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E–cigarettes for Smoking Cessation Guideline Update:

Technical report of evidence review and Summary of Findings

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Contents

Introduction

The Royal Australian College of General Practitioners produce clinical guidelines for GPs and other health professionals for a range of topics. In 2018, RACGP commissioned the Joanna Briggs Institute (JBI) and the JBI Adelaide GRADE Centre to assist with the update of the smoking cessation guideline. The RACGP requested this guideline be updated using GRADE methods. When using GRADE to develop guidelines, an evidence review is required where the end result is a GRADE Summary of Findings table, a summarised representation of the major synthesised findings along with a rating of the certainty in the synthesised evidence.

These Summary of Findings tables are then incorporated in Evidence to Decision Frameworks which the guideline panel work through to move from the evidence to making a recommendation, whilst ensuring that all the important aspects related to making structured recommendations are taken into account. This results in transparent recommendations that form the basis of any guideline.

This document provides the technical report of the evidence review and Summary of Findings table for the smoking cessation guideline update. It includes a description of the methods, a detailed assessment of the risk of bias of all included studies, an extraction of characteristics of each study, synthesised results per outcome and a summary of findings table per question including a rating of certainty in the evidence. This technical report addresses one clinical question for the smoking cessation guideline update; the question addressed is re the use of e-cigarettes for smoking cessation. A Cochrane review by Hartmann-Boyce et al. 2016 has been used as the current best available evidence to inform this question. The methods used for this technical report update those of Hartmann-Boyce 2016 et al.

General methods

Search strategy

OVID Medline and the Cochrane Controlled Register of Trials (CENTRAL) were searched from January 2016 to locate relevant studies. The search strategy used by Hartmann-Boyce et al. 2016 was reproduced in both of these citation databases. Ongoing studies (27) identified in the Cochrane review (pg 64) were also searched for individually. Members of the RACGP guideline panel were also contacted to identify any relevant trials.

Search terms

The following search strategies were used to locate studies. All searches were filtered to 1 January 2016 onwards.

Searches were conducted on 21st January 2019.

OVID Medline search

Search	Query	Records retrieved
#1	e-cig$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	1944
#2	electr$ cigar$.mp.	1581

#3	electronic nicotine.mp.	2250
#4	(vape or vaper or vapers or vaping).ti,ab.	345
#5	1 AND 2 AND 3 AND 4	1577
Limited to 2016 - current		

Cochrane CENTRAL search

Search	Query	Records retrieved
#1	e-cig* [All text] OR electr* cigar*[All text] OR electronic nicotine [All text] OR (vape or vaper or vapers or vaping) [title, abstract, keyword]	281
Limited to 2016 - current		

Study selection

Titles and abstracts of all records returned from database searching were screened in dependently by two members of the review team to determine if they met the inclusion criteria (see page 5). Inclusion was limited to Systematic reviews and randomised controlled trials (RCTs). Records to registered trials returned from the database searching were also assessed in full at their source (clinicaltrials.gov). The full text reports of potentially relevant studies were retrieved and reviewed independently by two members of the review team to confirm eligibility.
Where necessary, inclusion was determined by discussion between reviewers. Reasons for exclusion of any studies retrieved in full text were recorded by reviewers (see Appendix 1).

Risk of bias assessment

Where evidence/studies included from the Hartmann-Boyce et al. 2016 review is included, existing risk of bias assessments of relevant studies have been extracted and presented in this report to allow for ready completion of GRADE processes.

Reviewers independently assessed the risk of bias of additional RCTs (n = 11; one RCT Adriaens already appraised by Hartmann-Boyce et al. 2016) using the Cochrane tool (see Appendix 2). Assessment was based on method of randomisation, concealment of allocation, reasons for participant losses to follow-up, blinding, and selective outcome reporting.

Any disagreement between reviewers regarding assessment of risk of bias was resolved by discussion and achieving consensus between the reviewers.

Data extraction

Descriptive details and predetermined outcome data were extracted from each included RCT into individual tables of study characteristics.

Synthesis and meta-analysis

Meta-analyses from the Hartman-Boyce et al. 2016 Cochrane review was initially extracted. Additional data from more recently published trials has been incorporated to extend these meta-analyses. Statistical meta-analyses have been performed with Review Manager Software (RevMan V5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014).

Establishing certainty of the evidence

Summary of findings tables were developed using processes established by the GRADE working group and within the GRADEpro Guideline Development Tool software (GRADEpro GDT; McMaster University, 2015 (developed by Evidence Prime, Inc.), available from gradepro.org. The members of the review team discussed and reached consensus regarding each criterion for each outcome and comparison. The judgements relating to the GRADE criteria are therefore not final and the feedback of the guideline group on the judgements, particularly indirectness and imprecision, was requested; Summary of findings tables have been updated accordingly, based on the feedback received.

Results

This section presents the PICO question and selection and appraisal of studies located by the searching for this review. Extraction of relevant descriptive data and meta-analysis of smoking cessation data is also presented. Results pertinent to adverse events and safety of e-cigarettes are summarised in narrative.

Clinical question

Are electronic cigarettes effective aids for smoking cessation?

Criteria for inclusion and exclusion of studies

1. **Population**:
    - Smokers (all)
    - More dependent smokers
2. **Intervention**: electronic cigarette (e-cig).
3. **Comparison**: placebo, no intervention, NRT, or any pharmacotherapy
4. **Outcome**: Smoking cessation/abstinence, any reduction in smoking, cigarettes per day (CPD) reduced by 50%. Ideally biochemically validated rates were reported. Adverse events have also been included.
5. **Study designs:** RCTs, systematic reviews of RCTs.
6. **Other criteria:** Ideally 6 months follow up or longer, or at any lesser duration if the only reported.

Summary of Findings

Question: Nicotine containing e-cigarettes compared to NRT for smoking cessation

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Nicotine Replacement Therapy	With Nicotine Containing E-Cigarettes	Relative effect (95% CI)	Risk with Nicotine Replacement Therapy	Risk difference with Nicotine Containing E-Cigarettes
Smoking Cessation (follow up: range 8 weeks to 52 weeks; assessed with: Biochemically Validated (Expired Carbon Monoxide Concentration ≤ 10ppm))											
1498 (3 RCTs)	serious [a]	not serious	not serious [b]	serious [c]	none	⨁⨁◯◯ LOW	61/751 (8.1%)	103/747 (13.8%)	**RR 1.69** (1.26 to 2.28)	81 per 1,000	**56 more per 1,000** (21 more to 104 more)
50% CPD reduction											
0 (studies)						-			not estimable		

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Significant issues of contamination bias (participants using other interventions).

b. Participants of Lee et al. (2018) were patients presenting to the anaesthesia pre-operative clinic for elective surgery.

c. Confidence Intervals are relatively narrow (1.26 -2.28), However there are a low number of events, 164 events does not meet the Optimal Information Size threshold of 476.

Question: Nicotine containing e-cigarettes compared to placebo e-cigarettes for smoking cessation

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo E-Cigarettes	With Nicotine Containing E-Cigarettes		Risk with Placebo E-Cigarettes	Risk difference with Nicotine Containing E-Cigarettes
Smoking Cessation (follow up: range 3 weeks to 52 weeks; assessed with: Biochemical Validation (Expired Carbon Monoxide Concentrations ≤10ppm)											
787 (4 RCTs)	not serious	serious [a]	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	10/234 (4.3%)	45/553 (8.1%)	**RR 1.84** (0.95 to 3.62)	43 per 1,000	**36 more per 1,000** (2 fewer to 112 more)
50% reduction in CPD											
0 (studies)						-			not estimable		

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Statistical heterogeneity is low, but large variation in the estimates of treatment of effect.

b. The study by Felicone et al. (2019) included participants from an outpatient opioid maintenance clinic, who were currently receiving a buprenorphine/naloxone combination.

c. Confidence intervals are wide (0.94 - 3.62). There are also few events, 55 events does not meet the Optimal Information Size threshold of 611.

Question: Nicotine containing e-cigarettes compared to no intervention for smoking cessation

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With No Intervention	With Nicotine Containing E-Cigarettes	Relative effect (95% CI)	Risk with No Intervention	Risk difference with Nicotine Containing E-Cigarettes
Smoking Cessation (follow up: range 8 weeks to 16 weeks; assessed with: Biochemical Validation (Expired Carbon Monoxide Concentrations ≤ 10ppm))											
118 (2 RCTs)	serious [a]	serious [b]	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	3/39 (7.7%)	14/79 (17.7%)	**RR 4.93** (0.97 to 25.19)	77 per 1,000	**302 more per 1,000** (2 fewer to 1,861 more)
50% reduction in CPD											
0 (studies)						-			not estimable		

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Potential for contamination in the study by Carpenter et al. (2017) – control group registered use of e-cigs

b. Some concerns over statistical heterogeneity. Widely differing estimates of treatment effect.

c. Confidence Intervals are very large (0.97 - 25.19). Low number of events, 14 events does not meet the Optimal Information Size threshold of 172.

Question: Nicotine containing e-cigarettes and NRT compared to placebo e-cigarettes and NRT for smoking cessation

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Placebo E-Cigarettes and NRT	With Nicotine Containing E-Cigarettes and NRT	Relative effect (95% CI)	Risk with Placebo E-Cigarettes and NRT	Risk difference with Nicotine Containing E-Cigarettes and NRT
Smoking Cessation (follow up: range 8 weeks to 16 weeks; assessed with: Biochemical Validation (Expired Carbon Monoxide Concentrations ≤ 10ppm))											
1039 (2 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	22/519 (4.2%)	33/520 (7.5%)	**RR 1.77** (1.07 to 2.93)	42 per 1,000	**33 more per 1,000** (2 more to 82 more)
50% reduction in CPD											
0 (studies)						-			not estimable		

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Assessment of methodological quality in the study by Walker et al. (2019) was restricted as only the study protocol/abstract were made available.

b. Confidence Intervals are large (1.07 - 2.94). Low number of events, 61 events does not meet the Optimal Information Size threshold of 815.

Question: Nicotine containing e-cigarettes and NRT compared to NRT alone for smoking cessation

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With NRT Alone	With Nicotine Containing E-Cigarettes and NRT	Relative effect (95% CI)	Risk with NRT Alone	Risk difference with Nicotine Containing E-Cigarettes and NRT
Smoking Cessation (follow up: range 8 weeks to 16 weeks; assessed with: Biochemical Validation (Expired Carbon Monoxide Concentrations ≤ 10ppm))											
625 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	3/125 (2.4%)	33/520 (7.0%)	**RR 2.92** (0.91 to 9.33)	24 per 1,000	**46 more per 1,000** (2 fewer to 200 more)
50% reduction in CPD											
0 (studies)						-			not estimable		

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Assessment of methodological quality in the study by Walker et al. (2019) was restricted as only the study protocol/abstract were made available.

b. Confidence intervals are very large, ranging from 0.91 to 9.33. Low number of events, 38 events does not meet the optimal information size threshold of 332

Question: Nicotine containing e-cigarettes and/or NRT and/or financial incentives compared to usual care for smoking cessation

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Usual Care	With Nicotine Containing E-Cigarettes and/or NRT and/or financial incentive	Relative effect (95% CI)	Risk with Usual Care	Risk Nicotine Containing E-Cigarettes and/or NRT and/or financial incentive
Smoking Cessation (follow up: range 8 weeks to 16 weeks; assessed with: Biochemical Validation (Expired Carbon Monoxide Concentrations ≤ 10ppm))											
6006 (1 RCT)	very serious [a]	not serious	not serious	very serious [b]	none	⨁◯◯◯ VERY LOW	0/813 (0.0%)	38/5193 (0.7%)	**RR 12.07** (0.74 to 196.23)	0 per 1,000	**Incalculable**
50% reduction in CPD											
0 (studies)						-			not estimable		

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Halpern et al. (2018) at high risk of bias under the domains of performance, detection and attrition. Also at risk of contamination

b. Confidence intervals are very large, and range from 0.74 to 196.23. Low number of events, 38 events does not meet the optimal information size threshold of 18,726

Study selection

The search of PubMed and Cochrane CENTRAL returned 1858 records. Figure 1 presents the results of the process of study inclusion process conducted by the review team. Following screening of titles and abstracts, the full text of 20 studies were retrieved and assessed for eligibility. Reasons for exclusion of retrieved studies are presented in Appendix 1.

One study (Adriaens et al. 2014) was identified via hand searching of a retrieved systematic review and a further study was located and forwarded by a member of the RACGP guideline panel (Hajek et al. 2019). Overall, a further eleven (11) randomised trials were included in the review to add to the evidence available in the Hartmann-Boyce et al., review of 2016. Two of these studies (Cravo et al. 2016; Walele et al. 2016) reported adverse event/safety data only.

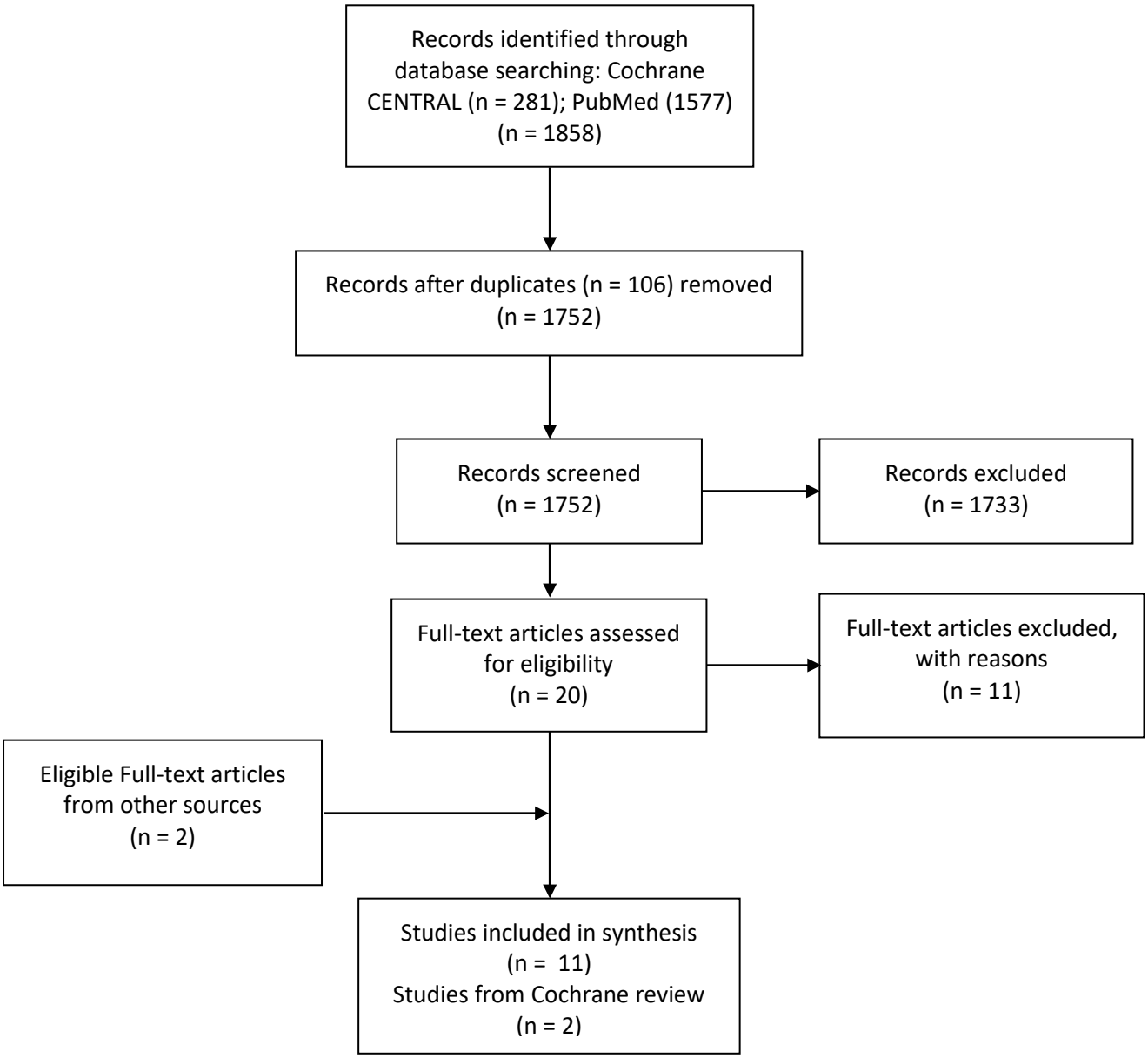


Figure 1: Flow diagram illustrating the results of database searching, citation screening and assessment and inclusion of full text studies (see Appendix 1 for reasons for exclusion of full text articles).

Two trials included in the Cochrane systematic review by Hartmann-Boyce et al. 2016 compared nicotine containing e-cigarettes to placebo e-cigarettes (Bullen et al. 2013; Caponnetto et al. 2013). One trial (Bullen et al. 2013) also included outcome data comparing nicotine containing e-cigarettes to NRT. Of the additional studies located, two (Felicone et al. 2019; Tseng et al. 2013) have been combined with the data comparing nicotine containing e-cigarettes vs. placebo e-cigarettes, and two (Hajek et al. 2019; Lee et al. 2018) have been combined with the outcome data comparing nicotine e-cigarettes vs. NRT. Two trials (Baldassarri et al. 2018; Walker et al. 2019) investigated combination therapy and compared NRT and nicotine containing e-cigarettes with NRT and placebo e-cigarettes. Finally, two new studies located during the study selection have provide outcome data comparing nicotine containing e-cigarettes to no-intervention (Adriaens et al. 2014; Carpenter et al. 2017).

Methodological quality

Overall the risk of bias of included studies, both from Hartmann-Boyce et al. 2016 and the newly identified RCTs was low, with the majority of the potential for bias coming from the unclear, or lack of reporting of domains. High risk of bias was noted for the domains of performance and detection bias, due to the lack of blinding that occurred. Often, the nature of the intervention did not permit blinding of participants or study personnel. However, as many outcomes were recorded through self-report, the risk of performance or detection bias remains high. Three studies (Hajek et al. 2019; Halpern et al. 2018; Lee et al. 2018) were at risk of contamination, as study participants recorded using the unassigned treatment prior to the reporting of the final outcome data, or at baseline. The study comparing combination therapy (Baldassarri et al. 2018) reported that the use of e-cigarettes was encouraged but not mandatory (Table 1).

Once included study (Walker et al. 2019) was only available as a conference abstract. After consulting the study protocol, the methodological quality of the study was assessed. However, the limited availability of study detail prevented complete assessment.

Allocation

Random assignment was generally well carried out, with the methods of randomisation reported in all but two studies. Whilst both Carpenter et al. (2017) and Felicone et al. (2019) report that randomisation had taken place, the methods of this procedure were not clearly documented to allow for assessment as low risk of bias.

Few studies provided methodological detail as how allocation to treatment groups was concealed. The majority of studies recording an ‘unclear’ risk of bias, as insufficient detail was provided to allow assessment as either low or high risk of bias.

Blinding

Blind assignment was also generally well performed and reported. One study (Walele et al. 2016) had an ‘unclear’ risk of bias, as blinding was stated to have occurred, but the methods of how blinding was achieved were not reported. Three studies meanwhile were appraised by the methods group as having a high risk of bias, as blinding was not achievable due to the study design, and participants were directly aware of the treatment group in which they were assigned.

Detection bias (biochemical validation of smoking outcomes)

Where the outcome of smoking cessation was reported, biochemical validation was utilised in all cases. Carbon monoxide concentrations in the breath were assessed and smoking cessation was confirmed if these concentrations fell below a certain threshold (unique to study). Of the studies that report cessation outcome data, all but one has low risk of detection bias. Hajek et al. 2019 did include biochemically validated smoking cessation outcome data, however, as this study also included outcome data related to adverse events and blinding of participants, personnel or assessors was not achieved, this domain was scored as high risk of bias.

The two studies that report adverse event outcome data only (Cravo et al. 2016; Walele et al. 2016), were reported as having an unclear risk of bias, due to insufficient information provided in text as to whether the outcome assessors were blind to participant assignment or not.

Incomplete outcome data

Overall, the included studies were at low risk of attrition bias. Few studies reported no withdrawals, or an even number of withdrawals between groups that were explained in narrative. Of the studies that recorded a low risk of bias, an intention to treat analysis was performed appropriately. Three studies (Carpenter et al. 2017; Cravo et al. 2016; Felicone et al. 2019) had an unclear risk of bias for this domain, due to no mention of an intention to treat analysis or for providing insufficient information to allow a rating of either high or low risk of bias.

Selective reporting

The majority of studies included reported an unclear risk of bias, due primarily to the study authors not referencing a study protocol, or where slight differences from the protocol were inadequately discussed in the final report. Hajek et al. (2019) had significant deviations from the protocol, including multiple outcomes pre-specified that were not addressed or discussed in the review, and is at a high risk of reporting bias. The study by Halpern et al. (2018) is also at high risk of reporting bias, as only participants who 'reported' abstinence were tested, to biochemically confirm their abstinence. This allows for participants who didn't want to provide samples to easily avoid this component of the study.

Other potential sources of bias

Two studies (Hajek et al. 2019; Lee et al. 2018) were at significant risk of contamination bias, as study participants reported using the unassigned treatment prior to the reporting of the outcome data. In both studies, the authors report the percentage of participants in each treatment group who used the non-assigned treatment. However, these participants have been combined in the outcome data for smoking cessation, and not discussed by the authors. As such, the studies are at significant risk of contamination. Additionally Baldassarri et al. (2018) outlined a period of observation following the initial intervention in which participants were permitted to use any available therapies for tobacco treatment. Participants in this study were also advised not to use the e-cigarette if the patch alone proved adequate to prevent withdrawal and smoking cravings. There is also the potential for some contamination in the study by Carpenter et al. (2017) however this was inadequately discussed by the study authors.

Table 1: Methodological quality summary: judgements extracted from Cochrane review (Hartmann-Boyce et al. 2016) and those of individual RCTs assessed for this report.

	Random sequence generation (selection bias)	Allocation Concealment (selection bias)	Blinding (performance and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Detection bias	Other bias
Adriaens 2014*	+	?	+	+	?	+	
Baldassarri 2018**	+	?	+	+	?	+	-
Bullen 2013*	+	+	+	+	+	+	
Caponnetto 2013*	+	+	+	+	?	+	
Carpenter 2017**	?	?	-	?	?	+	-
Cravo 2016**	+	?	+	?	?	?	?
Felicone 2019**	?	?	+	?	?	+	+
Hajek 2019**	+	?	-	+	-	-	-
Halpern**	+	?	-	+	-	-	-
Lee 2018**	+	+	-	+	+	+	-
Tseng 2016**	+	?	+	+	?	+	+
Walele 2016**	+	?	?	+	?	?	?
Walker 2019**	+	?	+	?	?	+	?

* Denotes study assessment extracted directly from Cochrane review Hartmann-Boyce et al. 2016.

**Denotes study assessment performed by review team. Corresponding details can be referred to in Table 2 below. + denotes low risk of bias, ? unclear risk of bias and – denotes high risk of bias. Where no indication is made (blank) data was not available (earlier version of Cochrane tool).

Table 2: Critical appraisal results of included RCTs assessed using the Cochrane Risk of Bias tool (see Appendix 2).

ID	Source of bias						
	Selection bias		Performance bias	Detection bias (validation)	Attrition bias	Reporting bias	Other
	Random sequence generation	Allocation concealment					
Baldassarri 2018	Random number generator with blocked randomization: **L**	Insufficient information to permit judgment of 'Low risk or High risk' : **U**	Investigators and participants blinded to treatment assignment: **L**	Primary outcome (CPD) by questionnaire. Exhaled CO measured (unclear who measured this outcome). Both measured at week 2, 4, 6, 8 and 24: **L**	Loss to follow-up at week 24 was 20%. There was no significant differences in loss to follow-up among all demographic factors except type of insurance however data not provided. ITT analysis conducted – assuming those lost to follow-up were smokers: **L**	No protocol was provided by the authors. **U**	Use of e-cigarettes was encouraged but not mandatory – at discretion of participants. Different smoking 'style' Longer/slower puff also required. 16 week period of observation during which participants were permitted to use any available therapies for tobacco treatment. **H**

ID	Source of bias						
	Selection bias		Performance bias	Detection bias (validation)	Attrition bias	Reporting bias	Other
	Random sequence generation	Allocation concealment					
Carpenter 2017	Authors state: Randomisation stratified by motivation to quit in the next 30 days (0-6 vs. 7-10 on a VAS scale) but proportioned 2:1 (ENDS: control) to increase precision estimates for e-cigarette uptake and usage. Randomisation Process not described: **U**	Insufficient information to permit judgment of 'Low risk or High risk' **U**	The study participants were not blinded to their treatment assignment. **H**	No information provided as to whether outcome assessors were blinded to participant treatments. However primary outcomes were measured using validated, biochemical means: **L**	Paper states : Assessment of cessation-related behaviours (quit attempts, abstinence) followed an intent-to treat approach' however no further information provided: **U**	Methods on how each primary outcome will be measured are not outlined in the protocol. Floating abstinence not mentioned in protocol, neither is product evaluation, motivation to quit and biomarkers of exposure: **U**	Potential for contamination between groups: **H**

ID	Source of bias						
	Selection bias		Performance bias	Detection bias (validation)	Attrition bias	Reporting bias	Other
	Random sequence generation	Allocation concealment					
Cravo 2016	Randomisation was performed using an Interactive Web Response System (IWRS; Almac Clinical Technologies). Age was selected as a stratification factor (21–39 years or ≥40 years). The stratified randomisation ensured balanced allocation of both age groups to the two study arms: **L**	Insufficient information to permit judgment of 'Low risk or High risk' **U**	Due to the nature of the intervention, blinding of subjects or personnel was not possible. However as the primary outcomes were all health outcomes biochemically validated, performance bias is unlikely: **L**	No information provided as to whether outcome assessors were blinded to participant treatments. **U**	Loss to follow up was relatively even between groups and these differences were discussed. There was one death in the intervention group (unrelated to intervention). However ITT not mentioned: **U**	All of the study's pre-specified outcomes in the protocol (NCT02029196) have been reported. But lacking detail as to what adverse events will be measured: **U**	Use of CCs in the EVP arm would not generally lead to termination although subjects were reminded to use only the EVP. Also This work was funded and supported by Fontem Ventures B.V. Funding bias? **U**

ID	Source of bias						
	Selection bias		Performance bias	Detection bias (validation)	Attrition bias	Reporting bias	Other
	Random sequence generation	Allocation concealment					
Felicone 2019	Authors state that they used a mixed factorial, simple randomization, double-blind study design. However the methods of randomization are not provided. Insufficient information to permit judgment of 'Low risk or High risk': **U**	Insufficient information to permit judgment of 'Low risk or High risk' **U**	Double-blinded: **L**	No information provided as to whether outcome assessors were blinded to participant treatments. However primary outcomes were measured using validated, biochemical means: **L**	Of those that were randomised 70.9% completed the 4-week follow-up session (n = 13 active;n= 9 placebo). Non-completers and completers did not differ on any demographic or smoking history characteristic shown in Table 1, but no ITT: **U**	No protocol was provided by the authors. **U**	None to report: **L**

ID	Source of bias						
	Selection bias		Performance bias	Detection bias (validation)	Attrition bias	Reporting bias	Other
	Random sequence generation	Allocation concealment					
Hajek 2019	Randomisation sequences (1:1 ratio in permuted blocks of 20, stratified according to trial site) were generated with the use of a pseudorandom number generator in Stata software and were embedded into an application that only revealed the next treatment assignment once a participant had been entered into the database: **L**	No information provided: **U**	Participants and personnel un-blinded due to nature of the intervention and some outcomes are likely to be influenced by lack of blinding: **H**	Whilst some outcomes were biochemically validated, and therefore not likely to be affected by the lack of blinding, other outcomes (AEs etc.) are likely to be affected by lack of blinding: **H**	Loss to follow-up is relatively even between groups (102/44 - ECIG) (83/439 - NRT). However discussion as to the patterns behind this attrition is lacking. Insufficient information to permit judgment of 'Low risk or High risk': **L**	Slight variances - Protocol mentions cost-efficacy; Smoking reduction in participants who did not achieve full abstinence; Treatment ratings; Adverse reactions. Protocols states to measure at 4, 24 and 52 weeks whereas paper measured at 4, 26, and 52 weeks: **H**	Risk of contamination between the groups. All Participants were asked to sign a commitment to not use the non-assigned treatment for at least 4 wks after their quit date. No details provided as to how this was enforced. Supplementary material provides number of people in each group who use the 'un-assigned' intervention **H**

ID	Source of bias						
	Selection bias		Performance bias	Detection bias (validation)	Attrition bias	Reporting bias	Other
	Random sequence generation	Allocation concealment					
Halpern 2018	Randomisation stratified according to employer recruited from. Unbalanced to achieve power for between group contrasts. **L**	Insufficient information to permit judgment of 'Low risk or High risk' **U**	Pragmatic trial using opt-out recruitment. Participants were informed of their group. 20% were 'engaged' with the program **H**	Sustained abstinence reported by participants on survey at months 1, 3 and 6. Biochemical confirmed by urine cotinine <20ng/ml. Where e-cig user > 20ng/ml, blood carboxyHb <4% accepted. Lab techs were blinded to treatment. Only subjects who 'reported' abstinence were tested. **H**	Significant loss to follow-up reported, however these numbers were balanced between groups. The authors report this as 'engaged' participants. Approximately 80% of participants randomly assigned to each group were not 'engaged' (logged in to trial website at least once). However an ITT was properly conducted: **L**	Only subjects who 'reported' abstinence were tested. Allows for participants who didn't want to provide samples to easily avoid it. All of the studies pre-specified outcomes were reported. **H**	NJOY provided e-cigarettes at no cost. Some potential for contamination as 9.6% of participants randomised to receive 'usual care' reported that they were currently using e-cigarettes. **H**

ID	Source of bias						
	Selection bias		Performance bias	Detection bias (validation)	Attrition bias	Reporting bias	Other
	Random sequence generation	Allocation concealment					
Lee 2018	Randomisation was computer-generated, with randomly permuted block sizes of 3 or 6, in a 2:1 ratio using the ralloc program in Stata version 13: **L**	Allocation was concealed by consecutively numbered, sealed, opaque envelopes: **L**	Due to the nature of the intervention, blinding of subjects was not possible. However, healthcare providers were blinded throughout the perioperative period: **H**	Outcome adjudicators were blinded wherever possible, but some participants unintentionally unblinded the investigators while reporting side-effects. Primary outcomes were measured using validated, biochemical means: **L**	Loss to follow up was 10% in the NRT group and 5% in the END group. However as the group sizes were small these were only 1 participant lost to follow-up for each group. Discussion is otherwise limited: **L**	All of the study's pre-specified outcomes in the protocol (NCT02482233) have been reported: **L**	Risk of contamination between groups. 30% of the participants randomised to NRT group used an e-cigarette between 30-days post-randomisation and 8-wks post-randomisation. 10% of the participants randomised to the END group used a form of NRT between 30-days post-randomisation and 8-weeks post-randomisation: **H**

ID	Source of bias						
	Selection bias		Performance bias	Detection bias (validation)	Attrition bias	Reporting bias	Other
	Random sequence generation	Allocation concealment					
Tseng 2016	Subjects were randomised. A randomisation scheme was computer generated by using randomly permuted blocks of sizes 2, 4, and 6: **L**	Blinding of the allocation of nicotine or placebo EC was ensured by the identical appearance of the ECS: **L**	The EC's used were identical in appearance to ensure that both personnel and participants were adequately blinded: **L**	No information stated in text as to the level of blinding for outcome assessors. However the primary outcomes were measured using validated, biochemical means: **L**	Loss to follow-up was relatively even in the two groups, ITT performed: **L**	No protocol was provided by the authors: **U**	None to report: **L**
Walele 2016	Randomisation of subjects to one of the four product use sequences was performed according to randomisation codes produced using the PROC PLAN procedure of SAS®version 9.4: **L**	Insufficient information to permit judgment of 'Low risk or High risk': **U**	Part 2 of this study was blinded. However the details as to the methods of blinding, and whether the study personnel were also blinded are absent from the report. Insufficient information to permit judgment of "Low risk or High risk': **U**	No information provided as to the blinding of the outcome assessors. However as the participants in part 1 were unblinded, and they were required to report any adverse-events, there is some concern. However, more information is required to permit a judgment of either 'Low risk or High risk': **U**	There were no withdrawals: **L**	This paper reports on safety assessment measures only (another paper reports on effects) and these are not mentioned in trial protocol: **U**	Study funded and supported by Fontem Ventures who are the manufacturer of the EVP prototype used in this study. Some authors are employees of the company. Funding bias? **U**

ID	Source of bias						
	Selection bias		Performance bias	Detection bias (validation)	Attrition bias	Reporting bias	Other
	Random sequence generation	Allocation concealment					
Walker 2019	Participants randomised by computer, using stratified block randomization: **L**	Insufficient information to permit judgment of 'Low risk or High risk' **U**	Participants/researchers were masked to the nicotine content of the e-cigarettes. However, for the group assigned to NRT alone, blinding could not be achieved: **H**	No information provided as to whether outcome assessors were blinded or not. However, the primary outcome was measured using standard, biochemically validated means: **L**	Insufficient information to permit judgment of 'Low risk or High risk' **U**	Insufficient information to permit judgment of 'Low risk or High risk' **U**	Insufficient information to permit judgment of 'Low risk or High risk' **U**

Included study characteristics

<table>
<tr><th>ID</th><th>Adriaens (2014)</th></tr>
<tr><td>Bibliographic reference</td><td>Adriaens K, Van Gucht D, Declerck P, Baeyens F. 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 Oct 29;11(11):11220-48.</td></tr>
<tr><td>Study type</td><td>3-arm, randomised controlled trial</td></tr>
<tr><td>Country</td><td>Belgium</td></tr>
<tr><td>Study Setting</td><td>Community and Laboratory</td></tr>
<tr><td>Number of participants</td><td>Total N: 50
>Intervention Group 1 (Joyetech eGo-C): n=16 >Intervention Group 2 (Kanger T2-CC): n=17 >Comparison (Conventional Cigarettes): n=17</td></tr>
<tr><td>Number of withdrawals</td><td>>Intervention Group 1 (Joyetech eGo-C): 1/16 (15 present at 8-week follow-up) >Intervention Group 2 (Kanger T2-CC): 1/17 (16 present at 8-week follow-up) >Comparison (Conventional Cigarettes): 1/17 (16 present at 8-week follow-up)</td></tr>
<tr><td>Patient characteristics</td><td>
<table>
<tr><th>Group</th><th>Gender (ratio female/male)</th><th>Age</th><th>% Employed</th><th># Cigarettes</th><th>FTCD</th><th>BDI</th><th>eCO</th></tr>
<tr><td>Ecig 1</td><td>7/9</td><td>44.75 (13.54)</td><td>78.75</td><td>20.13 (9.41)</td><td>5.81 (1.94)</td><td>6.81 (7.06)</td><td>19.13 (6.11)</td></tr>
<tr><td>Ecig2</td><td>10/6</td><td>46.06 (12.76)</td><td>71.25</td><td>20.63 (6.62)</td><td>6.31 (1.45)</td><td>6.14 (11.99)</td><td>17.38 (6.29)</td></tr>
<tr><td>Control</td><td>10/6</td><td>40.31 (13.21)</td><td>74.69</td><td>16.69 (5.49)</td><td>5.24 (1.62)</td><td>3.56 (4.34)</td><td>16.25 (8.92)</td></tr>
<tr><td>All groups</td><td>27/21</td><td>43.71 (13.13)</td><td>74.90</td><td>19.15 (7.41)</td><td>5.79 (1.70)</td><td>5.51 (8.35)</td><td>17.58 (7.17)</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Both intervention groups were provided with guidance on how to use the EC and instructed to use the EC ad libitum. Both groups were also provided with tobacco-flavoured e-liquid containing 18mg/ml nicotine.</td></tr>
<tr><td>Comparison</td><td>Tobacco Cigarettes (during first 8-weeks of study)
Note: After the 3rd lab session (week-8). This group were also provided with EC’s, but no instructions were provided. Therefore, all of the data extracted is only for the first 8-weeks of study, to compare EC’s versus no intervention.</td></tr>
<tr><td>Length of follow-up</td><td>8-weeks</td></tr>
<tr><td>Outcome measures/results</td><td>Cessation: measured but definition not provided, validated with expired CO (5ppm or less).
<table>
<tr><th>E-Cigs</th><th>Conventional Cigarettes</th></tr>
<tr><td>11/33</td><td>0/17</td></tr>
</table>
Adverse events and biomarkers: eCO, salivary cotinine, “complaints, made in online diaries”
<table>
<tr><th>Item relevant for</th><th>Complaints</th></tr>
<tr><td>Cigarette and e-cig</td><td>Bad taste
Dry mouth/throat
Irritated mouth/throat
Dizziness</td></tr>
</table>
</td></tr>
</table>

	Headache Nausea Increased heart rate/palpitations Increased weight Concerns about health risks **E-cig** Technical problems with unit
Source of funding	No external funding for this study was obtained. Electronic cigarettes and e-liquids were purchased at E-cig4U (`t Rond 10, 4285 DE Woudrichem, The Netherlands with balances of previous research funds obtained by Frank Baeyens
Additional comments	After two months, we observed that 34% of the e-cig groups had stopped smoking tobacco cigarettes, versus 0% of the control group (difference $p < 0.01$). This is how the values were extracted above.

ID	Baldassarri (2018)		
Bibliographic reference	Baldassarri SR, Bernstein SL, Chupp GL, Slade MD, Fucito LM, Toll BA. Electronic cigarettes for adults with tobacco dependence enrolled in a tobacco treatment program: A pilot study. Addictive Behaviors 2018 May;80:1-5.		
Study type	2-arm, randomised controlled trial		
Country	New Haven, Connecticut, United States		
Study Setting	Recruited from outpatient clinics and through referrals from medical providers		
Number of participants	Total N: 40 >Intervention Group (nicotine patch, counselling and nicotine E-cigarette): n=20 >Comparison (nicotine patch, counselling and non-nicotine E-cigarette): n=20		
Number of withdrawals	> Paper reports 20% loss to follow-up at week 24 however distribution across Intervention and Comparison Groups is not provided.		
Patient characteristics		**Overall (n=40)**	**Combination therapy including Nicotine E-cigarette (n=20)**	**Combination therapy including Non-Nicotine E-cigarette (n=20)**
	Age, mean (SD), years	53 (10.1)	52.2 (12.2)	53.8 (7.8)
	Female, No. (%)	21 (52.5)	8 (40)	13 (65)
	Non-white race, No. (%)	14 (35)	6 (15)	8 (20)
	Insurance, No. (%)			
	Medicaid	18 (45)	8 (40)	10 (50)
	Medicare	11 (27.5)	4 (20)	7 (35)
	Private	11 (27.5)	8 (40)	3 (15)
	Education, No. (%)			
	Less than high school	4 (10)	3 (15)	1 (5)
	High school	25 (62.5)	12 (60)	13 (65)
	College or University	6 (15)	1 (5)	5 (25)
	Graduate or Doctoral	5 (12.5)	4 (20)	1 (5)
	Employment status, No (%)			
	Unemployed	9 (22.5)	4 (20)	5 (25)
	Employed	14 (35)	8 (40)	6 (30)
	Retired	6 (15)	3 (15)	3 (15)
	Disabled	11 (27.5)	5 (25)	6 (30)
	Smoking characteristics			
	Baseline reported cigarettes smoked per day, mean (SD)	17 (11.5)	17 (10.9)	17 (12.4)

	Estimated pack-years, mean (SD)	36 (21.5)	35 (20.4)	38 (23.1)
	Fagerstrom Test Score, Mean (SD)	5.8 (2.1)	5.7 (2.0)	6.0 (2.2)
	Time to first cigarette <30m mins, No (%)	35 (87.5)	17 (85)	18 (90)
	Baseline exhaled carbon monoxide	19 (10.2)	19 (9.7)	19 (10.8)
Intervention	Participants received standard care consisting of a two-week supply of nicotine patches provided at each study visit for the first 8 weeks and counselling provided at the initial study visit and each subsequent study visit. Counselling consisted of intensive counselling sessions with an Advanced Practice Registered Nurse behavioural tobacco treatment specialist or a clinical psychologist trained in motivational interviewing techniques and tobacco dependence pharmacotherapy. The intervention group also received a 2nd generation eGO style E-cigarette (650 mAh battery, EVOD clearomizer, 3.7 V, 1.8Ωsingle bottom coil), provided with e-liquid (24 mg/ml nicotine strength, 70/30 propylene glycol/vegetable glycerin, tobacco flavour), and were instructed to use it as needed as a substitute for tobacco to try to satisfy cravings to smoke. If the patch alone proved adequate to prevent withdrawal and smoking cravings, the subject was advised not to use the EC. Use of the EC as a substitute for cigarette smoking was encouraged but not considered mandatory and was at the discretion of participants.			
Comparison	Standard care (as described above) and an E-cigarette (described above) but 0 mg/ml nicotine.			
Length of follow-up	24 weeks			
Outcome measures/ results	**Smoking status (defined by 7-day point prevalence abstinence and confirmed by exCO≤6 ppm) (measured at week 24)** Combination therapy including Nicotine E-cigarette: 4/20 Combination therapy including Non-Nicotine E-cigarette: 2/20 **Self-reported change in reported cigarettes per day (mean, sd) at week 24** Combination therapy including Nicotine E-cigarette: -5.5, 11.5 Combination therapy including Non-Nicotine E-cigarette: -8.04, 11.6 **Adverse events** The most commonly reported adverse events were cough (30%), sore throat (22.5%), increased appetite (17.5%), and vivid dreams (17.5%) (no significant differences by treatment group).			

Source of funding	Funding was provided by the Yale School of Medicine, Section of Pulmonary, Critical Care, and Sleep Medicine and the National Heart, Lung, and Blood Institute grant.
Additional comments	If the patch alone proved adequate to prevent withdrawal/cravings the subject was advised not to use the E-cigarette. 16 week period of observation during which subjects were permitted to use any available therapies for tobacco treatment.

ID	Bullen 2013 (Included in Cochrane Review)		
Bibliographic reference	Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. Lancet 2013;382 (9905):1629–37.		
Study type	3 parallel groups randomised controlled trial		
Country	New Zealand		
Study Setting	Research Unit		
Number of participants	Total N = 657 (Randomized as 4:4:1) >Nicotine Electronic Cigarette (NEC) group: n = 289 >NRT (PATCH) group: n = 295 >Placebo Electronic Cigarette (PEC) group: n = 73		
Number of withdrawals	*Lost to follow-up at 6 months:* >NEC: 43/289 >PATCH: 58/295 >PEC: 15/73 *Discontinued treatment:* > NEC: 2/289 >PATCH: 22/295 >PEC: 1/73		
Patient characteristics		**Nicotine e-cigarettes (n=289)**	**Patches (n=295)**	**Placebo e-cigarettes (n=73)**
	Age (years)	43·6 (12·7)	40·4 (13·0)	43·2 (12·4)
	Women	178 (62%)	182 (62%)	45 (62%)
	Ethnicity*			
	New Zealand Māori	95 (33%)	95 (32%)	23 (32%)
	Non-Māori	194 (67%)	200 (68%)	50 (68%)
	Education below year 12† or no qualification	150 (52%)	123 (42%)	38 (52%)
	Average number of cigarettes (including Roll Your Own) smoked per day	18.4 (7.2)	17.6 (6.0)	17.7 (5.6)
	Age started smoking (years)	15.6 (4.7)	15.2 (3.8)	15.7 (5.1)
	Number of years smoking continuously	25.9 (13.1)	23.5 (12.9)	24.8 (13.7)
	Type pf tobacco usually smoked			
	Factory made only	167 (58%)	167 (57%)	47 (64%)
	Roll Your Own	92 (32%)	92 (31%)	21 (29%)

	Both	30 (10%)	35 (12%)	5 (7%)
	Lives with other smokers	151 (52%)	149 *51%)	42 (58%)
	At least 1 quit attempt in past 12 months	158 (55%)	169 (57%)	39 (53%)
	FTND score	5.6 (2.0)	5.5 (2.0)	5.5 (2.0)
	FTND >5 (high dependence)	157 (54%)	162 (55%)	40 (55%)
	GN-SBQ score	20.1 (7.9)	20.1 (8.4)	21.4 (8.6)
	Self-efficacy to quit ‡	3.7 (1.0)	3.7 (0.9)	3.6 (1.0)
	AUTOS total score	22.6 (7.2)	23.1 (7.6)	23.4 (7.3)
	Data are mean (SD) or n (%). FTND=Fagerström test of nicotine dependence. GN-SBQ: Glover-Nilsson smoking behavioural questionnaire. AUTOS=autonomy over smoking scale; higher scores indicate greater dependence. *All non-Māori ethnicity categories aggregated as non-Māori.25 †Age 16 or 17 years. ‡Self-efficacy to quit=belief in ability to quit this time, measured on scale of 1 to 5, 1=very low, 5=very high.			
Intervention	>NEC: Elusion brand e-cigarettes with nicotine cartridges. Cartridges were labelled as 16mg nicotine per ml, but contained 10-16 mg nicotine per ml. >PATCH: 21mg/24-hour patch (Participants given vouchers to exchange at pharmacy). Instructions provided to participants to use the patches daily, from weeks 1 to 12. (No information provided about brand of patches).			
Comparison	>PEC: Elusion brand e-cigarettes with cartridges identical in appearance to NEC, however contained no active nicotine (0mg)			
Length of follow-up	6 months-post start of intervention			
Outcome measures/ results	**Sustained (≤ 5 cigarettes allowed) validated (exhaled breath carbon monoxide concentrations <10ppm) at 6 months post-intervention**			
	NEC	*PATCH*	*PEC*	
	21/289	17/295	3/73	
	≥ 50% self-reported reduction in baseline cigarettes at 6 months			
	Participants reporting any adverse events (AE)			
	Proportion of AEs that were serious			
	Proportion of unrelated AEs			

	Nicotine e-cigarettes		**Patches**		**Placebo e-cigarettes**	
	N	**%**	**N**	**%**	**N**	**%**
Total	137	100%	119	100%	36	100%
Event type						
Serious *	27	19·7%	14	11·8%	5	13·9%
Any non-serious event	110	80·3%	105	88·2%	31	86·1%

	Relation to study treatment Definitely 0 1 0·8% 0 Probably 1 0·7% 1 0·8% 1 2·8% Possibly 5 3·6% 4 3·4% 1 2·8% Unrelated 131 95·6% 113 95·0% 34 94·4% 107 participants in the nicotine e-cigarettes group had a total of 137 events. 96 participants in the patches group had a total of 119 events. 26 participants in the placebo group had a total of 36 events. Event rate was 0·8 events per person month in nicotine e-cigarettes group and patches group, and 0·9 in placebo e-cigarettes group. The difference between the rates in the nicotine e-cigarettes group and patches group were not significant (incidence rate ratio 1·05, 95% CI 0·82–1·34, p=0·7). * Serious adverse event by convention includes: death (n=1, in nicotine e-cigarettes group), life threatening illness (n=1, in nicotine e-cigarettes group), admission to hospital or prolongation of hospital stay (12% of all events in nicotine e-cigarettes group, 8% in patches group, and 11% in placebo e-cigarettes group), persistent or significant disability or incapacity, congenital abnormality, medically important (6% of all events in nicotine e-cigarettes group, 4% in patches group, and 3% placebo e-cigarettes group). No serious adverse events in any groups were related to product use.
Source of funding	Health Research Council of New Zealand
Additional comments	Telephone-based behavioural support was available to all participants, but only a few from each group chose to access this support. >NEC: 115/289 >PATCH: 106/295 >PEC 26/73

ID	Caponnetto 2013 (Included in Cochrane Review)				
Bibliographic reference	Caponnetto P, Campagna D, Cibella F, Morjaria JB, Caruso M, Russo C, 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.				
Study type	3-arm double blind randomised controlled trial				
Country	Italy				
Study Setting	Outpatient clinic				
Number of participants	Total N = 657 >Group A: (7.2mg of nicotine) n = 100 >Group B: (7.2mg of nicotine followed by 5.4mg of nicotine) n =100 >Group C: (0mg of nicotine) n =100				
Number of withdrawals	*Lost to follow-up at 6 months:* >Group A: 35/100 (65 remaining) >Group B: 37/100 (62 remaining) >Group C: 45/100 (55 remaining)				
Patient characteristics		**Overall Sample (N = 300)**	**Group A (N = 100)**	**Group B (N = 100)**	**Group C (N = 100)**	**P**
	Males/Females (No)	190/110	61/39	66/34	63/37	NS
	Age (years ± SD)	44 ± 12.5	45.9 ± 12.8	43.9 ± 12.2	42.2 ± 12.5	*
	Age at initiation (mean ± SD)	16.8 ± 3.9	16.4 ± 3.9	17.3 ± 4.3	16.9 ±	NS
	Education (No. %)					
	Low	93 (31%)	28 (28%)	32 (32%)	33 (33%)	
	Intermediate	160 (53%)	57 (57%)	59 (59%)	44 (44%)	0.055
	High	47 (16%)	15 (15%)	9 (9%)	23 (23%)	
	Pack/yr (median [IQ range])	24.9 [14.0-37.0]	24.0 [14.3-37.0]	25.3 [16.9-38.8]	25.5 [12.0-35.0]	NS
	Cig/day (median [IQ range])	20.0 [15.0-25.0]	19.0 [14.0-25.0]	21.0 [15.0-26.0]	22.0 [15.0-27.0]	NS
	Past attempts to quit (% yes)	51	56	48	47	NS
	Number past attempts to quit (mean ± SD)	0.6 ± 0.7	0.7 ± 0.8	0.5 ± 0.6	0.6 ± 0.7	NS
	eCO (median [IQ range])	20.0 (15.0-28.0)	19.0 (15.5 - 29.0)	22.0 (16.0 - 29.0)	19.5 (14.0 - 28.0)	NS
	FTND (mean ± SD)	5.8 ± 2.2	5.6 ± 2.3	6.0 ± 2.1	5.8 ± 2.2	NS
	GN-SBQ score (mean SD)	20.0 ± 7.2	20.5 ± 7.0	20.5 ± 7.5	19.0 ± 7.2	NS
	BDI (median [IQ range])	6.0 [2.0-12.0]	7.0 [2.0-12.5]	6.0 [3.0-12.5]	5.0 [1.0-11.5]	NS
	BAI (median [IQ range])	7.0 [3.0-14.0]	7.0 [3.0-14.5]	8.0 [3.0-14.0]	6.5 [2.0-15.5]	NS

	Legend: SD – standard deviation; IQR – interquartile range; Pack/yrs – pack-years; Cig/day – Cigarettes smoked per day; eCO – exhaled carbon monoxide; FTND – Fagerstrom Test of Nicotine Dependence; GN-SBQ- Glover-Nilsson Smoking Behavioral Questionnaire; BDI – Beck Depression Inventory; BAI – Beck Anxiety Inventory. Data are reported for the overall sample and separately for each treatment group. Differences among groups were evaluated by x2 test for categorical variables, one-way analysis of variance (ANOVA) and Fisher protected LSD for parametric variables, and Kruskal-Wallis test for non-parametric variables. *p = 0.04 between A and C groups (ANOVA).
Intervention	>Group A: Model 401 e-cigarette. 12 week supply of nicotine cartridges (7.2mg of nicotine) >Group B: Model 401 e-cigarette. 6 week supply of nicotine cartridges (7.2mg of nicotine) and a further 6 week supply of reduced nicotine cartridges (5.4mg of nicotine)
Comparison	>Group C: Model 401 e-cigarette. 12 week supply of no-nicotine cartridges, flavoured with "sweet tobacco aroma"
Length of follow-up	12 months-post start of intervention
Outcome measures/ results	**Validated (exhaled breath carbon monoxide concentrations <7ppm) at 6-months post-intervention** *A* *B* *C* 12/100 10/100 5/100 **Validated (exhaled breath carbon monoxide concentrations <7ppm) at 12-months post-intervention** *A* *B* *C* 13/100 9/100 4/100 **Recorded AEs thought to be related to tobacco smoking and EC at baseline and at each study visit (7 follow-up visits over 12 weeks, plus at 24 and 52 weeks) in 'study diaries'** Safety analyses included all participants who were using the product at their scheduled visit. Figure 8 shows the frequency distribution (%) of the five most commonly reported adverse events (AEs), separately for each study groups. Before using e-cigarettes, at baseline, the most frequently reported AEs were cough (26%; average for all study groups combined), dry mouth (22%), shortness of breath (20%), throat irritation (17%), and headache (17%). We performed a between-group evaluation at baseline, at week-12 and at week-52; no difference was found in frequency distribution of AEs among study groups at all the three time-points (χ2 test). However, for all the investigated AEs, a significant reduction in frequency of reported symptoms was observed compared to baseline. Of all symptoms that progressively decreased throughout the study with the use of e-cigarettes, shortness of breath was substantially reduced from 20 to 4% already by week-2.
Source of funding	Supported by a grant-in-aid from Lega Italiana AntiFumo. Author (RP) has received lecture fees and research funding from Pfizer and GlaxoSmithKline, manufacturers of stop smoking medications. He has served as a consultant for Pfizer and Arbi Group Srl, the distributor of the CategoriaTM e-Cigarette.
Additional comments	Meta-analysis of Hartmann-Boyce et al. has combined the data from groups A and B in their meta-analysis. The participants in group A were also significantly older than the participants in group C (p = 0.04). This study used a model of e-cigarette that is no longer produced.

ID	Carpenter (2017)
Bibliographic reference	Carpenter MJ, Heckman BW, Wahlquist AE, Wagener TL, Goniewicz ML, Gray KM, Froeliger B, Cummings KM. A naturalistic, randomized pilot trial of E-cigarettes: uptake, exposure, and behavioral effects. Cancer Epidemiology and Prevention Biomarkers. 2017 Nov 10.
Study type	Three-arm, randomised controlled trial
Country	United States
Study Setting	Recruited from community
Number of participants	Total: N = 68 Intervention 1 (E-Cig with 16mg/ml nicotine): n=25 Intervention 2 (E-Cig with 24mg/ml nicotine): n=21 Control (Conventional Cigarettes): n = 22
Number of withdrawals	Intervention 1: 6/25 (19 completed the study at 4-month follow-up) Intervention 2: 6/21 (15 completed the study at 4-month follow-up) Control: 6/22 (16 completed the study at 4-month follow-up)

Patient characteristics

	Control (n=22)	16mg ENDS (n=25)	24mg ENDS (n=21)	P
Age, mean (SD)	42.3 (14.2)	43.3 (14.4)	40.9 (12.3)	0.8
% Male	36%	28%	57%	0.1
Race				0.6
% White	59%	56%	48%	
% Black or African American	41%	40%	52%	
Income				0.8
Less than 25k	55%	48%	48%	
More than 25k	36%	48%	48%	
Education				0.04
Some HS	5%	12%	5%	
HS	41%	8%	43%	
Some college	36%	56%	52%	
College or greater	18%	24%	0%	
% Employed full or part time	68%	44%	52%	0.3
Age began smoking	15.8 (3.2)	18.4 (4.6)	19.0 (8.4)	0.2
% Lives with another smoker	27%	56%	33%	0.3
Cigarettes per Day	16.7 (11.3)	13.9 (4.9)	15.3 (8.3)	0.9

<table>
<tr><td></td><td>
<table>
<tr><td>Heaviness of Smoking (0-6)</td><td>3.1 (1.3)</td><td>2.6 (1.3)</td><td>2.9 (1.4)</td><td>0.6</td></tr>
<tr><td>% Quit Attempts in past year</td><td>45%</td><td>36%</td><td>19%</td><td>0.2</td></tr>
<tr><td>Lifetime # Quit Attempts</td><td>4.0 (3.4)</td><td>5.5 (8.0)</td><td>3.0 (4.4)</td><td>0.2</td></tr>
<tr><td>Motivation to Quit Smoking (0-10)</td><td>4.0 (3.9)</td><td>5.0 (3.8)</td><td>4.4 (3.1)</td><td>0.6</td></tr>
<tr><td>Confidence to Quit Smoking (0-10)</td><td>4.7 (3.0)</td><td>3.4 (3.0)</td><td>4.3 (3.1)</td><td>0.3</td></tr>
<tr><td>Ever used e-cigarette</td><td>9%</td><td>4%</td><td>33%</td><td>0.01</td></tr>
<tr><td>Anyone you know use an e-cigarette</td><td>55%</td><td>52%</td><td>57%</td><td>0.9</td></tr>
<tr><td>Intend to use e-cigarette in future (0-10)</td><td>5.4 (3.3)</td><td>5.6 (2.9)</td><td>5.5 (3.4)</td><td>0.9</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Intervention 1: E-cigarette with cartridges containing 16mg/ml of nicotine
Intervention 2: E-cigarette with cartridges containing 24mg/ml of nicotine
Note: Participants were offered cartridges of either tobacco or menthol flavouring. No information is provided as to the number of participants receiving each flavour, and this is not taken into consideration in the analysis.</td></tr>
<tr><td>Comparison</td><td>No active intervention, however participants were free to purchase e-cigarettes. According to the authors 14% of all control participants reported that they had purchased and used an e-cigarette prior to the 4-month follow-up.</td></tr>
<tr><td>Length of follow-up</td><td>4-month follow-up</td></tr>
<tr><td>Outcome measures/Results</td><td>Validated (expired CO <6ppm) smoking cessation at 4-months
<table>
<tr><th>Control</th><th>16mg/ml e-cigs</th><th>24mg/ml 3-cigs</th></tr>
<tr><td>1/22</td><td>1/25</td><td>2/21</td></tr>
</table>
Note: This data was only provided as percentage of participants in each group that achieved smoking cessation and was verified with CO expiration (4.6% - Control, 4.0% -16mg/ml, 9.5% - 21mg/ml)
Adverse Events
During the course of the study, 11 24mg ENDS participants (52%) reported a total of 21 adverse events, compared with 9 16mg ENDS participants (36%) who reported 17 adverse events, and compared with 8 control participants (36%) who reported a total of 29 events. Collapsed across both ENDS groups, the most common side effects reported were cough (32%), nausea (24%) and mouth/throat irritation (16%), and in the control group, headache (24%), cough (21%) and mouth/throat irritation (17%). None of the adverse events resulted in study termination, or, amongst ENDS participants, early discontinuation of sampling.</td></tr>
<tr><td>Source of funding</td><td>Funding provided by NIH R21 DA037407 (MJC), P01 CA200512 (KMC, MJC, MLG), UL1 TR001450, and P30 CA138313.</td></tr>
<tr><td>Additional comments</td><td>The authors state that “Our general aim was to approximate the real-world scenario in which smokers are exposed to e-cigarette and decide on their own if and how they will use them”. Participants randomized to the control-arm of the experiment were free to purchase and use e-cigarettes is they wished. The authors only state that “Participants who received the 24mg product were significantly more likely to report independent purchase of an ENDS product compared to those who received 16mg product and those in the control group (57% vs. 28% vs. 14%; $p<0.05$).</td></tr>
</table>

ID	Cravo (2016)
Bibliographic reference	Cravo AS, Bush J, Sharma G, Savioz R, Martin C, Craige S, Walele T. A randomised, parallel group study to evaluate the safety profile of an electronic vapour product over 12 weeks. Regulatory Toxicology and Pharmacology. 2016 Nov 15;81:S1-4.
Study type	Multicentre, 2-arm, parallel group, randomised controlled trial
Country	Wales, UK
Study Setting	Multicentre, clinical research units
Number of participants	Total N = 419 > EVP (Electronic-vapour product aka e-cigarette): n=306 > CC (Conventional Cigarette): n = 102 **NOTE:** A subgroup of 40 subjects at the Covance centre (referred to as Cohort 2) stayed in confinement for the first study week. Subjects requiring only the ambulatory visits were labelled Cohort 1. The confinement component was included in order to monitor and evaluate study outcomes in subjects using exclusively the allocated products. All outcomes have been presented considering all subjects.
Number of withdrawals	>EVP: 20/306 (286 participants completed study) >CC: 1/102 (101 participants completed study)
Patient characteristics	In order to be included in the study, subjects of either gender had to be between 21 and 65 years of age, with a body mass index in the range of 18e35 kg/m2, to have smoked 5e30 cigarettes per day (CPD) for at least one year (self-reported) and to be in good health (as determined by a medical history, a physical examination, a 12-lead electrocardiogram [ECG], lung function tests and clinical laboratory evaluations).

	Statistic	All subjects		Cohort 2	
		EVP (N =306)	CC (N = 102)	EVP (N = 32)	CC (N =8)
Age (years)					
	Mean ± SD	3.41 ± 10.6	35.1 ± 10.6	34.7 ± 12.2	40.6 ± 15.4
Sex					
Males	N (%)	168 (54.9%)	58 (56.9%)	22 (68.8%)	6 (75.0%)
Females	N (%)	138 (45.1%)	44 (43.1%)	10 (31.3%)	2 (25.0%)
BMI (kg/m²)					
	Mean ± SD	25.8 ± 3.9	25.3 ± 3.7	25.0 ± 3.1	23.6 ± 4.1
Body weight (kg)					
	Mean ± SD	75.6 ± 13.7	73.9 ± 13.6	75.4 ± 11.5	71.9 ± 14.8
eCO (ppm)					
	Mean ± SD	15.8 ± 6.3	16.7 ± 7.3	15.0 ± 5.4	15.1 ± 4.0
Daily cigarette use history					

	5-10 CPD	N (%)	109 (35.6%)	32 (31.4%)	12 (37.5%)	1 (12.5%)
	11-20 CPD	N (%)	172 (56.2%)	63 (61.8%)	17 (53.1%)	7 (87.5%)
	21-30 CPD	N (%)	25 (8.2%)	7 (6.9%)	3 (9.4%)	0 (0%)
	FTND classification					
	Mild	N (%)	91 (29.7%)	30 (29.4%)	13 (40.6%)	2 (25.0%)
	Moderate	N (%)	173 (56.5%)	55 (53.9%)	14 (43.8%)	6 (75.0%)
	Severe	N (%)	42 (13.7%)	17 (16.7%)	5 (15.6%)	0 (0%)
	ISO nicotine yield of CCs smoked (mg)					
		Mean ± SD	0.81 ± 0.13	0.81 ± 0.14	0.81 ± 0.15	0.73 ± 0.18
	ISO tar yield of CCs smoked (mg)					
		Mean ± SD	9.2 ± 1.5	9.2 ± 1.5	9.0 ± 1.6	8.3 ± 2.0
Intervention	E-vapour product (e-cigarette): Subjects randomised to the EVP arm could choose between two different e-liquids, which differed solely in their flavour: a menthol-flavoured e-liquid with 2.0% nicotine (2.7 mg nicotine/capsule) and a tobacco flavoured e-liquid with 2.0% nicotine (2.7 mg nicotine/capsule). Each capsule was expected to provide 40 to 60 puffs, depending on the user's puffing behaviour					
Comparison	Conventional Cigarettes: Subjects randomised to the CC arm used their own usual CC brand (representative of the UK market; mean ISO nicotine yield 0.81 mg and mean ISO tar yield 9.2 mg).					
Length of follow-up	12-weeks post-randomisation					
Outcome measures/results	**Adverse events**					

AE's (%) by severity and relationship to product	**EVP (n=306)**	**CC (n=102)**
Total	1515 (100%)	225 (100%)
SAEs (including deaths)	5 (0.3%)	0 (0%)
AEs leading to study withdrawal	2 (0.1%)	0 (0%)
AEs by severity		
Mild	449 (29.6%)	64 (28.4%)
Moderate	827 (54.6%)	129 (57.3%)
Severe	239 (15.8%)	32 (14.2%)
AEs by relationship to product		
Almost definitely related	19 (1.3%)	0 (0%)
Probably related	71 (4.7%)	0 (0%)

Possibly related	752 (49.6%)	0 (0%)
Unlikely to be related	246 (16.2%)	0 (0%)
Not related	427 (28.2%)	225 (100%)

	EVP (N=306)	**CC (N=102)**
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	85 (27.8%)	9 (8.8%)
Cough	52 (17.0%)	8 (7.8%)
Nasal congestion	14 (4.6%)	1 (1.0%)
Dry throat	9 (2.9%)	0
Rhinorrhea	4 (1.3%)	1 (1.0%)
Dyspnea	3 (1.0%)	0
Nervous system disorders		
Headache	145 (47.4%)	34 (33.3%)
Disturbance in attention	22 (7.2%)	2 (2.0%)
Dizziness	14 (4.6%)	2 (2.0%)
Gastrointestinal disorders		
Nausea	27 (8.8%)	1 (1.0%)
Toothache	21 (6.9%)	4 (3.9%)
Abdominal pain upper	19 (6.2%)	2 (2.0%)
Dyspepsia	16 (5.2%)	1 (1.0%)
Vomiting	15 (4.9%)	2 (2.0%)
Mouth ulceration	12 (3.9%)	0
Diarrhoea	11 (3.6%)	3 (2.9%)
Dry mouth	8 (2.6%)	0
Constipation	8 (2.6%)	4 (3.9%)
Abdominal discomfort	3 (1.0%)	0
Abdominal pain	3 (1.0%)	0
Oral pain	3 (1.0%)	0
Infection and infestation		
Nasopharyngitis	34 (11.1%)	8 (7.8%)
Upper respiratory tract infection	17 (5.6%)	8 (7.8%)
Gastroenteritis	10 (3.3%)	0
Influenza	7 (2.3%)	2 (2.0%)
Rhinitis	6 (2.0%)	0
Tonsillitis	4 (1.3%)	1 (1.0%)

	Oral herpes	3 (1.0%)	2 (2.0%)
	Psychiatric disorders		
	Nicotine dependence (craving and/or desire to smoke)	84 (27.5%)	13 (12.7%)
	Anger	23 (7.5%)	1 (1.0%)
	Depressed mood	20 (6.5%)	0
	Frustration	22 (7.2%)	1 (1.0%)
	Impatience	22 (7.2%)	2 (2.0%)
	Insomnia	14 (4.6%)	2 (2.0%)
	Middle insomnia	18 (5.9%)	1 (1.0%)
	Restlessness	17 (5.6%)	2 (2.0%)
	Anxiety	13 (4.2%)	0
	Sleep disorder	11 (3.6%)	2 (2.0%)
	Abnormal dreams	7 (2.3%)	0
	Nightmare	6 (2.0%)	1 (1.0%)
	Nervousness	4 (1.3%)	0
	General disorders and administration site conditions		
	Irritability	33 (10.8%)	1 (1.0%)
	Hunger	10 (3.3%)	0
	Fatigue	9 (2.9%)	1 (1.0%)
	Chest discomfort	9 (2.9%)	0
	Pain	3 (1.0%)	0
	Metabolism and nutrition disorders		
	Increased appetite	43 (14.1%)	1 (1.0%)
	Musculoskeletal and connective tissue disorders		
	Back pain	14 (4.6%)	4 (3.9%)
	Arthralgia	4 (1.3%)	0
	Musculoskeletal chest pain	3 (1.0%)	0
	Neck pain	3 (1.0%)	0
	Injury, poisoning and procedural complications		
	Ligament sprain	4 (1.3%)	0
	Reproductive system and breast disorders		
	Dysmenorrhea	12 (3.9%)	5 (4.9%)
	Skin and subcutaneous tissue disorders		
	Rash	6 (2.0%)	0
	Immune system disorders		
	Seasonal allergy	10 (3.3%)	6 (5.9%)
	Investigations		
	Weight increased	10 (3.3%)	1 (1.0%)
	Cardiac disorders		

	Palpitations	5 (1.6%)	0
	Blood and lymphatic system disorders		
	Lymphadenopathy	5 (1.6%)	0
	Ear and labyrinth disorders		
	Ear pain	3 (1.0%)	0
Source of funding	This work was funded and supported by Fontem Ventures B.V. Imperial Brands plc is the parent company of Fontem Ventures B.V., the manufacturer of the EVP prototype used in this study.		
Additional comments	Whilst this study does not present any outcome data related to smoking cessation or abstinence, it does provide significant information relevant to adverse events associated with e-cigarette use.		

ID	Felicone (2019)
Bibliographic reference	Nicholas J. Felicione, Paul Enlow, Daniel Elswick, Dustin Long, C.R. Sullivan, Melissa D. Blank, A pilot investigation of the effect of electronic cigarettes on smoking behavior among opioid-dependent smokers, Addictive Behaviors, 91, 2019, 45-50,
Study type	2-arm randomised controlled trial
Country	West Virgina, United States
Study Setting	Outpatient opioid-maintenance clinic
Number of participants	Total: N=25 >Nicotine E-Cig: n=14 >Placebo E-Cig: n=11
Number of withdrawals	>Nicotine E-Cig: 1/14 (13 completed the 4-week follow-up) >Placebo E-Cig: 2/11 (9 completed the 4-week follow-up)
Patient characteristics	Smokers were recruited from an outpatient opioid-maintenance clinic in West Virginia. They were currently receiving a buprenorphine/naloxone combination in sublingual form, and had maintained sobriety from opioids and all other illicit substances for at least 90 consecutive days as verified via urinalysis.

		N (%) or mean (SD)		
		Total sample (n=25)	**Placebo (n=11)**	**Active (n=14)**
Sex	*Male*	7 (28.0%)	2 (18.2%)	5 (35.7%)
Race / ethnicity	*Non-Hispanic (Caucasian)*	100%	100%	100%
Marital Status	*Single*	14 (56.0%)	5 (54.5%)	8 (57.1%)
	Divorced	1 (12.0%)	1 (9.1%)	2 (14.3%)
	Separated	1 (4.0%)	0 (0.0%)	1 (7.1%)
	Married	6 (28.0%)	4 (36.4%)	3 (21.4%)
Education	*Less than HS*	2 (8.0%)	1 (9.1%)	1 (7.1%)
	HS Graduate	11 (44.0%)	6 (54.5%)	5 (35.7%)
	Some College	11 (48.0%)	3 (27.3%)	7 (57.2%)
	College Graduate	1 (4.0%)	1 (9.1%)	0 (0.0%)
Employment	*Unemployed*	13 (52.0%)	7 (63.6%)	6 (42.9%)
	Student	2 (8.0%)	0 (0.0%)	2 (14.3%)
	Part-time	2 (8.0%)	0 (0.0%)	2 (14.3%)
	Full-time	8 (32.0%)	4 (36.4%)	4 (28.6%)
Age (years)		32.4 (8.7)	32.8 (8.9)	32.1 (8.9)

<table>
<tr><td></td><td><table>
<tr><td>Cigs per day</td><td>22.1 (9.7</td><td>21.0 (9.9)</td><td>22.9 (9.7)</td></tr>
<tr><td>Years smoking</td><td>11.5 (8.9)</td><td>13.5 (7.0)</td><td>9.8 (10.0)</td></tr>
<tr><td>CO Level (ppm)</td><td>25.4 (9.6)</td><td>21.9 (9.6)</td><td>28.1 (9.1)</td></tr>
<tr><td>FTND score</td><td>5.8 (2.0)</td><td>5.6 (2.3)</td><td>5.9 (1.7)</td></tr>
<tr><td>Quit ladder score</td><td>5.6 (1.0)</td><td>5.8 (1.0)</td><td>5.4 (1.0)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>E-cigarette with cartridges containing 18mg/ml of nicotine</td></tr>
<tr><td>Comparison</td><td>E-cigarette with cartridges containing no nicotine.
Note: All participants were allowed to choose the flavour of the e-liquid from tobacco (n=15) or menthol (n=10). The flavouring did not alter nicotine concentrations. No effect of flavour choice was observed on the outcome.</td></tr>
<tr><td>Length of follow-up</td><td>28 days</td></tr>
<tr><td>Outcome measures/ results</td><td>Validated (expired CO <8ppm) smoking cessation at 28-days post randomisation
<table><tr><th>Nicotine Containing E-Cigs</th><th>Placebo E-Cigs</th></tr><tr><td>0/14</td><td>2/11</td></tr></table></td></tr>
<tr><td>Source of funding</td><td>Source of funding not disclosed</td></tr>
<tr><td>Additional comments</td><td>It is important to note that the participants of this study were individuals with opioid use disorder, and were currently being treated with buprenorphine/naloxone, however these treatments were not for smoking cessation.</td></tr>
</table>

ID	Halpern 2019					
Bibliographic reference	Halpern, S.D., Harhay, M.O., Saulsgiver, K., Brophy, C., Troxel, A.B. and Volpp, K.G. A pragmatic trial of e-cigarettes, incentives, and drugs for smoking cessation. New England Journal of Medicine, 378, 2018, 2302-2310.					
Study type	Randomised Controlled Trial					
Country	United States					
Study Setting	Eligible participants were the employees and their spouses at 54 companies that used Vitality wellness programs					
Number of participants	Total: N=6006 >Usual care group: n = 813 >Free cessation aids group: n = 1588 >Free e-cigarettes group: n = 1199 >Reward incentives + free cessation aids group: n= 1198 >Redeemable deposit = free cessation aids group: n=1208					
Number of withdrawals	Loss to follow-up was not explicitly mentioned by the authors. The authors report this in terms of the number of 'engaged' participants. Being those participants who logged in to the trial website at least once. >Usual Care: 129/813 were engaged (84.1% were lost to follow-up) >Free cessation aids: 277/1588 (82.6% were lost to follow-up) >Free e-cigarettes: 253/1199 (78.9% were lost to follow-up) >Reward incentives + free cessation aids: 255/1198 (78.7% were lost to follow-up) >Redeemable deposit = free cessation aids: 277/1208 (77.1% were lost to follow-up)					
Patient characteristics		**Usual Care (n=813)**	**Free Cessation Aids (n=1588)**	**Free E-Cigarettes (n=1199)**	**Rewards + Free Cessation Aids (n=1198)**	**Redeemable Deposit + Free Cessation Aids (n=1208)**
	Median age (IQR) – yr	44.5 (35.6-53.7)	43.4 (34.5-52.7)	43.9 (35.0-52.8)	44.0 (34.6-52.6)	44.1 (34.4-54.0)
	Level of education – no. (%)					
	Did not complete high school	28 (3.4)	65 (4.1)	46 (3.8)	37 (3.1)	34 (2.8)
	High-school graduate	228 (28.0)	439 (27.6)	311 (25.9)	305 (25.5)	327 (27.1)
	Some college	309 (38.0)	511 (32.2)	441 (36.8)	447 (37.3)	425 (35.2)
	College degree	146 (18.0)	369 (23.2)	254 (21.2)	257 (21.5)	285 (23.6)
	Postgraduate degree	37 (4.6)	74 (4.7)	51 (4.3)	54 (4.5)	41 (3.4)
	Missing data	65 (8.0)	130 (8.2)	96 (8.0)	98 (8.2)	96 (7.9)
	Female sex – no. (%)	415 (51.0)	832 (52.4)	597 (49.8)	614 (51.3)	618 (51.2)
	Median duration of smoking (IQR) – yr	18.0 (10.0-29.0)	18.0 (10.0-29.0)	20.0 (10.0-27.0)	18.0 (10.0-28.0)	18.0 (10.0-28.8)
	Median no. of cigarettes smoked per day (IQR)	10.0 (5.0-15.0)	10.0 (5.0-15.0)	10.0 (5.0-15.0)	10.0 (5.0-15.0)	10.0 (5.0-15.0)

	Participant reported desire to quit – no. (%)					
	No plan to quit	74 (9.1)	147 (9.3)	109 (9.1)	120 (10.0)	100 (8.3)
	Want to quit later	490 (60.3)	994 (62.6)	754 (62.9)	725 (60.5)	744 (61.6)
	Want to quit, need help	238 (29.3)	425 (26.8)	315 (26.3)	333 (27.8)	344 (28.5)
	Missing data	11 (1.4)	22 (1.4)	21 (1.8)	20 (1.7)	20 (1.7)
	E-cigarette use – no. (%)					
	Never	317 (39.0)	677 (42.6)	461 (38.4)	495 (41.3)	452 (37.4)
	Past but not current use	169 (20.8)	367 (23.1)	299 (24.9)	271 (22.6)	294 (24.3)
	Current use	78 (9.6)	185 (11.6)	131 (10.9)	120 (10.0)	139 (11.5)
	Missing data	249 (30.6)	359 (22.6)	308 (25.7)	312 (26.0)	323 (26.7)
Intervention	>Free Cessation Aids: Participants provided with all forms of nicotine-replacement therapy, bupropion or varenicline, and – for participants who reported lack of success with these therapies – free NJOY e-cigarettes (20 chambers of 1.0-1.5% nicotine per week). >Free E-Cigarettes: Participants were provided with free e-cigarettes without the requirement that standard therapies had first been tried. >Rewards + Free Cessation Aids: Participants given a reward incentive worth $600 for achieving sustained abstinence, plus all the options in the free cessation aids group. >Redeemable Deposit + Free Cessation Aids: Participants given access to a deposit account worth $600 redeemable only if they became abstinent, plus all the options in the free cessation groups					
Comparison	Usual Care: Participants notified of their usual care resources, including information regarding the health benefits of smoking cessation, strategies to promote cessation and the opportunity to register for the SmokeFreeTXT program of the National Cancer Institute, a free text-messaging program that gives encouragement, advice, and tips for stopping smoking. All materials were in English.					
Length of follow-up	Longest period of follow-up was 12 months.					
Outcome measures/ results	The primary outcome was sustained smoking abstinence at 6-months post-target quit date, however outcome data was also available at 12-months. As the outcome of interest is abstinences at the longest available time point, this outcome data is presented. Only participants who self-reported that they had abstained were asked to provide a sample to biochemically confirm abstinence. This data has been collected from the Supplementary Material.					
		Usual Care (n=813)	**Free Cessation Aids (n=1588)**	**Free E-Cigarettes (n=1199)**	**Rewards + Free Cessation Aids (n=1198)**	**Redeemable Deposit + Free Cessation Aids (n=1208)**
	Biochemically confirmed smoking abstinences	0/813	4/1199	5/1588	13/1198	16/1208
Source of funding	Supported by a research grant from the Vitality Institute to the University of Pennsylvania Centre for Health Incentives and Behavioural Economics. E-Cigarettes were provided for NJOY at no cost.					
Additional comments	NJOY provided e-cigarettes at no cost. Some potential for contamination as 9.6% of participants randomised to receive 'usual care' reported that they were currently using e-cigarettes.					

<table>
<tr><th>ID</th><th colspan="4">Hajek 2019</th></tr>
<tr><td>Bibliographic reference</td><td colspan="4">Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, Li J, Parrott S, Sasieni P, Dawkins L, Ross L. A randomized trial of e-cigarettes versus nicotine-replacement therapy. New England Journal of Medicine. 2019 Jan 30.</td></tr>
<tr><td>Study type</td><td colspan="4">2-arm (multi-centre, but individually-randomised) randomised controlled trial</td></tr>
<tr><td>Country</td><td colspan="4">England UK.</td></tr>
<tr><td>Study Setting</td><td colspan="4">The Health and Lifestyle Research Unit that delivers the service for two London boroughs (Tower Hamlets and City of London), along with the Leicester and East Sussex services</td></tr>
<tr><td>Number of participants</td><td colspan="4">Total N = 886
Intervention (E-Cigarettes): n = 439
Comparison (NRT): n= 447</td></tr>
<tr><td>Number of withdrawals</td><td colspan="4">Intervention: 102/446 (342 remaining, 1 participant died during trial)
Comparison: 83/439 (356 remaining at 52 weeks, 1 participant died during trial)</td></tr>
<tr><td>Patient characteristics</td><td></td><td>E-Cigarettes (N=438)</td><td>NRT (N=446)</td><td>Total (N=884)</td></tr>
<tr><td></td><td>Median age (IQR) -yr</td><td>41 (33-53)</td><td>41 (33-51)</td><td>41 (33-52)</td></tr>
<tr><td></td><td>Female sex – no. (%)</td><td>211 (48.2)</td><td>213 (47.8)</td><td>424 (48.0)</td></tr>
<tr><td></td><td>Employed – no. (%)</td><td>299 (68.3)</td><td>316 (70.9)</td><td>615 (69.6)</td></tr>
<tr><td></td><td>Entitled to free prescriptions – no. (%)</td><td>181 (41.3)</td><td>179 (40.1)</td><td>360 (40.7)</td></tr>
<tr><td></td><td>Median no. of cigarettes per day (IQR)</td><td>15 (10-20)</td><td>15 (10-20)</td><td>15 (10-20)</td></tr>
<tr><td></td><td>Median expired CO level (IQR) - ppm</td><td>20 (13-27)</td><td>21 (13-28)</td><td>20 (13-28)</td></tr>
<tr><td></td><td>Score on the Fagerström Test for Cigarette Dependence †</td><td>4.5 ± 2.5</td><td>4.6 ± 2.4</td><td>4.6 ± 2.4</td></tr>
<tr><td></td><td>Past use of NRT – no. (%)</td><td>328 (74.9)</td><td>334 (74.9)</td><td>662 (74.9)</td></tr>
<tr><td></td><td>Past use of e-cigarettes – no. (%)</td><td>186 (42.5)</td><td>181 (40.6)</td><td>367 (41.5)</td></tr>
<tr><td>Intervention</td><td colspan="4">Multisession Behavioural Support (weekly one-on-one sessions and weekly monitoring of CO expiration concentration).
Participants also provided with e-cigarette starter pack and 30-ml bottle of Tobacco flavoured e-liquid (18mg nicotine per ml).
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. 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 further 10-ml bottle, but this was not offered proactively. Participants received oral and written information on how to operate the e-cigarette.</td></tr>
<tr><td>Comparison</td><td colspan="4">Multisession Behavioural Support (weekly one-on-one sessions and weekly monitoring of CO expiration concentration).
Participants were informed about the range of nicotine-replacement products and selected their preferred product. Use of combinations was encouraged (88% of NRT arm participants used NRT combinations - This comprised mostly patch plus one of the oral products). Based on products that participants</td></tr>
</table>

started to use on their TQD, nicotine patch was used by 84% of participants, followed by nicotine inhalator (37%), mouth spray (28%), mouth strips (15%), lozenge (9%), chewing gum (8%), microtabs (8%), and nasal spray (0.5%).
Switching to different NRT products during the first four weeks of treatment was common (59% of participants).
The way that nicotine replacement was provided differed slightly among trial sites.
("*While East Sussex and Leicester clients were able to receive their products at randomisation, we were concerned that if at the London site only NRT participants were asked to go to the local pharmacy and possibly pay the prescription charge while EC participants did not, this could generate a potential bias. To avoid this, the London participants selected their preferred NRT at their baseline session and were instructed to bring their NRT to their target quit date (TQD) session. After treatment allocation was revealed, participants allocated to NRT kept their NRT while those allocated to EC exchanged their NRT for the EC starter pack.*")

Length of follow-up

12 months (52 weeks post TQD)

Outcome measures/Results

Sustained (≤ 5 cigarettes allowed) validated (exhaled breath carbon monoxide concentrations <8ppm) at 12 months post-intervention

E-Cigarettes	NRT
79/438	44/446

Adverse reactions reported at least once N (%)

	E-Cigarettes (N=438)	NRT (N=446)
Nausea	137 (31)	169 (38)
Sleep disturbances	279 (64)	303 (68)
Throat/mouth irritation*	286 (65)	221 (51)

Source of funding

(Funded by the National Institute for Health Research and Cancer Research UK

Additional comments

Non-blinded study. Participants in both the intervention and control group were asked to sign a commitment to not use the non-assigned treatment for at least 4 weeks after their quit date. However, no details provided as to how this was enforced. Potential for contamination of results as described in the table below.

	E-Cigarettes (N=438)	NRT (N=446)
Use of non-allocated product within the initial 4 weeks		
Used for 5 or more consecutive days, N (%)	3 (0.7)	11 (2.5)
Use of non-allocated products at 6 months (excludes initial 4 weeks)		
Used for 5 or more consecutive days since week 4: N (%)	16 (3.6)	57 (12.8)
Length of non-allocated product use in weeks among users since previous assessment (0-20): Median (IQR)	3 (1-9)	8 (1-20)
Use of non-allocated products at 12 months (excludes initial 4 weeks)		
Used for 5 or more consecutive days since week 26: N (%)	14 (3.2)	77 (17.3)
Length of non-allocated product use in weeks among users since previous assessment (0-24): Median (IQR)	6.5 (0-12)	20 (6-24)
Length of other non-study stop-smoking medications (including single use)		

	Varenicline: N (%)	15 (3.4)	13 (2.9)
	Bupropion: N (%)	0 (0)	0 (0)

ID	Lee 2018
Bibliographic reference	Lee SM, Tenney R, Wallace AW, Arjomandi M. E-cigarettes versus nicotine patches for perioperative smoking cessation: a pilot randomized trial. PeerJ. 2018 Sep 28;6:e5609.
Study type	2-arm, parallel group, randomised controlled trial
Country	California, San Francisco, United States
Study Setting	San Francisco Veteran's Affairs Medical Centre, University of California
Number of participants	Total N = 30 > Electronic Nicotine Devices (END – e-cigarette): n =20 > Nicotine patches (NRT): n =10
Number of withdrawals	>END: 1 /10 (9 participants available at 6-month follow-up) >NRT: 1/20 (19 participants available at 6-month follow-up)
Patient characteristics	Participants were eligible if they presented to the anaesthesia preoperative (APO) clinic for elective surgery 3 or more days before surgery, were current cigarette smokers of more than two cigarettes per day having smoked at least once in the last 7 days.

	NRT group (n=10)	**END group (n=20**
Male	9 (90.0%)	18 (90.0%)
Age (years)	53 (10.6)	54 (12.7)
Height (cm)	179.8 (8.9)	180.7 (7.7)
Weight (kg)	92 (25.9)	97 (19.7)
Body mass index (kg/m²)	28.5 (7.9)	29.6 (5.8)
Race (white)	5 (50.0%)	11 (55.0%)
Ethnicity (latino)	0 (0%)	0 (0%)
General Surgery	3 (30.0%)	5 (25%)
Orthopaedic Surgery	2 (20.0%)	6 (30.0%)
Neurosurgery	1 (10.0%)	1 (5.0%)
Vascular Surgery	1 (5.0%)	0 (0.0%)
Other surgery type	4 (40.0%)	7 (35.0%)
Days seen prior to scheduled surgery	16.5 (9.5)	11.2 (7.9)
Diabetes	0 (0%)	2 (10.0%)
Hypertension	3 (30.0%)	7 (35.0%)
Heart Disease	0 (0%)	1 (5.0%)
COPD	1 (10.0%)	6 (30.0%)

<table>
<tr><td></td><td>
<table>
<tr><td>Cigarettes smoked per day</td><td>10.8 (6.6)</td><td>15.3 (10.5)</td></tr>
<tr><td>Number of years smoking</td><td>32 (16.4)</td><td>32 (15.6)</td></tr>
<tr><td>Pack-years smoking history</td><td>16.7 (12.1)</td><td>26.4 (27.0)</td></tr>
<tr><td>Fagerström score (out of 10)</td><td>2.5 (0.85)</td><td>3.7 (2.6)</td></tr>
<tr><td>Salivary cotinine (ng/ml)</td><td>130.1 (75.3)</td><td>209.6 (110.3)</td></tr>
<tr><td>Exhaled CO level (ppm)</td><td>16.1 (7.7)</td><td>21.7 (11.5)</td></tr>
<tr><td>FEV1 (L)</td><td>3.14 (1.35)</td><td>2.78 (1.11)</td></tr>
<tr><td>FVC (L)</td><td>3.52 (1.28)</td><td>4.03 (1.32)</td></tr>
<tr><td>FEV1/FVC ratio (%)</td><td>105% (81.3%)</td><td>68.2% (13.0%)</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>END (e-cigarettes): Participants received a 6-week supply of NJOY e-cigarettes (Scottsdale, AZ, USA) and were instructed to use the Bold (4.5%) e-cigarettes ad libitum for 3 weeks, the Gold (2.4%) e-cigarettes ad libitum for 2 weeks and the Study (0%) e-cigarettes ad libitum for the final week. The number of e-cigarettes issued corresponded to the reported baseline cigarettes smoked per day, calculated assuming one NJOY e-cigarette was equivalent to 10 cigarettes.</td></tr>
<tr><td>Comparison</td><td>NRT (nicotine patches): 6-week supply of Nicoderm CQR patches (5 weeks) and placebo patches (1 week) appropriate to baseline nicotine consumption. Those smoking an average of ten or more cigarettes per day were given the 21 mg/day patch for 3 weeks, the 14 mg/day patch for 1 week, the seven mg/day patch for 1 week, and the 0 mg/day patch for 1 week. Participants who reported smoking an average of less than 10 cigarettes per day at baseline were given the 14 mg/day patch for 3 weeks, the seven mg/day patch for 2 weeks, and the 0 mg/day patch for 1 week.</td></tr>
<tr><td>Length of follow-up</td><td>Follow-up was for 6 months post-randomization. However, at 6-months follow-up was only via telephone survey. Biochemical validation was only available for 8-weeks post randomization.</td></tr>
<tr><td>Outcome measures/Results</td><td>
Smoking cessation at day of surgery (biochemically validated)
Smoking cessation 30-days post-randomization (self-report)
Smoking cessation 8-weeks post-randomization (biochemically validated)
<table>
<tr><th>END</th><th>NRT</th></tr>
<tr><td>3/20</td><td>0/10</td></tr>
</table>
Smoking cessation 6-months post-randomization (self-report)
Adverse events
No participants in either group experienced severe adverse events at any time point. Adverse event rates were similar between groups on the day of surgery (50% in the NRT group experienced at least one adverse event compared to 53% in the END group, p = 1.0) and at 8-week follow-up (33% in the NRT group versus 50% in the END group, p = 0.45). No participants in either group experienced intraoperative complications. The rate of postoperative complications was similar in both groups (60% in the NRT group and 26% in the END group, p = 0.11). Common adverse events related to both NRT and END included headache, nausea, cough, and throat irritation, as shown below.
<table>
<tr><th></th><th>NRT group (n=10)</th><th>END group (n=20</th><th>P</th></tr>
<tr><td>Headache</td><td>4 (40%)</td><td>4 (20%)</td><td>0.38</td></tr>
</table>
</td></tr>
</table>

	Nausea	1 (10%)	5 (25%)	0.63
	Dry cough (persistent)	0 (0%)	2 (10%)	0.54
	Dry cough (intermittent)	1 (10%)	6 (30%)	0.37
	Palpitations	2 (20%)	0 (0%)	0.10
	Throat irritation	3 (30%)	5 (25%)	1.0
	Skin irritation	3 (30%)	2 (10%)	0.3
	Other	6 (60%)	7 (35%)	0.26
Source of funding	Internal UCSF Department of Anesthesia and Perioperative Care funds (San Francisco, California, United States of America) and the UCSF Resource Allocation Program grant, administered by the Helen Diller Family Comprehensive Cancer Center developmental funds from the National Cancer Institute Cancer Center Support Grant (P30 CA 82103-16). E-cigarettes were purchased from NJOY using these funds.			
Additional comments	This study is at significant risk of contamination between the groups. 30% of the participants randomised to the NRT group used an e-cigarette between 30-days post-randomisation and 8-weeks post-randomisation. 10% of the participants randomized to the END group used a form of NRT between 30-days post-randomisation and 8-weeks post-randomisation.			

ID	Tseng 2016				
Bibliographic reference	Tseng TY, Ostroff JS, Campo A, Gerard M, Kirchner T, Rotrosen J, Shelley D. A randomized trial comparing the effect of nicotine versus placebo electronic cigarettes on smoking reduction among young adult smokers. Nicotine & Tobacco Research. 2016 Jan 17;18(10):1937-43.				
Study type	2-arm; double blind randomised controlled trial				
Country	United States (New York City)				
Study Setting	Outpatient (in person baseline assessment, followed by 20-30minute telephone counselling session)				
Number of participants	Total: N = 100 Intervention (Nicotine EC): n = 50 Comparator (Placebo EC): n = 50				
Number of withdrawals	Intervention: 10/50 (40 completed week 3 assessment) Comparator: 11/50 (39 completed week 3 assessment)				
Patient characteristics	**Baseline variable**	**Mean ± *SD*, *n* (%)a**			
		Total (*N* = 99)	**Nicotine EC (*N* = 50)**	**Placebo EC (*N* = 49)**	***P*b**
	Demographics				
	Age in years	28.43±4.07	27.90±4.01	28.98±4.11	.789
	Gender				
	Female	32 (32.3%)	16 (32.0%)	16 (32.7%)	.945
	Male	67 (67.7%)	34 (68.0%)	33 (67.3%)	
	Education				
	HS degree or less	25 (25.3%)	9 (18.0%)	16 (32.7%)	.235
	Some college	39 (39.4%)	21 (42.0%)	18 (36.7%)	
	College or post-graduate degree	35 (35.4%)	20 (40.0%)	15 (30.6%)	
	Race/ethnicity				
	Non-Hispanic African American/black	30 (30.9%)	16 (32.7%)	14 (29.2%)	.514
	Non-Hispanic white	29 (29.9%)	17 (34.7%)	12 (25.0%)	
	Other non-Hispanic	14 (14.4%)	5 (10.2%)	9 (18.8%)	
	Hispanic of any race	24 (24.7%)	11 (22.4%)	13 (27.1%)	
	Tobacco use				
	Number of cigarettes per day	14.33±4.93	13.86±4.30	14.81±5.51	.343
	Time to first cigarette				
	5 minutes or less after waking	22 (23.4%)	10 (21.3%)	12 (25.5%)	.923
	6–30 minutes after waking	39 (41.5%)	19 (40.4%)	20 (42.6%)	
	31–60 minutes after waking	22 (23.4%)	12 (25.5%)	10 (21.3%)	
	>60 minutes after waking	11 (11.7%)	6 (12.8%)	5 (10.6%)	
	Made serious quit attempts (≥1 day) in last year	46 (46.5%)	25 (50%)	21 (42.9%)	.476

<table>
<tr><td></td><td>
<table>
<tr><td>How confident are you that you could quit smoking completely and stay quit (0–10 scale)</td><td>6.35±2.53</td><td>6.41±2.38</td><td>6.29±2.71</td><td>.809</td></tr>
<tr><td>Readiness to quit (1–10 scale, 1–8 apply to current smokers)</td><td>5.57±1.49</td><td>5.63±1.59</td><td>5.51±1.39</td><td>.685</td></tr>
<tr><td>Smoking behavioural dependence scale (11 items)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Mild</td><td>17 (17.2%)</td><td>9 (18.0%)</td><td>8 (16.3%)</td><td>.951</td></tr>
<tr><td>Moderate</td><td>51 (51.5%)</td><td>26 (52.0%)</td><td>25 (51.0%)</td><td></td></tr>
<tr><td>Strong to very strong</td><td>31 (31.3%)</td><td>15 (30.0%)</td><td>16 (32.7%)</td><td></td></tr>
</table>
EC = electronic cigarette; HS = high school.
a Values are means with standard deviations or n with percentages in the column.
b t tests were used for continuous variables and chi-square analyses were used for categorical variables.
</td></tr>
<tr><td>Intervention</td><td>Nicotine-containing EC (no information provided in text or supplementary material as to the concentration of nicotine in mg per ml)
Subjects were encouraged to replace cigarettes with as much or as little use of an EC as needed in order to reduce nicotine withdrawal symptoms. At the end of 1-week of EC use, subjects were asked to return for a 2-week supply of ECs and to complete a second in-person assessment. An end-of-intervention assessment was conducted 3 weeks after starting ECs.</td></tr>
<tr><td>Comparison</td><td>Non-nicotine-containing EC (placebo, no information provided as too flavour or EC cartridge)
Subjects were encouraged to replace cigarettes with as much or as little use of an EC as needed in order to reduce nicotine withdrawal symptoms. At the end of 1-week of EC use, subjects were asked to return for a 2-week supply of ECs and to complete a second in-person assessment. An end-of-intervention assessment was conducted 3 weeks after starting ECs.</td></tr>
<tr><td>Length of follow-up</td><td>3-weeks post-intervention</td></tr>
<tr><td>Outcome measures/Results</td><td>Self-reported reduction of at least 50% in the number of cigarettes/day smoked (3 weeks post-intervention)
Validated (exhaled breath carbon monoxide concentrations <8ppm) at 3 weeks post-intervention
<table>
<tr><th>Nicotine EC</th><th>Placebo</th></tr>
<tr><td>2/50</td><td>1/50</td></tr>
</table>
Adverse events
There was no difference in reported side effects between groups (34.1% for intervention and 17.5% for placebo group at week 1, P = .09; 22.5% for intervention and 10.3% for placebo group at week 3, P = .14; chi-square test) or between study time points in each group (P = .39 for intervention and P = .63 for placebo group; McNemar test). Common side effects included mouth or throat irritation, cough, insomnia or difficulty sleeping, abnormal dreams, headache and fatigue.</td></tr>
<tr><td>Source of funding</td><td>This work was supported by the National Center for Advancing Translational Sciences at the National Institutes of Health</td></tr>
<tr><td>Additional comments</td><td>This study only has outcome data for 3-weeks post-intervention</td></tr>
</table>

ID	Walele 2016
Bibliographic reference	Walele T, Sharma G, Savioz R, Martin C, Williams J. A randomised, crossover study on an electronic vapour product, a nicotine inhalator and a conventional cigarette. Part B: Safety and subjective effects. Regulatory Toxicology and Pharmacology. 2016 Feb 1;74:193-9.
Study type	Randomised, controlled, four-way crossover trial Part 1 compared the EVP (e-cigarette) (2.0% nicotine) to a conventional cigarette and a licensed nicotine inhalator. Part 1 was performed open-label Part 2 assessed the effect of increasing concentrations of nicotine in the eliquid used with the EVP (0%, 0.4%, 0.9%, 2.0%). Part 2 was performed blinded
Country	Wales, UK
Study Setting	Clinical setting
Number of participants	Total; N =24 **Part 1:** N=12 **Part 2:** N = 12
Number of withdrawals	No withdrawals
Patient characteristics	**Part 1** The mean age of subjects was 31.1 years and the mean BMI was 25.0 kg/m2. The mean FTND score was 4.3, indicating moderate nicotine dependence according to the FTND scale. Subjects smoked between 5 and 30 cigarettes per day (self-reported), for 6–20 years. At baseline (Day -2), urine cotinine levels were positive for all subjects, with NicAlert scores ranging from 4 to 6. Blood COHb levels ranged from 4.9 to 10.7% saturated haemoglobin and mean exhaled CO levels were at 22.9 (±9.3) ppm. Subjects were thus confirmed smokers. **Part 2** The mean age of subjects was 37.4 years and the mean BMI was 26.1 kg/m2. The mean FTND score was 3.6, which indicated moderate nicotine dependence according to that scale. Subjects smoked between 5 and 30 cigarettes per day (self-reported). The majority of subjects had smoked for 6–20 years; one subject had smoked for less than 6 years and five for over 20 years. Urine cotinine levels at baseline were positive for smoking for all subjects, with NicAlert scores ranging from 4 to 6. Blood COHb levels ranged from 4.1 to 10.5% saturated haemoglobin and mean exhaled CO levels were at 20.1 (±12.4) ppm. Subjects were thus confirmed smokers.
Intervention	**Part 1 – The participants were randomly assigned to one of four pre-defined sequences of product use. Each participant used each treatment for one daily use session** E-Cigarette (unflavoured) (2.0% nicotine) E-Cigarette (menthol flavoured) (2.0% nicotine) **Part 2 - The participants were randomly assigned to one of four pre-defined sequences of product use. Each participant used each treatment for one daily use session** E-Cigarette (2.0% nicotine) E-Cigarette (0.9% nicotine) E-Cigarette (0.4% nicotine)
Comparison	**Part 1 - The participants were randomly assigned to one of four pre-defined sequences of product use. Each participant used each treatment for one daily use session** NRT (Nicorette Inhaler – 15mg nicotine) Conventional Cigarette

	Part 2 - The participants were randomly assigned to one of four pre-defined sequences of product use. Each participant used each treatment for one daily use session E-Cigarette (0% nicotine)					
Length of follow-up	1-day					
Outcome measures/ results	**Adverse Events**					
			Part 1			
		UF2.0%	**FL2.0%**	**NIC15**	**CC**	**Overall**
		(N = 12)	**(N = 12)**	**(N = 12)**	**(N = 12)**	**(N = 12)**
	Number of AEs	2	3	7	0	12
	Number (%) subjects with ≥1 AE:	1 (8.3%)	3 (25.0%)	3 (25.0%)	0	5 (41.7%)
	Number (%) of subjects with AE/number of AEs by relationship					
	Related	1 (8.3%)/2	2 (16.7%)/2	3 (25.0%)/7	0	4 (33.3%)/11
	Unrelated	0	1 (8.3%)/1	0	0	1 (8.3%)/1
	Number (%) of subjects with AE/number of AEs by SOC					
	Gastrointestinal disorders					
	Glossodynia (related)	0	0	1 (8.3%)/1	0	1 (8.3%)/1
	Infection and infestation					
	Nasopharyngitis (unrelated)	0	1 (8.3%)/1	0	0	1 (8.3%)/1
	Respiratory, thoracic and mediastinal disorders:					
	Cough (related)	1 (8.3%)/2	1 (8.3%)/1	2 (16.7%)/5	0	2 (16.7%)/8
	Throat irritation (related)	0	1 (8.3%)/1	1 (8.3%)/1	0	2 (16.7%)/2

	Part 2				
	UF2.0%	**UF0.9%**	**UF0.4%**	**UF0%**	**Overall**
	(N = 12)	**(N = 12)**	**(N = 12)**	**(N = 12)**	**(N = 12)**
Number of AEs	6	3	3	1	13
Number (%) subjects with ≥1 AE:	3 (25.0%)	3 (25.0%)	3 (25.0%)	1 (8.3%)	7 (58.3%)
Number (%) of subjects with AE/number of AEs by relationship:					
Related	2 (16.7%)/3	1 (8.3%)/1	0	0	3 (25.0%)/4
Unrelated	1 (8.3%)/3	2 (16.7%)/2	3 (25.0%)/3	1 (8.3%)/1	4 (33.3%)/9
Number (%) of subjects with AE/number of AEs by SOC					
Gastrointestinal disorders:					
Toothache (unrelated)	0	1 (8.3%)/1	0	0	1 (8.3%)/1
General disorders and administration site conditions:					
Fatigue (unrelated)	1 (8.3%)/1	0	1 (8.3%)/1	0	2 (16.7%)/2
Musculoskeletal and connective tissue disorders:					
Myalgia (unrelated)	0	1 (8.3%)/1	0	0	1 (8.3%)/1
Musculoskeletal and connective tissue disorders:					
Dizziness (unrelated)	1 (8.3%)/1	0	0	1 (8.3%)/1	2 (16.7%)/2
Headache (unrelated)	0	0	2 (16.7%)/2	0	2 (16.7%)/2
Paraesthesia (unrelated)	1 (8.3%)/1	0	0	0	1 (8.3%)/1
Respiratory, thoracic and mediastinal disorders:					
Cough (related)	2 (16.7%)/3	1 (8.3%)/1	0	0	3 (25.0%)/4
Source of funding	Funded and supported by Fontem Ventures. Imperial Tobacco Group is the parent company of Fontem Ventures B.V., the manufacturer of the EVP prototype used in this study.				

<table>
<tr><th>ID</th><th>Walker 2019 (PROTOCOL AND CONFERENCE ABSTRACT ONLY)</th></tr>
<tr><td>Bibliographic reference</td><td>Walker N, Verbiest M, Kurdziel T, et al Effectiveness and safety of nicotine patches combined with e-cigarettes (with and without nicotine) for smoking cessation: study protocol for a randomised controlled trial BMJ Open 2019;9:e023659. doi: 10.1136/bmjopen-2018-023659</td></tr>
<tr><td>Study type</td><td>Pragmatic, three-arm, community-based randomised trial</td></tr>
<tr><td>Country</td><td>New Zealand</td></tr>
<tr><td>Study Setting</td><td>Community-based</td></tr>
<tr><td>Number of participants</td><td>Total; N =1,124
Nicotine patches alone: n=125
Nicotine patches plus nicotine containing e-cigarette: n=500
Nicotine patches plus placebo (nicotine-free e-cigarettes);N = 499</td></tr>
<tr><td>Number of withdrawals</td><td>Unable to report on loss-to follow up with available literature</td></tr>
<tr><td>Patient characteristics</td><td>Limited information provided in available literature
Participants eligible if they are a t least 18 years of age, able to provide verbal consent, have access to a telephone and prepared to use the trial treatments. Women who self-report that they were pregnant or breast feeding were excluded. As were people currently using NRT, had used an e-cigarette for smoking cessation for more than 1 week, any time in the last year or current users of non-nicotine based therapies (varenicline, buproprion etc.)</td></tr>
<tr><td>Intervention</td><td>Nicotine patches plus nicotine containing e-cigarette: 14 weeks of 21mg nicotine patches, 18mg nicotine-containing e-cigarettes and 6 weeks of weekly withdrawal-oriented behavioural support calls.
Nicotine patches plus placebo e-cigarette: 14 weeks of 21mg nicotine patches, nicotine-free e-cigarettes and 6 weeks of weekly withdrawal-oriented behavioural support calls.</td></tr>
<tr><td>Comparison</td><td>Nicotine patches alone: 14 weeks of 21mg nicotine patches and 6 weeks of weekly withdrawal-oriented behavioural support calls.</td></tr>
<tr><td>Length of follow-up</td><td>Primary outcome was at 6-months, however data was also collected at 12-months.</td></tr>
<tr><td>Outcome measures/Results</td><td>Even though 12-month outcome data was specified in the protocol, the conference abstract only reports 6-month outcome data.
<table>
<tr><th></th><th>NRT Alone</th><th>NRT + Nicotine E-Cig</th><th>NRT + Placebo E-Cig</th></tr>
<tr><td>Biochemically-confirmed abstinence at 6-months</td><td>3/125</td><td>35/500</td><td>20/499</td></tr>
</table></td></tr>
<tr><td>Source of funding</td><td>Trial was funded by a three year project grant from the Health Research Council of New Zealand.</td></tr>
</table>

Synthesis and meta-analysis

Validated smoking cessation

The original meta-analyses produced by Hartmann-Boyce et al. (2016) included outcome data for smoking cessation for two randomised controlled trials (Bullen et al. 2013; Caponnetto et al. 2013). One trial (Adriaens et al. 2014) was identified in this review but was not included in the formal analysis as outcome data was not available at 6-months. Eight of the ten additional studies identified that met our inclusion criteria have been combined with the data presented by Hartmann-Boyce et al. (2016).

Three studies were also identified that investigated e-cigarettes as part of a combination therapy intervention (Baldassarri et al. 2018; Halpern et al. 2018; Walker et al. 2019). This data has been presented separately to the studies presenting outcome data when e-cigarettes were used as the sole-intervention.

Nicotine dependency was assessed in most of the included studies using the Fagerstrom Test for Nicotine Dependence (FTND), a validated, self-administered survey. A score of 1-2 is classified as having a low dependence on nicotine. A score of 3-4 would be considered to have a low to moderate dependence on nicotine. A score of 5-7 would be moderately dependent on nicotine. A score of 8 and over would be highly dependent on nicotine. When assessing the dependence of the smokers included in the following meta-analyses FTND scores were considered where available. Where FTND scores were not provided for every study, cigarettes per day (CPD) were also used to compare and assess nicotine dependence at baseline.

Nicotine containing e-cigarette versus NRT

Two additional studies (Hajek et al. 2019; Lee et al. 2018) were identified and have been combined with the data presented by Hartmann-Boyce et al. (2016). As shown in Figure 2, Nicotine containing e-cigarettes were more effective than NRT for achieving biochemically validated smoking cessation, RR 1.69 (95%CI 1.26 – 2.28, $p < 0.05$). Cessation endpoints varied from 8 weeks up to 52 weeks.

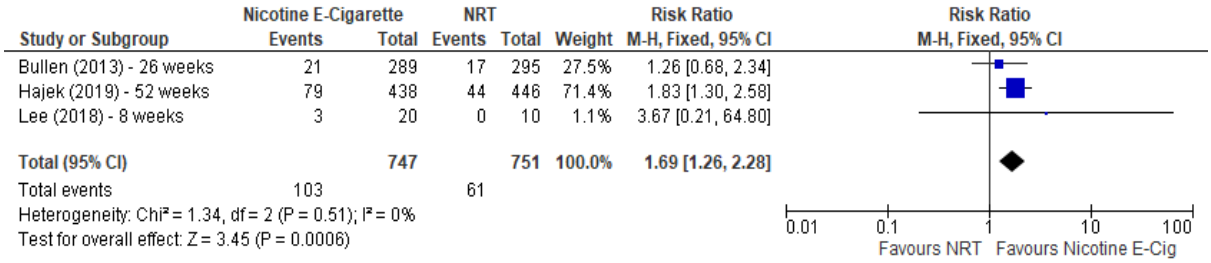


Figure 2: *Nicotine e-cigarettes vs. nicotine replacement therapy to achieve biochemically validated smoking cessation*

Study Heterogeneity

There is notable clinical heterogeneity that exists between these studies. The intervention dosage (expressed as either mg of nicotine per ml or as percentage of nicotine) and length of intervention usage varied significantly. Bullen et al. (2013) used a 12 week treatment period, where subjects randomised to the e-cigarette treatment were provided with an e-cigarette with 16mg/ml of nicotine whilst participants randomised to the NRT group received daily 21mg/24 hour nicotine patches. Hajek et al. (2019) compared participants using an 18mg/ml e-cigarette to those using any form (or combination of) NRT for the whole 52-week period. However, participants were only provided with

their assigned treatments for up to 3-months post-randomisation and were encouraged to purchase and keep using their assigned treatment after this time-point. Lee et al. (2018), used a range of e-cigarettes that contained a decreasing concentration of nicotine (4.5% for 3-weeks; 2.4% for 2-weeks and 0% for 1-week) over 6-weeks. This was compared to decreasing concentrations of nicotine-containing NRT, dependent on the average number of cigarettes the participants smoked per-day (reported at baseline). It should also be noted, that whilst Bullen et al. (2013) and Lee et al. (2018) validated smoking cessation where the concentration of carbon monoxide (CO) in expired breath was less than or equal to 10 ppm, Hajek et al. (2019) employed a stricter validation requirement, of CO concentrations of less than or equal to 8ppm.

Importantly, the studies by Hajek et al. (2019) and Lee et al. (2018) are at significant risk of contamination; in Hajek et al. (2019) the study authors note that participants were simply asked to sign a commitment to not use the non-assigned treatment for at least the first 4-weeks post-quit date; however, no details were provided as to how this was enforced. The authors included the percentages of participants in each group who reported using the non-assigned treatment at 52-weeks post-quit date. Of those assigned to receive NRT, 17.3% reported using an E-cigarette for at least 5-consecutive days since 26-weeks post-quit date and 2.9% reported using varenicline at least once. Comparatively, of those assigned to receive the e-cigarette, 3.2% reported using NRT for at least 5-consecutive days since 26-weeks post-quit date. Once again 3.4% reported that they used varenicline at least once. The study by Lee et al. (2018) is at similar contamination risk. 30% of the participants randomised to the NRT group used an e-cigarette between 30-days post-randomisation and 8-weeks post-randomisation. 10% of the participants randomized to the e-cigarette group used a form of NRT between 30-days post-randomization and 8-weeks post-randomisation. These factors have not been considered in the smoking cessation outcome data as presented in both studies.

Nicotine Dependency

All three studies included in the meta-analysis presented in Figure 2 include an average FTND score for the randomised participants. In the study by Bullen et al. (2013), those randomised to receive the nicotine containing e-cigarette reported an average FTND score of 5.6 ± 2.0, whilst those randomised to receive NRT reported an average score of 5.5 ± 2.0. Hajek et al. (2019) report that participants who received the nicotine e-cigarette responded with a score of 4.5 ± 2.5, and those who received the NRT with a score of 4.6 ± 2.4. Finally, Lee et al. (2018) reported that on average, those in the nicotine e-cigarette group responded with a score of 2.5 ± 0.85, and those in the NRT group responded with a score of 3.7 ± 2.6. This suggests that the participants involved in the studies by both Bullen et al. (2013) and Hajek et al. (2019), were more dependent smokers than those involved in the study by Lee et al. (2018).

Nicotine containing e-cigarette versus placebo e-cigarettes

Two additional studies (Tseng et al. 2016; Felicone et al. 2019) were identified and have been combined with the data presented by Hartmann-Boyce et al. (2016). As indicated in Figure 3, there is no significant difference between nicotine containing e-cigarettes and placebo e-cigarettes on biochemically validated smoking cessation RR 1.84 (95%CI 0.94 – 3.62, p = 0.08).

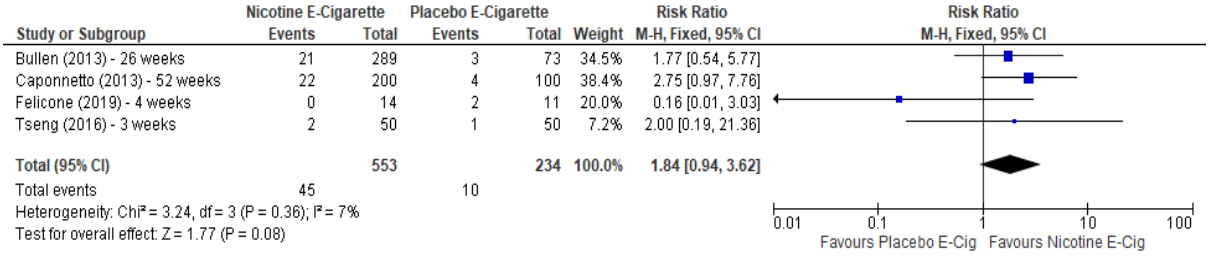


Figure 3: *Nicotine e-cigarettes vs. placebo e-cigarettes to achieve biochemically validated smoking cessation*

It is worth noting that participants included in the study by Felicone et al. (2019) were individuals with opioid use disorder and were receiving concurrent buprenorphine/naxloxone treatment. Due to inclusion of this subset of the population, consideration of 'indirectness' in the Summary of Findings (pg 7) has been rated as serious. Sensitivity analysis of the three trials excluding the study by Felicone et al (2019) increased the risk of smoking cessation relative to placebo e-cigarette RR 2.26 (95%CI 1.08, 4.73; Figure 4).

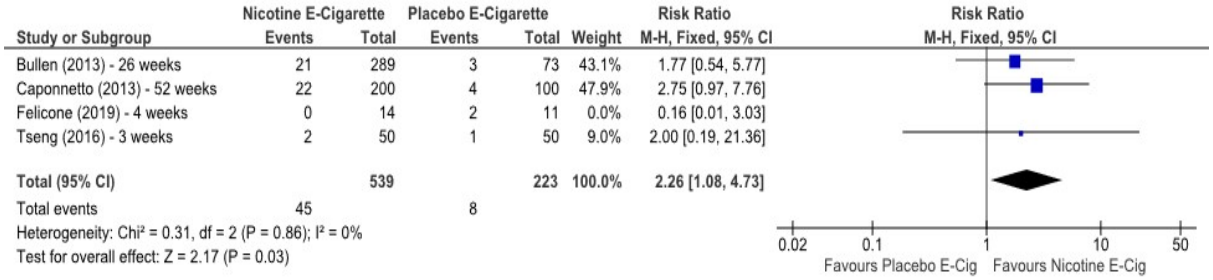


Figure 4: *Sensitivity analysis excluding the Felicone (2019) trial - Nicotine e-cigarettes vs. placebo e-cigarettes to achieve biochemically validated smoking cessation*

Study Heterogeneity

Notable clinical heterogeneity exists between the studies included in the meta-analysis (Figure 3). All studies included smoking cessation outcome data, biochemically validated through detection of expired CO. However, cessation 'cut-off' was different between studies, with smoking cessation being considered if the CO concentration was less than or equal to 10 (Bullen et al. 2013); 8 (Felicone et al. 2019; Tseng et al. 2016) and 7ppm (Caponnetto et al. 2013) respectively across studies. In addition, both Bullen et al. (2013) and Caponnetto et al. (2013) utilised a treatment period of 12 weeks, compared to the significantly shorter treatment periods used by Felicone et al. (2019) (2 weeks) and Tseng et al. (2016) (3 weeks).

The concentration of active nicotine in the e-cigarette also varied significantly between studies. Two studies (Bullen et al. 2013; Felicone et al. 2019) used concentrations of nicotine in the e-cigarette (16mg/ml and 18mg/ml respectively) that remained consistent through the study period. Caponnetto et al. (2013) however, included two treatment groups (combined in the meta-analysis), of these groups, one received e-cigarettes containing 7.2mg/ml for the whole 12 week trial period, the other received 7.2mg/ml for the first 6 weeks of the trial, which was then replaced with an e-cigarette containing 5.4mg/ml for the remaining 6 weeks of the trial. Tseng et al. (2016) provide no information in the text, or in any supplementary material as to the concentration of nicotine in mg/ml in the nicotine containing e-cigarettes.

Finally, it is important to note that the participants involved in the study by Felicone et al. (2019) were individuals with opioid use disorder. These participants used the assigned treatment concurrently with buprenorphine/naloxone.

Nicotine Dependency

When assessing the nicotine dependence in the four studies included in Figure 3, three studies included information on both FTND scores and CPD usage (Bullen et al 2013; Caponnetto et al. 2013; Felicone et al. 2019 & Tseng et al. 2016). Of these, the participants randomised to receive the nicotine containing e-cigarette responded with similar FTND dependency scores, 5.6 ± 2.0 (Bullen et al. 2013); 5.6 ± 2.3 and 6.0 ± 2.1 (Caponnetto et al. 2013) and 5.9 ± 1.7 (Felicone et al. 2019). These similarities are also observed in the FTND scores for those participants randomised to receive the placebo e-cigarette, 5.5 ± 2.0 (Bullen et al. 2013); 5.8 ± 2.2 (Caponnetto et al. 2013) and 5.6 ± 2.3 (Felicone et al. 2019). The smokers of these studies are argued to be similar in terms of their nicotine dependence. However, the study by Tseng et al. (2016) provided no information on FTND scores for the participants involved, instead reporting average CPD usage. Those randomized to receive the active e-cigarette reported an average CPD of 13.86 ± 4.3, whilst those receiving the placebo e-cigarette reported an average CPD of 14.81 ± 5.51. Compared to the CPD usage reported in the participants of Bullen et al. (2013) (18.4 ± 7.2 – Active; 17.6 ± 6.0 - Placebo) Caponetto et al. (2013) (19.0 IQR:14.0-25.0 and 21.0 IQR: 15.0 -26.0 – Active; 22.0 IQR15.0-27.0 - Placebo) and Felicone et al. (2019) (21.0 ± 9.9 – Active; 22.9 ± 9.7 - Placebo) it is arguable that the participants involved in the study by Tseng et al. (2016) did not have as high dependence compared to those involved in the other three studies.

Nicotine containing e-cigarette versus no intervention

Two studies were identified that compared active, nicotine containing e-cigarettes with no-intervention (Adriaens et al. 2014; Carpenter et al. 2017). The participants in the control arm for these studies continued to smoke conventional cigarettes (CC) of their own choosing. Cessation was once again assessed through biochemical validation of expired CO concentrations, at either less than or equal to 6ppm (Carpenter et al. 2017) or 5ppm (Adriaens et al. 2014; Figure 5).

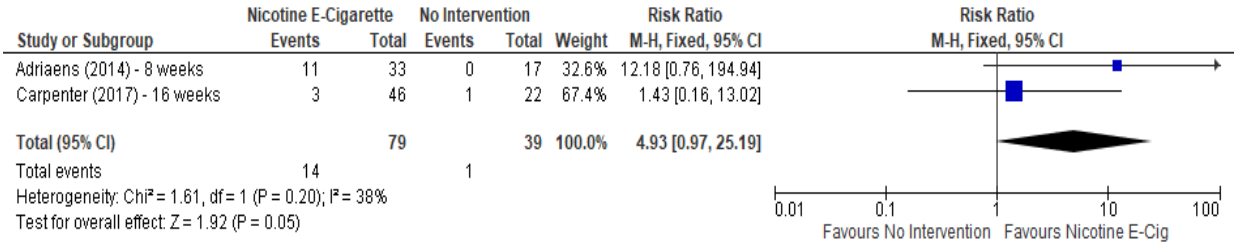


Figure 5: *Nicotine e-cigarettes vs. no intervention to achieve biochemically validated smoking cessation*

Study Heterogeneity

Heterogeneity between these studies is relatively low. The length of the treatment phases (active prescription of interventions) were similar, 2-weeks for Adriaens et al. (2014) and 3-weeks for Carpenter et al. (2017). There are some concerns as to the differences in nicotine concentrations utilised between studies. Adriaens et al. (2014) provided two types of e-cigarettes, however both contained 18mg/ml of nicotine (combined in above meta-analysis). Carpenter et al. (2017) had two treatment groups also (combined in above meta-analysis) with one group randomized to receive an e-cigarette containing 16mg/ml of nicotine, and the second to receive an e-cigarette containing 24mg/ml.

Carpenter et al. (2017) is also at risk of contamination. The participants that were randomised to the control-arm (continued to smoke CC's of own choosing) were free to purchase and use e-cigarettes if they wished. According to the data presented by the authors, 14% of the participants randomised to

the control group reported independent purchase of an e-cigarette. This contamination has not been considered by the authors in the presentation of their outcome data.

Nicotine Dependency

Whilst average FTND scores were not provided for the participants involved in the study by Carpenter et al. (2017), cigarettes per day (CPD) were. Participants in the control arm reported using 16.7 ± 11.3 CPD, participants assigned to the e-cigarette containing 16mg/ml and those assigned the e-cigarette containing 24mg/ml reported using 13.9 ± 4.9 and 15.3 ± 8.3 CPD, respectively. Adriaens et al. (2014) did provide information related to the FTND (titled FTCD). Participants randomised to the control arm reported using 16.7 ± 5.5 CPD and had a FTND of 5.24 ± 1.62. Those that were randomised to the first nicotine containing e-cigarette reported an average CPD of 20.1 ± 9.4 and an FTND score of 5.81 ± 1.94, whilst those randomised to the second nicotine containing e-cigarette reported an average CPD of 20.6 ± 66.2 and an FTND of 6.14 ± 11.99. This suggests that the participants involved in the study by Adriaens et al. (2014) were more dependent smokers compared to those involved in the study by Carpenter et al. (2017).

Nicotine containing e-cigarette and NRT versus placebo e-cigarette and NRT

Two studies were identified that compared active, nicotine containing e-cigarettes with nicotine free e-cigarettes (Baldassarri et al. 2018; Walker et al. 2019). Participants in in all arms were assigned NRT patches and ad libitim use of active e-cigarettes or control for the intervention period. Cessation was once again assessed through biochemical validation of expired CO concentrations, at either ≤ 6ppm (Baldassarri et al. 2018) or 9ppm (Walker et al. 2019). As shown in Figure 6, Nicotine containing e-cigarettes combined with nicotine patches (NRT) were more effective than nicotine-free e-cigarettes combined with NRT patches for achieving biochemically validated smoking cessation, RR 1.77 (95%CI 1.07 – 2.94, p < 0.05).

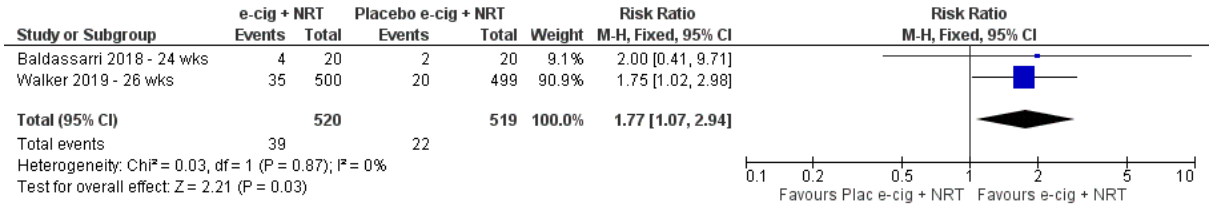


Figure 6: *Nicotine e-cigarettes with NRT vs. placebo e-cigarettes with NRT to achieve biochemically validated smoking cessation.*

Study Heterogeneity

There is low heterogeneity between the two studies. Both studies compared similar interventions, with slightly different concentrations of active nicotine in the e-cig (18mg/ml – Walker et al. 2019; 24mg/ml - Baldassarri et al. 2018) and NRT (21mg patch for both studies). However, where participants smoked 10 or fewer cigarettes per day, Baldassarri et al. (2018) utilised NRT containing 14mg/ml of nicotine. Baldassarri et al. (2018) also utilised a shorter active treatment period (8 weeks) compared to the treatment period of Walker (12 weeks).

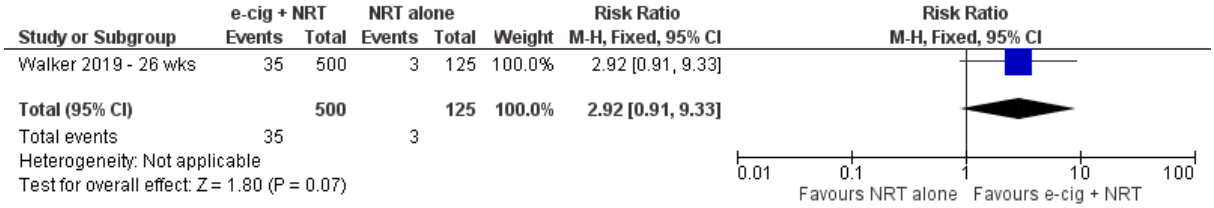
Nicotine Dependency

In the trial by Baldassarri et al (2018) participants were moderately dependent on nicotine; in the control, non-nicotine, e-cigarette group had mean FTND scores of 6.0 (± 2.2) and smoked 17 (± 12.4)

cigarettes/day, while participants in the active e-cigarette group had mean FNTD score of 5.7 (± 2.0) and similarly smoked 17 (± 10.9) cigarettes/day. Nicotine dependency in the trial by Walker et al. 2019 could not be determined (study protocol/abstract only).

Nicotine containing e-cigarette and NRT versus NRT alone

The study by Walker et al. (2019) also included a participant treatment group that had no access to e-cigarettes. Cessation was assessed through biochemical validation of expired CO concentrations at ≤ 9ppm. As identified in Figure 7, nicotine containing e-cigarettes combined with nicotine patches (NRT)



were not more effective than NRT patches alone for achieving biochemically validated smoking cessation, RR 2.92 (95%CI 0.91 - 9.33, p = 0.07)

Figure 7: *Nicotine e-cigarettes and NRT vs. NRT alone to achieve biochemically validated smoking cessation*

Nicotine Dependency

Nicotine dependency could not be determined (study protocol/abstract only).

Nicotine containing e-cigarette and/or NRT and/or financial incentive versus usual care

One study (Halpern et al. 2018) incorporated e-cigarettes in multiple combinations of cessation therapies. Four treatment groups were included, all of which had some form of e-cigarette usage and compared these combination therapies against usual care. Participants randomised to group 1 (Free Cessation Aids) received free access to all forms of NRT and pharmacotherapy, and if smoking cessation was not achieved using these therapies, then they were provided with free access to e-cigarettes. Participants in group 2 (Free E-Cigarettes) were provided free access to e-cigarettes without the requirement that they failed the traditional therapies first. Participants in group 3 (Rewards) received all the options available in the 'Free Cessation Aids' group, as well as $600 in redeemable rewards. Finally, participants in group 4 (Cash Reward) were provided with all the options available in the 'Free Cessation Aids' group, as well as $600 in redeemable funds.

As each intervention group in this study (Halpern et al. 2018) included some form of e-cigarette use, these four treatment groups have been combined in the meta-analysis presented in Figure 8. However, it must be noted that e-cigarettes were not utilised by every participant randomised to each group, and the cessation outcome data reported by the authors has not taken this into consideration. As reported by Halpern et al. the percentages of randomised participants who actually ordered the e-cigarettes for each group were as follows; 6% (Free Cessation Aids); 12% (Free E-Cigarettes); 8% (Rewards) and 11% (Cash Reward).

As can been seen from Figure 8, e-cigarettes as a factor in various combination therapies were not more effective than usual care for achieving biochemically validated smoking cessation, RR 12.07 (95%CI 0.74 – 196.23, p = 0.08).

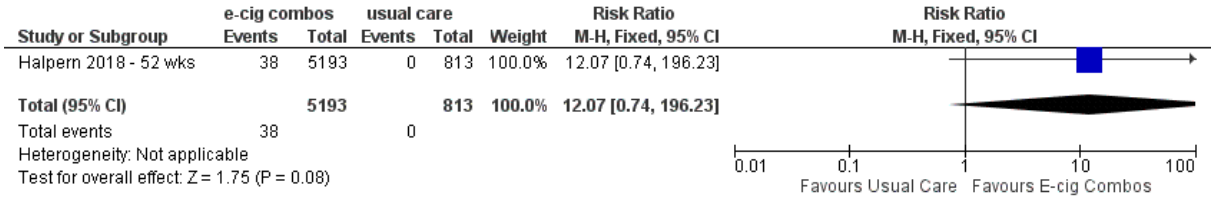


Figure 8: *Nicotine e-cigarettes and/or NRT and/or financial incentive vs. usual care to achieve biochemically validated smoking cessation*

Nicotine Dependency

FTND scores were collected at baseline, however CPD was recorded. The Median CPD for the participants in all 5 treatment groups was 10.0 (IQR 5.0-15.0), indicating that the participants involved in the study had a moderate dependence on nicotine.

Adverse events

As reported in the systematic review by Hartmann-Boyce et al. (2016), the most commonly reported adverse events (AEs) were mouth and throat irritation. Adverse events were recorded and reported narratively in all but one (Felicone et al. 2019) of the additional included studies. Overall, the most common adverse events associated with e-cigarette use were cough; dry/irritated mouth/throat; headache and nausea.

Adriaens et al. (2014), recorded AEs through self-reporting in online diaries. The only complaint that was unique to the e-cigarette group was related to technical problems with the e-cigarette unit. Otherwise, there was no significant difference in the proportion of AEs between the e-cigarette and the CC groups. The AEs common to both groups included bad taste; dry/irritated mouth/throat; dizziness; headache; nausea; increased heart rate; increased weight and shortness of breath.

Baldassarri et al (2018) note the most commonly reported AE among all participants were cough (30%), sore throat (22.5%), increased appetite (17.5%) and vivid dreams (17.5%). Data is not broken down by treatment group but the authors note that there were no significant differences between groups.

Bullen et al. (2013), do not provide descriptive information about the type of AE experienced in the study, but do categorize AEs as 'serious' or non-serious'. There were no significant differences in the proportion of participants experiencing either a serious or non-serious AE between treatment groups, and no serious adverse event was related to product use.

Caponnetto et al. (2013), have presented AE data combined between groups (nicotine containing versus placebo e-cigarette). Overall 26% of the study participants experienced cough; 22% shortness of breath; 20% throat irritation and 17% experienced a headache. Whilst no difference was found between the frequency and distribution of AEs among study groups at any time point, there was a decrease in reported AEs over time, compared to baseline.

Of the participants randomised to receive the nicotine containing e-cigarette in the study by Carpenter et al. (2017), 52% (24mg/ml) and 36% (16mg/ml) experienced at least one AE over the trial period. Collapsed across both e-cigarette groups, 32% of all e-cigarette assigned participants experienced

cough, 24% experienced nausea and 16% experienced mouth/throat irritation. No AE resulted in study termination.

Cravo et al. (2016) present comprehensive data on the number and type of AEs reported in e-cigarette using, or CC using participants. Overall, AEs considered to be 'mild' were reported by 29.6% of the e-cigarette using participants, moderate AEs were experienced by 54.6% of the participants and 15.8 % experienced severe AEs. These were not significantly different when compared to the AEs reported by the CC group. A greater percentage of participants in the e-cigarette group reported oropharyngeal pain (27.8%) compared to the CC group (8.8%) and cough (17.0% vs. 7.8%), however all other AEs remained relatively stable.

Hajek et al. (2019) report AE data for nausea, sleep disturbances and throat/mouth irritation (pre-specified in study protocol). Nausea was more common in the participants randomised to receive NRT (37.9%) compared to those receiving the e-cigarette (31.3%). Throat/mouth irritation was more common in the e-cigarette group (65.3% vs. 51.2%). Sleep disturbances were common in both groups (65% for e-cigarette vs. 68% for NRT).

Lee et al. report that the common AEs to both NRT and e-cigarettes usage were headaches (40% vs. 20%, respectively); nausea (10% vs. 25%); cough (10% vs. 30%) and throat irritation (30% vs 25%), however there were no significant differences in the rate of AE occurrence.

Tseng et al. (2016) provide narrative description only as to the type of AEs that were common to both the nicotine containing e-cigarettes and placebo e-cigarettes, being mouth/throat irritation, cough, insomnia, abnormal dreams, headache and fatigue. The authors report that there was no difference in AEs between groups (34.1% for intervention and 17.5% for placebo group at week 1, P = .09; 22.5% for intervention and 10.3% for placebo group at week 3, P = .14; chi-square test).

Finally, Walele et al. (2016) report that no participant reported a moderate or serious AE and no AEs lead to study withdrawal. The most common reported AEs were once again, cough; mouth/throat irritation; fatigue and headache. In Part 2 of the study, 58.3% of the participants reported a total of 13 AEs, all of which were evaluated as mild. The authors state that while no clear product trend was observed, most AEs occurred with the products containing the greater concentrations of nicotine.

Overall, nicotine containing e-cigarette usage is associated with the occurrence of some mild AE's. The most common of which include coughing; dry/irritated mouth/throat; nausea and insomnia. However, the occurrence of these AEs are comparable to the rates of AEs experienced when participants were using either NRT, CC or placebo e-cigarettes. As reported by Caponetto et al. (2013) AEs related to e-cigarette usage have the potential to decrease over time, however more study data is needed to validate this claim.

Appendix 1 – Excluded Studies

Studies excluded after full text assessment against eligibility criteria

Citation	Reason for exclusion
Cibella, F., et al. (2016). "Lung function and respiratory symptoms in a randomized smoking cessation trial of electronic cigarettes." Clinical Science **130**(21): 1929-1937.	Three arm RCT. Cessation not reported per arm. Outcomes are predominantly spirometric data and lung function.
Bullen, C., et al. (2018). "The effectiveness and safety of combining varenicline with nicotine e-cigarettes for smoking cessation in people with mental illnesses and addictions: study protocol for a randomised-controlled trial." BMC Public Health **18**(1): 596.	Protocol for trial of Varenicline vs Varenicline + e-cig
Ghosh, S. and M. B. Drummond (2017). "Electronic cigarettes as smoking cessation tool: are we there?" Current Opinion in Pulmonary Medicine **23**(2): 111-116.	Literature review. No additional studies identified.
Glasser, A. M., et al. (2017). "Overview of Electronic Nicotine Delivery Systems: A Systematic Review." American Journal of Preventive Medicine **52**(2): e33-e66.	Overview. No additional studies identified.
Klonizakis, M., et al. (2017). "Smokers making a quit attempt using e-cigarettes with or without nicotine or prescription nicotine replacement therapy: Impact on cardiovascular function (ISME-NRT) - a study protocol." BMC Public Health **17**(1): 293.	Study protocol only. Outcomes all cardiovascular physiological effects.
Liu, X., et al. (2018). "Efficiency and adverse events of electronic cigarettes: A systematic review and meta-analysis (PRISMA-compliant article)." Medicine **97**(19): e0324.	Systematic review and meta-analysis. No additional studies data beyond Hartmann-Boyce et al. 2016.
Meier, E., et al. (2017). "A Pilot Randomized Crossover Trial of Electronic Cigarette Sampling Among Smokers." Nicotine & Tobacco Research **19**(2): 176-182.	Ad libitum use of e-cig active vs placebo for 2 wks following 1 week of usual smoking. No cessation reported. Outcomes incl. satisfaction, cravings and behavioural dependence.
O'Brien, B., et al. 2015 E-cigarettes versus NRT for smoking reduction or cessation in people with mental illness: secondary analysis of data from the ASCEND trial. **13**:5.	Secondary analysis of data from Bullen et al. 2013. Focus is on subset with mental illness.
Rigotti, N. A., et al. (2018). "Association of E-cigarette use with smoking cessation among smokers who plan to quit after a hospitalization a prospective study." Annals of Internal Medicine **168**(9): 613-620.	Secondary analysis of RCT. Measures use of e-cigs 3mths after hospital discharge.
Tucker, M. R., et al. (2018). "Predicting short-term uptake of electronic cigarettes: effects of nicotine, subjective effects, and simulated demand." Nicotine & Tobacco Research **20**(10): 1265-1271.	Not RCT. Subjects randomised to 3 different dosages that all ultimately received for 2 weeks. No biochemical validation of cessation. Only CPD reported.

Citation	Reason for exclusion
Walele, T., et al. (2016). "A randomised, crossover study on an electronic vapour product, a nicotine inhalator and a conventional cigarette. Part A: Pharmacokinetics." Regulatory Toxicology & Pharmacology **74**: 187-192.	First paper from Walele trial (Part B is included). Here no cessation/safety data reported.

Appendix 2 – Cochrane tool

Cochrane tool and criteria to assess the risk of bias of randomised controlled trials*

Domain	Support for judgement	Review authors' judgement
Selection bias.		
Random sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias.		
Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Detection bias.		
Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
Attrition bias.		
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
Reporting bias.		
Selective reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other bias.		
Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

* Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

QUESTION

SHOULD NICOTINE CONTAINING E-CIGARETTES BE RECOMMENDED FOR SMOKING CESSATION?	
POPULATION:	Smokers who are interested in stopping smoking habits.
INTERVENTION:	Nicotine containing e-cigarettes alone, or in addition to a standard course of nicotine replacement therapy
COMPARISON:	Nicotine replacement therapy
MAIN OUTCOMES:	Biochemically validated smoking cessation.
SETTING:	Australian population
PERSPECTIVE:	The individual patient in which this recommendation will be made and the individual clinician who might be making this recommendation
CONFLICT OF INTERESTS:	Dr Colin Mendelsohn is a member of this guideline panel who has a potential conflict of interest regarding e-cigarettes. Dr Mendelsohn has been excluded from voting from the items presented in the following evidence to decision framework.

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Smoking causes a higher burden of disease than any other behavioural risk factor, representing 13% of the total burden in men and 9.3% in women (9% of the total burden of disease) in 2011 (Australian Institute of Health and Welfare, 2016). Tobacco smoking is responsible for the deaths of almost 18,762 Australians each year (Australian Institute of Health and Welfare, 2016) and smoking-related disease contributes as a comorbidity to many more. Below are the estimated percentages of all tobacco-caused or related deaths in Australia in 2011: (Australian Institute of Health and Welfare, 2016) - 36% of respiratory diseases - 75% of chronic obstructive pulmonary disease - 80% of lung cancers - 22% of cancers - 3.5% of endocrine disorders Australia has not met the 2018 National Tobacco Strategy target to reduce the national smoking rate to 10% of the population or halve the Indigenous smoking rate over the 2009 rate in the same time (Intergovernmental Committee on Drugs, 2012). Despite the decline in prevalence, smoking remains the behavioural risk factor responsible for the highest levels of preventable disease and premature death (Australian Institute of Health and Welfare, 2016).	

Smokers tend to report other lifestyle risk factors such as higher levels of alcohol consumption, lower daily fruit and vegetable intake and lower levels of exercise. There is extensive evidence that tobacco use contributes to poverty and inequality; encouraging smokers to quit has the potential to improve health and also to alleviate poverty (Australian Institute of Health and Welfare, 2016).

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

- ○ Trivial
- ● Small
- ○ Moderate
- ○ Large
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

Comparison 1: Nicotine containing e-cigarettes versus nicotine replacement therapy for smoking cessation

According to our evidence review, nicotine containing e-cigarettes are more effective than nicotine replacement therapy for smoking cessation. In absolute terms, for every 1000 people treated, 56 more (from 21 more to 104 more) will achieve biochemically validated smoking cessation using a nicotine containing e-cigarette compared to nicotine replacement therapy. No outcome data reported a 50% reduction in CPD.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Nicotine Replacement Therapy	Risk difference with Nicotine Containing E-Cigarettes
Smoking Cessation assessed with: Biochemically Validated (Expired Carbon Monoxide Concentration <= 10ppm) follow up: range 8 weeks to 52 weeks	1498 (3 RCTs)	⨁⨁◯◯ LOW[a,b,c]	**RR 1.69** (1.26 to 2.28)	Study population	
				81 per 1,000	**56 more per 1,000** (21 more to 104 more)

a. Significant issues of contamination bias and other types of bias (performance and detection) present.
b. Participants of Lee et al. (2018) were patients presenting to the anaesthesia pre-operative clinic for elective surgery.
c. Confidence Intervals are somewhat imprecise, ranging from a potentially small effect to a large effect (1.26 -2.28). However there are a low number of events, with 164 events not meeting the Optimal Information Size threshold of 476.

Comparison 2: Nicotine containing e-cigarettes versus placebo e-cigarettes for smoking cessation

According to our evidence review, it is unclear whether Nicotine containing e-cigarettes are more, less or equally effective as placebo e-cigarettes (no active nicotine) for smoking cessation. In absolute terms, for every 1000 people, 36 more (from 2 fewer to 112 more) will achieve biochemically validated smoking cessation using a nicotine containing e-cigarette compared to a placebo e-cigarette. No outcome data reported a 50% reduction in CPD. However this conclusion may be

ADDITIONAL CONSIDERATIONS

The overall judgement regarding how "substantial the desirable effects are" was made following review of all six comparisons included in this section.

One panel member raised the point that the desirable anticipated effects should be moderate, as the RR is in comparison to an already effective therapy, and the RR needs to be contextualised by this factor. As such, a judgment of small would be undervaluing the true effect.

After discussion with the panel, members were split as to whether the desirable effects were small or moderate. However, the panel were unanimous that regardless of whether the effect size is classified as small or moderate it is sufficiently large to be considered important given the

related to the small number of participants in the 4 RCTs and it should be noted that nicotine-containing e-cigarettes have been shown to be more effective than nicotine replacement therapy which itself has been shown to be effective against placebo in a large number of studies with thousands of participants.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Placebo E-Cigarettes	Risk difference with Nicotine Containing E-Cigarettes
Smoking Cessation assessed with: Biochemical Validation (Expired Carbon Monoxide Concentrations <=10ppm follow up: range 3 weeks to 52 weeks	787 (4 RCTs)	⨁◯◯◯ VERY LOW[a,b,c]	**RR 1.84** (0.95 to 3.62)	Study population	
				43 per 1,000	**36 more per 1,000** (2 fewer to 112 more)

a. Statistical heterogeneity is low, but large variation in the estimates of treatment of effect.
b. The study by Felicone et al. (2019) included participants from an outpatient opioid maintenance clinic, who were currently receiving a buprenorphine/naloxone combination.
c. Confidence intervals are wide (0.94 - 3.62). There are also few events, 55 events does not meet the Optimal Information Size threshold of 611.

Comparison 3: Nicotine containing e-cigarettes versus no intervention for smoking cessation

According to our evidence review, it is unclear whether Nicotine containing e-cigarettes are more, less or equally effective as no active-intervention for smoking cessation. In absolute terms, for every 1000 people, 302 more (from 2 fewer to 923 more) will achieve biochemically validated smoking cessation using a nicotine containing e-cigarette compared to no active intervention. No outcome data reported a 50% reduction in CPD However this conclusion may be related to the small number of participants in the 2 RCTs and is of limited relevance as the population of interest (smokers with nicotine dependence) are going to be offered some form of intervention.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with No Intervention	Risk difference with Nicotine Containing E-Cigarettes
				Study population	

health benefits of smoking cessation.

Notes:

Only a conference abstract and study protocol are available for the study by Walker et al.

Smoking Cessation assessed with: Biochemical Validation (Expired Carbon Monoxide Concentrations <=10ppm) follow up: range 8 weeks to 16 weeks	118 (2 RCTs)	⨁◯◯◯ VERY LOW[a,b,c]	**RR 4.93** (0.97 to 25.19)	77 per 1,000	**302 more per 1,000** (2 fewer to 923 more)

a. Potential for contamination in the study by Carpenter et al. (2017)
b. Some concerns over statistical heterogeneity. Widely differing estimates of treatment effect.
c. Confidence Intervals are very large (0.97 - 25.19). Low number of events, 14 events does not meet the Optimal Information Size threshold of 172.

Comparison 4: Nicotine containing e-cigarettes and NRT versus placebo e-cigarettes and NRT for smoking cessation

According to our evidence review, it appears that Nicotine containing e-cigarettes combined with nicotine replacement therapy are more effective than placebo e-cigarettes combined with nicotine replacement therapy for smoking cessation. In absolute terms, for every 1000 people, 33 more (from 3 more to 82 more) will achieve biochemically validated smoking cessation using a nicotine containing e-cigarette combined with NRT compared to a placebo e-cigarette combined with NRT.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Placebo E- Cigarettes and NRT	Risk difference with Nicotine Containing E-Cigarettes and NRT
Smoking Cessation assessed with: Biochemical Validation (Expired Carbon Monoxide Concentrations <=9ppm) follow up: range 24 weeks to 26 weeks	1039 (2 RCTs)	⨁⨁◯◯ LOW[a,b]	**RR 1.77** (1.07 to 2.94)	Study population	
				42 per 1,000	**33 more per 1,000** (3 more to 82 more)

a. Assessment of methodological quality in the study by Walker et al. (2019) was restricted as only the study protocol/abstract were made available.
b. Confidence Intervals are wide, ranging from a trivial benefit to a large benefit (1.07 - 2.94). Low number of events, 61 events does not meet the Optimal Information Size threshold of 815.

Comparison 5: Nicotine containing e-cigarettes and NRT versus NRT alone for smoking cessation

According to our evidence review, it is unclear whether Nicotine containing e-cigarettes combined with NRT are more, less or equally effective as NRT alone at achieving smoking cessation. In absolute terms, for every 1000 people, 46 more (from 2 fewer to 200 more) will achieve biochemically validated smoking cessation using combination e-cigarettes and NRT compared to NRT alone.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with NRT Alone	Risk difference with Nicotine Containing E-Cigarettes and NRT
Smoking Cessation assessed with: Biochemical Validation (Expired Carbon Monoxide Concentrations <=9ppm) follow up: mean 26 weeks	625 (1 RCT)	⨁⨁◯◯ LOW[a,b]	**RR 2.92** (0.91 to 9.33)	Study population	
				24 per 1,000	**46 more per 1,000** (2 fewer to 200 more)

a. Assessment of methodological quality in the study by Walker et al. (2019) was restricted as only the study protocol/abstract were made available.
b. Confidence intervals are very large, ranging from 0.91 to 9.33. Low number of events, 38 events does not meet the optimal information size threshold of 332

<u>Comparison 6:</u> Nicotine containing e-cigarettes and/or NRT and/or financial incentive versus usual care be used for smoking cessation?

According to our evidence review, it is unclear whether Nicotine containing e-cigarettes and/or NRT and/or financial incentive are more, less or equally as effective as usual care at achieving smoking cessation. However due to the significant imprecision encountered and the high rates of contamination observed, absolute terms are incalculable.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Usual Care	Risk difference with Nicotine Containing E-Cigarette and/or NRT and/or financial incentive
Smoking Cessation assessed with: Biochemical Validation (Anabasine Concentraions in Urine <3ng per ml) follow up: mean 52 weeks	6006 (1 RCT)	⨁◯◯◯ VERY LOW[a,b]	**RR 12.07** (0.74 to 196.23)	Study population	
				0 per 1,000,000	**0 fewer per 1,000,000** (0 fewer to 0 fewer)

a. Confidence intervals are very large, and range from 0.74 to 196.23. Low number of events, 38 events does not meet the optimal information size threshold of 18,726
b. Halpern et al. (2018) at high risk of bias under the domains of performance, detection and attrition. Also at risk of contamination

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	**<u>Comparison 1:</u> Nicotine containing e-cigarettes versus nicotine replacement therapy for smoking cessation**	
	<u>Comparison 2:</u> Nicotine containing e-cigarettes versus placebo e-cigarettes for smoking cessation	
	<u>Comparison 3:</u> Nicotine containing e-cigarettes versus no intervention for smoking cessation	
	<u>Comparison 4:</u> Nicotine containing e-cigarettes and NRT versus placebo e-cigarettes and NRT for smoking cessation	
	<u>Comparison 5:</u> Nicotine containing e-cigarettes and NRT versus NRT alone for smoking cessation	
	<u>Comparison 6:</u> Nicotine containing e-cigarettes and/or NRT and/or financial incentive versus usual care be used for smoking cessation	
	As reported in the systematic review by Hartmann-Boyce et al. (2016), the most commonly reported adverse events (AEs) were mouth and throat irritation during the trial period. Adverse events were recorded and reported narratively in all but one (Felicone et al. 2019) of the studies that have contributed to the above summary of findings tables. Overall, the most common adverse events associated with e-cigarette use were cough; dry/irritated mouth/throat; headache and nausea. These were all reported during the duration of the trial and there was no evidence on long term NRT use within these studies. Adriaens et al. (2014), recorded AEs through self-reporting in online diaries. The only complaint that was unique to the e-cigarette group was related to technical problems with the e-cigarette unit. Otherwise, there was no significant difference in the proportion of AEs between the e-cigarette and the CC groups. The AEs common to both groups included bad taste; dry/irritated mouth/throat; dizziness; headache; nausea; increased heart rate; increased weight and shortness of breath. Bullen et al. (2013), do not provide descriptive information about the type of AE experienced in the study, but do categorize AEs as 'serious' or 'non-serious'. There were no significant differences in the proportion of participants experiencing either a serious or non-serious AE between treatment groups, and no serious adverse event was related to product use. Caponnetto et al. (2013), have presented AE data combined between groups (nicotine containing versus placebo e-cigarette). Overall 26% of the study participants experienced cough; 22% shortness of breath; 20% throat irritation and 17% experienced a headache. Whilst no difference was found between the frequency and distribution of AEs among study groups at any time point, there was a decrease in reported AEs over time, compared to baseline. Of the participants randomised to receive the nicotine containing e-cigarette in the study by Carpenter et al. (2017), 52% (24mg/ml) and 36% (16mg/ml) experienced at least one AE over the trial period. When looking across both e-cigarette groups, 32% of all e-cigarette assigned participants experienced cough, 24% experienced nausea and 16% experienced mouth/throat irritation. No AE resulted in study termination.	Discussion with the panel focused on the lack of evidence that is currently available as to the long term effects of e-cigarette use. One panel member noted that it is reasonable to assume that the long term adverse effects of e-cigarette maybe be worse than long term use of NRT. Multiple studies have not found health concerns associated with long term NRT use, while no such studies yet exist for e-cigarettes. The evidence presented suggests that the immediate adverse effects associated with e-cigarette usage under 12 months, appears to be trivial. However some panel members raised the point

	Cravo et al. (2016) present comprehensive data on the number and type of AEs reported in e-cigarette using, or conventional cigarette (CC) using participants. Overall, AEs considered to be 'mild' were reported by 29.6% of the e-cigarette using participants, moderate AEs were experienced by 54.6% of the participants and 15.8 % experienced severe AEs. These were not significantly different when compared to the AEs reported by the CC group. A greater percentage of participants in the e-cigarette group reported oropharyngeal pain (27.8%) compared to the CC group (8.8%) and cough (17.0% vs. 7.8%), however all other AEs remained relatively stable. Hajek et al. (2019) report AE data for nausea, sleep disturbances and throat/mouth irritation (pre-specified in study protocol). Nausea was more common in the participants randomised to receive NRT (37.9%) compared to those receiving the e-cigarette (31.3%). Throat/mouth irritation was more common in the e-cigarette group (65.3% vs. 51.2%). Sleep disturbances were common in both groups (65% for e-cigarette vs. 68% for NRT). The authors state that there were 27 serious adverse events in the e-cigarette group, and 22 in the NRT group. Of these, there were 5 respiratory events in the e-cigarette group and 1 respiratory event in the NRT group. No serious adverse event was classified by the trial clinician as being related to product use. Lee et al. report that the common AEs to both NRT and e-cigarettes usage were headaches (40% vs. 20%, respectively); nausea (10% vs. 25%); cough (10% vs. 30%) and throat irritation (30% vs 25%), however there were no significant differences in the rate of AE occurrence. Tseng et al. (2016) provide narrative description only as to the type of AEs that were common to both the nicotine containing e-cigarettes and placebo e-cigarettes, being mouth/throat irritation, cough, insomnia, abnormal dreams, headache and fatigue. The authors report that there was no difference in AEs between groups (34.1% for intervention and 17.5% for placebo group at week 1, P = .09; 22.5% for intervention and 10.3% for placebo group at week 3, P = .14; chi-square test). Finally, Walele et al. (2016) report that no participant reported a moderate or serious AE and no AEs lead to study withdrawal. The most common reported AEs were once again, cough; mouth/throat irritation; fatigue and headache. In Part 2 of the study, 58.3% of the participants reported a total of 13 AEs, all of which were evaluated as mild. The authors state that while no clear product trend was observed, most AEs occurred with the products containing the greater concentrations of nicotine. Overall, nicotine containing e-cigarette usage is associated with the occurrence of some mild AE's. The most common of which include coughing; dry/irritated mouth/throat; nausea and insomnia. However, the occurrence of these AEs are comparable to the rates of AEs experienced when participants were using either NRT, CC or placebo e-cigarettes. As reported by Caponetto et al. (2013) AEs related to e-cigarette usage have the potential to decrease over time, however more study data is needed to validate this claim.	that more data was needed before they were happy to be confident that the adverse effects were in fact trivial, arguing that even for the immediate adverse effects associated with e-cigarette usage, the judgment must be 'Don't Know'. The Hajek study where there were 5 respiratory events in the e-cigarette group and 1 respiratory event in the NRT group was highlighted as an example of the lack of certainty about short term adverse effects. Given this lack of evidence on long term effects, and the questioning of some of the panel members on short term adverse events, the overall judgement of the panel is 'don't know.'
Balance of effects		

Does the balance between desirable and undesirable effects favour the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention	As discussed and presented in the summary of findings above, the balance of effects probably favours the intervention.	The panel were unanimous in the balance of effects probably favouring the intervention.
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ● Low ○ Moderate ○ High ○ No included studies	**<u>Comparison 1:</u> Nicotine containing e-cigarettes versus nicotine replacement therapy for smoking cessation**	Comparisons 1 and 5 were unanimously decided by the panel as being the equal most important comparisons of interest. This is why the certainty of the evidence has remained at low, despite outcomes under other comparisons being judged to have a very low certainty of evidence.
	The certainty of the evidence was deemed to be low, due to imprecision and issues with the methodological quality of the included studies.	
	<u>Comparison 2:</u> Nicotine containing e-cigarettes versus placebo e-cigarettes for smoking cessation	
	The certainty of the evidence for this comparison was deemed to be very low, due to significant heterogeneity between studies, indirectness (participants in the study by Felicone et al. (2019) were from an outpatient opioid maintenance clinic) and imprecision.	
	<u>Comparison 3:</u> Nicotine containing e-cigarettes versus no intervention for smoking cessation	
	The certainty of the evidence for this comparison was deemed to be very low, due to significant heterogeneity between studies, significant imprecision, and concerns over the methodological quality of the included study by Carpenter et al. (2017).	

	<u>Comparison 4:</u> Nicotine containing e-cigarettes and NRT versus placebo e-cigarettes and NRT for smoking cessation	One panel member raised the point that it is incorrect to consider the contamination of the contributing studies as a major factor worthy of downgrading the certainty of the evidence, as contamination occurred both ways, and it could be argued to actually increase the true estimate of effect. However, despite this factor, there were other methodological issues associated with this study that warranted the downgrading of the certainty to low. The panel were subsequently happy to leave the overall certainty of the evidence as low.
	The certainty of the evidence for this comparison was deemed to be low due to imprecision, and concerns over the methodological quality of the included studies. However these concerns are largely due to the inability to adequately appraise the data presented by Walker et al. (2019) as only the study protocol and conference abstract were available.	
	<u>Comparison 5:</u> Nicotine containing e-cigarettes and NRT versus NRT alone for smoking cessation	
	The certainty of the evidence was deemed to be low, due to imprecision and the inability to adequately appraise the methodological quality of the Walker et al. (2019) study, as only the study protocol and a conference abstract were made available.	
	<u>Comparison 6:</u> Nicotine containing e-cigarettes and/or NRT and/or financial incentive versus usual care be used for smoking cessation?	
	The certainty of the evidence was deemed to be very low, due to significant imprecision, and major concerns over the methodological quality of the one, included study.	

Values **Is there important uncertainty about or variability in how much people value the main outcomes?**		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or	Most smokers of conventional cigarettes have a nominal understanding of the health risks associated with smoking. Whilst most smokers might understand the presence of increased health risks, there is a lack of understanding demonstrated as to the magnitude of such health risks.	Multiple panel members wanted it noted that while smokers might be aware of the presence of increased health risks associated with smoking, they are generally

variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability		not aware of the magnitude of these health risks. Often under-valuing the true negative effects associated with continued smoking. These points have been noted in the 'research evidence' adjacent.
Acceptability **Is the intervention acceptable to key stakeholders?**		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Patient Perspective ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know **Clinician Perspective** ○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	After discussion with the guideline panel, it was unanimously decided that the acceptability of a recommendation for e-cigarettes needs to be separated into a patient and clinician perspective **Patient perspective** The large, societal acceptance of e-cigarettes (as identified in both the reviewed and extant literature) demonstrates that e-cigarettes, are an acceptable and widely used product among patients. **Clinician perspective** From the clinician perspective, acceptability of the product is also closely associated with the safety of the product. Long term effects of e-cigarette use are currently unknown and insufficiently researched at present. These factors may make clinicians feel that this is an unacceptable treatment to offer their patients, particularly in the absence of regulatory assessment of delivery devices and e-liquid and in the broader context of lack of clarity of regulation and legislation in this field. **Research Evidence** While no meta-analysis was performed to investigate the nature and severity of the AEs encountered, it is likely that nicotine containing e-cigarettes do not appear to increase the risk of AE's (in the short term) substantially beyond the potential for irritating the mouth/throat of its users. In a comprehensive systematic review by Glasser et al. (2016), 116 studies were identified that examined the impact of vaping on human health (this review combine's nicotine containing e-cigarettes with non-nicotine containing e-cigarettes). Glasser et al. (2016) report that e-cigarette use has no or minimal impact on many physiological measures (exhaled CO, complete blood count, body weight), with improvements in outcomes seen	One panel member stated that in comparison to the cost of smoking conventional cigarettes, e-cigarettes are actually a financial benefit to consumers. One panel member thought that the evidence was clear that larger percentages of the participants of the Hajek study continued to use e-cigarettes over the 12-month trial period, compared to the percentage of people who continued to use NRT. This point highlights the fact that it is clearly an

	for smokers switching to e-cigarettes from conventional cigarettes, such as reduced blood pressure, improved lung function and improved disease symptoms (asthma and chronic obstructive pulmonary disease). As reported by Ghosh and Drummond (2017) there is substantial heterogeneity in e-cigarette device design which leads to heterogeneity in the constituents of the vapour produced. Ghosh and Drummond (2017) state that "while the preponderance of data support that e-cigarettes generate toxic compounds at levels less than combustible cigarettes, it is unclear if these levels are below a threshold for harm." Some 'flavours' of the e-cigarette liquid are also more cytotxic than others, but overall, they are much less cytotoxic than cigarette smoke (Glasser et al. 2016). In cellular studies, exposure to vapour from an e-cigarette has been evidenced to increase anti-inflammatory process, oxidative stress, cell apoptosis and cell necrosis (Glasser et al. 2016). The Food and Drug Administration received 35 adverse event reports due to the passive exposure of e-cigarette vapour between January 2012 and December 2014 (Durmowicz et al. 2016). These included respiratory symptoms, eye irritation, headache, nausea, sore throat/irritation, dizziness, racing/irregular heart rate. As summarised in the review by Glasser et al. (2016), studies that observed the effects of second-hand vapour report that non-users may be exposed to nicotine, however the level of exposure is low. Compared to second-hand smoke, exposure to nicotine and other toxic compounds was significantly reduced in non-users. From 2012 to 2015 there were 92 reported overheating/fire/explosion events in the US related to e-cigarette use. Approximately half of these resulted in injuries, including (but not limited too) thermal burns, lacerations, smoke inhalation) Rudy et al. (2016). **Stigma** As identified in the systematic review by Glasser et al, (2017) social stigma of using e-cigarettes is a common, negative perception felt among e-cigarette users. **Financial burden and lack of regulation** As reviewed by Glasser et al. (2017), the e-cigarette market is expanding. In the U.S, e-cigarettes are widely available for purchase online, and approximately half of U.S tobacco outlets now sell e-cigarettes. In Australia, it is illegal to purchase nicotine containing e-cigarettes from any Australian retailer. However it is legal to use, and legal to import (except for in Queensland, where it appears it is illegal to use nicotine containing e-cigarettes). Where a nicotine containing e-cigarette is to be used for therapeutic uses (smoking cessation) the e-cigarette must be first registered with the TGA after a prescription is obtained from a doctor. E-cigarettes are not currently subsidised by the Pharmaceutical Benefits Scheme. There is limited research evidence available as to the impact of pricing on e-cigarette usage.	acceptable product from a consumer perspective. One panel member agreed that whilst it may be acceptable from the perspective of a patient to use an e-cigarette for smoking cessation. The lack of available evidence regarding the long term effects of e-cigarette use may prevent clinicians from finding it acceptable to recommend to their patients. In rebuttal, a panel member stated that as a clinician, if a patient found e-cigarettes acceptable, and they are willing to try them for smoking cessation, then they should be recommended as a therapy to those people. Another panel member argued that they were unhappy to recommend a product to a patient, if they didn't have all the information available, regarding said product. Furthermore, the patient reacts to the information that is provided to them,

		and when clinicians don't have all the relevant information it is unacceptable to recommend. One panel member noted that the regulatory environment of e-cigarettes currently, make clinicians uncomfortable with recommending such a product. Following the discussion from the panel, the acceptability from the clinician perspective was judged to be 'probably no'.
Feasibility **Is the intervention feasible to implement?**		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Patient perspective ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know **Clinician perspective**	**Patient perspective** It may be unfeasible for some patients to access the product due to the lack of regulation, and reliance on internet sales to purchase and obtain the product. **Clinician perspective** From the clinician perspective, due to the lack of regulation around the product, it might not be feasible to make a recommendation. There are also issues associated with prescribing an e-cigarette product, such as standard prescription forms for nicotine containing e-liquids and standard, approved, recommended devices being unavailable.	One panel member noted that whilst a prescription is needed to obtain an e-cigarette for use in Australia, most patients can access them quite easily from e-cigarette shops and via the internet. One member had an issue with the range of devices used in the studies included in the above

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		synthesis. Such a wide range and variety of devices used makes it difficult to feasibly recommend a particular device over another without further research. One panel member discussed the point that it has been demonstrated to be feasible to some patients in some circumstances. It may not be feasible for every patient in every circumstance but it is possible to get people to use e-cigarettes. Another panel member argued that it is clearly feasible, as people are already doing it. Stating that it is feasible with some barriers. Following the discussion from the panel, the feasibility from the clinician perspective was judged to be 'probably yes'.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know
ACCEPTABILITY (PATIENT)	No	Probably no	**Probably yes**	Yes		Varies	Don't know
ACCEPTABILITY (CLINICIAN)	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY (PATIENT)	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY (CLINICIAN)	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

For people who have tried to achieve smoking cessation with traditional therapies (nicotine replacement therapy, other pharmacotherapies etc.) but failed, are still motivated to quit smoking and have brought up e-cigarette usage with their GP, then e-cigarettes may be a reasonable intervention to recommend. However, this needs to be preceded by a evidence-informed shared-decision making process, whereby the patient is aware of the following caveats:

1. Due to the lack of available literature, the long term health effects of vaping are unknown.
2. E-cigarettes are currently not regulated in Australia and therefore the constituents of the vapour they produce has not been tested.
3. There is a lack of uniformity in delivery devices and the e-liquid constituents which increases the uncertainties associated with their usage.
4. In order to maximise possible benefit and minimise risk of harms dual use and long term use needs to be avoided

Justification

The evidence does suggest that e-cigarettes do promote biochemically validated smoking cessation for at least up to 12-month post quitting. However there is a significant lack of evidence for the efficacy and safety of these products after this time point.

Subgroup considerations

This recommendation may be more effective for smokers who are dependent on the behavioural/social components of smoking.
Perhaps we need to consider more dependant smokers who are interested in e-cigarettes.

Implementation considerations

Registration with the TGA (Therapeutic Goods Administration) would encourage further standardisation and regulation of e-cigarette availability and usage. Clinicians might be more accepting of recommending e-cigarettes with TGA testing and regulation. The current legislation and regulation of e-cigarettes varies state by state and this needs to be considered.

Research priorities

More research is needed to investigate the health risks associated with long term e-cigarette usage. Uncommon potentially serious adverse effects such as respiratory events also need further investigation.