National Institute for Health and Care Excellence

Final

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

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

NICE guideline NG209

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

November 2021

Final

These evidence reviews were developed by PHIGD

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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Contents

Appendices

Appendix A – Review protocols

Review protocol for effectiveness of e-cigarettes

ID	Field (based on PRISMA-P	Content
I	Review question	6.1a. What are the most effective and cost effective means of smoking cessation (including e-cigarettes[1])? 6.1b. Are e-cigarettes effective and cost effective for smoking harm reduction?
II	Type of review question	Intervention
III	Objective of the review	Electronic cigarettes (e-cigarettes) are a relatively new technology. Their effectiveness for harm reduction or cessation in relation to commonly used pharmacotherapies is not certain. For cessation, commonly used pharmacotherapies include NRTs, varenicline and bupropion. For harm reduction, only NRTs are commonly used in England. The relative effectiveness of these treatments compared with e-cigarettes is uncertain and may affect

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

		patient choice. This review aims to establish which interventions are the most effective and cost effective for cessation and harm reduction.
IV	Eligibility criteria – population/disease/condition/issue/domain	**Included**: 6.1a. Anyone aged 18 and over who smokes and wants to stop smoking (for the effectiveness at 6 months outcome and adverse events, also those who want to reduce their harm from smoking without stopping completely). 6.1b. Anyone aged 18 and over who smokes and wants to reduce their harm from smoking without stopping completely. **Excluded**: People who do not smoke Pregnant and breastfeeding women People aged 17 and under People who want to stop using smokeless tobacco but not smoking. **Setting**: All settings
V	Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	**Included**: 6.1a. Elements to be included in the NMA:

		• Varenicline • Bupropion • NRT single mode (use of either long-acting or short-acting NRT only) • NRT multi-mode (use of both a long-acting and short-acting NRT) • E-cigarettes • Placebo • Usual care • Waitlist. These may be used as monotherapy or in combination with each other or with behavioural support. 6.1b. • E-cigarettes **Excluded**: Therapies not licensed in the UK. Alternative and complementary therapies. Psychotherapies (unless included as co-treatment with an included smoking therapy). Therapies that are either smoked or contain tobacco.

VI	Eligibility criteria – comparator(s)/control or reference (gold) standard	**6.1a: see listed elements above** **6.1b:** NRT (either single- or multi-mode) No intervention or usual care. Placebo.

VII	Outcomes and prioritisation	**Quantitative outcomes**
		
		<u>6.1a.</u>
		
		<u>Critical outcomes</u>
		
		• Cessation: Smoking status at 6 months. Measured as:
		  ○ Abstinence from smoking (relative risk)
		• Cessation: Smoking status at more than 1 but less than 6 months (of e-cigarettes vs other included treatments). Measured as:
		  ○ Abstinence from smoking (relative risk)
		
		Where studies reported more than one cessation outcome, continuous/sustained abstinence was preferred, followed by prolonged abstinence, 30-day PPA, 7-day PPA and any other abstinence.
		
		<u>6.1b.</u>

		<u>Critical outcomes</u> • Harm reduction status at longest available follow-up (minimum 6 months). Measured as: a. Reduction in validated biochemical measures: i. Carbon monoxide in expired air or blood sample ii. Urinary cotinine iii. Anabasine and anatabine in urine. • Quit status: risk of quitting smoking, defined as per the critical cessation outcome above. <u>Important outcomes</u> • Reduction in smoking-related symptoms: • Cough • Phlegm • Shortness of breath • Wheezing <u>6.1a and 6.1b important outcomes</u> • Adverse or unintended (positive or negative) effects of e-cigarettes when used for cessation or harm reduction at any time point, including:

		○ Adverse effects such as headaches, nausea, throat irritation or dry mouth. • Health-related quality of life of using e-cigarettes for cessation or harm reduction (using validated patient-report measures, for example EQ-5D). **Cost/resource use associated with the intervention** The following outcomes will be extracted in reviews of the health economic evidence, where available: • cost per quality-adjusted life year • cost per unit of effect • net benefit • net present value • cost/resource impact or use associated with the intervention or its components
VIII	Eligibility criteria – study design	**Included study designs**: • Systematic reviews of included study designs • RCTs (including cluster RCTs) All non-randomised studies will be excluded. <u>Economic studies</u>:

		• Cost-utility (cost per QALY) • Cost benefit (i.e. net benefit) • Cost-effectiveness (Cost per unit of effect) • Cost minimization • Cost-consequence
IX	Other inclusion exclusion criteria	**Studies** This is a new review for the tobacco update. **Systematic Review** Relevant systematic reviews (SRs) identified from database searches will be citation searched. Highly relevant systematic reviews may be included as a primary source of data. These SRs will be assessed against the inclusion criteria for this protocol, and their quality will be assessed using the ROBIS tool. Where the SR is highly relevant and of high quality, details or data from the systematic review may be used. In addition to any SRs meeting the above criteria, other primary studies will be included if they were published after the publication date of the SR and meet the protocol inclusion criteria. Costing data will not be used for the purpose of the effectiveness review. Health economics reviews and modelling will be conducted by the York Health Economics Consortium (YHEC). Non-English language articles will be included as per the Bristol protocol.

		No country limit will be applied to this review.
X	Proposed sensitivity/sub-group analysis, or meta-regression	An upcoming publication will produce a network meta-analysis for the critical cessation outcome at 6 months, which will be incorporated into this review. This protocol has been aligned with that review where relevant. Pairwise comparisons will be carried out for all outcomes, including the critical harm reduction outcome. The following factors will be of interest in any subgroup or meta-regression analyses: • Psychiatric illness • Cardiovascular disease • COPD • Diabetes • Heavy smoking (>20 cigarettes / day) • Those with previous quit attempts • Generation of e-cigarette used
XI	Selection process – duplicate screening/selection/analysis	6.1a (6 month outcome): as per Bristol. 6.1a (short-term outcome) and 6.1b: The review will use the priority screening function within the EPPI-reviewer systematic reviewing software. Double screening will be carried out for 10% of titles and abstracts by a second reviewer. Disagreements will be resolved by discussion. Inter-rater reliability will be assessed and reported. If below 90%, a second round of 10% double screening will be considered. The study inclusion and exclusion lists will be checked with members of the PHAC to ensure no studies are excluded inappropriately.
XII	Data management (software)	6.1a (6 month outcome): as per Bristol.

		6.1a (short-term outcome) and 6.1b: EPPI Reviewer will be used: • to store lists of citations • to sift studies based on title and abstract • to record decisions about full text papers • to order freely available papers via retrieval function • to request papers via NICE guideline Information Services • to store extracted data Cochrane Review Manager 5 will be used to perform meta-analyses. Any meta-regression analyses will be undertaken using the R software package.
XIII	Information sources – databases and dates	6.1a: as per Bristol 6.1a (short-term outcome): Bristol's included study list (which does not select by follow-up length) will be searched. 6.1b: NICE will conduct a search using the following methods: • the databases listed below will be searched with an appropriate strategy. • forward citation searching and reference harvesting will be done using selected studies prioritised from the surveillance reviews, scoping searches or any relevant systematic reviews identified in the search process. **Database strategies** The principal search strategy is listed in Appendix A. The search strategy will take this broad approach: (((Ecigs OR Vaping) AND (Smoking Harm Reduction)) OR Multi-Tobacco Use) AND (RCTs OR Systematic Reviews) AND Limits

		Feedback on the principal database strategy will be sought from PHAC members. The principal search strategy will be developed in MEDLINE (Ovid interface) and then adapted, as appropriate, for use in the other sources listed, taking into account their size, search functionality and subject coverage. The databases will be: • Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley • Cochrane Database of Systematic Reviews (CDSR) via Wiley • Database of Abstracts of Reviews of Effects (DARE) legacy database via CRD https://www.crd.york.ac.uk/CRDWeb • Embase via Ovid • MEDLINE via Ovid • MEDLINE-in-Process (including Epub Ahead-of-Print) via Ovid • PsycINFO via Ovid **Database search limits** Database functionality will be used, where available, to exclude: • non-English language papers • animal studies • editorials, letters and commentaries • conference abstracts and posters • registry entries for ongoing or unpublished clinical trials • duplicates. Sources will be searched without any date limits. The database search strategies will use agreed study-type search filters, where available, to limit the results. The McMaster Therapy Best Balance filter will be used for RCTs and the health-evidence.ca Systematic Review filter will be used for SRs.

		Web of Science Forward citation searching and reference harvesting will be conducted using Web of Science (WOS) Core Collection. Only those references which NICE can access through its WOS subscription will be added to the search results. Duplicates will be removed in WOS before downloading. **Cost effectiveness evidence** A separate search will be done for cost effectiveness evidence. The following databases will be searched again with agreed study-type search filters applied to a strategy based on the one in Appendix A: • Embase via Ovid • MEDLINE via Ovid • MEDLINE-in-Process (including Epub Ahead-of-Print) via Ovid In addition, the following sources will be searched without study-type filters: • Campbell Collaboration via https://campbellcollaboration.org/library.html • EconLit via Ovid • HTA database via CRD https://www.crd.york.ac.uk/CRDWeb • NHS EED via CRD https://www.crd.york.ac.uk/CRDWeb **Website searching** The following websites will be searched with an appropriate strategy for SRs and RCTs: • Health Services/Technology Assessment Texts (HSTAT) https://www.ncbi.nlm.nih.gov/books/NBK16710 • NICE Evidence Search https://www.evidence.nhs.uk The websites of relevant organisations, including the ones below, will be browsed: • UK Centre for Tobacco and Alcohol Studies http://ukctas.net/index.html

		• University of Bath Tobacco Control Research Group https://researchportal.bath.ac.uk/en/organisations/uk-centre-for-tobacco-control-studies • University of Stirling Centre for Tobacco Control Research https://www.stir.ac.uk/about/faculties-and-services/health-sciences-sport/research/research-groups/centre-for-tobacco-control-research/publications The website results will be reviewed on screen and documents in English and that are potentially relevant will be added to the main EndNote file. **Quality assurance** The guidance Information Services team at NICE will quality assure the principal search strategy and peer review the strategies for the other databases. Any revisions or additional steps will be agreed by the review team before being implemented. Any deviations and a rationale for them will be recorded alongside the search strategies. **Search results** The database search results will be downloaded to EndNote before duplicates are removed using automated and manual processes. The de-duplicated file will be exported in RIS format for loading into EPPI-Reviewer for data screening.
XIV	Identify if an update	This question is a new question for the Tobacco update.
XV	Author contacts	Please see the guideline development page
XVI	Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual

XVII	Search strategy – for one database	For details please see appendix B.
XVIII	Data collection process – forms/duplicate	A standardised evidence table format will be used and published as appendix D (effectiveness evidence tables) or H (economic evidence tables).
XIX	Data items – define all variables to be collected	For details please see evidence tables in appendix D (effectiveness evidence tables) or H (economic evidence tables).
XX	Methods for assessing bias at outcome/study level	6.1a (6 month follow-up): as per Bristol 6.1a (short follow-up) and 6.1b: Standard study checklists will be used to critically appraise individual studies. For details please see Appendix H of Developing NICE guidelines: the manual The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ GRADE will be used to assess confidence in the findings from
XXI	Criteria for quantitative synthesis (where suitable)	6.1a: An NMA will be undertaken as per Bristol. 6.1a (short follow-up) and 6.1b: For details please see section 6.4 of Developing NICE guidelines: the manual.
XXII	Methods for analysis – combining studies and exploring (in)consistency	6.1a: If a network which includes e-cigarettes and two or more other treatment can be constructed, a network meta-analysis (NMA) will be conducted for the main outcome of smoking abstinence and harm reduction. This will include an assessment of consistency,

		the presence of which is assumed when conducting an NMA, to identify whether studies have different prevalence of effect modifiers. This will be a visual inspection unless high inconsistency is detected, when a formal approach will be used. 6.1a (short follow-up) and 6.1b: **Heterogeneity** Data from different studies will be pooled in a meta-analysis where they are investigating the same outcome and where the resulting meta-analysis may be useful for decision-making. Cluster and individual randomised controlled trials will be pooled. Randomised and non-randomised controlled studies investigating the same outcomes will be pooled. Results will be stratified by design (cluster, individual, randomised and non-randomised for a maximum of four groups stratified) and the P value of the interaction between study design and effect evaluated. A P value of <0.2 will be considered significant. If interaction is significant, results will be presented separately for each group, but if not, will be presented with one averaged effect estimate. It is anticipated that studies included in the review will be heterogeneous with respect to participants, interventions, comparators, setting and study design. Where significant between study heterogeneity in methodology, population, intervention or comparator is identified by the reviewer in advance of data analysis, random effects models will be used. If methodological heterogeneity is not identified in advance but the I2 value is ≥50%, random effects models will also be used. If the I^2 value is above 50%, heterogeneity will be judged to be serious and so will be downgraded by one level in GRADE. If the I^2 value is above 75%, heterogeneity will be judged to be very serious and will be downgraded by two levels in GRADE.

		If the studies are found to be too heterogeneous to be pooled statistically, a narrative synthesis will be conducted. **Imprecision** No minimally important difference (MID) thresholds relevant to this guideline were identified from the COMET database or other published source. MIDs were agreed by committee. Uncertainty is introduced where confidence intervals cross the MID threshold. If the confidence interval crosses one lower MID threshold, this indicates 'serious' risk of imprecision. Crossing both MID thresholds indicates 'very serious' risk of imprecision in the effect estimate. Where the MID is 'any significant change' there is effectively only one threshold (the line of no effect), and so only one opportunity for downgrading. In this instance, outcomes will be downgraded again if they are based on small samples (<300 people). MIDs for outcomes will be included in the methods section of the individual reviews.
XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details please see Appendix H of Developing NICE guidelines: the manual.
XXIV	Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
XXV	Rationale/context – Current management	For details please see the introduction to the evidence review.
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee will develop the guideline. The committee will be convened by Public Health Internal Guidelines Development (PH-IGD) team and chaired by Sharon Hopkins in line with section 3 of Developing NICE guidelines: the manual. Staff from Public Health Internal Guidelines Development team will undertake systematic literature searches, appraise the evidence, conduct meta-analysis where appropriate and draft the guideline in collaboration with the committee. Cost-effectiveness analysis will be

		conducted by YHEC where appropriate. For details please see Developing NICE guidelines: the manual.
XXVII	Sources of funding/support	PH-IGD is funded and hosted by NICE
XXVIII	Name of sponsor	PH-IGD is funded and hosted by NICE
XXIX	Roles of sponsor	NICE funds PH-IGD to develop guidelines for those working in the NHS, public health and social care in England.
XXX	PROSPERO registration number	[If registered, add PROSPERO registration number]

Appendix B – Literature search strategies

Cessation main search – searches completed by Thomas (2020)

Cessation re-run search – searches completed by NICE Information Services

The re-run searches were based on the strategy used by Thomas (2020), which was last updated on 22 January 2019. The searches were adapted to make them appropriate to the screening criteria for the NICE review. There was no new QA or peer review at NICE. The re-runs were completed on 14 November 2019.

The strategies were adapted as appropriate to the other databases listed in the protocol. Full details of all the search strategies are available in a separate document from the NICE Information Services team.

Search sources

Database name	Date searched	Database Platform	Database segment or version	No. of records
Cochrane Central Register of Controlled Trials (CENTRAL)	14/11/2019	Wiley	Cochrane Central Register of Controlled Trials Issue 11 of 12, November 2019	357
Cochrane Database of Systematic Reviews (CDSR)	14/11/2019	Wiley	Cochrane Database of Systematic Reviews Issue 11 of 12, November 2019	9
Embase	14/11/2019	Ovid	Embase 1974 to 2019 November 13	171
MEDLINE	14/11/2019	Ovid	Ovid MEDLINE(R) 1946 to November 13, 2019	263
MEDLINE-in-Process	14/11/2019	Ovid	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to November 13, 2019	222
MEDLINE-in-Process Epub Ahead-of-Print	14/11/2019	Ovid	Ovid MEDLINE(R) Epub Ahead of Print November 13, 2019, Ovid MEDLINE(R) Daily Update November 13, 2019	145
PsycINFO	14/11/2019	Ovid	PsycINFO 1806 to November Week 1 2019	128
Web of Science Core Collection	14/11/2019	Clarivate	Web of Science Core Collection = SCI-EXPANDED, SSCI, A&HCI, ESCI	414

Principal search strategy – as run in MEDLINE and adapted for other sources

Database(s): **Ovid MEDLINE(R)** 1946 to November 13, 2019

#	Searches	Results
1	Smoking/	137725
2	Tobacco Smoking/	757
3	Tobacco/	30121
4	Nicotine/	24976
5	Tobacco Products/	3626
6	Smoking Cessation/	27578
7	"Tobacco Use Cessation"/	1121
8	"Tobacco Use Disorder"/	10923
9	smokers/ or Ex-smokers/	1261
10	(smoking* or smoker*).ti,ab,kf.	215790
11	(tobacco* or cigar* or cigarette* or nicotine*).ti,ab,kf.	151473

12	((quit or quits or quitting* or stop or stops* or stopping* or stopped* or stoppage* or cease or ceases* or ceasing* or cessation* or cut or cuts or cutting or abstain* or abstinen* or giv* up or discontinu*) adj3 (smoker* or smoking* or tobacco* or cigar* or cigs or bidi or bidis or beedi or beedis or kretek* or hand roll* or handroll* or rollies or waterpipe* or water pipe* or dokha or dokhas or hookah or hookahs or hooka or hookas or shisha or shishas or sheesha or sheeshas)).ti,ab,kf.	32608
13	(antismok* or anti smok* or anti-smok* or exsmoker* or ex-smoker* or "ex smoker*").ti,ab,kf.	5627
14	or/1-13	330726
15	Nicotine Chewing Gum/	16
16	"tobacco use cessation devices"/	1694
17	Smoking cessation agents/	93
18	Bupropion/	2968
19	Varenicline/	1233
20	Nicotinic Agonists/	7185
21	(NRT or nicotine replacement*).ti,ab,kf.	3569
22	bupropion*.ti,ab,kf.	3741
23	(amfebutamone* or quomen* or wellbutrin* or zyban* or zyntabac*).ti,ab,kf.	186
24	varenicline*.ti,ab,kf.	1422
25	(champix* or chantix*).ti,ab,kf.	95
26	(nicotin* adj3 (replacement* or substitute* or gum* or inhaled* or inhaler* or inhalant* or inhalator* or spray* or lozenge* or tablet* or transdermal* or patch* or vaccin* or device* or gel* or pastil* or deliver* or sublingual* or therap* or treatment* or nasal* or microtab* or polacrilex* or product or products*)).ti,ab,kf.	11931
27	(nicorette* or niquitin* or nicotinell* or nicassist*).ti,ab,kf.	105
28	(nicotinic* adj3 agonist*).ti,ab,kf.	2152
29	(benzazepine* adj2 derivative*).ti,ab,kf.	70
30	nicotinic receptor partial agonist*.ti,ab,kf.	58
31	or/15-30	23066
32	Electronic Nicotine Delivery Systems/	2766
33	Vaping/	511
34	(electr* adj2 (cig* or nicotine* or device* or tobacco*)).ti,ab,kf.	10860
35	(ecig* or e-cig* or e-voke* or juul* or ENNDS).ti,ab,kf.	2514
36	(nicotine* adj4 (electr* or ENDS or aerosol* or ANDS)).ti,ab,kf.	899
37	(vape or vaper or vapers or vaping or vapor or vapour).ti,ab,kf.	23853
38	((tobacco* or nicotin* or cigar* or cigs) adj3 (dual* or multiple* or multi) adj3 ("use" or uses or user* or usage* or using*)).ti,ab,kf.	344
39	(polytobacco* or poly tobacco* or poly-tobacco* or multitobacco* or multi tobacco* or multi-tobacco*).ti,ab,kf.	93
40	or/32-39	35748
41	randomized controlled trial.pt.	494146
42	controlled clinical trial.pt.	93404
43	pragmatic clinical trial.pt.	1221
44	clinical trial.pt.	519103
45	clinical trial/ or clinical trial, phase i/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or controlled clinical trial/	585065
46	Random Allocation/	101120
47	randomized controlled trial/	494146
48	pragmatic clinical trial/	1221
49	Double-Blind Method/	154687
50	Single-Blind Method/	27623
51	Placebos/	34601
52	((clin* or randomi?ed) adj5 trial*).ti,ab,kf.	535977

53	((singl* or doubl* or trebl* or tripl*) adj5 (blind* or mask*)).ti,ab,kf.	153888
54	placebo*.ti,ab,kf.	190671
55	control groups/	1640
56	randomi?ation.ti,ab,kf.	30394
57	randomly.ab.	274416
58	(random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion or number* or place* or recruit* or subsitut* or treat*)).ab.	390723
59	drug therapy.fs.	2157239
60	trial.ti,ab,kf.	491894
61	groups.ab.	1700801
62	(control* adj3 (trial* or study or studies)).ab,ti.	433026
63	((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dummy*)).mp.	215629
64	(quasi adj (experimental* or random*)).ti,ab.	13695
65	((waitlist* or wait* list* or treatment as usual or TAU) adj3 (control or group)).ab.	4723
66	or/41-65	4578495
67	31 or 40	57518
68	14 and 67	17916
69	66 and 68	6568
70	Animals/ not (Animals/ and Humans/)	4609630
71	69 not 70	5502
72	limit 71 to (letter or historical article or comment or editorial or news or case reports)	346
73	71 not 72	5156
74	limit 73 to english language	4928
75	limit 74 to ed=20190121-20191114	263

Harm reduction main search – completed by NICE Information Services

The MEDLINE searches below were run after QA, peer review and consultation with the committee. The strategies were adapted as appropriate to the other databases listed in the protocol. Further searches were undertaken for grey literature using the websites listed in the protocol. Additional search results were obtained from the scoping searches undertaken before developing the protocol.

Full details of all the search strategies are available in a separate document from the NICE Information Services team.

Search sources

Database name	Date searched	Database Platform	Database segment or version	No. of records
Cochrane Central Register of Controlled Trials (CENTRAL)	24/07/2019	Wiley	Cochrane Central Register of Controlled Trials Issue 7 of 12, July 2019	262
Cochrane Database of Systematic Reviews (CDSR)	24/07/2019	Wiley	Cochrane Database of Systematic Reviews Issue 7 of 12, July 2019	8
Database of Abstracts of Reviews of Effects (DARE) - legacy	24/07/2019	CRD	Last updated 31 March 2015	17
Embase	24/07/2019	Ovid	Embase 1974 to 2019 July 23	337
MEDLINE	24/07/2019	Ovid	Ovid MEDLINE(R) 1946 to July 23, 2019	252
MEDLINE-in-Process (including	24/07/2019	Ovid	Ovid MEDLINE(R) Epub Ahead of Print July 23, 2019, Ovid MEDLINE(R)	90

Epub Ahead-of-Print)			In-Process & Other Non-Indexed Citations 1946 to July 23, 2019	
PsycINFO	24/07/2019	Ovid	PsycINFO 1806 to July Week 3 2019	542
Scoping searches	24/07/2019	-	-	6
Web of Science	24/07/2019	Clarivate	Web of Science Core Collection (1990-present)	327
Websites	24/07/2019	-	As in the protocol	11

Principal search strategy – as run in MEDLINE and adapted for other sources

Database(s): **Ovid MEDLINE(R)** 1946 to July 23, 2019

#	Searches	Results
1	Electronic Nicotine Delivery Systems/	2480
2	Vaping/	351
3	(ecig* or e-cig* or e-voke* or juul* or vape* or vaping* or ENNDS).ti,ab.	2311
4	(electronic* adj3 (tobacco* or nicotin* or cigar* or cigs or vapor* or vapour*)).ti,ab.	1799
5	((tobacco* or nicotin* or cigar* or cigs) adj3 (vapor* or vapour* or device* or inhalator* or inhaler*)).ti,ab.	662
6	(nicotin* and (ENDS or ANDS)).ti,ab.	241
7	(nicotin* adj3 deliver* system*).ti,ab.	282
8	or/1-7	3688
9	Smoking reduction/	26
10	Harm Reduction/	2742
11	Risk Reduction Behavior/	11630
12	Smokers/	914
13	(pre-quit* or prequit* or "pre quit*" or cut* down* or controlled smoking*).ti,ab.	2051
14	("Stop-start*" or stopstart* or "stop start*" or "cold turkey*").ti,ab.	189
15	((harm* or risk*) adj1 (cut or cuts* or cutting* or reduc* or declin* or limit* or decreas* or minimal* or minimis* or minimiz* or less* or lower* or small*)).ti,ab.	93025
16	((temporar* or short* or impermanent* or brief* or interim* or cautious* or planned* or schedul* or intention* or intend* or motivat* or abrupt* or sudden* or rapid* or immediate* or quick* or impulsive* or spontaneous* or unplann* or unstructur* or unprompt* or unmotivat* or unwilling* or unable* or unintention* or unintend* or unsustain* or unsuccess* or prolong* or maintain* or maintenance* or sustain* or consumption* or consum* or attempt* or fail* or incomplet* or partial*) adj3 (cut or cuts* or cutting* or abstain* or abstinen* or quit or quits* or quitting* or stop or stops* or stopping* or stopped* or stoppage* or cease or ceases* or ceasing* or cessation* or giv* up or discontinu* or reduc* or declin* or limit* or decreas* or minimal* or minimis* or minimiz*)).ti,ab.	205037
17	((tobacco* or cigar* or cigs or smoking* or smoker*) adj3 (cut or cuts* or cutting* or abstain* or abstinen* or quit or quits* or quitting* or stop or stops* or stopping* or stopped* or stoppage* or cease or ceases* or ceasing* or cessation* or giv* up or discontinu* or reduc* or declin* or limit* or decreas* or minimal* or minimis* or minimiz*)).ti,ab.	41137
18	(gradual* or withdraw* or substitut* or fading* or taper* or swap* or swop* or switch* or replace* or replacing*).ti,ab.	943923
19	((intention* or intend* or motivat* or impulsive* or spontaneous* or unplann* or unstructur* or unprompt* or unmotivat* or unwilling* or unable* or unintention* or unintend* or unsustain* or unsuccess* or attempt* or fail* or incomplet* or partial*) adj3 smoker*).ti,ab.	1562
20	or/9-19	1253036
21	8 and 20	1588
22	((tobacco* or nicotin* or cigar* or cigs) adj3 (dual* or multiple* or multi) adj3 ("use" or uses or user* or usage* or using*)).ti,ab.	316
23	(polytobacco* or poly tobacco* or poly-tobacco* or multitobacco* or multi tobacco* or multi-tobacco*).ti,ab.	73
24	or/21-23	1862

25	Animals/ not (Animals/ and Humans/)	4568770
26	24 not 25	1820
27	limit 26 to (letter or historical article or comment or editorial or news or case reports)	154
28	26 not 27	1666
29	limit 28 to english language	1598
30	randomized controlled trial.pt.	485715
31	randomi?ed.mp.	749931
32	placebo.mp.	186653
33	or/30-32	800073
34	29 and 33	192
35	(MEDLINE or pubmed).tw.	143252
36	systematic review.tw.	102263
37	systematic review.pt.	109542
38	meta-analysis.pt.	103021
39	intervention*.ti.	113402
40	or/35-39	338819
41	29 and 40	90
42	34 or 41	252

Harm reduction re-run search – completed by NICE Information Services

Database name	Date searched	Database Platform	Database segment or version	No. of records
Cochrane Central Register of Controlled Trials (CENTRAL)	13/11/2019	Wiley	Cochrane Central Register of Controlled Trials Issue 11 of 12, November 2019	18
Cochrane Database of Systematic Reviews (CDSR)	13/11/2019	Wiley	Cochrane Database of Systematic Reviews Issue 11 of 12, November 2019	0
Database of Abstracts of Reviews of Effects (DARE) - legacy			Legacy database – no need to rerun	x
Embase	13/11/2019	Ovid	Embase 1974 to 2019 November 12	30
MEDLINE	13/11/2019	Ovid	Ovid MEDLINE(R) 1946 to November 12, 2019	20
MEDLINE-in-Process (including Epub Ahead-of-Print)	13/11/2019	Ovid	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to November 12, 2019 Ovid MEDLINE(R) Epub Ahead of Print November 12, 2019, Ovid MEDLINE(R) Daily Update November 12, 2019	49
PsycINFO	13/11/2019	Ovid	PsycINFO 1806 to November Week 1 2019	42
Scoping searches	-	-	Not re-run	x
Web of Science	-	-	Not re-run	x
Websites	12/11/2019	-	As in the protocol	13

Database(s): **Ovid MEDLINE(R)** 1946 to November 12, 2019

#	Searches	Results
1	Electronic Nicotine Delivery Systems/	2764
2	Vaping/	510

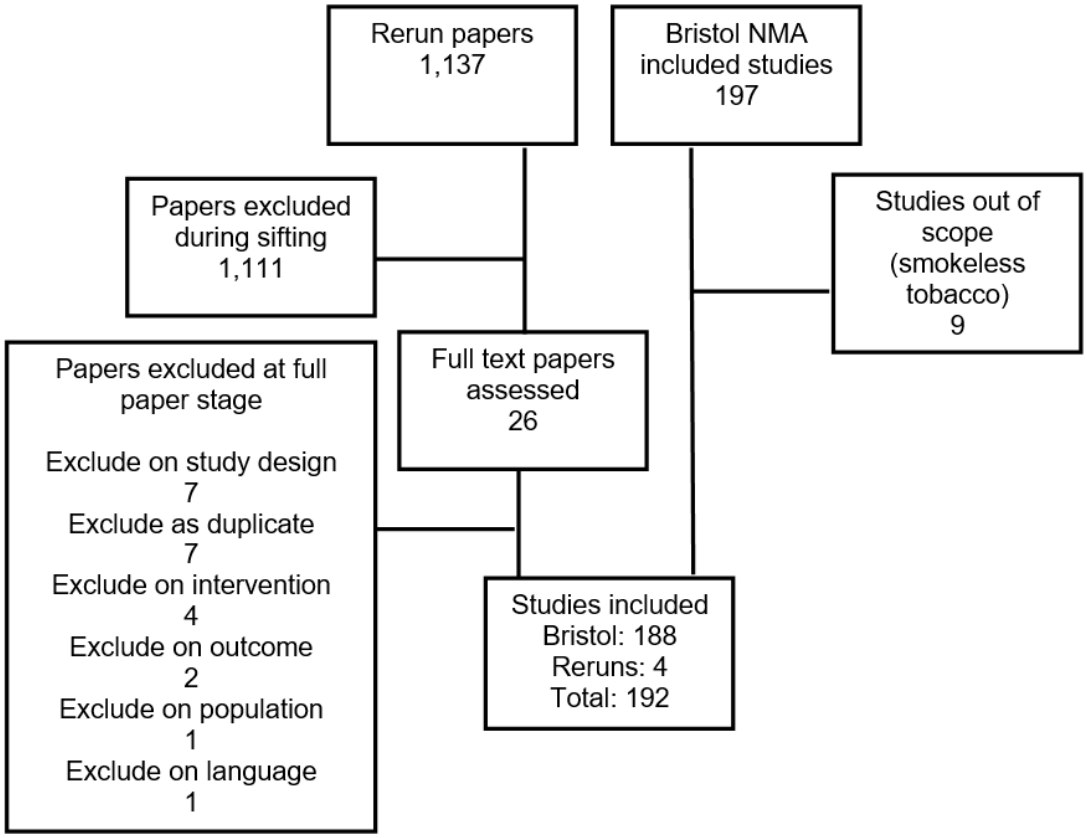
3	(ecig* or e-cig* or e-voke* or juul* or vape* or vaping* or ENNDS).ti,ab.	2600
4	(electronic* adj3 (tobacco* or nicotin* or cigar* or cigs or vapor* or vapour*)).ti,ab.	1963
5	((tobacco* or nicotin* or cigar* or cigs) adj3 (vapor* or vapour* or device* or inhalator* or inhaler*)).ti,ab.	696
6	(nicotin* and (ENDS or ANDS)).ti,ab.	262
7	(nicotin* adj3 deliver* system*).ti,ab.	309
8	or/1-7	4061
9	Smoking reduction/	39
10	Harm Reduction/	2846
11	Risk Reduction Behavior/	11935
12	Smokers/	1250
13	(pre-quit* or prequit* or "pre quit*" or cut* down* or controlled smoking*).ti,ab.	2094
14	("Stop-start*" or stopstart* or "stop start*" or "cold turkey*").ti,ab.	193
15	((harm* or risk*) adj1 (cut or cuts* or cutting* or reduc* or declin* or limit* or decreas* or minimal* or minimis* or minimiz* or less* or lower* or small*)).ti,ab.	95991
16	((temporar* or short* or impermanent* or brief* or interim* or cautious* or planned* or schedul* or intention* or intend* or motivat* or abrupt* or sudden* or rapid* or immediate* or quick* or impulsive* or spontaneous* or unplann* or unstructur* or unprompt* or unmotivat* or unwilling* or unable* or unintention* or unintend* or unsustain* or unsuccess* or prolong* or maintain* or maintenance* or sustain* or consumption* or consum* or attempt* or fail* or incomplet* or partial*) adj3 (cut or cuts* or cutting* or abstain* or abstinen* or quit or quits* or quitting* or stop or stops* or stopping* or stopped* or stoppage* or cease or ceases* or ceasing* or cessation* or giv* up or discontinu* or reduc* or declin* or limit* or decreas* or minimal* or minimis* or minimiz*)).ti,ab.	208737
17	((tobacco* or cigar* or cigs or smoking* or smoker*) adj3 (cut or cuts* or cutting* or abstain* or abstinen* or quit or quits* or quitting* or stop or stops* or stopping* or stopped* or stoppage* or cease or ceases* or ceasing* or cessation* or giv* up or discontinu* or reduc* or declin* or limit* or decreas* or minimal* or minimis* or minimiz*)).ti,ab.	42134
18	(gradual* or withdraw* or substitut* or fading* or taper* or swap* or swop* or switch* or replace* or replacing*).ti,ab.	957867
19	((intention* or intend* or motivat* or impulsive* or spontaneous* or unplann* or unstructur* or unprompt* or unmotivat* or unwilling* or unable* or unintention* or unintend* or unsustain* or unsuccess* or attempt* or fail* or incomplet* or partial*) adj3 smoker*).ti,ab.	1603
20	or/9-19	1274025
21	8 and 20	1769
22	((tobacco* or nicotin* or cigar* or cigs) adj3 (dual* or multiple* or multi) adj3 ("use" or uses or user* or usage* or using*)).ti,ab.	344
23	(polytobacco* or poly tobacco* or poly-tobacco* or multitobacco* or multi tobacco* or multi-tobacco*).ti,ab.	86
24	or/21-23	2066
25	Animals/ not (Animals/ and Humans/)	4609130
26	24 not 25	2021
27	limit 26 to (letter or historical article or comment or editorial or news or case reports)	170
28	26 not 27	1851
29	limit 28 to english language	1774
30	randomized controlled trial.pt.	494037
31	randomi?ed.mp.	766344
32	placebo.mp.	189864
33	or/30-32	817037
34	29 and 33	205
35	(MEDLINE or pubmed).tw.	149839
36	systematic review.tw.	107826

37	systematic review.pt.	116270
38	meta-analysis.pt.	107651
39	intervention*.ti.	116839
40	or/35-39	352166
41	29 and 40	98
42	34 or 41	272
43	limit 42 to ed=20190724-20191113	20

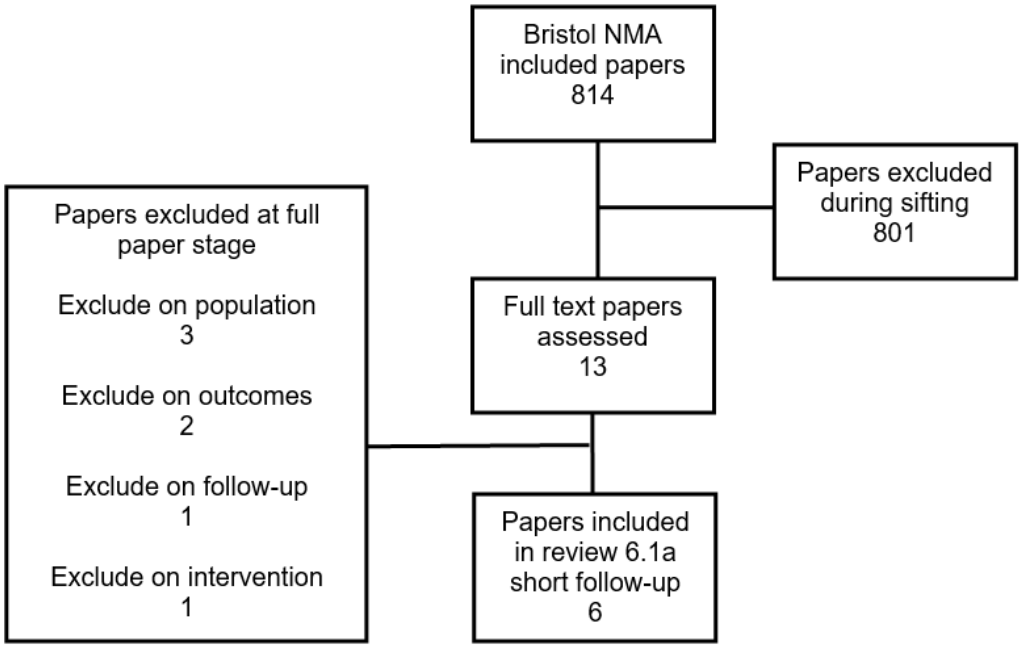
Appendix C – Evidence study selection

Cessation, relative effectiveness

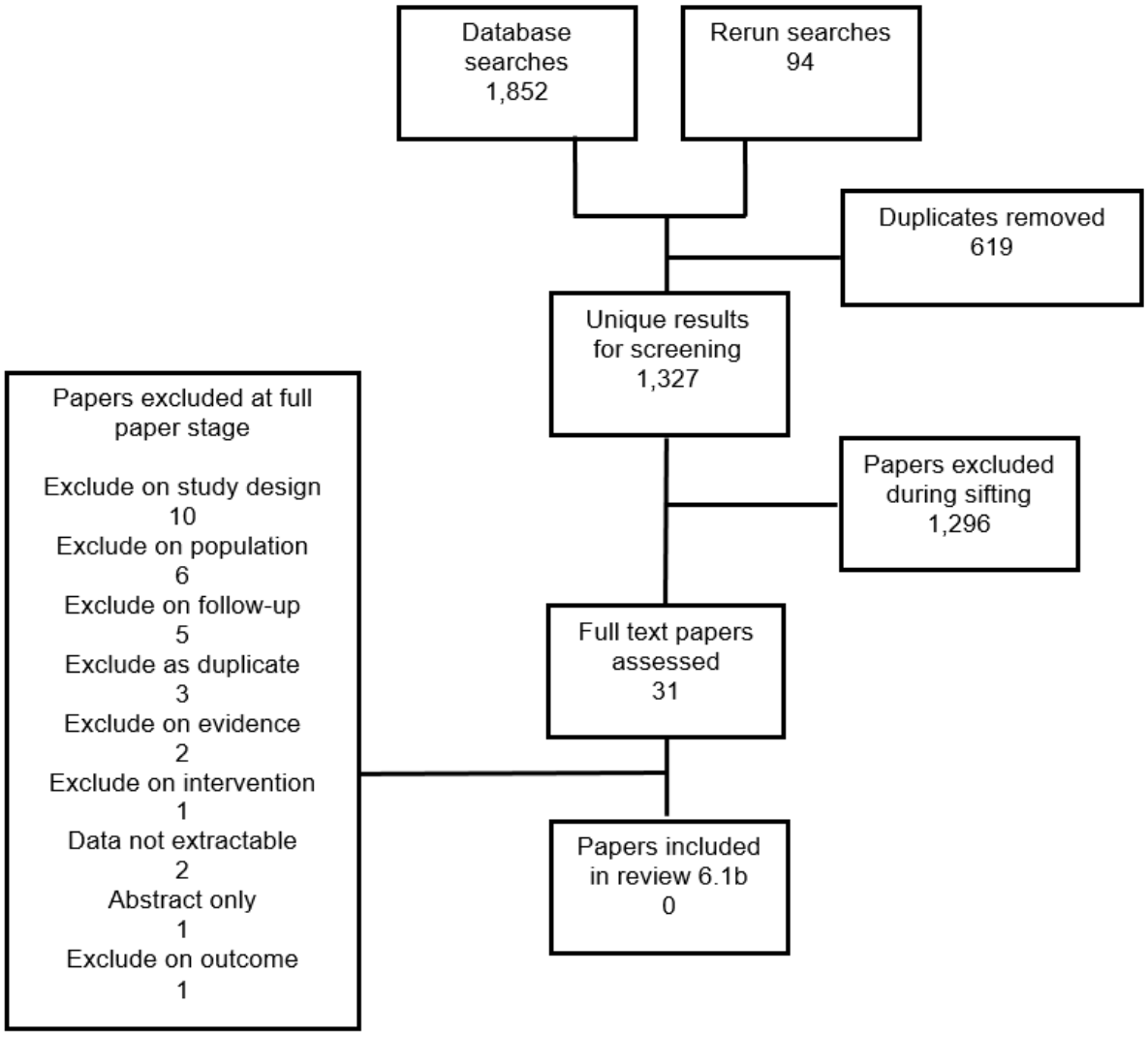
Thomas (2020) used for main analysis.



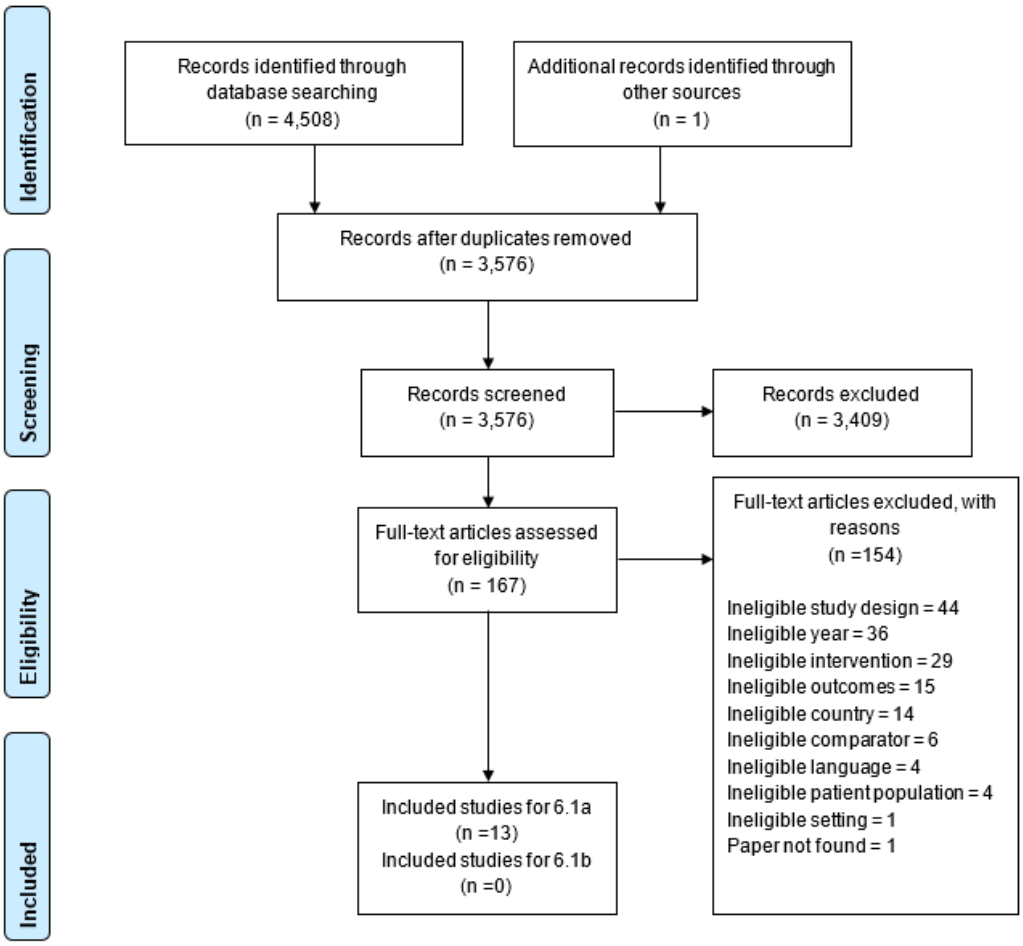
Cessation, short follow-up


Bristol NMA included papers 814
Papers excluded during sifting 801
Full text papers assessed 13
Papers excluded at full paper stage
Exclude on population 3
Exclude on outcomes 2
Exclude on follow-up 1
Exclude on intervention 1
Papers included in review 6.1a short follow-up 6

Harm reduction



Economic evidence study selection



Appendix D – Evidence tables

Cessation, relative effectiveness (including mental health subgroup)

The Thomas (2020) review updated a number of Cochrane evidence reviews. Table 13 and 14 indicate where included studies are reported in existing and freely available (hyperlinked) Cochrane reviews. Where study characteristics are not published elsewhere, study characteristics from Thomas (2020) and corresponding characteristics from studies identified in the rerun searches are included in table 15.

Table 1: Relative effectiveness studies – location of study characteristics

Cochrane review	Studies included
Cahill 2016	Anthenelli 2013 Anthenelli 2016A (as EAGLES 2016) Anthenelli 2016B (as EAGLES 2016) Aubin 2008 Baker 2016 Bolliger 2011 Carson 2014 Chengappa 2014 Cinciripini 2013 De Dios 2012 Ebbert 2015 Eisenberg 2016 Gonzales 2006 Gonzales 2014 Heydari 2012 Hughes 2011 Nahvi 2014 Nakamura 2007 Niaura 2008 Nides 2006 Rennard 2012 Rigotti 2010 Rose 2013 Steinberg 2011 Tashkin 2011 Tonstad 2006 Tsai 2007 Wang 2009 Westergaard 2015
Hartmann-Boyce 2016	Bullen 2013 Caponnetto 2013
Hartmann-Boyce 2018	Cummins 2016 Cunningham 2016 Heydari 2013 (as Heydari 2012) Lerman 2015 Jamrozik 1984 Segnan 1991 Tonnesen 1999 (as CEASE 1999)

Cochrane review	Studies included
Hughes 2014	Ahluwalia 2002 Aubin 2004 Blondal 1999 Collins 2004 Covey 2007 Cox 2012 Dalsgarð 2004 Eisenberg 2013 Evins 2001 Evins 2005 Evins 2007 Ferry 1992 Fossati 2007 George 2008 Gonzales 2001 Haggsträm 2006 Hall 2002 Hall 2011 Hertzberg 2001 Holt 2005 Jorenby 1999 Levine 2010 McCarthy 2008 Piper 2007 Piper 2009 Schmitz 2007 Schnoll 2010 Siddiqi 2013 Simon 2009 SMK20001 Tashkin 2001 Tonnesen 2003 Tonstad 2003 Uyar 2007 Wagena 2005 Zellweger 2005
Stead 2012	Ahluwalia 2006 Areechon 1988 Blondal 1997 Chan 2011 Cinciripini 1996 Cooney 2009 Cooper 2005 Daughton 1991 Daughton 1998 Daughton 1999/TNSG 1991 Dautzenberg 2001 Ehrsam 1991 Fagerstrom 1982 Fiore 1994A Fiore 1994B

Cochrane review	Studies included
	Glavas 2003B Glover 2002 Gourlay 1995 Gross 1995 Hall 1985 Hall 1987 Hand 2002 Harackiewicz 1988 Hays 1999 Herrera 1995 Hjalmarson 1984 Hjalmarson 1994 Hjalmarson 1997 Hughes 1999 Hughes 2003 Hurt 1990 Jensen 1991 Kalman 2006 Killen 1990 Killen 1997 Killen 1999 Kornitzer 1995 Leischow 1996 Lerman 2004 Lewis 1998 Llivina 1988 Malcolm 1980 Mori 1992 Nakamura 1990 Niaura 1994 Niaura 1999 Perng 1998 Pirie 1992 Puska 1995 Richmond 1993 Richmond 1994 Sachs 1993 Schneider 1983A (as Schneider 1985A) Schneider 1983B (as Schneider 1985B) Schneider 1995 Schneider 1996 Schnoll 2010A Schnoll 2010B Stapleton 1995 Sutherland 1992 Tonnesen 1993 Tonnesen 2000 Tonnesen 2006 Tønnesen 2012 Wallstrom 2000 Westman 1993

Cochrane review	Studies included
In table below	Andrews 2016 Aryanpur 2016 Ashare 2019 Baker 2006 Baldassarri 2018, and “cessation, short follow-up” below Binnie 2007 Bonevski 2018 Caldwell 2014 Caldwell 2016 Campbell 1983 Cinciripini 2018 Cooney 2007 Cooperman 2017 Dogar 2018 Ebbert 2014 Ebbert 2017 FernandezArias 2014 Gifford 2004 GlaxoSmithKline 2009 Hall 2006 Halpern 2018 Hanioka 2010 Hatsukami 2004 Holliday 2019 Horst 2005 Joseph 2004 Kalman 2011 Koegelenberg 2014 Myles 2004 Nides 2018 Okuyemi 2007 QuilezGarcia 1989 Ramon 2014 Ratner 2004 Reid 2008 Rohsenow 2017 SelmaBozkurtZincir 2013 Sharma 2018 Shiffman 2019 Steinberg 2009 Stockings 2014 Swanson 2003 Tulloch 2016 Vial 2002 Walker 2019 Williams 2012 Winhusen 2014 Wong 1999 Zernig 2008 ZYB40005

Cessation, adverse events

The Thomas (2020) review reported on adverse events of e-cigarettes. Table 14 indicates where included studies are reported in existing and freely available Cochrane reviews. Where study characteristics are not published elsewhere, study characteristics from Thomas (2020) are included in table 15.

Table 2: Adverse events studies – location of study characteristics

Studies	Full extraction table
Baldassarri 2018	In table below
Bullen 2013	Hartmann-Boyce 2016
Caponnetto 2013	Hartmann-Boyce 2016
Carpenter 2017	In table below
Cravo 2016	In table below
Hajek 2019	In table below
Lee 2018	See data extraction table under “Cessation, short follow-up”
Masiero 2018	See data extraction table under “Cessation, short follow-up”
Tseng 2016	In table below

Cessation data extraction

Table 15 details the study characteristics for studies included in the NMA or in the adverse events analysis (all from Thomas [2020]) and which are not reported in a freely available Cochrane review.

Table 3: Extraction tables for studies not in previous Cochrane reviews

Study	Study sponsor	Study design	Study duration (weeks)	Duration of drug treatment (weeks)	Location	Total N	Study arms	Risk of bias
Andrews 2016	National Health, Lung & Blood Institute of the National Institutes of Health	Cluster RCT	52	8	Georgia and South Carolina, USA	409	1. NRT Patch (24hrs) + Individual + Group Long Counselling 2. Waitlist	High risk
Aryanpur 2016	National Research Institute of Tuberculosis and Lung Diseases and Shahid Beheshti University of Medical Sciences, Abidi pharmaceutical company provided buperopion drug (Wellban) fund.	Parallel RCT	24	9	Tehran, Iran	210	1. Usual Care 2. Usual Care + Individual Counselling 3. Bupropion Standard + Individual Counselling	High risk
Ashare 2019	National Institute on Drug Abuse (R01 DA033681 and K24 DA045244) and through core services and support from the Penn Center for AIDS Research (P30 AI045008) and the Penn Mental Health AIDS Research Center (P30 MH097488). Pfizer provided medication and placebo free of charge.	Parallel RCT	24	12	Pennsylvania, USA	179	1. Varenicline (0.5-1.0mg/day) 2. Placebo	Low risk

Study	Study sponsor	Study design	Study duration (weeks)	Duration of drug treatment (weeks)	Location	Total N	Study arms	Risk of bias
Baldassarri 2018	Yale School of Medicine, Section of Pulmonary, Critical Care, and Sleep Medicine and the National Heart, Lung, and Blood Institute	Parallel RCT	24	16	Connecticut, USA	40	1. NRT Patch (24hrs) + Placebo e-cigarette + Individual Long Counselling 2. Electronic Cigarette High + NRT Patch (24hrs) + Individual Long Counselling	High risk
Binnie 2007	Local NHS Smoking Cessation Services (Smoking Concerns, Glasgow, UK) and the dental school	Parallel RCT	52		Glasgow, UK	118	1. NRT Choice 2. Usual Care	High risk
Bonevski 2018	National Health and Medical Research Council (NHMRC) of Australia (631055)	Parallel RCT	24		New South Wales, Australia	618	1. No Drug Treatment 2. NRT Choice + Individual + Telephone Short Counselling	High risk
Caldwell 2014	Health Research Council of New Zealand. Active Zonnic mouth-spray was provided by Niconovum	Parallel RCT	55	26	Wellington and Christchurch, New Zealand	1423	1. NRT Combo High + Individual Short Counselling 2. NRT Patch (24hrs) High + Individual Short Counselling	High risk
Caldwell 2016	The Health Research Council of New Zealand	Parallel RCT	28	24	Wellington, New Zealand	502	1. NRT Combo High + Individual + Telephone Short Counselling 2. NRT Patch (24hrs) High + Individual +	Low risk

Study	Study sponsor	Study design	Study duration (weeks)	Duration of drug treatment (weeks)	Location	Total N	Study arms	Risk of bias
							Telephone Short Counselling	
Campbell 1983	Health Education Council and Lundbeck Ltd, who also supplied the chewing gum	Parallel RCT	52	24	UK	1618	1. Usual Care 2. Usual Care 3. Placebo 4. NRT Gum Standard	Low risk
Carpenter 2017	National Institutes of Health; Oklahoma Tobacco Research Centre	Parallel RCT	16	3	USA	68	1. E-cigarette 2. Usual care	High risk
Cinciripini 2018	United States National Institutes of Health (NIH) and by The University of Texas MD Anderson's Cancer Center, funded by the National Cancer Institute (NCI)	Parallel RCT	53	12	Houston, Texas, USA	385	1. Varenicline Standard + Bupropion Standard + Individual + Telephone Short Counselling 2. Varenicline Standard + Individual + Telephone Short Counselling 3. Placebo + Individual + Telephone Short Counselling	Low risk
Cooney 2007	National Institute on Alcoholism and Alcohol Abuse and by the Department of Veterans Affairs	Parallel RCT	26	8	Connecticut, USA	133	1. NRT Patch (24hrs) High + Individual Long Counselling 2. No Drug Treatment + Individual Short Counselling	High risk

Study	Study sponsor	Study design	Study duration (weeks)	Duration of drug treatment (weeks)	Location	Total N	Study arms	Risk of bias
Cooperman 2017	National Institute on Drug Abuse (NIDA) Grant K23DA025049	Parallel RCT	24	12	New Jersey, USA	83	1. NRT + Individual Long Counselling 2. No Drug Treatment	High risk
Cravo 2016	Fontem Ventures B.V. Imperial Brands plc (tobacco organisation)	Parallel RCT	12	Unclear	Leeds and Wales, UK	419	1. E-cigarette 2. No drug treatment	High risk
Dogar 2018[76]	GRAND 2014, supported by Pfizer	Parallel RCT	25	12	Punjab, Pakistan	510	1. Varenicline Standard + Individual Long Counselling 2. Placebo + Individual Long Counselling	Low risk
Ebbert 2014	National Institutes of Health (NIH)	Parallel RCT	52	12	Minnesota, USA	506	1. Varenicline Standard + Bupropion Standard + Individual Short Counselling 2. Varenicline Standard + Individual Short Counselling	Low risk
Ebbert 2017	Pfizer	Parallel RCT	24	12	Minnesota, USA	93	1. Varenicline Standard + Individual Short Counselling 2. Placebo + Individual Short Counselling	High risk
FernandezArias 2014	University Complutense of Madrid	Parallel RCT	52	10	Madrid, Spain	291	1. NRT Patch (16hrs) Standard + Group Long Counselling 2. No Drug Treatment + Group Long Counselling	High risk

Study	Study sponsor	Study design	Study duration (weeks)	Duration of drug treatment (weeks)	Location	Total N	Study arms	Risk of bias
							3. NRT Patch (16hrs) Standard + Individual Short Counselling	
Gifford 2004	National Institutes of Health, National Cancer Institute, National Institutes of Health, National Institute on Drug Abuse and the Department of Veterans Affairs	Parallel RCT	52	7	Nevada, USA	76	1. No Drug Treatment + Individual + Group Long Counselling 2. NRT Patch (24hrs) High + Group Long Counselling	High risk
GlaxoSmithKline 2009	GlaxoSmithKline	Parallel RCT	24	12	Not reported in Thomas (2020)	723	1. NRT Lozenge Standard 2. Placebo 3. NRT Lozenge High 4. Placebo	Some concerns
Hall 2006	National Institute on Drug Abuse	Parallel RCT	76	10	California, USA	322	1. No Drug Treatment 2. NRT Patch (24hrs) + Individual Long Counselling	High risk
Halpern 2018	Grant from the Vitality Institute to the University of Pennsylvania Center for Health Incentives and Behavioral Economics	Parallel RCT	52	24	Pennsylvania, USA	6006	1. Usual Care 2. Mixed 3. Electronic Cigarette Low 4. Mixed 5. Mixed	High risk
Hanioka 2010	Fukuoka Dental College Grant and the Japanese Ministry of Health, Labor and Welfare	Parallel RCT	52	6	Hiroshima, Nagasaki, Japan	56	1. NRT Patch (24hrs) High + Individual Short Counselling 2. No Drug Treatment	Some concerns
Holliday 2019	NIHR	Parallel RCT	24	8	Newcastle, UK	80	1. E-cigarette (2nd generation, choice of	High

Study	Study sponsor	Study design	Study duration (weeks)	Duration of drug treatment (weeks)	Location	Total N	Study arms	Risk of bias
							strength and flavour) plus usual care. 2. Usual care (brief advice)	
Horst 2005	The American Legacy Foundation and the Via Christi Foundation	Open Label followed by Parallel RCT	36	36	Kansas, USA	50	1. NRT Patch (24hrs) High + Group Long Counselling 2. Placebo + Group Long Counselling	High risk
Joseph 2004	National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the Veterans Affairs (VA) Health Services Research and Development Center for Chronic Disease Outcomes Research	Wait-list RCT	76	52	Minnesota, USA	499	1. NRT Choice High + Individual + Telephone Long Counselling 2. Waitlist	High risk
Kalman 2011	National Institute of Drug Abuse, National Institute on Alcohol Abuse and Alocholism	Parallel RCT	24	8	Massachusetts, USA	143	1. NRT Patch (24hrs) High + Individual Counselling 2. Bupropion Standard + NRT Patch (24hrs) High + Individual Counselling	Some concerns
Koegelenberg 2014	Pfizer, New York, New York, and McNeil, Helsingborg, Sweden	Parallel RCT	24	14	Cape Town, Johannesburg, and Durban, South Africa	446	1. Varenicline Standard + NRT Patch (16hrs) Standard + Individual Short Counselling 2. Varenicline Standard + Individual Short Counselling	Some concerns

Study	Study sponsor	Study design	Study duration (weeks)	Duration of drug treatment (weeks)	Location	Total N	Study arms	Risk of bias
Lee 2018	Internal UCSF Department of Anaesthesia and Perioperative Care	Parallel RCT	26	6	California, USA	30	1. E-cigarette 2. NRT patch	Some concerns
Masiero 2018	Fondazione Umberto Veronesi (FUV)	Parallel RCT	12	12	Milan, Italy	210	1. E-cigarette 2. Placebo 3. No drug treatment (counselling)	Some concerns
Myles 2004	The Alfred Hospital Research Trust, GlaxoWellcome, Australia, Australian National Health and Medical Research Council	Parallel RCT	24	7	Australia	47	1. Bupropion Standard 2. Placebo	Low risk
Nides 2018	GlaxoSmithKline/McNeil AB	Parallel RCT	26	12	USA	1198	1. NRT Mouth Spray Standard 2. Placebo	Some concerns
Okuyemi 2007	Not reported in Thomas (2020)	Cluster RCT	24	8	Kansas and Missouri, USA	173	1. NRT Gum High + Individual + Telephone Counselling 2. No Drug Treatment	High risk
QuilezGarcia 1989	Not reported in Thomas (2020)	Parallel RCT	52	16	Alicante, Spain	106	1. NRT Gum Standard + Group Counselling 2. Placebo + Group Counselling 3. NRT Gum Standard + Individual Counselling	Some concerns
Ramon 2014	Pfizer	Parallel RCT	24	12	Barcelona, Spain	341	1. Varenicline Standard + NRT	Low risk

Study	Study sponsor	Study design	Study duration (weeks)	Duration of drug treatment (weeks)	Location	Total N	Study arms	Risk of bias
							Patch (24hrs) High + Individual Short Counselling 2. Varenicline Standard + Individual Short Counselling	
Ratner 2004	National Cancer Institute of Canada, Canadian Cancer Society, Canadian Institutes of Health Research, Social Sciences and Humanities Research Council of Canada and the Michael Smith Foundation for Health Research	Parallel RCT	62	16	British Columbia, Canada	237	1. Usual Care 2. NRT Gum + Individual + Telephone Short Counselling	High risk
Reid 2008	National Institute on Drug Abuse (NIDA)	Parallel RCT	26	8	New York, Florida, Michigan, North Carolina, South Carolina, California, USA	225	1. NRT Patch (24hrs) High + Group Counselling 2. Waitlist	High risk
Rohsenow 2017	National Institute on Drug Abuse and the Department of Veterans Affairs	Parallel RCT	24	13	Rhode Island, USA	137	1. Varenicline Standard + Individual Long Counselling 2. NRT Patch (24hrs) High + Individual Long Counselling	Some concerns
SelmaBozkurtZincir 2013	Not reported in Thomas (2020)	Parallel RCT	28	12	Istanbul, Turkey	251	1. Bupropion Standard 2. Varenicline Standard 3. NRT Choice	High risk

Study	Study sponsor	Study design	Study duration (weeks)	Duration of drug treatment (weeks)	Location	Total N	Study arms	Risk of bias
Sharma 2018	EU-FP7 and ICMR	Parallel RCT	24	6	National Capital Region of Delhi and Andhra Pradesh, India	800	1. NRT Gum + Individual Short Counselling 2. No Drug Treatment + Individual Short Counselling	High risk
Shiffman 2019	National Institute on Drug Abuse at the National Institutes of Health	Parallel RCT	24	8	Pittsburgh, USA	369	1. NRT gum 2mg plus behavioural counselling 2. Placebo plus behavioural counselling	Low risk
Steinberg 2009	Cancer Institute of New Jersey and the Robert Wood Johnson Foundation	Parallel RCT	26	26	New Jersey, USA	127	1. Bupropion Low + NRT Combo High 2. NRT Patch (24hrs) High	High risk
Steinberg 2011	Robert Wood Johnson Foundation, Pfizer	Parallel RCT	24	12	Moderate-sized urban center, USA	79	1. Varenicline Standard + Individual Short Counselling 2. Placebo + Individual Short Counselling	Low risk
Stockings 2014	Commonwealth Department of Health and Ageing, Australian Rotary Health, and the Hunter Medical Research Institute	Parallel RCT	24	14	New South Wales, Australia	205	1. Usual Care 2. NRT Choice + Individual + Telephone Short Counselling	High risk
Swanson 2003	Not reported in Thomas (2020)	Parallel RCT	52	9	Virginia, USA	140	1. NRT Patch (24hrs) + Group Long Counselling	High risk

Study	Study sponsor	Study design	Study duration (weeks)	Duration of drug treatment (weeks)	Location	Total N	Study arms	Risk of bias
							2. Bupropion + Group Long Counselling 3. Bupropion + NRT Patch (24hrs) + Group Long Counselling 4. No Drug Treatment + Group Long Counselling	
Tseng 2016	National Center for Advancing Translational Sciences at the National Institutes of Health	Parallel RCT	3	3	New York, USA	99	1. E-cigarette 2. Placebo	Some concerns
Tulloch 2016	Heart and Stroke Foundation of Ontario	Parallel RCT	52	24	Ontario, Canada	737	1. NRT Patch (24hrs) + Individual Short Counselling 2. NRT Combo + Individual Short Counselling 3. Varenicline Standard + Individual Short Counselling	High risk
Vial 2002	The Anti-Cancer Foundation of South Australia, The Queen Elizabeth Hospital Research Foundation and the University of South Australia	Parallel RCT	52	16	Adelaide, South Australia, Australia	102	1. NRT Patch (24hrs) 2. NRT Patch (24hrs) 3. No Drug Treatment	High risk
Walker 2019	Health Research Council of New Zealand	Parallel RCT	24	14	New Zealand	999	1. E-cigarette (2nd gen) plus NRT patch 21mg plus behavioural support	Low risk

Study	Study sponsor	Study design	Study duration (weeks)	Duration of drug treatment (weeks)	Location	Total N	Study arms	Risk of bias
							2. NRT patch 21mg plus behavioural support plus placebo e-cigarette	
Williams 2012	Pfizer	Parallel RCT	26	12	USA, Canada	128	1. Varenicline Standard + Individual Long Counselling 2. Placebo + Individual Long Counselling	Some concerns
Winhusen 2014	National Institute on Drug Abuse	Parallel RCT	28	10.4	Oregon, Pennsylvania, South Carolina, Florida, Montana, Arizona, California, Texas, USA	538	1. Bupropion Standard + NRT Inhalator + Individual Short Counselling 2. Usual Care	High risk
Wong 1999	DuPont Merck Pharmaceutical Company, Wilmington, Delaware	Parallel RCT	24	12	Minnesota, USA	100	1. Placebo + Individual Short Counselling 2. NRT Patch (24hrs) High + Individual Short Counselling	High risk
Zernig 2008	Styrian Regional Health Care System (Steiermaerkische Gebietskrankenkasse, STGKK), Austrian Science Fund	Parallel RCT	52	9	Graz, Austria	779	1. No Drug Treatment + Group Long Counselling 2. Bupropion Standard	High risk

Study	Study sponsor	Study design	Study duration (weeks)	Duration of drug treatment (weeks)	Location	Total N	Study arms	Risk of bias
ZYB40005	GlaxoSmithKline	Parallel RCT	52	33	USA	609	1. Bupropion Standard 2. Placebo	High risk

Cessation, short follow-up

The below data extraction tables are for analysis of effectiveness of e-cigarettes for cessation at 1-<6 months (conducted by NICE).

Baldassarri 2018

Bibliographic reference/s	**Baldassarri Stephen R, Bernstein Steven L, Chupp Geoffrey L, Slade Martin D, Fucito Lisa M, and Toll Benjamin A (2018) Electronic cigarettes for adults with tobacco dependence enrolled in a tobacco treatment program: A pilot study. Addictive Behaviors 80, 1-5**
Study name	Not reported
Registration	Not reported
Study type	RCT
Study dates	Not reported
Objective	To establish feasibility of adding an EC to outpatient tobacco treatment as part of a standard care regimen, to determine if there are differences in smoking behaviour and lung function changes between individuals receiving nicotine versus non-nicotine containing ECs, to characterize EC use patterns and perceptions in a real-world setting among treatment-seeking smokers; and to generate hypotheses regarding potential benefits, risks, and challenges of introducing ECs into tobacco treatment settings.
Country/ Setting	USA, Connecticut Outpatient treatment for smoking (pulmonary and primary care clinics, Tobacco Treatment service, referrals from medical providers)
Number of participants / clusters	40 participants (20 intervention, 20 placebo) Pilot study not powered to detect differences between the intervention and placebo control.
Attrition	20% (n = 8) loss-to-follow-up at 24 weeks. Difference between groups not reported. There were no significant differences in loss to follow-up among other demographic factors including age, race, gender, baseline number of cigarettes smoked per day, or FTND score. Those lost to follow-up were assumed to still be smokers (intention to treat)
Participant /community characteristics.	Participant characteristics at baseline. Differences between intervention and placebo control group not evaluated.

	Intervention (n=20)	**Placebo (n=20)**
Mean age years (SD)	52.2 (12.2)	53.8 (7.8)
Female (%)*	8 (40)	13 (65)
SES	Not reported	
Ethnicity non-white n (%)	6 (15)	8 (20)
Education less than high school n (%)	3 (15)	1 (5)
Education college, university or higher n (%)	5 (25)	6 (30)
Employment status unemployed n (%)	4 (20)	5 (25)
Fagerstrom Test Score*, mean (SD)	5.7 (2.0)	6.0 (2.2)
Baseline reported cigarettes smoked per day mean (SD)	17 (10.9)	17 (12.4)

Bibliographic reference/s	**Baldassarri Stephen R, Bernstein Steven L, Chupp Geoffrey L, Slade Martin D, Fucito Lisa M, and Toll Benjamin A (2018) Electronic cigarettes for adults with tobacco dependence enrolled in a tobacco treatment program: A pilot study. Addictive Behaviors 80, 1-5**	
Study name	Not reported	
	*Fagerström Test for Nicotine Dependence. Score 0-10, higher score indicates more intense addiction.	
Method of allocation	Randomised. Random number generator, 1:1 blocked randomisation (block size 8).	
Inclusion criteria	Age 18 years or older; Smoking 1 or more tobacco cigarettes per day; Willing to quit smoking.	
Exclusion criteria	Unstable psychiatric or medical conditions requiring hospitalization within the past 4 months; Acute coronary syndromes or stroke within the past 30 days; History of allergic reactions to adhesives; Women who were pregnant, nursing, or not practicing effective contraception; Current use of an EC for the purpose of stopping tobacco cigarette smoking.	
Intervention	**TIDieR Checklist criteria**	**Details**
	Brief Name	E-cigarette
	Rationale/theory/Goal	That nicotine e-cigarettes in combination with NRT and behavioural counselling will increase cessation among treatment-seeking smokers.
	Materials used	NRT: Subjects who smoked > 10 cigarettes per day were initially given the 21 mg patch, and subjects who smoked 10 or fewer cigarettes per day were given the 14 mg patch. All participants were given a two-week supply of nicotine patches at each study visit for the first 8 weeks of the study. E-cigarette: 2nd generation EC with e-liquid (24mg/ml [2.4% nicotine] strength, tobacco flavour). Instructed to use as needed. 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 study subjects. Counselling: The initial study visit and each subsequent study visit consisted of intensive counselling sessions (6 visits total, week 1, 2, 4, 6, 8, 24).
	Method of delivery	Counselling: Advanced Practice Registered Nurse (APRN) behavioural tobacco treatment specialist or a clinical psychologist trained in motivational interviewing techniques and tobacco dependence pharmacotherapy. Assignment blinded to both investigators and participants.
	Duration	Materials provided for first 8 weeks of study.
	Intensity	As needed (decided by participants)
	Planned treatment fidelity	As needed for first 8 weeks of study
	Other details	None reported

<table>
<tr><td>Bibliographic reference/s</td><td colspan="3">Baldassarri Stephen R, Bernstein Steven L, Chupp Geoffrey L, Slade Martin D, Fucito Lisa M, and Toll Benjamin A (2018) Electronic cigarettes for adults with tobacco dependence enrolled in a tobacco treatment program: A pilot study. Addictive Behaviors 80, 1-5</td></tr>
<tr><td>Study name</td><td colspan="3">Not reported</td></tr>
<tr><td rowspan="9">Comparison</td><td>TIDieR Checklist criteria</td><td colspan="2">Details</td></tr>
<tr><td>Brief Name</td><td colspan="2">Non-nicotine e-cigarette</td></tr>
<tr><td>Rationale/theory/Goal</td><td colspan="2">That e-cigarettes without nicotine may be less effective for cessation in treatment seeking smokers.</td></tr>
<tr><td>Materials used</td><td colspan="2">NRT: As for intervention

E-cigarette: 2nd generation EC with e-liquid (0mg/ml strength, tobacco flavour). Instructed to use as needed. 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 study subjects.

Counselling: As for intervention</td></tr>
<tr><td>Method of delivery</td><td colspan="2">As for intervention</td></tr>
<tr><td>Duration</td><td colspan="2">As for intervention</td></tr>
<tr><td>Intensity</td><td colspan="2">As for intervention</td></tr>
<tr><td>Planned treatment fidelity</td><td colspan="2">As for intervention</td></tr>
<tr><td>Other details</td><td colspan="2">None reported</td></tr>
<tr><td>Follow up</td><td colspan="3">8 weeks</td></tr>
<tr><td>Data collection</td><td colspan="3">Smoking status (7-day point prevalence abstinence confirmed by exhaled carbon monoxide of ≤6ppm).</td></tr>
<tr><td>Critical outcomes measures and effect size. (time points)</td><td colspan="3">Smoking abstinence (8 weeks) (validated by exhaled CO)
<table>
<tr><td></td><td>Nicotine e-cigarette (n=20)</td><td>Non-nicotine e-cigarette (n=20)</td><td>RR* (95% CI)</td></tr>
<tr><td>Number abstinent (%)</td><td>2 (10)</td><td>5 (25)</td><td>0.40 (0.09, 1.83)</td></tr>
</table>
*Calculated by analyst</td></tr>
<tr><td>Important outcomes measures and effect size. (time points)</td><td colspan="3">None reported</td></tr>
<tr><td>Statistical Analysis</td><td colspan="3">SAS v9.4 was utilized for the statistical analyses. Descriptive statistics were calculated by group to determine if statistical differences existed between the nicotine and non-nicotine EC participants. Fisher's exact test was used. Smoking abstinence was assessed by intention-to-treat analysis, assuming those lost to follow-up were smokers.</td></tr>
<tr><td>Risk of bias (ROB)
Overall ROB</td><td colspan="3">Smoking abstinence
<table>
<tr><th>Outcome</th><th>Judgement (Low / High / some concerns)</th><th>Comments</th></tr>
</table></td></tr>
</table>

Bibliographic reference/s	**Baldassarri Stephen R, Bernstein Steven L, Chupp Geoffrey L, Slade Martin D, Fucito Lisa M, and Toll Benjamin A (2018) Electronic cigarettes for adults with tobacco dependence enrolled in a tobacco treatment program: A pilot study. Addictive Behaviors 80, 1-5**		
Study name	Not reported		
	Risk of bias arising from the randomisation process	Low	Randomisation appears successful. Investigators and participants blinded to allocation.
	Risk of bias due to deviations from intended interventions (assignment)	Some concerns	Intention to treat analysis. Participants not aware of assigned intervention. Deviations from intended intervention (i.e. stopping using any of the intervention elements) not reported. Study looking at natural context.
	Missing outcome data	Low	20% loss to follow-up, spread across groups not reported. No evidence that outcome data biased by missing data.
	Risk of bias in measurement of the outcome	Low	Measurement of the outcome validated by exhaled CO. Same across groups.
	Risk of bias in selection of the reported result	Some concerns	Some data reported for group as a whole, or for quitters. Not across groups.
	Other sources of bias	None	
	Overall Risk of Bias	Some concerns	
	Other outcome details: None		
Source of funding	Funding for this study was provided by the Yale School of Medicine, Section of Pulmonary, Critical Care, and Sleep Medicine and the National Heart, Lung, and Blood Institute		
Comments	Participants paid $25 at intake and $50 at 24-week follow-up.		
Additional references	None		

Bullen 2013

Bibliographic reference/s	**Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, and Walker N (2013) Electronic cigarettes for smoking cessation: A randomised controlled trial. The Lancet 382(9905), 1629-1637**
Study name	Bullen 2013
Registration	New Zealand Clinical Trials Registry, number ACTRN12610000866000.
Study type	RCT
Study dates	2011-2013
Objective	To investigate whether e-cigarettes are more effective than nicotine patches at helping smokers to quit.
Country/ Setting	New Zealand, Auckland.
Number of participants / clusters	657 randomised 289 nicotine e-cigarettes 295 nicotine patches 73 placebo e-cigarettes 4:4:1 ratio

<table>
<tr><td>Bibliographic reference/s</td><td>Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, and Walker N (2013) Electronic cigarettes for smoking cessation: A randomised controlled trial. The Lancet 382(9905), 1629-1637</td></tr>
<tr><td>Study name</td><td>Bullen 2013</td></tr>
<tr><td></td><td>Power calculations done but cessation at lower levels than expected, so study was not powered for the results achieved.</td></tr>
<tr><td>Attrition</td><td>17% 48/289 nicotine e-cigarettes
27% 80/295 nicotine patches
22% 16/73 placebo e-cigarettes</td></tr>
<tr><td>Participant /community characteristics.</td><td>Participant characteristics at baseline

<table>
<tr><th></th><th>Nicotine e-cig (n=289)</th><th>NRT patch (n=295)</th><th>Nicotine free e-cig (n=73)</th></tr>
<tr><td>Mean age years (SD)</td><td>43.6 (12.7)</td><td>40.4 (12.0)</td><td>43.2 (12.4)</td></tr>
<tr><td>Female (%)*</td><td>178 (62)</td><td>182 (62)</td><td>45 (62)</td></tr>
<tr><td>SES (high) n (%)</td><td colspan="3">Not reported</td></tr>
<tr><td>Ethnicity non-Maori n (%)</td><td>194 (67)</td><td>200 (68)</td><td>50 (68)</td></tr>
<tr><td>Education below year 12 or no qualifications</td><td>150 (52)</td><td>123 (42)</td><td>38 (52)</td></tr>
<tr><td>Age started smoking (years, SD)</td><td>15.6 (4.7)</td><td>15.2 (3.8)</td><td>15.7 (5.1)</td></tr>
<tr><td>Fagerstrom Test Score*, mean (SD)</td><td>5.6 (2.0)</td><td>5.5 (2.0)</td><td>5.5 (2.0)</td></tr>
<tr><td>Number of years smoking continuously</td><td>25.9 (13.1)</td><td>23.5 (12.9)</td><td>24.8 (13.7)</td></tr>
</table>
Characteristics evenly balanced between treatment groups.</td></tr>
<tr><td>Method of allocation</td><td>Randomised. Computerised block randomisation (block size 9), stratified by ethnicity, sex, and level of nicotine dependence.
Not feasible to blind participants re e-cig vs NRT.</td></tr>
<tr><td>Inclusion criteria</td><td>• aged 18 years or older
• had smoked ten or more cigarettes per day for the past year,
• wanted to stop smoking, and could provide consent.</td></tr>
<tr><td>Exclusion criteria</td><td>• pregnant and breastfeeding women;
• people using cessation drugs or in an existing cessation programme;
• those reporting heart attack, stroke, or severe angina in the previous 2 weeks;
• those with poorly controlled medical disorders, allergies, or other chemical dependence</td></tr>
<tr><td>Intervention</td><td>
<table>
<tr><th>TIDieR Checklist criteria</th><th>Details</th></tr>
<tr><td>Brief Name</td><td>E-cigarette (intervention)</td></tr>
<tr><td>Materials used</td><td>Elusion e-cigarettes (second generation). 16 mg/ml (1.6% nicotine). Participants were couriered an e-cigarette, spare battery and charger and cartridges (unlabelled). Simple instructions for use as desired</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference/s	**Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, and Walker N (2013) Electronic cigarettes for smoking cessation: A randomised controlled trial. The Lancet 382(9905), 1629-1637**	
Study name	Bullen 2013	
		from one week before, until 12 weeks after chosen quit date. Quitline referral: all participants referred to Quitline, who called participants to offer telephone-based behavioural support.
	Procedures used	Instructed to use as needed via printed material.
	Provider	Provided by study free of charge
	Method of delivery	As needed by participant.
	Location	None
	Duration	12 weeks from quit date plus 1 week before
	Intensity	As needed by participant.
	Other details	None
Comparison	**TIDieR Checklist criteria**	**Details**
	Brief Name	Placebo e-cigarette
	Materials used	Elusion e-cigarettes (second generation). 0 mg per ml. Participants were couriered an e-cigarette, spare battery and charger and cartridges (unlabelled). Simple instructions for use as desired from one week before, until 12 weeks after chosen quit date. Quitline referral: As for intervention.
	Procedures used	As for intervention
	Provider	As for intervention
	Method of delivery	As for intervention
	Location	None
	Duration	As for intervention
	Intensity	As for intervention.
	Planned treatment fidelity	As for intervention
	Other details	None reported
Comparison	**TIDieR Checklist criteria**	**Details**
	Brief Name	NRT patch (control)
	Materials used	NRT: exchange cards for patches sent in mail, redeemable at pharmacies. Vouchers supplied to cover dispensing costs. Patches were 21mg/24hr. Quitline referral: all participants referred to Quitline, who called participants to offer telephone-based behavioural support.
	Procedures used	As for intervention
	Provider	As for intervention
	Method of delivery	As for intervention
	Location	As for intervention
	Duration	As for intervention
	Intensity	As for intervention
	Planned treatment fidelity	As for intervention
	Other details	None reported

<table>
<tr><td>Bibliographic reference/s</td><td>Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, and Walker N (2013) Electronic cigarettes for smoking cessation: A randomised controlled trial. The Lancet 382(9905), 1629-1637</td></tr>
<tr><td>Study name</td><td>Bullen 2013</td></tr>
<tr><td>Follow up</td><td>1 month and 3 months (main outcome 6 months reported in NMA)</td></tr>
<tr><td>Data collection</td><td>Smoking abstinence: continuous (self-reported abstinence over the whole follow-up period, allowing ≤5 cigarettes in total) verified by exhaled breath CO measurement (<10ppm).</td></tr>
<tr><td>Critical outcomes measures and effect size. (time points)</td><td>Smoking abstinence (1 month) (biochemically verified)
<table>
<tr><td></td><td>Nicotine e-cigarette (n=289)</td><td>NRT patch (n=295)</td><td>RR (95% CI)</td></tr>
<tr><td>Number abstinent (%)</td><td>67 (23.2)</td><td>47 (15.9)</td><td>1.46 (1.04, 2.04)</td></tr>
</table>
<table>
<tr><td></td><td>Nicotine e-cigarette (n=289)</td><td>Nicotine free e-cigarette (n=73)</td><td>RR (95% CI)</td></tr>
<tr><td>Number abstinent (%)</td><td>67 (23.2)</td><td>12 (16.4)</td><td>1.41 (0.81, 2.46)</td></tr>
</table>
Smoking abstinence (3 months) (biochemically verified)
<table>
<tr><td></td><td>Nicotine e-cigarette (n=289)</td><td>NRT patch (n=295)</td><td>RR (95% CI)</td></tr>
<tr><td>Number abstinent (%)</td><td>38 (13.1)</td><td>27 (9.2)</td><td>1.44 (0.90, 2.33)</td></tr>
</table>
<table>
<tr><td></td><td>Nicotine e-cigarette (n=289)</td><td>Nicotine free e-cigarette (n=73)</td><td>RR (95% CI)</td></tr>
<tr><td>Number abstinent (%)</td><td>38 (13.1)</td><td>5 (6.8)</td><td>1.92 (0.78, 4.70)</td></tr>
</table></td></tr>
<tr><td>Important outcomes measures and effect size. (time points)</td><td>None reported</td></tr>
<tr><td>Statistical Analysis</td><td>Intention to treat analysis (participants with unknown status were assumed to still be smoking). Treatment groups compared using Chi squared tests.</td></tr>
<tr><td>Risk of bias (ROB)
Overall ROB</td><td>Outcome name: smoking abstinence (intervention vs placebo)
<table>
<tr><th>Outcome</th><th>Judgement (Low / High / some concerns)</th><th>Comments</th></tr>
<tr><td>Risk of bias arising from the randomisation process</td><td>Low risk</td><td>Allocation sequence random and baseline characteristics evenly spread.</td></tr>
<tr><td>Risk of bias due to deviations from intended interventions (assignment)</td><td>Low risk</td><td>Participants not aware of intervention status. Unclear whether outcome assessor blinded. Unlikely that deviations arose from experimental context.</td></tr>
<tr><td>Missing outcome data</td><td>Low risk</td><td>Withdrawal moderate (17/22%). Per protocol</td></tr>
</table></td></tr>
</table>

Bibliographic reference/s	**Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, and Walker N (2013) Electronic cigarettes for smoking cessation: A randomised controlled trial. The Lancet 382(9905), 1629-1637**		
Study name	Bullen 2013		
			and ITT tests not significantly different.
	Risk of bias in measurement of the outcome	Low risk	Outcome measurement same between groups. Unclear whether outcome assessors blinded. Validation not easily influenced by knowledge of intervention.
	Risk of bias in selection of the reported result	Low risk	No indication that result selected from multiple outcomes. Protocol checked.
	Other sources of bias		
	Overall Risk of Bias	Low risk of bias	
	Other outcome details Smoking abstinence (intervention vs control): **Some concerns** **[**risk of bias due to deviations from intended interventions **some concerns** (withdrawal uneven and due to experimental context)**]**		
Source of funding	Health Research Council of New Zealand		
Comments	7 day point prevalence also reported but continuous abstinence preferred in protocol. One researcher has previously conducted research funded by Ruyan (an e-cigarette manufacturer) but this study was not funded by any e-cigarette or tobacco companies. Participants only had face to face contact with staff for outcome assessment.		
Additional references	None		

Hajek 2019

Bibliographic reference/s	**Hajek Peter, Phillips-Waller Anna, Przulj Dunja, Pesola Francesca, Myers Smith, Katie , Bisal Natalie, Li Jinshuo, Parrott Steve, Sasieni Peter, Dawkins Lynne, Ross Louise, Goniewicz Maciej, Wu Qi, and McRobbie Hayden J (2019) A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. 380(7), 629-637**
Study name	Not reported
Registration	ISRCTN60477608
Study type	RCT
Study dates	2015-2018
Objective	To investigate the effectiveness of e-cigarettes for smoking cessation among adults attending UK NHS stop smoking services, compared with NRT of choice.
Country/ Setting	UK Stop smoking services (London, Leicester and East Sussex)
Number of participants / clusters	886 participants Intervention: 439 Control: 447

<table>
<tr><td>Bibliographic reference/s</td><td colspan="2">Hajek Peter, Phillips-Waller Anna, Przulj Dunja, Pesola Francesca, Myers Smith, Katie , Bisal Natalie, Li Jinshuo, Parrott Steve, Sasieni Peter, Dawkins Lynne, Ross Louise, Goniewicz Maciej, Wu Qi, and McRobbie Hayden J (2019) A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. 380(7), 629-637</td></tr>
<tr><td>Study name</td><td colspan="2">Not reported</td></tr>
<tr><td></td><td colspan="2">Power calculations conducted: trial has 95% power if the true percentages of 1-year abstinence were 23.8% in the e-cigarette group and 14.0% in the nicotine replacement group or 85% power if the percentages were 17.0% and 10.0% in the respective groups.</td></tr>
<tr><td>Attrition</td><td colspan="2">4 week follow-up:
Intervention: 63/439 (14.4%)
Control: 91/447 (20.4%)
One participant in each arm died during the trial and so was excluded. Sample for analysis was 438 (intervention) and 446 (control)</td></tr>
<tr><td>Participant /community characteristics.</td><td colspan="2">Characteristics at baseline
<table>
<tr><th></th><th>Intervention</th><th>Control</th></tr>
<tr><td>Median age years (IQR)</td><td>41 (33-53)</td><td>41 (33-51)</td></tr>
<tr><td>Female (%)*</td><td>211 (48.2)</td><td>213 (47.8)</td></tr>
<tr><td>Entitled to free prescriptions (indicator of SES) n (%)</td><td>181 (41.3)</td><td>179 (40.1)</td></tr>
<tr><td>Ethnicity n (%)</td><td colspan="2">Not reported</td></tr>
<tr><td>Employment status employed n (%)</td><td>299 (68.3)</td><td>316 (70.9)</td></tr>
<tr><td>Fagerstrom Test Score*, mean (SD)</td><td>4.5 (2.5)</td><td>4.6 (2.4)</td></tr>
<tr><td>Baseline reported cigarettes smoked per day median (IQR)</td><td>15 (10-20)</td><td>15 (10-20)</td></tr>
</table>
No significant differences between the trial groups.</td></tr>
<tr><td>Method of allocation</td><td colspan="2">Randomised. 1:1 ratio in blocks of 20, stratified by trial site. A pseudorandom number generator in Stats was used, and next treatment assignment only revealed once participant had been entered into database.
Participants could not be blinded. Analysis of outcomes conducted with blinding to treatment assignments. Outcome assessor blinding not reported.</td></tr>
<tr><td>Inclusion criteria</td><td colspan="2">Adult smokers were invited to participate if they were not pregnant or breast-feeding, had no strong preference to use or not to use nicotine replacement or e-cigarettes, and were currently not using either type of product.</td></tr>
<tr><td>Exclusion criteria</td><td colspan="2">None reported</td></tr>
<tr><td>Intervention</td><td>TIDieR Checklist criteria</td><td>Details</td></tr>
<tr><td></td><td>Brief Name</td><td>E-cigarettes</td></tr>
<tr><td></td><td>Rationale/theory/Goal</td><td>That e-cigarettes may be effective for cessation in treatment-seeking adult smokers</td></tr>
<tr><td></td><td>Materials used</td><td>E-cigarette: “One Kit” second generation. E-cigarette starter kit containing an e-cigarette, five atomizers, UK adapter, spare battery and e-liquid (30ml bottle, tobacco flavour, 18mg/ml nicotine, 1.8%). E-cigarette is refillable.
42 participants received a different version of the e-cigarette device due to previous version being</td></tr>
</table>

Bibliographic reference/s	**Hajek Peter, Phillips-Waller Anna, Przulj Dunja, Pesola Francesca, Myers Smith, Katie , Bisal Natalie, Li Jinshuo, Parrott Steve, Sasieni Peter, Dawkins Lynne, Ross Louise, Goniewicz Maciej, Wu Qi, and McRobbie Hayden J (2019) A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. 380(7), 629-637**	
Study name	Not reported	
		discontinued during trial. Lower ohm atomizer and higher mAh battery, no other differences. Behavioural support: support involved weekly one-on-one sessions with expired carbon monoxide (eCO) monitoring for at least 4 weeks after quit date.
	Provider	Investigators purchased product and provided to participants. Behavioural support: delivered by local clinicians
	Method of delivery	As required
	Location	Not reported
	Duration	E-cigarette: 30ml e-liquid provided, after that participants advised to purchase their own products / liquid as suited them. If unable to purchase more liquid, one further 10ml bottle was provided (not offered proactively). Behavioural support: 4 weeks
	Intensity	E-cigarette: as needed Behavioural support: one-on-one, weekly
	Planned treatment fidelity	Participants committed to not use NRT for at least 4 weeks after quit date to minimise contamination.
	Other details	
Comparison	**TIDieR Checklist criteria**	**Details**
	Brief Name	NRT
	Rationale/theory/Goal	That NRT may be effective for cessation in treatment-seeking adult smokers
	Materials used	NRT: participants informed about the range of NRT products available. Encouraged to use combinations, typically patch and a faster-acting oral product. Participants selected their preferred product and were free to switch to other NRT products. Behavioural support: as for intervention.
	Provider	Unclear – NHS? Study states “the cost to the NHS of a 3-month supply of a single nicotine-replacement product is currently approximately £120”
	Method of delivery	As required
	Location	Not reported
	Duration	Supplies of NRT provided for up to 3 months
	Intensity	NRT: as needed Behavioural support: one-on-one, weekly
	Planned treatment fidelity	Participants committed to not use e-cigarettes for at least 4 weeks after quit date to minimise contamination
	Other details	
Follow up	4 weeks (main outcome 52 weeks to be included in NMA)	

<table>
<tr><td>Bibliographic reference/s</td><td>Hajek Peter, Phillips-Waller Anna, Przulj Dunja, Pesola Francesca, Myers Smith, Katie , Bisal Natalie, Li Jinshuo, Parrott Steve, Sasieni Peter, Dawkins Lynne, Ross Louise, Goniewicz Maciej, Wu Qi, and McRobbie Hayden J (2019) A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. 380(7), 629-637</td></tr>
<tr><td>Study name</td><td>Not reported</td></tr>
<tr><td>Data collection</td><td>Smoking abstinence (4 weeks): a self-report of no smoking from 2 weeks after the target quit date, plus an expired carbon monoxide level of less than 8 ppm at 4 weeks.
Data collector blinding not reported.</td></tr>
<tr><td>Critical outcomes measures and effect size. (time points)</td><td>Smoking abstinence (4 weeks) (validated by exhaled CO)
<table>
<tr><td></td><td>Nicotine e-cigarette (n=438)</td><td>NRT (n=446)</td><td>RR* (95% CI)</td></tr>
<tr><td>Number abstinent (%)</td><td>192 (43.8)</td><td>134 (30.0)</td><td>1.46 (1.22, 1.74)</td></tr>
</table>
*calculated by analyst (adjusted RR presented in the paper, but event data only extracted. Adjusted results are very similar to unadjusted)</td></tr>
<tr><td>Important outcomes measures and effect size. (time points)</td><td>None reported</td></tr>
<tr><td>Statistical Analysis</td><td>Smoking status was regressed onto trial group at each time point. Trial centre was adjusted in the paper but not extracted. Sensitivity analyses were conducted to investigate the effect of withdrawals. Stata used for analysis.</td></tr>
<tr><td>Risk of bias (ROB)
Overall ROB</td><td>Outcome name
<table>
<tr><th>Outcome</th><th>Judgement (Low / High / some concerns)</th><th>Comments</th></tr>
<tr><td>Risk of bias arising from the randomisation process</td><td>Low risk</td><td>Random allocation, concealed, no baseline differences.</td></tr>
<tr><td>Risk of bias due to deviations from intended interventions (assignment)</td><td>Some concerns</td><td>Participants aware of the intervention, no information on outcome assessor blinding (data analysis – blinded). Some deviations may have arisen (people wanting assignment to e-cig dropping out of NRT group) but attempt to reduce by recruiting people with no strong preference.</td></tr>
<tr><td>Missing outcome data</td><td>Low risk</td><td>Some withdrawals, sensitivity analysis indicates no impact on results.</td></tr>
<tr><td>Risk of bias in measurement of the outcome</td><td>Low risk</td><td>Measurement of outcome same between groups. No information on outcome assessor blinding but unlikely to influence outcome.</td></tr>
<tr><td>Risk of bias in selection of the reported result</td><td>Low risk</td><td>Result not selected from multiple measurements and analysed in accordance with protocol.</td></tr>
<tr><td>Other sources of bias</td><td colspan="2">None</td></tr>
<tr><td>Overall Risk of Bias</td><td colspan="2">Some concerns</td></tr>
<tr><td colspan="3">Other outcome details</td></tr>
</table></td></tr>
</table>

Bibliographic reference/s	**Hajek Peter, Phillips-Waller Anna, Przulj Dunja, Pesola Francesca, Myers Smith, Katie , Bisal Natalie, Li Jinshuo, Parrott Steve, Sasieni Peter, Dawkins Lynne, Ross Louise, Goniewicz Maciej, Wu Qi, and McRobbie Hayden J (2019) A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. 380(7), 629-637**
Study name	Not reported
Source of funding	National Institute for Health Research, Cancer Research UK Prevention Trials Unit
Comments	Participants who reported reduction / cessation were invited for validation. They were compensated £20 ($26 U.S.) for their travel and time at the 52-week validation visit.
Additional references	None

Halpern 2018

Bibliographic reference/s	**Halpern S D, Harhay M O, Saulsgiver K, Brophy C, Troxel A B, and Volpp K G (2018) A Pragmatic Trial of E-Cigarettes, Incentives, and Drugs for Smoking Cessation. New England Journal of Medicine 378(24), 2302-2310**
Study name	Not reported
Registration	NCT02328794
Study type	RCT
Study dates	2014-2017
Objective	To investigate how successful workplace smoking-cessation programs are when offered to all smokers, regardless of willingness to quit?
Country/ Setting	USA, Pennsylvania (unclear where workplaces are located) Workplace setting
Number of participants / clusters	6006 participants randomised to 5 different groups. Relevant groups are: E-cigarette: 1199 Usual care: 813 6000 participants provided 80% power to detect an increase of at least 5 percentage points above an assumed abstinence rate of 2.5% in free cessation aids group (main comparator, not relevant for this review so not extracted). Changes were smaller than this, so study not sufficiently powered.
Attrition	Participants were those who did not opt out of the study. Therefore attrition not relevant. Those who actively engaged (measured as those who logged on to the platform through which allocations were revealed and interventions explained) were: E-cigarette: 253 (21.1%) Usual care: 129 (15.9%)
Participant /community characteristics.	Characteristics at baseline

	Intervention (n=1199)	**Control (n=813)**
Median age years (IQR)	43.9 (35.0 – 52.8)	44.5 (35.6 – 53.7)
Female, n (%)	597 (49.8)	415 (51.0)
Education (high school or less), n (%)	357 (29.8)	256 (31.5)
SES (high) n (%)	Not reported	
Ethnicity	Not reported	
Baseline reported cigarettes smoked per day median (IQR)	10 (5 – 15)	10 (5 – 15)

Bibliographic reference/s	**Halpern S D, Harhay M O, Saulsgiver K, Brophy C, Troxel A B, and Volpp K G (2018) A Pragmatic Trial of E-Cigarettes, Incentives, and Drugs for Smoking Cessation. New England Journal of Medicine 378(24), 2302-2310**	
Study name	Not reported	
	Reported desire to quit, n (%): No plan to quit want to quit later want to quit, need help	 109 (9.1) 754 (62.9) 315 (26.3)	 74 (9.1) 490 (60.3) 238 (29.3)
	Characteristics are balanced across the groups.	
Method of allocation	Participants contacted minimum 4 times by email as opportunities to opt out. If they did not opt out, they were enrolled. Enrolled participants were randomly assigned, and stratified according to employer. Randomization probabilities unbalanced to achieve power to detect changes in the pre-planned comparisons.	
Inclusion criteria	Employees and their spouses at 54 companies that use Vitality wellness programs, who are 18 years old or over, and who reported current smoking on a health risk assessment within the previous year.	
Exclusion criteria	None reported.	
Intervention	**TIDieR Checklist criteria**	**Details**
	Brief Name	E-cigarette
	Materials used	Contact: participants sent brief descriptions of their assigned intervention and encouraged to sign into Web portal. Processes for obtaining e-cigarettes and for submitting samples for biochemical validation available on the portal. NJOY e-cigarette (including battery stick, USB charger, full chambers). Up to 20 chambers with **1.0 to 1.5% (10-15mg/ml)** nicotine per week in participants' chosen flavours provided free of charge. Additional resources: participants were notified of usual care resources that could be accessed through wellness websites for their companies. Also given opportunity to register for SmokeFreeTXT program (National Cancer Institute): a free text messaging program giving encouragement, advice and tips for stopping smoking.
	Provider	NJOY provided e-cigarettes free of charge until 6 months after quit date; participants' employer (for usual care information) and National Cancer Institute (for text messaging service)
	Method of delivery	E-cigarettes ordered directly through the trial website at no cost.
	Location	As decided by participants
	Duration	As needed until 6 months after quit date, and could then be purchased at own expense.
	Intensity	As required by participants
	Planned treatment fidelity	Not reported
	Other details	

<table>
<tr><td>Bibliographic reference/s</td><td colspan="2">Halpern S D, Harhay M O, Saulsgiver K, Brophy C, Troxel A B, and Volpp K G (2018) A Pragmatic Trial of E-Cigarettes, Incentives, and Drugs for Smoking Cessation. New England Journal of Medicine 378(24), 2302-2310</td></tr>
<tr><td>Study name</td><td colspan="2">Not reported</td></tr>
<tr><td rowspan="10">Comparison</td><td>TIDieR Checklist criteria</td><td>Details</td></tr>
<tr><td>Brief Name</td><td>Usual care</td></tr>
<tr><td>Materials used</td><td>Participants were notified of usual care resources that could be accessed through wellness websites for their companies. Also given opportunity to register for SmokeFreeTXT program (National Cancer Institute): a free text messaging program giving encouragement, advice and tips for stopping smoking.</td></tr>
<tr><td>Provider</td><td>Participants’ employer (for usual care information) and National Cancer Institute (for text messaging service)</td></tr>
<tr><td>Method of delivery</td><td>Through employer, employee-driven.</td></tr>
<tr><td>Location</td><td>Workplace; SmokeFreeTXT via phone.</td></tr>
<tr><td>Duration</td><td>Unclear – assumed that workplace interventions won’t stop at 6 months as they are run by workplace.</td></tr>
<tr><td>Intensity</td><td>As required by participants</td></tr>
<tr><td>Planned treatment fidelity</td><td>Not reported</td></tr>
<tr><td>Other details</td><td></td></tr>
<tr><td>Follow up</td><td colspan="2">1 and 3 months (main outcome 6 months included in NMA)</td></tr>
<tr><td>Data collection</td><td colspan="2">Survey asking about smoking.
Participants self-reporting a quit at any time point were contacted to provide biochemical confirmation.
Usual care: urine sample with cotinine level of less than 20ng/ml.
E-cigarette: urine sample with cotinine test as above. Where users had a positive cotinine sample, blood carboxyhaemoglobin level also assessed, and levels less than 4% considered to confirm a quit.

All samples evaluated by lab technicians who were unaware of group assignments. However, if different tests used for different study arms, assignment could become clear.</td></tr>
<tr><td>Critical outcomes measures and effect size. (time points)</td><td colspan="2">Smoking abstinence (1 month) (biochemically verified)
<table>
<tr><td></td><td>Nicotine e-cigarette (n=1199)</td><td>Usual care (n = 813)</td><td>RR* (95% CI)</td></tr>
<tr><td>Number abstinent (%)</td><td>28 (2.34)</td><td>9 (1.11)</td><td>2.11 [1.00, 4.45]</td></tr>
</table>
*Calculated by analyst

Smoking abstinence (3 month) (biochemically verified)
<table>
<tr><td></td><td>Nicotine e-cigarette (n=1199)</td><td>Usual care (n = 813)</td><td>RR* (95% CI)</td></tr>
<tr><td>Number abstinent (%)</td><td>20 (1.67)</td><td>2 (0.25)</td><td>6.78 [1.59, 28.93]</td></tr>
</table>
*Calculated by analyst</td></tr>
<tr><td>Important outcomes measures and effect size. (time points)</td><td colspan="2">None reported</td></tr>
</table>

Bibliographic reference/s	**Halpern S D, Harhay M O, Saulsgiver K, Brophy C, Troxel A B, and Volpp K G (2018) A Pragmatic Trial of E-Cigarettes, Incentives, and Drugs for Smoking Cessation. New England Journal of Medicine 378(24), 2302-2310**		
Study name	Not reported		
Statistical Analysis	Logistic regression to compare rates of sustained abstinence. Phase adjusted for in the analysis.		
Risk of bias (ROB) **Overall ROB**	**Outcome name: smoking abstinence**		
	Outcome	**Judgement (Low / High / some concerns)**	**Comments**
	Risk of bias arising from the randomisation process	Low risk	Allocation sequence random and baseline characteristics similar.
	Risk of bias due to deviations from intended interventions (assignment)	Some concerns	Participants were aware of their intervention; assessors of validation samples blinded. No information on changes due to experimental context.
	Missing outcome data	High risk	Most participants randomised did not engage with the study and so did not either take up the intervention or provide outcome data. People who engaged were more highly educated, more motivated to quit, more likely to be female. Outcomes are therefore out of all people eligible and notified of the intervention, not out of those who took up the intervention. This is likely to underestimate the absolute effects in all groups (as a proportion of people receiving the intervention).
	Risk of bias in measurement of the outcome	High risk	Measurement of the outcome varies across arms to accommodate continued nicotine intake in the intervention arm, probably to allow samples to be sent in post.
	Risk of bias in selection of the reported result	Low risk	Trial analysed according to protocol.
	Other sources of bias		
	Overall Risk of Bias	High risk of bias	
	Other outcome details: None		
Source of funding	Vitality Institute grant to University of Pennsylvania Center for health Incentives and Behavioral Economics.		
Comments	Participants were recruited in two phases due to insufficient powering from first phase. Participants are recruited through their workplaces, and so may be healthier than the general population, particularly the general population of people who smoke. Compensation was given for submitting urine and blood samples (urine: $25, blood $50 with exception of final 12 month follow-up which gave $100 for both samples from participants in Wave 2).		

Bibliographic reference/s	**Halpern S D, Harhay M O, Saulsgiver K, Brophy C, Troxel A B, and Volpp K G (2018) A Pragmatic Trial of E-Cigarettes, Incentives, and Drugs for Smoking Cessation. New England Journal of Medicine 378(24), 2302-2310**
Study name	Not reported
Additional references	None

Lee 2018

Bibliographic reference/s	**Lee S M, Tenney R, Wallace A W, and Arjomandi M (2018) E-cigarettes versus nicotine patches for perioperative smoking cessation: a pilot randomized trial. PeerJ 6, e5609**
Study name	None reported
Registration	Clinical trials: NCT02482233
Study type	RCT (pilot)
Study dates	2015-2016
Objective	To determine feasibility and acceptability of e-cigarettes, compared to nicotine patch, for perioperative smoking cessation in veterans
Country/ Setting	USA, California Preoperative clinic.
Number of participants / clusters	30 participants (20 intervention, 10 control). Not powered – small sample size as pilot study.
Attrition	At 8 weeks (time-point of interest): Intervention: 0 loss to follow-up Control: 1 (10%) lost to follow up. (not reachable)
Participant /community characteristics.	Patient demographics at baseline (all veterans)

	Intervention (n=20)	**Control (n=10)**
Mean age years (SD)	54 (12.7)	53 (10.6)
Female, n (%)*	2 (10)	1 (10)
SES	NR	
Ethnicity non-white, n (%)	9 (45)	5 (50)
Education	NR	
Comorbidities (diabetes or hypertension or heart disease or COPD)	16 (80)	4 (40)
Fagerstrom Test Score*, mean (SD)	3.7 (2.6)	2.5 (0.85)
Baseline reported cigarettes smoked per day mean (SD)	15.3 (10.5)	10.8 (6.6)

*Fagerström Test for Nicotine Dependence. Score 0-10, higher score indicates more intense addiction.

Statistical testing between groups not reported. Authors report that patient demographics were well balanced. E-cigarettes group had higher smoking disease burden and greater number of cigarettes smoked per day, and higher addiction levels.

Method of allocation	Randomized. Computer-generated randomisation (block size 3 or 6), 2:1 ratio (e-cigs: NRT). Participants could not be blinded. Healthcare providers and outcome adjudicators blinded where possible.

Bibliographic reference/s	**Lee S M, Tenney R, Wallace A W, and Arjomandi M (2018) E-cigarettes versus nicotine patches for perioperative smoking cessation: a pilot randomized trial. PeerJ 6, e5609**	
Study name	None reported	
Inclusion criteria	• People presenting to the anaesthesia preoperative (APO) clinic for elective surgery 3 or more days before surgery • current cigarette smokers of more than two cigarettes per day having smoked at least once in the last 7 days • people who could provide consent	
Exclusion criteria	• exclusive users of other forms of tobacco (e.g., pipe tobacco) or marijuana only • pregnant or breast-feeding women • people with an unstable cardiac condition (e.g., unstable angina, unstable arrhythmia) • people currently using smoking cessation pharmacotherapy • people already enrolled in a smoking cessation trial, • people currently using e-cigarettes on a daily basis	
Intervention	**TIDieR Checklist criteria**	**Details**
	Brief Name	E-cigarette
	Rationale/theory/Goal	First generation selected as widely available and it was not yet known that second generation were more satisfying (authors report).
	Materials used	Those allocated to the e-cigarette group received a 6-week supply of NJOY e-cigarettes (Scottsdale, AZ, USA) and were instructed to use the Bold (4.5% nicotine) e-cigarettes as needed for 3 weeks, the Gold (2.4% nicotine) e-cigarettes ad libitum for 2 weeks and the Study (0% nicotine) e-cigarettes as needed 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. The NJOY e-cigarette is a disposable first-generation e-cigarette that is available for purchase in shops and online. Also received: brief counselling by research team, brochure explaining the benefits of preoperative smoking cessation, referral to California Smokers' Helpline (online form triggering phone call to participant).
	Provider	Not reported
	Method of delivery	Materials given, and participants educated on use of products (product masked to investigator). Materials given, and then used as desired by participants. Materials stopped at 6 weeks and unused products returned. Participants asked to refrain from cigarettes and all study products at the end of the 6 weeks.
	Location	Veteran's Affairs Medical Centre
	Duration	6 weeks of treatment
	Intensity	As required

Bibliographic reference/s	**Lee S M, Tenney R, Wallace A W, and Arjomandi M (2018) E-cigarettes versus nicotine patches for perioperative smoking cessation: a pilot randomized trial. PeerJ 6, e5609**	
Study name	None reported	
	Planned treatment fidelity	As required
	Other details	
Comparison	**TIDieR Checklist criteria**	**Details**
	Brief Name	NRT
	Rationale/theory/Goal	Patch effective in perioperative patients, dose-tapering also effective.
	Materials used	Patients randomized to the NRT group received a 6-week supply of Nicoderm CQ 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. Also received: brief counselling by research team, brochure explaining the benefits of preoperative smoking cessation, referral to California Smokers' Helpline (online form triggering phone call to participant)
	Provider	Not reported
	Method of delivery	As for intervention
	Location	As for intervention
	Duration	As for intervention
	Intensity	As required
	Planned treatment fidelity	Not specified
	Other details	
Follow up	8 weeks (main outcome 6 months)	
Data collection	Baseline, day of surgery and 8 week follow-up data collection in person. CO and salivary cotinine tested at each visit. Smoking abstinence (7-day point prevalence): validated with exhaled CO (≤10ppm) and saliva sample, at 8 weeks.	
Critical outcomes measures and effect size. (time points)	**Smoking abstinence (8 weeks) (biochemically verified)**	

	Nicotine e-cigarette (n=20)	NRT (n=10)	RR* (95% CI)
Number abstinent (%)	3 (15)	0 (0)	3.67 (0.21, 64.80)**

*Calculated by analyst

**Revman automatically adds a fixed value to 0 cell counts to enable a RR to be calculated.

<table>
<tr><td>Bibliographic reference/s</td><td colspan="3">Lee S M, Tenney R, Wallace A W, and Arjomandi M (2018) E-cigarettes versus nicotine patches for perioperative smoking cessation: a pilot randomized trial. PeerJ 6, e5609</td></tr>
<tr><td>Study name</td><td colspan="3">None reported</td></tr>
<tr><td>Important outcomes measures and effect size. (time points)</td><td colspan="3">None</td></tr>
<tr><td>Statistical Analysis</td><td colspan="3">Intention to treat analysis – those lost to follow-up assumed to have continued smoking.
Descriptive statistics were calculated for baseline demographic variables. Categorical outcomes were analyzed using Fisher exact test. Histograms were constructed for continuous outcomes and visually assessed for distribution and analyzed using Student t test if normally distributed; Wilcoxon rank sum test was used for non-normally distributed variables. A two-tailed p value of <0.05 was considered significant. Stata version 13 (StataCorp LP, College Station, TX, USA) was used for all data management and analyses.</td></tr>
<tr><td>Risk of bias (ROB)
Overall ROB</td><td colspan="3">Smoking abstinence</td></tr>
<tr><td></td><td>Outcome</td><td>Judgement (Low / High / some concerns)</td><td>Comments</td></tr>
<tr><td></td><td>Risk of bias arising from the randomisation process</td><td>Some concerns</td><td>Allocation sequence concealed but differences suggest a potential problem with randomisation</td></tr>
<tr><td></td><td>Risk of bias due to deviations from intended interventions (assignment)</td><td>Low</td><td>Intention to treat analysis. Participants aware of intervention, but blinding conducted where possible. Deviations arising from experimental context unlikely.</td></tr>
<tr><td></td><td>Missing outcome data</td><td>Low</td><td>Minimal missing data, but small dataset and rare outcomes.</td></tr>
<tr><td></td><td>Risk of bias in measurement of the outcome</td><td>Low</td><td>Measure appropriate and the same across groups. Assessors not properly blinded but little power to change outcomes.</td></tr>
<tr><td></td><td>Risk of bias in selection of the reported result</td><td>Low</td><td>Outcomes as in protocol. No evidence of multiple measurements.</td></tr>
<tr><td></td><td>Other sources of bias</td><td colspan="2">None</td></tr>
<tr><td></td><td>Overall Risk of Bias</td><td colspan="2">Some concerns</td></tr>
<tr><td></td><td colspan="3">Other outcome details None</td></tr>
<tr><td>Source of funding</td><td colspan="3">Internal UCSF Department of Anaesthesia and Perioperative Care funds (San Francisco, California, United States of America) and the UCSF Resource Allocation Program grant.
E-cigarettes were purchased from NJOY using these funds. NJOY had no involvement in the design, execution, or analysis of the study.</td></tr>
<tr><td>Comments</td><td colspan="3">Participants received a $100 cheque after completion of 8-week follow-up.
If in-person visits were refused, data collection conducted by telephone, and validation of smoking could not be done.
Three participants allocated to NRT patch used e-cigarettes, and 2 allocated to e-cigarettes used nicotine patches. All analysed in the group they were originally allocated to.</td></tr>
</table>

Bibliographic reference/s	**Lee S M, Tenney R, Wallace A W, and Arjomandi M (2018) E-cigarettes versus nicotine patches for perioperative smoking cessation: a pilot randomized trial. PeerJ 6, e5609**
Study name	None reported
Additional references	None

Masiero 2018

Bibliographic reference/s	**Masiero M, Lucchiari C, Mazzocco K, Veronesi G, Maisonneuve P, Jemos C, Sale E O, Spina S, Bertolotti R, and Pravettoni G (2018) E-cigarettes May Support Smokers With High Smoking-Related Risk Awareness to Stop Smoking in the Short Run: Preliminary Results by Randomized Controlled Trial. Nicotine & Tobacco Research 11, 11**
Study name	None reported
Registration	NCT02422914
Study type	RCT
Study dates	2015-2016
Objective	To assess the efficacy of the use of e-cigarettes in a tobacco cessation program with a group of chronic smokers (smoking 10 or more cigarettes daily for 10 years or more) voluntarily involved in long-term lung cancer screening, using a randomized controlled trial.
Country/ Setting	Italy, Milan From a screening programme, outpatient
Number of participants / clusters	210 Intervention: 70 Placebo: 70 Control: 70 Power calculated for detecting a reduction in cigarettes per day – not a relevant outcome for this study.
Attrition	40/210 could not have data collected at follow-up (19%) Withdrawals per arm not reported and unable to work out exactly.
Participant /community characteristics.	Characteristics at baseline

	Intervention (n = 70)	**Placebo (n = 70)**	**Control (n = 70)**
Mean age years (SD)	62.8 (4.6)		
Female n (%)*	78 (37.1%)		
SES (high) n (%)	Not reported		
Ethnicity non-white n (%)	Not reported		
Fagerstrom Test Score*, mean (SD)	4.5 (1.788)	4.4 (1.878)	4.1 (1.954)
Baseline reported cigarettes smoked per day mean (SD)	19.2 (6.123)	19.2 (6.123)	19.3 (8.939)**

*Fagerström Test for Nicotine Dependence. Score 0-10, higher score indicates more intense addiction.

**reported as 9.3 but from other information available, assessed this as an error.

No significant differences between the groups.

Bibliographic reference/s	**Masiero M, Lucchiari C, Mazzocco K, Veronesi G, Maisonneuve P, Jemos C, Sale E O, Spina S, Bertolotti R, and Pravettoni G (2018) E-cigarettes May Support Smokers With High Smoking-Related Risk Awareness to Stop Smoking in the Short Run: Preliminary Results by Randomized Controlled Trial. Nicotine & Tobacco Research 11, 11**	
Study name	None reported	
Method of allocation	Randomised. Permuted block design (40 blocks of 6 subjects randomly assigned to an arm). Prepared by independent personnel unit.	
Inclusion criteria	• Having smoked at least 10 cigarettes a day for the past 10 years; • High motivation to stop smoking (High or Very High at the motivational questionnaire); • Not enrolled in other smoking cessation programs. The screening programme from which participants were drawn only includes adults aged 55 and over.	
Exclusion criteria	• Severe cardiovascular and respiratory diseases; • Use of psychotropic medication; • Current or past history of alcohol abuse; • Any use of NRTs or e-cigarettes.	
Intervention	**TIDieR Checklist criteria**	**Details**
	Brief Name	E-cigarette
	Materials used	E-cigarette: VP5 kit. E-cigarette (eGO-CE4 PIEFFE) with rechargeable battery and 1.6ml capacity atomizer. Nicotine liquid 8mg/ml (0.8% nicotine), tobacco flavour. 12 x 10ml liquid cartridges provided. No additional provided if participants ran out. Counselling: low intensity telephone counselling at week 1, 4, 8, 12. Around 10 minutes each. Counsellor provided information, supported participants' motivation, helped with coping mechanisms.
	Provider	E-cigarette: BioFumo provided to study. Materials provided to participants free of charge. Counselling: a trained psychologist.
	Method of delivery	Participants asked to consume no more than 1ml of liquid a day. Participants blinded to whether receiving intervention or placebo, but not blinded to control condition (not feasible)
	Location	Counselling by phone. E-cigarette use where needed
	Duration	12 weeks (E-cigarette use began 1 week before quit date, 11 weeks after. Final counselling phone call at 12 weeks)
	Intensity	As required
	Planned treatment fidelity	Participants asked to use only the liquid provided, and not to purchase more / different types of liquid. Participants returned any unused liquid after the end of the study.

<table>
<tr><td>Bibliographic reference/s</td><td colspan="3">Masiero M, Lucchiari C, Mazzocco K, Veronesi G, Maisonneuve P, Jemos C, Sale E O, Spina S, Bertolotti R, and Pravettoni G (2018) E-cigarettes May Support Smokers With High Smoking-Related Risk Awareness to Stop Smoking in the Short Run: Preliminary Results by Randomized Controlled Trial. Nicotine & Tobacco Research 11, 11</td></tr>
<tr><td>Study name</td><td colspan="3">None reported</td></tr>
<tr><td></td><td>Other details</td><td colspan="2">Participants were asked to refer to dedicated personnel (by phone, email, or on-site) for any issue that might arise in relation to e-cig use.</td></tr>
<tr><td>Placebo</td><td>TIDieR Checklist criteria</td><td colspan="2">Details</td></tr>
<tr><td></td><td>Brief Name</td><td colspan="2">Placebo e-cigarette</td></tr>
<tr><td></td><td>Materials used</td><td colspan="2">E-cigarette: VP5 kit. E-cigarette (eGO-CE4 PIEFFE) with rechargeable battery and 1.6ml capacity atomizer. Nicotine liquid 0mg/ml (0% nicotine), tobacco flavour. 12 x 10ml liquid cartridges provided. No additional provided if participants ran out.

Counselling: as for intervention</td></tr>
<tr><td></td><td>Provider</td><td colspan="2">As for intervention</td></tr>
<tr><td></td><td>Method of delivery</td><td colspan="2">As for intervention</td></tr>
<tr><td></td><td>Location</td><td colspan="2">As for intervention</td></tr>
<tr><td></td><td>Duration</td><td colspan="2">As for intervention</td></tr>
<tr><td></td><td>Intensity</td><td colspan="2">As for intervention</td></tr>
<tr><td></td><td>Planned treatment fidelity</td><td colspan="2">As for intervention</td></tr>
<tr><td></td><td>Other details</td><td colspan="2">Participants were asked to refer to dedicated personnel (by phone, email, or on-site) for any issue that might arise in relation to e-cig use.</td></tr>
<tr><td>Comparison</td><td>TIDieR Checklist criteria</td><td colspan="2">Details</td></tr>
<tr><td></td><td>Brief Name</td><td colspan="2">Control</td></tr>
<tr><td></td><td>Materials used</td><td colspan="2">Counselling: as for intervention</td></tr>
<tr><td></td><td>Provider</td><td colspan="2">Counselling: a trained psychologist.</td></tr>
<tr><td></td><td>Location</td><td colspan="2">Counselling by phone.</td></tr>
<tr><td></td><td>Duration</td><td colspan="2">Final counselling phone call at 12 weeks</td></tr>
<tr><td></td><td>Intensity</td><td colspan="2">Low: Around 10 minutes per phone call, 4 phone calls total.</td></tr>
<tr><td></td><td>Planned treatment fidelity</td><td colspan="2">Planned that participants do not use e-cigarettes at all.</td></tr>
<tr><td></td><td>Other details</td><td colspan="2"></td></tr>
<tr><td>Follow up</td><td colspan="3">3 months</td></tr>
<tr><td>Data collection</td><td colspan="3">Smoking abstinence: continuous smoking abstinence (self-reported abstinence over the previous month). Validated by exhaled CO. >5ppm considered not within normal limits
Data collectors blinded.</td></tr>
<tr><td>Critical outcomes measures and effect size. (time points)</td><td colspan="3">Smoking abstinence (3 months) (validated by exhaled CO)
<table>
<tr><td></td><td>Nicotine e-cigarette (n=70)</td><td>Non-nicotine e-cigarette (n=70)</td><td>RR* (95% CI)</td></tr>
<tr><td>Number abstinent (%)</td><td>15 (21.4)</td><td>13 (18.6)</td><td>1.15 [0.59, 2.24]</td></tr>
</table>
*Calculated by analyst</td></tr>
</table>

<table>
<tr><td>Bibliographic reference/s</td><td colspan="4">Masiero M, Lucchiari C, Mazzocco K, Veronesi G, Maisonneuve P, Jemos C, Sale E O, Spina S, Bertolotti R, and Pravettoni G (2018) E-cigarettes May Support Smokers With High Smoking-Related Risk Awareness to Stop Smoking in the Short Run: Preliminary Results by Randomized Controlled Trial. Nicotine & Tobacco Research 11, 11</td></tr>
<tr><td>Study name</td><td colspan="4">None reported</td></tr>
<tr><td></td><td colspan="4"><table><tr><td></td><td>Nicotine e-cigarette (n=70)</td><td>Control (n=70)</td><td>RR* (95% CI)</td></tr><tr><td>Number abstinent (%)</td><td>15 (21.4)</td><td>6 (8.6)</td><td>2.50 [1.03, 6.07]</td></tr></table>*Calculated by analyst</td></tr>
<tr><td>Important outcomes measures and effect size. (time points)</td><td colspan="4">None</td></tr>
<tr><td>Statistical Analysis</td><td colspan="4">Mann-Whitney U and Kruskal-Wallis H tests used to evaluate statistical differences in cigarette consumption. No sensitivity testing reported.</td></tr>
<tr><td>Risk of bias (ROB)
Overall ROB</td><td colspan="4">Outcome name: smoking abstinence (intervention vs placebo)<table><tr><th>Outcome</th><th>Judgement (Low / High / some concerns)</th><th>Comments</th></tr><tr><td>Risk of bias arising from the randomisation process</td><td>Low risk</td><td>Allocation sequence random, no differences in baseline characteristics.</td></tr><tr><td>Risk of bias due to deviations from intended interventions (assignment)</td><td>Low risk</td><td>Participants and personnel blinded.</td></tr><tr><td>Missing outcome data</td><td>Some concerns</td><td>Outcome data not available for all participants, unclear distribution. Unlikely that missingness depends on true value.</td></tr><tr><td>Risk of bias in measurement of the outcome</td><td>Low risk</td><td>Outcome measurement same across groups. Outcome assessors blinded.</td></tr><tr><td>Risk of bias in selection of the reported result</td><td>Some concerns</td><td>Unclear – protocol does not specify cessation outcome or thresholds</td></tr><tr><td>Other sources of bias</td><td colspan="2">None</td></tr><tr><td>Overall Risk of Bias</td><td colspan="2">Some concerns</td></tr></table>Other outcome details
Smoking abstinence (intervention vs control): Some concerns for deviations from intended interventions: participants not blinded, unclear whether deviations arose from experimental context. Overall judgement: High risk of bias (study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in of the result)</td></tr>
<tr><td>Source of funding</td><td colspan="4">Fondazione Umberto Veronesi (FUV) (a foundation for scientific progress)</td></tr>
<tr><td>Comments</td><td colspan="4">Primary outcome of the study is to look at smoking-related respiratory symptoms, not cessation.</td></tr>
</table>

Bibliographic reference/s	**Masiero M, Lucchiari C, Mazzocco K, Veronesi G, Maisonneuve P, Jemos C, Sale E O, Spina S, Bertolotti R, and Pravettoni G (2018) E-cigarettes May Support Smokers With High Smoking-Related Risk Awareness to Stop Smoking in the Short Run: Preliminary Results by Randomized Controlled Trial. Nicotine & Tobacco Research 11, 11**
Study name	None reported
Additional references	None

Harm reduction

No included papers.

Economic evidence profiles

Study	Annemans 2015 (Belgium)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: Cost-utility analysis (CUA) **Study design:** A two-quit BENESCO (Markov) model estimating cost-effectiveness **Approach to analysis:** The analysis considers smokers who make their 1st quit attempt (1QA) in year 1 followed by a 2nd quit attempt (2QA) in a subsequent year due to failure or relapse. The two-quit BENESCO model calculates lifetime healthcare costs and QALYs associated with smoking related morbidities: asthma exacerbation, COPD, CHD, lung cancer, stroke. Lifetime costs and QALYs are dependent on smoking status obtained from published literature	**Population:** 1,000 current smoker willing to quit (non-representative) **Intervention [a]:** 2QA varenicline: 1QA with varenicline followed by varenicline re-treatment in case of failure or relapse **Comparators [a]:** 2QA NRT: 1QA with NRT followed by NRT re-treatment in case of failure or relapse 2QA bupropion: 1QA with bupropion followed by bupropion re-treatment in case of failure or relapse 2QA placebo: 1QA with placebo followed by placebo re-treatment in case of failure or relapse	**Total population costs:** Not reported **Total cost per person:** Not reported **Intervention costs per person (12 weeks) (€):** Varenicline 246.81 Bupropion 170.40 NRT 230.77 **Healthcare costs 1st year (subsequent years) (€):** Stroke 16,501 (4,419) CHD 8,487 (2,148) Asthma exacerbation 2,861 COPD 2,186 (2,186)	**Total population QALYs (millions):** Not reported **QALYs per person:** Not reported **Incremental costs (total population) (€):** Compared with 2QA varenicline 2QA NRT - 275,000 2QA bupropion - 118,000 2QA placebo - 316,000 1QA varenicline - 237,000 **Incremental QALYs (total population):** Compared with 2QA varenicline 2QA NRT 74	**Incremental cost per QALY:** 2QA varenicline dominates all other interventions **Analysis of uncertainty:** Both one-way univariate analyses and probabilistic sensitivity analysis were performed. Univariate sensitivity analyses found discount rates, cost of NRT and relative risks of smoking related diseases in long term quitters were the most influential parameters. However, changes to these parameters did not affect the conclusions. Probabilistic sensitivity analysis indicated that the conclusions are robust.

Study	Annemans 2015 (Belgium)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
reporting 12-month abstinence rates. Annual healthcare costs per smoking related morbidity are obtained from published literature. Utilities associated with smoking-related diseases are obtained from published literature. These are in line with those reported in the one-quit BENESCO model. **Perspective:** Healthcare payer: public health care payer and the patient **Time horizon:** Lifetime (100 years or dead) **Treatment effect duration:** Lifetime health benefits **Discounting:** 3% cost discounted 1.5% effects discounted	1QA varenicline: 1QA with varenicline followed by 1QA with placebo	Lung cancer 10,765 (10,765) **Currency & cost year:** EUR (€); 2013	2QA bupropion 63 2QA placebo 193 1QA varenicline 111	
Data sources				
Health outcomes: Abstinence rates were derived from Cahill et al. (2013) as well as RCTs. Second line treatment efficacy for NRT and bupropion conservatively used the same value as first line treatment due to lack of evidence. **Quality-of-life weights:** Utility weights for health states are from published				

Study	Annemans 2015 (Belgium)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
data sources. These are the same as those reported in a previous BENESCO model (Annemans et al., 2009). **Cost sources:** Hospitalization costs of smoking-related diseases were obtained from the Belgium TCT database Annual follow-up costs were taken from literature. Drug costs were taken from the RIZIV/INAMI database and the CBIP. All cost prior to 2013 were inflated.				
Comments				
Source of funding: Pfizer Inc. **Limitations:** The model does not consider adverse events associated with the interventions. In addition, the model limits to only 5 smoking-related diseases and all risk ratios are kept constant for each smoking status for simplicity. **Other:** None.				
Overall applicability: Partly applicable **Overall quality: Minor limitations**				
Abbreviations: BENESCO: Benefit of smoking cessation on outcomes; CHD: Coronary heart disease; COPD: Chronic obstructive pulmonary disease; CUA: Cost utility analysis; ICER: Incremental cost-effectiveness ratio; LY: Life years NRT: Nicotine replacement therapy; QA: quit attempt; QALY: Quality-adjusted life year; RCT: randomised control trail				
(a) The length of treatment is not specified within the study. A 12-week treatment length is assumed in line with the cost per intervention.				

Study	Athanasakis 2012 (Greece)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: Cost-utility analysis (CUA) **Study design:** A BENESCO (Markov) model estimating cost-effectiveness **Approach to analysis:** The primary outcome is the ICER per QALY across the lifetime of the cohort. Treatment costs are applied for the first 12 weeks. The BENESCO model calculates lifetime	**Population:** 819,709 individuals making a single quit attempt **Intervention:** Varenicline (12 weeks) **Comparator(s):** Bupropion (12 weeks) NRT (12 weeks) Unaided cessation	**Total population costs (€, thousands):** Varenicline (12 weeks) 15,485,564 Bupropion (12 weeks) 15,654,958 NRT (12 weeks) 15,711,867 Unaided cessation 15,883,032 **Total cost per person (€):** *CALCULATED BY YHEC* [c] Varenicline (12 weeks) 18,891	**Total population QALYs:** Varenicline (12 weeks) 11,610,664 Bupropion (12 weeks) 11,582,961 NRT (12 weeks) 11,582,803 Unaided cessation 11,541,803 **QALYs per person:** *CALCULATED BY YHEC* [c] Varenicline (12 weeks)	**Incremental cost per QALY:** Varenicline dominates all other interventions **Cost per additional quitter (€)** [b]**:** Varenicline vs. bupropion 2,659 Varenicline vs. NRT 1015 **Analysis of uncertainty:** Both probabilistic sensitivity analysis (PSA) and deterministic sensitivity analysis (DSA) were performed. For an implicit €30,000 threshold, varenicline was cost-effective for 82.3%, 86.6%, and 85.2% of the Monte-Carlo iterations versus bupropion, NRT, and unaided cessation respectively. DSA found utilities after smoking-

Study	Athanasakis 2012 (Greece)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
healthcare costs and QALYs associated with smoking related morbidities: COPD, CHD, lung cancer, stroke. Lifetime costs and QALYs are dependent on smoking status obtained from published literature reporting 12-month abstinence rates. Annual healthcare costs per smoking related morbidity are obtained from published literature and updated to 2011 prices. All utility weights are taken from previous published data sources. **Perspective:** Societal security (third-party payer) **Time horizon:** Lifetime **Treatment effect duration:** Lifetime health benefits **Discounting:** 3% cost discounted 3% effects discounted		Bupropion (12 weeks) 19,098 NRT (12 weeks) 19,167 Unaided cessation 19,376 **Intervention costs per person [a]:** Not reported **Annual healthcare costs (€):** COPD 2,579.50 Lung cancer 12,261 CHD (first year/subsequent years) 12,233/1,240 **Currency & cost year:** EUR (€); 2011	14.2 Bupropion (12 weeks) 14.1 NRT (12 weeks) 14.1 Unaided cessation 14.1	related events, the discount rate, costs of events, and effectiveness of varenicline to be of significant influence. Varenicline remained dominant in a shorter timeframe of 20 years.

Study	Athanasakis 2012 (Greece)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Data sources				
Health outcomes: 1-year quit rates from two head to head RCTs, pooled in analysis by Nides (2008) for varenicline and bupropion. 1-year quit rates for NRT taken from 2 meta-analyses of trials, and for unaided cessation taken from Foulds et al. **Quality-of-life weights:** Utility weights for health states are taken from various published data sources, baseline utilities from Fiscella and Franks. **Cost sources:** Medication cost were taken from the Greek National Formulary, the cost of a physician's visit was based on official social security tariff and healthcare costs are taken from recent economic evaluation in the Greek healthcare setting.				
Comments				
Source of funding: Pfizer Inc. **Limitations:** Author recognised: Wider societal perspective not taken into account, abstinence rates may differ from clinical trials and only one quit attempt per person allowed in model. **Other:** None.				
Overall applicability: Partly applicable **Overall quality: Minor limitations**				
Abbreviations: BENESCO: Benefit of smoking cessation on outcomes; CHD: Coronary heart disease; COPD: Chronic obstructive pulmonary disease; CUA: Cost utility analysis; DSA: Deterministic sensitivity analysis; ICER: Incremental cost-effectiveness ratio; NRT: Nicotine replacement therapy; PSA: Probabilistic sensitivity analysis; QALY: Quality adjusted life year				
(a) Intervention costs included 12 weeks of medication and the cost of a single physicians visit at the initiation of treatment. These figures were not reported.				
(b) Considering only the costs of the smoking-cessation strategy.				
(c) Assumed to be total population costs/QALYS divided by population size (819,709).				

Study	Coward 2014 (Canada)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: Cost-utility analysis (CUA) **Study design:** A Markov model estimating cost-effectiveness	**Population:** Smokers between the age of 18 and 35, who are newly diagnosed with Crohn's disease and are anti-TNF naïve. The population size is not reported.	**Total population costs:** Not reported **Total cost per person (CAD$) (95% CI):** Varenicline (12 weeks) 55,614 (52,755 – 58,474) NRT + counselling	**Total population QALYs:** Not reported **QALYs per person (95% CI):** Varenicline (12 weeks) 3.70 (3.68 – 3.73)	**Incremental cost-effectiveness ratio (ICER):** Varenicline dominated all other interventions **Cost savings (5 years) compared with no program (CAD$):** Varenicline (12 weeks) 16,116,169 NRT + counselling

Study	Coward 2014 (Canada)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Approach to analysis: The aim of the analysis is to assess the cost-effectiveness of smoking cessation for patients with Crohn's disease (CD). The primary outcome is the cost per QALY gained across a 5-year time horizon. The model calculates healthcare costs and QALYs associated with the following health state: medical remission, does escalation of an anti-TNF, second anti-TNF surgery and death. These health states relate to CD progression and smoking related morbidities, such as lung cancer, stroke etc., are not included in the model. Hence, the focus of the study is the impact of smoking on CD progression. **Perspective:** Publicly funded healthcare system **Time horizon:** 5 years	**Intervention:** Varenicline (12 weeks) **Comparator(s):** NRT [b] + counselling [c] NRT Counselling No program [d]	58,878 (56,050 – 61,706) NRT 59,540 (56,732 – 62,347) Counselling 61,029 (58,246 – 63,812) No program 63,601 (60,865 – 66,337) **Intervention costs per person (CAD$):** Varenicline (12 weeks) 293.33 NRT + counselling 458.58 NRT 267.78 Counselling 190.80 No program 0.00 **Currency & cost year:** CAD ($); 2013	NRT + counselling 3.69 (3.66 – 3.72) NRT 3.69 (3.66 – 3.71) Counselling 3.68 (3.65 – 3.71) No program 3.67 (3.64 – 3.69)	9,530,069 NRT 8,194,286 Counselling 5,189,782 **Analysis of uncertainty:** Probabilistic sensitivity analysis was conducted to account for variation is effectiveness of smoking cessation programs. Varenicline remained the most cost-effective strategy until its effectiveness was reduced below 17.7%. In addition, a 10% decrease in anti-TNF effectiveness among smokers and a 0.3 decrease in utilities for flares leading to surgery and the health state "surgery" were assessed.

Study	Coward 2014 (Canada)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Treatment effect duration: 5 years **Discounting:** 5% discount rate [a]				
Data sources				
Health outcomes: Effectiveness data was taken from published data sources. **Quality-of-life weights:** Utility estimates were derived from Gregor (1997). **Cost sources:** Drug costs relating to CD were taken from the Alberta Blue Cross Interactive Drug Benefit List. Drug costs relating to smoking cessation were taken from published data sources. Surgery cost were taken from studies but the studies were not referenced.				
Comments				
Source of funding: Alberta-Innovates Health-Solutions. **Limitations:** The design cannot adequately control for confounding nor variation between clinical practices. The model does not consider long-term effects on cardiovascular disease, chronic lung disease and cancer. There was no variation in utilities for smokers and non-smokers. **Other:** None.				
Overall applicability: Partly applicable **Overall quality: Major limitations**				
Abbreviations: CD: Crohn's disease; CI: Confidence interval; CUA: Cost utility analysis; NRT: Nicotine replacement therapy; QALY: Quality-adjusted life years				
(a) A 5% discount rate was applied but it is unclear whether this is applied to costs, effects or both.				
(b) The nicotine patch is used; however, the length of use is not specified.				
(c) Individual counselling once a week for six weeks led by a healthcare professional.				
(d) Recommendation to quit smoking without any direct counselling or prescription of smoking cessation medication.				

Study	Hagen 2010 (Norway)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: Cost-effectiveness analysis (CEA) **Study design:**	**Population:** Current smoker of the Norwegian population. The population size is not reported. **Intervention [a]:**	**Total population costs:** Not reported **Total cost per person (kr):** Varenicline 863,650	**Total population LYs:** Not reported **LYs per person:** Varenicline 14.74	**Incremental cost-effectiveness ratio (ICER) (kr):** Compared with no treatment Varenicline 69,086

Study	Hagen 2010 (Norway)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
A Markov model estimating cost-effectiveness **Approach to analysis:** The primary outcome is the ICER per LY across the lifetime of the cohort. The Markov model calculates lifetime healthcare costs and LYs. Lifetime costs and LYs are dependent on efficacy estimates that are taken from a systematic review of literature. Treatment cost and an annual healthcare cost are obtained from published literature. **Perspective:** Not reported **Time horizon:** Lifetime (100 years or dead) **Treatment effect duration:** Lifetime health benefits **Discounting:** 4% costs discounted	Varenicline **Comparators [a]:** Bupropion NRT No treatment	 Bupropion 859,706 NRT 858,118 No treatment 853,977 **Intervention costs per person (kr) [b]:** Varenicline (105 days) 2,456 Bupropion (56 days) 1,103 NRT (90 days) 3,150 **Annual healthcare cost (kr) [c]:** 45,544 Last year of life 73,306 **Currency & cost year:** NOK (kr); 2009	Bupropion 14.69 NRT 14.62 No treatment 14.60	Bupropion 63,656 NRT 207,050 **Net health benefit:** Varenicline 0.121 Bupropion 0.079 NRT 0.012 **Analysis of uncertainty:** Both one-way and probabilistic sensitivity analysis was conducted. Results are most sensitive to changes in age, the price of varenicline, average healthcare expenses per person per year and choice of discount rate. However, changes to these parameters will not bring the ICER above the willingness to pay per life year of NOK 500,000. Probabilistic sensitivity analysis showed varenicline was the optimal choice when willingness to pay per life year was above NOK 116,000.

Study	Hagen 2010 (Norway)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
4% life years discounted				
Data sources				
Health outcomes: Efficacy estimates were taken from a systematic review (no further details as this was in Norwegian). **Quality-of-life weights:** N/A. **Cost sources:** Cost data used from published data sources.				
Comments				
Source of funding: Norwegian Directorate of Health. **Limitations:** Methodology of underlying efficacy estimates is not provided nor is the length of treatment. **Other:** None.				
Overall applicability: Partly applicable **Overall quality: Minor limitations**				
Abbreviations: CEA: Cost-effectiveness analysis; LY: Life year; NRT: Nicotine replacement therapy; QALY: Quality-adjusted life years				
(a) The dosage and treatment length for the intervention and comparators is not specified in the study. Length of treatment is specified when calculating costs; however, it is unclear whether this is the same for effectiveness.				
(b) It is assumed patients treated with varenicline and bupropion will have one visit to a GP in order to get a prescription. NRT is available over-the-counter.				
(c) It is assumed that annual healthcare costs are the same for smokers and non-smokers, and that healthcare costs are constant across age. A higher healthcare cost is applied to the last year of life for all persons, a cost of dying.				

Study	Hettle, 2012 (Europe)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: Cost-utility analysis (CUA) **Study design:** Three Markov models (BENESCO) that report ICERS and are populated with data from Austria, Germany and Hungary **Approach to analysis:**	**Population:** Cohort of 1,000 smokers per country, all with stable CVD. Divided into 3 groups: patients with CHD, patients with a history of stroke, patients with PVD	**Total population costs (€):** Austria Varenicline 17,730,771 Placebo 16,970,528 Germany Varenicline 32,278,318 Placebo 31,423,185 Hungary Varenicline 6,110,250 Placebo 5,771,339	**Total population QALYs (millions):** Austria Varenicline 5,316 Placebo 5,172 Germany Varenicline 5,243 Placebo 5,098 Hungary Varenicline 4,511 Placebo 4,405	**Incremental cost-effectiveness ratio per QALY gained (varenicline versus placebo) (€):** Payers perspective: Austria 5,278 Germany 5,867 Hungary 3,183 Societal perspective:

Study	Hettle, 2012 (Europe)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
The primary outcome is the incremental cost effectiveness ratio per QALY across the lifetime of the cohort. Treatment costs are applied for the first 12 weeks. The three BENESCO models calculate lifetime healthcare costs and QALYs associated with numerous smoking-related diseases (chronic heart disease (CHD), lung cancer, mouth cancer, stroke, peripheral vascular disease (PVD), Chronic Obstructive Pulmonary Disease (COPD)). . Lifetime costs and QALYs depend on smoking status, established from 12-month abstinence rates from a single double-blind RCT. Annual healthcare costs per smoking-related diseases are obtained from published literature and inflated to 2010 prices **Perspective:**	**Intervention:** Varenicline [a] plus counselling (12 weeks) [b] **Comparator(s):** Placebo plus counselling (12 weeks) [b]	**Total costs per person (€):** *CALCULATED BY YHEC* [d]*:* Austria Varenicline 17,731 Placebo 16,971 Germany Varenicline 32,278 Placebo 31,423 Hungary Varenicline 6,110 Placebo 5,771 **Intervention cost of per person (€):** Austria Varenicline 17,730,771 Placebo 16,970,528 Germany Varenicline 32,278,318 Placebo 31,423,185 Hungary Varenicline 6,110,250 Placebo 5,771,339 **Currency & cost year:** EUR (€); 2010 **Healthcare costs first year (subsequent year) (€):** Austria Stroke 3,722 (1,101)	**QALYs per person:** *CALCULATED BY YHEC* [d] Austria Varenicline 5.32 Placebo 5.17 Germany Varenicline 5.24 Placebo 5.10 Hungary Varenicline 4.51 Placebo 4.41 **% abstinent at 12 months:** Varenicline 19.2% Placebo 7.2%	In all countries, varenicline plus counselling was cost saving with positive incremental QALYs so dominant over placebo plus counselling **Analysis of uncertainty:** The probabilistic sensitivity analysis found that, in all scenarios and countries, varenicline remained cost-effective under a threshold of €12,500 per QALY gained.

Study	Hettle, 2012 (Europe)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
Payers perspective and societal perspective **Time horizon:** Lifetime (65 years) **Treatment effect duration:** Lifetime **Discounting:** Costs 3% per year Benefits 3% per year		CHD 2,085 (1,166) PVD 2,245 Stroke and CHD comorbidity 3,722 (1,166) PVD and stroke/PVD and CHD 3,848 Lung cancer 2,209 Mouth cancer 1,818 COPD 1,858 Annual unit cost of lost productivity 17,394 Germany Stroke 20,465 (6,055) CHD 4,955 (2,782) PVD 2,832		

Study	Hettle, 2012 (Europe)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
		Stroke and CHD comorbidity 20,465 (6,055) PVD and stroke/PVD and CHD 4,854 Lung cancer 9,344 Mouth cancer 7,384 COPD 2,244 Annual unit cost of lost productivity 15,873 Hungary Stroke 1,532 (2,010) CHD 1,670 (593) PVD 922 Stroke and CHD comorbidity 1,670 (728) PVD and stroke/PVD and CHD 1,418 Lung cancer		

Study	Hettle, 2012 (Europe)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
		3,874 Mouth cancer 3,123 COPD 815 Annual unit cost of lost productivity 3,016		
Data sources				
Health outcomes: % Abstinence rates after 52 weeks [c] from double-blind placebo RCT **Quality-of-life weights:** Numerous published studies from both included countries and countries not included in the study. **Cost sources:** Numerous country dependent published sources used, generally from national data registries, national tariff schemes and published studies.				
Comments				
Source of funding: Pfizer Ltd. **Limitations:** Only one quit attempt and one additional acute CVD event were permitted in the model. Additionally, some of the country-specific data was lacking and various assumptions were applied to the model. **Other:** This study is similar to Wilson, 2012				
Overall applicability: Partly applicable **Overall quality: Minor limitations**				
Abbreviations: BENESCO: Benefits of smoking cessation on outcomes; CHD: Coronary heart disease; COPD: Chronic obstructive pulmonary disease; CUA: Cost-utility analysis; CVD: Cardio-vascular disease; ICER: Incremental cost-effectiveness ratio; NRT: Nicotine replacement therapy; PVD: Peripheral vascular disease; QALY: Quality-adjusted life year; RCT: Randomised controlled trial				
(a) Varenicline was dosed at 0.5mg once a day for 3 days, 0.5mg twice a day for 4 days followed by 1.0mg twice a day for total of 12 weeks *(b)* Counselling was 12 weekly clinic visits lasting a maximum of 10 minutes, plus a single telephone call 3 days after the quit date *(c)* Abstinence was verified by a measurement of expired air carbon monoxide of less than or equal to 10 parts per million from weeks 9-52. *(d)* Assumed to be total population costs/QALYS divided by total population (1000).				

Study	Huber, 2018 (Germany)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: Cost-utility analysis (CUA) **Study design:** A Markov-based state transition return on investment model (EQUIPTMOD) was used and inputted with data from Germany **Approach to analysis:** The primary outcome is the incremental cost effectiveness ratio per QALY. Treatment costs are applied for the first 12 weeks for varenicline. The Markov model informs a return on investment model, together calculating lifetime healthcare costs and QALYs associated with numerous smoking-related diseases. Lifetime costs and QALYs depend on smoking status, established from a	**Population:** Current smokers in Germany **Intervention:** Varenicline (12 weeks) [a] **Comparator(s):** Zero investment[b]	**Intervention cost of per person (€):** Varenicline 293 Zero investment - **Incremental costs per smoker (€):** Prospective scenario 1[e]: Zero investment - Varenicline -0.02 Prospective scenario 2[f]: Zero investment - Varenicline -0.25 **Total lifetime population costs:** NR **Currency & cost year:** EUR (€), 2015	**Incremental QALYs per smoker:** Prospective scenario 1: Zero investment - Varenicline 0.0002 Prospective scenario 2: Zero investment - Varenicline 0.0031 **Risk ratio versus usual care:** Varenicline 2.27 **Total lifetime population QALYs:** NR	**Lifetime incremental cost-effectiveness ratio per QALY gained (€):** Prospective scenario 1: Zero investment - Varenicline Dominant (-77.81) Prospective scenario 2: Zero investment - Varenicline Dominant (-77.80) **Analysis of uncertainty:** There was no sensitivity analysis around only varenicline.

Study	Huber, 2018 (Germany)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
previous study. Annual healthcare costs per smoking-related diseases are obtained from published literature and inflated to 2015 prices **Perspective:** German public perspective **Time horizon:** Lifetime **Treatment effect duration:** Lifetime **Discounting:** Costs 3% per year Benefits 3% per year				
Data sources				
Health outcomes: Taken from systematic review, studies with self-reported abstinence were excluded (only studies with biochemical testing were included) **Quality-of-life weights:** NR **Cost sources:** Varenicline treatment cost calculated from German pharmacy pricing. Smoking-related disease costs were not reported.				
Comments				

Study	Huber, 2018 (Germany)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Source of funding: The European Community's Seventh Framework Programme under grant agreement no. 602270 (EQUIPT) **Limitations:** Author recognised: The model does not include possible costs or effects of adverse events of varenicline and not all smoking-related diseases are included. **Other:** None				
Overall applicability: Partly applicable **Overall quality: Major limitations**				
Abbreviations: CUA: Cost-utility analysis; CVD: Cardio-vascular disease; EQUIPTMOD: European study on quantifying utility of investment in protection from tobacco model; QALY: Quality-adjusted life-year;				
(a) Dosage not reported. Treatment began with starter kit before moving to maintenance. *(b)* Zero investment is 'do nothing', meaning no interventions are implemented *(c)* In prospective scenario 1, varenicline uptake was increased by 1% causing 57,915 more quit attempts (ie a population of 57,915 analysed). *(d)* In prospective scenario 2, varenicline uptake was increased to UK levels (by 14.49%) causing 839,188 more quit attempts (ie a population of ~800.000 analysed).				

Study	Kautianen 2017 (Finland)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: Cost-utility analysis (CUA) **Study design:** A two-quit BENESCO (Markov) model estimating cost-effectiveness **Approach to analysis:** The analysis considers smokers who make their 1st quit attempt (1QA) in	**Population:** 116,533 current smoker willing to make a quit attempt **Intervention** [a]**:** 2QA varenicline: 1QA with varenicline followed by varenicline re-treatment in case of failure or relapse **Comparators** [a]**:**	**Total population costs (€, millions):** 2QA varenicline 2,605 2QA bupropion 2,645 2QA NRT 2,618 2QA unaided 6,660	**Total population QALYs:** 2QA varenicline 1,835,400 2QA bupropion 1,831,805 2QA NRT 1,831,175 2QA unaided 1,823,452	**Incremental cost per QALY:** 2QA varenicline dominates all other interventions **Analysis of uncertainty:** Both one-way univariate analyses and probabilistic sensitivity analysis were performed. Univariate sensitivity analyses found discount rates, cost of NRT and relative risks of smoking related diseases in long term quitters were the most influential parameters. However, changes to these parameters did not affect the conclusions. Probabilistic sensitivity analysis indicated that the conclusions are robust.

Study	Kautianen 2017 (Finland)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
year 1 followed by a 2nd quit attempt (2QA) in a subsequent year due to failure or relapse. The two-quit BENESCO model calculates lifetime healthcare costs and QALYs associated with smoking related morbidities: asthma exacerbation, COPD, CHD, lung cancer, stroke. Lifetime costs and QALYs are dependent on smoking status obtained from published literature reporting first line 12-month abstinence rates and second line 12-month abstinence rates. Annual healthcare costs per smoking related morbidity are obtained from published literature. Utilities associated with smoking-related diseases are obtained from published literature. **Perspective:** Healthcare payer **Time horizon:**	2QA NRT: 1QA with NRT followed by NRT re-treatment in case of failure or relapse 2QA bupropion: 1QA with bupropion followed by bupropion re-treatment in case of failure or relapse 2QA unaided: 1QA unaided followed by a subsequent unaided attempt in the case of failure or relapse 1QA varenicline: 1QA with varenicline followed by 1QA with placebo	1QA varenicline 2,633 **Total cost per person (€):** *CALUCLATED BY YHEC* [b] 2QA varenicline 22,354 2QA bupropion 22,687 2QA NRT 22,466 2QA unaided 57,151 1QA varenicline 22,594 **Intervention costs per person (12 weeks) (€):** Varenicline [c] 379.04 Bupropion [c] 369.29 NRT 209.32 Unaided 0.00	1QA varenicline 1,829,742 **QALYS per person:** *CALUCLATED BY YHEC* [b] 2QA varenicline 15.8 2QA bupropion 15.7 2QA NRT 15.7 2QA unaided 15.6 1QA varenicline 15.7	Compared with 2QA NR, 2QA varenicline is 99.9% cost-effective at a willingness to pay threshold of 5,000€ per QALY.

Study	Kautianen 2017 (Finland)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Lifetime (100 years or dead) **Treatment effect duration:** Lifetime health benefits **Discounting:** 3% cost discounted 3% effects discounted		**Healthcare costs 1st year (subsequent years) (€):** Stroke 21,303 (14,429) CHD 11,657 (3,668) Asthma exacerbation 2,044 COPD 1,423 (1,423) Lung cancer 13,473 (1,824) **Currency & cost year:** EUR (€); 2013/2014		
Data sources				
Health outcomes: First line treatment efficacies were derived from the Cochrane systematic review (Cahill et al., 2013). Second line treatment efficacy for varenicline was from a RCT. Second line treatment efficacies for NRT and bupropion conservatively used the same value as first line treatment due to lack of evidence. **Quality-of-life weights:** Utility weights for health states are from published data sources. **Cost sources:** Unit costs were taken from Kapianen at al., Finnish version of NordDRGs and pharmaceuticals pricing board (PPB)				
Comments				
Source of funding: Pfizer Inc. **Limitations:** The model does not consider adverse events associated with the interventions. In addition, the model limits to only 5 smoking-related diseases and all risk ratios are kept constant for each smoking status for simplicity. **Other:** None.				
Overall applicability: Partly applicable **Overall quality: Minor limitations**				
Abbreviations: BENESCO: Benefits of smoking cessation on outcomes; CHD: Coronary heart disease; COPD: Chronic obstructive pulmonary disease; CUA: Cost utility analysis; ICER: Incremental cost-effectiveness ratio; LY: Life years NRT: Nicotine replacement therapy; QA: Quit attempt; QALY: Quality-adjusted life year; RCT: Randomised control trail				
(a) The length of treatment is not specified within the study. A 12-week treatment length is assumed in line with the cost per intervention.				
(b) Assumed to be total population costs/QALYS divided by total population (116,533).				

Study	Kautianen 2017 (Finland)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
(c) Intervention cost includes 1 GP visit				

Study	Knight 2012 (Belgium)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
Economic analysis: Cost-utility analysis (CUA) **Study design:** A BENESCO (Markov) model estimating cost-effectiveness **Approach to analysis:** The primary outcome is the ICER per QALY across the lifetime of the cohort. Treatment costs are applied for the first 24 weeks. The BENESCO model calculates lifetime healthcare costs and QALYs associated with smoking related morbidities: COPD, CHD, lung cancer, stroke. Lifetime costs and QALYs are dependent on smoking status obtained from published literature reporting 12-month	**Population:** 168,239 current smoking willing to quit with pharmacological agent **Intervention:** Varenicline (12+12 weeks) plus brief counselling [a] **Comparators:** Varenicline (12 weeks) plus brief counselling Bupropion (12 weeks) plus brief counselling Brief counselling alone	**Total population costs (€, millions):** Varenicline (12+12 weeks) plus brief counselling 1,946 Varenicline (12 weeks) plus brief counselling 1,941 Bupropion (12 weeks) plus brief counselling 1,957 Brief counselling alone 1,973 **Total cost per person (€):** *CALCULATED BY YHEC* [b] Varenicline (12+12 weeks) plus brief counselling 11,566 Varenicline (12 weeks) plus brief counselling 11,537 Bupropion (12 weeks) plus brief counselling	**Total population QALYs (millions):** Varenicline (12+12 weeks) plus brief counselling 3.102 Varenicline (12 weeks) plus brief counselling 3.097 Bupropion (12 weeks) plus brief counselling 3.089 Brief counselling alone 3.081 **QALYS per person:** *CALCULATED BY YHEC* [b] Varenicline (12+12 weeks) plus brief counselling 3.102 18.43 Varenicline (12 weeks) plus brief counselling 18.41	**Incremental cost per QALY:** **(€):** Varenicline (12 weeks) plus brief counselling vs. varenicline (12+12 weeks) plus brief counselling 1,101 per QAYL gained All other interventions were dominated **Analysis of uncertainty:** Probabilistic sensitivity analysis was used to investigate the stability of the ICER when comparing the extended and non-extended course of varenicline. The extended course had an ICER below 30,000 € per QALYS 81.7% of the time. 30.9% of the time the extended course dominated the non-extended course.

Study	Knight 2012 (Belgium)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
abstinence rates. Annual healthcare costs per smoking related morbidity are obtained from published literature and updated to 2011 prices. All utility weights are retained from existing publication where the BENESCO model was applied in a different population (USA). **Perspective:** Public health care **Time horizon:** Lifetime **Treatment effect duration:** Lifetime health benefits **Discounting:** 3% cost discounted 1.5% effects discounted		11,632 Brief counselling alone 11,727 **Intervention costs per person (€) [c]:** Varenicline (12+12 weeks) plus brief counselling 547.52 Varenicline (12 weeks) plus brief counselling 382.14 Bupropion (12 weeks) plus brief counselling 288.23 Brief counselling alone 205.08 **Healthcare costs (€, thousands):** Varenicline (12+12 weeks) plus brief counselling COPD: 531,045 Lung cancer: 165,923 CHD: 632,087 Stroke: 525,773	Bupropion (12 weeks) plus brief counselling 18.36 Brief counselling alone 18.31 **% abstinent at 12 months:** Varenicline (12+12 weeks) plus brief counselling 27.7% Varenicline (12 weeks) plus brief counselling 22.9% Bupropion (12 weeks) plus brief counselling 15.9% Brief counselling alone 9.3%	

Study	Knight 2012 (Belgium)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
		Varenicline (12 weeks) plus brief counselling COPD: 542,197 Lung cancer: 168,851 CHD: 636,576 Stroke: 529,035 Bupropion (12 weeks) plus brief counselling COPD: 558,461 Lung cancer: 173,121 CHD: 643,123 Stroke: 533,792 Brief counselling alone COPD: 573,795 Lung cancer: 177,147 CHD: 649,296 Stroke: 538,277 **Currency & cost year:** EUR (€); 2011		
Data sources				
Health outcomes: 1-year quit rates reported in Knight et al. (2012). **Quality-of-life weights:** Utility weights for health states are as published in Annemans et al. (2009). **Cost sources:** Publicly available costs from the national institute for health insurance (RIZIV/INAMI), published hospital costs for the appropriate				

Study	Knight 2012 (Belgium)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
All Patient Refined Diagnosis Related Group and two published studies; Annemans et al. (2009) and Muls et al. (1998). Costs were inflated to 2011 price were necessary.				
Comments				
Source of funding: Pfizer NV/SA. **Limitations:** Subjects in the (12+12 weeks) intervention group received an additional five brief counselling GP visits if they remained abstinent after the initial 12 weeks of treatment. Additionally, the model does not account for repeated quit attempts or include a wider societal perspective. **Other:** None.				
Overall applicability: Partly applicable **Overall quality: Minor limitations**				
Abbreviations: BENESCO: Benefits of smoking cessation on outcomes; CHD: Coronary heart disease; COPD: Chronic obstructive pulmonary disease; CUA: Cost-utility analysis; ICER: Incremental cost-effectiveness ratio; INAMI: Institut National D'assurance Maladie-Invalidité; QALY: Quality-adjusted life year; RIZM: Rijksinstituut voor Ziekte- en Invaliditeitsverzekering;				
(a) Brief counselling consists of 12 GP visits within the first 12 weeks. Subjects in the (12+12 weeks) intervention group received an additional five GP visits in the following 12-week period.				
(b) Assumed to be total population costs/QALYS divided by total population (168,239).				
(c) Starter pack was at quitters own expense for both varenicline and bupropion. Treatment following the starter pack were included plus GP visits.				

Study	Li 2019 (UK)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Li 2019 (UK) **Economic analysis:** Cost-effectiveness analysis (CEA) **Study design:**	**Population:** 886 adult smokers who sought help to quit at Stop-Smoking Services. A hypothetical cohort size of 1000 was used for the lifetime model. **Intervention:**	**Total population costs:** Not reported **Total cost per participant (SE) (£):** **12-Month** EC 1174 (147)	**Total population QALYs:** Nor reported **QALYS per participant (SE):** **12-Month** EC	**Estimated ICER (£) [d]:** EC compared with NRT **12-Month** 1,100 per QALY gained **Lifetime** 65 per QALY gained

Study	Li 2019 (UK)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
A Markov model to estimate cost-effectiveness alongside a randomised control trial (RCT) **Approach to analysis:** Cost-effectiveness was measured by an incremental cost-effectiveness ratio (ICER). 12-month analysis estimates for costs and utilities came from the RCT. The EuroQol 5 dimensions and 3 levels (EQ-5D-3L) questionnaire was administered at baseline, 3- and 12-month follow-up. Life-time analysis uses a Markov model with input from the RCT and published data sources. QALYs depend on smoking status establish from the RCT. **Perspective:**	E-cigarette (EC) + behavioural support [a] **Comparator:** Nicotine replacement therapy (NRT) + behavioural support [a]	NRT 1116 (163) **Lifetime** EC 3184 (169) NRT 3175 (161) **Treatment costs (SE) (£):** **12-Month** EC 105 (1) NRT 201 (4)	0.886 (0.008) NRT 0.882 (0.009) **Lifetime** EC 24.14 (0.31) NRT 24.28 (0.31) **% abstinent at 12 months [c,d]:** EC 18.0 NRT 9.9	**Analysis of uncertainty:** Cost-effectiveness acceptability curves estimated the probability of EC being cost-effective in comparison with NRT to be: **12-month** 87% at £20,00/QALY and 90% at £30,00/QALY **Lifetime** 85% at both 20,000/QALY and 30,000/QALY thresholds.

Study	Li 2019 (UK)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
NHS and PSS perspective **Time horizon:** 12-month and lifetime **Treatment effect duration:** 12-month and lifetime health benefits **Discounting:** 3.5% cost discounted 3.5% effects discounted		**Smoking cessation costs (SE) (£) [b]:** **12-Month** EC 48 (11) NRT 77 (13) **Health-care costs (SE) (£) [b]:** **12-Month** EC 1022 (147) NRT 839 (162) **Currency & cost year:** GBP (£); 2015/16		

Study	Li 2019 (UK)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Data sources				
Health outcomes: 1-year quit rates were used directly from RCT. **Quality-of-life weights**: EQ-5D utility values were based on a study of Health Survey for England data, with a sample size of 13,241. **Cost sources**: Costs were source from the NHS, NICE, PSSRU and government publications.				
Comments				
Source of funding: National Institute for Health Research and a grant from the Cancer Research UK Prevention Trials Unit. **Limitations:** The lifetime model did not take into consideration the possible long-term effects of using EC on health and personal finance due to lack of evidence. The RCT had a 35% missing data level which make cost-effectiveness less certain. The 6-month recall period for self-reported health-care services use could potentially cause recall bias. QALYs were derived based on smoking status, and were not disease specific. **Other:** None.				
Overall applicability: Directly applicable **Overall quality: Minor limitations**				
Abbreviations: EC: E-cigarette; EQ-5D-3L: EuroQol 5 dimensions and 3 levels; ICER: Incremental cost-effectiveness ratio; NRT: Nicotine replacement therapy; QALY: Quality-adjusted life year; RCT: Randomised control trial; SE: Standard error				
(a) All participants were offered six weekly behavioural support sessions at their Personal Social Services (SSS) as per standard practice, with the second session on the target quit date.				
(b) Smoking cessation help costs and health-care costs are self-reported service utilization and quantities at baseline, 6- and 12- month follow-up. These costs are not reported for a lifetime horizon.				
(c) Carbon monoxide (CO)-validated.				
(d) 1-year quit rates were applied to the first cycle of the lifetime model. An annual relapse rate of 10% was applied for the following 10 years and abstinence was subsequently assumed to be permanent.				
(e) Incremental costs and incremental QALYs were estimated using regression adjusting for baseline covariates and their respective baseline values. A generalized linear regression model controlled for utility value at baseline, age, gender, study site, entitlement of free prescriptions and FTCD at baseline.				

Study	Linden, 2010 (Finland)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: Cost-utility analysis	**Population:**	**Total population costs (€):** Varenicline	**Total population QALYs:**	**Incremental cost-effectiveness ratio per QALY gained (€):**

Study	Linden, 2010 (Finland)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
(CUA) **Study design:** A BENESCO (Markov) model that reports ICERS and is populated with data from Finland **Approach to analysis:** The primary outcome is the incremental cost effectiveness ratio per QALY across the lifetime of the cohort. Treatment costs are applied for the first 12 weeks for varenicline, 7 weeks for bupropion and there were no treatment costs for unaided cessation. The Markov model (BENESCO) calculates lifetime healthcare costs and QALYs associated with numerous smoking-related diseases. Lifetime costs and QALYs depend on smoking status, established from 12-month abstinence rates from two head to head RCTs of identical study design and a number of other studies. Annual	Current Finnish smokers making a single quit attempt (229,301) **Intervention:** Varenicline (12 weeks) plus single physician visit [a,b] **Comparator(s):** Bupropion (7 weeks) plus single physician visit [a,b] Unaided cessation	5,170,773,916 Bupropion 5,185,427,331 Unaided cessation 5,213,398,246 **Total cost per person (€):** *CALCULATED BY YHEC* [d] Varenicline 22,550 Bupropion 22,614 Unaided cessation 22,736 **Intervention cost of per person (€):** Varenicline 386.47 Bupropion 229.92 Unaided cessation - **Healthcare costs (€):** COPD (first year/subsequent year) 1,513/1,513	Varenicline 4,161,579 Bupropion 4,156,728 Unaided cessation 4,149,094 **Total QALYs per person:** *CALCULATED BY YHEC* [d] Varenicline 18.15 Bupropion 18.13 Unaided cessation 18.09 **% abstinent at 12 months:** Varenicline 22.5% Bupropion 15.7% Unaided cessation 5%	Varenicline dominates both bupropion and unaided cessation (lower total costs and higher total QALYs) **Analysis of uncertainty:** The 20-year time-horizon found ICER per QALYs of €8,791 and €7,791 for varenicline versus bupropion and unaided cessation respectively. The deterministic sensitivity analysis found that even with major changes of the input values, varenicline remained dominant below the ICER threshold of £30,000 (€33,200) over a lifetime horizon. The probabilistic sensitivity analysis found that, when the willingness-to-pay threshold was €10,000, varenicline was cost-effective compared with bupropion (unaided cessation) 65% (80%) of the time.

Study	Linden, 2010 (Finland)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
healthcare costs per smoking-related diseases are obtained from published literature and inflated to 2006 prices **Perspective:** Finnish societal perspective **Time horizon:** 20 years and lifetime **Treatment effect duration:** Lifetime **Discounting:** Costs 5% per year Benefits 5% per year		Lung cancer (first year/subsequent year) 14,348/642 CHD (first year/subsequent year) 10,343/11,828 Stroke (first year/subsequent year) 15,737/18,769 Severe asthma exacerbation 213 **Currency & cost year:** EUR (€); 2006 (apart from healthcare sub-index of Finnish cost-of-living index, 2007)		
Data sources				
Health outcomes: % Abstinence rates after 52 weeks from two varenicline versus bupropion head to head RCTs of identical study design [c] and also two other studies focussing on unaided cessation **Quality-of-life weights:** For smoking-related morbidities, these were derived from the Finnish general population using 15D weights. For general population and morbidities, these were estimated from the national representative Health 2000 Health Examination Survey database. **Cost sources:** Pharmacotherapy costs taken from SLD Price and Reimbursement Database on Human Prescription and Self-care Medicines. The treatment costs for COPD, lung cancer and asthma exacerbations were estimated from Finnish studies and costed with published Finnish unit costs. The treatment costs for CHD and stroke were derived from cost information from the Helsinki-Uusimaa hospital district.				
Comments				
Source of funding: Pfizer Oy, Finland. **Limitations:** Author recognised: Only one quit attempt per person allowed, only five smoking-related diseases included and persons not allowed to move between health states more than once a year. **Other:** None				
Overall applicability: Partly applicable **Overall quality: Minor limitations**				
Abbreviations: BENESCO: Benefits of smoking cessation on outcomes; CHD: Coronary heart disease; COPD: Chronic obstructive pulmonary disease; CUA: Cost-utility analysis; ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life-year; RCT: Randomised controlled trial				
(a) Dosage was not reported for either varenicline or bupropion.				

Study	Linden, 2010 (Finland)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
(b) Patients had a single physician visit at the initiation of treatment. *(c)* Abstinence determined by carbon monoxide test in weeks 9 to 52 for varenicline and bupropion, not reported for unaided cessation. *(d)* Assumed to be total population costs/QALYS divided by total population (229,301).				

Study	Lock, 2011 (UK)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
Economic analysis: Cost-utility analysis (CUA) **Study design:** A Markov model that reports ICERS and is populated with data from the UK **Approach to analysis:** The primary outcome is the incremental cost effectiveness ratio per QALY across the lifetime of the cohort. Treatment costs are applied for the first 12 weeks. The Markov model calculates lifetime healthcare costs and QALYs associated with numerous smoking-related diseases. Lifetime costs and QALYs depend on smoking status, established from 12-	**Population:** Current cigarette smokers with COPD **Intervention:** Varenicline (12 weeks) plus booklet and counselling [a,b] **Comparator(s):** Placebo (12 weeks) plus booklet and counselling	**Total population costs:** Not reported **Total cost per person (€):** Varenicline 14,978 Placebo 14,238 **Intervention cost of per person (€):** Varenicline 914 Placebo 723 **Healthcare costs (€):** Annual maintenance costs: Mild COPD 328 Moderate COPD 571 Severe COPD 1,339 Very severe COPD 4,391 Lung cancer and COPD 7,141 Death -	**Total population QALYs:** Not reported **QALYs per person:** Varenicline 5.78 Placebo 5.62 **% abstinent at 12 months:** Varenicline 18.6% Placebo 5.6%	**Incremental cost-effectiveness ratio per QALY gained (€):** Varenicline versus placebo 4,478 **Analysis of uncertainty:** There was limited sensitivity analysis around the UK model. At an implicit threshold of €30,000 per QALY gained, varenicline has a high probability of being cost-effective when compared with placebo.

Study	Lock, 2011 (UK)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
month abstinence rates from a double-blind placebo RCT. Annual healthcare costs per smoking-related diseases are obtained from published literature and inflated to 2010 prices **Perspective:** UK NHS **Time horizon:** 28 years, with mean starting age of 57 **Treatment effect duration:** Lifetime **Discounting:** Costs 3% per year Benefits 3% per year		Event specific costs: Non-severe exacerbation 452 Severe exacerbation 3,328 **Currency & cost year:** EUR (€); 2010		
Data sources				
Health outcomes: % Abstinence rates after 52 weeks from a 27-centre double-blind placebo RCT [c] **Quality-of-life weights:** Estimated according to the UK EQ-5D tariff, taken from previous model of natural history and economic impact of COPD (Borg et al, 2004) **Cost sources:** Numerous cost sources used, prices inflated to 2010 levels and GDP converted to EUR at 2010 exchange rates when necessary. 'Whenever possible, state-specific costs are derived from peer-reviewed publications containing country-specific sources'.				
Comments				
Source of funding: Pfizer Ltd. **Limitations:** Author recognised: Wider societal costs and costs to patients and care givers were not considered. Additionally, only one quit attempt was permitted and the model did not allow the reflection of the increasing rate of progression of COPD with age. **Other:** None				
Overall applicability: Partly applicable **Overall quality: Minor limitations**				
Abbreviations: BENESCO: Benefits of smoking cessation on outcomes; COPD: Chronic obstructive pulmonary disease; CUA: Cost-utility analysis; CVD: Cardio-vascular disease; ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life-year; RCT: Randomised controlled trial				

Study	Lock, 2011 (UK)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
(a) Dosage was 1 mg by mouth twice daily for 12 weeks, though first week was 0.5mg once daily for 3 days, 0.5mg twice daily for 4 days *(b)* Persons were given an educational booklet on smoking cessation and brief (≤10 mins) counselling sessions at a weekly clinic visit (12 total). Further clinic visits and telephone calls were made during the 40-week follow-up period *(c)* Abstinence determined by an end-expiratory exhaled CO measurement of less than or equal to 10 ppm from week 9 through to week 24, and week 52				

Study	von Wartburg, 2014 (Canada)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
Economic analysis: Cost utility analysis (CUA) **Study design:** Markov model (BENESCO model) based on efficacy data from randomised controlled trials (RCTs) **Approach to analysis:** Efficacy was based on a mixed-treatment comparison of three RCTs and a fourth study. One RCT estimated the efficacy of 12 weeks of maintenance therapy with varenicline or placebo using a double-blind approach. Costs of events and utility values associated to health states were taken from the literature.	**Population:** The initial population included all Canadian smokers who are assumed to make a quit attempt (25% of smokers = 1,275,481). **Intervention [a]:** 12 weeks of varenicline for smoking cessation plus 12 weeks of varenicline maintenance for quitters **Comparators [b]:** Varenicline for smoking cessation plus additional 12 weeks of placebo for quitters Bupropion for smoking cessation	**Total population costs (CAD$, millions) – Payer perspective:** Varenicline (12 weeks) 25,369 Varenicline (12+12 weeks) 25,426 Bupropion 25,510 NRT 25,705 Unaided cessation 25,746 **Total population costs (CAD$, millions) – Societal perspective:** Varenicline (12 weeks): 98,739 Varenicline (12+12 weeks) 98,902	**Total population QALYs (thousands):** Varenicline (12 weeks) 15,398 Varenicline (12+12 weeks) 15,413 Bupropion 15,376 NRT 15,374 Unaided cessation 15,342 **% abstinent at 12 months [d]:** Varenicline (12+12 weeks) 27.7% Varenicline (12 weeks) 22.9%	**Incremental cost-effectiveness ratio per QALY gained (direct costs only, CAD$) [e]:** Varenicline (12+12 weeks) versus varenicline (12 weeks) 3758 All other comparators dominated **Incremental cost-effectiveness ratio per QALY gained (direct and indirect costs, CAD$):** Varenicline (12+12 weeks) dominates all other comparators **Analysis of uncertainty** Probabilistic sensitivity analysis (PSA) showed that varenicline (12+12 weeks) had a 95% probability of being cost-effective at a willingness to pay threshold of CAD$30,000 per QALY compared with varenicline (12 weeks) and 100% compared with the other interventions (from the payer perspective).

Study	von Wartburg, 2014 (Canada)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Perspective: Both third-party payer and societal **Time horizon:** Lifetime **Treatment effect duration:** 1-year quit rates estimated from RCTs and lifetime benefits estimated with a Markov model **Discounting:** 5% for costs 5% for benefits	Nicotine replacement therapy (NRT) for smoking cessation Unaided cessation: no further description was provided	Bupropion 99,902 NRT 100,177 Unaided cessation: 101,730 **Currency & cost year:** CAD ($); 2009	Bupropion 15.9% NRT 15.4% Unaided cessation 5%	
Data sources				
Health outcomes: 1-year quit rates were derived from a mixed treatment comparison of 3 RCTs (Knight 2010) and for NRT were taken from a meta-analysis by Silagy, 2004. **Quality-of-life weights:** These were taken from published literature but no further details were given. **Cost sources:** Costs associated with smoking-related morbidities were taken from published literature but were not described. Costs of interventions were taken from Pharmastat, Public Claim Data for Québec				
Comments				
Source of funding: Financial support from Pfizer Canada, Inc. **Limitations:** Author-recognised limitations: Main limitations of the analysis were related to the BENESCO model. Also, subgroup analyses were not conducted and might have been relevant given the different impact on long-term benefits according to a person's age at time of quitting. **Other:** None				
Overall applicability: Partly applicable **Overall quality:** Minor limitations				
Abbreviations: CUA: Cost-utility analysis; NRT: Nicotine replacement therapy; PSA: Probabilistic sensitivity analysis; RCT: Randomised controlled trial; QALYs: Quality-adjusted life-years				
a) All Varenicline doses were 1mg twice daily. b) All interventions for smoking cessation were given for 12 weeks, doses not provided, NRT comprised of chewing gum, transdermal patches, nasal spray, inhalers and tablets. Studies of the additional comparators (bupropion, NRT and unaided cessation) are based on a population of smokers that are attempting to quit and not on quitters.				

Study	von Wartburg, 2014 (Canada)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness

c) This includes: tobacco consumption, which is composed of foregone tobacco sales (cigarette manufacturers) and foregone tobacco tax revenues (governments), future increases in healthcare costs resulting from increased survival proxied by the average value of healthcare consumption, cost savings from reduced second-hand smokers and smoke related fires, and productivity benefits from improved health and reduced absenteeism.

d) 1-year quit rates for Varenicline (12 + 12 weeks), Varenicline (12 weeks) and Bupropion were derived from a mixed treatment comparison of 3 RCTs which established abstinence through self-reported non-smoking and exhaled CO readings < 10 parts per million; the 1-year quit rates for NRT was obtained from a meta-analysis which confirmed abstinence through a combination of self-reported non-smoking and CO readings.

e) Cost-effectiveness driven by efficacy rates which result in a higher ratio of non-smoker to smokers and fewer smoking related comorbidities/deaths.

Study	Wilson, 2012 (Europe)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
Economic analysis: Cost-utility analysis (CUA) **Study design:** Four BENESCO (Markov) models that report ICERS and are populated with data from Belgium, Spain, Portugal and Italy **Approach to analysis:** The primary outcome is the incremental cost effectiveness ratio per QALY across the lifetime of the cohort. Treatment costs are applied for the first 12 weeks. The BENESCO model calculates lifetime healthcare costs and	**Population:** Cohort of 1,000 smokers per country, all with stable CVD. Divided into 3 groups: patients with CHD, patients with a history of stroke, patients with PVD **Intervention:** Varenicline [a] plus counselling (12 weeks) [b] **Comparator(s):** Placebo plus counselling (12 weeks) [b]	**Total population costs (€):** Belgium Varenicline 34,812,609 Placebo 33,828,993 Spain Varenicline 25,984,405 Placebo 25,239,643 Portugal Varenicline 28,201,146 Placebo 27,451,663 Italy Varenicline 26,581,362 Placebo 25,706,868 **Total costs per person (€):** *CALCULATED BY YHEC* [d] Belgium Varenicline 34,813 Placebo 33,829	**Total population QALYs (millions):** Belgium Varenicline 5,311 Placebo 5,150 Spain Varenicline 5,154 Placebo 5,010 Portugal Varenicline 5,231 Placebo 5,091 Italy Varenicline 5,296 Placebo 5,135 **QALYs per person:** *CALCULATED BY YHEC* [d]:	**Incremental cost-effectiveness ratio per QALY gained (varenicline versus placebo) (€):** Payers perspective: Belgium 6,120 Spain 5,151 Portugal 5,357 Italy 5,433 Societal perspective: In all countries, varenicline was dominant, becoming cost-saving and having positive incremental QALYs versus placebo **Analysis of uncertainty:** The one-way sensitivity analysis determined that assumptions on cost parameters did not exhibit a strong influence on outcomes. It also found time horizon had no significant influence. The probabilistic sensitivity analysis found that all

Study	Wilson, 2012 (Europe)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
QALYs associated with numerous smoking-related diseases (chronic heart disease (CHD), lung cancer, mouth cancer, stroke, peripheral vascular disease (PVD), Chronic Obstructive Pulmonary Disease (COPD)). Lifetime costs and QALYs depend on smoking status, established from 12-month abstinence rates from a single double-blind RCT. Annual healthcare costs per smoking-related diseases are obtained from published literature and inflated to 2010 prices **Perspective:** Payer perspective **Time horizon:** Lifetime (65 years) **Treatment effect duration:** Lifetime (65 years) **Discounting:**		Spain Varenicline 25,984 Placebo 25,240 Portugal Varenicline 28,201 Placebo 27,452 Italy Varenicline 26,581 Placebo 25,707 **Intervention cost of per person (€):** Belgium Varenicline 519 Placebo 272 Spain Varenicline 682 Placebo 321 Portugal Varenicline 665 Placebo 372 Italy Varenicline 575 Placebo 225 **Currency & cost year:** €, 2010 **Healthcare costs first year (subsequent year) (€):** Belgium	Belgium Varenicline 5.31 Placebo 5.15 Spain Varenicline 5.15 Placebo 5.01 Portugal Varenicline 5.23 Placebo 5.09 Italy Varenicline 5.30 Placebo 5.14 **% abstinent at 12 months:** Varenicline 19.2% Placebo 7.2%	countries had an ICER between willingness to pay thresholds of €4,000 and €10,000 per QALY gained.

Study	Wilson, 2012 (Europe)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
Costs 3% per year Benefits 3% per year		Stroke 15,580 (4,111) CHD/Stroke and CHD comorbidity 7,535 (1,895) PVD 4,098 PVD and stroke/PVD and CHD 7,024 Lung cancer 14,619 Mouth cancer 4,897 COPD 2,034 Annual unit cost of lost productivity 13,831 Spain Stroke 6,930 (4,974) CHD 11,692 (1,012) PVD 2,860 Stroke and CHD comorbidity		

Study	Wilson, 2012 (Europe)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
		11,692 (4,974) PVD and stroke/PVD and CHD 4,902 Lung cancer 16,971 Mouth cancer 4,349 COPD 2,880 Annual unit cost of lost productivity 10,585 Portugal Stroke 9,243 (899) CHD/Stroke and CHD comorbidity 19,504 (2,384) PVD 2,986 PVD and stroke/PVD and CHD 5,118 Lung cancer 10,959 Mouth cancer 2,003		

Study	Wilson, 2012 (Europe)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
		COPD 1,609 Annual unit cost of lost productivity 8,314 Italy Stroke 11,643 (4,398) CHD/Stroke and CHD comorbidity 13,313 (2,641) PVD 2,066 PVD and stroke/PVD and CHD 3,541 Lung cancer 16,971 Mouth cancer 3,092 COPD 5,347 Annual unit cost of lost productivity 11,750		
Data sources				
Health outcomes: % Abstinence rates after 52 weeks [c] from a single double-blind placebo RCT. **Quality-of-life weights:** Numerous country dependent published sources used, generally published studies. **Cost sources:** Numerous country dependent published sources used, generally published studies.				

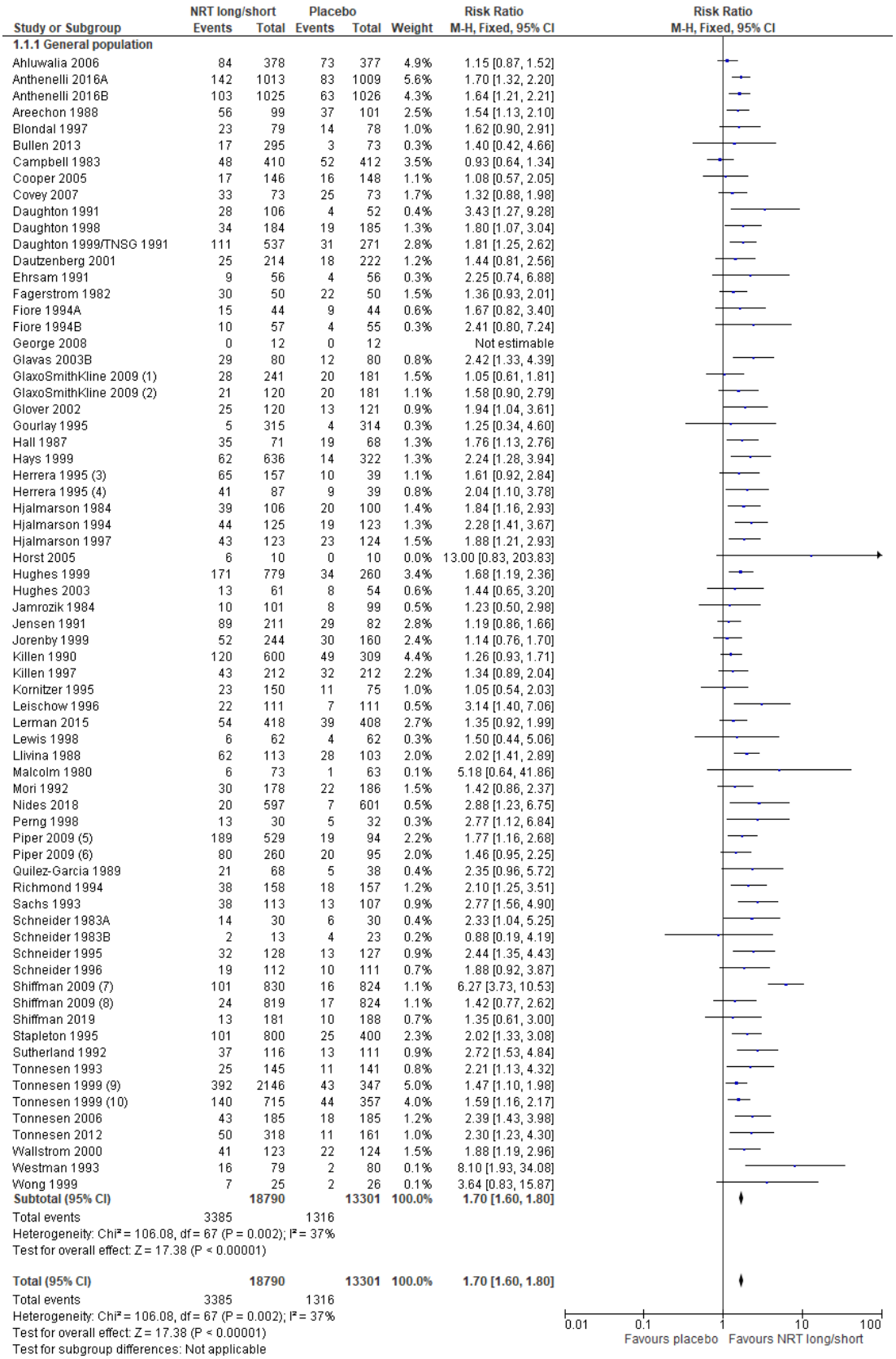
Study	Wilson, 2012 (Europe)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
Comments				
Source of funding: Pfizer Ltd. **Limitations:** Author recognised: Quit attempts and secondary non-fatal acute events limited to one per person. Risk estimates came from the UK and were adapted for smoking status based on outcomes of a US observational study. There was uncertainty regarding the true social cost of premature mortality and in the cost inputs since they were taken from many different sources. **Other:** Study is similar to Hettle, 2012				
Overall applicability: Partly applicable **Overall quality: Minor limitations**				
Abbreviations: BENESCO: Benefits of Smoking Cessation on Outcomes; CHD: Coronary heart disease; COPD: Chronic obstructive pulmonary disease; CUA: Cost-utility analysis; CVD: Cardio-vascular disease; ICER: Incremental cost-effectiveness ratio; NRT: Nicotine replacement therapy; PVD: Peripheral vascular disease; QALY: Quality-adjusted life-year; RCT: Randomised controlled trial				
(a) Varenicline was dosed at 0.5mg once a day for 3 days, 0.5mg twice a day for 4 days followed by 1.0mg twice a day for total of 12 weeks				
(b) Counselling was 12 weekly clinic visits lasting a maximum of 10 minutes, plus a single telephone call 3 days after the quit date				
(c) Abstinence was verified by a measurement of expired air carbon monoxide of less than or equal to 10 parts per million				
(d) Assumed to be total population costs/QALYS divided by total population (1,000).				

Appendix E – Forest plots

Cessation, relative effectiveness

Pairwise effectiveness evidence – cessation at 6 months

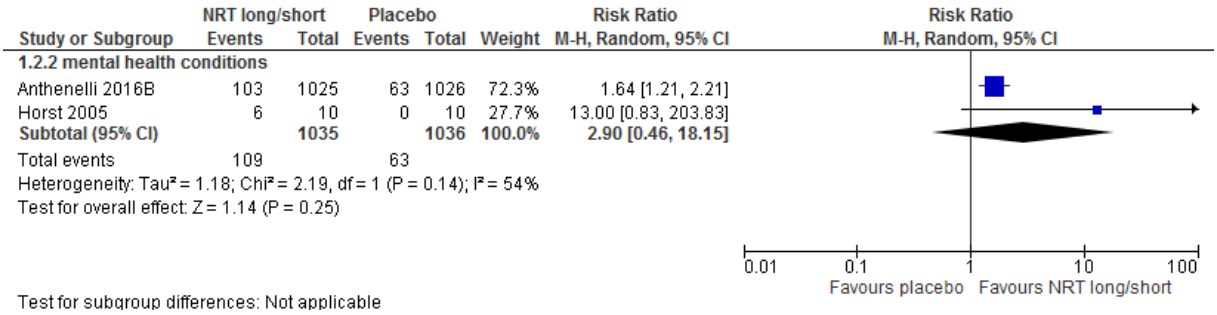
Figure 1: NRT long/short acting vs placebo



Footnotes

(1) Lozenge std
(2) Lozenge high
(3) Gum std
(4) Gum high
(5) Patch
(6) Lozenge
(7) Gum high
(8) Gum std
(9) NRT ns
(10) NRT patch

Figure 2: NRT long/short acting vs placebo (mental health subgroup)



Subgroup studies separated out from main analysis as they require random effects where the main analysis requires fixed effects.

Figure 3: NRT long/short acting vs no drug treatment

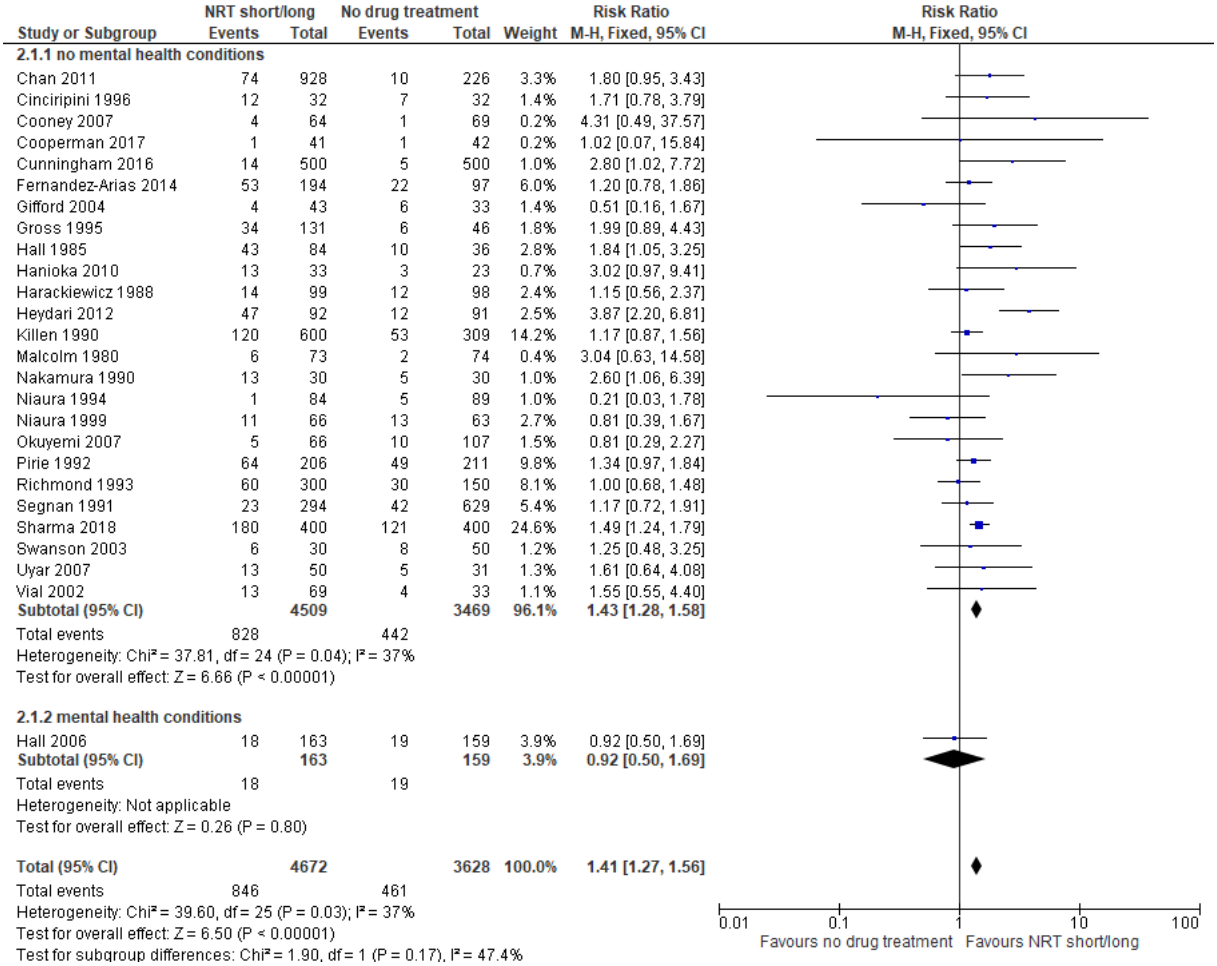


Figure 4: NRT long/short acting vs waitlist

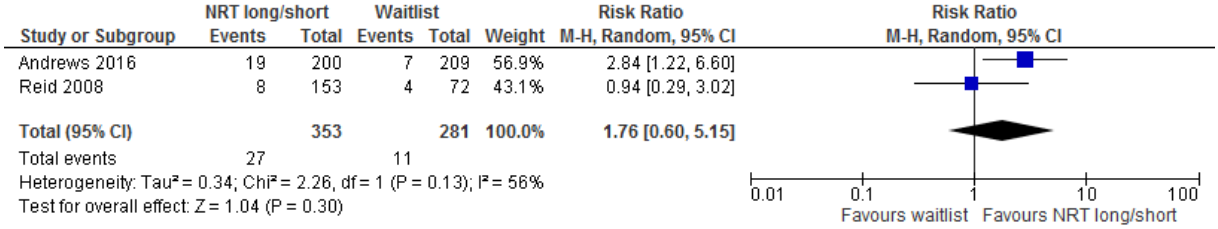


Figure 5: NRT long/short acting vs usual care

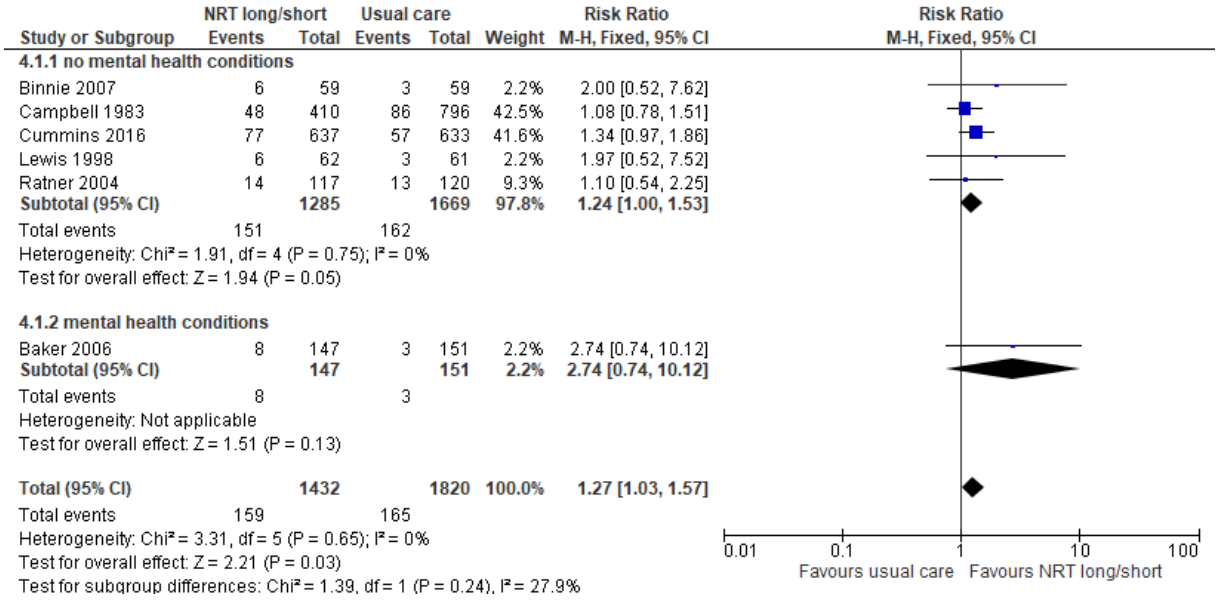


Figure 6: NRT long&short acting vs placebo

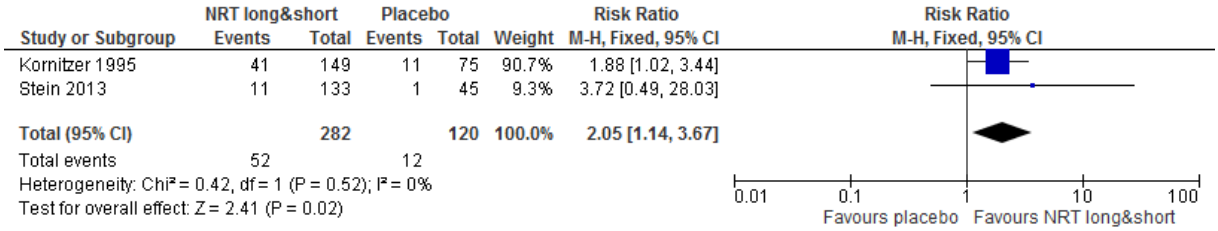
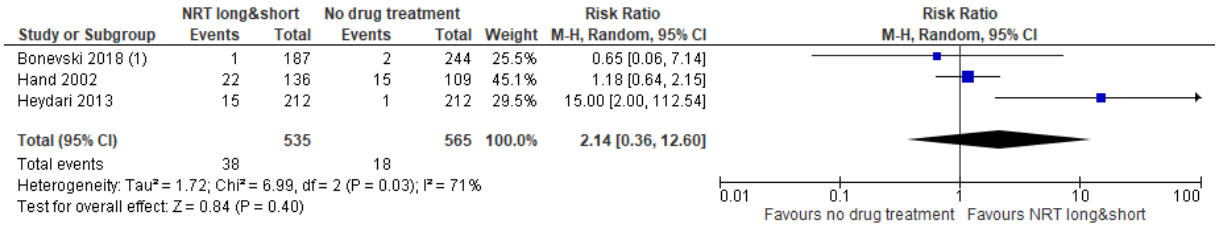


Figure 7: NRT long&short acting vs no drug treatment



Footnotes
(1) Study gives choice of NRT but recommends combination of long and short acting NRT

Figure 8: NRT long&short acting vs NRT long/short acting

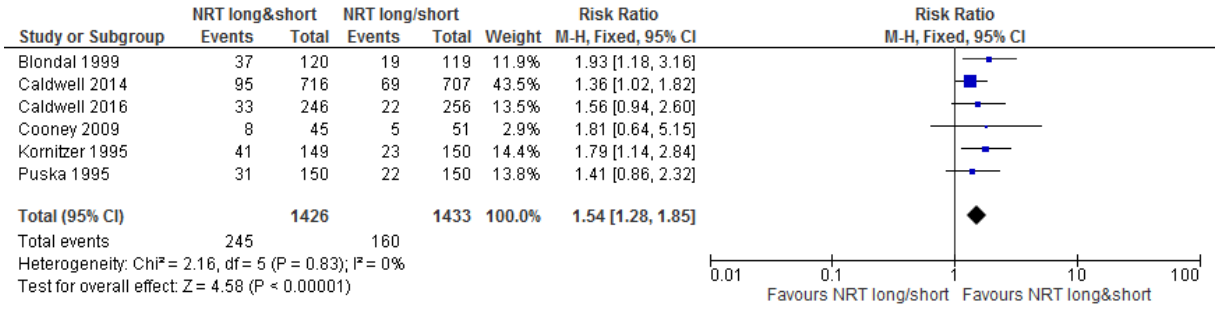


Figure 9: Bupropion vs placebo

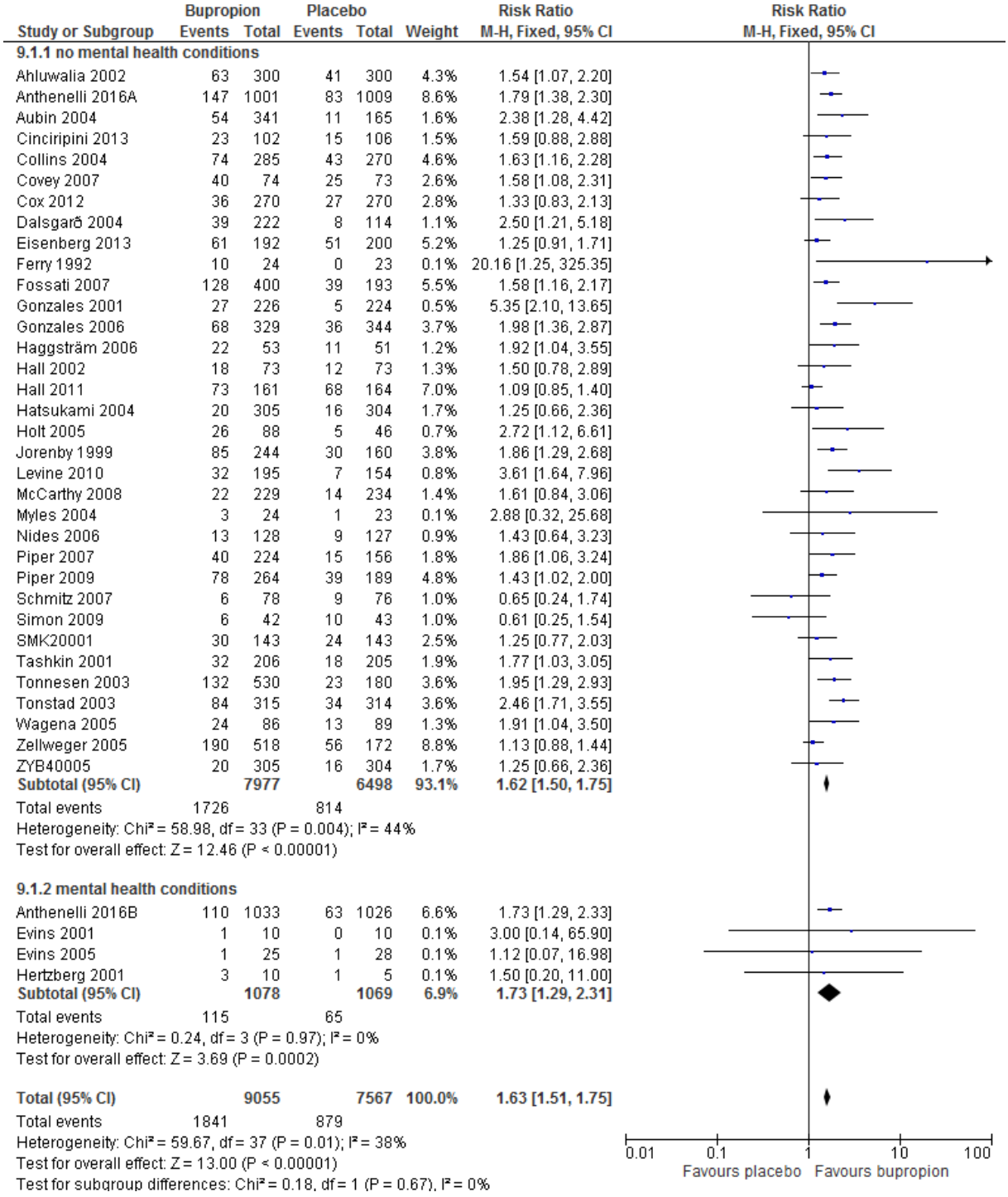


Figure 10: Bupropion vs no drug treatment

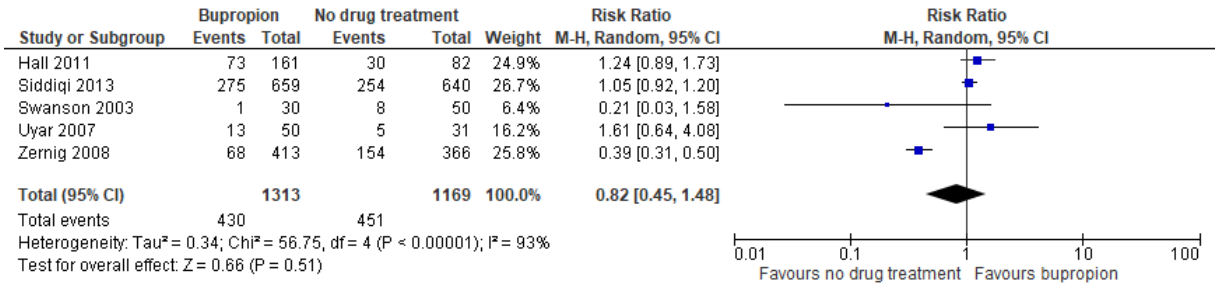


Figure 11: Bupropion vs usual care

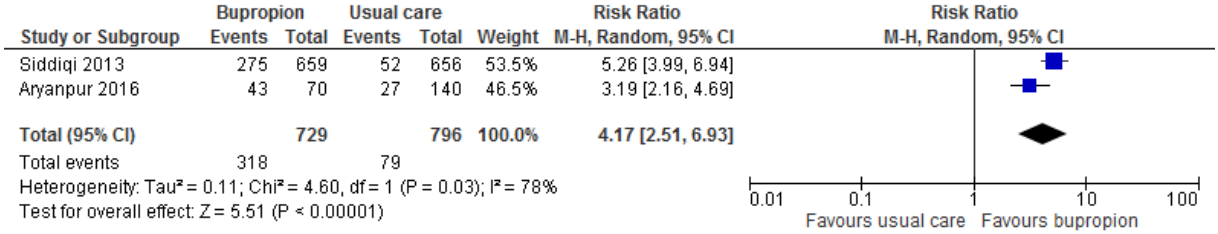
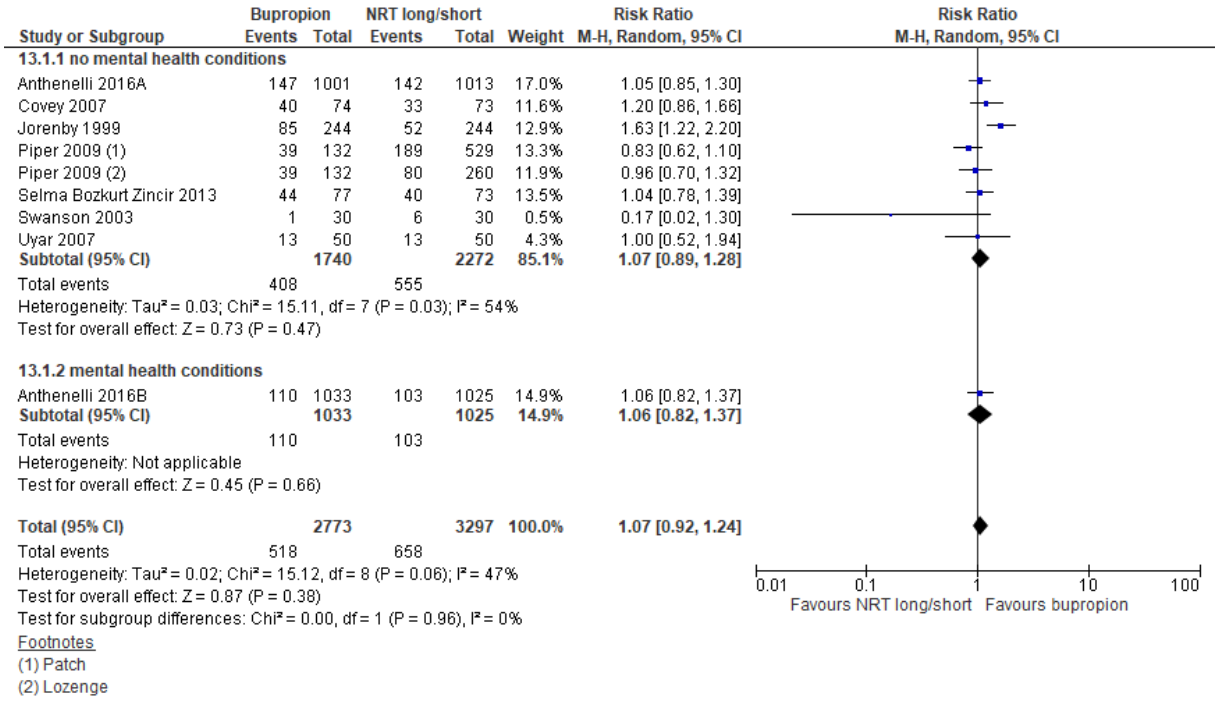


Figure 12: Bupropion vs NRT long/short acting



Footnotes
(1) Patch
(2) Lozenge

Figure 13: Varenicline vs placebo

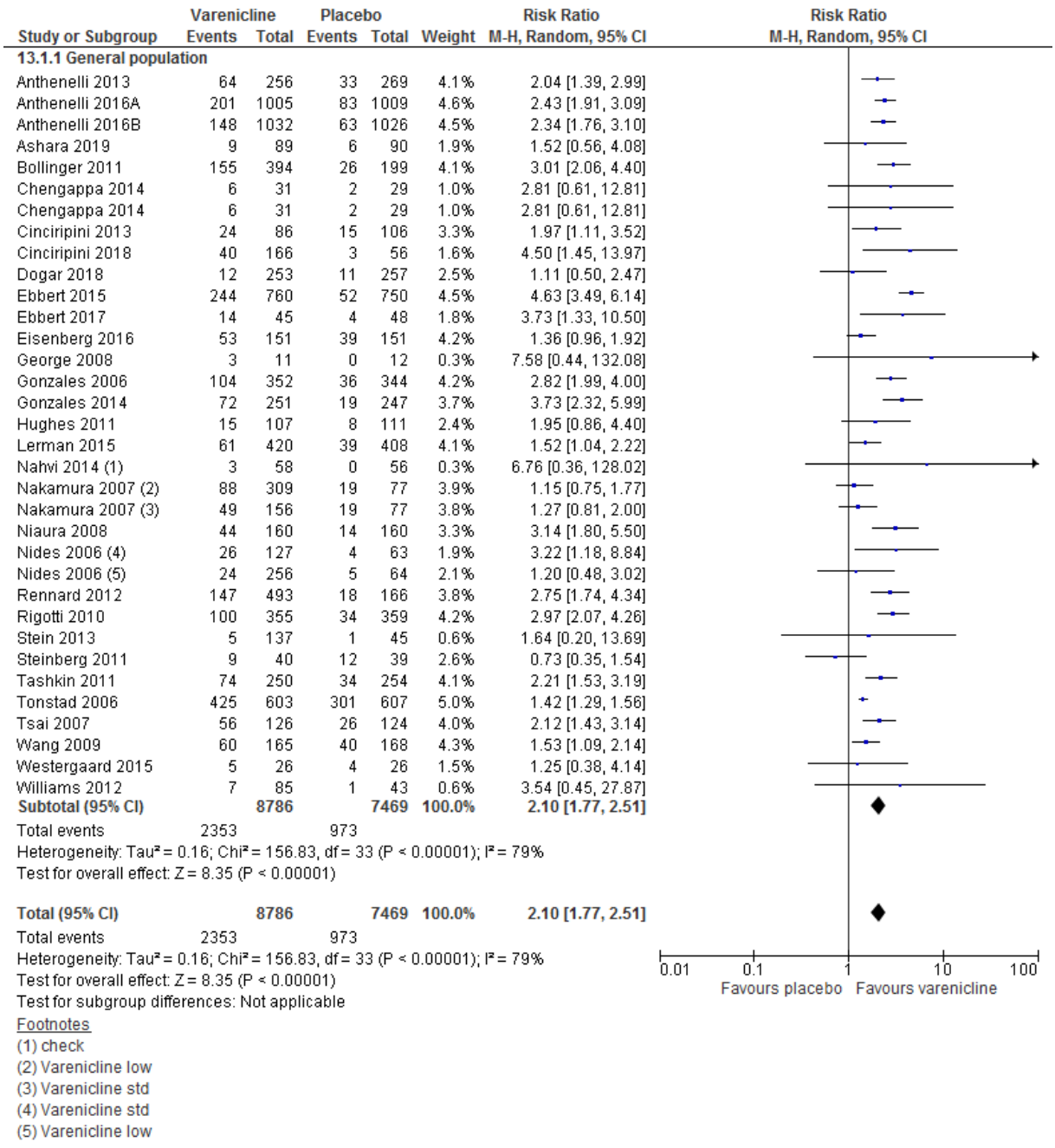
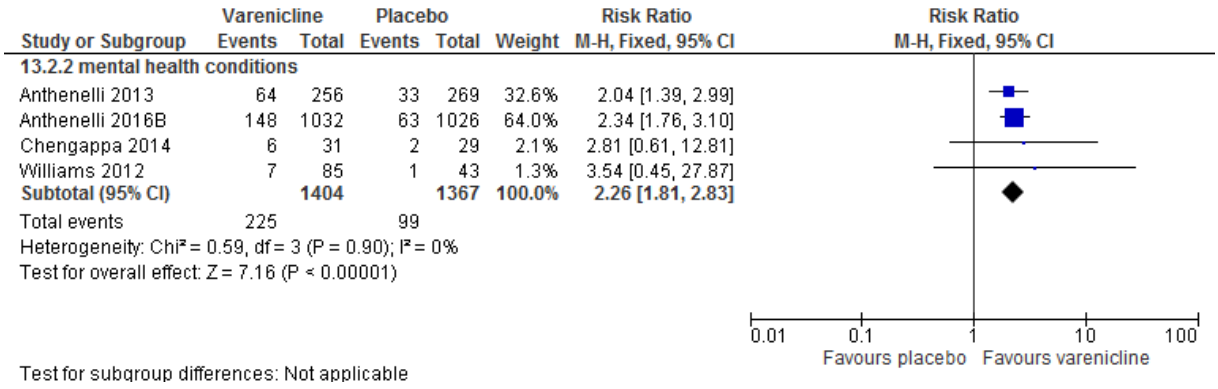


Figure 14: Varenicline vs placebo (mental health subgroup)



Subgroup studies separated out from main analysis as they require fixed effects where the main analysis requires random effects.

Figure 15: Varenicline vs no drug treatment

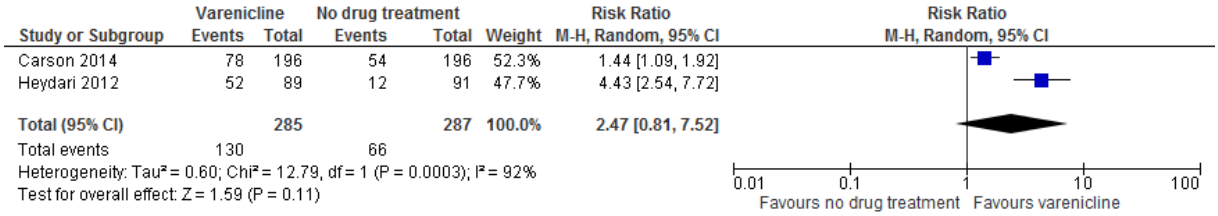


Figure 16: Varenicline vs NRT long/short acting

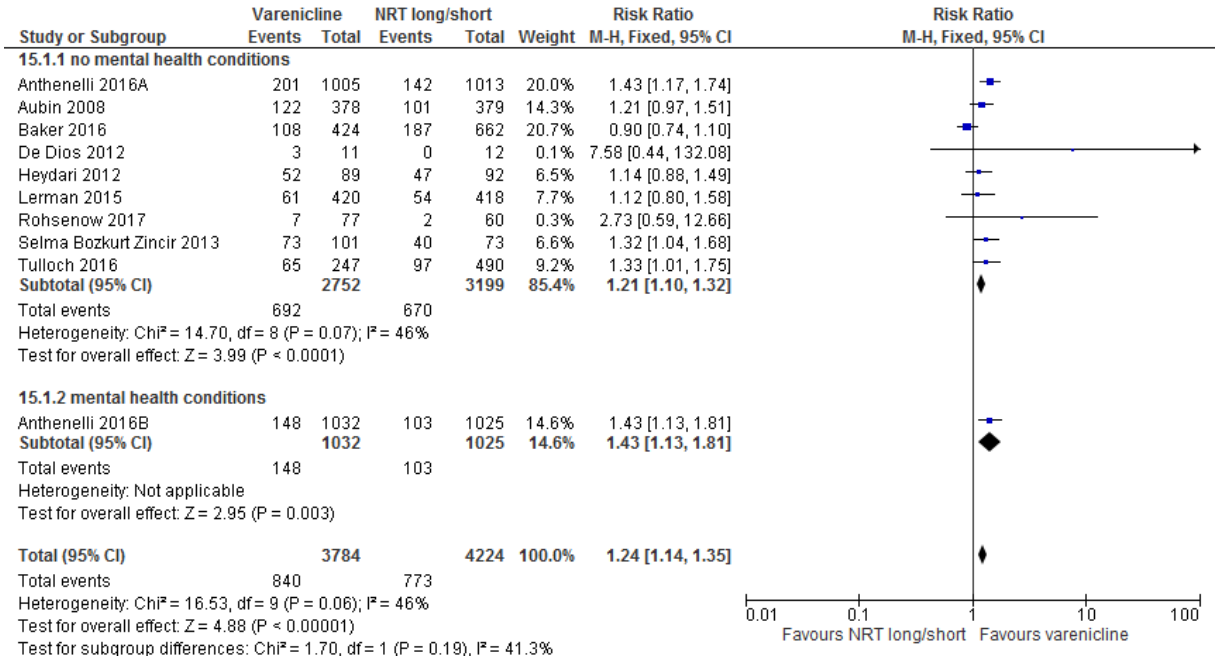


Figure 17: Varenicline vs bupropion

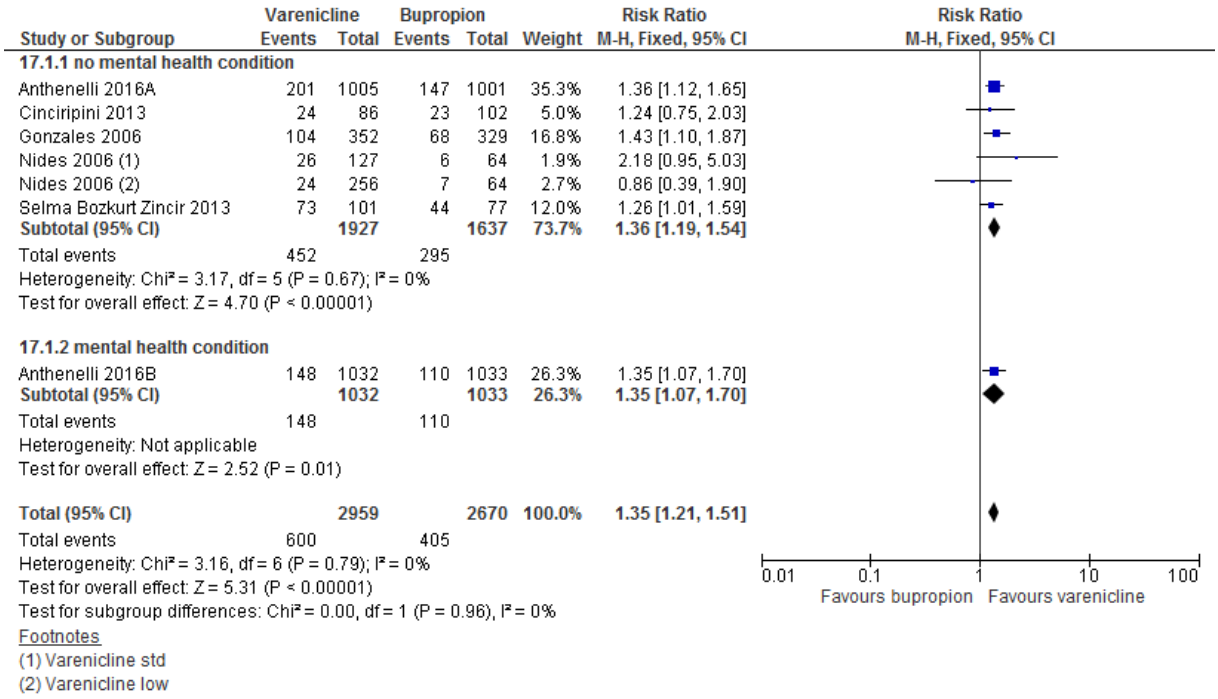


Figure 18: E-cigarette vs placebo e-cigarette

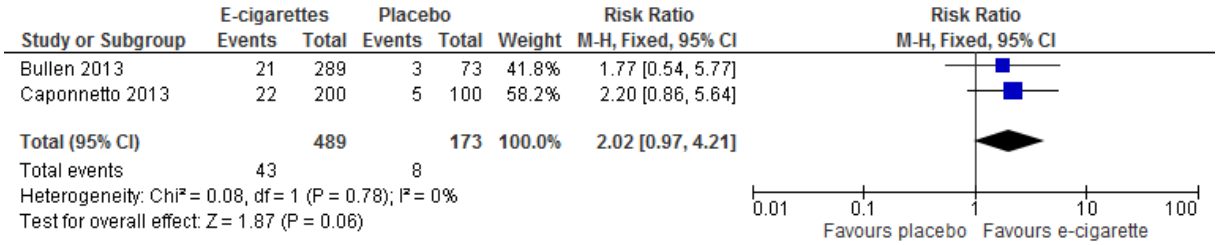


Figure 19: E-cigarette vs usual care

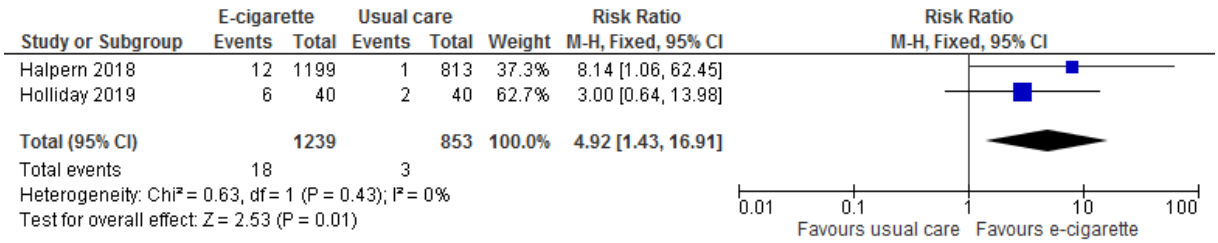


Figure 20: Bupropion + NRT long/short vs placebo

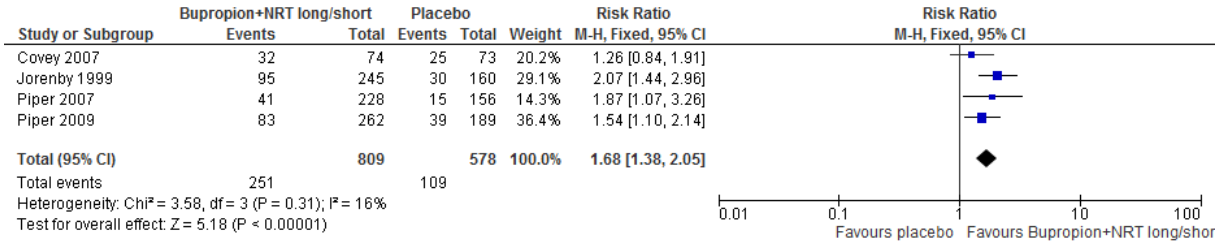


Figure 21: Bupropion + NRT long/short vs NRT long/short

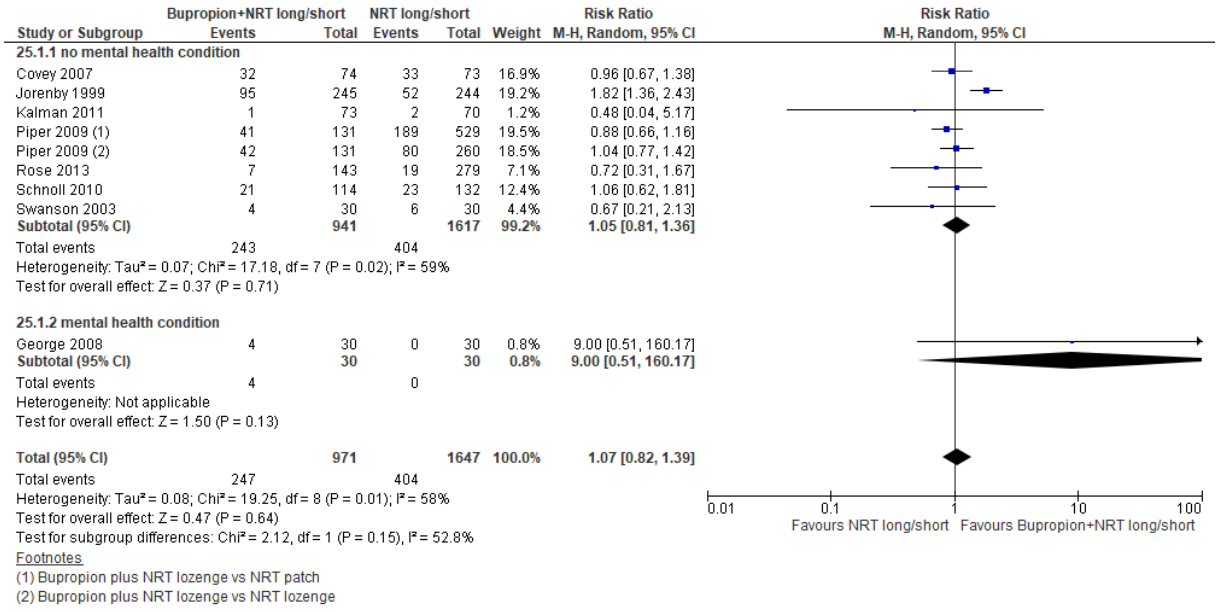


Figure 212: Bupropion + NRT long/short vs bupropion

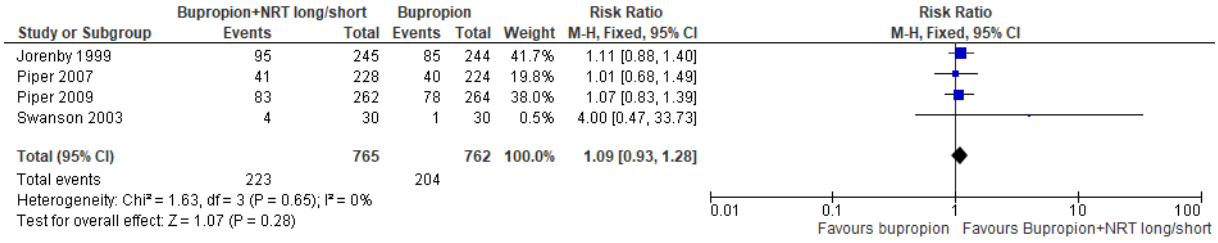


Figure 223: Bupropion + NRT long&short vs NRT long/short

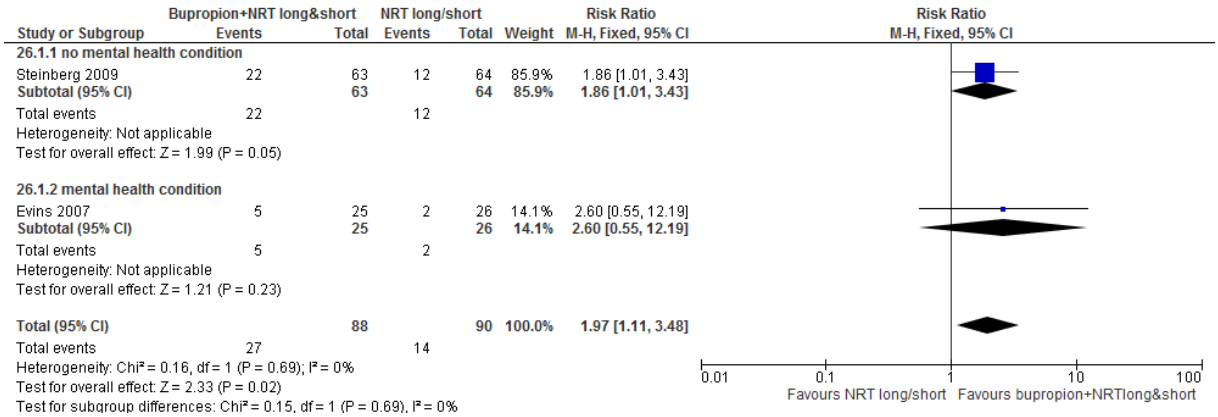


Figure 234: Varenicline + NRT long/short vs varenicline

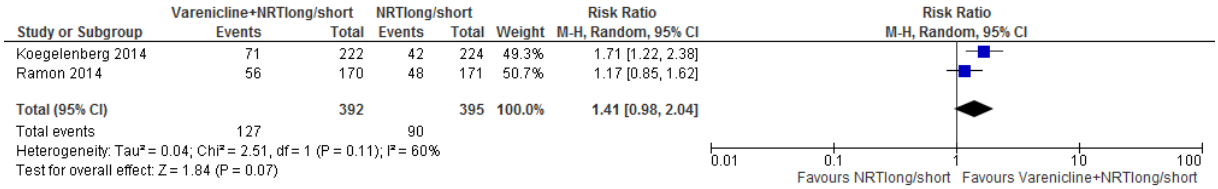


Figure 245: Varenicline + bupropion vs varenicline

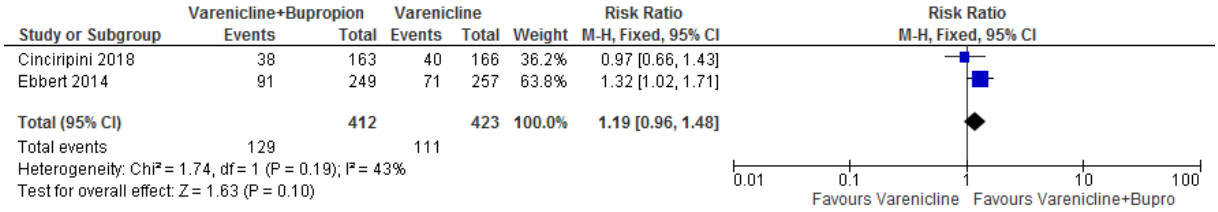
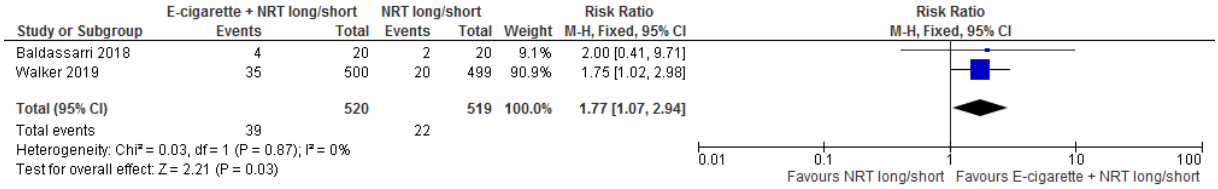


Figure 256: E- cigarette + NRT long/short vs NRT long/short



Funnel plots for meta-analyses with >10 studies (cessation at 6 months)

Figure 267: NRT long/short acting vs placebo

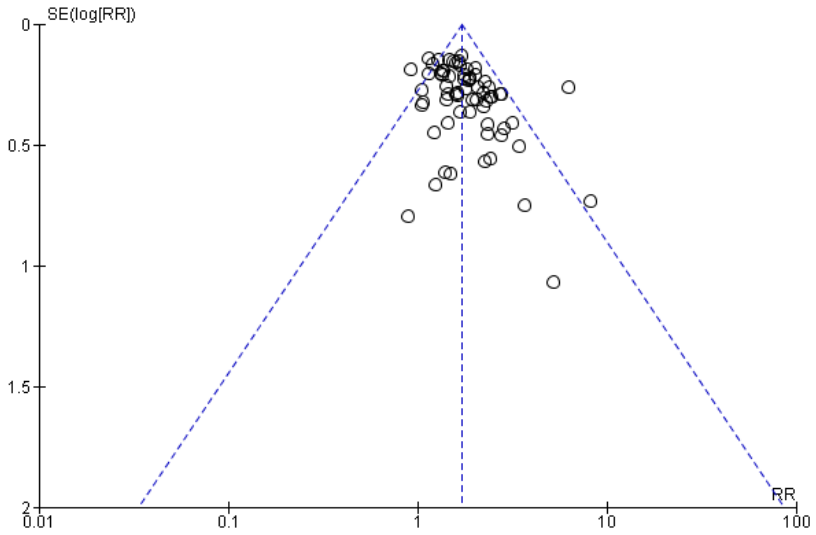


Figure 278: NRT long/short acting vs no drug treatment

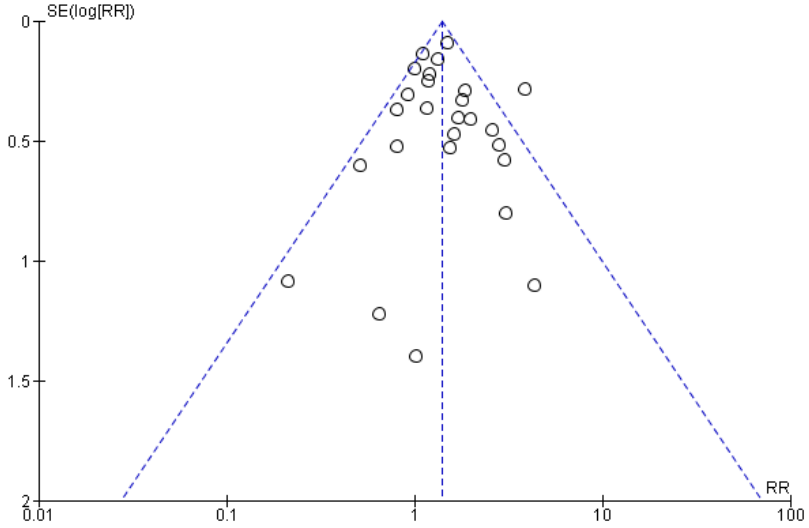


Figure 29: Bupropion vs placebo

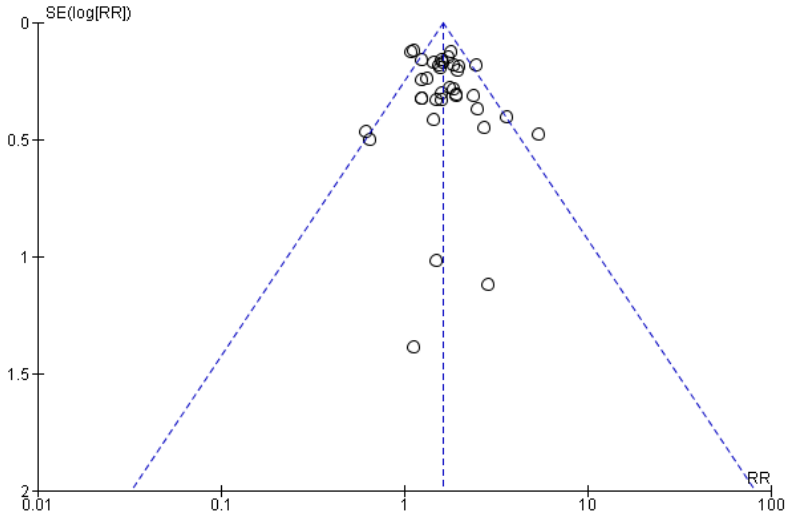


Figure 280: Varenicline vs placebo

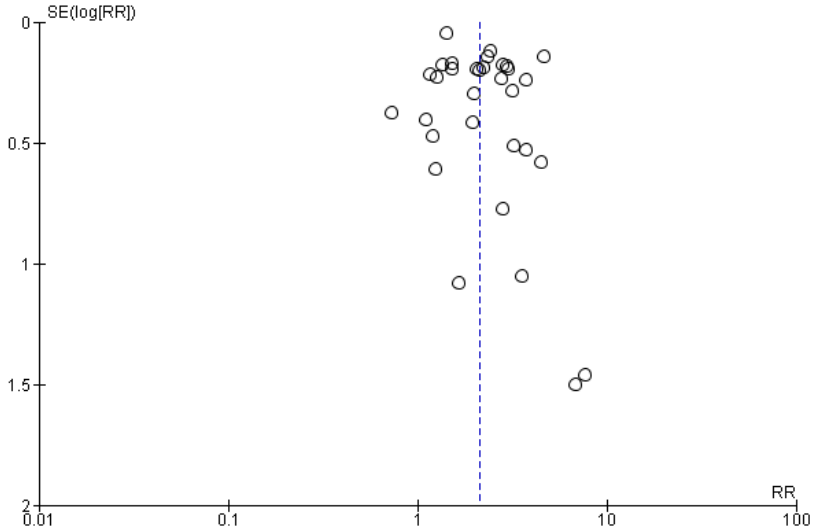
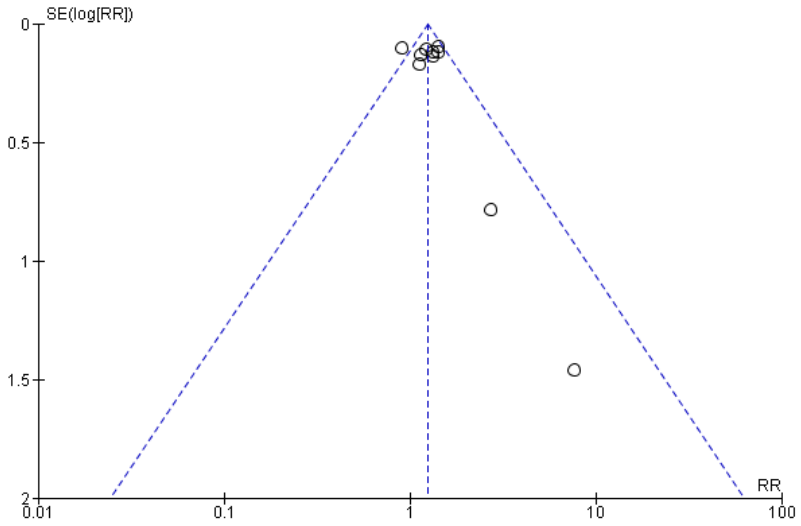


Figure 291: Varenicline vs NRT long/short



Pairwise adverse events evidence

Figure 302: E-cigarettes vs no drug treatment, headache

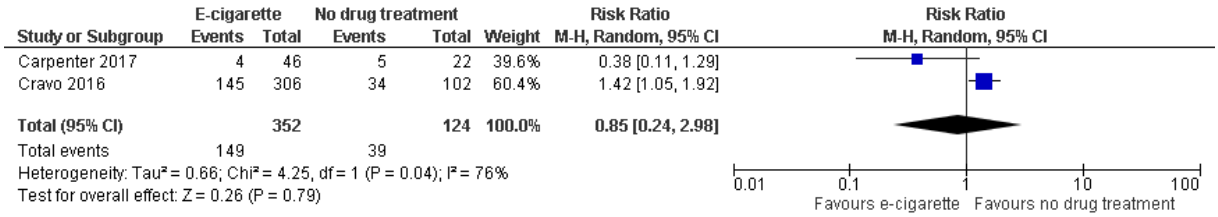


Figure 313: E-cigarettes vs no drug treatment, nausea

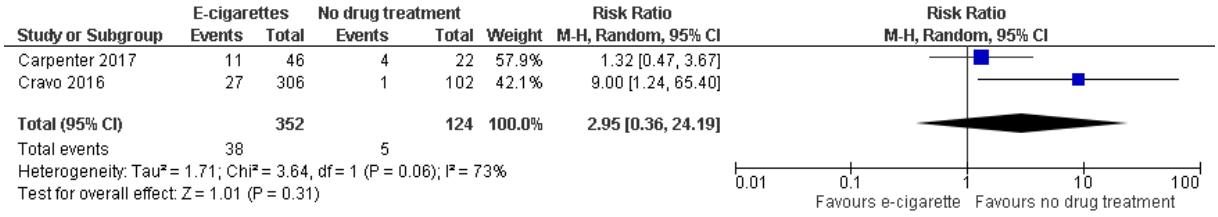
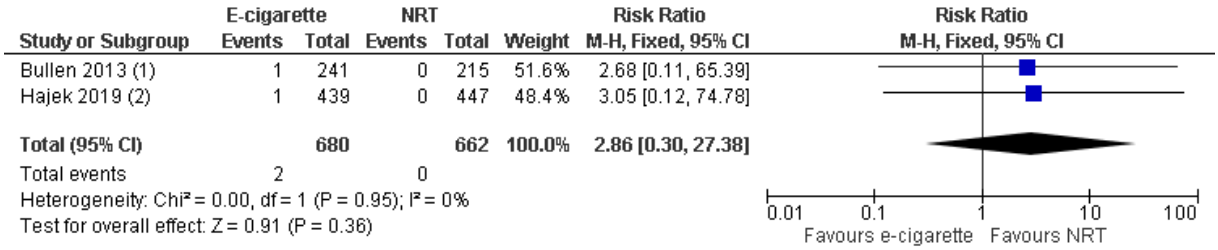
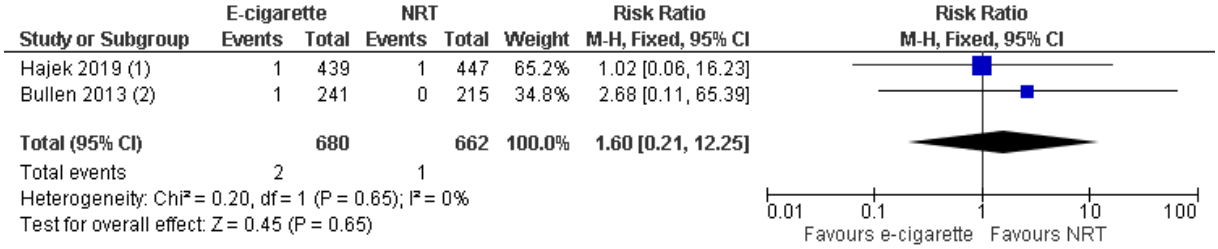


Figure 324: E-cigarettes vs NRT, cardiovascular death



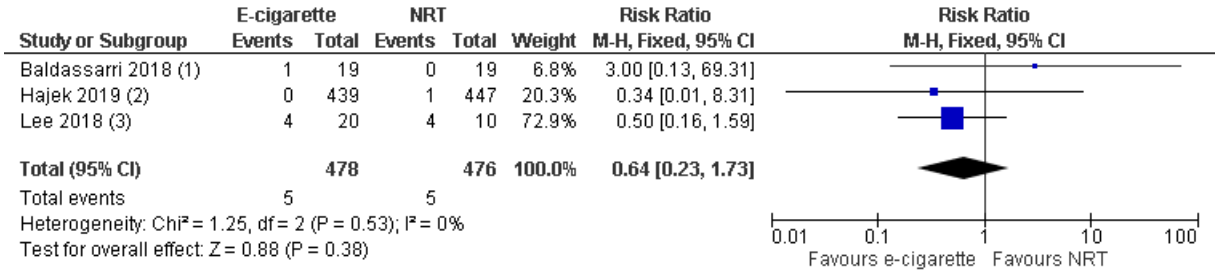
Footnotes
(1) NRT patch
(2) NRT choice

Figure 335: E-cigarettes vs NRT, death all causes



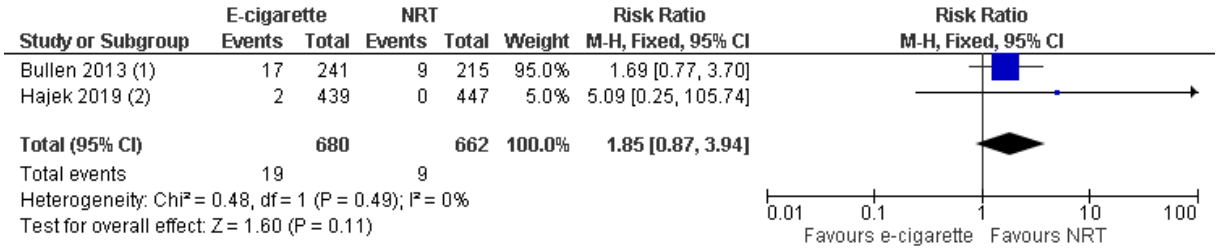
Footnotes
(1) NRT choice
(2) NRT patch

Figure 346: E-cigarettes vs NRT, headache



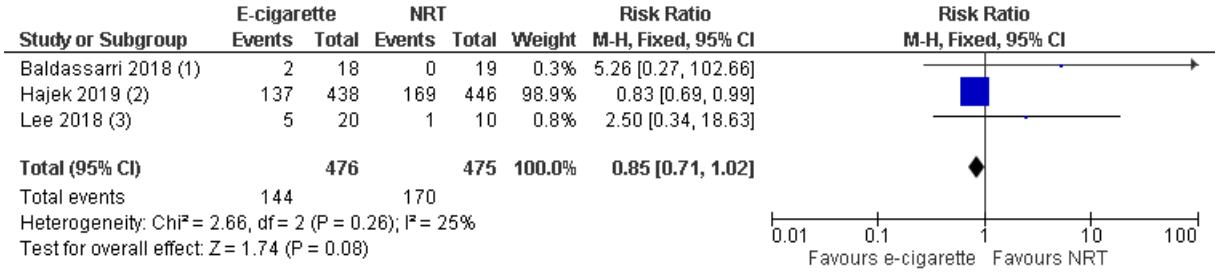
Footnotes
(1) E-cig plus NRT patch vs NRT patch
(2) NRT choice
(3) NRT patch

Figure 357: E-cigarettes vs NRT, hospitalisation



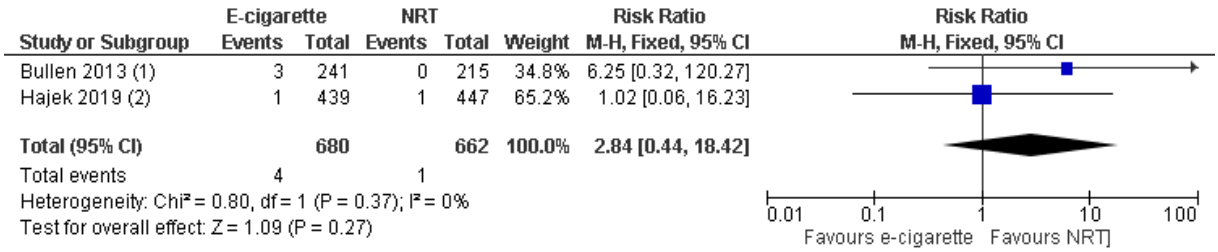
Footnotes
(1) NRT patch
(2) NRT choice

Figure 368: E-cigarettes vs NRT, nausea



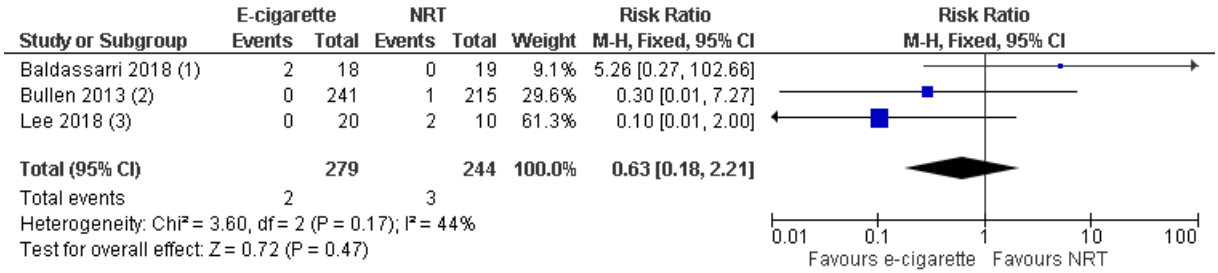
Footnotes
(1) E-cig plus NRT patch vs NRT patch
(2) NRT choice
(3) NRT patch

Figure39: E-cigarettes vs NRT, non-fatal MI



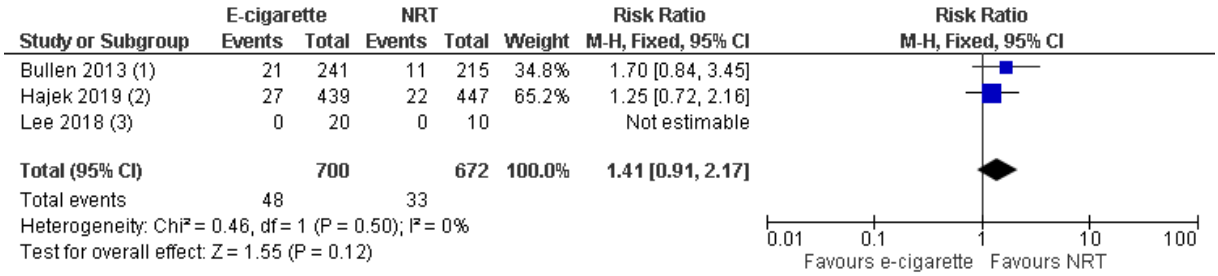
Footnotes
(1) NRT patch
(2) NRT choice

Figure 370: E-cigarettes vs NRT, palpitations



Footnotes
(1) E-cig plus NRT patch vs NRT patch
(2) NRT patch
(3) NRT patch

Figure 381: E-cigarettes vs NRT, serious adverse events



Footnotes
(1) NRT patch
(2) NRT choice
(3) NRT patch

Figure 392: E-cigarettes vs placebo e-cigarette, headache

Figure 403: E-cigarettes vs placebo e-cigarette, insomnia

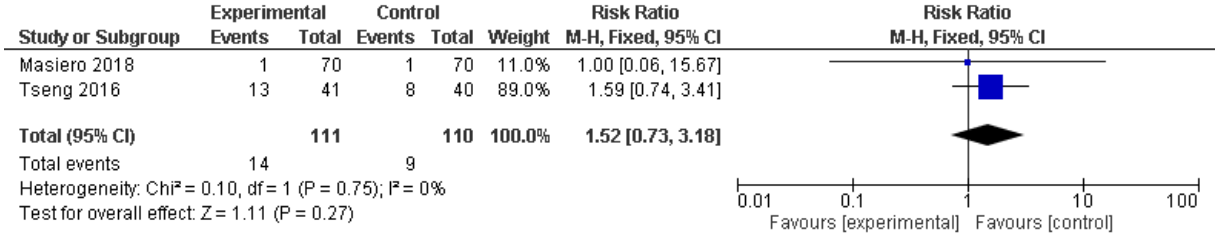
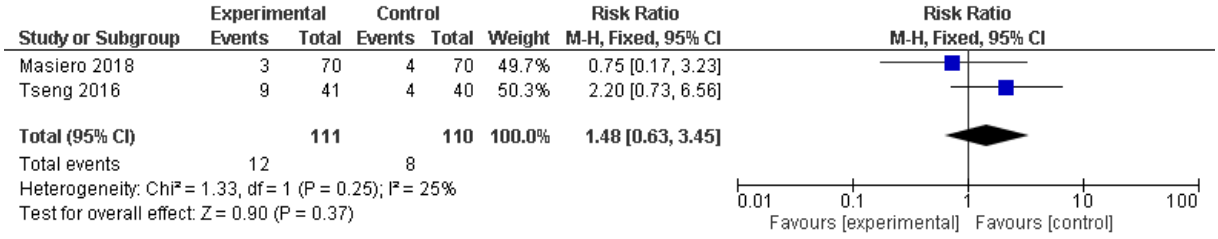


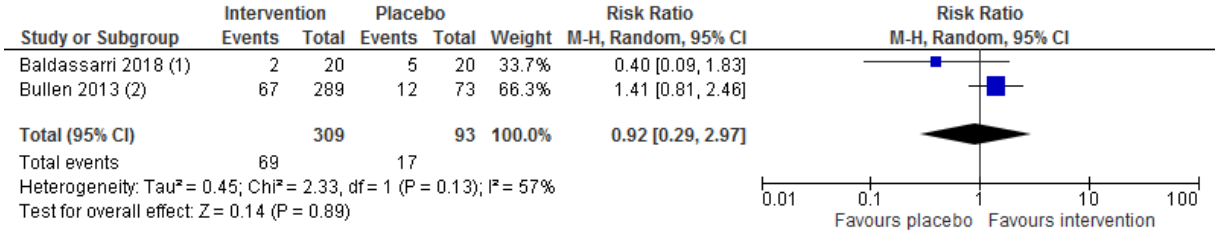
Figure 414: E-cigarettes vs placebo e-cigarette, nausea



Cessation, short follow-up

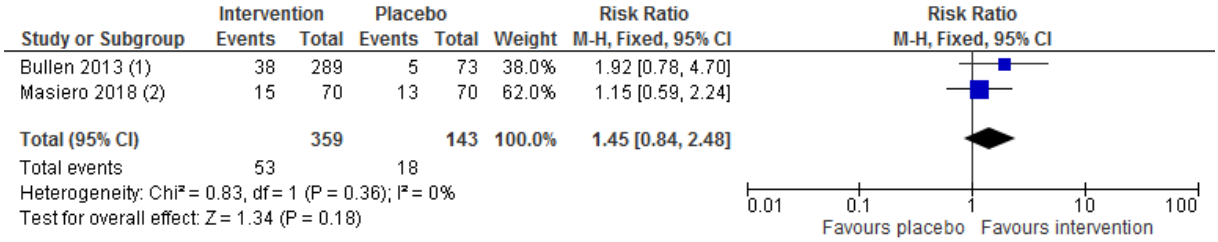
E-cigarettes vs placebo e-cigarette

Figure 425: Smoking abstinence 1-<3 months



Footnotes
(1) 8 week follow-up
(2) 1 month follow-up

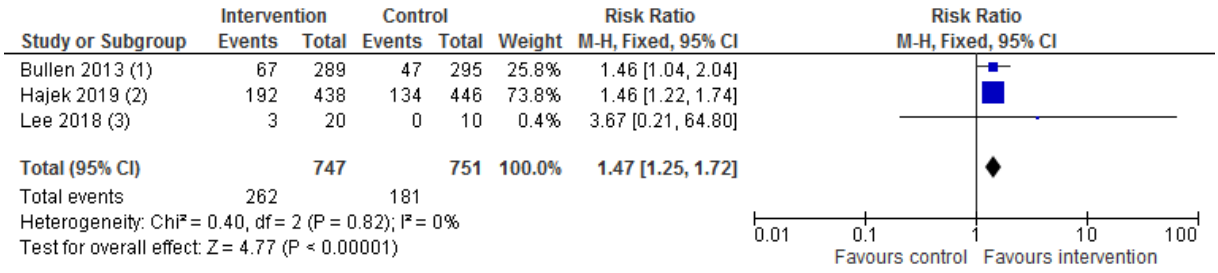
Figure 436: Smoking abstinence 3-<6 months



Footnotes
(1) 3 month follow-up
(2) 3 month follow-up

Nicotine e-cigarettes vs NRT

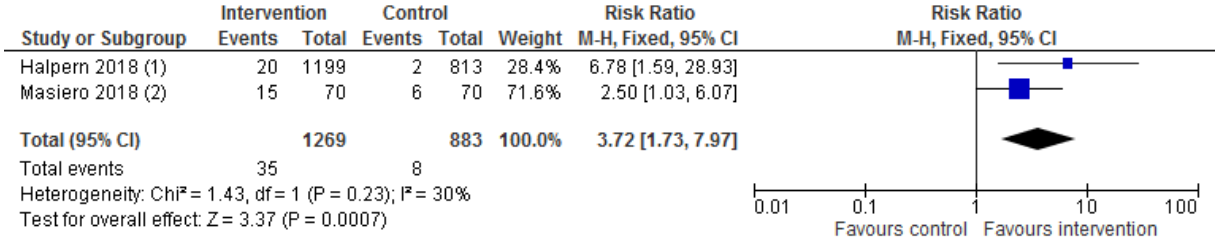
Figure 447: Smoking abstinence 1-<3 months



Footnotes
(1) 1 month follow-up; NRT patch control (long-acting)
(2) 4 week follow-up; NRT of choice (long- and short-acting recommended)
(3) 8 week follow-up; NRT patch control (long-acting)

Nicotine e-cigarettes vs no intervention

Figure 458: Smoking abstinence 3-<6 months



Footnotes
(1) 3 month follow-up, control is usual care
(2) 3 month follow-up, control is minimal counselling

Harm reduction

No meta-analysis could be conducted for harm reduction outcomes

Appendix F – GRADE tables

Cessation, relative effectiveness

- The first GRADE profile in this section (GRADE profile 1) is for the full NMA.
- GRADE profiles 2 to 34 are for individual pairwise comparisons within the NMA.
- GRADE profile 35 is for the mental health subgroup NMA.
- GRADE profiles 36 to 46 are for individual pairwise comparisons within the NMA for people with mental health conditions only.
- GRADE profiles 47 to 49 are for pairwise data of adverse events of e-cigarettes compared with other interventions (NRT) or placebo e-cigarette or no drug treatment.
- GRADE profiles 50 to 52 are for short-term follow-up cessation outcomes (e-cigarettes only)

GRADE profile 1: Full NMA

Quality assessment	No of patients across all arms in all studies	Confidence

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Cessation at 6 months (assessed with: biochemical validation)								
192	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision[3]	none	92,067	⊕⊕OO LOW

[1] 30.7% of studies were at high risk of bias (59/192) and 46.4% of studies had some concerns (89/192)
[2] A random effects model for between studies provided the best fit. However, a fixed effects model for between classes provided best fit so only downgraded by one level.
[3] It was possible to differentiate between treatments at a statistically significant level (statistical significance is the MID for the outcome of cessation) – see mileage chart for more details.

GRADE profile 2: NRT long/short acting vs placebo (Figure 1)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NRT long/short acting	Placebo	Relative (95% CI)	Absolute	
Cessation at 6 months (assessed with: biochemical validation)											
63[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3385/18790 (18%)	1316/13301 (9.9%)	RR 1.70 (1.6 to 1.8)	69 more per 1000 (from 59 more to 79 more)	⊕⊕⊕O MODERATE

[1] 64 studies in forest plot for illustration, but 1 study included no events so was not part of any calculations
[2] Minority of studies at high risk of bias, and studies with highest weight at low risk of bias. Most studies with some bias due to unclear reporting.

GRADE profile 3: NRT long/short acting vs no drug treatment (Figure 3)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NRT long/short acting	No drug treatment	Relative (95% CI)	Absolute	
Cessation at 6 months (assessed with: biochemical validation)											
26	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	846/4672 (18.1%)	461/3628 (12.7%)	RR 1.41 (1.27 to 1.56)	52 more per 1000 (from 34 more to 71 more)	⊕⊕OO LOW

[1] Most studies at high risk of bias, including study with a quarter of overall meta-analysis weight. Main concern is blinding.

GRADE profile 4: NRT long/short acting vs waitlist (Figure 4)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NRT long/short acting	Waitlist	Relative (95% CI)	Absolute	
Cessation at 6 months (assessed with: biochemical validation)											
2	randomised trials	very serious[1]	serious[2]	no serious indirectness	serious[3]	none	27/353 (7.6%)	11/281 (3.9%)	RR 1.76 (0.6 to 5.15)	30 more per 1000 (from 16 fewer to 162 more)	⊕OOO VERY LOW

[1] Both studies at high risk of bias for concerns about blinding
[2] I2 is 56%
[3] CI crosses MID

GRADE profile 5: NRT long/short acting vs usual care (Figure 5)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NRT long/short acting	Usual care	Relative (95% CI)	Absolute	
Cessation at 6 months (assessed with: biochemical validation)											
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	159/1432 (11.1%)	165/1820 (9.1%)	RR 1.27 (1.03 to 1.53)	24 more per 1000 (from 3 more to 52 more)	⊕⊕⊕O MODERATE

[1] Some risk of bias due to lack of blinding in the studies. One study with high weight at low risk.

GRADE profile 6: NRT long&short acting vs placebo (Figure 6)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NRT long&short acting	Placebo	Relative (95% CI)	Absolute	
Cessation at 6 months (assessed with: biochemical validation)											
2	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	52/282 (18.4%)	12/120 (10%)	RR 2.05 (1.14 to 3.67)	105 more per 1000 (from 14 more to 267 more)	⊕⊕⊕⊕ HIGH

[1] Some risk due to unclear reporting, but largest study at low risk.

GRADE profile 7: NRT long&short acting vs no drug treatment (Figure 7)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NRT long&short acting	No drug treatment	Relative (95% CI)	Absolute	
Cessation at 6 months (assessed with: biochemical validation)											
3	randomised trials	very serious[1]	very serious[2]	no serious indirectness	serious[3]	none	38/3535 (7.1%)	19/3565 (3.4%)	RR 2.14 (0.36 to 12.60)	38 more per 1000 (from 22 fewer to 390 more)	⊕OOO VERY LOW

[1] Both studies at high risk of bias due to poor blinding of participants, personnel and outcome assessors and one study with poor allocation concealment.
[2] I2 is 85%
[3] CI crosses MID

GRADE profile 8: NRT long&short acting vs waitlist

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NRT long&short acting	Waitlist	Relative (95% CI)	Absolute	
Cessation at 6 months (assessed with: biochemical validation)											
1	randomised trials	serious[1]	NA	no serious indirectness	serious[2]	none	21/251 (8.4%)	11/248 (4.4%)	RR 1.89 (0.93 to 3.83)	39 more per 1000 (from 3 fewer to 126 more)	⊕⊕OO LOW

[1] Study at high risk for poor blinding of participants and personnel.
[2] CI crosses MID

GRADE profile 9: NRT long&short acting vs usual care

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NRT long&short acting	Waitlist	Relative (95% CI)	Absolute	
Cessation at 6 months (assessed with: biochemical validation)											

1	randomised trials	serious[1]	NA	no serious indirectness	very serious2	none	2/105 (1.9%)	0/102 (0%)	RR 4.68 (0.24 to 99.98)	Not calculable	⊕OOO VERY LOW

[1] Some risk of bias due to lack of blinding in the study.
[2] CI crosses MID and <300 participants

GRADE profile 10: NRT long&short acting vs NRT long/short acting (Figure 8)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NRT long&short acting	NRT long/short acting	Relative (95% CI)	Absolute	
Cessation at 6 months (assessed with: biochemical validation)											
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	245/1426 (17.2%)	160/1433 (11.2%)	RR 1.54 (1.28 to 1.85)	60 more per 1000 (from 31 more to 95 more)	⊕⊕⊕O MODERATE

[1] One high weight study at risk due to incomplete outcome data but otherwise low risk of bias.

GRADE profile 11: Bupropion vs placebo (Figure 9)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bupropion	Placebo	Relative (95% CI)	Absolute	
Cessation at 6 months (assessed with: biochemical validation)											
38	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1841/9055 (20.3%)	879/7567 (11.6%)	RR 1.63 (1.51 to 1.75)	73 more per 1000 (from 59 more to 87 more)	⊕⊕⊕O MODERATE

[1] Some studies at risk due to lack of blinding, but most studies including high weight studies at low risk or with only some concerns due to unclear reporting.

GRADE profile 12: Bupropion vs no drug treatment (Figure 10)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bupropion	No drug treatment	Relative (95% CI)	Absolute	

Cessation at 6 months (assessed with: biochemical validation)											
5	randomised trials	very serious[1]	very serious[2]	no serious indirectness	serious[3]	none	430/1313 (32.7%)	451/1169 (38.6%)	RR 0.82 (0.45 to 1.48)	69 fewer per 1000 (from 212 fewer to 185 more)	⊕OOO VERY LOW

[1] Most studies - and most weight - at high risk of bias due to poor blinding or incomplete outcome data.
[2] I2 is 94%
[3] CI crosses MID

GRADE profile 13: Bupropion vs usual care (Figure 11)

Quality assessment							No of patients		Effect		Confidence
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Bupropion**	**Usual care**	**Relative (95% CI)**	**Absolute**	
Cessation at 6 months (assessed with: biochemical validation)											
2	randomised trials	serious[1]	very serious[2]	no serious indirectness	no serious imprecision	none	318/729 (43.6%)	79/796 (9.9%)	RR 4.17 (2.51 to 6.93)	315 more per 1000 (from 150 more to 589 more)	⊕OOO VERY LOW

[1] Studies at risk due to poor blinding of participants
[2] I2 is 78%

GRADE profile 14: Bupropion vs NRT long/short acting (Figure 12)

Quality assessment							No of patients		Effect		Confidence
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Bupropion**	**NRT short/long acting**	**Relative (95% CI)**	**Absolute**	
Cessation at 6 months (assessed with: biochemical validation)											
8	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	518/2773 (18.7%)	658/3296 (20%)	RR 1.07 (0.92 to 1.24)	14 more per 1000 (from 16 fewer to 48 more)	⊕⊕⊕O MODERATE

[1] CI crosses MID

GRADE profile 15: Varenicline vs placebo (Figure 13)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Varenicline	Placebo	Relative (95% CI)	Absolute	
Cessation at 6 months (assessed with: biochemical validation)											
31	randomised trials	no serious risk of bias[1]	very serious[2]	no serious indirectness	no serious imprecision	none	2353/8786 (26.8%)	973/7469 (13%)	RR 2.10 (1.77 to 2.51)	143 more per 1000 (from 100 more to 197 more)	⊕⊕OO LOW

[1] Vast majority of weight comes from studies at low risk or some concerns due to unclear reporting.
[2] I2 is 79%

GRADE profile 16: Varenicline vs no drug treatment (Figure 15)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Varenicline	No drug treatment	Relative (95% CI)	Absolute	
Cessation at 6 months (assessed with: biochemical validation)											
2	randomised trials	serious[1]	very serious[2]	no serious indirectness	serious[3]	none	130/285 (45.6%)	66/287 (23%)	RR 2.47 (0.81 to 7.52)	338 more per 1000 (from 44 fewer to 1000 more)	⊕OOO VERY LOW

[1] One study at high risk of bias due to concerns about blinding.
[2] I2 is 92%
[3] CI crosses MID

GRADE profile 17: Varenicline vs NRT long/short acting (Figure 16)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Varenicline	NRT long/short acting	Relative (95% CI)	Absolute	
Cessation at 6 months (assessed with: biochemical validation)											

10	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	840/3784 (22.2%)	773/4224 (18.3%)	RR 1.24 (1.14 to 1.35)	44 more per 1000 (from 26 more to 64 more)	⊕⊕⊕O MODERATE

[1] Some risk of bias from lack of blinding from 3 studies, one of which also had unclear allocation concealment. Most weight from trials at low or with some risk of bias.

GRADE profile 18: Varenicline vs NRT long&short acting

Quality assessment							No of patients		Effect		Confidence
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Varenicline**	**NRT long&short acting**	**Relative (95% CI)**	**Absolute**	
Cessation at 6 months (assessed with: biochemical validation)											
1	randomised trials	no serious risk of bias[1]	NA	no serious indirectness	very serious[2]	none	5/137 (3.6%)	11/133 (8.3%)	RR 0.44 (0.16 to 1.24)	46 fewer per 1000 (from 69 fewer to 20 more)	⊕⊕OO LOW

[1] Some unclear reporting in this study, but no serious risk of bias.
[2] CI crosses MID and <300 participants

GRADE profile 19: Varenicline vs bupropion (Figure 17)

Quality assessment							No of patients		Effect		Confidence
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Varenicline**	**Bupropion**	**Relative (95% CI)**	**Absolute**	
Cessation at 6 months (assessed with: biochemical validation)											
6	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	600/2959 (20.3%)	405/2670 (15.2%)	RR 1.35 (1.21 to 1.51)	53 more per 1000 (from 32 more to 77 more)	⊕⊕⊕⊕ HIGH

[1] One study with some risk from lack of participant blinding, but most meta-analysis weight is from studies with low risk of bias.

GRADE profile 20: E-cigarette vs placebo e-cigarette (Figure 18)

Quality assessment							No of patients		Effect		Confidence
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**E-cigarette**	**Placebo e-cigarette**	**Relative (95% CI)**	**Absolute**	
Cessation at 6 months (assessed with: biochemical validation)											

2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	43/489 (8.8%)	8/173 (4.6%)	RR 2.02 (0.97 to 4.21)	47 more per 1000 (from 1 fewer to 148 more)	⊕⊕⊕O MODERATE

[1] CI includes MID

GRADE profile 21: E-cigarette vs usual care (Figure 19)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	E-cigarette	Usual care	Relative (95% CI)	Absolute	
Cessation at 6 months (assessed with: biochemical validation)											
2	randomised trials	serious[1]	No serious inconsistency	no serious indirectness	no serious imprecision	none	18/1239 (0.65%)	3/853 (0.35%)	RR 4.92 (1.04 to 16.91)	14 more per 1000 (from 0 more to 56 more)	⊕⊕⊕O MODERATE

[1] Serious risk of bias due to incomplete outcome data in one study, and lack of blinding in the second study

GRADE profile 22: E-cigarette vs NRT long/short acting

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	E-cigarette	NRT short/long acting	Relative (95% CI)	Absolute	
Cessation at 6 months (assessed with: biochemical validation)											
1	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[1]	none	21/289 (7.3%)	17/295 (5.8%)	RR 1.26 (0.68 to 2.34)	15 more per 1000 (from 18 fewer to 77 more)	⊕⊕⊕O MODERATE

[1] CI crosses MID.

GRADE profile 23: Bupropion + NRT long/short vs placebo (Figure 20)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bupropion + NRT short/long	Placebo	Relative (95% CI)	Absolute	
Cessation at 6 months (assessed with: biochemical validation)											
4	randomised trials	no seriou	no serious inconsistency	no serious indirectness	no serious imprecision	None	251/809 (31%)	109/578	RR 1.68	128 more	⊕⊕⊕⊕ HIGH

		s risk of bias[1]						(18.9%)	(1.38 to 2.05)	per 1000 (from 72 more to 198 more)	

[1] One study at risk of bias due to incomplete outcome data, but majority of weight of meta-analysis comes from studies at low risk of bias or with some concerns due to unclear reporting.

GRADE profile 24: Bupropion + NRT long/short vs no drug treatment

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bupropion + NRT short/long	No drug treatment	Relative (95% CI)	Absolute	
Cessation at 6 months (assessed with: biochemical validation)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	None	4/30 (13.3%)	8/50 (16%)	RR 0.83 (0.27 to 2.53)	27 fewer per 1000 (from 117 fewer to 245 more)	⊕OOO VERY LOW

[1] Study at risk of bias due to incomplete outcome data.
[2] CI includes MID and <300 participants.

GRADE profile 25: Bupropion + NRT long/short vs usual care

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bupropion + NRT short/long	Usual care	Relative (95% CI)	Absolute	
Cessation at 6 months (assessed with: biochemical validation)											
1	randomised trials	very serious[1]	NA	no serious indirectness	no serious imprecision	None	28/267 (10.5%)	8/271 (3%)	RR 3.55 (1.65 to 7.65)	75 more per 1000 (from 19 more to 196 more)	⊕⊕OO LOW

[1] Study at high risk of bias due to blinding, and unclear reporting in most other areas

GRADE profile 26: Bupropion + NRT long/short vs NRT long/short (Figure 21)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bupropion + NRT short/long	NRT short/long	Relative (95% CI)	Absolute	
Cessation at 6 months (assessed with: biochemical validation)											

8	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	None	247/971 (25.4%)	404/1647 (24.5%)	RR 1.07 (0.82 to 1.39)	17 more per 1000 (from 44 fewer to 96 more)	⊕OOO VERY LOW

[1] Most weight from studies with some risk due to unclear reporting, but one large study at risk due to incomplete outcome data.
[2] I2 is 61%
[3] CI includes MID

GRADE profile 27: Bupropion + NRT long/short vs bupropion (Figure 22)

Quality assessment							No of patients		Effect		Confidence
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Bupropion + NRT short/long**	**Bupropion**	**Relative (95% CI)**	**Absolute**	
Cessation at 6 months (assessed with: biochemical validation)											
3[1]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	2123/765 (29.2%)	204/762 (26.8%)	RR 1.09 (0.93 to 1.28)	24 more per 1000 (from 19 fewer to 75 more)	⊕OOO VERY LOW

[1] 4 studies in forest plot for illustration, but 1 had no events so is not included in any calculations
[2] CI includes MID

GRADE profile 28: Bupropion + NRT long&short vs NRT long/short (Figure 23)

Quality assessment							No of patients		Effect		Confidence
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Bupropion + NRT short&long**	**NRT short/long**	**Relative (95% CI)**	**Absolute**	
Cessation at 6 months (assessed with: biochemical validation)											
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	27/88 (30.7%)	14/90 (15.6%)	RR 1.97 (1.11 to 3.48)	151 more per 1000 (from 17 more to 386 more)	⊕⊕⊕⊕ HIGH

GRADE profile 29: Varenicline + NRT long/short vs no drug treatment

Quality assessment							No of patients		Effect		Confidence
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Varenicline + NRT long/short**	**No drug treatment**	**Relative (95% CI)**	**Absolute**	
Cessation at 6 months (assessed with: biochemical validation)											

1	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[1]	none	6/148 (4.1%)	19/279 (6.8%)	RR 0.6 (0.24 to 1.46)	27 fewer per 1000 (from 52 fewer to 31 more)	⊕⊕⊕O MODERATE

[1] CI includes MID

GRADE profile 30: Varenicline + NRT long/short vs varenicline (Figure 24)

Quality assessment							No of patients		Effect		Confidence
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Varenicline + NRT long/short**	**Varenicline**	**Relative (95% CI)**	**Absolute**	
Cessation at 6 months (assessed with: biochemical validation)											
2	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	none	127/392 (32.4%)	90/395 (22.8%)	RR 1.41 (0.98 to 2.04)	93 more per 1000 (from 5 fewer to 237 more)	⊕⊕OO LOW

[1] I2 is 60%
[2] CI includes MID

GRADE profile 31: Varenicline + NRT long/short vs bupropion + NRT long/short

Quality assessment							No of patients		Effect		Confidence
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Varenicline + NRT long/short**	**Bupropion + NRT long/short**	**Relative (95% CI)**	**Absolute**	
Cessation at 6 months (assessed with: biochemical validation)											
1	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[1]	none	6/148 (4.1%)	7/143 (4.9%)	RR 0.83 (0.29 to 2.4)	8 fewer per 1000 (from 35 fewer to 69 more)	⊕⊕OO LOW

[1] CI includes MID and <300 participants

GRADE profile 32: Varenicline + bupropion vs placebo

Quality assessment							No of patients		Effect		Confidence
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Varenicline + bupropion**	**Placebo**	**Relative (95% CI)**	**Absolute**	
Cessation at 6 months (assessed with: biochemical validation)											

1	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	38/163 (23.3%)	3/56 (5.4%)	RR 4.35 (1.4 to 13.55)	179 more per 1000 (from 21 more to 672 more)	⊕⊕⊕⊕ HIGH

GRADE profile 33: Varenicline + bupropion vs Varenicline (Figure 25)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Varenicline + bupropion	Varenicline	Relative (95% CI)	Absolute	
Cessation at 6 months (assessed with: biochemical validation)											
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	129/412 (31.3%)	111/423 (26.2%)	RR 1.19 (0.96 to 1.48)	50 more per 1000 (from 10 fewer to 126 more)	⊕⊕⊕O MODERATE

[1] CI includes MID

GRADE profile 34: E-cigarette + NRT long/short vs NRT long/short (Figure 26)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	E-cigarette + NRT long/short	NRT long/short	Relative (95% CI)	Absolute	
Cessation at 6 months (assessed with: biochemical validation)											
2	randomised trials	serious[1]	No serious inconsistency	no serious indirectness	no serious imprecision[2]	none	39/520 (7.5%)	22/519 (4.2%)	RR 1.77 (1.07 to 2.94)	33 more per 1000 (from 3 more to 82 more)	⊕⊕⊕O MODERATE

[1] One study is at risk of bias due to incomplete outcome data, incomplete allocation concealment information in the other study (with higher weight).

GRADE profile 35: Mental health subgroup full NMA

Quality assessment							No of patients across all arms in all studies	Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Cessation at 6 months (assessed with: biochemical validation)								

13	randomised trials	very serious[1]	serious[2]	no serious indirectness	serious[3]	none	5,875	⊕OOO VERY LOW

[1] 46% of studies (6/13) were at high risk of bias.
[2] A random effects model for between studies provided the best fit. However, a fixed effects model for between classes provided best fit so only downgraded by one level.
[3] It was not possible to differentiate between treatments at a statistically significant level (statistical significance is the MID for the outcome of cessation) other than placebo and usual care – see mileage chart for more details.

GRADE profile 36: Mental health subgroup - NRT long/short acting vs placebo (Figure 2)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	NRT long/short acting	Placebo	Relative (95% CI)	Absolute	
Cessation at 6 months - mental health conditions											
2	randomised trials	no serious risk of bias[1]	serious[2]	no serious indirectness	serious[3]	none	109/1035 (10.5%)	63/1036 (6.1%)	RR 2.90 (0.46 to 18.15)	116 more per 1000 (from 22 fewer to 1000 more)	⊕⊕OO LOW

[1] Majority of weight from trial at low risk of bias
[2] I2 is 54%
[3] CI crosses MID (line of no effect)

GRADE profile 37: Mental health subgroup - NRT long/short acting vs no drug treatment (Figure 3)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	NRT long/short acting	No drug treatment	Relative (95% CI)	Absolute	
Cessation at 6 months - mental health conditions											
1	randomised trials	serious[1]	NA	no serious indirectness	serious[2]	none	18/163 (11%)	19/159 (11.9%)	RR 0.92 (0.5 to 1.69)	10 fewer per 1000 (from 60 fewer to 82 more)	⊕⊕OO LOW

[1] Study at high risk of bias due to lack of blinding
[2] CI includes the MID (line of no effect)

GRADE profile 38: Mental health subgroup - NRT long/short acting vs usual care (Figure 5)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	NRT long/short acting	Usual care	Relative (95% CI)	Absolute	
Cessation at 6 months - mental health conditions											
1	randomised trials	serious[1]	NA	no serious indirectness	very serious[2]	none	8/147 (5.4%)	3/151 (2%)	RR 2.74 (0.74 to 10.12)	35 more per 1000 (from 5 fewer to 181 more)	⊕OOO VERY LOW

[1] Study at risk of bias from blinding
[2] CI includes the MID and <300 participants

GRADE profile 39: Mental health subgroup - NRT long&short acting vs usual care

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NRT long&short acting	Waitlist	Relative (95% CI)	Absolute	
Cessation at 6 months (assessed with: biochemical validation)											
1	randomised trials	serious[1]	NA	no serious indirectness	very serious[2]	none	2/105 (1.9%)	0/102 (0%)	RR 4.68 (0.24 to 99.98)	Not calculable	⊕OOO VERY LOW

[1] Some risk of bias due to lack of blinding in the study.
[2] CI crosses MID and <300 participants

GRADE profile 40: Mental health subgroup - Bupropion vs placebo (Figure 9)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Bupropion	Placebo	Relative (95% CI)	Absolute	
Cessation at 6 months - mental health conditions											
4	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	115/1078 (10.7%)	65/1069 (6.1%)	RR 1.73 (1.29 to 2.31)	44 more per 1000 (from 18 more to 80 more)	⊕⊕⊕⊕ HIGH

[1] Study with majority weight at low risk of bias

GRADE profile 41: Mental health subgroup - Bupropion vs NRT long/short acting

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Bupropion	NRT short/long acting	Relative (95% CI)	Absolute	
Cessation at 6 months - mental health conditions											
1	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[1]	none	110/1033 (10.6%)	103/1025 (10%)	RR 1.06 (0.82 to 1.37)	6 more per 1000 (from 18 fewer to 37 more)	⊕⊕⊕O MODERATE

[1] CI includes MID (line of no effect)

GRADE profile 42: Mental health subgroup - Varenicline vs placebo (Figure 14)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Varenicline	Placebo	Relative (95% CI)	Absolute	
Cessation at 6 months - mental health conditions											

4	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	225/1404 (16%)	99/1367 (7.2%)	RR 2.26 (1.81 to 2.83)	91 more per 1000 (from 59 more to 133 more)	⊕⊕⊕⊕ HIGH

[1] No studies at high risk of bias, studies with majority weight at low risk of bias

GRADE profile 43: Mental health subgroup - Varenicline vs NRT long/short acting

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Varenicline	NRT long/short acting	Relative (95% CI)	Absolute	
Cessation at 6 months - mental health conditions											
1	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	148/1032 (14.3%)	103/1025 (10%)	RR 1.43 (1.13 to 1.81)	43 more per 1000 (from 13 more to 81 more)	⊕⊕⊕⊕ HIGH

GRADE profile 44: Mental health subgroup - Varenicline vs bupropion

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Varenicline	Bupropion	Relative (95% CI)	Absolute	
Cessation at 6 months - mental health condition											
1	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	148/1032 (14.3%)	110/1033 (10.6%)	RR 1.35 (1.07 to 1.7)	37 more per 1000 (from 7 more to 75 more)	⊕⊕⊕⊕ HIGH

GRADE profile 45: Mental health subgroup - Bupropion + NRT long/short acting vs NRT long/short acting

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Bupropion + NRT short/long	NRT short/long	Relative (95% CI)	Absolute	
Cessation at 6 months - mental health condition											
1	randomised trials	serious[1]	NA	no serious indirectness	very serious[2]	none	4/30 (13.3%)	0/30 (0%)	RR 9 (0.51 to 160.17)	-	⊕OOO VERY LOW

[1] No information on randomisation or allocation concealment.
[2] CI includes MID (line of no effect) and <300 participants

GRADE profile 46: Mental health subgroup - Bupropion + NRT long & short acting vs NRT long/short acting

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Bupropion + NRT short&long	NRT short/long	Relative (95% CI)	Absolute	
Cessation at 6 months - mental health condition											

1	randomised trials	serious[1]	NA	no serious indirectness	very serious[2]	none	5/25 (20%)	2/26 (7.7%)	RR 2.6 (0.55 to 12.19)	123 more per 1000 (from 35 fewer to 861 more)	⊕OOO VERY LOW

[1] Randomisation and allocation concealment not described.
[2] CI includes MID (line of no effect) and <300 participants

Adverse events, e-cigarettes

GRADE profile 47: E-cigarette vs no drug treatment – adverse events pairwise data (Figure 30 - 31)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	E-cigarette	No drug treatment	Relative (95% CI)	Absolute	
Abnormal dreams, 12 week follow-up											
1 a	randomised trials	serious[1]	NA	no serious indirectness	very serious[2]	none	7/306 (2.3%)	0/102 (0%)	RR 5.03 (0.29 to 87.35)	-	⊕OOO VERY LOW
Anxiety, 12 week follow-up											
1 a	randomised trials	serious[1]	NA	no serious indirectness	very serious[2]	none	13/306 (4.2%)	0/102 (0%)	RR 9.06 (0.54 to 151.04)	-	⊕OOO VERY LOW
Arrhythmia, 12 week follow-up											
1 a	randomised trials	serious[1]	NA	no serious indirectness	very serious[2]	none	1/306 (0.33%)	0/102 (0%)	RR 1.01 (0.04 to 24.52)	-	⊕OOO VERY LOW
Death (all causes), 12 week follow-up											
1 a	randomised trials	serious[1]	NA	no serious indirectness	serious[3]	none	1/306 (0.33%)	0/102 (0%)	RR 1.01 (0.04 to 24.52)	-	⊕⊕OO LOW
Dry Mouth, 12 week follow-up											
1 a	randomised trials	serious[1]	NA	no serious indirectness	very serious[2]	none	8/306 (2.6%)	0/102 (0%)	RR 5.7 (0.33 to 97.96)	-	⊕OOO VERY LOW
Fatigue, 12 week follow-up											
1 a	randomised trials	serious[1]	NA	no serious indirectness	very serious[2]	none	9/306 (2.9%)	1/102 (0.98%)	RR 3 (0.38 to 23.39)	20 more per 1000 (from 6 fewer to 220 more)	⊕OOO VERY LOW
Headache, 12-16 week follow-up											
2 a, b	randomised trials	serious[4]	very serious[5]	no serious indirectness	very serious[2]	none	149/352 (42.3%)	39/124 (31.5%)	RR 0.85 (0.24 to 2.98)	47 fewer per 1000 (from 239 fewer to 623 more)	⊕OOO VERY LOW
Insomnia, 12 week follow-up											
1 a	randomised trials	serious[1]	NA	no serious indirectness	very serious[2]	none	14/306 (4.6%)	2/102 (2%)	RR 2.33 (0.54 to 10.09)	26 more per 1000 (from 9 fewer to 178 more)	⊕OOO VERY LOW
Irritability, 12 week follow-up											
1 a	randomised trials	serious[1]	NA	no serious indirectness	no serious imprecision	none	33/306 (10.8%)	1/102 (0.98%)	RR 11 (1.52 to 79.41)	98 more per 1000 (from 5 more to	⊕⊕⊕O MODERATE

										769 more)	
Nausea, 12-16 week follow-up											
2 a, b	randomised trials	serious[4]	serious[6]	no serious indirectness	very serious[2]	none	38/352 (10.8%)	5/124 (4%)	RR 2.95 (0.36 to 24.19)	79 more per 1000 (from 26 fewer to 935 more)	⊕OOO VERY LOW
Serious Adverse Events, 12 week follow-up											
1 a	randomised trials	serious[1]	NA	no serious indirectness	very serious[2]	none	5/306 (1.6%)	0/102 (0%)	RR 3.69 (0.21 to 66.17)	-	⊕OOO VERY LOW
Skin Rash, 12 week follow-up											
1 a	randomised trials	serious[1]	NA	no serious indirectness	very serious[2]	none	6/306 (2%)	0/102 (0%)	RR 4.36 (0.25 to 76.75)	-	⊕OOO VERY LOW
Sleep Disorders, 12 week follow-up											
1 a	randomised trials	serious[1]	NA	no serious indirectness	very serious[2]	none	11/306 (3.6%)	2/102 (2%)	RR 1.83 (0.41 to 8.13)	16 more per 1000 (from 12 fewer to 140 more)	⊕OOO VERY LOW
Withdrew from study due to AE, 12 week follow-up											
1 a	randomised trials	serious[1]	NA	no serious indirectness	very serious[2]	none	3/306 (0.98%)	1/102 (0.98%)	RR 1 (0.11 to 9.51)	0 fewer per 1000 (from 9 fewer to 83 more)	⊕OOO VERY LOW

[1] Study was at high risk for different rates of missing outcome data between groups.
[2] CI crosses both MIDs (0.8 and 1.25)
[3] CI crosses MID (line of no effect)
[4] One study at high risk for different rates of missing outcome data between groups; the other study for unclear reporting on outcome measurement
[5] I2 is 76%
[6] I2 is 73%

a) Cravo 2016
b) Carpenter 2017

GRADE profile 48: E-cigarette vs NRT – adverse events pairwise data (Figure 32 - 39)

Quality assessment							No of patients		Effect		Confidence
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**E-cigarette**	**NRT**	**Relative (95% CI)**	**Absolute**	
Abnormal dreams, 24 week follow-up											
1 a	randomised trials	serious[1]	NA	no serious indirectness	very serious[2]	none	4/18 (22.2%)	3/19 (15.8%)	RR 1.41 (0.36 to 5.43)	65 more per 1000 (from 101 fewer to 699 more)	⊕OOO VERY LOW
Anxiety, 24 week follow-up											
1 a	randomised trials	serious[1]	NA	no serious indirectness	very serious[2]	none	0/18 (0%)	1/19 (5.3%)	RR 0.35 (0.02 to 8.09)	34 fewer per 1000 (from 52 fewer to 373 more)	⊕OOO VERY LOW
Cardiovascular Death, 12-24 week follow-up											
2 b, c	randomised trials	no serious risk of bias[3]	no serious inconsistency	no serious indirectness	serious[4]	none	2/680 (0.29%)	0/662 (0%)	RR 2.86 (0.3 to 27.38)	-	⊕OOO MODERATE

Death (all causes) , 12-24 week follow-up											
2 b, c	randomised trials	no serious risk of bias[3]	no serious inconsistency	no serious indirectness	serious[4]	none	2/680 (0.29%)	1/662 (0.15%)	RR 1.6 (0.21 to 12.25)	1 more per 1000 (from 1 fewer to 17 more)	⊕⊕⊕O MODERATE
Depression, 24 week follow-up											
1 c	randomised trials	no serious risk of bias[3]	NA	no serious indirectness	very serious[2]	none	1/439 (0.23%)	0/447 (0%)	RR 3.05 (0.12 to 74.78)	-	⊕⊕OO LOW
Fatigue, 24 week follow-up											
1 a	randomised trials	serious[1]	NA	no serious indirectness	very serious[2]	none	1/18 (5.6%)	1/19 (5.3%)	RR 1.06 (0.07 to 15.64)	3 more per 1000 (from 49 fewer to 771 more)	⊕OOO VERY LOW
Headache, 8-24 week follow-up											
3 a, c, d	randomised trials	no serious risk of bias[5]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/478 (1%)	5/476 (1.1%)	RR 0.64 (0.23 to 1.73)	4 fewer per 1000 (from 8 fewer to 8 more)	⊕⊕OO LOW
Hospitalisation, 12-24 week follow-up											
2 b, c	randomised trials	no serious risk of bias[3]	no serious inconsistency	no serious indirectness	serious[6]	none	19/680 (2.8%)	9/662 (1.4%)	RR 1.85 (0.87 to 3.94)	12 more per 1000 (from 2 fewer to 40 more)	⊕⊕⊕O MODERATE
Insomnia, 24 week follow-up											
1 a	randomised trials	serious[1]	NA	no serious indirectness	very serious[2]	none	1/18 (5.6%)	2/19 (10.5%)	RR 0.53 (0.05 to 5.33)	49 fewer per 1000 (from 100 fewer to 456 more)	⊕OOO VERY LOW
Nausea, 8-24 week follow-up											
3 a, c, d	randomised trials	no serious risk of bias[5]	no serious inconsistency	no serious indirectness	serious[6]	none	144/476 (30.3%)	170/475 (35.8%)	RR 0.85 (0.71 to 1.02)	54 fewer per 1000 (from 104 fewer to 7 more)	⊕⊕⊕O MODERATE
Non-fatal MI, 12-24 week follow-up											
2 b, c	randomised trials	no serious risk of bias[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/680 (0.59%)	1/662 (0.15%)	RR 2.84 (0.44 to 18.42)	3 more per 1000 (from 1 fewer to 26 more)	⊕⊕OO LOW
Non-fatal Stroke, 24 week follow-up											
1 b	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[2]	none	2/241 (0.83%)	0/215 (0%)	RR 4.46 (0.22 to 92.44)	-	⊕⊕OO LOW
Palpitations, 8-24 week follow-up											
3 a, b, d	randomised trials	no serious risk of bias[5]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/279 (0.72%)	3/244 (1.2%)	RR 0.63 (0.18 to 2.21)	5 fewer per 1000 (from 10 fewer to 15 more)	⊕⊕OO LOW
Pruiritus, 24 week follow-up											
1 a	randomised trials	serious[1]	NA	no serious indirectness	very serious[2]	none	1/18 (5.6%)	0/19 (0%)	RR 3.16 (0.14 to 72.84)	-	⊕OOO VERY LOW
Serious Adverse Events, 8-24 week follow-up											
3[7] b-d	randomised trials	no serious risk of bias[3]	no serious inconsistency	no serious indirectness	serious imprecision[6]	none	48/700 (6.9%)	33/672 (4.9%)	RR 1.41 (0.91 to 2.17)	20 more per 1000 (from 4	⊕⊕⊕O MODERATE

										fewer to 57 more)	
Skin Rash, 8 week follow-up											
1 d	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[2]	none	2/20 (10%)	3/10 (30%)	RR 0.33 (0.07 to 1.68)	201 fewer per 1000 (from 279 fewer to 204 more)	⊕⊕OO LOW
Sleep Disorders, 24 week follow-up											
1 c	randomised trials	no serious risk of bias[3]	NA	no serious indirectness	no serious imprecision[8]	none	279/438 (63.7%)	303/446 (67.9%)	RR 0.94 (0.85 to 1.03)	41 fewer per 1000 (from 102 fewer to 20 more)	⊕⊕⊕⊕ HIGH
Suicidal Ideation, 24 week follow-up											
1 c	randomised trials	no serious risk of bias[3]	NA	no serious indirectness	very serious[2]	none	1/439 (0.23%)	0/447 (0%)	RR 3.05 (0.12 to 74.78)	-	⊕⊕OO LOW
Transient Ischemic Attack, 12-24 week follow-up											
2[7] b, c	randomised trials	no serious risk of bias[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/680 (0%)	1/662 (0.15%)	RR 0.34 (0.01 to 8.31)	1 fewer per 1000 (from 1 fewer to 11 more)	⊕⊕OO LOW

[1] Study had higher attrition from e-cigarette group than the NRT group
[2] CI crosses both MIDs (0.8 and 1.25)
[3] Although blinding of participants not conducted, may have little impact on results as both are active treatments.
[4] CI crosses MID (line of no effect)
[5] One study had uneven attrition, but only has minority of weight in meta-analysis
[6] CI crosses one MID
[7] One study had no events so did not contribute data to this outcome, therefore no forest plot has been produced
[8] CI is within both MID thresholds

a) Baldassarri 2018
b) Bullen 2013
c) Hajek 2019
d) Lee 2018

GRADE profile 49: E-cigarette vs placebo e-cigarette – adverse events pairwise data (Figure 40 - 42)

Quality assessment							No of patients		Effect		Confidence
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**E-cigarette**	**Placebo e-cigarette**	**Relative (95% CI)**	**Absolute**	
Abnormal dreams, 3 week follow-up											
1 a	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[1]	none	14/41 (34.1%)	8/40 (20%)	RR 1.71 (0.81 to 3.62)	142 more per 1000 (from 38 fewer to 524 more)	⊕⊕⊕O MODERATE
Cardiovascular Death, 3-24 week follow-up											
2[2] a, b	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	1/282 (0.35%)	0/97 (0%)	RR 0.72 (0.03 to 17.42)	-	⊕⊕⊕O MODERATE
Death (all causes), 3-24 week follow-up											
2[2] a, b	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	1/282 (0.35%)	0/97 (0%)	RR 0.72 (0.03 to 17.42)	-	⊕⊕⊕O MODERATE

Fatigue, 3 week follow-up											
1 a	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[5]	none	11/41 (26.8%)	7/40 (17.5%)	RR 1.53 (0.66 to 3.56)	93 more per 1000 (from 59 fewer to 448 more)	⊕⊕OO LOW
Headache, 3-4 week follow-up											
2 a, c	randomised trials	no serious risk of bias[6]	no serious inconsistency	no serious indirectness	very serious[5]	none	13/111 (11.7%)	13/110 (11.8%)	RR 0.98 (0.5 to 1.92)	2 fewer per 1000 (from 59 fewer to 109 more)	⊕⊕OO LOW
Hospitalisation, 24 week follow-up											
1 b	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[5]	none	17/241 (7.1%)	4/57 (7%)	RR 1.01 (0.35 to 2.87)	1 more per 1000 (from 46 fewer to 131 more)	⊕⊕OO LOW
Insomnia, 3-4 week follow-up											
2 a, c	randomised trials	no serious risk of bias[6]	no serious inconsistency	no serious indirectness	very serious[5]	none	14/111 (12.6%)	9/110 (8.2%)	RR 1.52 (0.73 to 3.18)	43 more per 1000 (from 22 fewer to 178 more)	⊕⊕OO LOW
Nausea, 3-4 week follow-up											
2 a, c	randomised trials	no serious risk of bias[6]	no serious inconsistency	no serious indirectness	very serious[5]	none	12/111 (10.8%)	8/110 (7.3%)	RR 1.48 (0.63 to 3.45)	35 more per 1000 (from 27 fewer to 178 more)	⊕⊕OO LOW
Non-fatal MI, 24 week follow-up											
1 b	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[5]	none	3/241 (1.2%)	1/57 (1.8%)	RR 0.71 (0.08 to 6.7)	5 fewer per 1000 (from 16 fewer to 100 more)	⊕⊕OO LOW
Non-fatal Stroke, 24 week follow-up											
1 b	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[5]	none	2/241 (0.83%)	0/57 (0%)	RR 1.2 (0.06 to 24.62)	-	⊕⊕OO LOW
Palpitations, 3-24 week follow-up											
2[2] a, b	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	4/282 (1.4%)	4/97 (4.1%)	RR 0.98 (0.26 to 3.64)	1 fewer per 1000 (from 31 fewer to 109 more)	⊕⊕OO LOW
Serious Adverse Events, 3-52 week follow-up											
3[2] a, b, d	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	21/482 (4.4%)	4/197 (2%)	RR 1.24 (0.44 to 3.48)	5 more per 1000 (from 11 fewer to 50 more)	⊕⊕OO LOW

[1] CI crosses one MID
[2] Only one study contributed data as other study/ies had no events in either arm, therefore no forest plot has been produced
[3] CI crosses MID (line of no effect)
[4] CI crosses MID (line of no effect) and <300 participants
[5] CI crosses both MIDs (0.8 and 1.25)
[6] For one study attrition distribution unclear, and protocol does not specify cessation outcome or thresholds. However very small weight in meta-analysis.

a) Tseng 2016
b) Bullen 2013
c) Masiero 2018

d) Caponnetto 2013

Cessation, short follow-up

GRADE profile 50 E-cigarettes vs placebo e-cigarette, smoking cessation (Figure 43 - 44)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Nicotine e-cigarette	Placebo e-cigarette	Relative (95% CI)	Absolute	
Smoking abstinence 1-<3 month follow-up (follow-up 4-8 weeks; assessed with: Exhaled CO)											
2 (a, b)	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	none	69/309 (22.3%)	17/93 (18.3%)	RR 0.92 (0.29 to 2.97)	15 fewer per 1000 (from 130 fewer to 360 more)	⊕⊕OO LOW
Smoking abstinence 3-<6 month follow-up (follow-up 3 months; assessed with: Exhaled CO)											
2 (b, c)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	53/359 (14.8%)	18/143 (12.6%)	RR 1.45 (0.84 to 2.48)	57 more per 1000 (from 20 fewer to 186 more)	⊕⊕⊕O MODERATE

[1] I2 is over 50%
[2] CIs cross the line of no effect (MID) but >300 participants
a) Baldassarri 2018
b) Bullen 2013
c) Masiero 2018

GRADE profile 51: E-cigarettes vs NRT, smoking cessation (Figure 45)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Nicotine e-cigarette	NRT short- or long-acting	Relative (95% CI)	Absolute	
Smoking abstinence 1-<3 month follow-up (follow-up 4-8 weeks; assessed with: Exhaled CO)											
3 (b, d, e)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	262/747 (35.1%)	181/751 (24.1%)	RR 1.47 (1.25 to 1.72)	113 more per 1000 (from 60 more to 174 more)	⊕⊕⊕O MODERATE
Smoking abstinence 3-<6 month follow-up (follow-up 3 months; assessed with: Exhaled CO)											
1 (b)	randomised trials	serious[1]	NA	no serious indirectness	serious[3]	none	38/289 (13.1%)	27/295 (9.2%)	RR 1.44 (0.9 to 2.29)	40 more per 1000 (from 9 fewer to 118 more)	⊕⊕OO LOW

[1] Participants can't be blinded to intervention status, could affect expectations.
[2] One study pre-operative setting, could differ in motivation from general population. Smallest study so not sufficient to downgrade.
[3] CI crosses line of no effect (MID) but >300 participants

b) Bullen 2013

d) Hajek 2019

e) Lee 2018

GRADE profile 52: E-cigarettes vs no/minimal intervention, smoking cessation (Figure 46)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Nicotine e-cigarette	No intervention	Relative (95% CI)	Absolute	
Smoking abstinence 1-<3 month follow-up (follow-up 1 months; assessed with: urinary cotinine and blood carboxyhaemoglobin)											
1 (f)	randomised trials	serious[1]	NA	serious[2]	serious[3]	none	28/1199 (2.3%)	9/813 (1.1%)	RR 2.11 (1 to 4.45)	12 more per 1000 (from 0 more to 38 more)	⊕OOO VERY LOW
Smoking abstinence 3-<6 month follow-up (follow-up 3 months; assessed with: Exhaled CO)											
2 (f, g)	randomised trials	serious[4]	no serious inconsistency	serious[5]	no serious imprecision	none	35/1269 (2.8%)	8/883 (0.91%)	RR 3.72 (1.73 to 7.97)	25 more per 1000 (from 7 more to 63 more)	⊕⊕OO LOW

[1] Measurement of the outcome was different across study arms. Most participants did not engage with the intervention - likely to underestimate effectiveness.
[2] Study takes place in working population which may be systematically different from general population
[3] CI crosses line of no effect (MID) but >300 participants
[4] In one study, measurement of the outcome was different across study arms and most participants did not engage with the intervention - likely to underestimate effectiveness. In the other study missing data may have biased the results.
[5] The larger study takes place in working population which may be systematically different from general population

f) Halpern 2018

g) Masiero 2018

Harm reduction

No evidence to GRADE

Appendix G – Excluded studies

Cessation

Public health studies, relative effectiveness and adverse events

Original searches and sifting conducted by Thomas (2020).

Public health studies, short follow-up

Study Citation	Reason for excluding
Adriaens K, Van Gucht , D , Declerck P, and Baeyens F (2014) 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 11(11), 11220-11248	Exclude on population: participants had no intention of stopping smoking
Caponnetto P, Campagna D, Cibella F, Morjaria J B, Caruso M, Russo C, and Polosa R (2013) EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. Plos One 8(6), e66317	Exclude on population: participants had no intention of stopping smoking
Carpenter M J, Heckman B W, Wahlquist A E, Wagener T L, Goniewicz M L, Gray K M, Froeliger B, and Cummings K M (2017) A Naturalistic, Randomized Pilot Trial of E-Cigarettes: Uptake, Exposure, and Behavioral Effects. Cancer Epidemiology, and Biomarkers & Prevention 26(12), 1795-1803	Exclude on population: participants had no intention of stopping smoking
Cravo A S, Bush J, Sharma G, Savioz R, Martin C, Craige S, and Walele T (2016) A randomised, parallel group study to evaluate the safety profile of an electronic vapour product over 12 weeks. Regulatory Toxicology and Pharmacology 81, S1-S14	Exclude on outcomes: does not measure any cessation outcomes
Eisenhofer J, Makanjuola T, Martinez V, Thompson-Lake D G, Rodgman C, DeBrule D S, Graham D P, De La Garza , and Ii R (2015) Efficacy of electronic cigarettes for smoking cessation in veterans. Drug and Alcohol Dependence 156, e63-e64	Exclude on follow-up: longest follow-up is 3 weeks
Felicione N J, Enlow P, Elswick D, Long D, Rolly Sullivan, C , and Blank M D (2018) A pilot investigation of the effect of electronic cigarettes on smoking behavior among opioid-dependent smokers. Addictive Behaviors. ,	Exclude on outcomes: no effectiveness data
Tseng T Y, Ostroff J S, Campo A, Gerard M, Kirchner T, Rotrosen J, and Shelley D (2016) A Randomized Trial Comparing the Effect of Nicotine Versus Placebo Electronic Cigarettes on Smoking Reduction Among Young Adult Smokers. Nicotine & Tobacco Research 18(10), 1937-1943	Exclude on intervention: intention is to reduce harm only

Public health rerun search - cessation

Study Citation	Reason for excluding
Aldi Giulia A, Bertoli Giuly, Ferraro Francesca, Pezzuto Aldo, and Cosci Fiammetta (2018) Effectiveness of pharmacological or psychological interventions for smoking cessation in smokers with major depression or depressive symptoms: A systematic review of the literature. Substance abuse 39(3), 289-306	Exclude on study design – systematic review
Aveyard Paul, Lindson Nicola, Tearne Sarah, Adams Rachel, Ahmed Khaled, Alekna Rhona, Banting Miriam, Healy Mike, Khan Shahnaz,	Exclude on intervention – choice of interventions

Rai Gurmail, Wood Carmen, Anderson Emma C, Ataya-Williams Alia, Attwood Angela, Easey Kayleigh, Fluharty Megan, Freuler Therese, Hurse Megan, Khouja Jasmine, Lacey Lindsey, Munafo Marcus, Lycett Deborah, McEwen Andy, Coleman Tim, Dickinson Anne, Lewis Sarah, Orton Sophie, Perdue Johanna, Randall Clare, Anderson Rebecca, Bisal Natalie, Hajek Peter, Homsey Celine, McRobbie Hayden J, Myers-Smith Katherine, Phillips Anna, Przulj Dunja, Li Jinshuo, Coyle Doug, Coyle Katherine, and Pokhrel Subhash (2018) Nicotine preloading for smoking cessation: the Preloading RCT. Health technology assessment (Winchester, and England) 22(41), 1-84	means can't identify what intervention is being investigated
Bold Krysten W, Zweben Allen, Fucito Lisa M, Piepmeier Mary E, Muvvala Srinivas, Wu Ran, Gueorguieva Ralitza, and O'Malley Stephanie S (2019) Longitudinal Findings from a Randomized Clinical Trial of Varenicline for Alcohol Use Disorder with Comorbid Cigarette Smoking. Alcoholism, and clinical and experimental research 43(5), 937-944	Exclude as duplicate
Caponnetto Pasquale, DiPiazza Jennifer, Cappello Giorgio Carlo, Demma Shirin, Maglia Marilena, and Polosa Riccardo (2019) Multimodal Smoking Cessation in a Real-Life Setting: Combining Motivational Interviewing With Official Therapy and Reduced Risk Products. Tobacco use insights 12, 1179173X19878435	Exclude on study design – not randomised
Clyde Matthew, Pipe Andrew, Els Charl, Reid Robert, Fu Angel, Clark Alexa, and Tulloch Heather (2018) Nicotine metabolite ratio and smoking outcomes using nicotine replacement therapy and varenicline among smokers with and without psychiatric illness. Journal of psychopharmacology (Oxford, and England) 32(9), 979-985	Exclude as duplicate
Cropley M, Theadom A, Pravettoni G, and Webb G (2008) The effectiveness of smoking cessation interventions prior to surgery: a systematic review. Nicotine & tobacco research 10(3), 407-412	Exclude on study design – systematic review
Cunningham John A, Kushnir Vladyslav, Selby Peter, Tyndale Rachel F, Zawertailo Laurie, and Leatherdale Scott T (2018) Beyond Quitting: Any Additional Impact of Mailing Free Nicotine Patches to Current Smokers?. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 20(5), 654-655	Exclude as duplicate
Doran N, Dubrava S, and Anthenelli R M (2019) Effects of varenicline, depressive symptoms, and region of enrollment on smoking cessation in depressed smokers. Nicotine and Tobacco Research 21(2), 156-162	Exclude as duplicate
Drovandi Aaron D, Teague Peta-Ann, Glass Beverley D, and Malau-Aduli Bunmi (2018) A systematic review investigating the impact of modified varenicline regimens on smoking cessation. Journal of Smoking Cessation 13(1), 44-54	Exclude on study design – systematic review
Etter J-F, and Stapleton Ja (2006) Nicotine replacement therapy for long-term smoking cessation: a meta-analysis. Tobacco control 15(4), 280-285	Exclude on study design – systematic review
Gilbody S, Peckham E, Bailey D, Arundel C, Heron P, Crosland S, Fairhurst C, Hewitt C, Li J S, Parrott S, Bradshaw T, Horspool M, Hughes E, Hughes T, Ker S, Leahy M, McCloud T, Osborn D, Reilly J, Steare T, Ballantyne E, Bidwell P, Bonner S, Brennan D, Callen T, Carey A, Colbeck C, Coton D, Donaldson E, Evans K, Herlihy H, Khan W, Nyathi L, Nyamadzawo E, Oldknow H, Phiri P, Rathod S, Rea J, Romain-Hooper C B, Smith K, Stribling A, and Vickers C (2019) Smoking cessation for people with severe mental illness (SCIMITAR plus): a pragmatic randomised controlled trial. Lancet Psychiatry 6(5), 379-390	Exclude on intervention – choice of interventions means can't identify what intervention is being investigated

Gray Kevin M, Baker Nathaniel L, McClure Erin A, Tomko Rachel L, Squeglia Lindsay M, Saladin Michael E, and Carpenter Matthew J (2019) Efficacy and Safety of Varenicline for Adolescent Smoking Cessation: A Randomized Clinical Trial. JAMA pediatrics ,	Exclude on population – participants 14-21 and most too young to match protocol.
Hall Sharon M, Humfleet Gary L, Gasper James J, Delucchi Kevin L, Hersh David F, and Guydish Joseph R (2018) Cigarette Smoking Cessation Intervention for Buprenorphine Treatment Patients. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 20(5), 628-635	Exclude on intervention – all participants received buprenorphine which is excluded
Noor F, Koegelenberg C F. N, Esterhuizen T M, and Irusen E M (2017) Predictors of treatment success in smoking cessation with varenicline combined with nicotine replacement therapy v. varenicline alone. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde 108(1), 45-49	Exclude as duplicate
Okuyemi Ks, Thomas Jl, Warren J, Guo H, and Ahluwalia Js (2010) Relationship between smoking reduction and cessation among light smokers. Nicotine & tobacco research 12(10), 1005-1010	Exclude on outcome – cigarettes per day
Peckham Emily, Arundel Catherine, Bailey Della, Crosland Suzanne, Fairhurst Caroline, Heron Paul, Hewitt Catherine, Li Jinshuo, Parrott Steve, Bradshaw Tim, Horspool Michelle, Hughes Elizabeth, Hughes Tom, Ker Suzy, Leahy Moira, McCloud Tayla, Osborn David, Reilly Joseph, Steare Thomas, Ballantyne Emma, Bidwell Polly, Bonner Susan, Brennan Diane, Callen Tracy, Carey Alex, Colbeck Charlotte, Coton Debbie, Donaldson Emma, Evans Kimberley, Herlihy Hannah, Khan Wajid, Nyathi Lizwi, Nyamadzawo Elizabeth, Oldknow Helen, Phiri Peter, Rathod Shanaya, Rea Jamie, Romain-Hooper Crystal-Bella, Smith Kaye, Stribling Alison, Vickers Carinna, and Gilbody Simon (2019) A bespoke smoking cessation service compared with treatment as usual for people with severe mental ill health: the SCIMITAR+ RCT. Health technology assessment (Winchester, and England) 23(50), 1-116	Exclude on intervention – choice of interventions means can't identify what intervention is being investigated
Schlam Tanya R, Baker Timothy B, Smith Stevens S, Cook Jessica W, and Piper Megan E (2019) Anxiety Sensitivity and Distress Tolerance in Smokers: Relations with Tobacco Dependence, Withdrawal, and Quitting Success. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco ,	Exclude as duplicate
Underner M, Perriot J, Brousse G, de Chazeron , I , Schmitt A, Peiffer G, Harika-Germaneau G, and Jaafari N (2019) Stopping and reducing smoking in patients with schizophrenia. Encephale 45(4), 345-356	Exclude on language – not available in English
Windle Sarah B, Dehghani Payam, Roy Nathalie, Old Wayne, Grondin Francois R, Bata Iqbal, Iskander Ayman, Lauzon Claude, Srivastava Nalin, Clarke Adam, Cassavar Daniel, Dion Danielle, Haught Herbert, Mehta Shamir R, Baril Jean-Francois, Lambert Charles, Madan Mina, Abramson Beth L, Eisenberg Mark J, and Investigators Evita (2018) Smoking abstinence 1 year after acute coronary syndrome: follow-up from a randomized controlled trial of varenicline in patients admitted to hospital. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 190(12), E347-E354	Exclude as duplicate
Wu P, Wilson K, Dimoulas P, and Mills Ej (2006) Effectiveness of smoking cessation therapies: a systematic review and meta-analysis. BMC public health 6,	Exclude on study design – systematic review
Zarghami Mehran, Taghizadeh Fatemeh, Sharifpour Ali, and Alipour Abbas (2018) Efficacy of Smoking Cessation on Stress, Anxiety, and Depression in Smokers with Chronic Obstructive Pulmonary Disease: A Randomized Controlled Clinical Trial. Addiction & health 10(3), 137-147	Exclude on outcome – outcome is not validated

Zhong Zhaoshuang, Zhao Shijie, Zhao Yan, and Xia Shuyue (2019) Combination therapy of varenicline and bupropion in smoking cessation: A meta-analysis of the randomized controlled trials. Comprehensive psychiatry 95, 152125	Exclude on study design – systematic review

Economic studies

Study Citation	Reason for excluding
Akehurst RL, Piercy J. Cost-effectiveness of the use of transdermal Nicorette patches relative to GP counselling and nicotine gum in the prevention of smoking-related diseases. Br J Med Econ. 1994;7(I):115-22.	Ineligible Publication Date
Akehurst R, Piercy J. Cost-effectiveness of the use of Nicorette nasal spray to assist quitting smoking among heavy smokers. Br J Med Econ. 1994; 7(II):155-84.	Ineligible Publication Date
Ali A, Kaplan CM, Derefinko KJ, Klesges RC. Smoking cessation for smokers not ready to quit: Meta-analysis and cost-effectiveness analysis. Am J Prev Med. 2018;55(2):253-62.	Ineligible Country
Institute for Quality and Efficiency in Health Care. Health economic evaluation of venlafaxine, duloxetine, bupropion, and mirtazapine compared to further prescribable pharmaceutical treatments. Cologne, Germany: 2013. Available from: https://www.ncbi.nlm.nih.gov/books/NBK385761/.	Ineligible outcomes
Annemans L, Nackaerts K, Bartsch P, Prignot J, Marbaix S. Cost effectiveness of varenicline in Belgium, compared with bupropion, nicotine replacement therapy, brief counselling and unaided smoking cessation: A BENESCO Markov cost-effectiveness analysis. Clin Drug Investig. 2009;29(10):655-65.	Ineligible Publication Date
Anonymous. Varenicline effective for smoking cessation. J Fam Pract. 2006;55(10):848-49.	Ineligible Publication Date
Anonymous. Smoking cessation: Nicotine replacement works. US Pharm. 1995;20(6):84.	Ineligible Publication Date
Antonanzas F, Portillo F. Economic evaluation of pharmacotherapies for smoking cessation. Gac Sanit. 2003;17(5):393-403.	Ineligible Language
Antonopoulos MS, Bercume CM. Varenicline (Chantix): A new treatment option for smoking cessation. Pharmacol Therapeut. 2007;32(1):20.	Ineligible Outcomes
Aveyard P, Parsons A, Begh R. Smoking cessation 4: Antidepressants for smoking cessation - Bupropion and nortriptyline. Prim Care Cardiovasc J. 2010;3(1):32-34.	Unobtainable
Bae JY, Kim CH, Lee EK. Evaluation of cost-utility of varenicline compared with existing smoking cessation therapies in South Korea. Value Health. 2009;12 (Suppl 3):S70-3.	Ineligible Country
Baker CL, Ding Y, Ferrufino CP, Kowal S, Tan J, Subedi P. A cost-benefit analysis of smoking cessation prescription coverage from a US payer perspective. ClinicoEcon. 2018;10:359-70.	Ineligible Outcomes
Baker CL, Pietri G. A cost-effectiveness analysis of varenicline for smoking cessation using data from the EAGLES trial. ClinicoEcon. 2018;10:67-74.	Ineligible Country
Barnett PG, Wong W, Jeffers A, Hall SM, Prochaska JJ. Cost-effectiveness of smoking cessation treatment initiated during psychiatric hospitalization: Analysis from a randomized, controlled trial. J Clin Psychiatry. 2015;76(10):e1285-e91.	Ineligible Intervention
Barnett PG, Ignacio RV, Kim HM, Geraci MC, Essenmacher CA, Hall SV, et al. Cost-effectiveness of real-world administration of tobacco	Ineligible Study Design

pharmacotherapy in the United States Veterans Health Administration. Addiction. 2019;114(8):1436-45.	
Barnett PG, Wong W, Hall S. The cost-effectiveness of a smoking cessation program for out-patients in treatment for depression. Addiction. 2008;103(5):834-40.	Ineligible Intervention
Barnett PG, Wong W, Jeffers A, Munoz R, Humfleet G, Hall S. Cost-effectiveness of extended cessation treatment for older smokers. Addiction. 2014;109(2):314-22.	Ineligible Patient Population
Bauld L, Boyd KA, Briggs AH, Chesterman J, Ferguson J, Judge K, et al. One-year outcomes and a cost-effectiveness analysis for smokers accessing group-based and pharmacy-led cessation services. Nicotine Tob Res. 2011;13(2):135-45.	Ineligible Study Design
Berndt N, Bolman C, Lechner L, Max W, Mudde A, de Vries H, et al. Economic evaluation of a telephone- and face-to-face-delivered counseling intervention for smoking cessation in patients with coronary heart disease. Eur J Health Econ. 2016;17(3):269-85.	Ineligible Intervention
Bolin K, Lindgren B, Willers S. The cost utility of bupropion in smoking cessation health programs: Simulation model results for Sweden. Chest. 2006;129(3):651-60.	Ineligible Publication Date
Bolin K, Mork A-C, Willers S, Lindgren B. Varenicline as compared to bupropion in smoking-cessation therapy--Cost-utility results for Sweden 2003. Respir Med. 2008;102(5):699-710.	Ineligible Publication Date
Bolin K, Mork A-C, Wilson K. Smoking-cessation therapy using varenicline: The cost-utility of an additional 12-week course of varenicline for the maintenance of smoking abstinence. J Eval Clin Pract. 2009;15(3):478-85.	Ineligible Patient Population
Bolin K, Wilson K, Benhaddi H, de Nigris E, Marbaix S, Mork A-C, et al. Cost-effectiveness of varenicline compared with nicotine patches for smoking cessation--Results from four European countries. Eur J Public Health. 2009;19(6):650-4.	Ineligible Publication Date
Boyd KA, Briggs AH. Cost-effectiveness of pharmacy and group behavioural support smoking cessation services in Glasgow. Addiction. 2009;104(2):317-25.	Ineligible Intervention
Bullen C, Verbiest M, Galea-Singer S, Kurdziel T, Laking G, Newcombe D, et al. 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. 2018;18(1):596.	Ineligible Study Design
Carpenter CR. Promoting tobacco cessation in the military: An example for primary care providers. Mil Med. 1998;163(8):515-8.	Ineligible Setting
Cohen DR, Fowler GH. Economic implications of smoking cessation therapies: A review of economic appraisals. Pharmacoeconomics. 1993;4(5):331-44.	Ineligible Intervention
Cole S, Suter C, Nash C, Pollard J. Impact of a temporary NRT enhancement in a state quitline and web-based program. Am J Health Promot. 2018;32(5):1206-13.	Ineligible Study Design
Cook R, Davidson P, Martin R, Centre ND. E-cigarettes helped more smokers quit than nicotine replacement therapy. BMJ (Clinical research ed.). 2019;365:l2036.	Ineligible Study Design
Cornuz J, Gilbert A, Pinget C, McDonald P, Slama K, Salto E, et al. Cost-effectiveness of pharmacotherapies for nicotine dependence in primary care settings: A multinational comparison. Tob Control. 2006;15(3):152-9.	Ineligible Publication Date
Cornuz J, Pinget C, Gilbert A, Paccaud F. Cost-effectiveness analysis of the first-line therapies for nicotine dependence. Eur J Clin Pharmacol. 2003;59(3):201-6.	Ineligible Publication Date

Crealey GE, McElnay JC, Maguire TA, O'Neill C. Costs and effects associated with a community pharmacy-based smoking-cessation programme. Pharmacoeconomics. 1998;14(3):323-33.	Ineligible Intervention
Croghan IT, Offord KP, Evans RW, Schmidt S, Gomez-Dahl LC, Schroeder DR, et al. Cost-effectiveness of treating nicotine dependence: The Mayo Clinic experience. Mayo Clin Proc. 1997;72(10):917-24.	Ineligible Intervention
Curry SJ, Grothaus LC, McAfee T, Pabiniak C. Use and cost effectiveness of smoking-cessation services under four insurance plans in a health maintenance organization. N Engl J Med. 1998;339(10):673-9.	Ineligible Intervention
Daly AT, Deshmukh AA, Vidrine DJ, Prokhorov AV, Frank SG, Tahay PD, et al. Cost-effectiveness analysis of smoking cessation interventions using cell phones in a low-income population. Tob Control. 2019;28(1):88-94.	Ineligible Intervention
Dey P, Foy R, Woodman M, Fullard B, Gibbs A. Should smoking cessation cost a packet? A pilot randomized controlled trial of the cost-effectiveness of distributing nicotine therapy free of charge. Br J Gen Pract. 1999;49(439):127-8.	Ineligible Outcomes
Earl-Slater A, Walley T. Smoking cessation and bupropion. BR J Clin Gov. 2001;6(1):69-74.	Ineligible Publication Date
Ebbert JO, Wyatt KD, Hays JT, Klee EW, Hurt RD. Varenicline for smoking cessation: Efficacy, safety, and treatment recommendations. Patient Prefer Adherence. 2010;4:355-62.	Ineligible Study Design
Ekpu VU, Brown AK. The economic impact of smoking and of reducing smoking prevalence: Review of evidence. Tobacco use insights. 2015;8:1-35.	Systematic Review
Fairchild AL, Bayer R. Smoke and fire over e-cigarettes: As nations adopt regulatory measures for e-cigarettes, it is imperative to understand how approaches to risk, cost-benefit, and trade-offs have shaped interpretations of evidence. Science. 2015;347(6220):375-76.	Ineligible Study Design
Faulkner MA. Smoking cessation: An economic analysis and review of varenicline. ClinicoEcon. 2009;1:25-34.	Systematic Review
Feenstra TL, Hamberg-van Reenen HH, Hoogenveen RT, Rutten-van Molken MPMH. Cost-effectiveness of face-to-face smoking cessation interventions: A dynamic modeling study. Value Health. 2005;8(3):178-90.	Ineligible Publication Date
Feldman M, James U, Carvalho B, Underwood MR. Single-session hypnotherapy for smoking cessation: A cost-effective alternative? Eur J Gen Pract. 2002;8(2):73-74.	Ineligible Intervention
Fellows JL, Bush T, McAfee T, Dickerson J. Cost effectiveness of the Oregon quitline "free patch initiative". Tob Control. 2007;16(Suppl 1):I47-I52.	Ineligible Intervention
Fiscella K, Franks P. Cost-effectiveness of the transdermal nicotine patch as an adjunct to physicians' smoking cessation counseling. JAMA. 1996;275(16):1247-51.	Ineligible Comparator
Getsios D, Marton JP, Revankar N, Ward AJ, Willke RJ, Rublee D, et al. Smoking cessation treatment and outcomes patterns simulation: A new framework for evaluating the potential health and economic impact of smoking cessation interventions. Pharmacoeconomics. 2013;31(9):767-80.	Ineligible Study Design
Gilbert AR, Pinget C, Bovet P, Cornuz J, Shamlaye C, Paccaud F. The cost effectiveness of pharmacological smoking cessation therapies in developing countries: A case study in the Seychelles. Tob Control. 2004;13(2):190-5.	Ineligible Comparator

Godfrey C. The economic and social costs of lung cancer and the economics of smoking prevention. Monaldi Arch Chest Dis. 2001;56(5):458-61.	Ineligible Publication Date
Godfrey C, Fowler G. Pharmacoeconomic considerations in the management of smoking cessation. Drugs. 2002;62(Suppl 2):63-70.	Ineligible Study Design
Godfrey C, Parrott S, Coleman T, Pound E. The cost-effectiveness of the English smoking treatment services: Evidence from practice. Addiction. 2005;100(Suppl 2):70-83.	Ineligible Study Design
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Halpern MT, Dirani R, Schmier JK. The cost effectiveness of varenicline for smoking cessation. Manag Care Interface. 2007;20(10):18-25.	Ineligible Publication Date
Halpin HA, McMenamin SB, Rideout J, Boyce-Smith G. The costs and effectiveness of different benefit designs for treating tobacco dependence: Results from a randomized trial. Inquiry. 2006;43(1):54-65.	Ineligible Comparator
Hartmann-Boyce J, Begh R, Aveyard P. Electronic cigarettes for smoking cessation. BMJ (Online). 2018;360:j5543.	Ineligible Study Design
Healey A, Roberts S, Sevdalis N, Goulding L, Wilson S, Shaw K, et al. A cost-effectiveness analysis of stop smoking interventions in substance-use disorder populations. NicotineTob Res. 2019;21(5):623-30.	Ineligible Study Design
Heitjan DF, Asch DA, Ray R, Rukstalis M, Patterson F, Lerman C. Cost-effectiveness of pharmacogenetic testing to tailor smoking-cessation treatment. Pharmacogenomics J. 2008;8(6):391-9.	Ineligible Publication Date
Higashi H, Barendregt JJ. Cost-effectiveness of tobacco control policies in Vietnam: The case of personal smoking cessation support. Addiction. 2012;107(3):658-70.	Ineligible Patient Population
Hill A. A cost-effectiveness evaluation of single and combined smoking cessation interventions in Texas. Tex Med. 2006;102(8):50-5.	Ineligible Publication Date
Hillis WS. Smoking cessation strategies: Nicotine replacement therapy (NRT) and the cardiovascular patient. Br J Cardiol. 2000;7(12):792-800.	Ineligible Publication Date
Hind D, Tappenden P, Peters J, Kenjegalieva K. Varenicline in the management of smoking cessation: A single technology appraisal. Health Technol Assess. 2009;13(Suppl 2):9-13.	Systematic Review
Hojgaard B, Olsen KR, Pisinger C, Tonnesen H, Gyrd-Hansen D. The potential of smoking cessation programmes and a smoking ban in public places: Comparing gain in life expectancy and cost effectiveness. Scand J Public Health. 2011;39(8):785-96.	Ineligible Study Design
Hoogendoorn M, Welsing P, Rutten-van Molken MPMH. Cost-effectiveness of varenicline compared with bupropion, NRT, and nortriptyline for smoking cessation in the Netherlands. Curr Med Res Opin. 2008;24(1):51-61.	Ineligible Publication Date

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Igarashi A, Goto R, Suwa K, Yoshikawa R, Ward AJ, Moller J. Cost-effectiveness analysis of smoking cessation interventions in Japan using a discrete-event simulation. Appl Health Econ Health Policy. 2016;14(1):77-87.	Ineligible Country
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Institute for Quality and Efficiency in Health Care. Health economic evaluation of venlafaxine, duloxetine, bupropion, and mirtazapine compared to further prescribable pharmaceutical treatments. Cologne, Germany: 2013. Available from: https://www.iqwig.de/download/G09-01_Abschlussbericht_Kosten-Nutzen-Bewertung-von-Venlafaxin-Duloxetin....pdf.	Ineligible Language
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Javitz HS, Swan GE, Zbikowski SM, Curry SJ, McAfee TA, Decker D, et al. Return on investment of different combinations of bupropion SR dose and behavioral treatment for smoking cessation in a health care setting: An employer's perspective. Value Health. 2004;7(5):535-43.	Ineligible intervention
Johnson CD, Lucas LM, Uchishiba MA. Efficacy and cost-effectiveness analysis of NRT patches vs. once-daily bupropion SR: A retrospective chart review. J Pharm Tech. 2001;17(4):140-46.	Ineligible patient population
Kahende JW, Loomis BR, Adhikari B, Marshall L. A review of economic evaluations of tobacco control programs. IJERGQ. 2009;6(1):51-68.	Systematic Review
Keating GM, Lyseng-Williamson KA. Varenicline: A pharmacoeconomic review of its use as an aid to smoking cessation. Pharmacoeconomics. 2010;28(3):231-54.	Systematic Review
Keating GM, Lyseng-Williamson KA. Pharmacoeconomic spotlight on varenicline as an aid to smoking cessation. CNS Drugs. 2010;24(9):797-800.	Ineligible outcomes
Keiding H. Cost-effectiveness of varenicline for smoking cessation. Expert Rev Pharmacoecon Outcomes Res. 2009;9(3):215-21.	Ineligible study design
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McGhan WF, Smith MD. Pharmacoeconomic analysis of smoking-cessation interventions. Am J Health Syst Pharm. 1996;53(1):45-52.	Ineligible Publication Date
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McNeill A, Armstrong M. The impact of amfebutamone (bupropion) on National Health Service smoking cessation services. Pharm J. 2000;265(7126):860-62.	Ineligible study design

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Murphy JM, Mahoney MC, Cummings KM, Hyland AJ, Lawvere S. A randomized trial to promote pharmacotherapy use and smoking cessation in a Medicaid population (United States). Cancer Causes Control. 2005;16(4):373-82.	Ineligible study design
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Ong MK, Glantz SA. Free nicotine replacement therapy programs vs implementing smoke-free workplaces: A cost-effectiveness comparison. Am J Public Health. 2005;95(6):969-75.	Ineligible comparator
Orme ME, Hogue SL, Kennedy LM, Paine AC, Godfrey C. Development of the health and economic consequences of smoking interactive model. Tob Control. 2001;10(1):55-61.	Ineligible outcomes
Oster G, Huse DM, Delea TE, Colditz GA. Cost-effectiveness of nicotine gum as an adjunct to physician's advice against cigarette smoking. JAMA. 1986;256(10):1315-8.	Ineligible intervention
Park DJ, Kim YH, Kim EJ. Cost-utility analysis of varenicline versus existing smoking cessation strategies in Korea. Value Health. 2014;17(7):A726.	Ineligible study design
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Parry O, Kenicer M, Haw S, Richmond R, Isles C. A 56-year-old arteriopath who is unable to stop smoking. Coron Health Care. 1998;2(4):215-20.	Ineligible study design
Peckham E, Brabyn S, Cook L, Tew G, Gilbody S. Smoking cessation in severe mental ill health: What works? An updated systematic review and meta-analysis. BMC Psychiatry. 2017;17(1):252.	Ineligible study design
Prochazka AV. Review: Bupropion and nortriptyline each increase smoking cessation rates. Evid Based Med. 2005;10(3):88.	Ineligible study design
Quist-Paulsen P, Lydersen S, Bakke PS, Gallefoss F. Cost effectiveness of a smoking cessation program in patients admitted for coronary heart disease. Eur J Cardiovasc Prev Rehabil. 2006;13(2):274-80.	Ineligible intervention
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Rejas GJ, Sicras MA, Navarro AR, De LJA. Budgetary impact analysis of reimbursement varenicline in the smoking cessation treatment of patients with cardiovascular diseases, chronic obstructive pulmonary disease or type-2 diabetes mellitus: A national health system perspective in Spain. Value Health. 2014;17(7):A478-9.	Ineligible study design
Roddy E. ABC of smoking cessation: Bupropion and other non-nicotine pharmacotherapies. BMJ. 2004;328(7438):509-11.	Ineligible outcomes
Ruger JP, Lazar CM. Economic evaluation of pharmaco-and behavioral therapies for smoking cessation: A critical and systematic review of empirical research. Annu Rev Public Health. 2012;33:279-305.	Systematic Review
Salize HJ, Merkel S, Reinhard I, Twardella D, Mann K, Brenner H. Cost-effective primary care-based strategies to improve smoking cessation: more value for money. Arch Intern Med. 2009;169(3):230-6.	Ineligible intervention
Saul JE, Lien R, Schillo B, Kavanaugh A, Wendling A, Luxenberg M, et al. Outcomes and cost-effectiveness of two nicotine replacement treatment delivery models for a tobacco quitline. IJERGQ. 2011;8(5):1547-59.	Ineligible intervention
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Shanahan M, Doran C, Gates J, Shakeshaft A, Mattick RP. The cost effectiveness of pharmacotherapies for smoking cessation: Necessary but not sufficient? Appl Health Econ Health Policy. 2003;2(2):76-8.	Ineligible Publication Date
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Stevermer J. Cost-effectiveness of the nicotine patch. J Fam Pract. 1996;43(2):125-6.	Ineligible Publication Date
Sung H-Y, Penko J, Cummins SE, Max W, Zhu S-H, Bibbins-Domingo K, et al. Economic impact of financial incentives and mailing nicotine patches to help Medicaid smokers quit smoking: A cost-benefit analysis. Am J Prev Med. 2018;55(6 Suppl 2):S148-S58.	Ineligible intervention

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Thao V, Nyman JA, Nelson DB, Joseph AM, Clothier B, Hammett PJ, et al. Cost-effectiveness of population-level proactive tobacco cessation outreach among socio-economically disadvantaged smokers: Evaluation of a randomized control trial. Addiction. 2019;114(12):2206-16.	Ineligible intervention
Thomas D, Farrell M, McRobbie H, Tutka P, Petrie D, West R, et al. The effectiveness, safety and cost-effectiveness of cytisine versus varenicline for smoking cessation in an Australian population: A study protocol for a randomized controlled non-inferiority trial. Addiction. 2018;114(5):923-33.	Ineligible intervention
Thomas KH. ONGOING How do smoking cessation medicines compare with respect to their neuropsychiatric safety: A systematic review, network meta-analysis and cost effectiveness analysis.: 2015. Available from: https://www.journalslibrary.nihr.ac.uk/programmes/hta/155818#/.	Ineligible Study Design
Tosanguan J, Chaiyakunapruk N. Cost-effectiveness analysis of clinical smoking cessation interventions in Thailand. Addiction. 2016;111(2):340-50.	Ineligible Country
Tousoulis D. Smoking cessation and health economics. Hell J Cardiol. 2016;57(Jan-Feb):67-69.	Ineligible Study Design
Tran K, Asakawa K, Cimon K, Moulton K, Kaunelis D, Pipe A, et al. Pharmacologic-based strategies for smoking cessation. Ottawa, Canada: 2009. Available from: https://www.cadth.ca/media/pdf/H0486_Smoking_Cessation_tr_e.pdf.	Ineligible Publication Date
Tran MT, Holdford DA, Kennedy DT, Small RE. Modeling the cost-effectiveness of a smoking-cessation program in a community pharmacy practice. Pharmacotherapy. 2002;22(12):1623-31.	Ineligible Publication Date
Tsevat J. Impact and cost-effectiveness of smoking interventions. Am J Med. 1992;93(1A):43S-47S.	Ineligible Study Design
Van den Bruel A, Cleemput I, Van Linden A, Schoefs D, Ramaekers D, Bonneux L. Effectiveness and cost-effectiveness of treatments for smoking cessation. Brussels, Belgium: 2004. Available from: https://www.kce.fgov.be/en/effectiveness-and-cost-effectiveness-of-treatments-for-smoking-cessation.	Ineligible language
van Rossem C, Spigt M, Smit ES, Viechtbauer W, Mijnheer KK, van Schayck CP, et al. Combining intensive practice nurse counselling or brief general practitioner advice with varenicline for smoking cessation in primary care: Study protocol of a pragmatic randomized controlled trial. Contemp Clin Trials. 2015;41:298-312.	Ineligible intervention
Van Schayck CP, Kaper J, Wagena EJ, Wouters EF, Severens JL. The cost-effectiveness of antidepressants for smoking cessation in chronic obstructive pulmonary disease (COPD) patients. Addiction. 2009;104(12):2110-17.	Ineligible Publication Date
Vemer P, Rutten-van Molken MPMH, Kaper J, Hoogenveen RT, van Schayck CP, Feenstra TL. If you try to stop smoking, should we pay for it? The cost-utility of reimbursing smoking cessation support in the Netherlands. Addiction. 2010;105(6):1088-97.	Ineligible Study Design
Walker N, Verbiest M, Kurdziel T, Laking G, Laugesen M, Parag V, et al. Effectiveness and safety of nicotine patches combined with e-	Ineligible Study Design

cigarettes (with and without nicotine) for smoking cessation: Study protocol for a randomised controlled trial. BMJ Open. 2019;9(2):e023659.	
Wang D, Connock M, Barton P, Fry-Smith A, Aveyard P, Moore D. 'Cut down to quit' with nicotine replacement therapies in smoking cessation: A systematic review of effectiveness and economic analysis. Health Technol Assess. 2008;12(2):iii-135.	Ineligible Publication Date
Warner KE. Cost effectiveness of smoking-cessation therapies. Interpretation of the evidence-and implications for coverage. Pharmacoeconomics. 1997;11(6):538-49.	Ineligible intervention
Wasley MA, McNagny SE, Phillips VL, Ahluwalia JS. The cost-effectiveness of the nicotine transdermal patch for smoking cessation. Prev Med. 1997;26(2):264-70.	Ineligible intervention
West R. Bupropion SR for smoking cessation. Expert Opin Pharmacother. 2003;4(4):533-40.	Ineligible Study Design
Whitley HP, Moorman KL. Varenicline: A review of the literature and place in therapy. Pharm Pract. 2007;5(2):51-8.	Ineligible Outcomes
Wilkes S. The use of bupropion SR in cigarette smoking cessation. Int J Chron Obstruct Pulmon Dis. 2008;3(1):45-53.	Ineligible Outcomes
Winning A. Topic: Bupropion (Zyban) for smoking cessation. J Clin Excel. 2001;3(3):161-64.	Ineligible Publication Date
Woolacott NF, Jones L, Forbes CA, Mather LC, Sowden AJ, Song FJ, et al. The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: A systematic review and economic evaluation. Health Technol Assess. 2002;6(16):1-245.	Systematic Review
Xenakis JG, Kinter ET, Ishak KJ, Ward AJ, Marton JP, Willke RJ, et al. A discrete-event simulation of smoking-cessation strategies based on varenicline pivotal trial data. Pharmacoeconomics. 2011;29(6):497-510.	Ineligible Country
Xiao D, Chu S, Wang C. Smoking cessation in Asians: Focus on varenicline. Patient Prefer Adherence. 2015;9:579-84.	Ineligible Country
Zawertailo L, Mansoursadeghi-Gilan T, Zhang H, Hussain S, Le Foll B, Selby P. Varenicline and bupropion for long-term smoking cessation (the MATCH study): Protocol for a real-world, pragmatic, randomized controlled trial. JMIR Res Protoc. 2018;7(10):e10826.	Ineligible Study Design
Zawertailo L, Pavlov D, Ivanova A, Ng G, Baliunas D, Selby P. Concurrent e-cigarette use during tobacco dependence treatment in primary care settings: Association with smoking cessation at three and six months. Nicotine Tob Res. 2017;19(2):183-89.	Ineligible Study Design
Zimovetz EA, Wilson K, Samuel M, Beard SM. A review of cost-effectiveness of varenicline and comparison of cost-effectiveness of treatments for major smoking-related morbidities. J Eval Clin Pract. 2011;17(2):288-97.	Systematic Review

Harm reduction

Public health studies

Study Citation	Reason for excluding
Adriaens K, Van Gucht , D , Declerck P, and Baeyens F (2014) Effectiveness of the Electronic Cigarette: An Eight-Week Flemish Study with Six-Month Follow-up on Smoking Reduction, Craving and	Data not extractable – adverse event data cannot

Experienced Benefits and Complaints. International Journal of Environmental Research and Public Health 11(11), 11220-11248	be extracted. Follow-up under 6 months.
Adriaens Karolien, Van Gucht , Dinska , Declerck Paul, and Baeyens Frank (2014) 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 11(11), 11220-48	Exclude as duplicate
Brown Jennifer, Brown Brandon, Schwiebert Peter, Ramakrisnan Kalyanakrishnan, and McCarthy Laine H (2014) In adult smokers unwilling or unable to quit, does changing from tobacco cigarettes to electronic cigarettes decrease the incidence of negative health effects associated with smoking tobacco? A Clin-IQ. Journal of patient-centered research and reviews 1(2), 99-101	Exclude on study design – non-systematic review.
Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, and Williman J (2013) Do electronic cigarettes help smokers quit? Results from a randomized controlled trial. European respiratory society annual congress, 2013 sept 7-11, barcelona, and spain 42, 215s [P1047]	Exclude as abstract only – full text not available. Also clear that aim of intervention is cessation, not harm reduction
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.	Data not extractable – ranges not reported so conclusions cannot be drawn.
Campagna Davide, Cibella Fabio, Caponnetto Pasquale, Amaradio Maria Domenica, Caruso Massimo, Morjaria Jaymin B, Malerba Mario, and Polosa Riccardo (2016) Changes in breathomics from a 1-year randomized smoking cessation trial of electronic cigarettes. European journal of clinical investigation 46(8), 698-706	Exclude on evidence – results split by quit or reduction success, not by allocation
Cibella Fabio, Campagna Davide, Caponnetto Pasquale, Amaradio Maria Domenica, Caruso Massimo, Russo Cristina, Cockcroft Donald W, and Polosa Riccardo (2016) Lung function and respiratory symptoms in a randomized smoking cessation trial of electronic cigarettes. Clinical science (London, and England : 1979) 130(21), 1929-37	Exclude on evidence – results split by quit or reduction success, not by allocation
D'Ruiz Carl D, Graff Donald W, and Robinson Edward (2016) Reductions in biomarkers of exposure, impacts on smoking urge and assessment of product use and tolerability in adult smokers following partial or complete substitution of cigarettes with electronic cigarettes. BMC public health 16, 543	Exclude on population – not clear whether participants want to reduce harm. Forced switch means cessation is being measured.
D'Ruiz Carl D, O'Connell Grant, Graff Donald W, and Yan X Sherwin (2017) Measurement of cardiovascular and pulmonary function endpoints and other physiological effects following partial or complete substitution of cigarettes with electronic cigarettes in adult smokers. Regulatory toxicology and pharmacology : RTP 87, 36-53	Exclude on population – not clear whether participants want to reduce harm. Forced switch means cessation is being measured.
Eissenberg T (2010) Electronic nicotine delivery devices: ineffective nicotine delivery and craving suppression after acute administration. Tobacco Control 19(1), 87-88	Exclude on follow-up – follow-up under 6 months and adverse events not reported.
El Dib , Regina , Suzumura Erica A, Akl Elie A, Gomaa Huda, Agarwal Arnav, Chang Yaping, Prasad Manya, Ashoorion Vahid, Heels-Ansdell Diane, Maziak Wasim, and Guyatt Gordon (2017) Electronic nicotine delivery systems and/or electronic non-nicotine delivery systems for tobacco smoking cessation or reduction: a systematic review and meta-analysis. BMJ open 7(2), e012680	Exclude on study design – systematic review. Included studies screened for inclusion
Gentry Sarah, Forouhi Nita G, and Notley Caitlin (2019) Are Electronic Cigarettes an Effective Aid to Smoking Cessation or Reduction Among Vulnerable Groups? A Systematic Review of	Exclude on study design – systematic review. Included

Quantitative and Qualitative Evidence. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 21(5), 602-616	studies screened for inclusion
Kumral T L, Salturk Z, Yildirim G, Uyar Y, Berkiten G, Atar Y, and Inan M (2016) How does electronic cigarette smoking affect sinonasal symptoms and nasal mucociliary clearance?. B-ENT 12(1), 17-21	Exclude on population – participants all willing to quit
Leduc Charlotte, and Quoix Elisabeth (2016) Is there a role for e-cigarettes in smoking cessation?. Therapeutic advances in respiratory disease 10(2), 130-5	Exclude on study design – non-systematic review
Lee Seung-Hwa, Ahn Sang-Hyun, and Cheong Yoo-Seock (2019) Effect of Electronic Cigarettes on Smoking Reduction and Cessation in Korean Male Smokers: A Randomized Controlled Study. Journal of the American Board of Family Medicine : JABFM 32(4), 567-574	Exclude on population – participants were motivated to stop smoking entirely or reduce cigarette consumption, not analysed separately
Lindson-Hawley N, Hartmann-Boyce J, Fanshawe Tr, Begh R, Farley A, and Lancaster T (2016) Interventions to reduce harm from continued tobacco use. Cochrane Database of Systematic Reviews (10),	Exclude on study design – systematic review. Included studies screened for inclusion
Liu Xing, Lu Wan, Liao Sheng, Deng Zhongliang, Zhang Zhongrong, Liu Yun, and Lu Weizhong (2018) Efficiency and adverse events of electronic cigarettes: A systematic review and meta-analysis (PRISMA-compliant article). Medicine 97(19), e0324	Exclude on study design – systematic review. Included studies screened for inclusion
Masiero Marianna, Lucchiari Claudio, Mazzocco Ketti, Veronesi Giulia, Maisonneuve Patrick, Jemos Costantino, Sale Emanuela Omodeo, Spina Stefania, Bertolotti Raffaella, and Pravettoni Gabriella (2019) E-cigarettes May Support Smokers With High Smoking-Related Risk Awareness to Stop Smoking in the Short Run: Preliminary Results by Randomized Controlled Trial. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 21(1), 119-126	Exclude on population – participants were all highly motivated to quit
McRobbie Hayden, Bullen Chris, Hartmann-Boyce Jamie, and Hajek Peter (2014) Electronic cigarettes for smoking cessation and reduction. The Cochrane database of systematic reviews (12), CD010216	Exclude on study design – systematic review. Included studies screened for inclusion (and more recent version of review identified and screened)
Meier Ellen, Wahlquist Amy E, Heckman Bryan W, Cummings K Michael, Froeliger Brett, and Carpenter Matthew J (2017) A Pilot Randomized Crossover Trial of Electronic Cigarette Sampling Among Smokers. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 19(2), 176-182	Exclude on follow-up – follow-up is 2 weeks and no adverse events data reported.
O'Brien Brigid, Knight-West Oliver, Walker Natalie, Parag Varsha, and Bullen Christopher (2015) E-cigarettes versus NRT for smoking reduction or cessation in people with mental illness: secondary analysis of data from the ASCEND trial. Tobacco induced diseases 13(1), 5	Exclude on population – participants all willing to quit
Polosa Riccardo, Campagna Davide, and Sands Mark F (2016) Counseling patients with asthma and allergy about electronic cigarettes: an evidence-based approach. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, and & Immunology 116(2), 106-11	Exclude on study design – non-systematic review
Rahman Muhammad Aziz, Hann Nicholas, Wilson Andrew, Mnatzaganian George, and Worrall-Carter Linda (2015) E-cigarettes and smoking cessation: evidence from a systematic review and meta-analysis. PloS one 10(3), e0122544	Exclude on study design – systematic review. Also considers cessation rather than harm reduction

Tseng Tuo-Yen, Ostroff Jamie S, Campo Alena, Gerard Meghan, Kirchner Thomas, Rotrosen John, and Shelley Donna (2016) A Randomized Trial Comparing the Effect of Nicotine Versus Placebo Electronic Cigarettes on Smoking Reduction Among Young Adult Smokers. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 18(10), 1937-1943	Exclude on follow-up – follow-up is 3 weeks and no adverse events data reported (although study reportedly collects this data)
Vanderkam P, Boussageon R, Underner M, Langbourg N, Brabant Y, Binder P, Freche B, and Jaafari N (2016) Efficacy and security of electronic cigarette for tobacco harm reduction: Systematic review and meta-analysis. Presse Medicale 45(11), 971-985	Exclude on study design – systematic review. Also considers cessation rather than harm reduction
Veldheer S, Yingst J, Midya V, Hummer B, Lester C, Krebs N, Hrabovsky S, Wilhelm A, Liao J, Yen M S, Cobb C, Eissenberg T, and Foulds J (2019) Pulmonary and other health effects of electronic cigarette use among adult smokers participating in a randomized controlled smoking reduction trial. Addictive Behaviors 91, 95-101	Exclude on follow-up – follow-up is 1 and 3 months. Adverse events data reported but for group as a whole, not comparatively
Walele Tanvir, Sharma Girish, Savioz Rebecca, Martin Claire, and Williams Josie (2016) 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 : RTP 74, 193-9	Exclude on follow-up – follow-up is 5 days. No adverse event data.
Walele Tanvir, Sharma Girish, Savioz Rebecca, Martin Claire, and Williams Josie (2016) A randomised, crossover study on an electronic vapour product, a nicotine inhalator and a conventional cigarette. Part A: Pharmacokinetics. Regulatory toxicology and pharmacology : RTP 74, 187-92	Exclude on intervention – intervention allocation was enforced, so measured cessation

Public health rerun search – harm reduction

Study Citation	Reason for excluding
Walker Natalie, Parag Varsha, Verbiest Marjolein, Laking George, Laugesen Murray, and Bullen Christopher (2019) Nicotine patches used in combination with e-cigarettes (with and without nicotine) for smoking cessation: a pragmatic, randomised trial. The Lancet. Respiratory medicine.	Exclude on outcome – cessation outcomes only. Population motivated to quit.

Appendix H – Research recommendations

Research recommendation 1

What are the short or long-term health effects of e-cigarette use? Are there any specific health effects relating to use in pregnancy, or use by children and young people?

Why this is important

The extensive harms of smoking are well known, and it is considered unlikely that use of e-cigarettes could cause similar levels of harm. For people who don't smoke, it is unlikely that inhaling vapour from an e-cigarette is as low risk as not doing so, although the extent of that potential risk is not yet known. E-cigarettes are relatively new devices and it is important to understand whether e-cigarettes cause any health harms or benefits aside from their potential to reduce smoking-related harm.

Rationale for research recommendation

Importance to 'patients' or the population	E-cigarettes are relatively new devices and are a popular choice as a smoking cessation aid. Many users perceive them to be less harmful than cigarettes ('Adult Smoking Habits in the UK: 2017').
Relevance to NICE guidance	It is important to understand whether e-cigarettes cause any health effects aside from their potential to reduce smoking-related harm.
Relevance to the NHS	Although smoking levels have fallen, smoking is linked to over half a million hospital admissions each year (NHS Long Term Plan).
National priorities	The extensive harms of smoking are well known and it is important to identify safe and effective means to support people to quit.
Current evidence base	There is a lack of evidence on the health effects of e-cigarette use.
Equality considerations	More secondary school pupils have tried e-cigarettes at least once (22%) than have tried cigarettes at least once (18%) ('Statistics on smoking, England – 2016'). It is currently estimated that almost a quarter of women smoke in pregnancy. (NHS Long Term Plan)

Modified PICO table

Population	People who use e-cigarettes, (nicotine and non - nicotine containing) including women who are pregnant and children and young people aged 12 and over, and who: • Have never smoked

	• Used to smoke and are using e-cigarettes to stop smoking or to prevent relapse
Intervention	Use of e-cigarettes (nicotine containing and non-nicotine containing)
Comparator	No use of e-cigarettes or tobacco containing products
Outcome	Short and long-term health effects (intended or unintended, positive or negative)

Research recommendation 3

How can effective and cost-effective interventions to support people to stop smoking be modified to improve engagement with and accessibility for under-served groups? How acceptable are these interventions to these groups?

Why this is important

In some under served population groups, smoking prevalence is high and although these groups may be motivated to stop smoking, they may experience additional challenges to successfully quitting (see the Equality Impact Assessment). No evidence was identified by the reviews to demonstrate how to tailor effective and cost effective interventions to ensure that they are engaging and accessible for under served groups, or how acceptable those interventions may be for those groups. This is a gap in the evidence which needs to be addressed in order to reduce inequalities in health in this area.

Rationale for research recommendation

Importance to 'patients' or the population	Smokers from under-served groups may be motivated to stop smoking but may experience additional challenges to successfully quitting.
Relevance to NICE guidance	Limited evidence was identified by the reviews to demonstrate how to tailor effective and cost effective interventions for these groups.
Relevance to the NHS	Smoking prevalence is higher in some under-served groups and it important these are addressed to address inequalities in health.
National priorities	High
Current evidence base	Limited evidence in this area was identified by the reviews but some evidence was provided through expert testimony.
Equality considerations	Despite being motivated to quit smoking, some under-served groups have a higher prevalence of smoking and experience additional challenges to successfully quitting.

Modified PICO table

Population	Under served groups in which smoking prevalence is higher than in the general population, and in which additional challenges to

	quitting smoking are experienced. For example: people from socio-economically disadvantaged groups including pregnant women from those groups. lesbian, gay, bisexual and trans people; people with learning disabilities.
Intervention	Smoking cessation interventions
Comparator	Other interventions No intervention
Outcome	Abstinence from smoking Uptake of stop smoking support in groups of interest Views and experiences of those delivering and those receiving interventions to support smoking cessation.

Research recommendation 4

How can people with mental health conditions be supported effectively to stop smoking (at individual and system level)? What are the challenges and opportunities and how can they be addressed?

Why this is important

Smoking prevalence remains disproportionately high among people with mental health conditions compared to the general population, despite evidence that smoking cessation strategies that may be effective for the general population may also work for people with mental health conditions. Both evidence and expert testimony highlighted that the development of further support strategies that target specific barriers to smoking cessation at an individual and at a system level need to be developed. This is an important gap in the evidence which needs to be addressed in order to reduce inequalities in this area.

Rationale for research recommendation

Importance to ‘patients’ or the population	Smoking prevalence is higher among people with mental health conditions, including those in mental health settings, than among the general population. However, evidence highlights that they are motivated to quit smoking.
Relevance to NICE guidance	There is a need for further evidence to inform the development of recommendations to support people with mental health conditions to quit smoking using tailored approaches.
Relevance to the NHS	There may be some inequalities in prescribing practices for some pharmacotherapies and variation in implementation of, and use of, stop smoking support.

National priorities	The NHS Long Term Plan outlines a universal smoking cessation offer as part of specialist mental health services for long term users of these services.
Current evidence base	Some evidence was identified relating to interventions to support smoking cessation in people with mental health conditions using specifically tailored approaches, but evidence on how to support people at an individual and system level so that they can benefit from those interventions is in general lacking.
Equality considerations	Smoking prevalence is high among people with mental health conditions. Despite being motivated to quit smoking, people with mental health conditions may face additional challenges to successfully quitting.

Modified PICO table

Population	People with mental health conditions, including those in mental health settings.
Intervention	Smoking cessation interventions (individual or system based)
Comparator	Other intervention No intervention
Outcome	Abstinence from smoking Uptake of stop smoking support in people with mental health conditions

Research recommendation 6

Are nicotine-containing e-cigarettes effective and safe for harm reduction when used alongside tobacco products to cut down on smoking (dual use approach)?

Why this is important

No evidence was identified on the effectiveness of e-cigarettes as a means of harm reduction. The committee noted that the link between harm reduction (temporary abstinence or cutting down numbers of cigarettes per day) and health benefits is still uncertain. However dual use of e-cigarettes alongside tobacco products is relatively common among current smokers. It is therefore important to determine if the use of nicotine-containing e-cigarettes as a means of harm reduction is effective and safe.

Rationale for research recommendation

Importance to ‘patients’ or the population	Some current smokers use nicotine containing e-cigarettes alongside tobacco products as a means of cutting down on the number of

	cigarettes they smoke, in the belief it will reduce the harms of smoking. It is therefore important to establish if the use of nicotine -containing e-cigarettes for this purpose is both effective and safe.
Relevance to NICE guidance	No evidence was found on the effectiveness of e-cigarettes as a means of harm reduction and so the committee did not make recommendations on their use for this purpose. Further research in this area would help to address this gap in the evidence.
Relevance to the NHS	As some smokers are dual users of both nicotine-containing e-cigarettes and tobacco products, it is important to be able to provide accurate information and advice on the effectiveness and safety of a dual use approach as a means of reducing harm from smoking.
National priorities	Dual use of e-cigarettes alongside tobacco products is relatively common among regular smokers. In 2019 the 'Adult smoking habits in the UK 'survey found that 5.7% respondents overall used e-cigarettes but 15.5% of current smokers used them alongside tobacco products.
Current evidence base	No evidence was found on the effectiveness of e-cigarettes as a means of harm reduction. In addition, the link between harm reduction (temporary abstinence or cutting down numbers of cigarettes per day) and health benefits is still uncertain
Equality considerations	There is a.social gradient in smoking that in 2018 ranged from about 8% in the most affluent to over 40% among those with multiple indicators of disadvantage. Some smokers use nicotine-containing e-cigarettes alongside tobacco products as they believe it will reduce the harms of smoking, so it is important to determine if nicotine containing e-cigarettes are effective and safe as a means of harm reduction.

Modified PICO table

Population	Current smokers who also use nicotine-containing e-cigarettes alongside tobacco products in an effort to reduce the harms of smoking.
Intervention	Use of nicotine-containing e-cigarettes for harm reduction.

Comparator	Other intervention No intervention
Outcome	Harm reduction Safety outcomes

Research recommendation 7

Does the effectiveness of nicotine-containing e-cigarettes as an aid to stopping smoking vary according to the amount of nicotine they contain or the frequency of use?

Why this is important

The committee recognised the need for evidence about the factors that may influence the use of nicotine containing e-cigarettes, including the amount of nicotine they contain and how frequently they are used.

Rationale for research recommendation

Importance to 'patients' or the population	Where people use nicotine containing e-cigarettes as an aid to smoking cessation, it is important they do so in a way that provides them with enough nicotine for this be effective. There are different types and generations of e-cigarettes available and e-liquids are available in many different nicotine strengths, It can therefore be difficult to equate the amount of nicotine the e-cigarettes need to provide to replace the amount usually consumed in tobacco products.
Relevance to NICE guidance	The amount of nicotine in e-cigarettes and the frequency with which they need to be used to deliver enough nicotine, are among several factors that may influence the acceptability of e-cigarettes and may therefore impact on their effectiveness as an aid to smoking cessation
Relevance to the NHS	It is important that those giving advice and support on stopping smoking understand how practical issues such as this may impact on the effectiveness of nicotine-containing e-cigarettes as an aid to smoking cessation.
National priorities	In 2019 the survey of Adult smoking habits in the UK found that almost 3 million people in Great Britain used e-cigarettes. Around half of these used them as means of stopping smoking.
Current evidence base	The committee recognised the need for evidence about factors that may influence the use of nicotine containing e-cigarettes.

Importance to 'patients' or the population	Where people use nicotine containing e-cigarettes as an aid to smoking cessation, it is important they do so in a way that provides them with enough nicotine for this be effective. There are different types and generations of e-cigarettes available and e-liquids are available in many different nicotine strengths, It can therefore be difficult to equate the amount of nicotine the e-cigarettes need to provide to replace the amount usually consumed in tobacco products.
Equality considerations	The committee heard from expert testimony that there is a social gradient in smoking prevalence that is paralleled by a social gradient in nicotine intake and dependence, This is due to inter-related and complex factors and in part reflects a higher dependence on nicotine. To help address smoking related inequalities in health, it is therefore important to determine if the effectiveness of nicotine-containing e-cigarettes as an aid to stopping smoking varies according to the amount of nicotine they contain and the frequency of use.

Modified PICO table

Population	Current smokers
Intervention	Nicotine-containing e-cigarettes containing varying amounts of nicotine and used in varying frequencies.
Comparator	Not applicable
Outcome	Smoking cessation outcomes.

Research recommendation 8

Do the flavours used in nicotine-containing e-cigarettes have an impact on their effectiveness as an aid to stopping smoking, and are there any adverse effects associated with them?

Why this is important

The committee recognised the need for evidence about factors that may influence the use of nicotine-containing e-cigarettes. When they are used as an aid to stopping smoking, it is important that they are sufficiently palatable for people to continue using them for long enough for them to be effective, without having any adverse effects.

Rationale for research recommendation

Importance to 'patients' or the population	Nicotine-containing e-cigarettes are a relatively new and popular choice of smoking cessation aid. It is important that they are sufficiently palatable so that people continue using them for long enough for them to be effective, without any adverse effects.
Relevance to NICE guidance	The flavours used in e-cigarettes are among several factors that may influence the acceptability of nicotine-containing e-cigarettes and may therefore impact on their effectiveness as an aid to smoking cessation.
Relevance to the NHS	It is important that those giving advice and information on stopping smoking, understand if flavours have an impact on the effectiveness of nicotine containing e-cigarettes and if there are any adverse effects associated with them.
National priorities	The extensive harms of smoking are well-known and it is important to identify safe and effective means to support people to quit.
Current evidence base	Flavours in nicotine-containing e-cigarettes were not specifically considered in the evidence reviews carried out for this guideline. However, the committee were aware that there are ongoing discussions around consumer preferences relating to flavours and that this may be a factor that influences the effectiveness of these products.
Equality considerations	The committee heard from expert testimony that there is evidence that ex-smokers from more disadvantaged backgrounds use e-cigarettes for longer periods than more affluent ex-smokers, possibly reflecting higher levels of dependence on tobacco. It is therefore important for these groups in particular, to determine if the flavours used in nicotine-containing e-cigarettes impact on their effectiveness as an aid to stopping smoking, and if are there any adverse effects associated with them.

Modified PICO table

Population	Current smokers.
Intervention	Flavoured nicotine-containing
Comparator	Non-flavoured nicotine-containing e-cigarettes.

Outcome	Smoking cessation outcomes Adverse effects

Appendix I – Network Meta-analysis

Context

Network meta-analysis methods for review question: What are the most effective and cost effective means of smoking cessation (including e-cigarettes)?

The results of conventional pairwise meta-analyses of direct evidence alone do not help to fully inform which treatment for smoking cessation is most effective. A large number of discrete pairwise comparisons can also be difficult to interpret. Direct comparisons between each of the treatments of interest may also not be available, particularly where technologies are relatively new (for example, e-cigarettes).

To overcome these issues, a Bayesian network meta-analysis (NMA) was performed. Advantages of performing this type of analysis are as follows:

- It allows the synthesis of evidence on multiple treatments compared directly and indirectly without breaking randomisation. If treatment A has never been compared to treatment B in a head to head trial, but these two interventions have been compared to a common comparator, then an indirect treatment comparison can be derived using the relative effects of the two treatments versus the common comparator. Indirect estimates can be calculated whenever there is a path linking two treatments through a set of common comparators. All the randomised evidence is considered simultaneously within the same model.
- For every intervention in a connected network, a relative effect estimate (with its 95% credible intervals, CrIs) between any two interventions can be estimated. These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on all relevant evidence, whilst appropriately accounting for uncertainty. Ranks of interventions may also be calculated.
- Estimates from the NMA can be used to directly parameterise treatment effectiveness in cost-effectiveness modelling of multiple treatments.

Conventional fixed effect meta-analysis assumes that the relative effect of one treatment compared to another is the same across an entire set of trials. In a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

NMA assumes that the included studies are similar in terms of factors that might interact with the intervention effects (effect modifiers). So, the relative effect of intervention B vs intervention A would be expected to be similar in all of the studies (if they had included A and B interventions). This assumption is the same as that made in conventional pairwise meta-analysis, but we have to be particularly careful that the studies making different comparisons do not differ in effect modifiers (the data are consistent)[b]. We can assess this assumption by measuring statistical heterogeneity, and also by checking if the direct and indirect estimates are in agreement when there are loops of evidence in the network (e.g. an ABC triangle of evidence).

Study selection and data collection

For full details see the protocol (Appendix A).

[b] Dias D, Ades AE, Welton NJ, Jansen A, Sutton AJ. Network meta-analysis for decision-making. Wiley. 2018.

Thomas (2020) conducted an NMA to investigate the effectiveness and neuropsychiatric safety of smoking cessation medicines. This NICE review uses the effectiveness data and NMA models from Thomas' (2020) review, as well as results of NICE-conducted rerun searches, to inform the effectiveness of smoking cessation treatments. The following changes were made to Thomas' (2020) work as a result of the inclusion and exclusion criteria specified by the NICE committee:

- Studies of treatments for cessation of smokeless tobacco – as opposed to smoked tobacco – were excluded.
- Interventions were reclassified. Doses and modes of the same treatment were combined into a single class, with the exception of NRT which was then split into "NRT long or short" and "NRT long and short".
- Results have been summarised as risk ratios (rather than odds ratios, which were used by the Thomas (2020) study). The conversion was conducted using an additional piece of modelling code which incorporates the log odds and precision of the log odds. The prevalence used to obtain these was the total number of cessation events in placebo arms of included studies out of the total number of participants in those arms. This was repeated for the subgroup using only studies included in that subgroup analysis:

Code to convert odds ratios to risk ratios:

```
A ~ dnorm(log odds, precision of log odds)
for (k in 1:nClass) { logit(T[k]) <- A + D[k] }
RR[1] <- 1
for (k in 2:nClass) {
RR[k] <- T[k]/T[1]
}
for (c in 1:(nClass-1)) {
for (k in (c+1):nClass) {
RRR[c,k] <- T[k]/T[c]
}
```

Behavioural interventions: Behavioural interventions are not the focus of this review question, which considers pharmacological treatments, NRT and e-cigarettes. Behavioural intervention-only arms were classed as "no drug treatment", along with arms where no intervention was given. Therefore the "no drug treatment" class represents a variety of different situations. There are also no "drug + behavioural intervention" nodes in the NMA, as the additive effect of behavioural interventions are not under investigation. Instead, arms with drug and behavioural interventions combined are allocated to class dependent on the drug only, for example varenicline + counselling is allocated to the class varenicline. For most included studies, behavioural interventions are equal across arms with the only difference being the drug intervention. However, some studies investigated behavioural plus drug intervention vs no intervention. In these cases, the effect of the drug + behavioural intervention is attributed solely to the drug in the NMA. Investigations were done into the studies included in the network to assess the extent to which this occurred, presented in table 16. The summary of this exercise is that:

- Most studies include counselling.

- Of these, most studies include counselling in both arms, meaning that the drug is being tested as an adjunct to behavioural interventions.
- A minority of studies did not have similar counselling in both arms (see table 16).
- The spread of these studies across classes is somewhat even (higher number of studies investigating NRT are uneven, but most other interventions have small numbers of studies meaning percentages are relatively even).

Table 4: Frequency of drug + behavioural intervention vs no intervention comparisons

Broad intervention class	Studies comparing drug + behavioural vs nothing* (n/total, [%])
NRT	8/119 (7)
Bupropion	0/44 (0)
Varenicline	0/41 (0)
E-cigarette	0/5 (0)
Bupropion + NRT	1/11 (9)
Varenicline + NRT	0/3 (0)
Varenicline + bupropion	0/2 (0)
E-cigarette + NRT long/short acting	0/2 (0)

*nothing *includes usual care, waitlist, no treatment – anything without drug and without counselling*
The number of studies adds up to more than 189 (the total number of included studies) because some papers contain more than two arms, and therefore more than 2 comparisons.

The results of this NMA are to be considered in conjunction with other evidence, particularly on e-cigarettes, presented in this review and other reviews for this guideline update:

- Safety of e-cigarettes (other existing reviews on pharmacotherapies and NRT, and review on long-term health effects of e-cigarette question [Review M])
- Adverse events of e-cigarettes (adverse events of e-cigarettes as presented in this review)
- Acceptability, and barriers and facilitators to use (review on barriers and facilitators to using e-cigarettes [Review L])

Methodology

Thomas (2020) used a random effects model between studies and fixed effect model for treatment within class.

Due to the removal of the smokeless tobacco studies and the reclassification of treatments within classes (mainly affecting NRT, which were reclassified into *long- or short acting* and *long- and short-acting* rather than according to mode and dose), tests were undertaken to determine the model with the best fit. It was anticipated that a random effects model between studies was still required, but both a fixed effect and a random effect for treatment within class was run. Results of this test are presented in Table 17. A test of model fit was also conducted for the subgroup analysis on groups with mental health conditions. Results of this test are presented in Table 18.

Analysis for both the main analysis and the subgroup analysis was undertaken following Bayesian statistics principles and conducted using Markov chain Monte Carlo simulation

techniques implemented in WinBUGS 1.4.3[c]. Results were synthesised using NMA code provided by Thomas (2020). Convergence was satisfactory after 10,000 iterations. A further 50,000 iterations were run on two chains, with priors as defined by Thomas (2020).

Thomas (2020) concluded that removing studies at high risk of bias from the NMA yielded findings that were in line of those in the main analysis. Restricting to studies at low risk of bias gave wider credible intervals for most effect estimates, with particular effect on e-cigarettes. It was therefore decided that only the main analysis would be conducted for this review.

Table 5: Model fit statistics for cessation outcome main analysis

Model	Between study heterogeneity – standard deviation (95% CrI)	Between intervention within class standard deviation (95% CrI)	Residual deviance (95% CrI)*	DIC
Random study effects and random intervention effects within class	SD between studies (sd.D): 0.1412 (0.02676, 0.2837)	SD within class (sd): 0.3958 (0.3316, 0.4675)	420.7 (367.6, 476.3)	2665.630
Random study effects and fixed intervention effects within class	sd 0.401 (0.341, 0.470)	NA	420.5 (368.9, 476.6)	2654.850
	Deviance information criteria (DIC) – lower values preferred			

* The number of datapoints this should be compared with is 423. This indicates that both models fit the data well.

Both models have a similar deviance information criterion (DIC, a measure of model fit), with the fixed effects model DIC being slightly higher. As the DIC is not 3+ points lower in the random effects model (see methods chapter), the fixed effects model was preferred.

Table 6: Model fit statistics for cessation outcome mental health subgroup

Model	Between study heterogeneity – standard deviation (95% CrI)	Between intervention within class standard deviation (95% CrI)	Residual deviance (95% CrI)*	DIC
Random study effects and random intervention effects within class	SD between studies (sd.D): 2.365 (0.3083, 4.792)	SD within class (sd): 0.3359 (0.0090, 1.325)	25.59 (13.44, 41.88)	143.027

[c] Lunn, D.J., Thomas, A., Best, N., and Spiegelhalter, D. (2000) WinBUGS — a Bayesian modelling framework: concepts, structure, and extensibility. Statistics and Computing, 10:325–337.

Model	Between study heterogeneity – standard deviation (95% CrI)	Between intervention within class standard deviation (95% CrI)	Residual deviance (95% CrI)*	DIC
Random study effects and fixed intervention effects within class	0.382 (0.01548, 1.89)		27.41 (15.93, 43.65)	145.828
	Deviance information criteria (DIC) – lower values preferred			

* The number of datapoints this should be compared with is 28. This indicates that both models fit the data well.

Both models have a similar deviance information criterion (DIC, a measure of model fit), and as the DIC is not 3+ points lower in the random effects model (see methods chapter), the fixed effects model was preferred.

Results

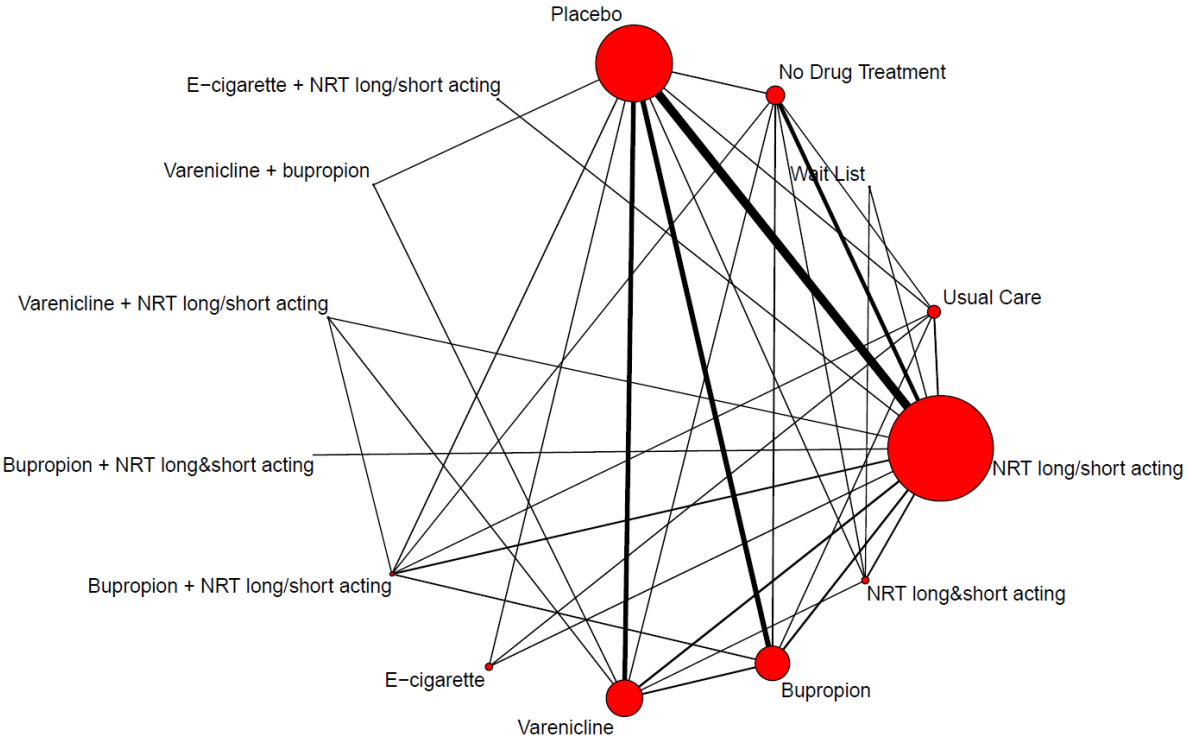
Main analysis: Abstinence at 6 months

Thomas (2020) identified evidence on interventions from 197 trials. Nine trials were removed from the evidence supplied by Thomas (2020), as they considered cessation of smokeless tobacco and therefore were outside of the scope of this review. Four additional studies were identified in rerun searches. 192 studies were included. The network of direct evidence is displayed in Figure 50.

The NMA results are a combination of indirect and, where available, direct estimates for each comparison. These are displayed in the upper diagonal of table 20 (mileage chart). Pairwise meta-analysis was also conducted for each comparison and displayed in the lower diagonal of the mileage chart. Comparisons for placebo, no drug treatment, waitlist and usual care to each other was not conducted, because these were not considered to be useful for making recommendations.

Table 21 displays the median rank and 95% CrI for each treatment. Ranks span from 1 (worst) to 14 (best). Rankings are also displayed in histograms (Figure 51). Relative risks of all treatments compared to placebo are displayed in a caterpillar plot (Figure 52).

Figure 46: Network for cessation outcome, where direct evidence was available



Note: The size of nodes is proportional to the number of people in the network who were randomised to a particular treatment. The thickness of connecting lines is proportional to the number of studies directly comparing 2 treatments.

Table 7: Detail of arms

Arm 1	Arm 2	Number of studies (including 0 events both arms)	Number of participants
NRT long/short	Placebo	64	32,091
NRT long/short	No drug treatment	26	8,300
NRT long/short	Waitlist	2	634
NRT long/short	Usual care	6	3,252
NRT long & short	Placebo	2	392
NRT long & short	No drug treatment	3	7,100
NRT long & short	Waitlist	1	299
NRT long & short	Usual care	1	207
NRT long & short	NRT long/short	6	2,859
Bupropion	Placebo	38	16,622
Bupropion	No drug treatment	5	2,482
Bupropion	Usual care	2	1,525

Arm 1	Arm 2	Number of studies (including 0 events both arms)	Number of participants
Bupropion	NRT long/short	8	6,069
Varenicline	Placebo	31	16,255
Varenicline	No drug treatment	2	572
Varenicline	NRT long/short	10	8,008
Varenicline	NRT long & short	1	270
Varenicline	Bupropion	6	5,629
E-cigarette	Placebo e-cigarette	2	662
E-cigarette	Usual care	2	2,092
E-cigarette	NRT long/short	1	584
Bupropion + NRT long/short	Placebo	4	1,387
Bupropion + NRT long/short	No drug treatment	1	80
Bupropion + NRT long/short	Usual care	1	538
Bupropion + NRT long/short	NRT long/short	8	2,618
Bupropion + NRT long/short	Bupropion	4	1,527
Bupropion + NRT long & short	NRT long/short	2	178
Varenicline + NRT long/short	No drug treatment	1	427
Varenicline + NRT long/short	Varenicline	2	787
Varenicline + NRT long/short	Bupropion + NRT long/short	1	291
Varenicline + Bupropion	Placebo	1	219
Varenicline + Bupropion	Varenicline	2	835
E-cigarette + NRT long/short	NRT long/short	2	1,039

Table 8: Mileage chart of pairwise [lower diagonal, RR 95%CI] and NMA [upper diagonal, posterior median RR 95% CrI] estimates for cessation

Treatment	Placebo	No drug treatment	Waitlist	Usual care	NRT l/s	NRT l&s	B	V	E-cig	B + NRT l/s	B + NRT l&s	V + NRT l/s	V+B	E-cig+ NRT l/s
Placebo					**1.83 [1.67, 2.01]**	**2.71 [2.10, 3.40]**	**1.73 [1.52, 1.95]**	**2.27 [2.01, 2.55]**	**2.25 [1.33, 3.58]**	**1.93 [1.50, 2.46]**	**3.51 [1.77, 5.59]**	**2.58 [1.68, 3.70]**	**2.75 [1.73, 4.05]**	**2.93 [1.52, 4.80]**
No drug treatment					**1.30 [1.11, 1.53]**	**1.91 [1.46, 2.49]**	**1.22 [1.01 1.49]**	**1.60 [1.32, 1.96]**	1.60 [0.93, 2.61]	**1.37 [1.02, 1.82]**	**2.48 [1.24, 4.08]**	**1.83 [1.16, 2.71]**	**1.94 [1.19, 2.98]**	**2.07 [1.07, 3.49]**
Waitlist					1.48 [0.83, 2.86]	**2.22 [1.18, 4.21]**	1.39 [0.77, 2.73]	**1.83 [1.01, 3.59]**	1.82 [0.84, 4.07]	1.56 [0.83, 3.14]	**2.79 [1.17, 6.45]**	**2.08 [1.02, 4.39]**	**2.21 [1.06, 4.78]**	2.35 [1.00, 5.41]
Usual care					**2.61 [1.92, 3.57]**	**3.84 [2.62, 5.62]**	**2.46 [1.79, 3.40]**	**3.23 [2.32, 4.50]**	**3.21 [1.82, 5.42]**	**2.75 [1.90, 4.01]**	**4.97 [2.39, 8.76]**	**3.67 [2.18, 5.92]**	**3.91 [2.25, 6.46]**	**4.16 [2.05, 7.46]**
NRT l/s	**1.70 [1.60, 1.80]**	**1.41 [1.27, 1.56]**	1.76 [0.60, 5.15]	**1.27 [1.03, 1.53]**		**1.48 [1.16, 1.48]**	0.94 [0.82, 1.08]	**1.24 [1.08, 1.41]**	1.23 [0.73, 1.95]	1.05 [0.82, 1.34]	1.91 [0.97, 3.05]	1.41 [0.92, 2.02]	1.50 [0.94, 2.22]	1.60 [0.84, 2.61]
NRT l&s	**2.05 [1.14, 3.67]**	2.14 [0.36, 12.60]	1.89 [0.93, 3.83]	4.68 [0.24, 99.98]	**1.54 [1.28, 1.85]**		**0.64 [0.50, 0.84]**	0.84 [0.65, 1.10]	0.84 [0.48, 1.40]	0.72 [0.51, 1.00]	1.30 [0.64, 2.20]	0.96 [0.59, 1.47]	1.02 [0.61, 1.61]	1.08 [0.55, 1.87]
B	**1.62 [1.50, 1.74]**	0.82 [0.45, 1.48]	-	**4.17 [2.51, 6.93]**	1.07 [0.92, 1.24]	-		**1.31 [1.12, 1.54]**	1.31 [0.76, 2.10]	1.12 [0.86, 1.44]	**2.03 [1.02, 3.29]**	1.50 [0.96, 2.17]	1.59 [0.99, 2.38]	1.69 [0.88, 2.82]
V	**2.10 [1.77, 2.51]**	2.47 [0.81, 7.52]	-	-	**1.24 [1.14, 1.35]**	0.44 [0.16, 1.24]	**1.35 [1.21, 1.51]**		1.00 [0.58, 1.60]	0.85 [0.65, 1.11]	1.55 [0.78, 2.50]	1.14 [0.75, 1.62]	1.22 [0.77, 1.78]	1.29 [0.70, 2.15]
E-cig	2.02 [0.97, 4.21]	-	-	**4.92 [1.04, 16.91]**	1.26 [0.68, 2.34]	-	-	-		0.86 [0.51, 1.51]	1.54 [0.69, 3.14]	1.14 [0.61, 2.15]	1.22 [0.63, 2.34]	1.29 [0.59, 2.66]
B + NRT l/s	**1.68 [1.38, 2.05]**	0.83 [0.27, 2.53]	-	**3.55 [1.65, 7.65]**	1.07 [0.82, 1.39]	-	1.09 [0.93, 1.28]	-	-		1.81 [0.89, 3.09]	1.33 [0.83, 2.04]	1.42 [0.84, 2.26]	1.51 [0.76, 2.64]
B + NRT l&s	-	-	-	-	**1.97 [1.11, 3.48]**	-	-	-	-	-		0.74 [0.39, 1.57]	0.79 [0.41, 1.71]	0.84 [0.37, 1.93]
V + NRT l/s	-	-	-	-	0.60 [0.24, 1.46]	-	-	1.41 [0.98, 2.04]	-	0.83 [0.29, 2.40]	-		1.06 [0.60, 1.93]	1.13 [0.54, 2.18]
V+B	**4.35 [1.40, 13.55]**	-	-	-	-	-	-	1.19 [0.96, 1.48]	-	-	-	-		1.07 [0.50, 2.11]
E-cig + NRT l/s	-	-	-	-	**1.77 [1.07, 2.94]**	-	-	-	-	-	-	-	-	

Bold is statistical significance
B: Bupropion; V: Varenicline; E-cig: E-cigarette; NRT l/s: NRT long or short acting; NRT l&s: NRT long and short acting
Lower diagonal: pairwise results comparing intervention (column 1) with control (row 1). RR higher than one favour column 1 treatment (higher cessation in that group) (for example varenicline vs NRT l/s is RR 1.24 (95% CrI 1.14, 1.35).
Upper diagonal: NMA results comparing intervention (row 1) with control (column 1). RR higher than one favour row 1 treatment (higher cessation in that group) (for example varenicline vs NRT l/s is RR 1.24 (95% CrI 1.08, 1.41).

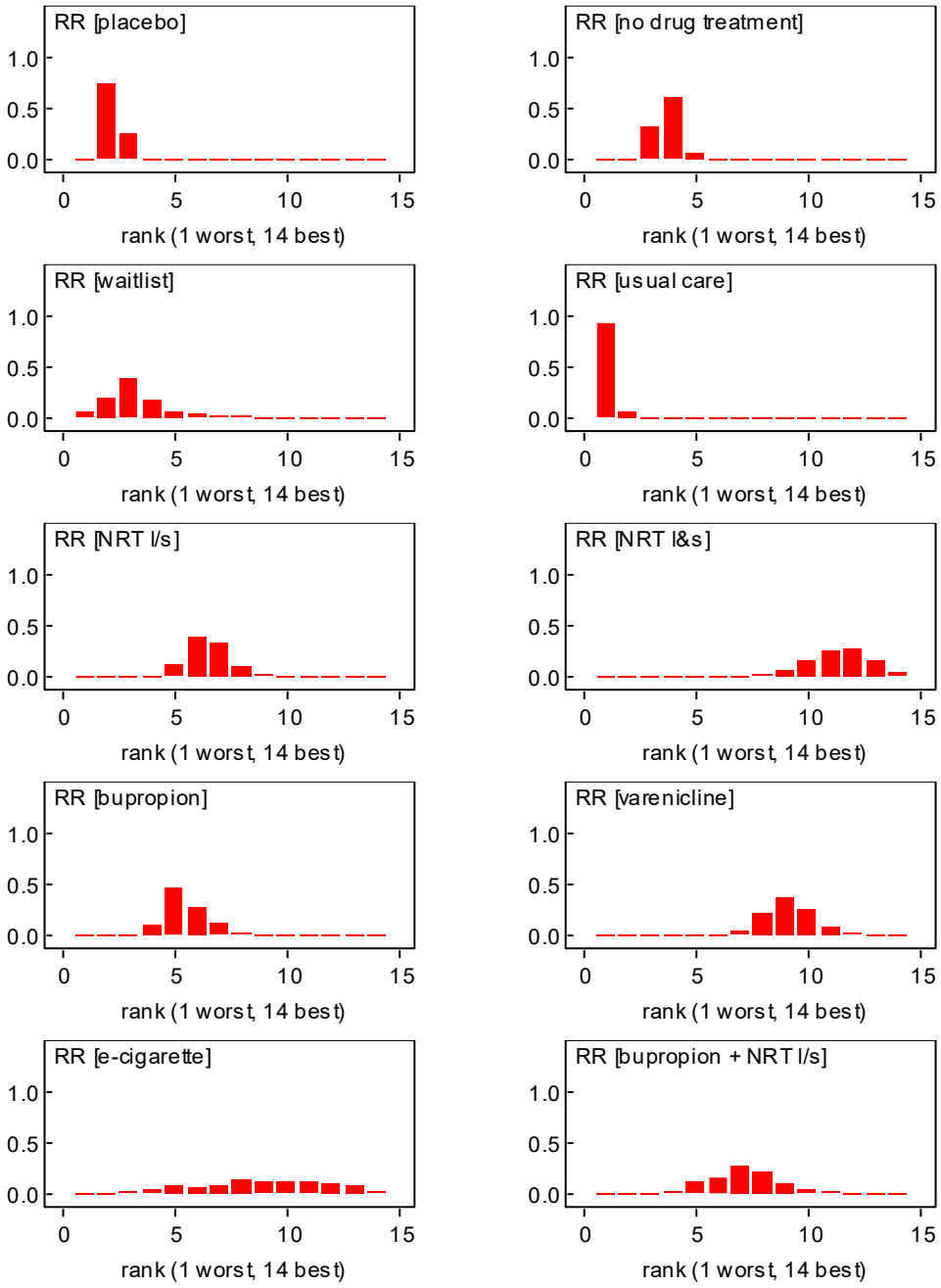
CrI: credible intervals; RR: relative risk; NMA: network meta-analysis

Table 9: Median treatment rank and 95% CrI (1-14, 14 is best, 1 is worst)

Treatment	Median (95% CrI) treatment rank
Placebo	2 (2, 3)
No Drug Treatment	4 (3, 5)
Wait List	3 (1, 9)
Usual Care	1 (1, 2)
NRT long/short acting	6 (5, 8)
NRT long&short acting	11 (8, 14)
Bupropion	5 (4, 8)
Varenicline	9 (7, 11)
E-cigarette	9 (4, 14)
Bupropion + NRT long/short acting	7 (4, 10)
Bupropion + NRT long &short acting	14 (6, 14)
Varenicline + NRT long/short acting	11 (5, 14)
Varenicline + bupropion	12 (6, 14)
E-cigarette + NRT long/short acting	12 (5, 14)

CrI: Credible intervals

Figure 47: Histograms of treatment rankings (1 is worst, 14 is best)



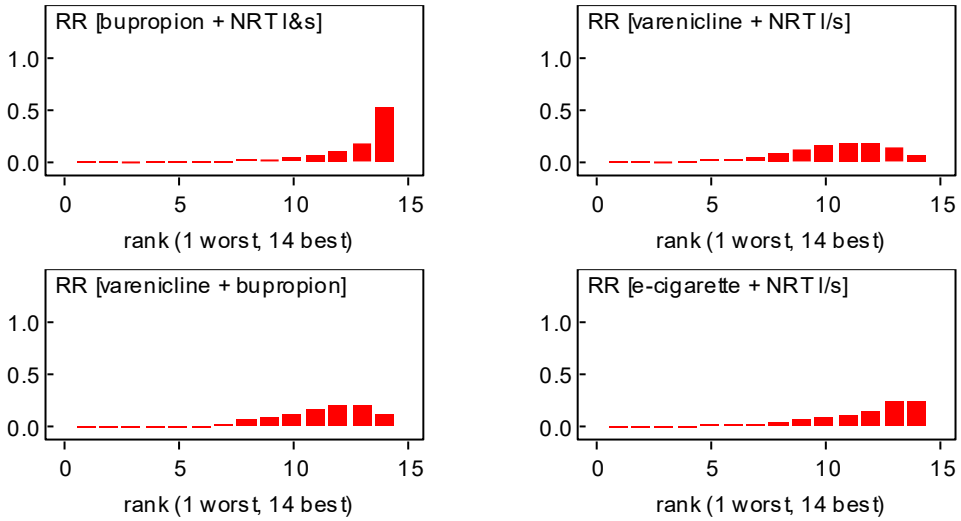
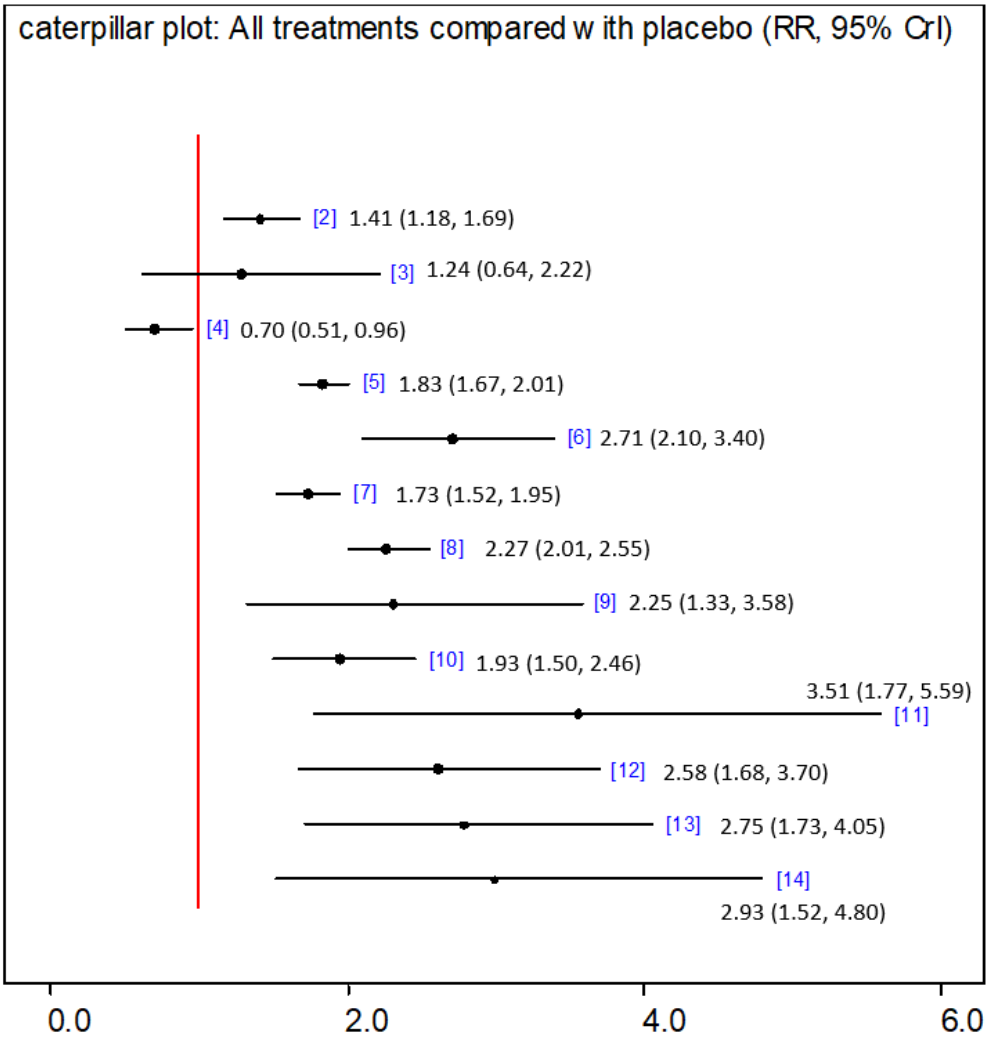


Figure 48: Caterpillar plot, all interventions compared with placebo (median risk ratio [RR] and 95% CrI)



NICE class list

1. Placebo

2. No Drug Treatment
3. Wait List
4. Usual Care
5. NRT long/short acting
6. NRT long&short acting
7. Bupropion
8. Varenicline
9. E-cigarette
10. Bupropion + NRT long/short acting
11. Bupropion + NRT long &short acting
12. Varenicline + NRT long/short acting
13. Varenicline + bupropion
14. E-cigarette + NRT long/short acting

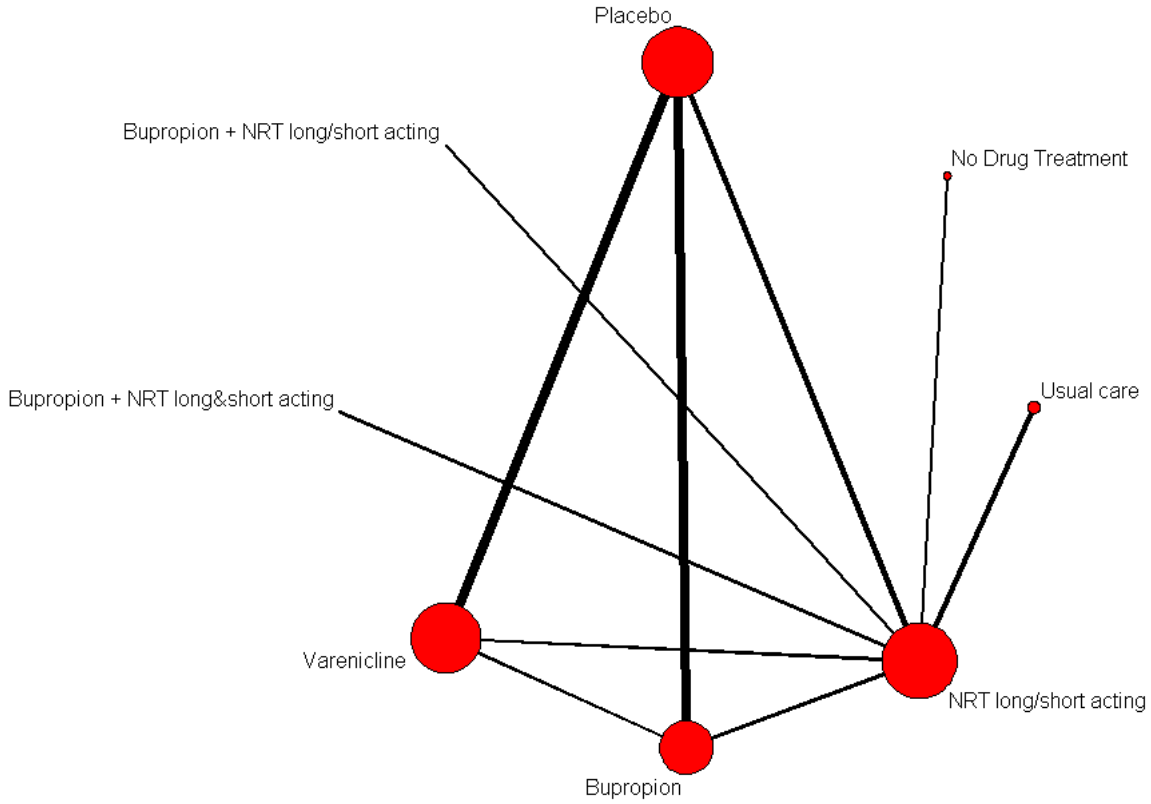
Mental health subgroup: Difference in abstinence at 6 months

Of the 192 trials included in the main analysis, 13 took place in populations with mental health conditions. These 13 studies formed a network which included varenicline, bupropion, NRT long/short acting, NRT long & short acting, bupropion + NRT long/short acting and bupropion + NRT long & short acting in addition to usual care, no drug treatment and placebo. There were no treatments which were disconnected.

The NMA results are a combination of indirect and, where available, direct estimates for each comparison. These are displayed in the upper diagonal of table 23 (mileage chart). Pairwise meta-analysis was also conducted for each comparison and displayed in the lower diagonal of the mileage chart. Comparisons for placebo, no drug treatment and usual care to each other was not conducted, because these were not considered to be useful for making recommendations.

Table 24 displays the median rank and 95% CrI for each treatment. Ranks span from 1 (worst) to 9 (best). Rankings are also displayed in histograms (Figure 54). Relative risks of all treatments compared to placebo are displayed in a caterpillar plot (Figure 55).

Figure 49: Network for cessation outcome, where direct evidence was available



Note: The size of nodes is proportional to the number of people in the network who were randomised to a particular treatment. The thickness of connecting lines is proportional to the number of studies directly comparing 2 treatments.

Table 10: Detail of arms – Mental health subgroup

Arm 1	Arm 2	Number of studies (including 0 events both arms)	Number of participants
NRT long/short	Placebo	2	2,071
NRT long/short	No drug treatment	1	322
NRT long/short	Usual care	1	298
NRT long&short	Usual care	1	207
Bupropion	Placebo	4	2,147
Bupropion	NRT long/short	1	2,058
Varenicline	Placebo	4	2,771
Varenicline	NRT long/short	1	2,057
Varenicline	Bupropion	1	2,065
Bupropion + NRT long/short	NRT long/short	1	60

Arm 1	Arm 2	Number of studies (including 0 events both arms)	Number of participants
Bupropion + NRT long & short	NRT long/short	1	51

Table 11: Mileage chart of pairwise [lower diagonal, RR 95%CI] and NMA [upper diagonal, posterior median RR 95% CrI] estimates for cessation

Treatment	Placebo	No drug treatment	Usual care	NRT l/s	NRT l&s	B	V	B + NRT l&s	B + NRT l/s
Placebo				**1.89 [1.06, 5.40]**	3.97 [0.16, 7.92]	1.79 [0.85, 4.01]	**2.29 [1.33, 4.34]**	4.24 [0.83, 7.63]	**7.0 [1.95, 7.98]**
No drug treatment				0.94 [0.44, 3.30]	1.61 [0.07, 8.50]	0.88 [0.24, 3.51]	1.12 [0.34, 4.35]	1.85 [0.37, 7.66]	3.01 [0.81, 11.09]
Usual care				2.52 [0.66, 18.69]	3.71 [0.38, 30.04]	2.34 [0.37, 19.47]	2.97 [0.50, 24.72]	4.93 [0.71, 41.0]	**7.77 [1.14, 67.09]**
NRT l/s	2.90 [0.46, 18.15]	0.92 [0.5, 1.69]	3.85 [0.97, 15.35]		1.72 [0.08, 5.46]	0.96 [0.29, 1.89]	1.22 [0.42, 2.28]	1.96 [0.46, 4.41]	3.19 [0.99, 6.18]
NRT l&s	-	-	4.68 [0.24, 99.98]	-		0.50 [0.15, 11.67]	0.61 [0.22, 14.52]	1.04 [0.19, 24.19]	1.57 [0.43, 38.77]
B	1.73 [0.29, 2.31]	-	-	1.06 [0.82, 1.37]	-		1.27 [0.57, 3.06]	2.22 [0.44, 6.15]	**3.53 [1.02, 7.93]**
V	**2.26 [1.81, 2.83]**	-	-	**1.43 [1.13, 1.81]**	-	**1.35 [1.07,1.70]**		1.78 [0.35, 4.15]	2.81 [0.82, 5.17]
B + NRT l&s	-	-	-	2.6 [0.55, 12.19]	-	-	-		1.48 [0.44, 7.76]
B + NRT l/s	-	-	-	9.0 [0.51, 160.17]	-	-	-	-	

Bold is statistical significance
B: Bupropion; V: Varenicline; NRT l/s: NRT long or short acting; NRT l&s: NRT long and short acting
Lower diagonal: pairwise results comparing intervention (column 1) with control (row 1). RR higher than one favour column 1 treatment (higher cessation in that group) (for example bupropion vs NRT l/s is RR 1.06 (95% CrI 0.82, 1.37).
Upper diagonal: NMA results comparing intervention (row 1) with control (column 1). RR higher than one favour row 1 treatment (higher cessation in that group) (for example bupropion vs NRT l/s is RR 0.96 (95% CrI 0.29, 1.89).
CrI: credible intervals; RR: relative risk; NMA: network meta-analysis

Table 12: Median treatment rank and 95% CrI (1-9, 9 is best, 1 is worst)

Treatment	Median (95% CrI) treatment rank
Placebo	2 (1, 4)
No Drug Treatment	5 (1, 8)
Usual Care	1 (1, 6)
NRT long/short acting	5 (3, 7)
NRT long & short acting	7 (1, 9)
Bupropion	4 (2, 7)

Treatment	Median (95% CrI) treatment rank
Varenicline	6 (2, 8)
Bupropion + NRT long &short acting	7 (2, 9)
Bupropion + NRT long / short acting	9 (5, 9)

CrI: Credible intervals

Figure 50: Histograms of treatment rankings (9 is best, 1 is worst)

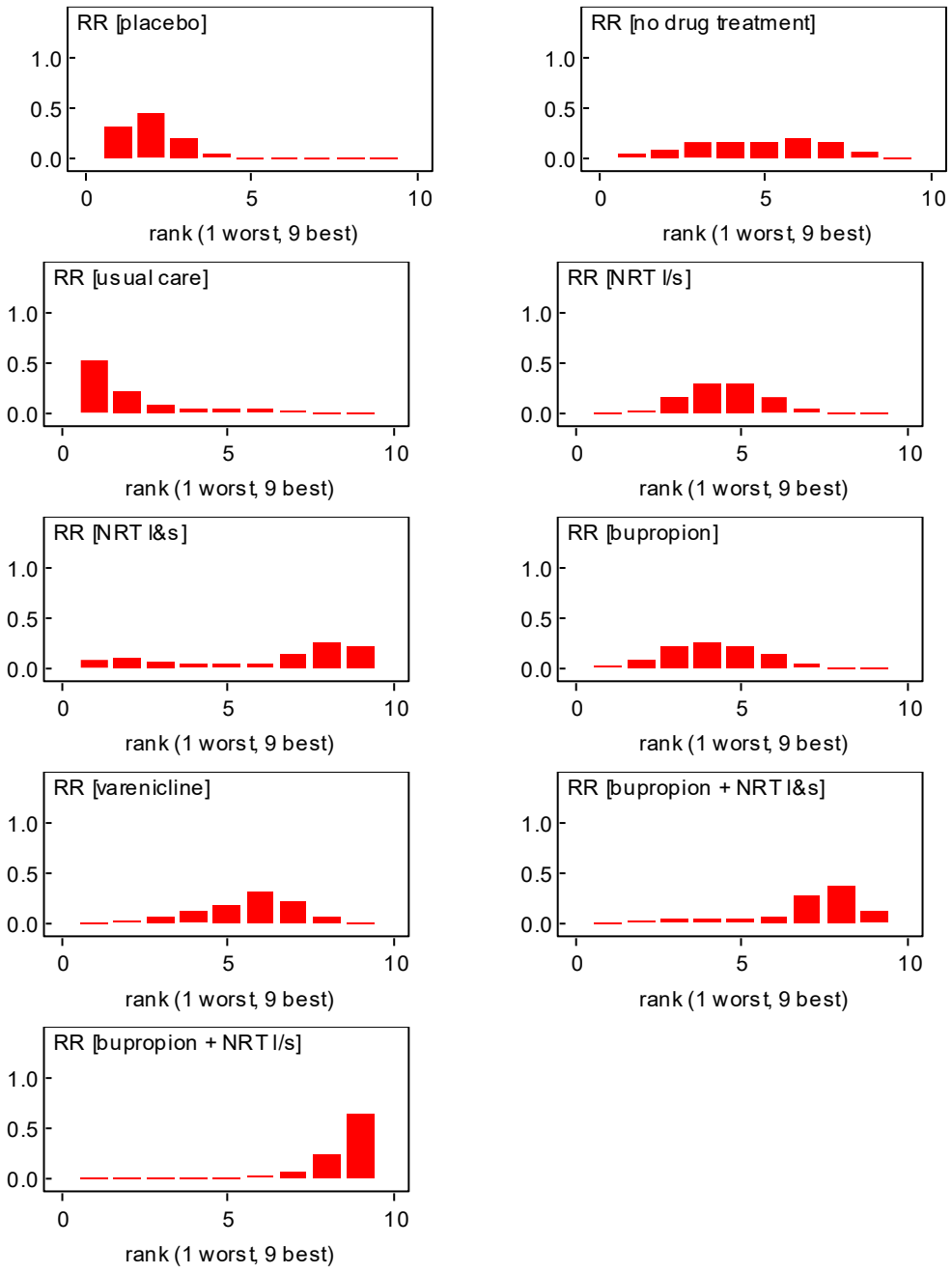
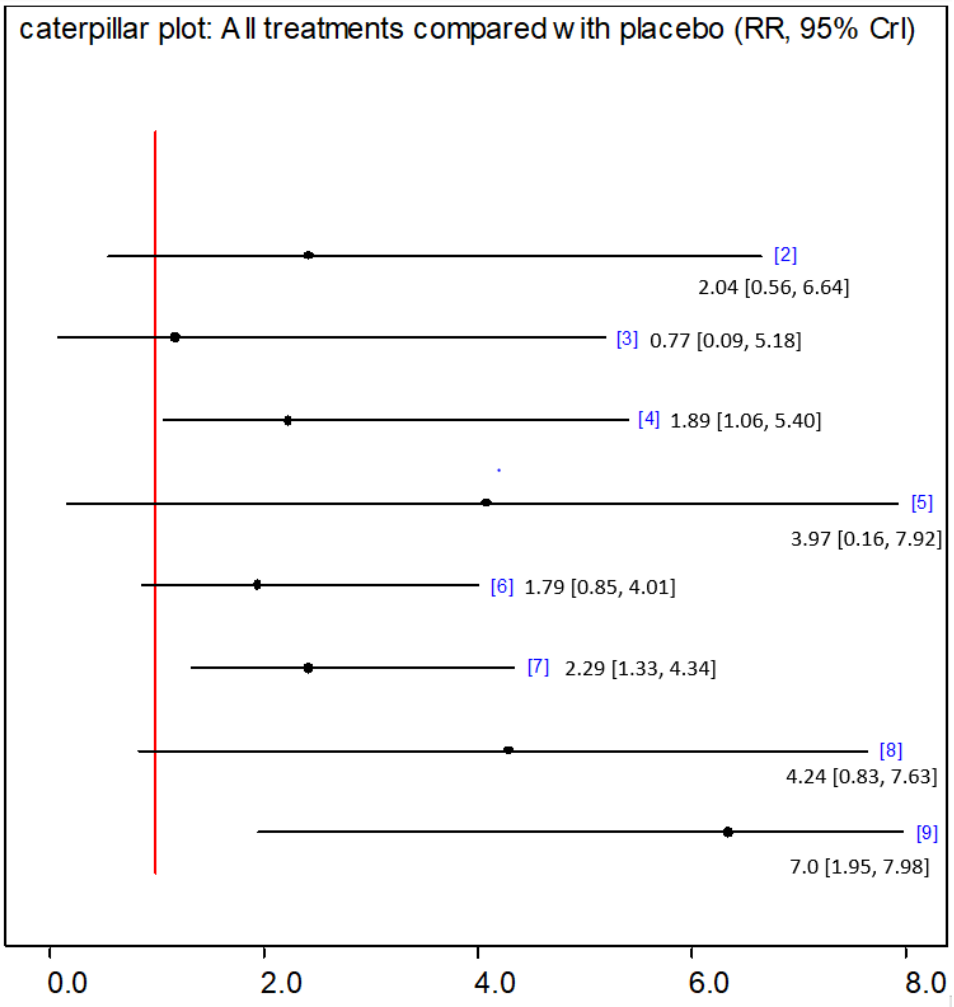


Figure 51: Caterpillar plot, all interventions compared with placebo (risk ratio [RR] and 95% CrI)



NICE class list

1. Placebo
2. No Drug Treatment
3. Usual Care
4. NRT long/short acting
5. NRT long&short acting
6. Bupropion
7. Varenicline
8. Bupropion + NRT long&short acting
9. Bupropion + NRT long/short acting

Appendix J – Network Meta-analysis inconsistency checks

Methods

To assess whether there is any statistical evidence of inconsistency, we fitted inconsistency models (the unrelated mean effects (UME) model) for each population, and compared model fit (posterior mean residual deviance and Deviance Information Criteria (DIC)) and estimates of between studies heterogeneity (sd). We also inspected the posterior mean contribution of each observation to the residual deviance to identify particular observations with lack of fit and plotted these for the inconsistency model vs the consistency model (Dev-Dev plots). Points falling far below and to the right of the 45º line indicate studies/treatments of potential concern. If there was an indication of inconsistency in the model fit and/or Dev-Dev plots, we explored this further using node-splitting. Node-splitting removes a particular edge (defined by 2 treatments) from the network diagram and estimates a treatment effect using only studies which directly compare those 2 treatments (direct estimate) (but sharing the heterogeneity estimate across the full network). An indirect estimate is obtained using an NMA model for the remaining network of evidence and the direct and indirect estimates are compared to obtain a p-value against a hypothesis of consistency. Small values of the p-value indicate evidence of inconsistency. Note, however, that since there are many edges that we could conduct node-splitting for, some will have small p-values by chance. We therefore interpret the p-values accordingly to allow for multiple testing (p-values need to be sufficiently less than 0.05 to indicate potential inconsistency).

Comparing Inconsistency and Consistency Models (Global Check for Inconsistency)

Table 25 gives model fit statistics for the consistency and inconsistency models, both assuming random study effects and each intervention effect set equal to it's class effect (the model found to be most parsimonious in the NMA). Because the fixed class model essentially assumes that interventions in the same class have the same effect, the inconsistency (UME) model was run at the class level.

Model fit is good for both populations (posterior mean deviance is less than the number of data-points). The DIC measure is a combination of model fit and model complexity, and we prefer models with lower DIC. On both measures, model fit is not improved by fitting the inconsistency (UME) model. However, for both populations the between studies standard deviation is lower for the inconsistency model, suggesting that some of the heterogeneity has been explained by relaxing the consistency assumption. This effect is stronger for the full population.

Table 13: Model fit statistics for consistency and inconsistency models

Model	Posterior Mean Residual Deviance*	Deviance Information Criteria (DIC)	Between Studies sd, posterior median (95%CrI)
FULL POPULATION			
Consistency Model	420.2	2666.0	0.41 (0.35, 0.48)
Inconsistency (UME) Model	428.8	2672.1	0.36 (0.30, 0.43)
MENTAL HEALTH SUBGROUP			
Consistency Model	26.9	143.1	0.32 (0.01, 1.56)

Model	Posterior Mean Residual Deviance*	Deviance Information Criteria (DIC)	Between Studies sd, posterior median (95%CrI)
Inconsistency (UME) Model	26.9	143.3	0.35 (0.01, 1.63)

Table 25: Model fit statistics for the consistency NMA model and the inconsistency (Unrelated Mean Effects Model) model at the class level. Results are shown separately for the full population and the mental health subgroup. *Compare the posterior mean residual deviance with 425 data-points for the Full-NMA and 28 data-points for the MH-NMA.

Figure 52: Network for cessation outcome, where direct evidence was available

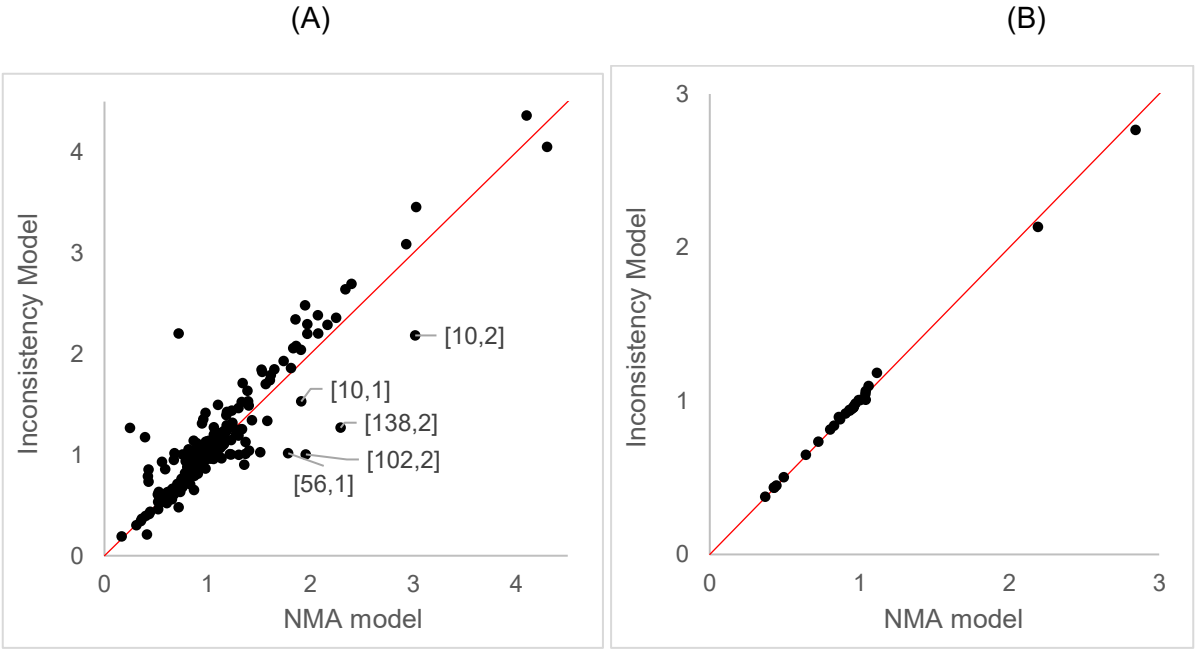


Figure 56: Dev-Dev plots showing the contribution of each observation to the posterior mean residual deviance under the inconsistency (UME) model compared with the consistency NMA model for (A) Full population and (B) MH-subgroup.

Inspecting the Dev-Dev plots (Fig 1) we see no evidence of inconsistency in the MH-NMA (Fig 1b), but some data-points are highlighted in the Full-NMA (Fig 1a). The observations are labelled by study and arm, so [138,2] is arm 2 of study 138. Table 2 shows which treatments are compared in the labelled observations. This highlights classes 2,4,5,7,10 as potential sources of inconsistency. Fig. 2 shows the network diagram for the full population at the class level. It can be seen there are several loops of evidence involving these 5 classes. We can therefore run node-splitting models for each pair of classes in the set {2,4,5,7,10}.

Table 14: Observations highlighted in the Dev-Dev plot for the full population (Fig 56A)

Label	Study (Arms)	Study Design (class level)	Study Design (intervention level)
[10,1], [10,2]	10 (Arms 1 and 2)	No drug treatment vs bupropion	No drug treatment vs bupropion standard

[138,2]	138 (Arm 2)	No drug treatment vs NRT long/short vs bupropion vs bupropion + NRT long/short	No drug treatment vs NRT patch (24 hours) ns vs bupropion ns vs bupropion ns + NRT patch (24 hrs) ns
[102,2]	102 (Arm 2)	No drug treatment vs usual care	No drug treatment vs usual care
[56,1]	56 (Arm 1)	Usual care vs NRT long/short	Usual care vs NRT gum ns
			No drug treatment vs bupropion standard

See figure 50.

Node-Splitting (Local Check for Inconsistency)

Figure 57 shows the results of node-splitting for each pair of classes where there is both direct and indirect evidence. Model fit does not improve and heterogeneity does not reduce for each of the node-split pairs. The p-values suggest there is some evidence of inconsistency when the 2v4 (p=0.0004) and the 4v5 (p=0.00004) contrasts are “split” from the network. This indicates that the 2-4-5 evidence loop may be inconsistent. Intervention 2 is usual care, 4 is waitlist and 5 is NRT long or short. Studies involved in this loop were checked for any data extraction and intervention classification errors. Study characteristics were also considered to see whether there was excessive methodological heterogeneity in this area of the NMA.

Conclusions from the Inconsistency Analysis

In the full population, there is some evidence of inconsistency on the 2-4-5 evidence loop, and a few studies have been identified as having particularly poor fit in the NMA consistency model. However, we note that relaxing the consistency assumption does not improve heterogeneity or model fit substantially. We believe this is due to the high levels of heterogeneity that exists in this data, so that the inconsistency observed isn’t over and above the differences between studies within comparisons, and may simply be a feature of the high levels of heterogeneity seen in this network.

The results of the investigation into the inconsistency was not able to fully explain the inconsistency. Minor data extraction errors were corrected in several identified studies – these errors are not expected to have affected the results, these have been corrected. Arms in two studies had classification errors and were reclassified from NRT long or short to NRT long and short. There was an imbalance in the intensity of the behavioural elements between arms in around a third of the 35 identified studies. This could affect the results, but it is unclear to what extent the 2-4-5 loop is affected by this issue more than the rest of the network. In some of the studies, the behavioural element was more intensive in the treatment (drug) arm, whereas in others it was more intensive in the no drug treatment or usual care arm. Some of the individual studies, for example Zernig (2008) comparing bupropion with no drug treatment, had results which were unexpected – in this case, showing no drug treatment to be significantly more effective than bupropion. This may be explained by the no drug treatment arm receiving an intensive behavioural intervention.

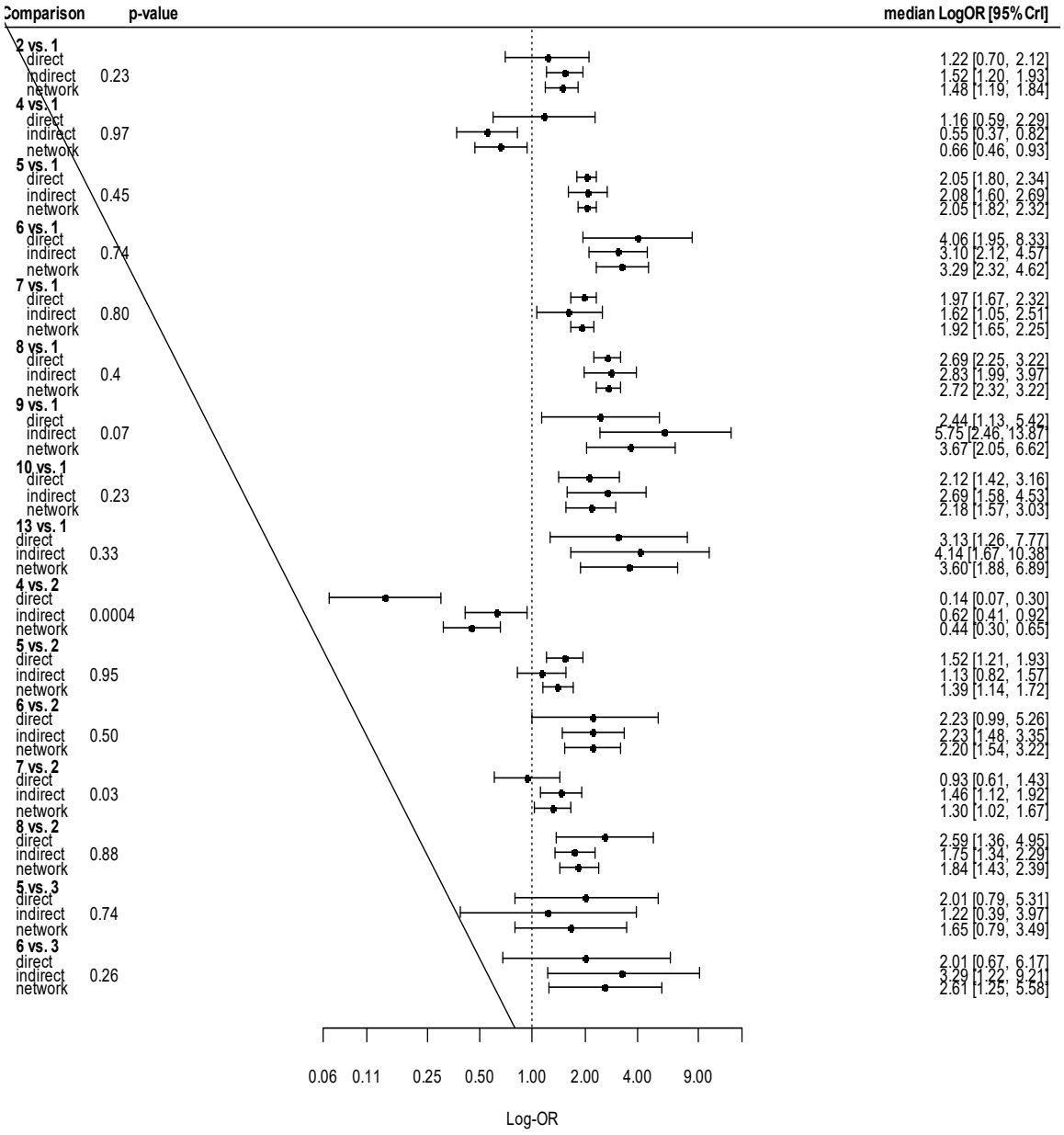
It was concluded that heterogeneity was not likely to be greater than throughout the rest of the NMA. The observed inconsistency could be a matter of chance based on heterogeneous data.

There was no evidence of inconsistency for the MH population, but note that there are no evidence loops that do not consist of multi-arm trials, and so no scope for inconsistency.

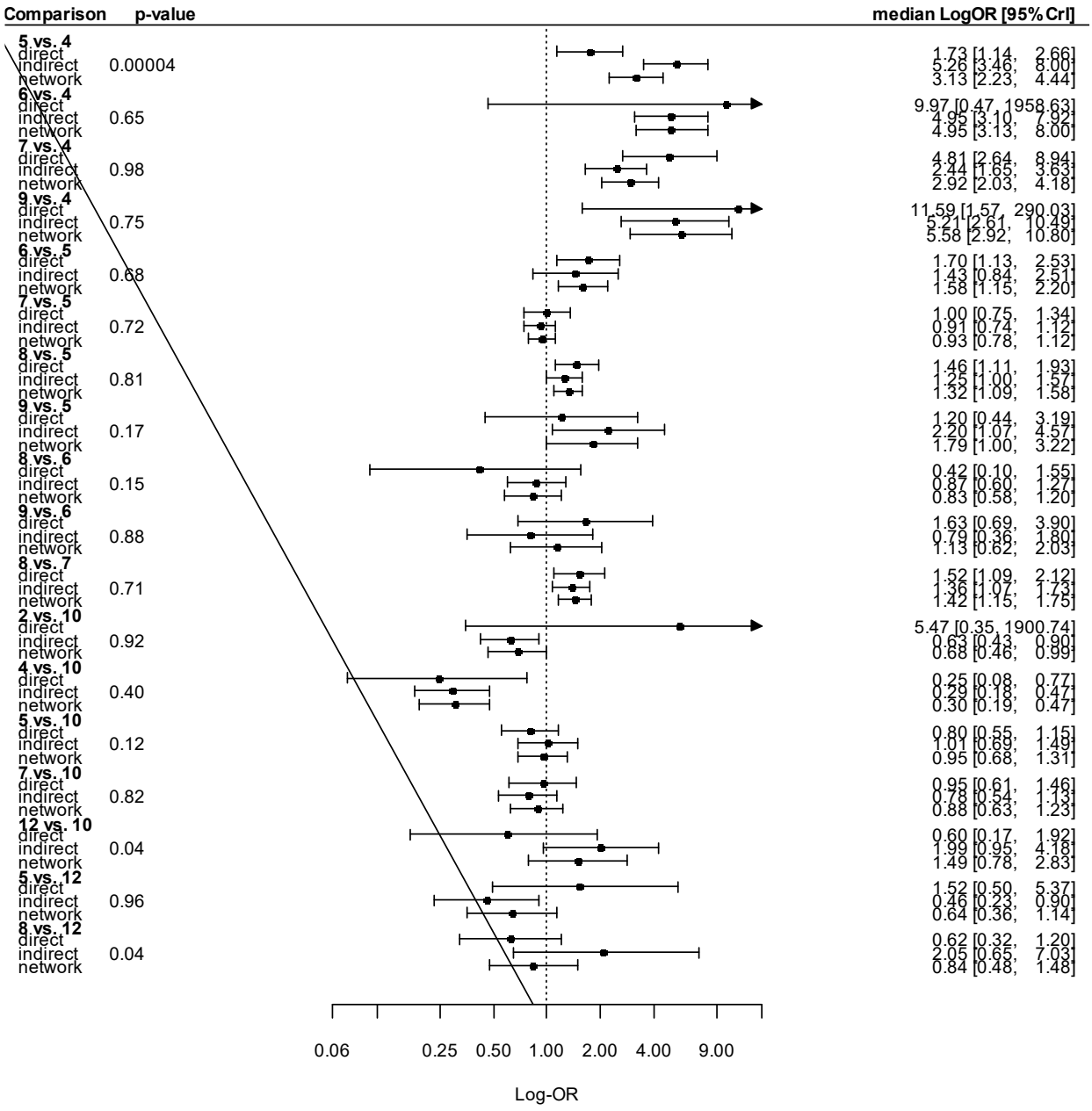
Figure 53: Network for cessation outcome, where direct evidence was available

Node-splitting models indicated by the contrast that is "split", for the full population. Direct and indirect estimates are displayed as well as the estimate from the NMA consistency model. Bayesian p-values are reported, interpreted as the probability that the direct estimate exceeds the indirect estimate. Very small values (much less than 0.05) of the p-value indicate evidence of inconsistency. (A): full NMA; (B): subgroup NMA.

(A)



(B)


Comparison
p-value
median LogOR [95% CrI]
5 vs. 4
direct
indirect 0.00004
network
1.73 [1.14, 2.66]
5.26 [3.46, 8.00]
3.13 [2.23, 4.44]
6 vs. 4
direct
indirect 0.65
network
9.97 [0.47, 1958.63]
4.95 [3.10, 7.92]
4.95 [3.13, 8.00]
7 vs. 4
direct
indirect 0.98
network
4.81 [2.64, 8.94]
2.44 [1.65, 3.63]
2.92 [2.03, 4.18]
9 vs. 4
direct
indirect 0.75
network
11.59 [1.57, 290.03]
5.21 [2.61, 10.49]
5.58 [2.92, 10.80]
6 vs. 5
direct
indirect 0.68
network
1.70 [1.13, 2.53]
1.43 [0.84, 2.51]
1.58 [1.15, 2.20]
7 vs. 5
direct
indirect 0.72
network
1.00 [0.75, 1.34]
0.91 [0.74, 1.12]
0.93 [0.78, 1.12]
8 vs. 5
direct
indirect 0.81
network
1.46 [1.11, 1.93]
1.25 [1.00, 1.57]
1.32 [1.09, 1.58]
9 vs. 5
direct
indirect 0.17
network
1.20 [0.44, 3.19]
2.20 [1.07, 4.57]
1.79 [1.00, 3.22]
8 vs. 6
direct
indirect 0.15
network
0.42 [0.10, 1.55]
0.87 [0.60, 1.27]
0.83 [0.58, 1.20]
9 vs. 6
direct
indirect 0.88
network
1.63 [0.69, 3.90]
0.79 [0.36, 1.80]
1.13 [0.62, 2.03]
8 vs. 7
direct
indirect 0.71
network
1.52 [1.09, 2.12]
1.36 [1.07, 1.73]
1.42 [1.15, 1.75]
2 vs. 10
direct
indirect 0.92
network
5.47 [0.35, 1900.74]
0.63 [0.43, 0.90]
0.68 [0.46, 0.99]
4 vs. 10
direct
indirect 0.40
network
0.25 [0.08, 0.77]
0.29 [0.18, 0.47]
0.30 [0.19, 0.47]
5 vs. 10
direct
indirect 0.12
network
0.80 [0.55, 1.15]
1.01 [0.69, 1.49]
0.95 [0.68, 1.31]
7 vs. 10
direct
indirect 0.82
network
0.95 [0.61, 1.46]
0.78 [0.54, 1.13]
0.88 [0.63, 1.23]
12 vs. 10
direct
indirect 0.04
network
0.60 [0.17, 1.92]
1.99 [0.95, 4.18]
1.49 [0.78, 2.83]
5 vs. 12
direct
indirect 0.96
network
1.52 [0.50, 5.37]
0.46 [0.23, 0.90]
0.64 [0.36, 1.14]
8 vs. 12
direct
indirect 0.04
network
0.62 [0.32, 1.20]
2.05 [0.65, 7.03]
0.84 [0.48, 1.48]
0.06
0.25
0.50
1.00
2.00
4.00
9.00
Log-OR

Sensitivity analysis for NMA

As noted in the committee discussion the committee noted that there are currently only a small number of e-cigarette published studies and a sensitivity analysis of the NMA was completed that included the 6 month (self-report) outcomes in the recent Hajek (2019) study of e-cigarettes compared with NRT long/short acting. An NMA allows the synthesis of multiple treatments, indirect estimates can be found where there is any path linking through comparators in the network. This may be seen in the findings for this sensitivity analysis where the addition of one study that compared e-cigarettes with NRT long/short acting results in findings that change the estimates across more than these two nodes.

The mileage chart for this sensitivity analysis.

Treatment	Placebo	No drug treatment	Waitlist	Usual care	NRT l/s	NRT l&s	B	V	E-cig	B + NRT l/s	B + NRT l&s	V + NRT l/s	V+B	E-cig+ NRT l/s
Placebo					**1.83 [1.67, 2.01]**	**2.59 [2.02, 3.24]**	**1.73 [1.53, 1.96]**	**2.26 [2.0, 2.55]**	**2.79 [1.82, 3.99]**	**1.91 [1.47, 2.45]**	**3.51 [1.77, 5.50]**	**2.57 [1.66, 3.70]**	**2.75 [1.70, 4.07]**	**2.94 [1.52, 4.83]**
No drug treatment					**1.31 [1.11, 1.56]**	**1.85 [1.40, 2.41]**	**1.24 [1.01 1.52]**	**1.61 [1.32, 1.99]**	**1.99 [1.27, 2.96]**	**1.37 [1.01, 1.84]**	**2.50 [1.25, 4.14]**	**1.84 [1.16, 2.76]**	**1.96 [1.19, 3.02]**	**2.1 [1.07, 3.55]**
Waitlist					1.51 [0.84, 2.95]	**2.31 [1.17, 4.12]**	1.43 [0.78, 2.83]	**1.87 [1.02, 3.69]**	**2.29 [1.13, 4.81]**	1.58 [0.83, 3.21]	**2.86 [1.19, 6.57]**	**2.12 [1.02, 4.54]**	**2.26 [1.06, 4.93]**	2.41 [1.00, 5.58]
Usual care					**2.66 [1.96, 3.67]**	**3.75 [2.56, 5.52]**	**2.52 [1.83, 3.51]**	**3.29 [2.36, 4.62]**	**4.04 [2.44, 6.48]**	**2.78 [1.90, 4.08]**	**5.07 [2.43, 9.08]**	**3.74 [2.21, 6.08]**	**3.99 [2.27, 6.66]**	**4.27 [2.08, 7.74]**
NRT l/s	**1.69 [1.60, 1.80]**	**1.39 [1.26, 1.54]**	1.76 [0.60, 5.15]	**1.27 [1.03, 1.57]**		**1.41 [1.11, 1.76]**	0.95 [0.82, 1.09]	**1.24 [1.08, 1.41]**	1.52 [0.99, 2.18]	1.04 [0.80, 1.34]	1.91 [0.97, 3.06]	1.41 [0.91, 2.03]	1.50 [0.92, 2.24]	1.61 [0.83, 2.63]
NRT l&s	**2.05 [1.14, 3.67]**	3.58 [0.24, 52.79]	1.89 [0.93, 3.83]	-	**1.54 [1.28, 1.85]**		**0.67 [0.52, 0.88]**	0.88 [0.68, 1.14]	1.08 [0.70, 1.57]	0.74 [0.53, 1.04]	1.36 [0.67, 2.30]	1.00 [0.61, 1.54]	1.06 [0.63, 1.69]	1.14 [0.57, 1.97]
B	**1.62 [1.50, 1.74]**	0.84 [0.41, 1.69]	-	**4.17 [2.51, 6.93]**	1.08 [0.93, 1.24]	-		**1.31 [1.12, 1.53]**	**1.61 [1.04, 2.35]**	1.10 [0.84, 1.43]	**2.02 [1.02, 3.29]**	1.49 [0.95, 2.17]	1.59 [0.97, 2.39]	1.7 [0.87, 2.83]
V	**2.10 [1.77, 2.51]**	2.47 [0.81, 7.52]	-	-	**1.24 [1.14, 1.35]**	0.44 [0.16, 1.24]	**1.35 [1.21, 1.51]**		1.23 [0.79, 1.79]	0.84 [0.64, 1.11]	1.55 [0.78, 2.52]	1.14 [0.74, 1.63]	1.22 [0.76, 1.79]	1.3 [0.67, 2.17]
E-cig	2.02 [0.97, 4.21]	-	-	**4.92 [1.04, 16.91]**	**1.39 [1.14, 1.69]**	-	-	-		0.69 [0.44, 1.12]	1.26 [0.59, 2.37]	0.92 [0.53, 1.62]	0.99 [0.54, 1.76]	1.05 [0.50, 2.02]
B + NRT l/s	**1.68 [1.38, 2.05]**	0.61 [0.03, 14.65]	-	**3.55 [1.65, 7.65]**	1.07 [0.81, 1.42]	-	1.08 [0.92, 1.26]	-	-		1.83 [0.90, 3.15]	1.35 [0.83, 2.08]	1.44 [0.84, 2.31]	1.54 [0.77, 2.70]
B + NRT l&s	-	-	-	-	**1.97 [1.11, 3.48]**	-	-	-	-	-		0.74 [0.39, 1.58]	0.79 [0.40, 1.71]	0.84 [0.37, 1.93]
V + NRT l/s	-	-	-	-	0.60 [0.24, 1.46]	-	-	1.41 [0.98, 2.04]	-	0.83 [0.29, 2.40]	-		1.07 [0.59, 1.90]	1.14 [0.54, 2.22]
V+B	**4.35 [1.40, 13.55]**	-	-	-	-	-	-	1.19 [0.96, 1.48]	-	-	-	-		1.07 [0.50, 2.14]

Treatment	Placebo	No drug treatment	Waitlist	Usual care	NRT l/s	NRT l&s	B	V	E-cig	B + NRT l/s	B + NRT l&s	V + NRT l/s	V+B	E-cig+ NRT l/s
E-cig + NRT l/s	-	-	-	-	**1.77 [1.07, 2.94]**	-	-	-	-	-	-	-	-	

Bold is statistical significance
B: Bupropion; V: Varenicline; E-cig: E-cigarette; NRT l/s: NRT long or short acting; NRT l&s: NRT long and short acting
Lower diagonal: pairwise results comparing intervention (column 1) with control (row 1). RR higher than one favour column 1 treatment (higher cessation in that group).
Upper diagonal: NMA results comparing intervention (row 1) with control (column 1). RR higher than one favour row 1 treatment (higher cessation in that group).
CrI: credible intervals; RR: relative risk; NMA: network meta-analysis

The median treatment rank (95%CrI), for this sensitivity analysis; 14 is best, 1 is worst.

Treatment	Median (95% CrI) treatment rank
Placebo	2 (2, 3)
No Drug Treatment	4 (3, 5)
Wait List	3 (1, 8)
Usual Care	1 (1, 2)
NRT long/short acting	6 (5, 8)
NRT long&short acting	11 (8, 13)
Bupropion	5 (4, 8)
Varenicline	9 (7, 11)
E-cigarette	12 (7, 14)
Bupropion + NRT long/short acting	7 (4, 10)
Bupropion + NRT long &short acting	14 (6, 14)
Varenicline + NRT long/short acting	11 (5, 14)
Varenicline + bupropion	11 (5, 14)
E-cigarette + NRT long/short acting	12 (5, 14)

CrI: Credible intervals

Economic sensitivity analysis

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

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

Table: Cost effectiveness results per person – scenario analysis including Hajek et al 2019 study

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

Appendix K – Expert testimony

Expert testimony 1: Socioeconomic inequalities

Section A: Developer to complete	
Name:	Martin Jarvis
Role:	Academic
Institution/Organisation (where applicable): **Contact information:**	Department of Behavioural Science and Health University College London 1 -19 Torrington Place London WC1E 6BT
Guideline title:	Tobacco: preventing uptake, promoting quitting and treating dependence (update)
Guideline Committee:	PHAC F
Subject of expert testimony:	Tackling the health inequalities caused by smoking: socioeconomic inequalities
Evidence gaps or uncertainties:	Evidence has been sought for effectiveness of various interventions for smoking cessation. Effectiveness by socioeconomic status (or income level, or occupation) was not identified. Please provide information on the following areas: • Are there particular subgroups at higher risk of smoking? • Are there specific barriers to cessation, or to accessing cessation services, among these groups? What are these barriers? • How can barriers be approached in a UK context (by local authorities, commissioners, health professionals, voluntary and community sector organisations)? Please note that we make recommendations at local rather than national levels. Policy, legislation and regulation should therefore not be the focus of the presentation.

	Please also note that although there may be complex and interlinked issues, the scope of this guideline is limited to tobacco, and particularly tobacco cessation.

Section B: Expert to complete

Summary testimony:	[Please use the space below to summarise your testimony in 250–1000 words. Continue over page if necessary]

People who are disadvantaged are more likely to become smokers, and having started smoking, less likely to give up. Disadvantage takes many forms – including material, cultural, and family circumstances, and personal well-being, giving rise to a social gradient in smoking that currently (2018) goes from about 8% in the most affluent to over 40% among those with multiple indicators of disadvantage. This gradient is paralleled by a social gradient in nicotine intake and dependence, which constitutes a major barrier to successful cessation. The social gradients in prevalence, nicotine dependence and cessation arise in late adolescence or early adulthood and persist through the life course.

The factors that generate and sustain the social gradient in smoking are complex and interrelated. They include parental smoking behaviour and the cultural norms and expectations embedded in the local social milieu. Disadvantaged smokers are no less likely to be motivated to give up smoking, but are less likely to succeed in a cessation attempt. This may reflect both higher nicotine dependence and the stresses inherent in their conditions of living.

E-cigarettes have become the preferred aid to smoking cessation, greatly outstripping a prescription from a doctor or use of NHS smoking cessation services. These disruptive products have great potential to address social inequalities in health attributable to cigarette smoking. There is evidence that ex-smokers from more disadvantaged backgrounds use e-cigarettes for longer periods after cessation than more affluent ex-smokers, possibly reflecting higher levels of dependence on tobacco.

The potential of e-cigarettes to contribute to the decline of cigarette smoking is currently not being fully realised. E-cigarettes are at present available as consumer products rather than medically licenced devices. While this may constitute an important part of their appeal, barriers to their use by disadvantaged smokers include cost and unreliable information, as well as unhelpful attitudes from health professionals. Use of e-cigarettes shows cross-elasticities with cigarettes, making it important to give them favourable tax treatment.

References to other work or publications to support your testimony' (if applicable):

Jarvis MJ & Wardle J. (2006) Social patterning of individual health behaviours: the case of cigarette smoking. Chapter 11 pages 225-237 in Marmot M & Wilkinson R. Social Determinants of Health, 2nd Edition, OUP

Disclosure:
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.

None to declare
Declaration of interests: Please complete NICE's declaration of interests (DOI) form and return it with this form. **Note: If giving expert testimony on behalf of an organisation**, please ensure you use the DOI form to declare your own interests and also those of the organisation – this includes any financial interest the organisation has in the technology or comparator product; funding received from the manufacturer of the technology or comparator product; or any published position on the matter under review. The declaration should cover the preceding 12 months and will be available to the advisory committee. For further details, see the NICE policy on declaring and managing interests for advisory committees and supporting FAQs.

Expert testimony papers are posted on the NICE website with other sources of evidence when the draft guideline is published. Any content that is academic in confidence should be highlighted and will be removed before publication if the status remains at this point in time.

Expert testimony 2: Inequalities by sexual orientation (1)

Section A: Developer to complete	
Name:	Sarah Jackson
Role:	Senior Research Fellow
Institution/Organisation (where applicable): **Contact information:**	UCL Tobacco and Alcohol Research Group Research Department of Behavioural Science and Health University College London Tel: 0207 679 8312 Email: s.e.jackson@ucl.ac.uk
Guideline title:	Tobacco: preventing uptake, promoting quitting and treating dependence (update)
Guideline Committee:	PHAC F
Subject of expert testimony:	Tackling the health inequalities caused by smoking: LGBT groups
Evidence gaps or uncertainties:	Evidence has been sought for effectiveness of various interventions for smoking cessation.

	Effectiveness specifically in LGBT groups was not identified in the evidence. Please provide information on the following areas: • Are there particular subgroups at higher risk of smoking? • Are there specific barriers to cessation, or to accessing cessation services, in LGBT groups? What are these barriers? • How can these barriers be approached in a UK context (by local authorities, commissioners, health professionals, voluntary and community sector organisations)? Please note that we make recommendations at local rather than national levels. Policy, legislation and regulation should therefore not be the focus of the presentation. Please also note that although there may be complex and interlinked issues, the scope of this guideline is limited to tobacco, and particularly tobacco cessation.

Section B: Expert to complete	
Summary testimony:	[Please use the space below to summarise your testimony in 250–1000 words. Continue over page if necessary]

Are there particular subgroups at higher risk of smoking?

In the UK, smoking prevalence is higher among lesbian, gay, and bisexual people (LGB) than in the general population. The most recent available data from the Annual Population Survey (1) indicate that smoking prevalence in 2017* was 23.1% among people who identified as gay or lesbian and 23.3% among those who identified as bisexual; around 1.5 times higher than in heterosexual (straight) people (15.9%) [*the official statistics on the proportion of people identifying as each sexual orientation for 2018 are not yet available].

There are currently limited data (particularly in the UK) on smoking prevalence in trans and non-binary people. The data that do exist suggest that these groups are also more likely to smoke than cisgender people (2,3).

Recent evidence (4) has shown a narrowing in the smoking prevalence gap between the general population and some (but not all) LGB groups. This could be a result of improving social attitudes towards LGBT people. However, this has not consistently been observed across surveys (1).

While LGB people are more likely than straight people to smoke, LGB smokers and straight smokers appear to be equally motivated to stop smoking or make a quit attempt (4).

Are there specific barriers to cessation, or to accessing cessation services, in LGBT groups? What are these barriers?

There are several factors that may contribute to higher smoking prevalence and make cessation more difficult among sexual minority groups.

Discrimination and mental health

For some LGBT people, smoking may be a mechanism for coping with “minority stress” caused by exposure to prejudice, discrimination, harassment and victimisation (5,6). Homophobia, biphobia and transphobia remain prevalent in schools, the workplace, and healthcare services. LGBT people may not be out to their family or may be estranged from them because of their sexual orientation. LGBT people still face high levels of hate crime, most of which goes unreported. These experiences can result in high stress levels. Smoking may be used as a means of coping with this stress. Quitting smoking may be more difficult or less of a priority in this context.

LGBT people are disproportionately more likely to experience poor mental health due to social pressures and prejudices. In 2018:

- Half of LGBT people (52%) said they had experienced depression in the last year
- One in eight LGBT people aged 18-24 (13%) said they had attempted to take their own life in the last year
- 41% of non-binary people, 20% of LGBT women and 12% of GBT men said they had harmed themselves in the last year (7)

Smoking prevalence among people with common mental health conditions remains around 50% higher than among those without despite their higher desire to quit (8).

Social influence

Smoking is a socially contagious behaviour and is initiated and maintained through social networks (9). For many LGBT people, safe places for social gathering have traditionally been bars and similar establishments where there is a culture of smoking (10). Given the

high levels of social exclusion experienced by sexual minority groups, it is also plausible that smoking persists due to fear of exclusion from the social group if the behaviour stops (11,12).

Industry interference

LGBT smoking has also been encouraged by decades of targeted marketing from the tobacco industry with a number of companies investing heavily in the promotion and depiction of smoking in LGBT media. Other techniques have included sponsorship of pride events, silencing boycotts with large pay-outs and giving away free cigarettes in LGBT venues (13,14).

Intersectionality with other high-risk smoking groups

Those who self-define as LGBT are also more likely to belong to other groups with higher smoking rates. As mentioned above, LGBT people are more likely than heterosexuals to have mental health problems. They are also more likely to be single (15), socioeconomically disadvantaged (16), and more likely to experience homelessness (17), all of which are associated with higher smoking prevalence.

Difficulty accessing services

LGBT people also face problems accessing health services. In January 2016 a report by the

Women and Equalities Select Committee into 'Transgender Equality' concluded that "the NHS is letting down trans people" noting a number of areas such as a lack of staff training around gender identity and a failure to combat transphobia (18). This sentiment is echoed throughout LGBT patient experience research which has repeatedly identified sexual orientation as a reason for delaying access to services (7).

Behavioural support can increase the likelihood that a quit attempt will be successful (19,20), so it is vital that LGBT people feel able to access stop smoking services and are feel supported when they do so. The evidence around LGBT people accessing health care services suggests that currently this is not always the case (7) (also see 'Smoking in Trans and Non Binary Communities'; available from LGBT Foundation on request).

Coming out to health care professionals appears to be beneficial. One in five LGBT people (19%) aren't out to any healthcare professional about their sexual orientation when seeking general medical care (7). Across all primary care services, the needs of LGBT people are more likely to be met when they disclosed their sexual orientation and/or trans status to their health care professionals (21).

However, last year, the LGBT Patient Survey found that only 53% of LGB people had a positive response to disclosing their sexual orientation, while only 44% of trans people had a positive response to disclosing their trans status, to a health care professional ('LGBT Patient Survey'; available from LGBT Foundation on request). A large majority (80%) of trans people report experiencing anxiety before a medical appointment due to fears of insensitivity, misgendering (being referred to as the incorrect gender) and discrimination ('LGBT Patient Survey'; available from LGBT Foundation on request).

<u>How can these barriers be approached in a UK context (by local authorities, commissioners, health professionals, voluntary and community sector organisations)?</u>

Making services welcoming for LGBT people

When a service is designed for everyone it does not necessarily cater to the needs of everyone. Discrimination or a lack of understanding of LGBT issues (including

misgendering or a lack of awareness that people can have a same sex partner) could prevent a smoker from accessing or returning to a service.

It is likely that most LGBT people do not need an LGBT specific smoking cessation service. Rather, they need the mainstream service to be a safe place for them to be themselves without fear of discrimination, being misgendered or having to explain or justify their identity. This potential can be reduced by having staff trained in LGBT awareness and providing visible signs of LGBT acceptance within services and more broadly in campaigns and health initiatives.

There are many simple steps that can be taken to make a service visibly LGBT friendly:

- Displaying LGBT posters and literature in GP receptions, pharmacies etc.
- Healthcare professionals wearing rainbow lanyards
- Appropriate posters signposting to LGBT support (as you would for carers, or people with mental health conditions)
- Including LGBT people in campaign communications
- For events, providing labels that give people the chance to share their preferred pronouns (she/her, he/him, they/them) alongside their name

It is also important to create an accepting atmosphere by ensuring staff have a relaxed and welcoming attitude, and avoiding assumptions that everyone is heterosexual or cisgender (e.g. assuming that all service users will have opposite sex partners).

These simple steps to inclusion can act as marks of acceptance improve engagement with services and boost confidence in service users by breaking down perceived barriers (22).

Engaging in LGBT outreach activities

Above and beyond making services LGBT friendly, there are other things that can be done to proactively target LGBT smokers and offer them the support they need to quit:

- Work with local LGBT organisations to reach the local LGBT community
- Work with the local LGBT community to embed smoke-free spaces in events and festivals (e.g. prides) and recruit LGBT people to stop smoking services

Sexual orientation and trans status monitoring

In terms of evaluation, evidence on the LGBT population has traditionally been limited by a lack of routine monitoring of sexual orientation in public services (23). The Sexual Orientation Monitoring Information Standard, published last year, provides a standardised format for recording the sexual orientation of patients/service users (24). Monitoring sexual orientation and trans status is important because it enables health and social care bodies to better understand the needs of the local population and to target services more effectively and efficiently. There is a real lack of evidence about the needs and experiences of LGBT people in general, and trans people in particular.

Monitoring, correctly implemented, is the best way to address this lack of evidence and ensure LGBT people's needs and experiences are heard. Monitoring also gives the patient or service user a safe and familiar way to disclose their identity.

At present other characteristics such as age, ethnicity and marital status are monitored. Additional questions around sexual orientation and trans status can be easily integrated into existing demographic forms for the purpose of compliance with the Equality Act 2010 and the Public Sector Equality Duty.

Special considerations for certain LGBT smokers

In providing cessation support to LGBT smokers, certain considerations may be relevant for trans people and people living with HIV.

Trans people. A trans person only requires self-identification in order to be considered trans, but many trans people also seek hormone replacement therapy (HRT) as part of their transition process. Before a person begins HRT, they must quit smoking due to the health risks of concurrent smoking and hormone use (25). In the case of trans women taking HRT there is potential tobacco use will impact the efficacy of their treatment. Trans people wishing to undergo gender affirming surgeries should also be aware of the significant risk factor during and after any surgery. Smokers are 30% more likely to die after any surgery and more likely to experience major complications such as wound infection and cardiovascular events (26).

People living with HIV. Gay, bisexual, and other men who have sex with men are the population most affected by HIV. There are higher levels of smoking among people with HIV than in the general population (27). Smoking has a much greater impact on life expectancy than HIV infection – but the two conditions combine to threaten the health of HIV positive smokers. It is not appropriate to prescribe bupropion (Zyban) to someone on anti-HIV drugs due to the way the two drugs interact (28). Anti-HIV drugs can reduce the level of bupropion in the blood and may require a much higher dosage to be effective.

For examples of good practice at a local level see this briefing by ASH and the LGBT Foundation:

Action on Smoking and Health (ASH) and LGBT Foundation. *Supporting your local LGBT community to quit smoking*. 2020.

References to other work or publications to support your testimony (if applicable):

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5. Slater ME, Godette D, Huang B, Ruan WJ, Kerridge BT. Sexual Orientation-Based Discrimination, Excessive Alcohol Use, and Substance Use Disorders Among Sexual Minority Adults. LGBT Health. 2017;4(5):337–44.

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Disclosure:
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.

None.

Declaration of interests: Please complete NICE's declaration of interests (DOI) form and return it with this form.

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confidence should be highlighted and will be removed before publication if the status remains at this point in time.

Expert testimony 3: Inequalities by sexual orientation (2)

Section A: Developer to complete	
Name:	Ben Heyworth
Role:	Macmillan Survivorship Network Manager / Survivorship Network
Institution/Organisation (where applicable): **Contact information:**	The Christie Hospital NHS Foundation Trust Consultant in LGBT and Smoking Cessation GMHSCP/LGBT Foundation
Guideline title:	Tobacco: preventing uptake, promoting quitting and treating dependence (update)
Guideline Committee:	PHAC F
Subject of expert testimony:	Tackling the health inequalities caused by smoking: LGBT groups
Evidence gaps or uncertainties:	Evidence has been sought for effectiveness of various interventions for smoking cessation. Effectiveness specifically in LGBT groups was not identified in the evidence. Please provide information on the following areas: • Are there particular subgroups at higher risk of smoking? • Are there specific barriers to cessation, or to accessing cessation services, in LGBT groups? What are these barriers? • How can these barriers be approached in a UK context (by local authorities, commissioners, health professionals, voluntary and community sector organisations)? Please note that we make recommendations at local rather than national levels. Policy, legislation and regulation should therefore not be the focus of the presentation.

	Please also note that although there may be complex and interlinked issues, the scope of this guideline is limited to tobacco, and particularly tobacco cessation.

Section B: Expert to complete

Summary testimony:	[Please use the space below to summarise your testimony in 250–1000 words. Continue over page if necessary]

- **Are there particular subgroups at higher risk of smoking?**

Smoking rates are higher among LGBT (lesbian, gay, bisexual, transgender) communities when compared to their heterosexual counterparts. The 2014 Integrated Household Survey found that:

- 25.3% of LGB people smoked compared to 18.4% of heterosexual people.
- Lesbian women were the most likely to smoke, with smoking prevalence at 30.71%. This compares to 21.86% of bisexual women, 24.59% of gay men and 26.26% of bisexual men.

There is not enough formal research data in the UK to support anecdotal evidence that trans people have higher smoking rates than cis people. However, A study in the US (CDHS, 2004) found smoking prevalence to be at 30.7% among their trans population.

Given the clear inter-relationship between higher smoking rates and mental health, and evidence for poor mental health amongst trans people (Somerville, C. 2015), on balance it seems likely that trans people are disproportionally more likely to be adversely affected by tobacco addiction.

There is some recent evidence to suggest that the gap is starting to narrow.

Some evidence (Blosnich, 2011) suggests that BME LGBT individuals have higher smoking rates compared to heterosexual BME groups, and that smoking prevalence is higher amongst disabled LGBT people (Guasp, 2012).

- **Are there specific barriers to cessation, or to accessing cessation services, in LGBT groups? What are these barriers?**
- **How can these barriers be approached in a UK context (by local authorities, commissioners, health professionals, voluntary and community sector organisations)?**

Research has shown that LGBT people are more likely to have negative experiences accessing healthcare services and as a result of this may be reluctant to access them. E.g. There is evidence of direct discrimination from HCPs directed towards LGBT people.

- 5% of patient facing staff have witnessed colleagues either provide a poor service or discriminate against a service users because they are LGB, in the last five years. (Somerville, C. 2015)
- 18% of trans people avoided treatment for fear of negative reaction. (Government Equalities Office. 2018)

However, whilst there is evidence to suggest LGBT specific stop smoking service can be effective (Harding, 2004), there is limited evidence from potential service users that they are more likely to use this service than an inclusive mainstream practice (Heyworth, 2017).

Therefore, my recommendation is that mainstream smoking cessation services should be enabled to become 'actively inclusive' of LGBT people and 'actively promote' their service to LGBT. This will require a programme of education and training for service providers that focuses on LGBT people and goes above and beyond the mandated equality and diversity training which is often rudimentary and of limited effectiveness when dealing with significant health inequalities.

It will also require the embedding of sexual orientation and trans status monitoring into the reporting of operational activity and outcomes from all smoking cessation services.

I do not recommend setting up specific smoking cessation services exclusively for the LGBT community, however, where services for mental health, sexual health, drugs and alcohol exist specifically for LGBT people, it would be appropriate to train staff around "Very Brief Advice" for smoking cessation, as individuals accessing these services are more likely to be affected by tobacco addiction. It may also be feasible for Smoking Cessation professionals to outreach into these services, or into other VCSE groups working with LGBT people.

For local authorities and health and social care organisations that may be involved in organising Stop Smoking campaigns, these programmes should be developed to be inclusive of LGBT communities and target LGBT communities specifically. This can be done by ensuring LGBT representation is embedded into the campaign assets – visual cues such as rainbow flags/pin badges, or testimony from members of the LGBT community are all simple ways that this can be achieved. Stereotypical images of LGBT people should be avoided.

LGBT social spaces are often centred around bars, clubs and events such as Pride. Local authorities who licence public spaces should consider the impact of the high visibility of smoking at these events, and encourage organisers to embed a "smoke-free" policy even if the event takes place outside – passive smoking can be a real issue in crowded spaces and there is anecdotal evidence to suggest individuals making quit attempts relapse back into smoking at public events, festivals and parties (Heyworth, 2017).

Whilst this falls outside the scope of this review, I would take this opportunity to remind the panel that the tobacco industry has a long history of target marketing towards the LGBT community and we must be extremely vigilant. We have had several instances of tobacco industry funding supporting activity within the LGBT community in the past 12 months. We must ensure that LGBT organisations, both in the health sector and elsewhere, are aware of this and that they must be encouraged not intersect with the tobacco industry in any way.

References to other work or publications to support your testimony' (if applicable):

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Disclosure:
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.

None

Declaration of interests: Please complete NICE's declaration of interests (DOI) form and return it with this form.

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Expert testimony 4: Inequalities for people with mental illness

Section A: Developer to complete	
Name:	Mary Yates
Role:	Nurse Consultant
Institution/Organisation (where applicable): **Contact information:**	South London and Maudsley NHS Foundation Trust Addictions Management Team Marina House 1st Floor, 63-65 Denmark Hill, London SE5 8RS
Guideline title:	Tobacco: preventing uptake, promoting quitting and treating dependence (update)
Guideline Committee:	PHAC F
Subject of expert testimony:	Tackling the health inequalities caused by smoking: mental health
Evidence gaps or uncertainties:	Evidence has been sought for effectiveness of various interventions for smoking cessation. Effectiveness specifically in groups with mental illness was limited. Please provide information on the following areas: • Are there specific barriers to cessation, or to accessing cessation services, in people with mental illness? What are these barriers? • How can stop smoking support be tailored or better delivered to people with mental illness in the community? • How can barriers be approached in a UK context (by local authorities, commissioners, health professionals, voluntary and community sector organisations)? Please note that we make recommendations at local rather than national levels. Policy, legislation and regulation should therefore not be the focus of the presentation. Please also note that although there may be complex and interlinked issues, the scope of

	this guideline is limited to tobacco, and particularly tobacco cessation.

Section B: Expert to complete
Summary testimony:

Although sick smokers are hiding in plain sight in mental health services, at food banks, in prisons and on the streets, there are numerous barriers preventing engagement in tobacco dependence treatment. These barriers exist at all levels in the system and are underpinned by poor staff knowledge and skills, fractured care pathways and a culture that regularly undermines rather than promotes health. All smokers need to quit as soon as possible and for good. The desire to quit is evident in people with mental health problems just as it is with other smokers.

Systems to screen for smoking and provide very brief advice (VBA) have improved recently but there is still room for improvement. Connecting smokers to specialist support services, prescribing nicotine replacement therapy (NRT), varenicline or bupropion is seldom achieved.

In smokefree mental health services tobacco withdrawal symptoms are often confused with common mental health symptoms and consequently are rarely appropriately managed. Prompt access to NRT in smokefree services is problematic, and when provided it usually falls short of what is needed for heavily dependent smokers. Smokers need fingertip control over NRT, restrictions on access during and after hospital stays make it an unlikely recipe for success. Failure to implement comprehensive smokefree policies, with all cues to smoke removed, increases the risk of starting to smoke or relapsing during a hospital stay.

- Recognising tobacco dependence as a chronic relapsing mental health condition, that if left untreated will lead to a toll of preventable disease and premature death is the first step to address this issue. As the leading cause of mortality in people with serious mental illness it must be adequately commissioned and resourced.

- The standard treatment programme needs to be adapted (~12 weeks) to accommodate the unique needs of smokers with mental health problems.

- Children who live with smokers are up to three times more likely to become smokers themselves compared with children of non-smoking households. Routine screening, provision of very brief advice (VBA) and referral for smoking cessation support for parents/adults and siblings of young people using mental health services can reduce this risk.

- Perinatal mental health services need to collaborate with midwifery/health visitor colleagues to support smokefree pregnancy and smokefree homes.

- Smokers with serious mental health problems spend around one third of their income on tobacco. Consequently, they are trapped in poverty. It is logical to assume that welfare advisors trained in VBA, can connect smokers with smoking cessation support.

- Around half of those diagnosed with a psychotic illness, are smokers. It follows that a prevention intervention delivered at the point of entry to the psychosis care pathway deflecting the individual from starting to use tobacco is pragmatic.

- Patients taking clozapine can potentially reduce their medication by up to 50% if they quit. Targeted smoking cessation support delivered within clozapine clinics removes multiple barriers. If prescriptions for varenicline, bupropion or NRT are provided together with clozapine, it is easier for the smoker to succeed.

- Patients on olanzapine depot must stay in clinic for three hours after administration of their injection, this provides an opportunity to provide smoking cessation support.

- People with long term conditions who are using the Improving Access to Psychological Therapies (IAPT) care pathway, could access smoking cessation support after completion of their psychological intervention.

- Patients who cut down or quit during admission to a smokefree hospital risk relapse at the point of discharge. This risk can be reduced if the hospital-based tobacco dependence advisor maintains support to build on health gains after return to the community.
- Considering the high rate of smoking among staff and residents in care homes, bespoke support should be targeted in these settings.
- Fire safety personnel trained to ensure consistent messaging around the benefits of switching from smoking to vaping has potential to nudge smokers onto a smokefree pathway.
- Health and wellbeing events utilising social media, local care networks and pop-up clinics in venues where people with mental health problems frequent offers a way into services for hard to reach sections of the community.
- Collaboration with carers forums can prove invaluable, so that families are clear about how to help rather than hinder smokefree success.
- Free electronic cigarette starter packs may help some smokers find a safer route out of tobacco dependence, since the initial outlay is a common barrier.
- Engagement with Illegal Tobacco Control initiatives are important to share intelligence and protect vulnerable people.
- Routine carbon monoxide testing has the potential to change conversations health care professionals (HCP) have with smokers.
- As an 'over the counter' medication NRT can be dispensed by registered nurses without waiting for prescription, early intervention maximises smokers comfort, and kick-starts the route to recovery.

Currently HCP graduate without completion of basic smoking awareness training. If all HCP completed VBA training as an undergraduate, this would provide a good platform from which to progress. Induction should focus on systems and processes at local level.

The arrangements for access to smoking cessation treatment is fragmented. When behavioural support is provided by one service and medication by another, this doesn't work for anyone. A one stop shop approach is essential to success. Commissioning of smoking cessation services must be an integral part of mental health care pathways, appropriately resourced, placing varenicline, bupropion and NRT on a par with other evidence-based treatments. Myths around the use of varenicline need to be challenged and agile access to e-cigarettes, the most popular way of quitting is a priority if we are to close the gap.

Shared record keeping is vital. The current arrangements offers poor connectivity between the local authority smoking cessation services and mental health services. Therefore, when people on critical medications (clozapine/olanzapine) are cutting down or quitting the mental health care team are not always in step with the programme or aware of outcomes.

Smokers with mental health problems **need to quit** – smoking is the single largest cause of the 10-20-year gap in life expectancy between people with a mental health condition and people without. Quitting enhances mental health and supports recovery. Smokers with mental health problems are more likely to **want to quit** than those who do not have a mental health problem. Smokers with mental health problems **can quit** – provided they have access to evidence based treatments and behavioural support, they are just as likely to succeed.

References to other work or publications to support your testimony' (if applicable):

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Disclosure: Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.
Not applicable
Declaration of interests: Please complete NICE's declaration of interests (DOI) form and return it with this form. **Note: If giving expert testimony on behalf of an organisation**, please ensure you use the DOI form to declare your own interests and also those of the organisation – this includes any financial interest the organisation has in the technology or comparator product; funding received from the manufacturer of the technology or comparator product; or any published position on the matter under review. The declaration should cover the preceding 12 months and will be available to the advisory committee. For further details, see the NICE policy on declaring and managing interests for advisory committees and supporting FAQs.

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Expert testimony 5: MHRA

Section A: Developer to complete	
Name:	Jo Lyn Chooi and Helena Bird
Role:	Senior Medical Assessor/ E-cigarette Notifications Compliance Coordinator
Institution/Organisation (where applicable): **Contact information:**	Vigilance and Risk Management of Medicines (VRMM), MHRA, 10 South Colonnade, Canary Wharf, London, E14 4PU
Guideline title:	Tobacco: preventing uptake, promoting quitting and treating dependence (update)

Guideline Committee:	PHAC F
Subject of expert testimony:	MHRA safety monitoring of e-cigarettes
Evidence gaps or uncertainties:	Evidence has been sought for the long-term health effects of e-cigarettes and the adverse events of e-cigarettes when used for cessation or harm reduction. Limited evidence was identified, which was inconclusive. Please provide information on the following areas: • Briefly, how does the regulation of e-cigarettes differ from the regulation of licensed medicines? What is the current situation of e-cigarettes and MHRA licensing for cessation / harm reduction in the UK? • What data on adverse events of e-cigarettes has been collected through the Yellow Card scheme, and what are the conclusions? • What data on e-cigarette and vaping associated lung injury (EVALI) has been collected through the Yellow Card scheme, and what are the conclusions? • Is there anything else relating to e-cigarettes that the MHRA considers it would be useful for the NICE Guideline Committee to know? Please also note that although there may be complex and interlinked issues, the scope of this guideline is limited to tobacco, and particularly tobacco cessation.

Section B: Expert to complete	
Summary testimony:	[Please use the space below to summarise your testimony in 250–1000 words. Continue over page if necessary]

The Tobacco and Related Product Regulations (TRPR) came into force in 2016 which regulates nicotine-containing e-cigarettes and refills. This introduced a notification scheme requiring all products to be notified to the MHRA and restrictions on strength, product capacity and ingredients. The notification scheme requires information on ingredients, their toxicity and emissions data to be submitted. Yellow Card reporting for e-cigarettes was also launched. The TRPR applies to consumer products and not products which hold a medicinal license. TRPR regulations implement the European Union Tobacco Products Directive.

In order to make a medicinal claim such as harm reduction or smoking cessation an e-cigarette manufacturer would have to apply for a medicinal license. This requires a greater level of data to be submitted, has a longer time frame and a much high cost associated than the notification scheme.

The MHRA carry out signal detection to look for new safety information associated with e-cigarette use. This uses disproportionality analyses and certain criteria to highlight events of interest. Signals are then validated to assess causality (including looking at strength of evidence and other data sources) and prioritised to set a time frame for regulatory action.

A total of 115 reports have been collected to date via the Yellow Card scheme with 340 reactions. 23 of these reports were reported prior to the regulations with non-notified products.

In April 2019 the FDA published a statement relating to a connection between e-cigarettes and seizures particularly in youth and young adults (127 reports). Seizures are a known effect of nicotine toxicity and this statement was issued at time when increased use of e-cigarettes amongst USA youth had been observed.

The highest number of reactions was reported within the respiratory category. Generally, reactions tended to be non-serious. Following signal detection activities on data accrued so far, the evidence is insufficient to suggest further regulatory action needs to be taken at this point in time. The situation is regularly monitored and may change depending on new information received.

The EVALI review so far indicates there is not a similar volume and trends of cases in the UK as USA. The number of confirmed EVALI cases in the USA exceeds 2000 to date, while in the UK there has been 1 case meeting US criteria for EVALI so far and 1 potential case. In the UK there have been fewer reports of serious respiratory events, in a more diverse pattern of events over a longer period of time.

Yellow Card data was also examined for reports of possible pathologies hypothesised as being the potential mechanism for EVALI. However, there has been insufficient evidence to confirm if any of these pathologies represent EVALI.

MHRA is conducting further activities to gather further information on EVALI. MHRA has devised a set of UK criteria for identifying cases of EVALI. An article was published in the MHRA's monthly Drug Safety Update bulletin (27 January 2020) to request Yellow Card reporting of adverse events with e-cigarettes. Targeted communications were sent to organisations for clinicians most likely to encounter EVALI cases. A follow-up form to gather detailed information about cases has also been devised. The review is ongoing.

References to other work or publications to support your testimony' (if applicable):

MHRA Drug Safety Update: E-cigarette use or vaping: reporting suspected adverse reactions, including lung injury https://www.gov.uk/drug-safety-update/e-cigarette-use-or-vaping-reporting-suspected-adverse-reactions-including-lung-injury Tobacco and Related Product Regulations: http://www.legislation.gov.uk/uksi/2016/507/contents/made MHRA E-Cigarette webpage: https://www.gov.uk/guidance/e-cigarettes-regulations-for-consumer-products
Disclosure: Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.
No past or current links to, or funding from, the tobacco industry,
Declaration of interests: Please complete NICE's declaration of interests (DOI) form and return it with this form. **Note: If giving expert testimony on behalf of an organisation**, please ensure you use the DOI form to declare your own interests and also those of the organisation – this includes any financial interest the organisation has in the technology or comparator product; funding received from the manufacturer of the technology or comparator product; or any published position on the matter under review. The declaration should cover the preceding 12 months and will be available to the advisory committee. For further details, see the NICE policy on declaring and managing interests for advisory committees and supporting FAQs.

Expert testimony papers are posted on the NICE website with other sources of evidence when the draft guideline is published. Any content that is academic in confidence should be highlighted and will be removed before publication if the status remains at this point in time.

Appendix L – Health economic quality assessment

Annemans, Lieven et al. "Cost-effectiveness of retreatment with varenicline after failure with or relapse after initial treatment for smoking cessation." Preventive medicine reports vol. 2 189-95. 14 Mar. 2015, doi:10.1016/j.pmedr.2015.03.004		
Guidance topic: Smoking cessation		**Question no: 6.1a**
Section 1: Applicability (relevance to specific review questions and the NICE reference case)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Current smokers willing to quit
1.2 Are the interventions appropriate for the review question?	Yes	Pharmacological agents
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	Belgium context
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	Healthcare payer
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	Intervention and health state costs included
1.6 Are all future costs and outcomes discounted appropriately?	No	3% for costs, 1.5% for benefits
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Partly	QALYs are included but the method was not described
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	No	Societal costs and benefits are not included
1.9 Overall judgement: Partly applicable		
Section 2: Study limitations (the level of methodological quality)		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Markov model
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Lifetime
2.3 Are all important and relevant outcomes included?	Yes	QALYs were calculated

2.4 Are the estimates of baseline outcomes from the best available source?	Yes	From published data sources; used in previous BENESCO model
2.5 Are the estimates of relative intervention effects from the best available source?	Partly	First line treatment efficacies derived using meta-analysis; second line treatment efficacy for varenicline from RCT; other second line treatment efficacies made by assumption
2.6 Are all important and relevant costs included?	Yes	Healthcare costs included
2.7 Are the estimates of resource use from the best available source?	Yes	Published data sources and through discussion with a group of Belgian clinicians
2.8 Are the unit costs of resources from the best available source?	Yes	Detailed cost sources provided that were validated through discussion with a group of Belgian clinicians
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	Incremental costs and QALYs
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Both univariate and probabilistic sensitivity analysis were performed
2.11 Is there any potential conflict of interest?	No	
2.12 Overall assessment: Minor limitations		
Other comments: None		
Abbreviations: BENESCO: Benefit of smoking cessation on outcomes; QALY: Quality-adjusted life year; RCT: Randomised control trial		

Athanasakis, Kostas et al. "Cost-Effectiveness Of Varenicline Versus Bupropion, Nicotine-Replacement Therapy, And Unaided Cessation In Greece". Clinical Therapeutics, vol 34, no. 8, 2012, pp. 1803-1814. Elsevier BV, doi:10.1016/j.clinthera.2012.07.002		
Guidance topic: Smoking cessation		**Question no: 6.1a**
Section 1: Applicability (relevance to specific review questions and the NICE reference case)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Individuals making a single quit attempt
1.2 Are the interventions appropriate for the review question?	Yes	Pharmacological agents

1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	Greek context
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	Societal security (third-party payer)
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	Intervention and health state costs included
1.6 Are all future costs and outcomes discounted appropriately?	Partly	3% for costs, 3% for benefits
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Partly	QALYs are included but the method was not described
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	No	Societal costs and benefits are not included
1.9 Overall judgement: Partly applicable		
Section 2: Study limitations (the level of methodological quality)		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Markov model
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Lifetime
2.3 Are all important and relevant outcomes included?	Yes	Healthcare outcomes included
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	Taken from Hellenic Statistical Authority and WHO European Detailed Mortality Database
2.5 Are the estimates of relative intervention effects from the best available source?	Partly	Main interventions from pooled data from two head to head trials. Unaided cessation from separate study.
2.6 Are all important and relevant costs included?	Yes	Healthcare costs included

2.7 Are the estimates of resource use from the best available source?	Yes	Taken from recent economic evaluations in Greek healthcare setting
2.8 Are the unit costs of resources from the best available source?	Yes	Taken from Greek National Formulary and other sources
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	Incremental cost and incremental QALYs are reported
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Both probabilistic sensitivity analysis and deterministic sensitivity analysis were conducted
2.11 Is there any potential conflict of interest?	No	
2.12 Overall assessment: Minor limitations		
Other comments: None		
Abbreviations: QALY: Quality-adjusted life-year		

Coward, Stephanie et al. "Funding A Smoking Cessation Program For Crohn'S Disease: An Economic Evaluation". American Journal Of Gastroenterology, vol 110, no. 3, 2015, pp. 368-377. Ovid Technologies (Wolters Kluwer Health), doi:10.1038/ajg.2014.300.		
Guidance topic: Smoking cessation		**Question no: 6.1a**
Section 1: Applicability (relevance to specific review questions and the NICE reference case)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Partly	Current smokers with Crohn's disease (CD)
1.2 Are the interventions appropriate for the review question?	Yes	Pharmacological agents
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	Canadian context
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	Publicly funded healthcare system

1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	No	Smoking related morbidities not included
1.6 Are all future costs and outcomes discounted appropriately?	No	5% discount rate – unclear whether this is for costs, benefits or both.
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Partly	QALYs are included but the method was not described
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	No	Societal costs and benefits are not included
1.9 Overall judgement: Partly applicable		
Section 2: Study limitations (the level of methodological quality)		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Markov model
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	5-year time horizon; captures CD progression costs and outcomes
2.3 Are all important and relevant outcomes included?	Party	QALYs were calculated but did not included smoking related morbidities
2.4 Are the estimates of baseline outcomes from the best available source?	Unsure	Not reported
2.5 Are the estimates of relative intervention effects from the best available source?	No	Non-pharmacological effectiveness rate from observational studies. In additional, interventions use different sources without meta-analysis
2.6 Are all important and relevant costs included?	Partly	Healthcare costs relating to Crohn's disease were included but costs relating to smoking morbidities were not included

2.7 Are the estimates of resource use from the best available source?	Unsure	Not reported
2.8 Are the unit costs of resources from the best available source?	Partly	Surgery costs were not referenced. Drug costs were from published data sources or the Alberta Blue Cross Interactive Drug Benefit List
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	Incremental cost-effectiveness ratios (ICERs)
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Probabilistic sensitivity analysis was conducted
2.11 Is there any potential conflict of interest?	No	
2.12 Overall assessment: Major limitations		
Other comments: None		
Abbreviations: CD: Crohn's disease; ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life-year		

Hagen, G., T. Wisloff, and M. Klemp. "Niph Systematic Reviews." Cost-Effectiveness of Varenicline, Bupropion and Nicotine Replacement Therapy for Smoking Cessation. Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH) **Copyright (c)2010 by The Norwegian Institute of Public Health (NIPH). 2010. Print**		
Guidance topic: Smoking cessation		**Question no: 6.1a**
Section 1: Applicability (relevance to specific review questions and the NICE reference case)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Current smokers willing to quit
1.2 Are the interventions appropriate for the review question?	Yes	Pharmacological agents
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	Norwegian context
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	No	Perspective is not reported. Assumed healthcare payer

1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Partly	Health state costs are not included
1.6 Are all future costs and outcomes discounted appropriately?	Partly	4% for costs, 4% for benefits
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	No	LY are used an the primary outcome
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	No	Societal costs and benefits are not included
1.9 Overall judgement: Partly applicable		
Section 2: Study limitations (the level of methodological quality)		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Markov model
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Lifetime (100 years or dead)
2.3 Are all important and relevant outcomes included?	Partly	LY were calculated but not QALYs
2.4 Are the estimates of baseline outcomes from the best available source?	Partly	Recently published study
2.5 Are the estimates of relative intervention effects from the best available source?	Unsure	Systematic review reported in Norwegian
2.6 Are all important and relevant costs included?	Partly	Treatment and an average annual health care expense included
2.7 Are the estimates of resource use from the best available source?	Unsure	Made by assumption and treatment guidelines
2.8 Are the unit costs of resources from the best available source?	Yes	Published data sources
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	Incremental cost-effectiveness ratios (ICERs)

2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Both probabilistic sensitivity analysis and deterministic sensitivity analysis were conducted
2.11 Is there any potential conflict of interest?	No	
2.12 Overall assessment: Minor limitations		
Other comments: None.		
Abbreviations: ICER: Incremental cost-effectiveness ratio; LY: Life years; QALY: Quality-adjusted life-year		

Hagen, G., T. Wisloff, and M. Klemp. "Niph Systematic Reviews." Cost-Effectiveness of Varenicline, Bupropion and Nicotine Replacement Therapy for Smoking Cessation. Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH) **Copyright (c)2010 by The Norwegian Institute of Public Health (NIPH). 2010. Print**		
Guidance topic: Smoking cessation		**Question no: 6.1a**
Section 1: Applicability (relevance to specific review questions and the NICE reference case)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Current smokers willing to quit
1.2 Are the interventions appropriate for the review question?	Yes	Pharmacological agents
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	Norwegian context
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	No	Perspective is not reported. Assumed healthcare payer
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Partly	Health state costs are not included
1.6 Are all future costs and outcomes discounted appropriately?	Partly	4% for costs, 4% for benefits
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	No	LY are used an the primary outcome

1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	No	Societal costs and benefits are not included
1.9 Overall judgement: Partly applicable		
Section 2: Study limitations (the level of methodological quality)		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Markov model
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Lifetime (100 years or dead)
2.3 Are all important and relevant outcomes included?	Partly	LY were calculated but not QALYs
2.4 Are the estimates of baseline outcomes from the best available source?	Partly	Recently published study
2.5 Are the estimates of relative intervention effects from the best available source?	Unsure	Systematic review reported in Norwegian
2.6 Are all important and relevant costs included?	Partly	Treatment and an average annual health care expense included
2.7 Are the estimates of resource use from the best available source?	Unsure	Made by assumption and treatment guidelines
2.8 Are the unit costs of resources from the best available source?	Yes	Published data sources
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	Incremental cost-effectiveness ratios (ICERs)
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Both probabilistic sensitivity analysis and deterministic sensitivity analysis were conducted
2.11 Is there any potential conflict of interest?	No	
2.12 Overall assessment: Minor limitations		
Other comments: None.		
Abbreviations: ICER: Incremental cost-effectiveness ratio; LY: Life years; QALY: Quality-adjusted life-year		

Hettle R, Wilson K, Peter T, Ezernieks J, Hackl D, Wolf C. Cost-effectiveness of varenicline compared to placebo as an aid to smoking cessation in patients with cardiovascular disease. Open Pharmacoeconomics and Health Economics Journal. 2012;4(1):8-17.

Guidance topic: Smoking cessation		**Question no: 6.1**
Section 1: Applicability (relevance to specific review questions and the NICE reference case)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Partly	Cohort is smokers with history of CVD
1.2 Are the interventions appropriate for the review question?	Yes	Varenicline plus counselling
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	Set in European countries: Austria, Germany and Hungary
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	From payers perspective, with societal perspective also included
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	Many CVD related disease states included
1.6 Are all future costs and outcomes discounted appropriately?	Partly	3% for costs, 3% for benefits
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Partly	QALYs are included but the method was not described
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	Direct costs and some societal costs like productivity included
1.9 Overall judgement: Partly applicable		
Section 2: Study limitations (the level of methodological quality)		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Uses BENESCO model which is common in this topic

2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Lifetime
2.3 Are all important and relevant outcomes included?	Yes	Health outcomes reported
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	Population based on the characteristics of those in the varenicline arm of the RCT
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	Double-blind placebo RCT
2.6 Are all important and relevant costs included?	Yes	Intervention and CVD disease costs reported
2.7 Are the estimates of resource use from the best available source?	Partly	Generally from published economic evaluations
2.8 Are the unit costs of resources from the best available source?	Partly	Many different country-specific sources used
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	ICERs reported
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Some one-way (based on CVD sub-groups) and full probabilistic sensitivity analyses
2.11 Is there any potential conflict of interest?	No	None reported, funded by Pfizer Ltd
2.12 Overall assessment: Minor limitations		
Other comments: None		
Abbreviations: BENESCO: Benefits of smoking cessation on outcomes; CVD: Cardio-vascular disease; ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life-year; RCT: Randomised controlled trial		

Huber, Manuel B. et al. "Cost-Effectiveness Of Increasing The Reach Of Smoking Cessation Interventions In Germany: Results From The EQUIPTMOD". Addiction, vol 113, 2017, pp. 52-64. Wiley, doi:10.1111/add.14062.	
Guidance topic: Smoking cessation	**Question no: 6.1**

Section 1: Applicability (relevance to specific review questions and the NICE reference case)	Yes/partly/no/unclear/NA	Comments
1.1 Is the study population appropriate for the review question?	Yes	Cohort is smokers in Germany
1.2 Are the interventions appropriate for the review question?	Partly	Varenicline versus current investment (standard care). Unclear what standard care entails, or how much it costs
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	Set in Germany, an EU country
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	German public perspective
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	CHD, stroke, lung cancer, COPD all included
1.6 Are all future costs and outcomes discounted appropriately?	Partly	3% for costs, 3% for benefits
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Partly	QALYs are included but the method was not described
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Partly	No productivity/payer costs included
1.9 Overall judgement: Partly applicable		
Section 2: Study limitations (the level of methodological quality)		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Partly	Uses a Markov model to feed a return on investment model
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Lifetime time horizon
2.3 Are all important and relevant outcomes included?	Yes	Incremental health outcomes reported
2.4 Are the estimates of baseline outcomes from the best available source?		

2.5 Are the estimates of relative intervention effects from the best available source?	Partly	
2.6 Are all important and relevant costs included?	Yes	Intervention costs and related-disease costs included
2.7 Are the estimates of resource use from the best available source?	No	Sources not reported
2.8 Are the unit costs of resources from the best available source?	No	Sources not fully reported
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	ICERs reported
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	No	No sensitivity analysis around varenicline
2.11 Is there any potential conflict of interest?	No	None reported, funded by a grant from the European Community's Seventh Framework Programme
2.12 Overall assessment: Major limitations		
Other comments: None		
Abbreviations: CHD: Coronary heart disease; COPD: Chronic obstructive pulmonary disease; ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life year;		

Kautiainen, Kirsi et al. "Re-Treatment With Varenicline Is A Cost-Effective Aid For Smoking Cessation". Journal Of Medical Economics, vol 20, no. 3, 2016, pp. 246-252. Informa UK Limited, doi:10.1080/13696998.2016.1249485.		
Guidance topic: Smoking cessation		**Question no: 6.1a**
Section 1: Applicability (relevance to specific review questions and the NICE reference case)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Current smokers willing to quit
1.2 Are the interventions appropriate for the review question?	Yes	Pharmacological agents
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	Finnish context

1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	Healthcare payer
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	Intervention and health state costs included
1.6 Are all future costs and outcomes discounted appropriately?	Partly	3% for costs, 3% for benefits
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Partly	QALYs are included but the method was not described
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	No	Indirect costs are not included
1.9 Overall judgement: Partly applicable		
Section 2: Study limitations (the level of methodological quality)		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Markov model
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Lifetime
2.3 Are all important and relevant outcomes included?	Yes	QALYs were calculated
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	From published data source (Koskinen et al.)
2.5 Are the estimates of relative intervention effects from the best available source?	Partly	First line treatment efficacies derived using meta-analysis; second line treatment efficacy for varenicline from RCT; other second line treatment efficacies made by assumption
2.6 Are all important and relevant costs included?	Yes	Healthcare costs included
2.7 Are the estimates of resource use from the best available source?	Yes	From medical experts and published literature
2.8 Are the unit costs of resources from the best available source?	Yes	Detailed cost sources provided
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	Incremental costs per QALY
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Both univariate and probabilistic sensitivity analysis were performed
2.11 Is there any potential conflict of interest?	No	

2.12 Overall assessment: Minor limitations	
Other comments: None	
Abbreviations: RCT: Randomised control trail; *QALY: quality-adjusted life year*	

Study identification **Knight, Chris et al (2012). The cost-effectiveness of an extended course (12+12 weeks) of varenicline plus brief counselling compared with other reimbursed smoking cessation interventions in Belgium, from a Public Payer perspective.. Acta clinica Belgica. 67. 416-22. 10.2143/ACB.67.6.2062706.**		
Guidance topic: Smoking cessation		**Question no: 6.1a**
Section 1: Applicability (relevance to specific review questions and the NICE reference case)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Current smoker willing to make a quit attempt
1.2 Are the interventions appropriate for the review question?	Yes	Pharmacological agents
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	Belgium context
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	Healthcare payer
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	Intervention and health state costs included
1.6 Are all future costs and outcomes discounted appropriately?	No	3% for costs, 1.5% for benefits
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Partly	QALYs are included but the method was not described
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	No	Societal costs and benefits are not included
1.9 Overall judgement: Partly applicable		
Section 2: Study limitations (the level of methodological quality)		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Markov model

2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Lifetime
2.3 Are all important and relevant outcomes included?	Yes	QALYs were calculated
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	From a previous BENESCO model; methodology excluded
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	From a previous BENESCO model; methodology excluded
2.6 Are all important and relevant costs included?	Yes	Healthcare costs included
2.7 Are the estimates of resource use from the best available source?	Yes	Publicly available data
2.8 Are the unit costs of resources from the best available source?	Yes	RIZIV/INAMI prices
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	Lifetime incremental costs per QALY were included
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	Probabilistic sensitivity analysis was conducted but reported details were limited. No deterministic sensitivity analysis was conducted.
2.11 Is there any potential conflict of interest?	No	
2.12 Overall assessment: Minor limitations		
Other comments: None		
Abbreviations: BENESCO: Benefits of smoking cessation on outcomes; *QALY: quality-adjusted life year*		

Study identification **Li J, Hajek P, Pesola F, Wu Q, Phillips-Waller A, Przulj D*, et al.* Cost-effectiveness of e-cigarettes compared with nicotine replacement therapy in stop smoking services in England (TEC study): a randomized controlled trial. Addiction. 2019**		
Guidance topic: Smoking cessation		**Question no: 6.1a**
Section 1: Applicability (relevance to specific review questions and the NICE reference case)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Current smokers willing to quit
1.2 Are the interventions appropriate for the review question?	Yes	E-cigarettes

1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	UK context
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	NHS and PSS
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	Intervention and healthcare costs included
1.6 Are all future costs and outcomes discounted appropriately?	Yes	3.5% for costs, 3.5% for benefits
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	EQ-5D utility values based in a study of Health Survey for England data.
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	No	Societal costs and benefits are not included
1.9 Overall judgement: Directly applicable		
Section 2: Study limitations (the level of methodological quality)		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	RCT followed by a Markov model
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Both 12 month and lifetimes horizons were used
2.3 Are all important and relevant outcomes included?	Partly	Potential adverse safety outcomes associated with e-cigarettes are not included
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	RCT
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	RCT
2.6 Are all important and relevant costs included?	Partly	Potential costs associated with e-cigarettes are not included
2.7 Are the estimates of resource use from the best available source?	Yes	RCT

2.8 Are the unit costs of resources from the best available source?	Yes	RCT
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	Incremental cost and incremental QALYs are reported
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	Probabilistic sensitivity analysis was conducted
2.11 Is there any potential conflict of interest?	No	
2.12 Overall assessment: Minor limitations		
Other comments: None		
Abbreviations: EQ-5D: EuroQol 5 dimensions; NHS: National Health Service; PSS: Personal Social Services; QALY: quality-adjusted life-year; RCT: randomised controlled trial		

Study identification **Li J, Hajek P, Pesola F, Wu Q, Phillips-Waller A, Przulj D*, et al.* Cost-effectiveness of e-cigarettes compared with nicotine replacement therapy in stop smoking services in England (TEC study): a randomized controlled trial. Addiction. 2019**		
Guidance topic: Smoking cessation		**Question no: 6.1a**
Section 1: Applicability (relevance to specific review questions and the NICE reference case)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Current smokers willing to quit
1.2 Are the interventions appropriate for the review question?	Yes	E-cigarettes
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	UK context
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	NHS and PSS
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	Intervention and healthcare costs included
1.6 Are all future costs and outcomes discounted appropriately?	Yes	3.5% for costs, 3.5% for benefits

1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	EQ-5D utility values based in a study of Health Survey for England data.
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	No	Societal costs and benefits are not included
1.9 Overall judgement: Directly applicable		
Section 2: Study limitations (the level of methodological quality)		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	RCT followed by a Markov model
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Both 12 month and lifetimes horizons were used
2.3 Are all important and relevant outcomes included?	Partly	Potential adverse safety outcomes associated with e-cigarettes are not included
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	RCT
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	RCT
2.6 Are all important and relevant costs included?	Partly	Potential costs associated with e-cigarettes are not included
2.7 Are the estimates of resource use from the best available source?	Yes	RCT
2.8 Are the unit costs of resources from the best available source?	Yes	RCT
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	Incremental cost and incremental QALYs are reported
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	Probabilistic sensitivity analysis was conducted
2.11 Is there any potential conflict of interest?	No	

2.12 Overall assessment: Minor limitations
Other comments: None
Abbreviations: EQ-5D: EuroQol 5 dimensions; NHS: National Health Service; PSS: Personal Social Services; QALY: quality-adjusted life-year; RCT: randomised controlled trial

Lock, K et al (2011) A cost-effectiveness model of smoking cessation based on a randomised controlled trial of varenicline versus placebo in patients with chronic obstructive pulmonary disease, Expert Opinion on Pharmacotherapy,12:17, 2613-2626, DOI: 10.1517/14656566.2011.628935		
Guidance topic: Smoking cessation		**Question no: 6.1**
Section 1: Applicability (relevance to specific review questions and the NICE reference case)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Partly	Cohort is cigarette smokers with COPD
1.2 Are the interventions appropriate for the review question?	Yes	Varenicline plus counselling and booklet
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	Set in UK
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	NHS perspective
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	COPD exacerbations included
1.6 Are all future costs and outcomes discounted appropriately?	Yes	3% for costs, 3% for benefits
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	QALYs are derived from UK EQ-5D tariff
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Partly	No societal/payer costs included
1.9 Overall judgement: Partly applicable		
Section 2: Study limitations (the level of methodological quality)		

2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Uses a Markov model
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	28 year horizon, with mean starting age of 57, so almost lifetime
2.3 Are all important and relevant outcomes included?	Yes	Health outcomes reported
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	Population based on the characteristics of those in the varenicline arm of the RCT
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	From 27-centre double-blind placebo RCT
2.6 Are all important and relevant costs included?	Yes	Intervention and COPD disease costs reported
2.7 Are the estimates of resource use from the best available source?	Yes	Taken from peer-reviewed, country specific source
2.8 Are the unit costs of resources from the best available source?	Yes	Taken from peer-reviewed, country specific source
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	ICERs reported
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	Limited sensitivity analysis around the UK. Only probabilistic analysis included.
2.11 Is there any potential conflict of interest?	No	None reported, funded by Pfizer Ltd
2.12 Overall assessment: Minor limitations		
Other comments: None		
Abbreviations: BENESCO: Benefits of smoking cessation on outcomes; CHD: Coronary heart disease; COPD: Chronic obstructive pulmonary disease; CUA: Cost-utility analysis; CVD: Cardio-vascular disease; NRT: Nicotine replacement therapy; PVD: Peripheral vascular disease; QALY: Quality-adjusted life-year; RCT: Randomised controlled trial		

von Wartburg M, Raymond V, Paradis PE. The long-term cost-effectiveness of varenicline (12-week standard course and 12 + 12-week extended course) vs. other smoking cessation strategies in Canada. Int J Clin Pract. 2014;68(5):639-46		
Section 1: Applicability (relevance to specific review questions and the NICE reference case)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Quitters after 12 weeks of varenicline
1.2 Are the interventions appropriate for the review question?	Yes	Varenicline maintenance for quitters
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	No	Canadian context
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	Both a payer and a societal perspective were adopted
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	Quit rates were calculated and smoking-related morbidities were estimated
1.6 Are all future costs and outcomes discounted appropriately?	No	5% for costs, 5% for benefits
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Partly	QALYs are included but the method was not described
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	Costs and benefits to cigarette manufacturers and governments were also considered
1.9 Overall judgement: Partly applicable		
Section 2: Study limitations (the level of methodological quality)		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	A Markov model estimated the long-term prognosis of smoking-related morbidities
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Lifetime
2.3 Are all important and relevant outcomes included?	Yes	QALYs were calculated

2.4 Are the estimates of baseline outcomes from the best available source?	Yes	Mixed-treatment comparison of randomised controlled trials (RCTs)
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	RCTs
2.6 Are all important and relevant costs included?	Yes	All relevant direct costs were included
2.7 Are the estimates of resource use from the best available source?	Unclear	Sources of resource use were not fully described
2.8 Are the unit costs of resources from the best available source?	Yes	Unit costs for interventions were taken from standard Canadian tariffs
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	Incremental cost-effectiveness ratios (ICERs) were presented
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Probabilistic sensitivity analysis (PSA)
2.11 Is there any potential conflict of interest?	None	
2.12 Overall assessment: Minor limitations		
Other comments: None		
Abbreviations: ICER: Incremental cost-effectiveness ratio; PSA: Probabilistic sensitivity analysis; QALY: quality-adjusted life-year; RCT: randomised controlled trial		

Wilson, Koo et al. "An Economic Evaluation Based On A Randomized Placebo-Controlled Trial Of Varenicline In Smokers With Cardiovascular Disease: Results For Belgium, Spain, Portugal, And Italy". European Journal Of Preventive Cardiology, vol 19, no. 5, 2011, pp. 1173-1183. SAGE Publications, doi:10.1177/1741826711420345.		
Guidance topic: Smoking cessation		**Question no: 6.1**
Section 1: Applicability (relevance to specific review questions and the NICE reference case)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Partly	Cohort is smokers with history of CVD

1.2 Are the interventions appropriate for the review question?	Yes	Varenicline plus counselling
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	Set in European countries: Italy, Belgium, Portugal and Spain
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	From payers perspective, with societal perspective also included
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	Many CVD related disease states included
1.6 Are all future costs and outcomes discounted appropriately?	Partly	3% for costs, 3% for benefits
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Partly	QALYs are included but the method was not described
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	Direct costs and some societal costs like productivity included
1.9 Overall judgement: Partly applicable		
Section 2: Study limitations (the level of methodological quality)		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Uses BENESCO model which is common in this topic
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Lifetime
2.3 Are all important and relevant outcomes included?	Yes	Health outcomes reported
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	Taken from many country-specific published sources
2.5 Are the estimates of relative intervention effects from the best available source?	Partly	From a single double-blind placebo RCT, but adapted from UK adaption of US study

2.6 Are all important and relevant costs included?	Yes	Intervention and CVD disease costs reported
2.7 Are the estimates of resource use from the best available source?	Partly	Taken from many country-specific published sources
2.8 Are the unit costs of resources from the best available source?	Partly	Taken from many country-specific published sources
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	ICERs reported
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Full one-way and probabilistic sensitivity analyses
2.11 Is there any potential conflict of interest?	No	None reported, funded by Pfizer Ltd
2.12 Overall assessment: Minor limitations		
Other comments: None		
Abbreviations: BENESCO: Benefits of smoking cessation on outcomes; CVD: Cardio-vascular disease; ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life-year; RCT: Randomised controlled trial		