National Institute for Health and Care Excellence

Final

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

[N] Evidence reviews for smoking relapse prevention

NICE guideline NG209

Evidence reviews underpinning recommendations 1.17.1 to 1.17.2, 1.17.6 to 1.17.7, 1.22.1 to 1.22.2, and research recommendations in the NICE guideline

November 2021

Final

These evidence reviews were developed by PH-IGD

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.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN: 978-1-4731-4347-0

Contents

Smoking relapse prevention

Review question

Which interventions are effective and cost effective for preventing a relapse in people who have recently quit smoking?

Introduction

Several treatments can help smokers make a successful quit attempt, but many of those who initially successfully quit relapse over time. Preventing relapse in people who have quit smoking is important for health benefits to be realised. Several interventions have been proposed to help prevent relapse. This review aims to identify which behavioural or pharmacotherapy interventions are most effective at preventing a relapse in those who have quit smoking recently, defined as at any point in the past.

There is no clear definition of a relapse prevention intervention distinct from extended cessation treatment. In principle, resuming smoking any time after a quit date may be defined as a relapse. Relapse prevention is often, however, intended to refer to preventing relapse after an acute treatment phase is successfully completed. Both types of relapse – at any point after a quit date, and after successful completion of a treatment phase – are included in this review.

This review was completed by the Cochrane Tobacco Addiction Group (TAG) in October 2019 for NICE (Livingstone-Banks *et al.*, 2019)[a]. Throughout, figures and sections of text have been taken directly from the Cochrane work, or had minor amendments to wording, and are presented here in the standard NICE format.

PICO table

Table 1: PICO information for relapse prevention review

Domain	Detail
Population	People aged 12 and over: • who have quit smoking on their own or • who are undergoing enforced abstinence, whether or not they intend to quit permanently or • who are participating in treatment programmes to assist initial cessation. **Excluded**: • People aged 11 and under. • People who used smokeless tobacco and have quit.
Intervention	**Included**: Interventions which have a stated and measured aim of preventing relapse. Interventions may include the following as monotherapies, or in combination with each other: • Behavioural interventions (for example individual, group, telephone support, information materials, text messaging or online support) • Pharmacological interventions (bupropion, varenicline, NRT only) • E-cigarettes

[a] Livingstone-Banks J, Norris E, Hartmann-Boyce J, West R, Jarvis M, Chubb E, Hajek P. Relapse prevention interventions for smoking cessation. Cochrane Database of Systematic Reviews 2019, Issue 2. Art. No.: CD003999. DOI: 10.1002/14651858.CD003999.pub5.

Domain	Detail
	• Incentives **Excluded**: • Other forms of nicotine containing products or medicines • Alternative and complementary therapies • Tobacco containing products
Comparator	• No intervention or placebo. • A shorter intervention or intervention not explicitly to prevent relapse. • Usual care. • An included intervention.
Outcome	**Critical outcomes** Smoking status at longest available follow-up (minimum of 6 months follow-up). Measured as abstinence from smoking (relative risk). *Where continued abstinence is presented, this is preferred over point-prevalence abstinence. Point prevalence measures will only be used where no continuous measure is reported.* *Where biochemically validated measures are available (i.e. saliva cotinine / carbon monoxide validation), these will be preferred to self-reported measures. Self-reported measures will only be used where no validated measure is reported.* **Important outcomes** These will be extracted only if the study also reports a critical outcome. Health-related quality of life (using validated patient-report measures, for example EQ-5D).
Study designs	Systematic reviews of RCTs RCTs

RCT – Randomised controlled trial

Methods and process

This evidence review was developed using the methods and processes described in Developing NICE guidelines: the manual (2018). Further methods are detailed in the methods chapter for this guideline. Methods specific to this review are described in 'Synthesis and appraisal of public health studies', and in the review protocol in Appendix A.

The following adaptations have been made to Livingstone-Banks (2019) to ensure the methods for this review are consistent with methods used in other reviews for the Tobacco guideline, and with the protocol for this review:

- Removal of quasi-randomised trials and trials from non-OECD countries
- Removal of a study assessing rimonabant
- Application of fixed- or random-effects meta-analysis based on methods described in the methods chapter for this guideline
- Completion of GRADE evidence profiles according to the methods chapter for this guideline

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

Agreed minimally important differences (MIDs) are used in this review and are presented in Table 2.

Table 2: Minimal Important Differences (MIDs) agreed

Outcome	Importance	MID
Abstinence from smoking	Critical	Statistical significance
Health-related quality of life	Important	Published MID if one available (e.g. SF-12 has published MID of 6.8 points; SF-36 of 2-4 points) Otherwise default: Dichotomous outcomes: 25% increase or 20% decrease (RR 0.8 to 1.25) Continuous outcomes: 0.5*standard deviation

Risk of bias

Livingstone-Banks (2019) used the *Cochrane Risk of Bias tool* to assess risk of bias. This tool assesses random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; and incomplete outcome data.

Studies were considered to be at high risk of attrition bias (incomplete outcome data) when lack of information meant that post-randomisation dropouts could not be included in denominators, or when less than 50% of participants were followed up at six months or longer, or when there was a difference between groups in follow-up rate of 20% or more. Had studies of pharmacotherapies not used a placebo, they would have been considered to be at high risk of performance bias (blinding of participants/personnel), but in the case of behavioural interventions where blinding of participants was not possible, other study characteristics such as similar amounts of contact between conditions, or participants not knowing about other conditions, which may indicate that performance bias is less likely were considered. Studies were judged to be at high risk of detection bias (blinding of outcomes assessors) when no biochemical validation was used and the intervention arm received more face-to-face contact than the control arm, as differential misreport was considered a possibility in these cases.

The systematic review by Livingstone-Banks (2019) was assessed using the Risk of Bias in Systematic Reviews *ROBIS* tool, in accordance with the NICE Manual (see Appendix D).

Randomised controlled trial (RCT) evidence from this review was assessed using the *Cochrane Risk of Bias (ROB) tool*, rather than the *Cochrane ROB 2.0 tool* recommended by NICE. As such, assessments of overall risk of bias of studies in this review were revised to align with judgments that would be derived from the use of this preferred tool as follows:

- High risk of bias: The Cochrane ROB checklist contains a judgement for high risk of bias in at least one domain, or unclear risk for multiple domains in a way that substantially lowers confidence in the result.
- Some concerns: The Cochrane ROB checklist contains a judgement for unclear risk in at least two domains, but not to be at high risk of bias for any domain.
- Low risk of bias: The Cochrane ROB checklist contains no judgements of high risk of bias for any domain and is at unclear risk of bias in no more than one domain.

- All GRADE ratings start at ‘high’, are compared to the ideal study design and are downgraded as appropriate.
- Assessments for Risk of Bias in GRADE were drawn from the RoB tool assessment.

See Appendix F for full GRADE tables.

Identification of public health evidence

Included studies

This is a new review for this guideline. Livingstone-Banks (2019) searched the Cochrane Tobacco Addiction Group trials register, clinicaltrials.gov, and the ICTRP in May 2019 for studies mentioning relapse prevention or maintenance in their title, abstracts, or keywords. Livingstone-Banks (2019) checked for relevance all reports of studies with 'relapse prevention' or 'maintenance' or 'relapse near prevent*' in title, abstract or keywords.

Livingstone-Banks (2019) included both studies that randomly assigned people already abstaining from smoking, and studies abstaining smokers before quitting. In studies that randomly assigned smokers before quitting:

- Only studies that explicitly identified in their titles or abstracts a focus on relapse prevention or maintenance were included
- Studies of exercise, aversive smoking, or incentives were excluded because the interventions used are similar, whether described as relapse prevention or not.
- Most interventions for hospitalised participants were excluded because studies generally did not describe whether participants were already abstinent or not, and interventions typically contained a mixture of cessation and relapse prevention components.

81 studies (69,094 participants) were included in the Cochrane review, five of which were new to this Cochrane update. Seven studies (including one of the five which were new for this update) were excluded due to being quasi-randomised, taking place in non-OECD countries, or including interventions which were excluded from the protocol, leaving 74 studies in total. 15 studies were judged to be at low risk of bias, 13 with some concerns, and 46 at high risk of bias. 50 studies included abstainers, and 25 studies helped people to quit and then tested treatments to prevent relapse (one study, Schmitz 1999, did both). 26 studies among those randomising abstainers focused on special populations who were abstinent because of pregnancy (18 studies), hospital admission (5 studies), or military service (3 studies). Most studies used behavioural interventions that tried to teach people skills to cope with the urge to smoke or followed up with additional support. Twenty-three tested extended pharmacotherapy either in combination with behavioural support or alone.

Excluded studies

See Appendix K for a full list of studies excluded by Livingstone-Banks (2019) and a list of the studies included in that review but excluded in this NICE review.

Details of public health studies included in the evidence review

Table 3: Summary of studies randomly assigning abstainers – special populations (n = 26). Ordered by date within populations.

Study	Population	Intervention	Comparison	Outcome(s)	Risk of bias
Ershoff 1995 USA	Pregnant ex-smokers N=171	Self-help booklets. During pregnancy only.	Minimal self-help (tip sheet)	7 day PPA Cotinine validation	Low risk
Secker-Walker 1995 USA	Pregnant ex-smokers N=165	Individual counselling. During pregnancy and post-partum.	Usual care	Abstinence Cotinine/creatine ratio validation	High risk

Study	Population	Intervention	Comparison	Outcome(s)	Risk of bias
Lowe 1997 USA	Pregnant ex-smokers N=78	Individual counselling, self-help materials, enhanced social support and materials (buddy). During pregnancy only	Usual care (including nurse advice)	Continued abstinence Saliva thiocyanate validation	High risk
Secker-Walker 1998 USA	Pregnant ex-smokers N=116	Individual counselling. During pregnancy only.	Usual care (physician)	Sustained abstinence CO ≤6ppm and urinary cotinine validation	High risk
McBride 1999 USA	Pregnant ex-smokers N=897	1. letter, health concerns and motivation, self-help book, relapse prevention kit 2. telephone counselling, MI[a] approach 3. 1 plus extra calls. During pregnancy and post-partum.	Self-help booklet	7 day PPA Validation: saliva cotinine requested by mail, < 20 ng/mL. Only self-reported rates	Some concerns
Hajek 2001 UK	Pregnant ex-smokers N=249	Advice, pamphlet, prompt notes. During pregnancy only.	Usual care (midwife)	Abstinence (prolonged for 12 weeks) Validation: CO ≤ 10 ppm	High risk
McBride 2004 USA	Pregnant ex-smokers N=316	1. Counselling calls for woman only, MI[a], relapse prevention kit 2. 1 for woman plus partner, plus calls and cessation support to partner. During pregnancy and post-partum.	Usual care (provider advice and mailed self-help)	7 day PPA Validation: saliva cotinine requested by mail, only self-reported rates reported	High risk
Pbert 2004 USA	Pregnant ex-smokers N=168	Guideline based, 4As training for staff, practice management system, inter-clinic communication.	No training, usual care (clinic providers)	30 day PPA Validation: saliva cotinine ≤ 20 ppm	High risk
Morasco 2006 USA	Pregnant ex-smokers N=33	Individual counselling (psychotherapy) and phone calls. During pregnancy only.	Usual care	7 day PPA Validation: CO ≤ 8 ppm	High risk
Ruger 2008 USA	Pregnant ex-smokers	MI at home visits, tailored self-help materials.	Usual care	Quit Validation: salivary cotinine, but cut-off	High risk

Study	Population	Intervention	Comparison	Outcome(s)	Risk of bias
	N=57	During pregnancy only.		and percentage validated not specified	
Reitzel 2010 USA	Pregnant ex-smokers (low income) N=251	1. Telephone-based counselling (motivational enhancement and social cognitive approach) 2. 1, plus in-person counselling. During pregnancy and post-partum.	Usual care	Continuous abstinence Validation: CO < 10 ppm and/or cotinine < 20 ng/mL	High risk
Brandon 2012 USA	Pregnant ex-smokers N=504	'Forever-free' self-help booklets by post. During pregnancy and post-partum.	Leaflets (not content customised for pregnancy)	7 day PPA Validation: CO < 8 ppm and Cotinine < 10 ng/mL or self-report (distance dependent)	High risk
Levine 2016 USA	Pregnant ex-smokers N=300	STARTS enhanced cognitive behavioural intervention. Unclear intervention duration	SUPPORT time and attention-controlled comparison	Sustained abstinence Validation: CO < 8 ppm or cotinine 15 ng/mL at 52 weeks postpartum	Low risk
Pollak 2016 USA	Pregnant ex-smokers N=382	In person session, phone calls (risk dependent intensity) plus Forever Free booklet. During pregnancy and post-partum.	Self-help "Forever Free" booklet and newsletters	Continuous abstinence Validation: CO < 10 ppm and cotinine < 0.5 mg/dL	High risk
Coleman-Cowger 2018 USA	Pregnant ex-smokers (low income) N=128	Standard care plus phone-based continuing care (MI[a] techniques and 5 A's). During pregnancy and post-partum.	Standard care only	7 day PPA Validation: Urine cotinine	High risk
Severson 1997 USA	Post-partum ex-smokers N=1026	Counselling, self-help materials, information pack. Intervention initiated after birth.	Information pack only	Sustained abstinence No validation	High risk
Ratner 2000 Canada	Post-partum ex-smokers N=251	Counselling session (in-person and telephone), skills training, self-help pamphlets. Intervention initiated after birth.	Usual care	Continuous abstinence Validation: CO < 10 ppm for participants interviewed in person. Data collectors blind	Some concerns

Study	Population	Intervention	Comparison	Outcome(s)	Risk of bias
Van't Hof 2000 USA	Post-partum ex-smokers N=277	Individual counselling, reinforcement, written materials. Intervention initiated after birth.	Usual care (nurse)	Abstinence (assume PP) Validation: none (assessment by phone, no details of blinding of assessor)	High risk
Cummins 2016 USA	Hospital inpatients N=1270	1. Standard care plus NRT patches 2. Standard care plus telephone counselling 3. Standard care plus NRT patches and telephone counselling	Standard care (brief bedside intervention)	30 day PPA Validation: Cotinine < 10 ng/mL at 6 months	Some concerns
Brandstein 2012 USA	Hospital inpatients N=126	Brief bedside intervention plus NRT patches, telephone counselling and self-help materials	Brief bedside intervention	Prolonged abstinence Validation: Self-report plus saliva sample bogus pipeline test	High risk
Hajek 2002 UK	Hospital inpatients (following MI[b] or CABG[c]) N=540	Control plus CO reading, information booklet, quiz, buddy offer.	Verbal advice, 'Smoking and Your Heart' booklet	Sustained abstinence Validation: saliva cotinine < 20 ng/mL (CO used at 6 weeks follow-up and for visits at 12 months)	Some concerns
Hasuo 2004 Japan	Hospital inpatients N=106	In-hospital counselling, and calls post discharge	In-hospital counselling only	Abstinence (assume PP) Validation: Urine cotinine	Low risk
Schmitz 1999 USA	Hospital inpatients (coronary artery disease) N=160	Coping skills sessions (including stress management), homework	Health belief model Smoking-related health information sessions	PP abstinence Validation: CO < 9 ppm, urine cotinine < 10 ng/mL	High risk
Klesges 1999 USA	Military recruits N=18,010	Single group session, interactive (health effects, role-play)	General health video	Abstinence (not defined No validation	Some concerns
Conway 2004 USA	Military recruits N=1682	1. Flyers, cognitive behavioural material, general health information by mail over 1 year 2. Access to helpline on relapse preventing	No intervention	30 day PPA No validation	High risk

Study	Population	Intervention	Comparison	Outcome(s)	Risk of bias
Klesges 2006 USA	Military recruits N=10164 (approx.)	Sessions on smoking, role playing, single session of NRT gum	General health video	Sustained abstinence No validation	High risk

(a) PPA, point prevalent abstinence
(b) MI, motivational interviewing
(c) Coronary Artery Bypass Graft

Table 4: Summary of studies randomly assigning abstainers – unselected populations (behavioural) (n = 16)

Study	Population	Intervention	Comparison	Outcome(s)	Risk of bias
Killen 1990 USA	Unaided abstainers N=1218	4x3 factorial design. Nicotine gum: 1. as needed 2. fixed schedule 3. placebo gum 4. no gum Combined with a self-help booklet plus one of: a. 7 more booklets of choice, weekly b. 7 more booklets randomly selected c. no further contact	See interventions	7 day PPA Validation: saliva cotinine < 20 ng/mL, except for participants who had moved away	High risk
Fortmann 1995 USA	Unaided abstainers N=1044	Factorial trial, combining an incentive with: 1. Nicotine gum 2. Self-help materials 3. Nicotine gum and self-help materials 4. incentive only	See interventions	PP abstinence Validation: CO < 9 ppm, salivary cotinine < 20 ng/mL	High risk
Brandon 2000 USA	Unaided abstainers N=584	2x2 factorial design: 1. self-help booklets over time (Stay Quit, previous version of Forever Free) 2. information about a hotline 3. both 4. minimal contact (one booklet only)	See interventions	7 day PPA Validation: CO < 10 ppm for participants living within 75 miles of laboratory	High risk
Brandon 2004 USA	Unaided abstainers N=481	2x2 factorial design: 1. self-help booklets over time (Forever Free)	See interventions	7 day PPA Validation: CO for 21 local quitters, no	Some concerns

Study	Population	Intervention	Comparison	Outcome(s)	Risk of bias
		2. Self-help booklets all at once 2. Letters over time 3. Single booklet 4. minimal contact (one booklet only)		misreporting identified	
Borland 2004 Australia	Unaided abstainers N=215	Quit pack, tailored advice letters	Quit pack only	Sustained abstinence Not validated	Low risk
Powell 1981 USA	Assisted abstainers N=51	Cessation programme (meetings and aversive smoking) plus: 1. 4-week support group 2. telephone contact system	Cessation programme only	Abstinence, not defined Not validated	High risk
Stevens 1989 USA	Assisted abstainers N=587	Weekly meetings plus: 1. Skills development, coping strategies 2. Discussion group, social support	Weekly meeting only	Sustained abstinence Validation: saliva thiocyanate < 0.8 mg/mL or cotinine < 5 ng/mL	Some concerns
Razavi 1999 Belgium	Assisted abstainers N=334	Cessation programme (behavioural and NRT patch). Successful also had: 1. monthly group discussion led by counsellor 2. group discussion, led by former smoker	Cessation programme only	Sustained abstinence Validation: CO < 10 ppm and urine cotinine ≥ 317 ng/mL required	Low risk
Smith 2001 USA	Assisted abstainers N=677	Brief cessation advice (including NRT patches and booklet “Clearing the Air”) plus: 1. cognitive-behavioural skills training 2. MI and group counselling	Brief cessation advice (including NRT patches and booklet “Clearing the Air”) only	7 day PPA Validation: CO < 10 ppm	High risk
Mermelstein 2003 USA	Assisted abstainers N=341	Telephone counselling sessions	Telephone counselling, non-specific	7 day PPA No validation	Some concerns

Study	Population	Intervention	Comparison	Outcome(s)	Risk of bias
Mayer 2010 Belgium	Assisted abstainers N=275	Cessation program plus workplace group counselling	Cessation program, plus phone counselling	Continuous abstinence Validation: CO < 10 ppm, urinary cotinine ≤ 317 ng/mL	High risk
McNaughton 2013 Canada	Assisted abstainers N=44	Cessation (varenicline and Interactive Voice Response calls); continued calls	Cessation (varenicline and Interactive Voice Response calls)	Prolonged abstinence Validation: CO < 10 ppm	Some concerns
Blyth 2015 UK	Assisted abstainers N=1404	Forever Free self-help booklets	Single leaflet (Learning to Stay Stopped)	Continuous abstinence Validation: CO < 10 ppm	Low risk
McDaniel 2015 USA	Assisted abstainers N=1785	1. Quitline TEQ-20 2. Quitline TEQ-10 Both with interactive voice response	Standard treatment	30 day PPA No validation	High risk
Hayes 2018 USA	Assisted abstainers N=577	Smoke-free Kids mailed parenting program	No treatment	30 day PPA No validation	High risk
Veldheer 2018 USA	Assisted abstainers N=115	Self-directed relapse prevention materials	Single information booklet on cigarettes	7 day PPA Validation: exhaled CO	Some concerns

(d) PPA, point prevalent abstinence
(e) MI, motivational interviewing

Table 5: Summary of studies randomly assigning abstainers – unselected populations (pharmacological) (n = 10)

Study	Population	Intervention	Comparison	Outcome(s)	Risk of bias
Killen 1990	As for entry in Table 4				High risk
Fortmann 1995	As for entry in Table 4				High risk
Hays 2001 USA	Abstainers following cessation pharmacotherapy N=429	Bupropion, advice, self-help and brief counselling plus extended bupropion 300mg/day for 45 weeks	Bupropion, advice, self-help and brief counselling plus placebo	Continuous abstinence Validation: CO ≤ 10 ppm	Low risk
Hurt 2003 USA	Abstainers following cessation pharmacotherapy N=578	NRT patch (8 weeks at a dose of 22, 33 or 44 mg/day), brief advice, self-help	NRT patch (8 weeks at a dose of 22, 33 or 44 mg/day), brief advice, self-help	Abstinence (assumed PP) Validation: CO < 8 ppm	High risk

Study	Population	Intervention	Comparison	Outcome(s)	Risk of bias
		materials plus extended bupropion 300 mg/day for 6 months	materials plus placebo		
Killen 2006 USA	Abstainers following cessation pharmacotherapy N=362	Combination bupropion and NRT patch (bupropion 300 mg for 11 weeks, nicotine patch for 10 weeks), individual relapse prevention skills plus extended bupropion (150 mg for 14 weeks)	Combination bupropion and NRT patch (bupropion 300 mg for 11 weeks, nicotine patch for 10 weeks), individual relapse prevention skills plus bupropion tapering to placebo	Continuous abstinence Validation: CO (10 people not required to provide samples)	Low risk
Tonstad 2006 USA	Abstainers following cessation pharmacotherapy N=1210	Varenicline (1 mg × 2 daily for 12 weeks) and clinic visits	Placebo	Sustained abstinence Validation: CO ≥ 10 ppm	Low risk
Covey 2007 USA	Abstainers following cessation pharmacotherapy N=289	1. Bupropion (300 mg) and nicotine gum (2 mg, use as needed to manage craving) for 16 weeks 2. Bupropion and placebo gum 3. Nicotine gum and placebo pill (150 mg bupropion for first week) 4. Double placebo	See interventions	Time to relapse Validation: CO ≤ 8 ppm at each visit	Low risk
Croghan 2007 USA	Abstainers following cessation pharmacotherapy N=405	Single-therapy abstainers were randomly assigned to continue cessation therapy or placebo for 9	See interventions	Point prevalence abstinence Validation: CO ≤ 8 ppm	Low risk

Study	Population	Intervention	Comparison	Outcome(s)	Risk of bias
		months. Combined therapy abstainers randomly assigned to 4 groups: combination, placebo and single therapy, or double placebo			
Hays 2009 USA	Abstainers following cessation pharmacotherapy N=110 (with alcoholism)	Brief ongoing counselling and NRT patch (8 weeks), plus bupropion (50 mg/day first 3 d, then 300 mg/d until week 52)	Brief ongoing counselling and NRT patch (8 weeks), plus placebo	Continuous abstinence Validation: CO < 8 ppm	High risk
Evins 2014 USA	Abstainers following cessation pharmacotherapy N=87	Varenicline plus CBT	Placebo plus CBT	Continuous abstinence Validation: CO < 9 ppm at week 52	High risk

(f) PPA, point prevalent abstinence
(g) CBT, cognitive behavioural therapy

Table 6: Summary of studies randomly assigning smokers (behavioural) (n = 25)

Study	Population	Intervention	Comparison	Outcome(s)	Risk of bias
Hall 1984 USA	Smokers N=135	Group behavioural treatment, aversive smoking, skills training	Matched for contact time. Aversive smoking, general discussion, skills discussion discouraged in the control.	PP abstinence Validation: CO < 10 ppm, plasma thiocyanate < 85 ng/mg and confirmation from significant other	High risk
Davis 1986 USA	Smokers N=45	Group cognitive behavioural skills training	1. Enhanced control, matched for contact time. General discussion 2. General cessation package only	PP abstinence Validation: CO	High risk
Curry 1988 USA	Smokers N=139	1. Group relapse prevention meetings.	1. Relapse prevention workbooks	Abstinence Validation: saliva thiocyanate	High risk

Study	Population	Intervention	Comparison	Outcome(s)	Risk of bias
		2. Group absolute abstinence meetings.	2. Absolute abstinence workbooks. Matched for contact time.	and two collateral verifiers	
Emmons 1988 USA	Smokers N=49	Cessation programme with relapse prevention focus. Cognitive coping, role play. Weekly sessions.	Matched for contact time, general cessation programme.	Validation: saliva thiocyanate ≤ 85 microg/mL	High risk
Buchkremer 1991 1 Germany	Smokers N=256	Tailored NRT patch plus weekly group sessions, plus: 1. additional relapse training 2. additional late booster sessions	1. Tailored NRT patch plus weekly group sessions 2. Tailored NRT patch plus weekly group sessions plus fixed dose NRT patch	PP Abstinence Validation: random urine nicotine, 'almost 100% conformity', no correction	High risk
Buchkremer 1991 2 Germany	Smokers N=185	Tailored NRT patch plus weekly group sessions, plus: 1.relapse coping training 2. modified relapse coping training	Tailored NRT patch plus weekly group sessions plus 1. individualised NRT patch 2. fixed dose NRT patch	PP abstinence Validation: random urine, 'almost 100% conformity', no correction	High risk
Becona 1997 Spain	Smokers N=76	8 weekly sessions of motivational contract, nicotine fading, stimulus control plus relapse prevention problem solving.	As for intervention without relapse prevention	Abstinence not defined. Validation: CO < 8 ppm during therapy, informants during follow-up	Some concerns
Schroter 2006 Germany	Smokers N=79	Group sessions on relapse prevention (skills training, coping strategies)	Group sessions on standard behavioural cessation. Matched for contact time.	Abstinence (not defined). No validation.	High risk
Niaura 1999 USA	Smokers N=120	Individual counselling sessions, self-help manual; (Freedom from smoking for	Individual counselling sessions, self-help manual; (Freedom from smoking for you	Sustained abstinence Validation: CO < 8 ppm	High risk

Study	Population	Intervention	Comparison	Outcome(s)	Risk of bias
		you and your family), plus: 1. CBT with cue exposure 2. CBT with cue exposure plus nicotine gum	and your family), plus: a. brief CBT (control for 1) b. CBT and nicotine gum (control for 2; matched for contact time)		
Schmitz 1999 USA	Smokers N=160 (with or at risk of CAD[j])	Individual sessions, coping skills relapse prevention	Individual sessions on health belief model. Matched for contact time.	PPA Validation: CO < 9 ppm, urine cotinine < 10 ng/mL	High risk
Killen 1984 USA	Smokers N=64	Cessation intervention plus: 1. NRT gum extended 2. Skills training for relapse prevention 3. 1 plus 2	See interventions	Abstinence for 4 weeks Validation: CO < 8 ppm	Low risk
Brandon 1987 USA	Smokers N=39	Cessation intervention plus relapse prevention sessions with advice, self-monitoring, coping exercises.	Cessation intervention plus single assessment session	Abstinence (assume PP) Validation: CO only during treatment	High risk
Hall 1987 USA	Smokers N=139	Intensive behavioural treatment, relapse prevention skills training	Low contact condition: group quitting techniques	Abstinence (assume PP) Validation: thiocyanate < 95 mm/L (unless marijuana use reported), CO < 8 ppm, significant other	High risk
Shoptaw 2002 USA	Smokers undergoing methadone maintenance N=175	NRT patch plus group counselling (21 mg nicotine patch for 12 weeks)	NRT patch only	PPA Validation: CO ≤ 8 ppm, urine cotinine < 30 ng/mL	Low risk
Hall 1985 USA	Smokers N=84	Intensive behavioural treatment plus NRT gum (2 mg nicotine gum available for 6 months)	Low contact behavioural treatment plus NRT gum	Abstinence (assume PP) Validation: CO < 10 ppm, thiocyanate < 85 mg/mL	High risk

Study	Population	Intervention	Comparison	Outcome(s)	Risk of bias
Lifrak 1997 USA	Smokers N=69	NRT patch plus high intensity CBT for relapse prevention	NRT patch plus moderate intensity meetings	7 day PPA Validation: urine cotinine for some participants, but no corrections made for misreporting	High risk
Lando 1996 USA	Smokers N=1083	Cessation programme plus telephone counselling	Cessation programme only	7 day PPA Validation: random half of quitters validated by saliva cotinine < 20 ng/mL at 12 months 91% confirmed	High risk
Segan 2011 Australia	Smokers N=698	Quitline services before and after quitting plus additional calls	Quitline services before and after quitting	Continuous abstinence No validation	High risk
Unrod 2016 USA	Smokers N=3458	1. Repeated mailings of self-help booklets (Forever Free) 2. Single mass mailing of same self-help booklets	Standard mail intervention	7 day PPA Validation not described.	High risk
Simmons 2018 USA	Smokers N=1874	1. Intensive repeated mailings of self-help booklets (10 x booklets) 2. Standard repeated mailings of self-help booklets (8 x booklets)	Single self-help cessation booklet	7 day PPA No validation	High risk
Japuntich 2006 USA	Smokers N=284	Bupropion (300 mg for 9 weeks), individual counselling sessions, assessment calls plus access to Comprehensive Health Enhancement Support System for Smoking Cessation and	Bupropion (300 mg for 9 weeks),individual counselling sessions, assessment calls only	PPA Validation: CO ≤ 10 ppm	Some concerns

Study	Population	Intervention	Comparison	Outcome(s)	Risk of bias
		Relapse Prevention (CHESS SCRP)			
Wetter 2011 USA	Smokers N=302	NRT patch (21 mg/d), group counselling sessions, computer-delivered treatment	NRT patch, group counselling sessions only	7 day PPA Validation: CO < 10 ppm	Some concerns
Hicks 2017 USA	Smokers with chronic PTSD N=11	QUIT4EVER (Stay Quit Coach app) and contingency management app	Contingency management app only	7 day PPA Validation: Cotinine < 10 ng/mL	High risk
Durmaz 2019 Turkey	Smokers N=132	Counselling, support booklet, relapse prevention component plus WhatsApp messages	Counselling, support booklet, relapse prevention component only	Continuous abstinence No validation.	Low risk
Joseph 2011 USA	Smokers N=443	NRT (patch; gum; lozenge, provision modelled on common clinical practice) and telephone calls for extended time period.	NRT (patch; gum; lozenge, provision modelled on common clinical practice) and telephone calls for short time period	6 months prolonged abstinence. No validation.	Low risk

(h) PPA, point prevalent abstinence
(i) CBT, cognitive behavioural therapy
(j) Coronary Artery Disease

To note for all study characteristics tables, outcome measures were taken at different follow-up points, but all were at least 6 months after randomisation. For full details, see the published Cochrane review.

Funding information

Cochrane are not aware of any studies included in this review linked to or funded by tobacco organisations.

Data synthesis

Grouping of results

Studies of interventions for relapse prevention may randomly assign people who have already quit, or they may randomly assign smokers before their quit attempt and provide a general smoking cessation intervention to all participants, with an additional component provided for those randomly assigned to relapse prevention. These studies are presented separately due to methodological strengths of randomly assigning abstainers.

Randomly assigning abstainers

Type of abstainer

Studies were divided into groups according to the population being studied:

- Those who had stopped smoking where it was prohibited or discouraged for a set amount of time ('special populations') due to factors such as:
  - Pregnancy
  - Hospital stay
  - Military training
- Ex-smokers recruited from the general population, dependent on the circumstances of their quit:
  - Assisted abstainers (those who have quit through a formal treatment programme)
  - Unaided abstainers (those who have quit without a formal treatment programme)

Type of intervention

Studies were then divided into those assessing behavioural interventions and those assessing pharmacotherapy, due to anticipated differences in results.

Livingstone-Banks (2019) classified behavioural interventions into intensive and less intensive categories. Intensive interventions involved repeated face-to-face contact, usually aimed at teaching clients to identify tempting situations and to apply a range of coping skills and cognitive strategies assumed to be of help in resisting relapse. Less intensive interventions usually attempted to teach these skills via written materials and could involve one brief face-to-face session and telephone contacts.

Randomly assigning smokers

Studies randomly assigning smokers would have been divided into those assessing behavioural interventions and those assessing pharmacotherapy, due to anticipated differences in results. However, there were no studies assessing only pharmacotherapy.

Behavioural interventions were divided into time-matched interventions with and without the relapse prevention elements, and those that looked at the effect of extended participant contact. For studies with more than two arms, the most intensive versus the least intensive were included in the main meta-analysis. The least intensive intervention is referred to as the 'control'.

Subgroup analysis

For analyses of studies randomising abstainers, subgroup analyses were conducted grouping studies by the duration of prior abstinence of participants. Livingstone-Banks (2019) grouped studies based on whether, on delivery of the relapse prevention intervention, participants had been abstinent for four or more weeks, less than four weeks, or if prior abstinence varied or was not adequately specified.

Sensitivity analysis

Livingstone-Banks (2019) conducted a sensitivity analysis removing studies conducted in countries outside of the OECD (Organisation for Economic Co-operation and Development) from any analyses in which they were included and explained that removing these studies did not meaningfully change the results of the relevant analyses. However, for consistency with other reviews and to ensure applicability, these studies were removed from this review altogether.

Livingstone-Banks (2019) also conducted sensitivity analyses – for meta-analyses of studies randomising abstainers – of duration of prior abstinence. Duration of less than 4 weeks was presented separately from 4 weeks or more. This split was chosen to align with the Russell Standard definition of a successful quit, which is reached at 4 weeks from quit date.

Where serious heterogeneity was present in spite of subgroup analysis, sensitivity analysis by risk of bias was conducted.

Quality of life

Cochrane TAG checked included studies for any results measuring change in health-related quality of life. No included studies reported this outcome.

Adverse events

Adverse events of the included interventions were not included in this review. For behavioural interventions, the committee did not believe it to be plausible that relapse prevention skill teaching would lead to adverse events. For the pharmacological interventions, the best adverse event data came from the large clinical trials using these medications as cessation aids, reported in systematic reviews and licensing information:

- Varenicline: Varenicline BNF entry; Varenicline for smoking cessation (TA123); Cochrane review on nicotine receptor partial agonists (Cahill, 2016)
- Bupropion: Bupropion Hydrochloride BNF entry;
- NRT: Review of effects of nicotine in secondary care (PH48)*; Effectiveness of smoking cessation interventions in mental health services (PH48)*; Cochrane review on NRT (Hartmann-Boyce, 2018)
- E-cigarettes: Please see review on effectiveness of treatments for smoking cessation.

*These reviews are being updated in this 2021 update of the Tobacco guideline.

Meta-Analysis

All meta-analyses are taken from Livingstone-Banks (2019). Amendments were made to comply with the methods chapter for this guideline. Sensitivity analyses by risk of bias and funnel plots to assess publication bias were conducted by the NICE review team. More detail about the meta-analysis (studies excluded, details of pooling etc.) are below:

Pregnancy (Figures 1-4, 25; GRADE profile 1):

Some studies in this area were excluded from the meta-analysis:

- Coleman-Cowger (2018) included current and recently-quit pregnant smokers but did not report outcomes separately for each group (results not reported in Livingstone-Banks 2019).
- Data could not be extracted from Pbert (2004) in a comparable format to pool with the other studies, but it did not detect any significant effect of behavioural intervention on spontaneous quitters at delivery; the postpartum non-smoking rate was higher in the usual care group (results not reported in Livingstone-Banks 2019).
- Levine (2016) had the same level of contact between the two intervention groups, so the study was not included in the meta-analysis. However, it did not detect an effect in favour of either group (n = 300, RR 0.80, 95% CI 0.53 to 1.20).

Hospital inpatients (Figures 5-6; GRADE profile 2):

Behavioural: Results were pooled from four studies and the behavioural arm of Cummins 2016.

Pharmacological: NRT results from Brandstein 2012 were pooled with two arms from Cummins 2016 (NRT and NRT plus telephone counselling).

Military recruits:

- Livingstone-Banks (2019) did not pool results because denominators were unclear and reported results were corrected for clustering.
- In all three studies, the period of enforced abstinence did give rise to a higher quit rate than the spontaneous rate expected in these populations of young smokers:
    - Klesges 2006 reported a statistically significant effect. With adjustments for clustering and predictors, the result for continuous abstinence at one year was odds ratio (OR) 1.23 (95% CI 1.07 to 1.41, n = 33,215). Crude abstinence rates were 15.47% versus 13.74%.
    - Klesges 1999: An earlier study of 25,996 participants reported 18% abstinence in the intervention group compared with 17% in the control group, however the denominators for these percentages were unclear.
    - Conway 2004: A study of 2781 female naval recruits provided the intervention after the end of training and did not detect an effect of mail (RR 1.03, 95% CI 0.93 to 1.14) or phone intervention (RR 0.93, 95% CI 0.84 to 1.04); fewer than 3% of participants called the helpline for counselling.

Behavioural interventions for unaided abstainers (Figures 7-8; GRADE profile 3):

All studies in this meta-analysis investigated low intensity interventions.

Pharmacological interventions for short-term unaided abstainers (Figure 9; GRADE profile 4)

In both of these studies, the period of unassisted abstinence was short, and these studies were distinct from the studies investigating pharmacological interventions in assisted abstainers, in which a more extended period of abstinence was required before the relapse prevention phase was initiated.

Behavioural interventions for assisted abstainers (Figures 10-12, 23; GRADE profile 5):

This meta-analysis compared the most intensive intervention with the least intensive control in the studies with more than two arms, except in McDaniel 2015, where two intervention arms of differing intensities were listed separately compared with a split control group. Livingstone-Banks (2019) report that using different comparison conditions did not change the conclusion.

No publication bias was observed in the funnel plot.

Pharmacological interventions for assisted abstainers (Figure 13-16; GRADE profile 6):

Varenicline vs placebo: Two studies investigating the effect of varenicline were not meta-analysed due to populations being heterogeneous (Tonstad 2006 in a general population, Evins 2014 in a population with diagnosed schizophrenia or bipolar disease), and interventions being heterogeneous (Evins 2014 supported by a tapering schedule of relapse prevention focused CBT, Tonstad 2006 a drug-only intervention).

Smokers, contact time matched (Figure 17-18; GRADE profile 7):

In ten studies, intervention and control conditions were matched for the amount of contact. Eight used a group format for behavioural intervention (Hall 1984; Davis 1986; Curry 1988; Emmons 1988; Buchkremer 1991 1; Buchkremer 1991 2; Becona 1997; Schroter 2006) and two used an individual counselling format (Niaura 1999; Schmitz 1999). Three provided pharmacotherapy in all treatment conditions (Emmons 1988; Buchkremer 1991 1; Buchkremer 1991 2). In one study, a factorial design was used to test nicotine gum against no gum (Niaura 1999).

Smokers, contact time not matched - behavioural (Figure 19-20; GRADE profile 8-9):

Face to face: Seven studies compared longer and shorter programmes. The relative intensity of the common cessation programme and of the additional relapse prevention component was variable. Studies were subgrouped according to whether the control group received more than four sessions. Only two studies had control groups with four or fewer sessions (Hall 1985, Lifrak 1997).

Separate meta-analysis was conducted for other modes of contact.

Smokers, contact time not matched – combined behavioural and pharmacological (Figure 21; GRADE profile 9)

One study combined NRT with proactive telephone counselling for extended time periods compared with short time periods (Joseph 2011)

Economic evidence

Included studies

2,439 records were assessed against the eligibility criteria for review question.

2,410 records were excluded based on information in the title and abstract. One reviewer assessed all of the records and a second reviewer blind-screened 10% of the records. The level of agreement between the two reviewers was 100%.

The full-text papers of 29 documents were retrieved and assessed and 9 studies (reported in 11 documents) were assessed as meeting the eligibility criteria. One reviewer assessed all of the full texts and a second reviewer blind-screened 10% of the records. The level of agreement between the two reviewers was 100%. 9 studies (reported in 11 documents) were included.

Excluded studies

18 full text documents were excluded for this question. The documents and the reasons for their exclusion are listed in Appendix K – Excluded studies. Documents were excluded for the following reasons: ineligible outcomes (n=11), ineligible patient population (n=6) and ineligible intervention (n=1). The selection process is shown in Appendix G.

Summary of studies included in the economic evidence review

The studies are presented by sub-group. Table 7 presents 5 studies that used data from randomly assigned abstainers. Table 8 presents 1 study that used effectiveness data for the interventions from both randomly assigned abstainers and other participants assigned before their quit date. Table 9 presents 3 studies that used effectiveness data for the main interventions being assessed, from studies that randomly assigned abstainers, but also used effectiveness data for some comparators from other studies, which assigned participants after their quit date.

Table 7: Summary of the studies that randomly assigned abstainers and were included in the economic evidence review for preventing relapse (n=5)

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Blyth 2015 (UK) Population: Carbon monoxide (CO)-verified, 4-week quitters treated in National Health Service (NHS) Stop Smoking Clinics Sample size: 1,404 quitters Study aim: to evaluate the effectiveness and cost-effectiveness	Minor limitations [a]	Directly applicable [b]	None	**Mean costs per participant [c]** **Provision of: Forever Free Booklets**: £20.78. **NHS costs (12 months)** Forever Free booklet: £553.78 Leaflet: £657.95 [d] **NHS + individual medication costs (12 months)**	**Quality-adjusted life years (QALYs) (12 months)** Forever Free booklet: 0.753 (standard deviation (SD) 0.204) Leaflet: 0.747 (SD 0.196) **Proportion of prolonged abstinence (12 months)**	**Incremental costs [e] (mean; 95% confidence interval)** *Forever Free booklet vs leaflet* NHS perspective: –£84.49 (–£280.96 to £111.98) NHS perspective plus participant medication costs:	Difference in QALYs was not reported.	**Incremental net benefit (assuming a QALY value of £20,000)** Forever Free booklet NHS perspective: £74.79 NHS plus participant medication costs: £78.20	A non-parametric bootstrap analysis was conducted to estimate cost-effectiveness acceptability curves (CEACs). The CEAC showed that there is a large uncertainty associated with the baseline result, as the Forever Free booklet intervention has only a 64.4% probability of being cost-effective at a £20,000 per QALY threshold (NHS perspective) and a

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
of a set of eight Forever Free booklets in preventing smoking relapse in short-term quitters Intervention: Full pack of eight Forever Free booklets • Booklet 1 is a brief summary of all issues relevant to smoking relapse prevention • The remaining seven booklets provide more extensive information on important issues for relapse prevention Comparator:				Forever Free booklet: £578.14 Leaflet: £674.87	Forever Free booklet: 36.9% Leaflet: 38.6% Difference not statistically significant.	–£87.89 (–£284.33 to £108.54)			66.1% probability using the NHS plus participant medication costs perspective.

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
The Leaflet "Learning to Stay Stopped" containing brief but comprehensive information on issues related to smoking relapse									

Abbreviations: CEAC: cost-effectiveness acceptability curve; CO: carbon monoxide; NHS: National Health Service; QALYs: Quality-adjusted life-years; RCT: randomised controlled trial; SD: standard deviation; UK: United Kingdom

a) The analysis was based on an economic evaluation conducted alongside a randomised controlled trial (RCT) with a large sample size, which should have ensured high internal validity. A relatively short time horizon was considered and some future savings and benefits might have been omitted. Higher incremental costs in the control arm may have been due to an outlier.
b) The analysis was conducted in the UK and from the NHS perspective.
c) NHS costs included booklet costs (intellectual property, adaptation, printing and postage), *and* healthcare resources (NHS Stop Smoking Clinic visits and phone calls, stop smoking aids and materials, GP visits, and hospital admissions. Individual medication costs were stop smoking aids paid for by individuals.
d) The major difference in costs was due to increased hospital admissions in the control arm (£221.67 vs. £338.08) where one person in the control group reported spending 98 days in hospital. Use of other healthcare resources was similar across both arms.
e) Results adjusted for covariates in seemingly unrelated regression analysis.

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Bolin 2009 (Sweden) Population: All adult smokers motivated to	Minor limitations [a]	Partly applicable [b]	Effectiveness rates were imputed from a study by Tonstad *et al*. [c]	**Intervention Cost (per patient)** [d] Varenicline (12 weeks): €452 Varenicline (12 + 12	Only incremental QALYs were reported	**Incremental costs (all patients, men)** Varenicline (12 + 12 weeks) vs	**Incremental QALYs (all patients, men)** Varenicline (12 + 12 weeks) vs	**Incremental cost per QALY (excluding indirect effects)** Varenicline (12 + 12 weeks) vs	Both univariate and stochastic sensitivity analyses were conducted.

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
quit (25% of the smoking population) Cohort size: 168,844 males and 208,737 females Study aim: to evaluate the cost-effectiveness of an additional 12-week treatment with varenicline for abstainers who had successfully completed an initial 12-week treatment Intervention Varenicline (12 + 12 weeks): for smoking cessation plus 12 weeks of varenicline maintenance for quitters			The time horizon is assumed to be 50-year	weeks): €705		varenicline (12 weeks) Intervention costs: €42,733,723 Health care costs [e]: -€13,162,508 **Incremental costs (all patients, women)** Varenicline (12 + 12 weeks) vs varenicline (12 weeks) Intervention costs: €52,830,477 Health care costs: -€18,996,258	varenicline (12 weeks): 4,185 **Incremental QALYs (all patients, women)** Varenicline (12 + 12 weeks) vs varenicline (12 weeks): 4,760	varenicline (12 weeks) Men: €7,066 Women: €7,108 **Incremental cost per QALY (including indirect effects)** Varenicline (12 + 12 weeks) vs varenicline (12 weeks) Men: €24,149 Women: €24,436	The time-horizon of the analysis was the parameter with the largest impact on results. For example, when decreasing the time horizon to 10 years, the incremental cost per QALY for varenicline (12 + 12 weeks) increased to €93,583 for men and €141,197 for women [f]. The stochastic sensitivity analysis showed that at a threshold of €25,000 per QALY the probability for varenicline (12 + 12 weeks) to be cost-effective was over 80% for both men and women (this was only presented graphically).

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Comparator Varenicline (12 weeks): for smoking cessation plus 12 weeks of placebo for quitters									

Abbreviations: QALYs: Quality-adjusted life-years; RCT: randomised controlled trial

a) Minor limitation due to level of reporting: no description was provided regarding production and consumption costs; results only reported incremental values rather than total costs and QALYs per patient, which would have been more useful.
b) The interventions considered appear relevant to the UK context, but caution is required in transferring the results of this study to the UK given the differences in prices between the UK and Sweden.
c) The study conducted a randomised control trial (RCT) on smokers who had successfully quit after an initial 12-week varenicline therapy. The 1210 ex-smokers were randomized to a 12-week double-blind treatment phase of either varenicline or placebo.
d) Intervention costs include drug cost, GP visits and motivational support (nurse).The difference between initial 12-week treatment and subsequent 12-week treatment is not proportion (i.e. double) result of the necessity to titrate the initial treatment schedule, and a reduction in the proportion of subjects randomized to the second phase of the study.
e) Healthcare costs were assigned for treatment of smoking related comorbidities which included COPD, Lung cancer, coronary heart disease, and stroke. Quit rates are the key driver in differences to healthcare costs as these affect the number of smokers and smoking related comorbidities throughout the model.
f) Longer term time horizons apply increased costs, disutility and life years lost due to smoking related morbidities when compared with shorter time horizons. Interventions associated with higher quit rates are more cost-effective when time horizons are increased, and less cost-effective when they are decreased.

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Brandon 2003 (USA) Population: Ex-smokers who	Major limitations [d]	Partly applicable [e]	The study provided inadequate information about the	NR	**Percentage of participants smoking at 12-month follow-up** [f]	NR	NR	**Cost (per person) of relapse prevention during the 12-**	Not investigated

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
self-reported abstaining from smoking for at least 7 days at the time of the baseline questionnaire. Sample size: 584 Study aim: to assess the cost per relapse avoided in the USA using data from a randomised controlled trial (RCT) Interventions: • Mailings only [a]: a series of "Stay Quit" booklets sent regularly over a 12-month period • Hotline only [b]: access to a toll-free telephone hotline			sources of data and the study methods		Subgroup abstinent < 3 months at baseline: Mailings: 11.9% No mailings: 35.0% Subgroup abstinent for 3 to 7 months at baseline: Mailings: 11.9% No mailings: 8.9% Subgroup abstinent for 7 to 18 months at baseline: Mailings: 7.0% No mailings: 4.0% Subgroup abstinent for more than 18 months at baseline: Mailings: 4.0% No mailings: 5.1%			**month follow-up** Mailings vs no mailings Whole sample: $174 Participants who had been abstinent for less than 3 months at baseline: $126	

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
number with trained operators • Combination of mailings and hotline Comparator: • No intervention [c]									

Abbreviations: CEA: cost-effectiveness analysis; NR: not reported; RCT: randomised clinical trial; USA: United States of America

a) Participants in the repeated-mailings intervention received a series of "Stay Quit" booklets through the mail. A booklet was mailed immediately after enrolment and at 1, 2, 3, 5, 7, 9, and 12 months thereafter. The first booklet included an introduction to the basic relapse-prevention principles and techniques, similar to the information packet sent to participants in the other two interventions. The remaining seven booklets included more extensive information on a topic related to maintaining abstinence.
b) Participants assigned to the hotline intervention received the same relapse-prevention material as participants in the control condition, plus a laminated wallet card with the toll-free telephone hotline number. The card instructed participants to call the number for any of the following reasons: to ask questions about smoking or remaining abstinent; if they were experiencing a smoking-related crisis; if they had "slipped"; or if they just needed to talk to someone. Operators were trained to assess the caller's current situation, provide advice based on relapse-prevention theory and research, and provide social support. Although telephone calls were intended to be subject-initiated, a backup strategy was employed for proactive calls to participants who did not call the hotline over any 3-month period. Participants had access to the hotline for 12 months.
c) A minimum contact control condition comprising a single mailing of basic smoking cessation and relapse-prevention advice.
d) The study was a feasibility study and did not report detailed methods and sources of data, particularly with respect to the economic side of the analysis, making assessment of the study quality difficult.
e) The interventions under examination might be relevant to the UK context, but caution is required when transferring the results of this study given the differences in prices and health care systems between the USA and the UK.
f) Smoking status was identified through a self-completed questionnaire at 12 months, which was returned by 76% (446) subjects, with equivalent return rates across trial arms.

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Brandon 2004 & Chirikos 2004 (USA) Population: individuals who had abstained from smoking for at least 1 week, any current smoker who reported planning to quit within the next 6 months and any former smoker who had been abstinent for no more than 6 months Sample size: 431 Study aim: to assess the cost-effectiveness of smoking relapse prevention interventions designed to	Minor limitations [c]	Partly applicable [d]	The same analysis was reported in two publications. The main study was Brandon 2004.	NR	NR	**Incremental costs** [e] Massed mailing vs MCC: $21.25 Repeated letters vs MCC: $26.00 Repeated mailing vs MCC: $43.94	**Incremental 24-month abstinence** [f] Massed mailing vs MCC: 11.4% Repeated letters vs MCC: 2.4% Repeated mailing vs MCC: 12.2% **Incremental QALYs** [g] Massed mailing vs MCC: 0.2561 Repeated mailing vs MCC: 0.2741 QALYs for repeated letters vs MCC were not calculated as there was no statistically significant difference	**Incremental cost per 24-month abstinence** Massed mailing vs MCC: $186 Repeated mailing vs MCC: $360 **Incremental cost per QALY** Massed mailing vs MCC: $83 Repeated mailing vs MCC: $160	NR

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
keep quitters from resuming the use of cigarettes Interventions: • Massed mailing: eight "Forever Free" booklets (FFB) [a] at study enrolment. No further contact until the 12-month follow-up. • Repeated letters [b]: A single FFB followed by seven brief letters sent at the same intervals as the booklets were sent to the repeated-mailings group (1, 2,							between the interventions.		

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
3, 5, 7, 9, and 12 months). • Repeated mailings: participants received the series of eight FFB through the mail. A booklet was mailed immediately after a participant enrolled and then at 1, 2, 3, 5, 7, 9, and 12 months. Comparator: • Minimum contact comparison (MCC): participants received only a single FFB at the time of enrolment.									

Abbreviations: CUA: cost-utility analysis; FFB: Forever Free booklets; MCC: minimum contact comparison; QALYs: quality-adjusted life years

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

a) The Forever Free booklets covered topics including (a) an introduction and description of nicotine dependence, (b) the stages of quitting, (c) situations that are high risk for relapse, (d) ways of coping with urges to smoke, (e) suggestions for making lifestyle changes, and (f) the abstinence violation effect and ways to handle initial slip.
b) The letters included (a) two short paragraphs of supportive messages (e.g., "Congratulations, and keep up the good work," "Remember that quitting smoking is the single most important health decision that most people can make"), (b) emphasized the importance of continued commitment (e.g., "If you keep trying, you can succeed"), and (c) encouraged another quitting attempt if relapse had occurred (e.g., "Most people require several attempts at quitting, so please don't give up").
c) There may have been self-selection as participants responded to advisements for relapse prevention programs and may not be representative of the overall population of ex-smokers; the study relied on self-reported outcomes and didn't confirm abstinence medically; the racial and ethnic distribution of the sample may not be representative of the general population (92% Caucasian).
d) The interventions under examination might be relevant for the UK context, but caution is required when transferring the results of this study given the differences in prices and health care systems between the USA and the UK.
e) Intervention costs included materials (booklets), time and-motion estimates of clerical input weighted by the hourly wage rate of US correspondence clerks, an estimate of other overhead expenses, and costs of smoking cessation methods. Costs associated with smoking related morbidities *were not* included.
f) Abstinence was assessed at 12, 18 and 24 months via a questionnaire.
g) QALYs were calculated by applying utility weights from the literature by smoking status.

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Brandon 2012 (USA) Population: Pregnant women who smoked for at least one year before pregnancy and had quit, or in anticipation of	Minor limitations [c]	Partly applicable [d]	The series of FFBs were also used in the following studies: Blyth (2015), Brandon (2003) (referred to as "Stay Quit Forever") and Brandon (2004)	**Total cost per participant** [e] FFB: $53.60	**Percentage abstinent** [f] At 8 months post-partum FFB: 69.6% UCC: 58.5% At 12 months post-partum FFB: 66.2% UCC: 58.6%	NR	NR	**Incremental cost per additional abstinence at 12 months post-partum** FFB vs UCC: $248	NR

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
quitting, during pregnancy Sample size: 504 Study aim: to test a series of self-help booklets designed to prevent smoking relapse in pregnant and postpartum women Intervention: • 10 Forever Free Booklets [a] (FFB): participants received the series of relapse prevention booklets, mailed until 8 months postpartum. The original FFBs were									

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
customised to pregnancy and there was greater emphasis on social support and pregnancy-specific stressors Comparator: • Usual care control (UCC): women received 2 high-quality publications, a copy of the National Cancer Institute Booklet, “Clearing the Air”, and the American Cancer Society pamphlet “Living Smoke-free for You and Your Baby” [b]									

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

Abbreviations: CEA: cost-effectiveness analysis; FFB: Forever Free booklets; RCT: randomised clinical trial; UCC: usual care control.

a) *FFBs include information about the nature of tobacco dependence, instruction in the use of cognitive and behavioural skills to deal with urges to smoke, awareness of high-risk "triggers" to smoke, strategies for managing an initial slip or lapse, and specific health information. The series included 2 pregnancy specific booklets: "A Time of Change" delivered shortly before a participant's due date, and "Partner Support" designed to be shared with the participant's partner. Booklets were distributed in a sequence and timing designed to provide timely content over the pregnancy and postpartum period. The full FFB package included 4 booklets (Overview; Smoking Urges; Smoking and Health; A Time of Change) mailed over equal intervals between the date of a participant's enrolment in the study and her expected due date, and 5 booklets (What If You Have a Cigarette? Smoking, Stress and Mood; Lifestyle Balance; Smoking and Weight; Life Without Cigarettes) mailed at 1, 2, 3, 4, 6, and 8 months postpartum. The "Partner Support" booklet was mailed with the first booklet, including instructions to deliver it to the participant's primary partner.*

b) *The National Cancer Institute Booklet, "Clearing the Air" was a 36-page, comprehensive guide toward quitting smoking, with seven pages dedicated to relapse prevention. However, the content was not customized for pregnant or postpartum women. The American Cancer Society pamphlet "Living Smoke-free for you and your baby" described the benefits of quitting smoking during pregnancy and staying abstinent after the baby is born.*

c) *The study presented some minor limitations associated with the self-selection of participants (the study sample may not be representative of the overall population of ex-smokers), the reliance on self-reported outcomes; and the fact that treatment was significantly more effective only in the subgroup of women from low-income households.*

d) *The interventions under examination might be relevant for the UK context, but caution is required when transferring the results of this study given the differences in prices and health care systems between the USA and the UK.*

e) *Costs include printing and delivery of booklets; labour costs associated with enrolling and tracking users; postage; and other supplies and overheads. Costs of usual care are not reported.*

f) *7 day point-prevalence abstinence – assessed via questionnaire. Carbon monoxide and saliva was confirmed in a sub-sample who reported abstinence at any one of the follow up points and lived with 100 mile radius (22 women), these being 95% consistent with self-reported figures.*

Table 8: Summary of a randomised controlled trial that randomly assigned abstainers and smokers before their quit date and that was included in the economic evidence review for preventing relapse (n=1)

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Ruger 2008 (USA) Population: Low-income pregnant women (less than 28 weeks gestation), receiving prenatal care Sample size (baseline non-smokers): 57 Study aim: to estimate the cost-effectiveness of motivational interviewing (MI) compared with usual care (UC) for low-income pregnant women Intervention	Minor limitations [c]	Partly applicable [d]	An economic evaluation alongside a randomised controlled trial (RCT) with a lifetime modelling time horizon	**Cost of intervention (per patient)** [e] MI: US$309.20 UC: US$4.85	**Relapse prevention rate (per patient)** [f] MI: 0.43 UC: 0.18 **Total LYs** [g] **(per patient)** MI: 0.61 UC: 0.26 **Total QALYs (per patient)** MI: 0.83 UC: 0.35	**Incremental costs** MI vs UC: US$304	**Incremental effects** Additional relapse prevented MI vs UC: 0.25 **Incremental life-years** MI vs UC: 0.36 **Incremental QALYs** MI vs UC: 0.49	**Incremental cost per relapse prevented** MI vs UC: US$1,217 **Incremental cost per LY saved** MI vs UC: US$851 **Incremental cost per QALY gained** MI vs UC: US$628	Univariate and multivariate sensitivity analyses were carried out on selected inputs. The inclusion of maternal medical cost savings for MI (=$6000 per participant) resulted in MI dominating usual care for relapse prevention. The inclusion of $1000 neonatal cost savings for MI during the first year of life resulted in the MI intervention dominating usual care for relapse prevention. Increasing MI's effectiveness by around 15%

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
MI: • Individually tailored to each woman's stage of readiness • Delivered by public health nurses • Women received an average of three home visits • Sessions lasted 1 hour • Participants received a self-help smoking cessation manual [a] Comparator UC: • Standard prenatal care from the woman's health-care provider at the clinic site [b]									resulted in an approximately 36% decrease in the incremental cost per QALY ratio. In two-way sensitivity analyses, MI was still relatively cost-effective for relapse prevention ($17,300/QALY saved) even if it cost as much as $2,000/participant and was less effective.

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

Abbreviations: MI: motivational interviewing; NHS: National Health Service; RCT: randomised controlled trial; UC: usual care; UK: United Kingdom.

a) The MI sessions: 1) educated clients about the impact of smoking on mothers, foetuses, and new-borns; 2) helped clients evaluate their smoking behaviour; 3) helped increase self-efficacy for smoking cessation and abstinence; 4) provided information on reducing exposure to environmental tobacco smoke and set goals on changes in smoking; and 5) provided feedback about household nicotine levels.
b) An up-to-5-minute intervention outlined the harmful effects of smoking during and after pregnancy. Self-help materials were also provided.
c) The study enrolled a small sample of a restricted patient population (low-income) in a specific geographic location meaning results may not be generalizable to the population; there is uncertainty in the data on long-term morbidity and mortality for children related to smoking-related illnesses.
d) The study was carried out in the USA thus caution is required when extrapolating the study results to the UK setting.
e) Costs components for the base case analysis were limited to intervention costs only (staff time, training time, self-help material costs, cost of analysing environmental nicotine use in MI. Neonatal healthcare resources during first year of life (intensive care, acute conditions, chronic conditions) and maternal healthcare resources (treatment for cardiovascular and lung disease) were included in a scenario analysis by identifying costs for smokers/ non-smokers from literature sources.
f) Self-reported abstinence over in the last 30 days.
g) Quit rates were converted into Life Years and QALYs using data from published literature (American Cancer Society's Cancer Prevention Study. Separate estimates were obtained for female smokers and former smokers by age group and duration of quitting using a Markov model which allowed for a 35% probability of relapse after 1-year.

Table 9: Summary of the studies used information from multiple trials that randomly assigned abstainers and smokers after their quit date and that were included in the economic evidence review for preventing relapse (n=3)

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Knight 2010 (USA) Population: All adult smokers motivated to quit (25% of smoking population) Cohort size: 11.9 million subjects Study aim: to estimate the cost-effectiveness of an extended (12 + 12 weeks) course of varenicline using the Benefits of Smoking Cessation on Outcomes (BENESCO) model	Minor limitations [b]	Partly applicable [c]	None	**Intervention Cost (per patient)** [d] Varenicline (12 + 12 weeks): $603.89 Varenicline (12 weeks): $370.96 Bupropion: $264.40 NRT: $405.47 Unaided cessation: $0 **Lifetime costs [e] (per population, millions)** Varenicline (12 + 12 weeks): $328,528 Varenicline (12 weeks): $328,279 Bupropion: $330,689 NRT: $332,622	**Lifetime QALYs (1000s)** Varenicline (12 + 12 weeks): 174,630 Varenicline (12 weeks): 174,373 Bupropion: 173,999 NRT: 173,970 Unaided cessation : 173,413 1-year quit rates [f]: Varenicline (12 + 12 weeks): 27.7%% Varenicline (12 weeks): 22.9% Bupropion: 15.9% NRT 15.4% Unaided	**Incremental population lifetime costs (millions) vs varenicline (12 weeks)** Varenicline (12 + 12 weeks): $249 [g] Bupropion: $2,161 NRT: $1,933 Unaided cessation: $661	**Incremental population QALYs (1000s) vs varenicline (12 weeks)** Varenicline (12 + 12 weeks): 257 Bupropion: -631 NRT: -29 Unaided cessation: -554	**Incremental cost per QALY vs varenicline (12 weeks)** Varenicline (12 + 12 weeks): $972 Varenicline (12 + 12 weeks) dominated all the other interventions	The probabilistic sensitivity analysis (PSA) showed that varenicline (12 + 12 weeks) had a 73% probability of being cost-effective at a willingness to pay threshold of $30,000 per QALY

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Intervention [a] Varenicline (12 + 12 weeks): 12 weeks for smoking cessation plus 12 weeks of varenicline for maintenance Comparator Varenicline (12 weeks): 12 weeks for smoking cessation plus 12 weeks of placebo Bupropion: 12 weeks for smoking cessation Nicotine replacement therapy (NRT): 12 weeks for smoking cessation Unaided cessation: no				Unaided cessation: $333,283	cessation 5%.				

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
further description was given									

Abbreviations: BENESCO: Benefits of Smoking Cessation on Outcomes; NRT: nicotine replacement therapy; PSA: probabilistic sensitivity analysis; QALYs: Quality-adjusted life-years; RCT: randomised controlled trial

a) All Varenicline cessation and maintenance doses were 1mg taken twice daily. Details on the dose of bupropion was not provided. NRT treatments included chewing gum, transdermal patches, nasal spray, inhalers and tablets, information on dose is not provided.
b) The study was based on valid sources of effectiveness data and the use of a Markov model that estimated lifetime costs and QALYs represents a strength of the analysis. Some more recent efficacy data would have been useful.
c) The interventions considered appear to be relevant to the UK context, but caution is required in transferring the results of this study given the differences in prices between the USA and the UK.
d) After 12 weeks of varenicline, it is assumed 63% of subjects will commence a further 12 weeks for maintenance. Hence, varenicline (12 + 12 weeks) costs are calculated as two times the 12 week course for 63% of subjects and one times the cost for the remained. A physician visit is included for each 12 week period.
e) The BENESCO model includes costs of smoking relating comorbidities (lung cancer, stroke, coronary heart disease, chronic obstructive pulmonary disease and asthma). All treatment costs for smoking related morbidities are drawn from published literature. Differences in lifetime costs are driven by differences in quit rates which impact on the ratio of smokers/non-smokers throughout the model. No indirect costs were included e.g. increased productivity, second hand smoke effects etc.
f) 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.
g) Incremental costs driven by higher intervention costs at delivery which exceeded cost savings due to reductions in smoking related comorbidities.

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Taylor (2011) & Coleman (2010) (UK) Population: Smokers who	Minor limitations [c]	Directly applicable [d]	The study was based on a health technology assessment (Coleman 2010).	**Total costs (per patient)** [e] Bupropion: £6,755	**QALYs (per patient)** [f] Bupropion: 12.76	**Incremental costs (per patient)** Bupropion vs no	**Incremental QALYs (per patient)** Bupropion vs no	**Incremental cost per QALY** [g]	All model inputs were varied across reasonable and published ranges of values. Base case results were robust to

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
had recently initiated quit attempts ('recent quitters') representative of England and Wales population. Sample size: hypothetical cohort of 1000 quitters. Study aim: To determine the incremental cost-effectiveness of nicotine replacement therapy (NRT), bupropion and varenicline for preventing relapse to smoking among abstinent smokers Interventions:			Time horizon: Lifetime	No intervention: £6,822 NRT: £7,050 No intervention: £7,039 Varenicline: £6,794 No intervention: £6,704	No intervention: 12.69 NRT: 12.63 No intervention: 12.58 Varenicline: 12.79 No intervention: 12.75 **12 month abstinence rates:** Bupropion: 37% No intervention: 29% NRT: 23% No intervention: 18% Varenicline: 41%	intervention: -£68 NRT vs no intervention: £12 Varenicline vs no intervention: £90	intervention: 0.07 NRT vs no intervention: 0.04 Varenicline vs no intervention: 0.04	Bupropion dominates no intervention NRT vs no intervention: £265 Varenicline vs no intervention: £2106	wide ranges of variations. Cost-effectiveness ratios only exceeded the UK National Institute of Health and Care Excellence (NICE) benchmark of £20,000 per QALY when drug treatment effects were postulated to last for no longer than 1 year; or, for NRT and varenicline, when efficacy was reduced to 10% of that observed in clinical trials.

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
• Bupropion: one daily tablet for 6 days followed by 2 daily tablets for a 7 week period • Nicotine replacement therapy (NRT): 12 weeks of daily nicotine patches [a] • Varenicline: 2 tablets daily for 77 days Comparator: No intervention [b]					No intervention : 36%				

Abbreviations: CUA: cost-utility analysis; HTA: health technology assessment; NHS: National Health Service; NRT: nicotine replacement therapy; UK: United Kingdom.

a) It was recommended that 15mg patches were used daily for 8 weeks, followed by 10mg patches used daily for 2 weeks, then 5mg patches used daily for 2 weeks. It was assumed unlikely that the full recommended course would be used, therefore an average patch use of 60.48% was assumed for the costings.

b) All interventions were compared to "no intervention". However, the abstinence rates for the "no intervention" arm differed slightly across comparisons as these were obtained from separate systematic reviews. Different underlying abstinence rates explain slight difference in total costs/QALYs for "no intervention".

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

c) The study was based on a health technology assessment with a robust methodology. Some conservative assumptions were applied which may have resulted in underestimating incremental cost-effectiveness.
d) The study was carried out in the UK and included the relevant population. Hence, it is directly applicable.
e) Cost components included intervention costs and healthcare resources for smoking related morbidities (lung cancer, stroke, coronary heart disease, myocardial infarction, COPD).
f) Quality of life detriments were applied to smoking related comorbidities (lung cancer, stroke, coronary heart disease, myocardial infarction, COPD). Life years were based on age-specific mortality rates for smokers and non-smokers.
g) Differences in incremental costs and QALYs were driven by higher quit rates resulting in fewer smokers and smoking related comorbidities/deaths in the intervention arms.

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Von Wartburg 2014 (Canada) Population: Adult smokers who are assumed to make a quit attempt within the next 30 days Cohort size: 1,275,481 Study aim: to estimate the cost-effectiveness	Minor limitations [c]	Partly applicable [d]	The study used the same model and efficacy rates as Knight et al. (2010) but applied the BENSCO model to a Canadian population.	**Lifetime costs (millions) – Payer perspective [e]** Varenicline (12 weeks): Can$25,369 Varenicline (12 + 12 weeks): Can$25,426 Bupropion: Can$25,510 NRT: Can$25,705 Unaided cessation: Can$25,746	**Lifetime QALYs (1000s)** Varenicline (12 weeks) 15,398 Varenicline (12 + 12 weeks) 15,413 Bupropion 15,376 NRT 15,374 Unaided cessation 15,342 **1-year quit rates [g]:**	**Lifetime costs (millions) – Payer perspective (vs varenicline 12 weeks)** Varenicline (12 + 12 weeks) : Can$56 Bupropion: Can$140 NRT: Can$336 Unaided cessation: Can$376	**Incremental QALYs (1000s) vs varenicline (12 + 12 weeks)** Varenicline (12 weeks): -15 Bupropion: -37 NRT: -39 Unaided cessation: -71	**Incremental cost per QALY - Payer perspective [h]** Varenicline (12 + 12 weeks) vs varenicline (12 weeks): Can$3,758 Varenicline (12 + 12 weeks) dominated all the other interventions. **Incremental cost per QALY - Societal perspective**	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 Can$30,000 per QALY compared with varenicline (12 weeks) and 100% compared with the other interventions (from the payer perspective).

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
of an extended (12 + 12 weeks) course of varenicline using the Benefits of Smoking Cessation on Outcomes (BENESCO) model Intervention: Varenicline [a] (12 + 12 weeks) Smoking cessation for 12 weeks plus additional 12 weeks of Varenicline maintenance for quitters Comparator: Varenicline (12 weeks) for smoking cessation plus 12 weeks placebo maintenance for quitters				**Lifetime costs (millions) – Societal perspective** [f] Varenicline (12 weeks): Can$98,739 Varenicline (12 + 12 weeks): Can$98,902 Bupropion: Can$99,902 NRT: Can$100,177 Unaided cessation: Can$101,730	Varenicline (12 weeks): 22.9%, Varenicline (12+12 weeks): 27.7% Bupropion: 15.9%, NRT: 15.4%, Unaided cessation: 5%.	**Lifetime costs (millions) – Societal perspective (vs varenicline 12 – 12 weeks)** Varenicline (12 weeks): Can$645 Bupropion: Can$1,807 NRT: Can$2,082 Unaided cessation: Can$3,635		Varenicline (12 + 12 weeks) was dominant compared with all the other options.	

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Additional comparators [b]: Bupropion (12 weeks) for smoking cessation Nicotine replacement therapy (NRT) (12 weeks) for smoking cessation Unaided cessation: no further description was provided									
Abbreviations: CUA: cost-utility analysis; NRT: nicotine replacement therapy; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; RCT: randomised controlled trial									

a) All Varenicline cessation and maintenance doses were 1mg taken twice daily.
b) Details on the dose of bupropion was not provided. NRT comprised of chewing gum, transdermal patches, nasal spray, inhalers and tablets, doses were not provided.
c) The study was based on multiple RCTs. When required, conservative assumptions were made.
d) The interventions considered appear relevant to the UK context, but caution is required in transferring the results of this study given the differences in prices between Canada and the UK.
e) Cost components of the payer perspective included intervention costs (drug costs and a single GP visit) and healthcare resources to treat smoking related comorbidities (lung cancer, stroke, coronary heart disease, chronic obstructive pulmonary disease and asthma)
f) The cost components for the wider societal perspective included all those for the payer perspective and the following indirect costs: productivity benefits from improved health & reduced absenteeism, reduced tax from tobaccos sales, cost savings from reduced second-hand smoker and smoke related fires.

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
g) 1-year quit rates for Varenicline (12 + 12 weeks), Varenicline (12 weeks) and Bupropion were derived from a mixed treatment comparison of 3 RCTs which established abstinence through self-reported non-smoking and exhaled CO readings < 10 parts per million; the 1-year quit rates for NRT was obtained from a meta-analysis which confirmed abstinence through a combination of self-reported non-smoking and CO readings. h) Cost-effectiveness driven by efficacy rates which result in a higher ratio of non-smoker to smokers and fewer smoking related comorbidities/deaths.									

Economic model

The economic model used to assess the cost-effectiveness of relapse prevention interventions was an adapted version of the model previously used to inform NICE guidelines on smoking cessation [NG92]. The NG92 economic model has since been updated to inform separate questions in the current NICE scope for the new tobacco guideline, specifically on smoking cessation in the general population. It adopts an NHS/PSS perspective and in addition calculates the lost productivity due to work absenteeism for each comorbidity using a human capital approach. Two further adaptations for the relapse prevention analysis were required: first, the model was restructured such that the population entering the model was defined as "former-smokers" rather than "current smokers"; and second, the effectiveness of interventions was measured in terms of preventing smoking relapses, rather than promoting successful quit attempts.

Model Structure

The adapted relapse prevention economic model includes the same health states and structure as the cessation model for this update, these being "former smoker", "current smoker" and "dead" and is depicted in **Figure 1**. The relapse prevention model differed from the cessation model as the population enter the model in the "former smoker" rather than the "current smoker" health state. The economic analysis was conducted for two specific populations: (i) assisted abstainers, who had achieved abstinence through a formal smoking cessation intervention, and (ii) unaided abstainers who had achieved abstinence without a formal smoking cessation intervention. The effectiveness of relapse prevention interventions is included in the model as the probability of the population transitioning from the "former smoker" to "current smoker" health state after the first 12-month cycle. This probability was informed by effectiveness evidence on relapse prevention.

After the first 12-months, populations transition between each health state in annual cycles across a lifetime (100-year) time horizon. The transitions between health states are determined by the natural rate of cessation and relapse in the population each year. The model structure and epidemiological inputs after the initial 12-months are identical to the updated NG92 cessation model, with is described in full elsewhere (Report R).

The model includes six smoking related comorbidities: lung cancer (LC), coronary heart disease (CHD), myocardial infarction (MI), stroke, chronic obstructive pulmonary disease (COPD), and asthma. It uses published literature sources to establish the prevalence of LC, CHD, MI, stroke and COPD, and incidence of asthma, for smokers and non-smokers by age and gender. Each comorbidity has an associated NHS treatment cost and disutility. These costs and disutilities are applied based on prevalence and incidence rates for each cycle and summed to estimate lifetime costs and QALYs across all cycles. The model also calculates the lost productivity due to work absenteeism for each comorbidity using a human capital approach. This multiplies the percentage of days absent from work due to smoking related morbidities by mean ONS (2019) wage estimates per age and gender (ONS, 2019)[b]. A similar model structure has been used in past cost-effectiveness models for smoking interventions (PHG10, PHG45, Taylor *et al.* 2011[c].

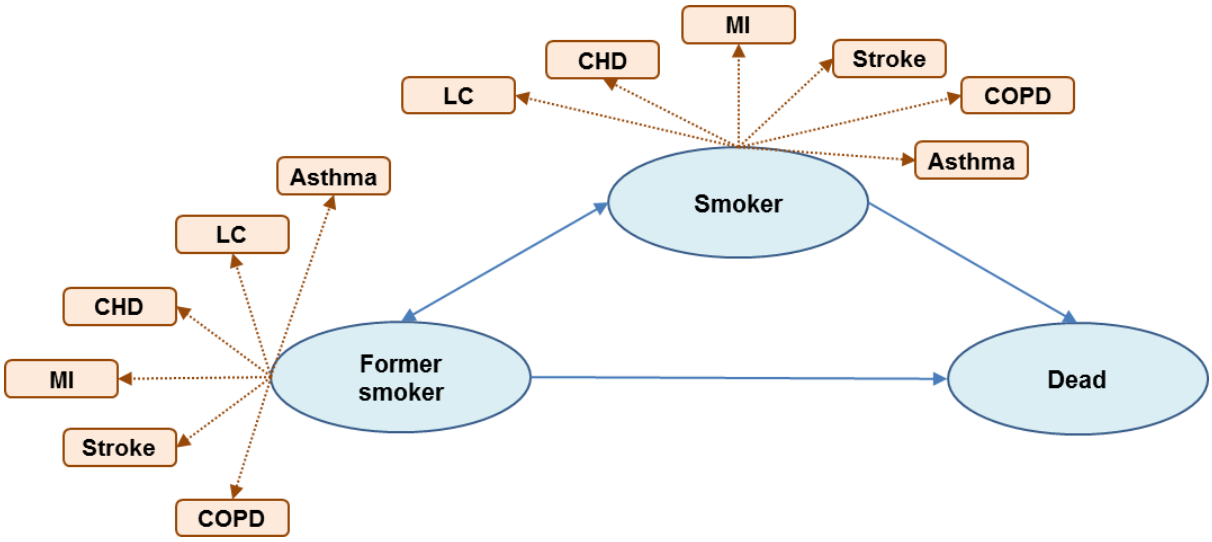
The model calculates the average lifetime costs, lifetime QALYs, and subsequent cost-effectiveness across all adult populations. Average outcomes are calculated across all populations between the ages of 12 and 100. This age range was selected as it represented

[b] ONS. Employment and labour market. People in work. . Office for National Statistics (ONS). 2019.
[c] Taylor M, Leonardi-Bee J, Agboola S, McNeill A, Coleman T. Cost effectiveness of interventions to reduce relapse to smoking following smoking cessation. Addiction. 2011 Oct;106(10):1819-1826.

the youngest and oldest ages where we could identify smoking related prevalence rates. For people aged 12 to 15 smoking was defined as smoking at least one cigarette per week based on the Action on Smoking and Health (ASH) fact sheet on young people and smoking[d]. For people aged 16 to 100 smoking was defined by self-reported status as a current, ex or non-smoker in the Health Survey for England (2019) report[e].

Average outcomes across the population are calculated by obtaining results for each specific age and applying a weighted average based on the number of people of that age in the UK population as reported by the ONS (2019) (16). For example, the model obtains results for populations specifically aged 12, then aged 13, then aged 14, 15, 16 and so on until the final age of 100. Results for people aged 12, 13, 14, …, 100 are then multiplied by the percentage of people aged 12, 13, 14 , …, 100 and summed across all ages.

Figure 1: Model structure



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

Model Parameters

All model parameter values are as reported in the economic modelling report for smoking cessation in the general population (Report Q) with the exception of intervention effectiveness (i.e. the probability of smoking abstinence) and intervention costs which were applied specifically for the relapse prevention interventions.

Assisted Abstainers

Effectiveness estimates for a population of assisted abstainers were obtained using results from the meta-analyses reported in this evidence review. The meta-analyses reported the relative risks for six interventions versus a relevant comparator indicated below:

[d] ASH. Action on Smoking and Health. Young People and Smoking. September 2019. . 2019.
[e] Health Survey for England 2018. Adults' health-related behaviours data tables (version 2). [database on the Internet]2019 [cited 03/09/2020]. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/2018.

1. Low intensity behavioural support
2. High intensity behavioural support
3. NRT short acting
4. Bupropion
5. Varenicline
6. NRT+bupropion

Unaided abstainers

Effectiveness estimates for unaided abstainers who had achieved abstinence without a formal smoking cessation intervention were obtained from the NICE evidence review N. The analysis was limited to two interventions for which effectiveness evidence was available:

1. Low intensity behavioural support
2. NRT gum

Note: The comparators were usual care and placebo for low intensity behaviour support and NRT gum respectively.

A detailed description of the model with full results and sensitivity analyses is provided in a separate economic modelling report 9Report R).

Results

The results are reported for the basecase analyses. Findings from the deterministic and probabilistic sensitivity analyses are also reported. Full details can be found in the separate economic modelling report (ref).

Assisted abstainers

Basecase results

With the exception of low intensity behaviour support, all other interventions were cost effective at a threshold of £20,000 per QALY. Moreover in the case of pharmacotherapies, the interventions were dominant (i.e. less costly and more effective than the comparator). By contrast, low intensity behaviour support was dominated (i.e. it produced fewer QALYs and was more costly than the comparator). The results for the six interventions included in the basecase analysis are shown in Table 10.

Table 10: Cost effectiveness results (per person) for assisted abstainers in the basecase analyses

	Intervention		Comparator		ICER
Intervention	**Total Costs**	**Total QALYs**	**Total Costs**	**Total QALYs**	**(£/QALY)**
Low intensity behaviour support	£10,480	15.37	£10,375	15.39	£105/-0.02 **Dominated**
High intensity behaviour support	£10,713	15.39	£10,465	15.37	£248/0.02 **£12,690**
NRT short acting	£10,731	15.30	£10,732	15.29	-£1/0.01 **Dominant**
Bupropion	£10,660	15.33	£10,701	15.30	-£40/0.04 **Dominant**
Varenicline	£10,185	15.50	£10,255	15.43	-£70/0.07 **Dominant**
NRT + Bupropion	£10,835	15.29	£10,798	15.27	£36/0.02 **£1,463**

Deterministic sensitivity analyses

Deterministic sensitivity analyses were used to investigate the sensitivity of the results to changes in the value of individual parameters in the model. The parameters included were: effectiveness estimates where the RR was varied to equal the value of the 95% upper and lower confidence intervals; intervention costs which were increased and decreased by 25% of the value used in the base case analysis; and the natural rate of smoking relapse per year which was changed from 0% in the base case to 10%. DSA were also conducted for the time horizon which was reduced to 5-years, for increased (5% costs, 5% QALYs) and decreased (1.5% costs, 1.5% QALYs) discount rates; utility values which were set equal for smokers

and non-smoker; and disutility and cost per smoking related comorbidities which were increased and decreased by 25%.

Low intensity behaviour support – there was considerable uncertainty in CE results when modifying effectiveness estimated. The DSA that applied the upper 95% CI changed low intensity behavioural support from being a dominated (i.e. more costly and less effective) to being dominant (i.e. less costly and more effective) versus usual care. Results for all of the other DSAs were robust with low intensity behavioural support remaining dominated by usual care.

High intensity behavioural support analysis – again there was considerable uncertainty in the cost-effectiveness results when the intervention effectiveness was modified: when set to the lower 95% CI the intervention was dominated by usual care equal but when set to the upper 95% CI the intervention was dominant versus usual. The results were also sensitive to relapse rates, which resulted in an ICER above the £20,000 threshold when the relapse was increased to 5% annually. High intensity behavioural support was not cost-effective for a younger population aged 20 due to reductions in incremental QALYs. However, results were consistent when varying intervention and comorbidity costs by 25%, with the ICER remaining below £20,000 for these DSAs. The ICER for high intensity behavioural support decreased slightly to £11,618 when including additional costs in the comparator equal to the costs of low intensity behavioural support (£21), the ICER decreased further to £7,582 when increasing the comparator costs to £100 per person.

NRT short acting - there was considerable uncertainty in the cost-effectiveness results when the effectiveness estimates were modified: when set to the lower 95% CI the results changed with NRT being dominated (costlier, less effective) by placebo; in contrast the upper 95% CI resulted in NRT being dominant (less costly, more effective) versus placebo . Results for all the other DSAs were robust with NRT remaining dominant or resulting in ICERs below the £20,000 threshold.

Bupropion - the cost-effectiveness results were not robust when modifying the effectiveness estimates; where the DSA applied the lower 95% CI bupropion was dominated by placebo. In contrast, when the upper 95% CI was applied, the ICER was dominant, with bupropion resulting in substantial cost savings of -£211 and health benefits of 0.09 per person. Results for all of the other DSAs were robust with bupropion remaining dominant or resulting in ICERs below the £20,000 threshold.

Varenicline – the cost effectiveness results for varenicline were robust with varenicline remaining dominant or resulting in ICERs well below the £20,000 threshold in all the DSAs.

NRT + Bupropion - there was considerable uncertainty in the cost-effectiveness results when the effectiveness estimates were modified: when set to the lower 95% CI NRT + bupropion was dominated by placebo i.e. costlier and less effective. In contrast, when set to the upper 95% CI NRT + bupropion was dominant versus placebo i.e. less costly and more effective. Results were robust for the majority of other DSAs with NRT plus bupropion remaining cost-effective versus placebo.

Probabilistic Sensitivity analyses

A PSA was conducted to explore the impact of randomly varying the value of the parameters in the model within a plausible range on the results produced by the model. The key output of the PSA is the probability the intervention is identified as cost effective vs the comparator across all random samples. The PSA was run for 3000 iterations. The results of the PSA are shown in Table 11.

Varenicline and bupropion were identified as being cost effective versus placebo in 94% and 98% of PSA iterations respectively. Low intensity behaviour support was cost-effective in 14.2% of the 3,000 iterations (Table X).

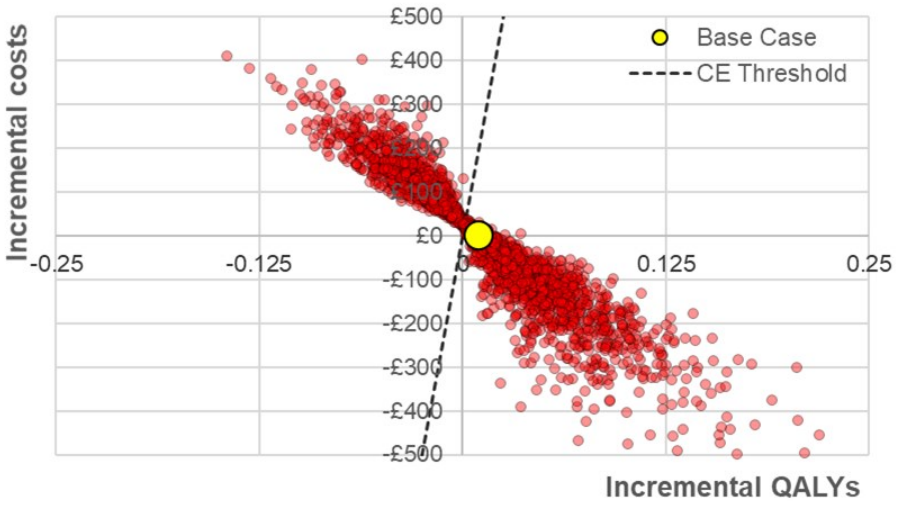
Table 11: Basecase ICERs and Probability of Cost Effectiveness of interventions versus the comparator (assisted abstainers)

	Basecase	PSA (3,000 iterations)
Intervention	**ICER (£/QALY)**	**Probability cost effective vs comparator**
Low intensity behaviour support	£105/-0.02 **Dominated**	14.2%
High intensity behaviour support	£248/0.02 **£12,690**	55.9%
NRT short acting	-£1/0.01 **Dominant**	57.7%
Bupropion	-£40/0.04 **Dominant**	93.5%
Varenicline	-£70/0.07 **Dominant**	97.8%
NRT + Bupropion	£36/0.02 **£1,463**	73.6%

The PSA results for NRT short acting versus placebo and varenicline vs placebo and illustrated in Figures X and Y below.

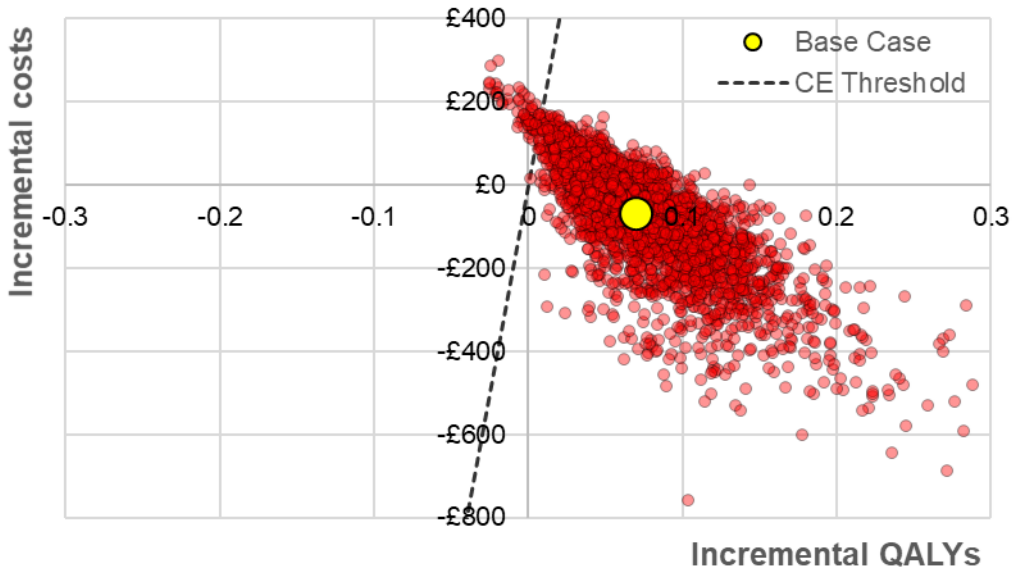
NRT short acting was identified as being cost-effective in 57.7% of the 3,000 iterations, with placebo being cost-effective in the remaining 42.3%. This reflects the results from the NICE effectiveness reviews where the lower 95% confidence interval for the RR of smoking cessation for NRT short acting versus placebo was below the line of no effect. There was considerable uncertainty regarding whether NRT short acting resulted in costs or savings vs. placebo with incremental NHS costs ranging between -£500 and £400 (Figure X).

Figure X: Scatterplot of weighted average incremental costs and QALYs for NRT short acting versus placebo (assisted abstainers)



In contrast, varenicline was identified as being cost-effective in 97.8% of the 3,000 iterations, with placebo being cost-effective in the remaining 2.2% (Fig Y). These results were driven by results from the NICE effectiveness reviews where the 95% confidence interval for the RR of smoking cessation for varenicline versus placebo was above the line of no effect. Incremental NHS costs ranged from -£800 to £250, with varenicline being cost saving versus placebo in the majority of PSA iterations.

Figure Y: Scatterplot of weighted average incremental costs and QALYs for Varenicline versus placebo (assisted abstainers)



Unaided Abstainers

Basecase results

The cost-effectiveness results found that low intensity behavioural support was dominant versus usual care being associated with a health benefit of 0.02 QALYs and incremental healthcare cost savings of £54. The analysis also found that NRT gum was dominant being

associated with a health benefit of 0.04 QALYs and healthcare cost savings of £141 see Table 12).

Table 12: Cost-effectiveness results per person for unaided abstainers in the basecase

	Intervention		Comparator		ICER
Intervention	**Total costs**	**Total QALYs**	**Total costs**	**Total QALYs**	**(£/QALY)**
Low intensity behaviour support	£10,553	15.35	£10,606	15.32	-£54/-0.02 **Dominant**
NRT gum	£10,807	15.27	£10,949	15.22	-£141/0.04 **Dominant**

Deterministic sensitivity analysis

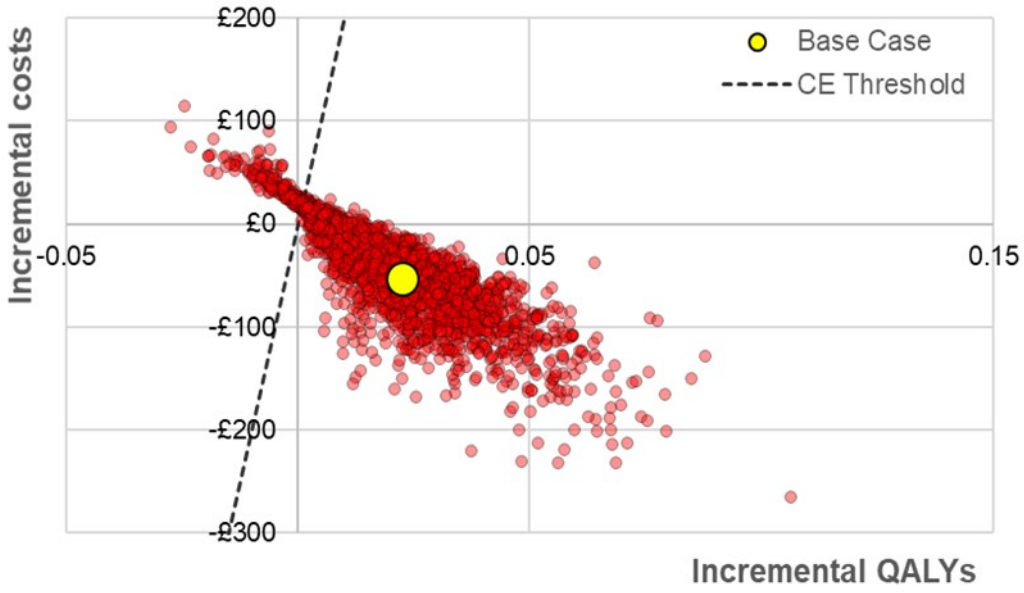
Low intensity behaviour support - the cost-effectiveness results were robust for all but one of the DSAs with low intensity support remaining the cost-effective strategy versus usual care. The only DSA where low intensity behavioural support was not cost-effective in unaided abstainers was when the lower 95% CI for effectiveness was applied. In this case the intervention was less effective and therefore dominated by usual care given the costs associated with intervention delivery.

NRT gum - the base case results were robust across all DSAs, with NRT gum remaining dominant versus placebo in each instance (i.e. less costly, more effective).

Probabilistic sensitivity analysis

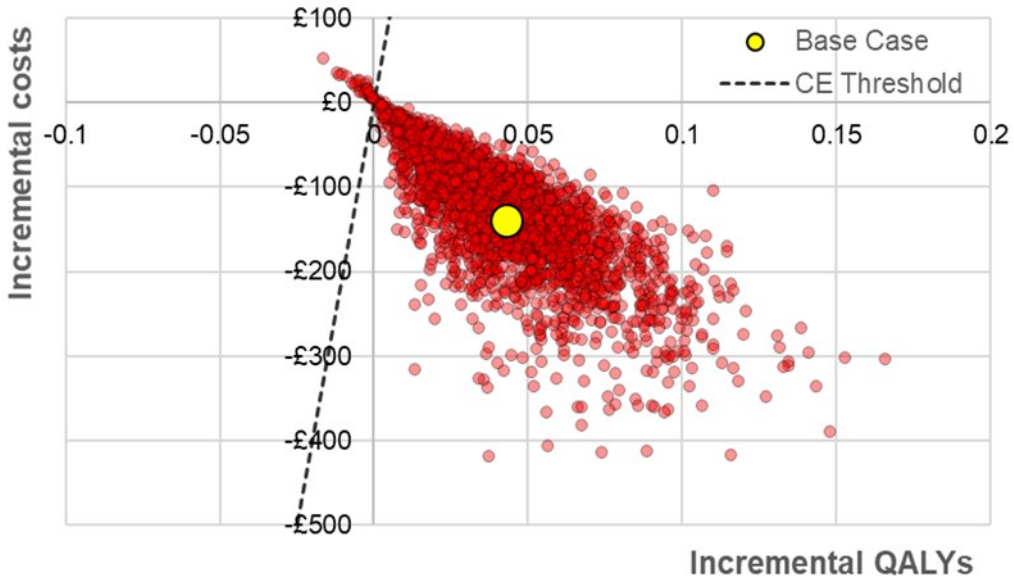
For the population of unaided abstainers, the PSA identified low intensity behavioural support as being the cost-effective strategy in 92.8% of the 3,000 iterations, with usual care being cost-effective in the remaining 7.2% The results of the PSA are illustrated in Figure Y.

Figure Y: Scatterplot of weighted average incremental costs and QALYs for low intensity behaviour support versus usual care (unaided abstainers)



For the population of unaided abstainers, the PSA identified NRT gum as being the cost-effective strategy in 99% of the 3,000 iterations, with placebo being cost-effective in the remaining 1% The results of the PSA are illustrated in Figure 10.

Figure Y: Scatterplot of weighted average incremental costs and QALYs for NRT gum versus placebo (unaided abstainers)



Summary of the evidence

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

Table 13: Evidence summary

Outcome	Population	Summary	Confidence	GRADE profile
Cessation (prevention of relapse)	Pregnant and post-partum ex-smokers	An effect was not detected of **behavioural interventions** on not smoking at last follow-up prior to delivery, or longest follow-up. • At last follow-up prior to delivery effects were not significantly different by type of intervention (self-help intervention, individual counselling or telephone counselling). • At longest follow-up, effects were not significantly different by timing of intervention (during pregnancy, during pregnancy and continuing post-partum, initiated after birth) or by prior abstinence length (less than 4 weeks, equal to or more than 4 weeks, not reported).	Last follow-up prior to delivery: LOW (8 studies) Longest follow-up: VERY LOW (13 studies)	1
	Hospitalised smokers	An effect was not detected of **behavioural interventions** or **pharmacotherapy** on not smoking at longest follow-up.	Behavioural: MODERATE (4 studies) Pharmacotherapy: MODERATE (2 studies)	2
	Unaided abstainers	An effect was not detected of **behavioural interventions** on not smoking at longest follow-up. • Those with a prior abstinence of less than 4 weeks had lower levels of cessation than those where prior abstinence was unclear or not reported but neither were significant.	LOW (5 studies)	3
	Unaided abstainers	**Nicotine gum** was effective for not smoking compared with placebo at 12 month follow-up.	MODERATE (2 studies)	4
	Assisted abstainers	An effect was not detected of **behavioural interventions** on not smoking at longest follow-up. • Effects were not significantly different by intensity of the intervention (low intensity, high intensity), or by prior abstinence length (less than 4 weeks, equal to or more than 4 weeks, not reported).	LOW (10 studies)	5
	Assisted abstainers	An effect was not detected of **NRT**, **bupropion or combination NRT and bupropion** on not smoking 12+ months/longest follow-up after quit date compared with placebo. • For **NRT** and for **bupropion**, effects were not significantly	NRT: MODERATE (2 studies) Bupropion: MODERATE	6

Outcome	Population	Summary	Confidence	GRADE profile
		different by mode or duration of intervention. • For **bupropion**, effects were not significantly different by prior abstinence length (less than 4 weeks, equal to or more than 4 weeks, not reported). Extended **varenicline** is effective for not smoking at 12+ months after quit date in the general population and in those diagnosed with severe mental illness.	(6 studies) Combination NRT and bupropion: VERY LOW (2 studies) Varenicline: General population: HIGH (1 study) Mental health population: MODERATE (1 study)	
	Smokers	Contact time matched: An effect was not detected of **relapse prevention by group/individual therapy or self-help format** as an adjunct to a cessation program on not smoking at longest follow-up.	Group/individual therapy: LOW (10 studies) Self-help: VERY LOW (1 study)	7
	Smokers	Contact time not matched: An effect was not detected of relapse prevention **face to face** interventions as adjuncts to cessation programmes on not smoking at longest follow-up. • Effects were not significantly different by intensity of control group intervention (more than four sessions, four sessions or less).	Face to face: LOW (7 studies)	8
	Smokers	Contact time not matched: Relapse prevention elements by **other modes** as adjuncts to cessation programmes are effective for not smoking at longest follow-up compared with cessation programmes only. • Effects were not significantly different by mode of additional component (telephone, print-based, computer or mobile phone). An effect was not detected of additional proactive **telephone counselling and NRT** on not smoking at longest follow-up.	Other modes: LOW (8 studies) Combination behavioural and NRT: MODERATE (1 study)	9

Health economics evidence statements

Evidence statements for the studies that randomly assigned abstainers and were included in the economic evidence review for preventing relapse during pregnancy (n=5)

- One health technology assessment (HTA) (Blyth, 2015) concluded that it is unclear whether the provision of a set of eight "Forever Free" booklets (FFB) for the prevention of smoking relapse is cost-effective compared with a single leaflet offering brief but comprehensive information on issues relating to smoking relapse, cravings and triggers, in a UK context. Although the estimated mean incremental net benefit was positive (£74.79), the probability of cost-effectiveness was estimated to be 64.4%, showing some uncertainty in study results. The economic evaluation was based on a randomised controlled trial (RCT). The trial found that there was no statistically significant difference in prolonged abstinence between the intervention and the control group. Slightly higher NHS costs were identified in the control group, largely due to increased hospital admissions where one person reported spending 98 days in hospital. The analysis was assessed as directly applicable to the review question with minor limitations.
- One cost-utility analysis (Bolin, 2009) found that 12 weeks of varenicline followed by a further 12-week course for successful quitters (varenicline 12 + 12 weeks) is a cost-effective alternative compared with varenicline for 12 weeks alone (not followed by 12-week maintenance for quitters) in a Swedish context. The analysis was based on a Markov model (BENESCO model) with a 50-year time horizon using effectiveness data from an RCT. It was found that varenicline (12 + 12 weeks) was associated with an incremental cost per quality-adjusted life year (QALY) of €7,066 in men and €7,108 in women from the health care sector perspective. The stochastic sensitivity analysis suggested that the probability of varenicline (12 + 12 weeks) being cost-effective at a willingness to pay threshold of US$30,000 was more than 80% for both men and for women. The authors concluded that varenicline (12 + 12 weeks) is a cost-effective alternative compared with varenicline 12 weeks in the Swedish context. The analysis was assessed as partly applicable to the review question with minor limitations.
- Brandon (2003) found a mailing intervention to be highly cost-effective in preventing relapse for former smokers when compared with a hotline intervention or no intervention, in a USA context. The economic evaluation estimated that the cost per relapse avoided at any point during the 12-month follow-up with mailings vs no mailings was $174 in the whole sample and $126 for the subgroup of participants who had been abstinent for less than 3 months at baseline. The authors suggested that if disseminated widely, such an approach had the potential to make a significant public health impact. The study was assessed as partly applicable to the review question. There were major limitations, as the study was a feasibility study and did not report detailed methods and sources of data, particularly with respect to the economic side of the analysis, making quality assessment difficult.
- Brandon (2004) and Chirikos (2004) reported that the mailing of eight high content Forever Free Booklets (FFB) for smoking relapse prevention was highly cost-effective when compared with the mailing of low content repeated letters or a minimum content comparison (MCC) in a population of ex-smokers in the USA. The frequency of contact (low contact massed mailing or high contact repeated mailing) of the eight FFBs did not affect the outcome. The incremental costs were $21.25 with massed mailed FFB vs MCC, $26.00 with repeated letters vs MCC, and $43.94 with repeated mailing FFB vs MCC. The incremental 24-month abstinence rate was 11.4% with massed mailing FFB vs MCC, 2.4% with repeated letters vs MCC, and 12.2% with repeated mailing FFB vs MCC. The incremental QALYs were 0.2561 with massed mailing FFB vs MCC and 0.2741 with repeated mailing FFB vs MCC. Compared with a minimal intervention, the incremental cost per QALY gained was $83 with massed mailing FFB and $16 with repeated mailing FFB. The analysis was assessed as partly applicable to the review question, with some minor limitations.
- Brandon (2012) found that, in the USA, a series of 10 self-help booklets (FFB) designed to prevent smoking relapse in pregnant and postpartum women increased percentage

abstinence compared with 2 existing smoking cessation booklets as a usual care control (UCC). The self-help FFB had a total cost per user of $53.60. At 8 months post-partum the abstinence rates were 69.6% with FFB and 58.5% with UCC; at 12 months post-partum the abstinence rates were 66.2% with FFB and 58.6% with UCC. The incremental cost per each additional abstinence at 12 months post-partum with FFB vs UCC were $248. Additional healthcare resource usage was not included in the analysis and the total cost of usual care was not reported. The analysis was assessed as partly applicable to the review question, with some minor limitations.

Summary of a trial that randomly assigned abstainers and smokers before their quit date and that was included in the economic evidence review for preventing relapse during pregnancy (n=1)

- One economic evaluation (Ruger 2008) found that the use of individually tailored motivational interviewing (MI) for smoking relapse prevention in low-income pregnant women was cost-effective compared with usual care (UC), in the USA. It estimated that the intervention costs for MI for relapse prevention compared with UC were $85 per life-year (LYs) saved and $628/QALY saved. Including savings in maternal medical costs in sensitivity analyses resulted in cost savings for MI for relapse prevention compared with UC. Among low-income pregnant women, MI helps prevent relapse at relatively low cost, and may be cost-saving when net medical cost savings are considered. The analysis was assessed as partly applicable to the review question, with some minor limitations.

Summary of the studies used information from multiple of trials that randomly assigned abstainers and smokers before their quit date and that were included in the economic evidence review for preventing relapse during pregnancy (n=3)

- One cost-effectiveness analysis (Knight, 2010) found that 12 weeks of varenicline followed by a further 12-week course for successful quitters (varenicline 12 + 12 weeks) was a highly cost-effective alternative compared with currently available smoking cessation options including varenicline for 12 weeks alone (not followed by 12-week maintenance for quitters), nicotine replacement therapy (NRT) or bupropion, in a USA context. The analysis was based on a lifetime Markov model (BENESCO model) that used quit rates on the basis of a mixed treatment comparison of three RCTs. Varenicline (12 + 12 weeks) led to an incremental cost per QALY of $972 compared with initial varenicline alone. All the other options were dominated by varenicline (12 + 12 weeks). Cost-effectiveness results were driven by initial treatment costs and increased quit rates reducing the number of smoking related comorbidities and smoking related deaths across model's lifetime time horizon. Probabilistic sensitivity analysis (PSA) suggested a 73% likelihood that varenicline (12 + 12 weeks) would be cost-effective at a willingness to pay of $30,000 per QALY. The authors concluded that varenicline (12 + 12 weeks) was a highly cost-effective alternative compared with currently available smoking cessation interventions in the USA. The analysis was assessed as partly applicable to the review question with minor limitations.
- Taylor (2011) and Coleman (2010) concluded that when compared with no intervention, NRT, bupropion and varenicline are highly cost-effective for relapse prevention in a UK context. The study used a Markov model with a hypothetical population of 1,000 recent quitters. Quit rates at 6 and 12-months were obtained from systematic reviews. Total costs and QALYs were £6755 and 12.76 with bupropion, £7,050 and 12.63 with NRT, and £6,794 and 12.79 with varenicline, respectively. Bupropion dominated no intervention. The incremental cost per QALY gained for NRT versus no intervention was £265 and for varenicline versus no intervention was £2,106. Cost-effectiveness results were driven by healthcare costs and QALYs assigned to smoking related comorbidities. Interventions remained cost-effective for all sensitivity analyses varying treatment costs. For sensitivity analyses applying 10% effectiveness rates, bupropion remained cost-effective whereas NRT and varenicline exceeded the £20,000 cost per QALY threshold. Overall, the study was robust based on its detailed rigorous methods and its selection of conservative

assumptions, supported by an extensive sensitivity analysis. The study was assessed as directly applicable to the research question, with minor limitations.

- Von Wartburg (2014) found that 12 weeks of varenicline followed by a further 12-week course for successful quitters (varenicline 12 + 12 weeks) was highly cost-effective compared with standard varenicline treatment (12 weeks only). Both varenicline (12 + 12 weeks) and varenicline (12 weeks) dominated alternative smoking cessation interventions (NRT and bupropion). The analysis was based on the lifetime BENESCO model using the same quit rates as Knight (2010) and applying costs for a Canadian setting. From the payer perspective varenicline (12 + 12 weeks) led to an incremental cost per QALY of Can$3,758 compared with standard varenicline treatment. For a societal perspective which included indirect health and productivity costs, varenicline (12 + 12 weeks) was dominant compared with all alternatives. Cost-effectiveness was driven by increased quit rates reducing the number of smoking related comorbidities and smoking related deaths across model's lifetime time horizon. Probabilistic sensitivity analysis (PSA) showed that varenicline (12 + 12 weeks) had a 95% probability of being cost-effective at a willingness to pay threshold of Can$30,000 per QALY compared with varenicline (12 weeks) and 100% compared with the other interventions (from the payer perspective).The analysis was assessed as partly applicable to the review question with minor limitations.
- One directly applicable cost-utility analysis with minor limitations found that several pharmacotherapies (short acting NRT, bupropion, varenicline) combined with behaviour support were dominant (i.e. less costly and more effective than the comparator). NRT+bupropion and high intensity behaviour support were also cost effective at the threshold of £20,000/QALY with ICERS of £1,463/QALY and £12,960/QALY respectively. In contrast low intensity behaviour support was dominated meaning it was less effective and more costly than the comparator. Uncertainty in parameter values was explored using DSAs and PSAs. Varenicline and bupropion were identified as being cost effective versus placebo in 94% and 98% of PSA iterations respectively. Low intensity behaviour support was cost-effective in 14.2% of the 3,000 iterations. NRT short acting, NRT + bupropion and high intensity behaviour support were identified as being cost-effective in 57.7%, 73.6% and 55.9% respectively of the 3,000 iterations.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that not smoking was the most important outcome for this review, and that validated outcomes were more reliable than self-report. The committee discussed the relapse curve – demonstrating higher levels of relapse initially which then level out over time – and the fact that not smoking at least 6 months after quit date was more likely to be indicative of a longer term quit than outcomes measured before that point.

Confidence in the evidence

Overall results

The committee noted that some of the results in this review were unexpected, as very few of the studies effectively prevented relapse. They discussed possible reasons for the lack of conclusive effectiveness of most of the interventions. It was noted that a proportion of the studies were conducted more than 20 years ago (for example, 6 out of the 18 studies on pregnancy). Practice has changed since then and although this might be particularly important for behavioural interventions, pharmacological interventions might also be affected. For example, it was previously more common to use single mode or low dose NRT as illustrated by Forman (1995) and Killen (1990) who used NRT gum with 2mg nicotine which is now considered to be a low dose. The committee agreed that in their experience,

behavioural interventions reflecting current best practice and treatments at high enough dose levels might be more effective in preventing relapse.

The committee also considered the precision of the effect estimates. They noted that point estimates were often in the direction of a positive intervention effect, but confidence intervals overlapped the line of no effect. When this overlap was small, the committee discussed the importance of not disregarding the result. This was particularly important if the result was supported by a number of studies of reasonable quality, and where the effect was reflective of the committee's experiences as well as being biologically plausible due to the result aligning with similar results in other areas or being supported by knowledge of biological systems.

The committee discussed the risk of bias in the studies and agreed that the risks observed would generally be expected to inflate effect estimates. Due to the general observation that most intervention effects were not statistically significant according to these studies, the committee agreed that the risk of bias did not appear to have caused false positive results. They did not think it likely that the risk of bias had masked a true negative effect.

Concept of relapse prevention

The committee discussed the difficulty of identifying all studies investigating relapse prevention. Studies in this review were required to include terms about relapse, maintenance or recurrence (see Appendix B for search strategies). The committee noted that some studies looking at "extending or prolonging abstinence" may not have been included.

The committee discussed that the included studies, whilst all having the aim of preventing relapse, defined relapse differently. Some studies assumed that relapse prevention starts from day 1 of a quit attempt and so is an integral part of cessation, while others looked at relapse prevention starting after a successful quit had been achieved (for example, by being abstinent at the end of a cessation programme). After discussion the committee agreed that although relapse prevention does begin at day 1 of a quit attempt, this is considered to be part of the cessation approach. They agreed that the focus of this review and any recommendations as a result of it should be on longer term relapse prevention. For this reason, the committee focussed on evidence where relapse was clearly additional to cessation and delivered at a later point (this included behavioural interventions for assisted abstainers [Figure 11, GRADE profile 5], and pharmacotherapy for assisted abstainers [Figure 13-16, GRADE profile 6]). There is a paucity of evidence on this type of longer term relapse prevention. The committee discussed the importance of relapse prevention in those who are pregnant and the continuation of providing this support after pregnancy. Review [J] reviewed nicotine replacement therapies and e-cigarettes in pregnancy. The committee developed a recommendation relating to preventing relapse after pregnancy in the discussion of this review.

Varenicline

When considering the evidence on the effectiveness of varenicline for relapse prevention (Evins 2014 and Tonstad 2006; GRADE profile 6), the committee agreed that the studies were too different in population and intervention to combine the studies in meta-analysis (Tonstad 2006 in general population, Evins 2014 in a population with diagnosed serious mental illness; Evins 2014 supported by a tapering schedule of relapse prevention focused CBT, Tonstad 2006 a drug-only intervention). These studies were considered individually. The committee had some confidence that extending the prescription of varenicline for people who had successfully quit while using varenicline could increase likelihood of being abstinent from smoking at 6 or more months, both in the general population and also in people with serious mental illness.

Buproprion

There were six studies (Hayes 2009, Hays 2001, Hurt 2003, Covey 2007, Croghan 2007, Killen 2006) on the effectiveness of bupropion for relapse prevention. These studies had a wide range of treatment periods from 14 weeks to 52 weeks) Two studies considered bupropion and NRT (Covey 2007, Croghan 2007) for relapse prevention. These studies, or the meta-analysis of these studies did not show a significant increase in not smoking.

NRT

Two studies (Fortmann 1995, Killen 1990) showed that short-acting NRT (gum, 2mg) was effective for preventing relapse. However, these studies recruited people who had quit in the past 48 hours, and so the committee classed this as an integrated part of the cessation attempt (GRADE profile 4). Two further studies (Covey 2007, Croghan 2007) recruited people who were abstainers following a formal cessation programme lasting either eight weeks or three months. These studies did not show a significant increase in not smoking after use of short-acting NRT for an extended period after quitting (GRADE profile 6). The committee discussed the limited evidence in this area and that these studies were of a short acting NRT, many of those who use NRT to try and stop smoking use a mixture of long and short-acting. They discussed that in their experience extending use of NRT may help people remain abstinent, particularly if more than one mode is used (usually combining patches with a fast-acting form of NRT).

Gaps in the evidence

No evidence on e-cigarettes for relapse prevention was identified. Furthermore, more evidence is needed on preventing relapse to smoking over the long term in people who have successfully quit, as opposed to having just started a quit attempt, to provide conclusive results. All the included studies focussed on adults, so it is not clear whether effectiveness differs for those aged 12-17.

Benefits and harms

The committee discussed that there are clear benefits for preventing a relapse. They expressed the need for interventions that help to reduce the large number of people who successfully quit in the very short term but return to smoking, particularly if this is due to not being able to access treatments for long enough to consolidate a quit. In comparison to relapsing to smoking, the potential harms of extending treatment are considerably smaller. The committee discussed that in their experience, if people experience side effects of these treatments, they often reduce over time. That means that people may find extending use of treatments that they have already used for cessation easier than commencing or changing treatment. The committee agreed the importance of sustaining a quit attempt by prevention of relapse. They discussed that a substantial number of people do not manage to quit in their first attempts at doing so. They discussed and agreed the importance of discussing the ways of preventing relapse. The committee agreed the limitations in the evidence available, they further noted that the pharmacotherapies in the included studies are all those that are currently used as options for cessation support. They agreed that this enabled them to make a recommendation to offer those aiming to prevent relapse of a quit attempt the opportunity for further pharmacotherapy that may help prevent relapse.

Cost effectiveness and resource use

The committee discussed evidence from 9 published cost effectiveness studies (reported in 11 documents). Two studies were considered directly applicable and seven partly applicable to the review question. Eight studies were considered to have minor limitations and 1 study potentially serious limitations. Studies differed in who was entered into the trial and when.

The committee considered those studies that randomly allocated abstainers to be methodologically more aligned with the review question.

The studies showed that a range of interventions covering varenicline, bupropion and NRT patches, motivational interviewing and booklets were cost-effective for relapse prevention. Four of the studies included a probabilistic sensitivity analysis. Three of these assessed pharmacotherapies and showed that the probability of cost effectiveness was highest for 12 + 12 weeks of varenicline (range 73% - 95% depending on the willingness to pay threshold) and dominated other pharmacotherapies. The fourth, a study of the provision of eight "Forever Free" booklets, showed the results were uncertain as to whether they were cost effective compared with a brief, but comprehensive, leaflet (probability cost effective 64.4%).

The committee noted two of the published studies considered pregnant populations and both reported positive findings. The study by Brandon et al (2012) comparing 10x Forever Free booklets with usual care reported an incremental cost of US$248 per additional abstainer. The study by Ruger et al (2008) which compared motivational interviewing with usual care reported an incremental cost of US$628 per QALY gained.

The committee were also presented with the results of the de novo economic model. In populations who had achieved assisted smoking abstinence through a smoking cessation intervention the results showed high intensity behavioural support was cost-effective versus usual care. Similarly, short acting NRT products, bupropion, varenicline, and combination therapy with NRT and bupropion were all cost-effective versus placebo. Low intensity behavioural support was the only intervention that was not cost-effective in this population.

The committee observed that the PSA for assisted abstainers identified very low levels of uncertainty in the cost-effectiveness results for varenicline and bupropion where, at a threshold of £20,000/QALY, 94% and 98% of PSA iterations were cost-effective versus placebo respectively. In contrast there was a very high level of uncertainty in the cost-effectiveness results for low intensity behaviour support where only 14.2% of the iterations were cost effective. The probability of cost effectiveness for high intensity behaviour support, NRT short acting, and combination NRT+Bupropion was 56%, 58% and 74% respectively.

The committee discussed bupropion and whilst the evidence showed it is an effective and cost effective method they commented that it had fallen out of favour and is not widely used. They agreed it would need to be marketed to encourage its use.

The committee considered how to interpret the cost effectiveness evidence in light of the effectiveness evidence. They were mindful that these two types of evidence draw on different paradigms: Where evidence of effectiveness centres around point estimates, confidence intervals and binary decisions based on statistical significance, assessing cost effectiveness builds in the uncertainty of point estimates and other parameters relevant to the analysis and uses sensitivity analyses to explore the impact of these uncertainties on the results.

Reflecting on the totality of the evidence, and noting that the interventions assessed for relapse are all those currently used for cessation, the committee decided to make a recommendation to offer those aiming to prevent relapse the opportunity for further pharmacotherapy that may help prevent relapse.

Other factors the committee took into account

The committee discussed the fact that telephone contact, print-based support, and computer / mobile interventions for relapse prevention in smokers (GRADE profile 9) appears effective. This is mainly due to the print-based support subgroup within the meta-analysis, which is contributed to by a study about which they had serious concerns due to abstinence not being biochemically validated (Unrod 2016). In addition, the same interventions investigated in different scenarios in this review do not show effectiveness. Lack of confidence in this

evidence combined with the committee's experience that repeated mailings are a somewhat outdated practice meant they chose not to recommend this intervention.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.17.1 to 1.17.2, 1.17.6 to 1.17.7, 1.22.1 to 1.22.2, and the research recommendations on relapse prevention and relapse prevention after enforced, temporary quit. Other evidence supporting these recommendations can be found in the evidence reviews on cessation and harm-reduction treatments (review K).

Included study list

Becona 1997

Becona E, Vazquez FL. Does using relapse prevention increase the efficacy of a program for smoking cessation? An empirical study. Psychological Reports 1997;81(1):291-6. [CRSREF: 2963097]

Blyth 2015

* Blyth A, Maskrey V, Notley C, Barton GR, Brown TJ, Aveyard P, et al. Effectiveness and economic evaluation of self-help educational materials for the prevention of smoking relapse: randomised controlled trial. Health Technology Assessment 2015;19(59):1-70. [CRSREF: 9969606]

Maskrey V, Blyth A, Brown TJ, Barton GR, Notley C, Aveyard P, et al. Self-help educational booklets for the prevention of smoking relapse following smoking cessation treatment: a randomized controlled trial. Addiction 2015;110(12):No Pagination Specified. [CRSREF: 9969607]

Notley C, Blyth A, Maskrey V, Karavadra B, Brown T, Holland R, et al. Self-help materials for smoking relapse prevention: a process evaluation of the SHARPISH randomized controlled trial. Journal of Public Health 2018;40(1):98-105.

Song F, Bachmann MO, Aveyard P, Barton GR, Brown TJ, Maskrey V, et al. Relapse to smoking and health-related quality of life: secondary analysis of data from a study of smoking relapse prevention. Plos ONE 2018;13(11):e0205992.

Song F, Holland R, Barton GR, Bachmann M, Blyth A, Maskrey V, et al. Self-help materials for the prevention of smoking relapse: study protocol for a randomized controlled trial. Trials 2012;13:69. [CRSREF: 9969608]

Borland 2004

Borland R, Balmford J, Hunt D. The effectiveness of personally tailored computer-generated advice letters for smoking cessation. Addiction 2004;99:369-77. [CRSREF: 2963099]

Brandon 1987

Brandon TH, Zelman DC, Baker TB. Effects of maintenance sessions on smoking relapse: delaying the inevitable? Journal of Consulting and Clinical Psychology 1987;55:780-2. [CRSREF: 2963101]

Brandon 2000

Brandon TH, Collins BN, Juliano LM, Lazev AB. Preventing relapse among former smokers: a comparison of minimal interventions through telephone and mail. Journal of Consulting and Clinical Psychology 2000;68:103-13. [CRSREF: 2963103]

Brandon 2004

* Brandon TH, Meade CD, Herzog TA, Chirikos TN, Webb MS, Cantor AB. Efficacy and cost-effectiveness of a minimal intervention to prevent smoking relapse: dismantling the effects of amount of content versus contact. Journal of Consulting and Clinical Psychology 2004;72:797-800. [CRSREF: 2963105]

Chirikos TN, Herzog TA, Meade CD, Webb MS, Brandon TH. Cost-effectiveness analysis of a complementary health intervention: the case of smoking relapse prevention. International Journal of Technology Assessment in Health Care 2004;20:475-80. [CRSREF: 2963106]

Brandon 2012

Brandon TH, Simmons VN, Meade CD, Quinn GP, Lopez Khoury EN, Sutton SK, et al. Self-help booklets for preventing postpartum smoking relapse: a randomized trial. American Journal of Public Health 2012;102(11):2109-15. [CRSREF: 9969610]

Brandstein 2012

Brandstein K. A proactive smoking cessation intervention with hospitalized smokers: a randomized controlled trial. Dissertation Abstracts International 2012;72(8-B):4600. [CRSREF: 9969612]

Buchkremer 1991 1

Buchkremer G, Minneker E, Block M. Smoking-cessation treatment combining transdermal nicotine substitution with behavioral therapy. Pharmacopsychiatry 1991;24:96-102. [CRSREF: 2963108]

Buchkremer 1991 2

Buchkremer G, Minneker E, Block M. Smoking-cessation treatment combining transdermal nicotine substitution with behavioral therapy. Pharmacopsychiatry 1991;24:96-102. [CRSREF: 2963110]

Coleman-Cowger 2018

Coleman-Cowger VH, Mark KS, Rosenberry ZR, Koszowski B, Terplan M. A pilot randomized controlled trial of a phone-based intervention for smoking cessation and relapse prevention in the postpartum period. Journal of Addiction Medicine 2018;12(3):193-200.

Conway 2004

* Conway TL, Woodruff SI, Edwards CC, Elder JP, Hurtado SL, Hervig LK. Operation Stay Quit: evaluation of two smoking relapse prevention strategies for women after involuntary cessation during US Navy recruit training. Military Medicine 2004;169:236-42. [CRSREF: 2963112]

Edwards CC, Woodruff SI, Conway TL. Operation Stay Quit: preventing smoking relapse among US Navy women. American Journal of Health Behavior 1999;23(5):352-5. [CRSREF: 2963113]

Covey 2007

Covey LS, Glassman AH, Jiang H, Fried J, Masmela J, LoDuca C, et al. A randomized trial of bupropion and/or nicotine gum as maintenance treatment for preventing smoking relapse. Addiction 2007;102(8):1292-302. [CRSREF: 2963115]

Croghan 2007

comparison of a nicotine inhaler and bupropion for smoking cessation and relapse prevention. Mayo Clinic Proceedings 2007;82(2):186-95. [CRSREF: 2963117]

Cummins 2016

Cummins S, Zhu SH, Gamst A, Kirby C, Brandstein K, Klonoff-Cohen H, et al. Nicotine patches and quitline counseling to help hospitalized smokers stay quit: study protocol for a randomized controlled trial. Trials 2012;13(1):128. [CRSREF: 9969616]

* Cummins SE, Gamst AC, Brandstein K, Seymann GB, Klonoff-Cohen H, Kirby CA, et al. Helping hospitalized smokers: a factorial RCT of nicotine patches and counseling. American Journal of Preventive Medicine 2016;51(4):578-86. [CRSREF: 9969617]

Curry 1988

Curry SJ, Marlatt GA, Gordon J, Baer JS. A comparison of alternative theoretical approaches to smoking cessation and relapse. Health Psychology 1988;7(6):545-56. [CRSREF: 2963119]

Davis 1986

Davis JR, Glaros AG. Relapse prevention and smoking cessation. Addictive Behaviors 1986;11:105-14. [CRSREF: 2963121]

Durmaz 2019

Durmaz S, Ergin I, Durusoy R, Hassoy H, Caliskan A, Okyay P. WhatsApp embedded in routine service delivery for smoking cessation: effects on abstinence rates in a randomized controlled study. BMC Public Health 2019;19(1):387.

Emmons 1988

Emmons KM, Emont SL, Collins RL, Weidner G. Relapse prevention versus broad spectrum treatment for smoking cessation: a comparison of efficacy. Journal of Substance Abuse 1988;1:79-89. [CRSREF: 2963123]

Ershoff 1995

Ershoff DH, Quinn VP, Mullen PD. Relapse prevention among women who stop smoking early in pregnancy: a randomized clinical trial of a self-help intervention. American Journal of Preventive Medicine 1995;11(3):178-84. [CRSREF: 2963125]

Evins 2014

* Evins AE, Cather C, Pratt SA, Pachas GN, Hoeppner SS, Goff DC, et al. Maintenance treatment with varenicline for smoking cessation in patients with schizophrenia and bipolar disorder: a randomized clinical trial. JAMA 2014;311(2):145-54. [CRSREF: 9969619]

Evins AE, Hoeppner SS, Schoenfeld DA, Hoeppner BB, Cather C, Pachas GN, et al. Maintenance pharmacotherapy normalizes the relapse curve in recently abstinent tobacco smokers with schizophrenia and bipolar disorder. Schizophrenia Research 2017;183:124-9.

NCT00621777. A study of varenicline for prevention of relapse to smoking in patients with schizophrenia (SCRP). clinicaltrials.gov/ct2/show/NCT00621777 (first received 2015). [CRSREF: 9969620]

Thorndike AN, Achtyes ED, Cather C, Pratt S, Pachas GN, Hoeppner S, et al. Weight gain and 10-year cardiovascular risk with sustained tobacco abstinence in smokers with serious mental illness: a subgroup analysis of a randomized trial. Journal of Clinical Psychiatry 2016;77(3):e320-6. [CRSREF: 9969621]

Fortmann 1995

Fortmann SP, Killen JD. Nicotine gum and self-help behavioral treatment for smoking relapse prevention: results from a trial using population-based recruitment. Journal of Consulting and Clinical Psychology 1995;63(3):460-8. [CRSREF: 2963127]

Hajek 2001

Hajek P, West R, Lee A, Foulds J, Owen L, Eiser JR, et al. Randomized controlled trial of a midwife-delivered brief smoking cessation intervention in pregnancy. Addiction 2001;96(3):485-94. [CRSREF: 2963129]

Hajek 2002

Hajek P, Taylor TZ, Mills P. Brief intervention during hospital admission to help patients to give up smoking after myocardial infarction and bypass surgery: randomised controlled trial. BMJ 2002;324:87-9. [CRSREF: 2963131]

Hall 1984

Hall SM, Rugg D, Tunstall C, Jones RT. Preventing relapse to cigarette smoking by behavioral skill training. Journal of Consulting and Clinical Psychology 1984;52(3):372-82. [CRSREF: 2963133]

Hall 1985

Hall SM, Killen JD. Psychological and pharmacological approaches to smoking relapse prevention. NIDA Research Monograph 1985;53:131-43. [CRSREF: 2963135]

* Hall SM, Tunstall C, Rugg D, Jones R, Benowitz N. Nicotine gum and behavioral treatment in smoking cessation. Journal of Consulting and Clinical Psychology 1985;53:256-8. [CRSREF: 2963136]

Hall 1987

* Hall SM, Tunstall CD, Ginsberg D, Benowitz NL, Jones RT. Nicotine gum and behavioral treatment: a placebo controlled trial. Journal of Consulting and Clinical Psychology 1987;55(4):603-5. [CRSREF: 2963138]

Hasuo 2004

Hasuo S, Tanaka H, Oshima A. Efficacy of a smoking relapse prevention program by postdischarge telephone contacts: a randomized trial. Nippon Koshu Eisei Zasshi 2004;51:403-12. [CRSREF: 2963144]

Hayes 2018

Hayes KA, Jackson C, Dickinson DM, Miller AL. Providing antismoking socialization to children after quitting smoking: does it help parents stay quit? American Journal of Health Promotion 2018;32(5):1257-63. [CRSREF: 9969623]

Hays 2001

Abel GA, Hays JT, Decker PA, Croghan GA, Kuter DJ, Rigotti NA. Effects of biochemically confirmed smoking cessation on white blood cell count. Mayo Clinic Proceedings 2005;80:1022-8. [CRSREF: 2963146]

Cox LS, Patten CA, Niaura RS, Decker PA, Rigotti N, Sachs DPL, et al. Efficacy of bupropion for relapse prevention in smokers with and without a past history of major depression. Journal of General Internal Medicine 2004;19:828-34. [CRSREF: 2963147]

Durcan MJ, Deener G, White J, Johnston JA, Gonzales D, Niaura R, et al. The effect of bupropion sustained-release on cigarette craving after smoking cessation. Clinical Therapeutics 2002;24(4):540-51. [CRSREF: 2963148]

Durcan MJ, Johnston JA, White J, Gonzales D, Sachs DP, Rigotti N, et al. Bupropion SR for relapse prevention: a "slips-allowed" analysis. American Journal of Health Behavior 2004;28:456-63. [CRSREF: 2963149]

Gonzales D, Bjornson W, Durcan MJ, White JD, Johnston JA, Buist AS, et al. Effects of gender on relapse prevention in smokers treated with bupropion SR. American Journal of Preventive Medicine 2002;22(4):234-9. [CRSREF: 2963150]

* Hays JT, Hurt RD, Rigotti NA, Niaura R, Gonzales D, Durcan MJ, et al. Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation. A randomized, controlled trial. Annals of Internal Medicine 2001;135:423-33. [CRSREF: 2963151]

Hurt RD, Wolter TD, Rigotti N, Hays JT, Niaura R, Durcan MJ, et al. Bupropion for pharmacologic relapse prevention to smoking - predictors of outcome. Addictive Behaviors 2002;27(4):493-507. [CRSREF: 2963152]

Hays 2009

* Hays JT, Hurt RD, Decker PA, Croghan IT, Offord KP, Patten CA. A randomized, controlled trial of bupropion sustained-release for preventing tobacco relapse in recovering alcoholics. Nicotine and Tobacco Research 2009;11(7):859-67. [CRSREF: 9969624]

Hurt RD, Patten CA, Offord KP, Croghan IT, Decker PA, Morris RA, et al. Treating nondepressed smokers with alcohol dependence in sustained full remission: nicotine patch therapy tailored to baseline serum cotinine. Journal of Studies on Alcohol 2005;66(4):506-16. [CRSREF: 9969625]

Hicks 2017

Hicks TA, Thomas SP, Wilson SM, Calhoun PS, Kuhn ER, Beckham JC. A preliminary investigation of a relapse prevention mobile application to maintain smoking abstinence among individuals with posttraumatic stress disorder. Journal of Dual Diagnosis 2017;13(1):15-20. [CRSREF: 9969627]

Hurt 2003

Hurt RD, Krook JE, Croghan IT, Loprinzi CL, Sloan JA, Novotny PJ, et al. Nicotine patch therapy based on smoking rate followed by bupropion for prevention of relapse to smoking. Journal of Clinical Oncology 2003;21:914-20. [CRSREF: 2963156]

Japuntich 2006

Japuntich SJ, Zehner ME, Smith SS, Jorenby DE, Valdez JA, Fiore MC, et al. Smoking cessation via the internet: a randomized clinical trial of an internet intervention as adjuvant treatment in a smoking cessation intervention. Nicotine & Tobacco Research 2006;8 Suppl 1:S59-67. [CRSREF: 2963158]

Joseph 2011

Joseph AM, Fu SS, Lindgren B, Rothman AJ, Kodl M, Lando H, et al. Chronic disease management for tobacco dependence: a randomized, controlled trial. Archives of Internal Medicine 2011;171(21):1894-900. [CRSREF: 2963160]

Killen 1984

* Killen JD, Maccoby N, Taylor CB. Nicotine gum and self-regulation training in smoking relapse prevention. Behavior Therapy 1984;15:234-48. [CRSREF: 2963164]

Killen 1990

Killen JD, Fortmann SP, Newman B, Varady A. Evaluation of a treatment approach combining nicotine gum with self-guided behavioral treatments for smoking relapse prevention. Journal of Consulting and Clinical Psychology 1990;58:85-92. [CRSREF: 2963166]

Killen 2006

Killen JD, Fortmann SP, Murphy GM Jr, Hayward C, Arredondo C, Cromp D, et al. Extended treatment with bupropion SR for cigarette smoking cessation. Journal of Consulting and Clinical Psychology 2006;74(2):286-94. [CRSREF: 2963168]

Klesges 1999

Klesges RC, Haddock CK, Lando H, Talcott GW. Efficacy of forced smoking cessation and an adjunctive behavioral treatment on long-term smoking rates. Journal of Consulting and Clinical Psychology 1999;67:952-8. [CRSREF: 2963170]

Klesges 2006

* Klesges RC, Debon M, Vander Weg MW, Haddock CK, Lando HA, Relyea GE, et al. Efficacy of a tailored tobacco control program on long-term use in a population of U.S. military troops. Journal of Consulting & Clinical Psychology 2006;74(2):295-306. [CRSREF: 2963172]

Klesges RC, Sherrill-Mittleman D, Ebbert JO, Talcott GW, Debon M. Tobacco use harm reduction, elimination, and escalation in a large military cohort. American Journal of Public Health 2010;100(12):2487-92. [CRSREF: 2963173]

Lando 1996

* Lando HA, Pirie PL, Roski J, McGovern PG, Schmid LA. Promoting abstinence among relapsed chronic smokers: the effect of telephone support. American Journal of Public Health 1996;86:1786-90. [CRSREF: 2963175]

Levine 2016

Katz MH. Preventing smoking relapse after delivery - maintaining a pregnant pause. JAMA Internal Medicine 2016;176(4):452. [CRSREF: 9969629]

Kolko RP, Emery RL, Cheng Y, Levine MD. Do psychiatric disorders or measures of distress moderate response to postpartum relapse prevention interventions? Nicotine & Tobacco Research 2017;19(5):615-22. [CRSREF: 9969630]

* Levine MD, Cheng Y, Marcus MD, Kalarchian MA, Emery RL. Preventing postpartum smoking relapse: a randomized clinical trial. JAMA Internal Medicine 2016;176(4):443-52. [CRSREF: 9969631]

Levine MD, Marcus MD, Kalarchian MA, Cheng Y. Strategies to Avoid Returning to Smoking (STARTS): a randomized controlled trial of postpartum smoking relapse prevention interventions. Contemporary Clinical Trials 2013;36(2):565-73. [CRSREF: 9969632]

Lifrak 1997

Lifrak P, Gariti P, Alterman A, Volpicelli J, O'Brien C. Combining individual relapse prevention counseling with a transdermal nicotine patch for smoking cessation. Journal of Addictive Diseases 1994;13(4):251. [CRSREF: 2963177]

* Lifrak P, Gariti P, Alterman AI, McKay J, Volpicelli J, Sparkman T, et al. Results of two levels of adjunctive treatment used with the nicotine patch. American Journal of Addiction 1997;6:93-8. [CRSREF: 2963178]

Lowe 1997

Lowe JB, Windsor R, Balanda KP, Woodby L. Smoking relapse prevention methods for pregnant women: a formative evaluation. American Journal of Health Promotion 1997;11:244-6. [CRSREF: 2963180]

Mayer 2010

Mayer C, Vandecasteele H, Bodo M, Primo C, Slachmuylder JL, Kaufman L, et al. Smoking relapse prevention programs and factors that predict abstinence: a controlled study comparing the efficacy of workplace group counselling and proactive phone counselling. Journal of Smoking Cessation 2010;5(1):83-94. [CRSREF: 2963182]

McBride 1999

McBride CM, Curry SJ, Lando HA, Pirie PL, Grothaus LC, Nelson JC. Prevention of relapse in women who quit smoking during pregnancy. American Journal of Public Health 1999;89:706-11. [CRSREF: 2963184]

McBride 2004

McBride CM, Baucom DH, Peterson BL, Pollak KI, Palmer C, Westman E, et al. Prenatal and postpartum smoking abstinence - a partner-assisted approach. American Journal of Preventive Medicine 2004;27(3):232-8. [CRSREF: 2963186]

McDaniel 2015

McDaniel AM, Vickerman KA, Stump TE, Monahan PO, Fellows JL, Weaver MT, et al. A randomised controlled trial to prevent smoking relapse among recently quit smokers enrolled in employer and health plan sponsored quitlines. BMJ Open 2015;5(6):e007260. [CRSREF: 9969634]

McNaughton 2013

McNaughton B, Frohlich J, Graham A, Young QR. Extended interactive voice response telephony (IVR) for relapse prevention after smoking cessation using varenicline and IVR: a pilot study. BMC Public Health 2013;13:824. [CRSREF: 9969636]

Mermelstein 2003

Mermelstein R, Hedeker D, Wong SC. Extended telephone counseling for smoking cessation: does content matter? Journal of Consulting and Clinical Psychology 2003;71:565-74. [CRSREF: 2963188]

Morasco 2006

Morasco BJ, Dornelas EA, Fischer EH, Oncken C, Lando HA. Spontaneous smoking cessation during pregnancy among ethnic minority women: a preliminary investigation. Addictive Behaviors 2006;31(2):203-10. [CRSREF: 2963190]

Niaura 1999

Niaura R, Abrams DB, Shadel WG, Rohsenow DJ, Monti PM, Sirota AD. Cue exposure treatment for smoking relapse prevention: a controlled clinical trial. Addiction 1999;94(5):685-96. [CRSREF: 2963192]

Pbert 2004

Pbert L, Ockene JK, Zapka J, Ma YS, Goins KV, Oncken C, et al. A community health center smoking-cessation intervention for pregnant and postpartum women. American Journal of Preventive Medicine 2004;26(5):377-85. [CRSREF: 2963194]

Pollak 2016

Pollak KI, Fish LJ, Lyna P, Peterson BL, Myers ER, Gao X, et al. Efficacy of a nurse-delivered intervention to prevent and delay postpartum return to smoking: the quit for two trial. Nicotine & Tobacco Research 2016;18(10):1960-6. [CRSREF: 9969638]

Powell 1981

Powell DR, McCann BS. The effects of a multiple treatment program and maintenance procedures on smoking cessation. Preventive Medicine 1981;10:94-104. [CRSREF: 2963196]

Ratner 2000

Johnson JL, Ratner PA, Bottorff JL, Hall W, Dahinten S. Preventing smoking relapse in postpartum women. Nursing Research 2000;49:44-52. [CRSREF: 2963198]

* Ratner PA, Johnson JL, Bottorff JL, Dahinten S, Hall W. Twelve-month follow-up of a smoking relapse prevention intervention for postpartum women. Addictive Behaviors 2000;25:81-92. [CRSREF: 2963199]

Ratner PA, Johnson JL, Bottorff JL. Smoking relapse and early weaning among postpartum women: is there an association? Birth 1999;26(2):76-82. [CRSREF: 2963200]

Razavi 1999

Razavi D, Vandecasteele H, Primo C, Bodo M, Debrier F, Verbist H, et al. Maintaining abstinence from cigarette smoking: effectiveness of group counselling and factors predicting outcome. European Journal of Cancer 1999;35:1238-47. [CRSREF: 2963202]

Reitzel 2010

Heppner WL, Ji L, Reitzel LR, Reitzel L, Castro Y, Correa-Fernandez V, et al. The role of prepartum motivation in the maintenance of postpartum smoking abstinence. Health Psychology 2011;30(6):736-45. [CRSREF: 2963204]

* Reitzel LR, Vidrine JI, Businelle MS, Kendzor DE, Costello TJ, Li Y, et al. Preventing postpartum smoking relapse among diverse low-income women: a randomized clinical trial. Nicotine & Tobacco Research 2010;12(4):326-35. [CRSREF: 2963205]

Ruger 2008

Ruger JP, Weinstein MC, Hammond SK, Kearney MH, Emmons KM. Cost-effectiveness of motivational interviewing for smoking cessation and relapse prevention among low-income pregnant women: a randomized controlled trial.. Value in Health 2008;11:191-8. [CRSREF: 2963207]

Schmitz 1999

Schmitz JM, Spiga R, Rhoades HM, Fuentes F. Smoking cessation in women with cardiac risk: a comparative study of two theoretically based therapies. Nicotine & Tobacco Research 1999;1(1):87-94. [CRSREF: 2963209]

Schroter 2006

Schroter M, Collins SE, Frittrang T, Buchkremer G, Batra A. Randomized controlled trial of relapse prevention and a standard behavioral intervention with adult smokers. Addictive Behaviors 2006;31(7):1259-64. [CRSREF: 2963211]

Secker-Walker 1995

Secker-Walker RH, Solomon LJ, Flynn BS, Skelly JM, LePage SS, Goodwin GD, et al. Smoking relapse prevention counseling during prenatal and early postnatal care. American Journal of Preventive Medicine 1995;11:86-93. [CRSREF: 2963213]

Secker-Walker 1998

Secker-Walker RH, Solomon LJ, Flynn BS, Skelly JM, Mead PB. Smoking relapse prevention during pregnancy. A trial of coordinated advice from physicians and individual counseling. American Journal of Preventive Medicine 1998;15:25-31. [CRSREF: 2963215]

Segan 2011

Segan CJ, Borland R. Does extended telephone callback counselling prevent smoking relapse? Health Education Research 2011;26(2):336-47. [CRSREF: 2963217]

Severson 1997

* Severson HH, Andrews JA, Lichtenstein E, Wall M, Akers L. Reducing maternal smoking and relapse: long-term evaluation of a pediatric intervention. Preventive Medicine 1997;26:120-30. [CRSREF: 2963219]

Wall MA, Severson HH, Andrews JA, Lichtenstein E, Zoref L. Pediatric office-based smoking intervention - Impact on maternal smoking and relapse. Pediatrics 1995;96:622-8. [CRSREF: 2963220]

Shoptaw 2002

Shoptaw S, Rotheram-Fuller E, Yang X, Frosch D, Nahom D, Jarvik ME, et al. Smoking cessation in methadone maintenance. Addiction 2002;97:1317-28. [CRSREF: 2963224]

Simmons 2018

Simmons VN, Sutton SK, Meltzer LR, Unrod M, Meade CD, Brandon TH. Long-term outcomes from a self-help smoking cessation randomized controlled trial. Psychology of Addictive Behaviors 2018;32(7):710-4.

Smith 2001

Smith SS, Jorenby DE, Fiore MC, Anderson JE, Mielke MM, Beach KE, et al. Strike while the iron is hot: can stepped-care treatments resurrect relapsing smokers? Journal of Consulting and Clinical Psychology 2001;69:429-39. [CRSREF: 2963226]

Stevens 1989

* Stevens VJ, Hollis JF. Preventing smoking relapse, using an individually tailored skills-training technique. Journal of Consulting and Clinical Psychology 1989;57:420-4. [CRSREF: 2963228]

Tonstad 2006

Bolin K, Mörk 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. Journal of Evaluation in Clinical Practice 2009;15:478-85. [CRSREF: 2963234]

Evins AE, Hoeppner SS, Schoenfeld DA, Hoeppner BB, Cather C, Pachas GN, et al. Maintenance pharmacotherapy normalizes the relapse curve in recently abstinent tobacco smokers with schizophrenia and bipolar disorder. Schizophrenia Research 2017;183:124-9.

Hajek P, Tønneson P, Arteaga C, Russ C, Tonstad S. Varenicline in prevention of relapse to smoking: effect of quit pattern on response to extended treatment. Addiction 2009;104:1597-602. [CRSREF: 2963235]

Knight C, Howard P, Baker CL, Marton JP. The cost-effectiveness of an extended course (12 + 12 weeks) of varenicline compared with other available smoking cessation strategies in the United States: an extension and update to the BENESCO model. Value in Health 2010;13(2):209-14. [CRSREF: 2963236]

Knight CJ, Howard PA, Baker CL. An evaluation of the cost-effectiveness of an extended course of varenicline in preventing smokers who have quit from relapsing [PSM3]. Value in Health 2007;10(6):A472. [CRSREF: 2963237]

Lee JH, Jones PG, Bybee K, O'Keefe JH. A longer course of varenicline therapy improves smoking cessation rates. Preventive Cardiology 2008;11(4):210-4. [CRSREF: 2963238]

O'Brien CP. Varenicline as maintenance therapy. Current Psychiatry Reports 2007;9(5):348-8. [CRSREF: 2963239]

* Tonstad S, Tonnesen P, Hajek P, Williams KE, Billing CB, Reeves KR. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. JAMA 2006;296:64-71. [CRSREF: 2963240]

Unrod 2016

Unrod M, Simmons VN, Sutton SK, Cummings KM, Celestino P, Craig BM, et al. Relapse-prevention booklets as an adjunct to a tobacco quitline: a randomized controlled effectiveness trial. Nicotine & Tobacco Research 2016;18(3):298-305. [CRSREF: 9969642]

Van't Hof 2000

Van't Hof SM, Wall MA, Dowler DW, Stark MJ. Randomised controlled trial of a postpartum relapse prevention intervention. Tobacco Control 2000;9 Suppl 3:III64-6. [CRSREF: 2963242]

Veldheer 2018

Veldheer S, Hrabovsky S, Yingst J, Sciamanna C, Berg A, Foulds J. The use of self-directed relapse prevention booklets to assist in maintaining abstinence after a 6-week group smoking cessation treatment program: a randomized controlled trial. Health Education & Behavior 2018;45(2):190-7.

Wetter 2011

Wetter D, McClure J. A randomized clinical trial of a palmtop computer-delivered treatment for smoking relapse prevention among women. Psychology of Addictive Behaviours 2011;25(2):365-71. [CRSREF: 2963246]

Health economics included studies

Blyth A, Maskrey V, Notley C, Barton GR, Brown TJ, Aveyard P, et al. Effectiveness and economic evaluation of self-help educational materials for the prevention of smoking relapse: Randomised controlled trial. Health Technol Assess. 2015;19(59):hta19590.

Bolin K, Mork AC, 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.

Brandon TH, Herzog TA, Webb MS. It ain't over till it's over: The case for offering relapse prevention interventions to former smokers. Am J Med Sci. 2003;326(4):197-200.

Brandon TH, Meade CD, Herzog TA, Chirikos TN, Webb MS, Cantor AB. Efficacy and cost-effectiveness of a minimal intervention to prevent smoking relapse: Dismantling the effects of amount of content versus contact. J Consult Clin Psychol. 2004;72(5):797-808.

Brandon TH, Simmons VN, Meade CD, Quinn GP, Lopez Khoury EN, Sutton SK, et al. Self-help booklets for preventing postpartum smoking relapse: A randomized trial. Am J Public Health. 2012;102(11):2109-15.

Chirikos TN, Herzog TA, Meade CD, Webb MS, Brandon TH. Cost-effectiveness analysis of a complementary health intervention: The case of smoking relapse prevention. Int J Technol Assess Health Care. 2004;20(4):475-80.

Coleman T, Agboola S, Leonardi-Bee J, Taylor M, McEwen A, McNeill A. Relapse prevention in UK Stop Smoking Services: Current practice, systematic reviews of effectiveness and cost-effectiveness analysis. Health Technol Assess. 2010;14(49):hta14490.

Knight C, Howard P, Baker CL, Marton JP. The cost-effectiveness of an extended course (12 + 12 weeks) of varenicline compared with other available smoking cessation strategies in the

United States: An extension and update to the BENESCO model. Value Health. 2010;13(2):209-14.

Ruger JP, Weinstein MC, Hammond SK, Kearney MH, Emmons KM. Cost-effectiveness of motivational interviewing for smoking cessation and relapse prevention among low-income pregnant women: A randomized controlled trial. Value Health. 2008;11(2):191-8.

Taylor M, Leonardi-Bee J, Agboola S, McNeill A, Coleman T. Cost effectiveness of interventions to reduce relapse to smoking following smoking cessation. Addiction. 2011;106(10):1819-26.

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

Appendices

Appendix A – Review protocols

Review protocol for smoking relapse prevention

ID	Field (based on PRISMA-P	Content
I	Review question	Which interventions are effective and cost effective for preventing a relapse in people who have recently quit smoking[6]?
II	Type of review question	Intervention
III	Objective of the review	Preventing relapse in people who have quit smoking is important in order for health benefits to be realised. This review aims to identify which interventions are most effective at preventing a relapse in those who have quit smoking recently, defined as at any point in the past
IV	Eligibility criteria – population/disease/condition/issue/domain	**Included**: People aged 12 and over: • who have quit smoking on their own or • who are undergoing enforced abstinence, whether or not they intend to quit permanently or • who are participating in treatment programmes to assist initial cessation.

[6] Throughout, smoking refers to the use of all smoked tobacco products.

		Excluded: People aged 11 and under. People who used smokeless tobacco and have quit. **Setting:** Any setting
V	Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	**Included:** Interventions which have a stated and measured aim of preventing relapse. Interventions may include the following as monotherapies, or in combination with each other: - Behavioural interventions (for example individual, group, telephone support, information materials, text messaging or online support) - Pharmacological interventions (bupropion, varenicline, NRT only) - E-cigarettes[7] - Incentives **Excluded**: Other forms of nicotine containing products or medicines Alternative and complementary therapies

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

		Tobacco containing products
VI	Eligibility criteria – comparator(s)/control or reference (gold) standard	**Included**: No intervention or placebo. A shorter intervention or intervention not explicitly to prevent relapse. Usual care. An included intervention.
VII	Outcomes and prioritisation	**Quantitative outcomes** <u>Critical outcomes</u> Smoking status at longest available follow-up (minimum of 6 months follow-up). Measured as: • Abstinence from smoking (relative risk) Where continued abstinence is presented, this is preferred over point-prevalence abstinence. Point prevalence measures will only be used where no continuous measure is reported. Where biochemically validated measures are available (i.e. saliva cotinine / carbon monoxide validation), these will be preferred to self-reported measures. Self-reported measures will only be used where no validated measure is reported. Risk ratio will be adjusted for cluster randomised trials. <u>Important outcomes</u>

		These will be extracted only if the study also reports a critical outcome. • Health-related quality of life (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**: <u>Comparative studies</u>: • Systematic reviews of randomised controlled trials (RCTs) • RCTs (including cluster RCTs) Study must have a minimum follow-up of 6 months from quit date to ascertain successful relapse prevention.

		Economic studies: • Cost-utility (cost per QALY) • Cost benefit (i.e. net benefit) • Cost-effectiveness (Cost per unit of effect) • Cost minimization • Cost-consequence **Excluded study designs**: • Cohort studies • Cross-sectional surveys • Correlation studies • Case control studies • Qualitative studies
IX	Other inclusion exclusion criteria	**Studies** This is a new review for the tobacco update. **Systematic Review**

		This review is being conducted by Cochrane by updating Relapse prevention interventions for smoking cessation. No language restriction will be applied. Only studies carried out in OECD countries will be included.
X	Proposed sensitivity/sub-group analysis, or meta-regression	Data will be presented separately for studies that randomly assigned abstainers and studies that randomly assigned participants before quit date. The following factors will be of interest in any meta-regression or subgroup analysis: • How does the type and intensity of the intervention influence effectiveness? • How does effectiveness vary according the type of quit (spontaneous quitters such as pregnant women vs people who smoke seeking smoking cessation treatment; enforced vs voluntary quit). • How does effectiveness vary between groups based on duration of quit (people who quit less than 4 weeks ago vs people who quit more than 4 weeks ago)? • Is effectiveness different when comparing first generation (cig-a-like), second generation (vape pen) and third generation ('mod') devices?
XI	Selection process – duplicate screening/selection/analysis	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)	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. Qualitative data will be summarised using secondary thematic analysis. A matrix approach will be used to compare findings with quantitative evidence.
XIII	Information sources – databases and dates	**Effectiveness** As in protocol to the Cochrane review. **Cost effectiveness** NICE will conduct a search using the following methods: • the databases listed below will be searched with an appropriate strategy. • the websites listed below will be searched or browsed with an appropriate strategy. • selected studies that are potentially relevant to the current review will be identified from the bibliography of previous NICE reviews. **Database strategies** The principal search strategy is listed in Appendix A. The search strategy will take this broad approach: (smoking cessation OR varenicline OR bupropion OR vaping OR NRT) AND (relapse prevention OR treatment failure OR patient compliance) AND CE filter AND Limits The cost effectiveness filter will be the standard filter used by NICE.

		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: • Campbell Collaboration via https://campbellcollaboration.org/library.html • EconLit via Ovid • Embase via Ovid • HTA legacy database via CRD https://www.crd.york.ac.uk/CRDWeb/ • MEDLINE ALL via Ovid • NHS EED legacy database via CRD https://www.crd.york.ac.uk/CRDWeb **Database search limits** Database functionality will be used, where available, to exclude: • animal studies • editorials, letters and commentaries • conference abstracts and posters • registry entries for ongoing or unpublished clinical trials • duplicates. No language or date limits will be applied. **Websites** The following websites will be searched with an appropriate strategy: • 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: • Action on Smoking and Health (ASH) http://ash.org.uk/home • Local Government Association https://www.local.gov.uk

		• National Centre for Smoking Cessation and Training http://www.ncsct.co.uk • Northern Ireland Assembly http://www.niassembly.gov.uk/ • Public Health England https://www.gov.uk/government/organisations/public-health-england • Royal College of Nursing https://www.rcn.org.uk • Royal College of Physicians https://www.rcplondon.ac.uk • Scottish Government https://www.gov.scot • UK Centre for Tobacco and Alcohol Studies http://ukctas.net/index.html • University of Bath Tobacco Control Research Group**Error! Hyperlink reference not valid.** http://www.bath.ac.uk/health/research/tobacco-control • 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 • Welsh Government https://gov.wales/?lang=en • World Health Organization Europe http://www.euro.who.int/en/health-topics/disease-prevention/tobacco The website results will be reviewed on screen and documents that are potentially relevant will be added to EndNote. **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.
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	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 quantitative evidence synthesis. GRADE-CERQual will be used to assess confidence in the findings from qualitative evidence syntheses.
XXI	Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual

XXII	Methods for analysis – combining studies and exploring (in)consistency	**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 I^2 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	NA – Cochrane review used

Appendix B – Literature search strategies

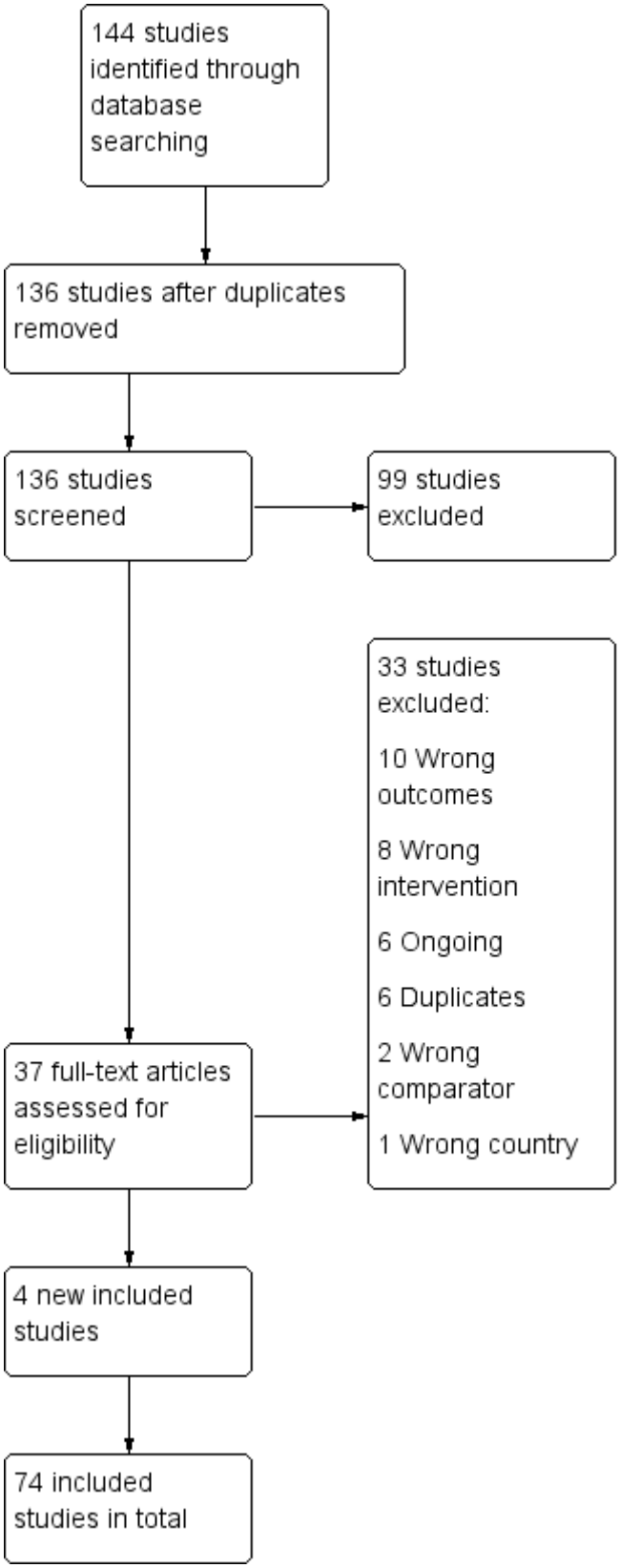
Cochrane TAG searched the Cochrane Tobacco Addiction Group register of trials, which includes the results of comprehensive searches of electronic bibliographic databases and conference abstracts, and the clinical trials registries clinicaltrials.gov and the ICTRP. They checked for relevance all reports of studies with 'relapse prevention' or 'maintenance' or 'relapse near prevent*' in title, abstract or keywords (see full search terms below).

At the time of the search in May 2019, the Register included the results of searches of the Cochrane Central Register of Controlled trials (CENTRAL), issue 1, 2018; MEDLINE (via OVID) to update 20190409; Embase (via OVID) to week 201915; PsycINFO (via OVID) to update 20190401. See the Tobacco Addiction Group website for full search strategies and list of other resources searched.

Cochrane Register of Studies search strategy:

#1 relapse prevention:TI,AB,MH,EMT,XKY
#2 maintenance:TI,AB,MH,EMT,XKY
#3 (relapse NEAR prevent*):TI,AB,MH,EMT,XKY
#4 (relapse* NEAR smok*):TI,AB,MH,EMT,XKY
#5 recurrence:MH,XKY
#6 #1 OR #2 OR #3 OR #4 OR #5

Appendix C – Public health evidence study selection



To note: The above is all related to the update search carried out in May 2019, not previous searches. Of the new studies identified by Cochrane, only one additional was excluded by

NICE (‘1 Wrong country’; Campos 2018). The other studies excluded by NICE were identified through previous searches and so are not captured above.

Study selection process carried out by Cochrane TAG. Discrepancies between this review and Cochrane’s published review are due to application of additional NICE criteria. See “Public health evidence”.

Appendix D – Public health evidence tables

Please see *Relapse prevention interventions for smoking cessation* (Livingstone-Banks, 2019)[h] for full evidence tables.

Livingstone-Banks 2019 (Cochrane Systematic Review)

Bibliographic reference	**Livingstone-Banks J, Norris E, Hartmann-Boyce J, West R, Jarvis M, Chubb E, Hajek P. Relapse prevention interventions for smoking cessation. Cochrane Database of Systematic Reviews 2019, Issue 2. Art. No.: CD003999. DOI: 10.1002/14651858.CD003999.pub5.**
Review question	Cochrane review to determine whether specific interventions for relapse prevention reduce the proportion of recent quitters who return to smoking. This review was updated specifically for use in the Tobacco Update and taking into account the requirements of that update.
Study inclusion characteristics	Randomised or quasi-randomised controlled trials with a minimum follow-up of six months from quit date.
Intervention	Any interventions to prevent relapse. This could include any kind of behavioural intervention or pharmacological intervention.
Comparison	No intervention Shorter intervention Intervention not oriented towards relapse prevention.
Location/setting	USA: 59 Germany: 3 UK: 3 Australia: 2 Belgium: 2 Canada: 2 Turkey: 2 Japan: 1 Spain: 1 Setting included inpatient settings, smoking cessation services, community settings, maternity settings.
Search strategy	Literature searches were conducted in May 2019. The Cochrane Tobacco Addiction Group register of trials was searched.
Included studies	81 studies were included in the review (n = 69,094), including five studies new for this update.
Assessment of study quality	Quality assessment criteria (using Cochrane Collaboration's tool) included: • Random sequence generation (selection bias) • Allocation concealment (selection bias) • Blinding of participants and personnel (performance bias bias) • Blinding of outcome assessment (detection bias) • Incomplete outcome data (attrition bias) • Other potential risks of bias

[h] Livingstone-Banks J, Norris E, Hartmann-Boyce J, West R, Jarvis M, Hajek P. Relapse prevention interventions for smoking cessation. Cochrane Database of Systematic Reviews 2019, Issue 2. Art. No.: CD003999. DOI: 10.1002/14651858.CD003999.pub5.

Bibliographic reference	**Livingstone-Banks J, Norris E, Hartmann-Boyce J, West R, Jarvis M, Chubb E, Hajek P. Relapse prevention interventions for smoking cessation. Cochrane Database of Systematic Reviews 2019, Issue 2. Art. No.: CD003999. DOI: 10.1002/14651858.CD003999.pub5.**		
Outcomes measures and effect size	The main outcome of interest is abstinence at at least six months from randomisation. Preferred: prolonged or multiple point prevalence abstinence Accepted: point prevalence abstinence Health-related quality of life was also included.		
Statistical analysis	To investigate heterogeneity, they used the I^2 statistic. A value greater than 50% may be considered to indicate substantial heterogeneity. The reviewers used risk ratios to summarise individual study outcomes and to determine estimates of pooled effect. They estimated a pooled weighted average of risk ratios with 95% confidence intervals, using a Mantel-Haenszel random-effects model to account for the expected variability in the interventions delivered; for comparisons of pharmacological interventions, a fixed-effect model. Predefined subgroups: • At the request of NICE, for analyses of studies randomising abstainers, we conducted subgroup analyses grouping studies by the duration of prior abstinence of participants. We grouped studies based on whether participants had been abstinent for four or more weeks, less than four weeks, or if prior abstinence varied or was not adequately specified. • At the request of NICE, we conducted a sensitivity analysis removing studies conducted in countries outside of the OECD (Organisation for Economic Co-operation and Development) from any analyses in which they were included. This was intended to ensure the relevance of the results to a UK healthcare setting.		
Risk of bias (ROB) **Overall ROB**	**Domain**	**Concerns (Low / High / unclear)**	**Rationale for concern**
	Study eligibility criteria	Low concern	Eligibility criteria clear, documented, realistic and appropriate.
	Identification and selection of studies	Low concerns	Search strategy appropriate and included a range of sources. Two authors identified potentially eligible studies for inclusion
	Data collection and study appraisal	Low concerns	Duplicate data extraction, clear characteristics extracted. Thresholds of validation methods not reported studies included in the most recent update. Risk of bias was assessed using Cochrane Collaboration's tool for assessing risk of bias.
	Synthesis and findings	Low concerns	Review addresses heterogeneity appropriately (but differently from pre-specified approach for this guideline). Publication bias not discussed. Bias addressed through the GRADE process.
	Overall Risk of Bias	Low risk of bias	
	Other details: None		

Bibliographic reference	**Livingstone-Banks J, Norris E, Hartmann-Boyce J, West R, Jarvis M, Chubb E, Hajek P. Relapse prevention interventions for smoking cessation. Cochrane Database of Systematic Reviews 2019, Issue 2. Art. No.: CD003999. DOI: 10.1002/14651858.CD003999.pub5.**
Source of funding	National Institute for Health Research (NIHR), via Cochrane Infrastructure and Cochrane Programme Grant funding to the Cochrane Tobacco Addiction Group.
Comments	- This review included quasi randomised studies, which were not included in the NICE protocol. Three quasi randomised studies were removed. - This review included all types of cessation pharmacotherapies, but the NICE protocol specified only NRT, varenicline and bupropion. One study investigating impact of rimonabant on relapse prevention was removed. - This review included studies from any country, but the NICE protocol specified studies conducted in OECD countries. Three studies from non-OECD countries (Malaysia, Brazil, China) were removed. - NICE recommends using Cochrane ROB 2.0 to assess risk of bias. Summary risk for the tool used by the Cochrane review (high, unclear, low) were converted to summary risk used for the ROB 2.0 tool (high, some concerns, low) as per the methods chapter.

Appendix E – Forest plots

Abstainers randomly assigned

Pregnant and postpartum ex-smokers (unaided)

Behavioural interventions

Figure 2: Not smoking at delivery/last follow-up prior to delivery – type of intervention

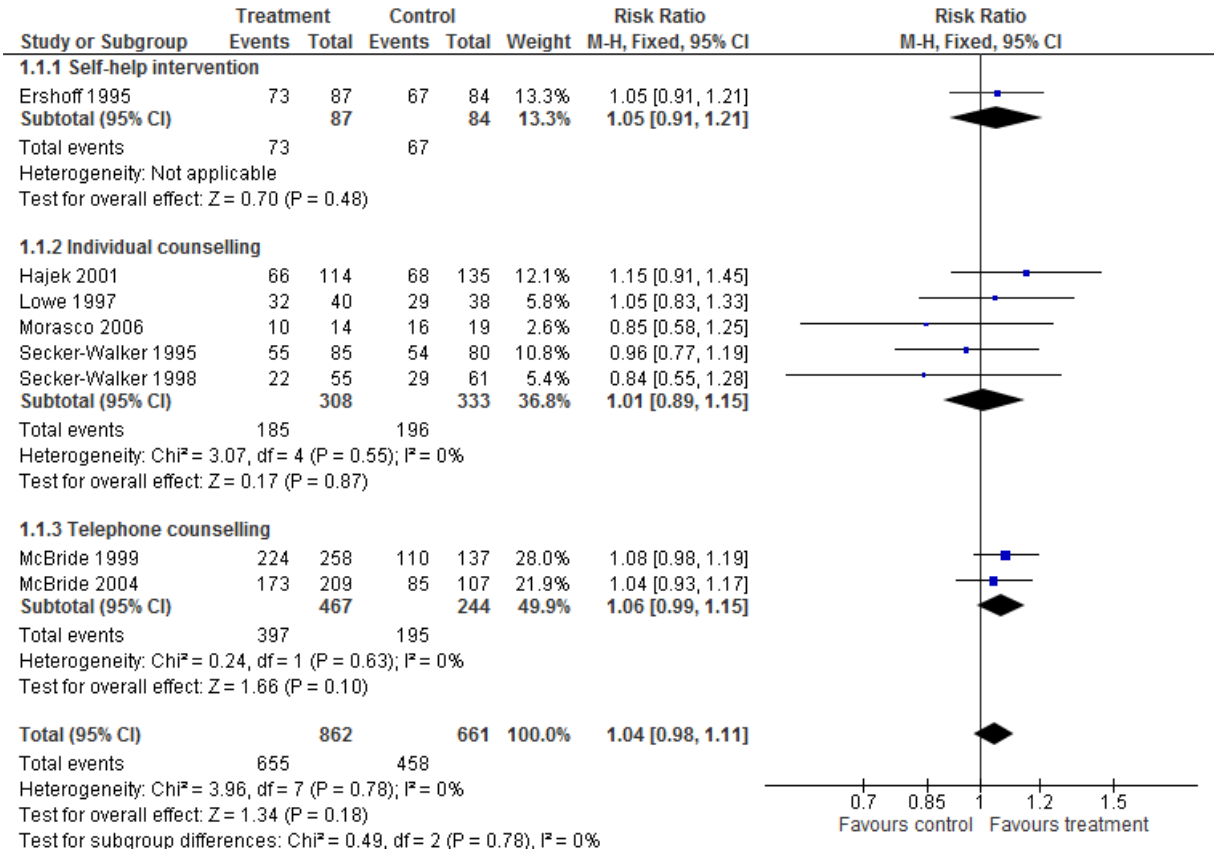
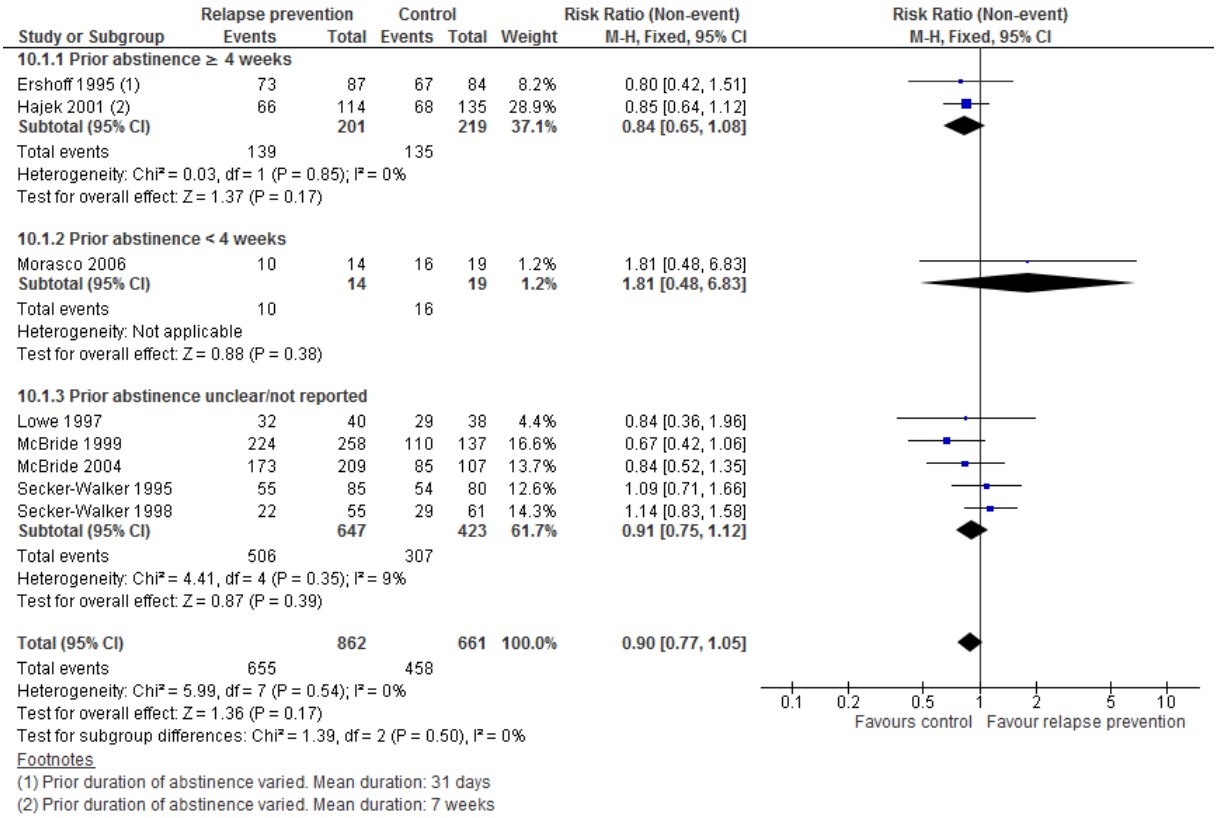


Figure 3: Not smoking at delivery/last follow-up prior to delivery – sensitivity analysis by prior abstinence length



Footnotes

(1) Prior duration of abstinence varied. Mean duration: 31 days

(2) Prior duration of abstinence varied. Mean duration: 7 weeks

Figure 4: Not smoking at longest follow-up after delivery – timing of intervention

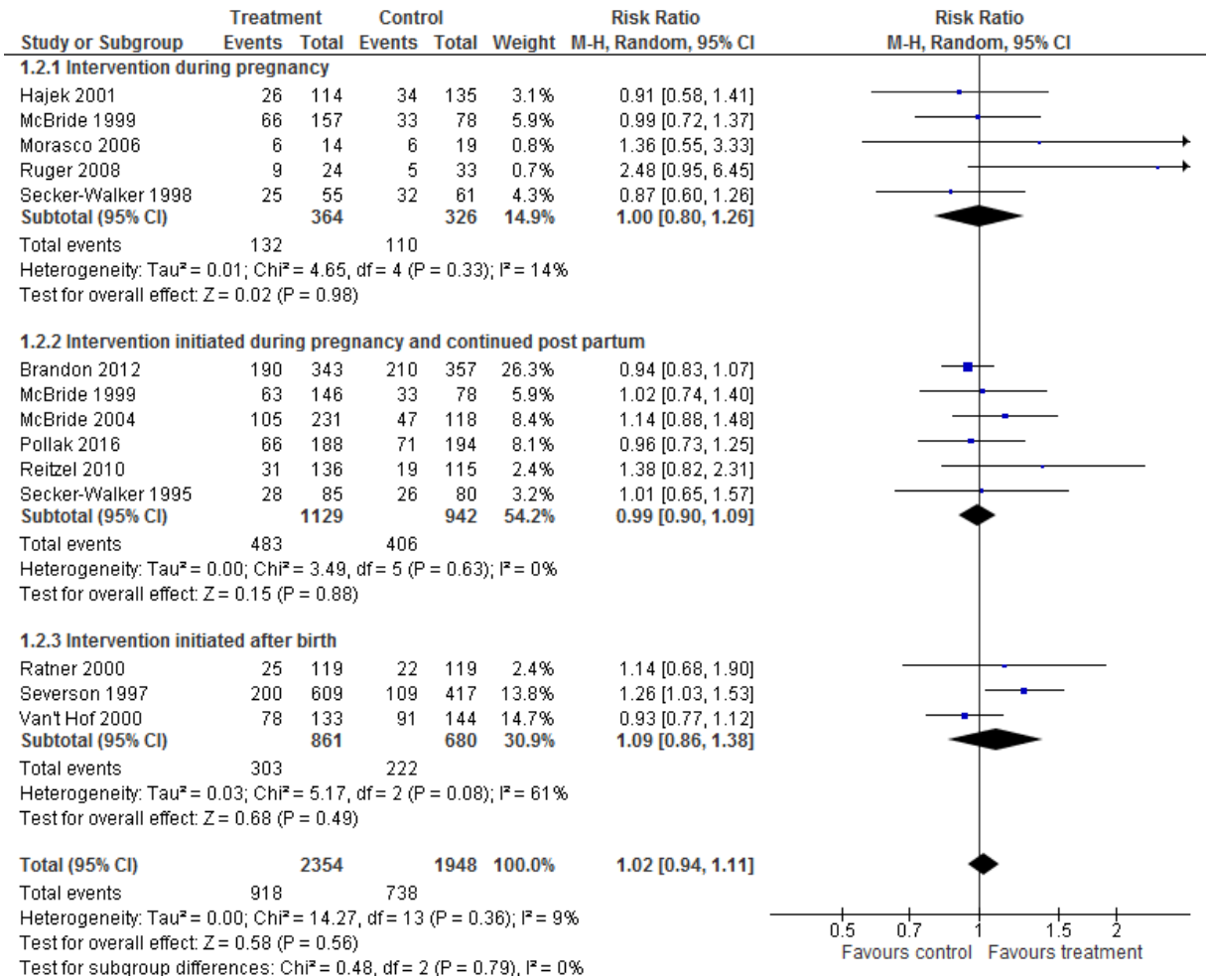
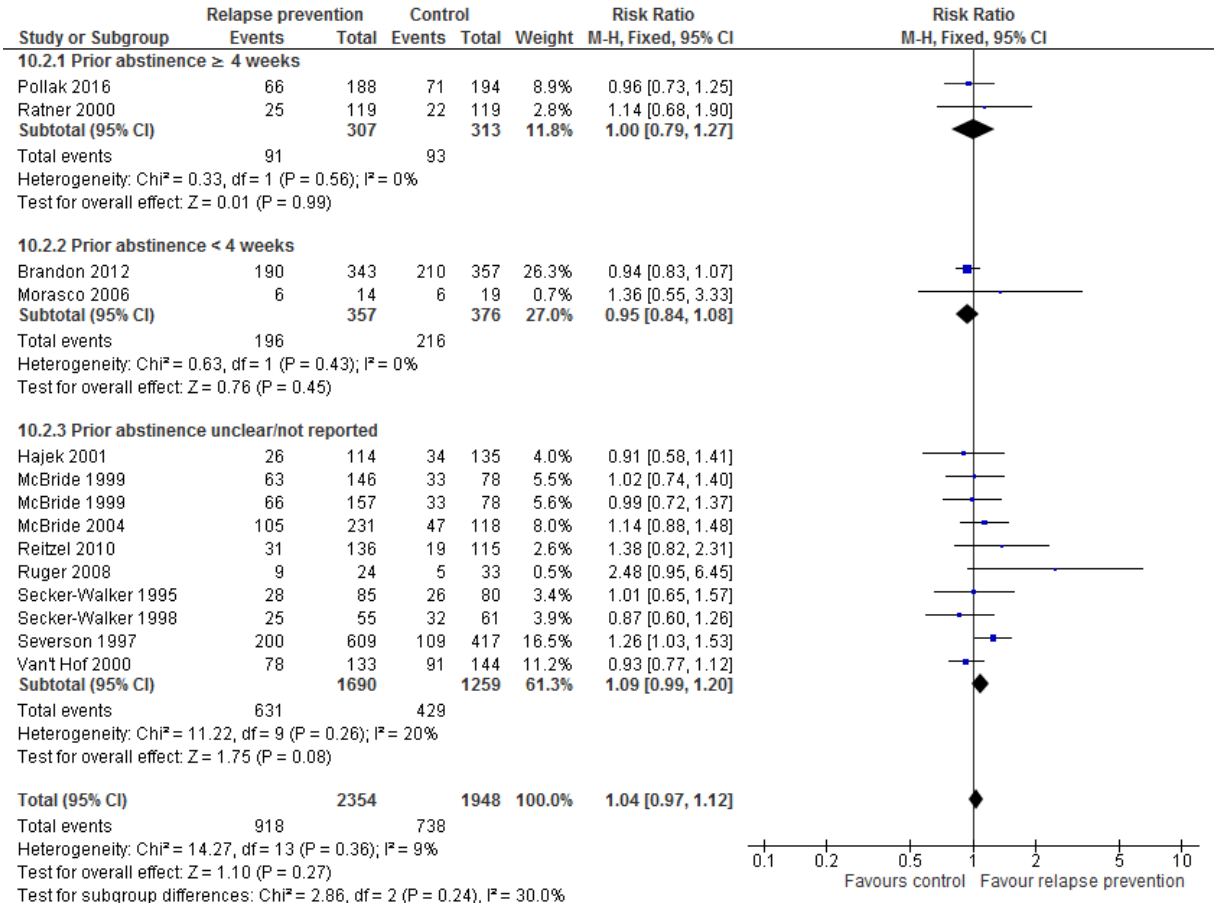


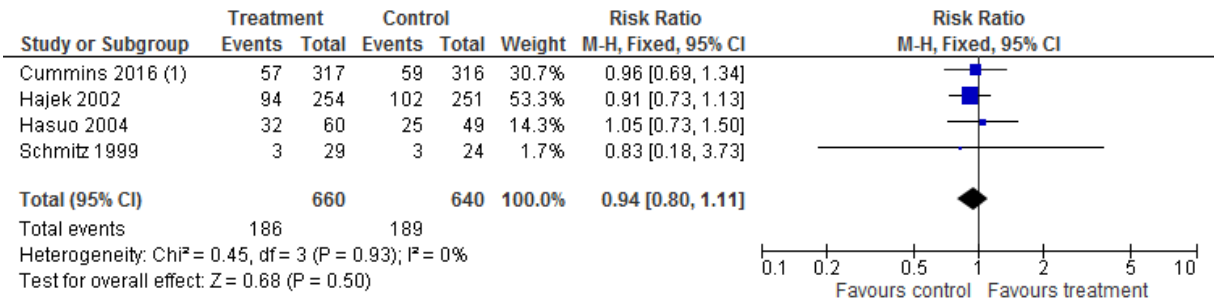
Figure 5: Not smoking at longest follow-up after delivery – sensitivity analysis by prior abstinence length



Hospitalised smokers (unaided)

Behavioural interventions

Figure 6: Not smoking at longest follow-up

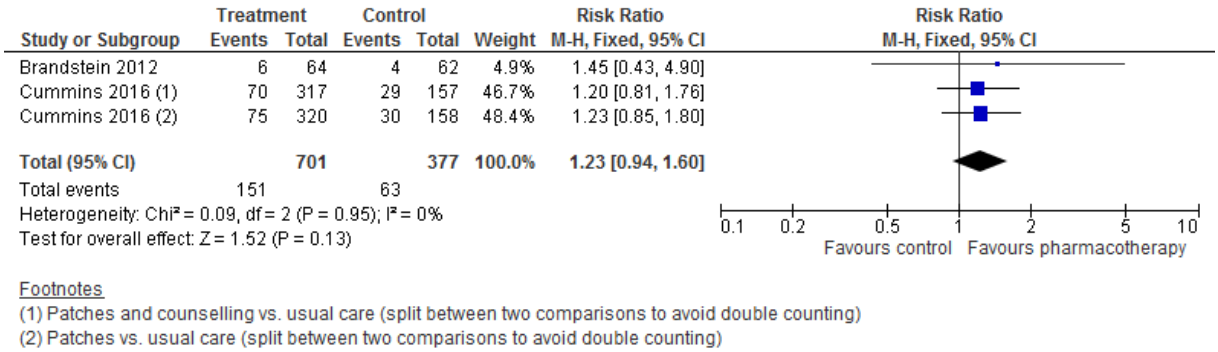


Footnotes
(1) Counselling vs. usual care (one arm of three)

Sensitivity analysis by prior abstinence duration cannot be conducted due to all studies having unclear abstinence duration.

Pharmacotherapy interventions

Figure 7: Not smoking at longest follow-up



Footnotes
(1) Patches and counselling vs. usual care (split between two comparisons to avoid double counting)
(2) Patches vs. usual care (split between two comparisons to avoid double counting)

Sensitivity analysis by prior abstinence duration cannot be conducted due to all studies having unclear abstinence duration.

General population – unaided abstainers

Behavioural interventions

Figure 8: Not smoking at longest follow-up

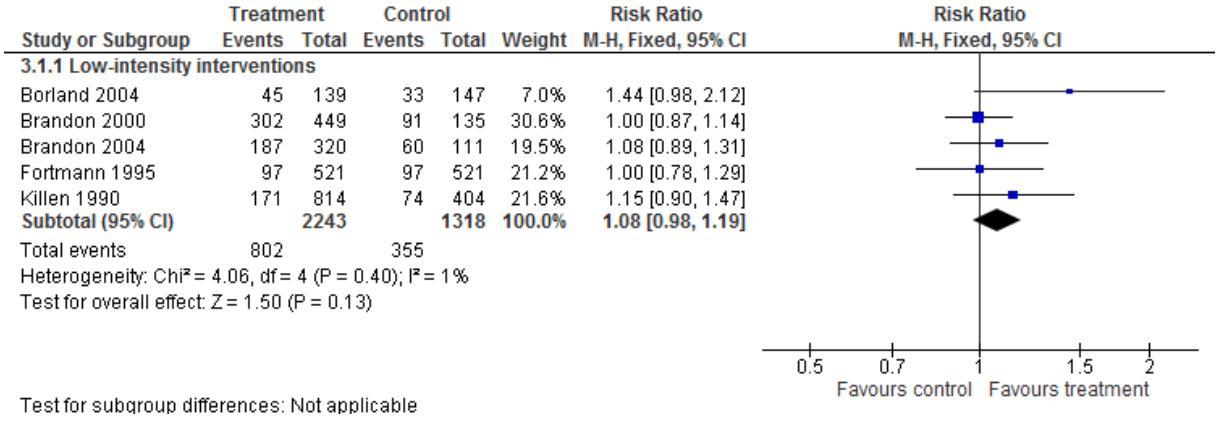
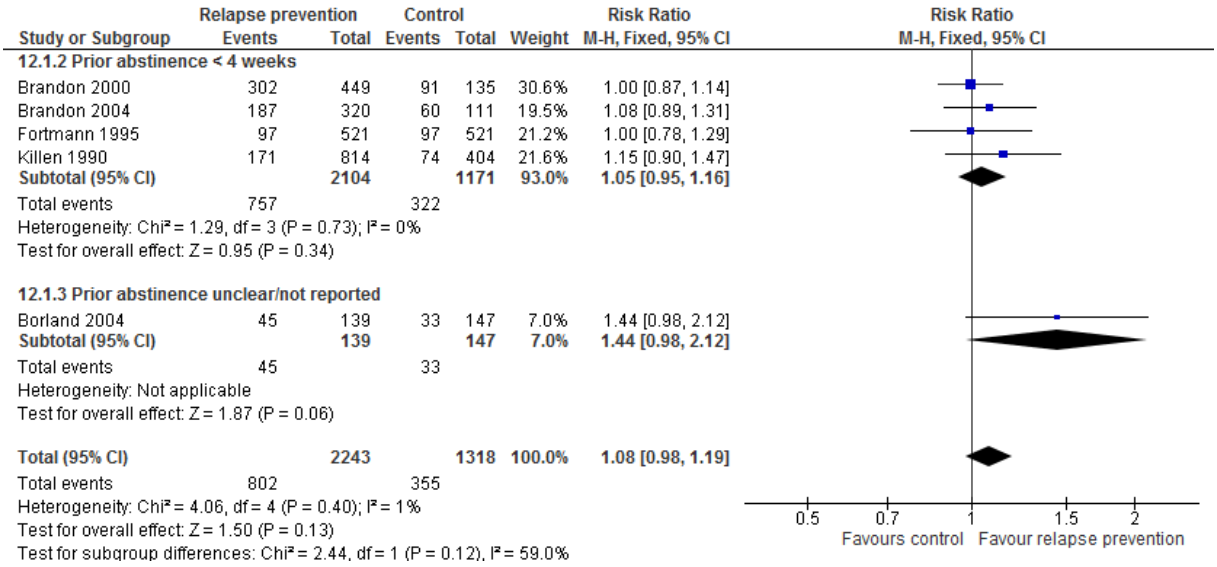
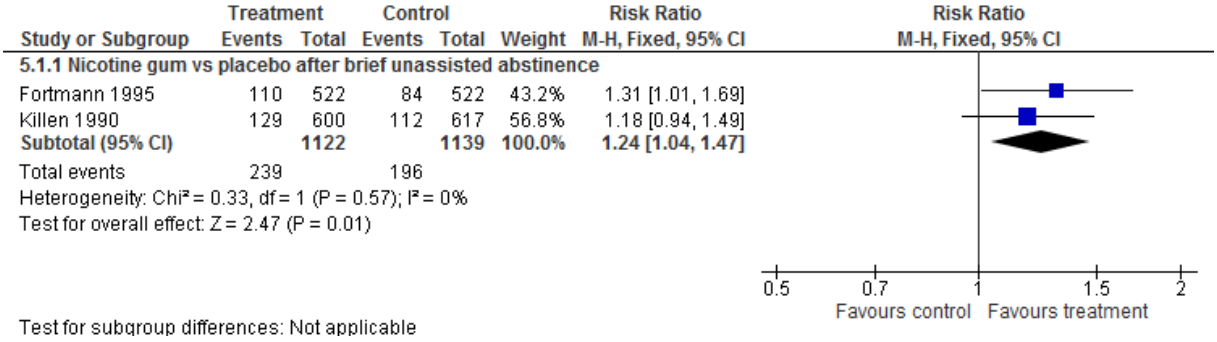


Figure 9: Not smoking at longest follow-up – sensitivity by prior abstinence length



Pharmacotherapy interventions

Figure 10: NRT vs placebo, not smoking 12 months after quit date

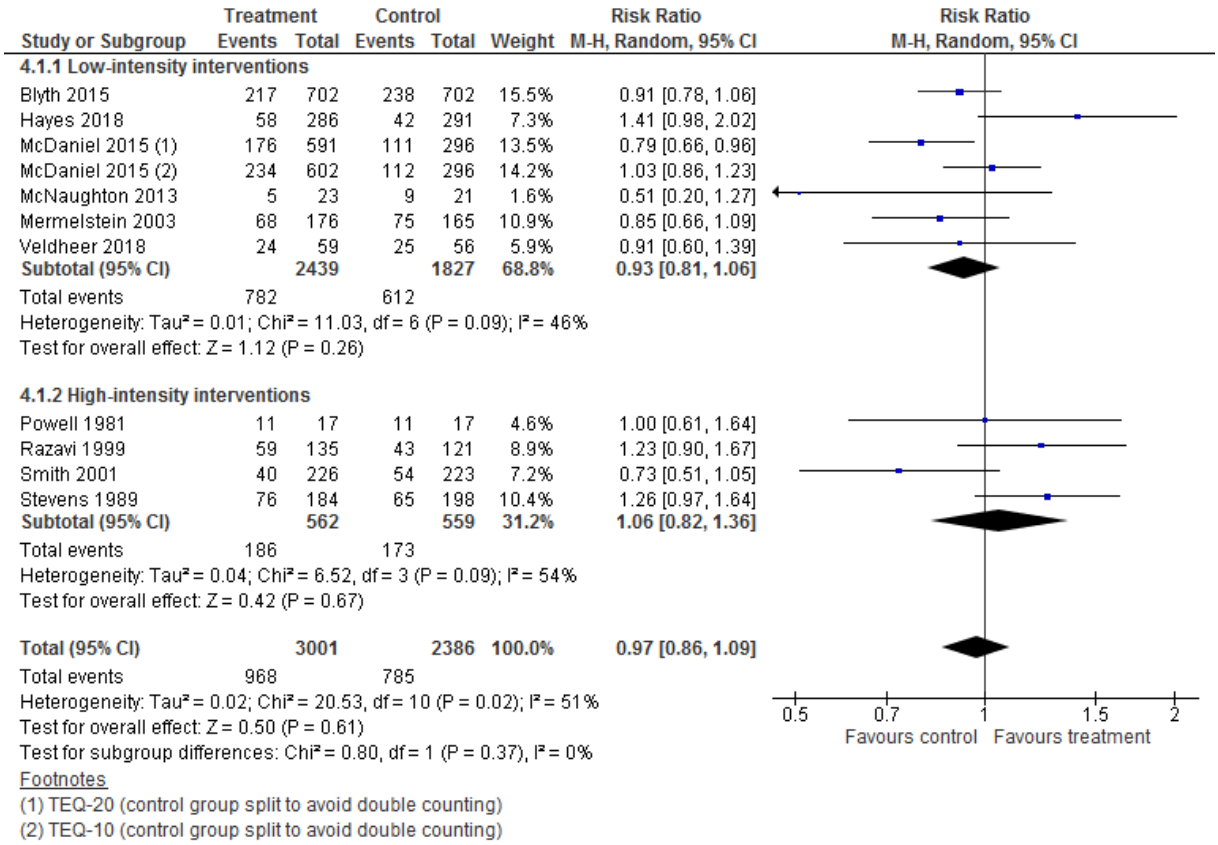


Sensitivity analysis by prior abstinence duration cannot be conducted due to all studies having abstinence durations below 4 weeks.

General population – assisted abstainers

Behavioural interventions

Figure 11: Not smoking at longest follow-up – by intensity of intervention

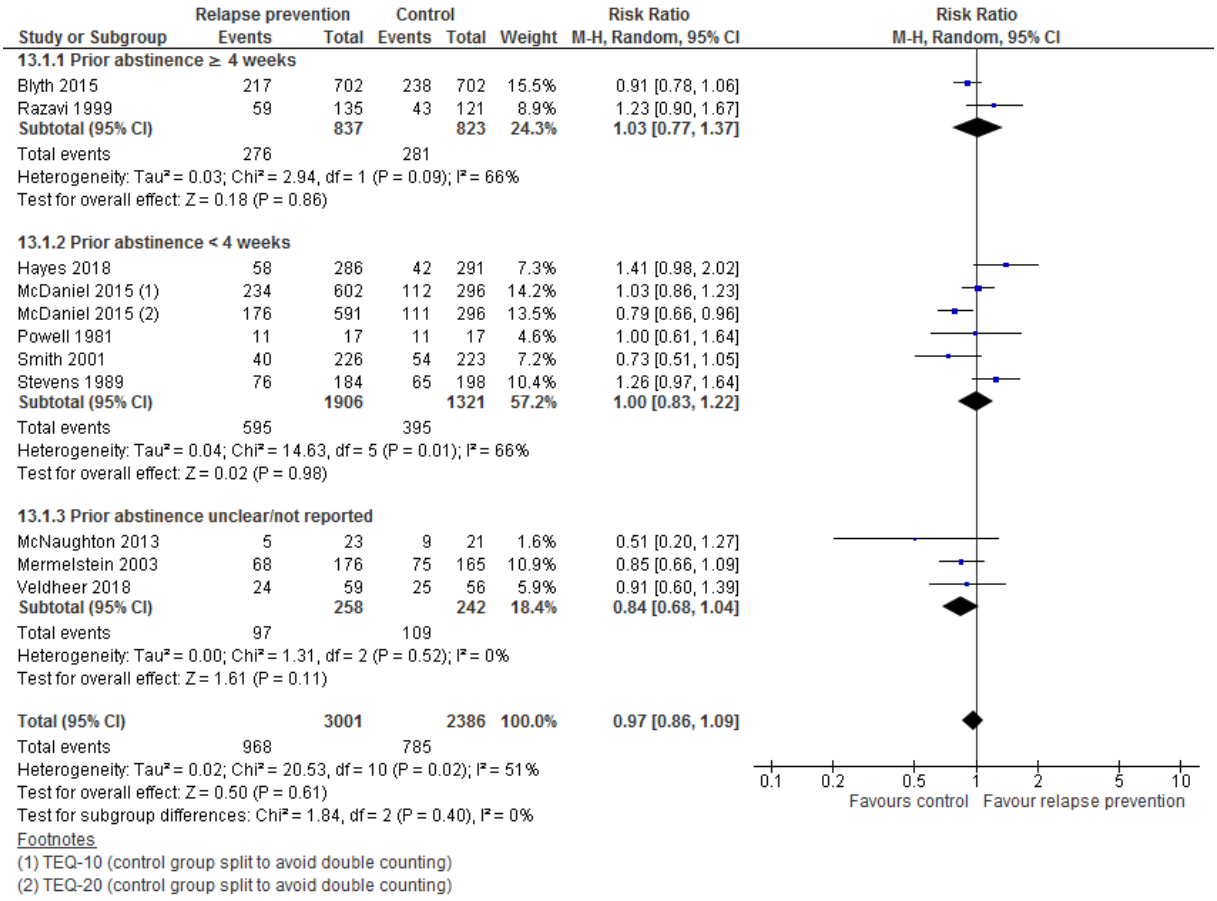


Footnotes

(1) TEQ-20 (control group split to avoid double counting)

(2) TEQ-10 (control group split to avoid double counting)

Figure 12: Not smoking at longest follow-up – sensitivity by prior abstinence length

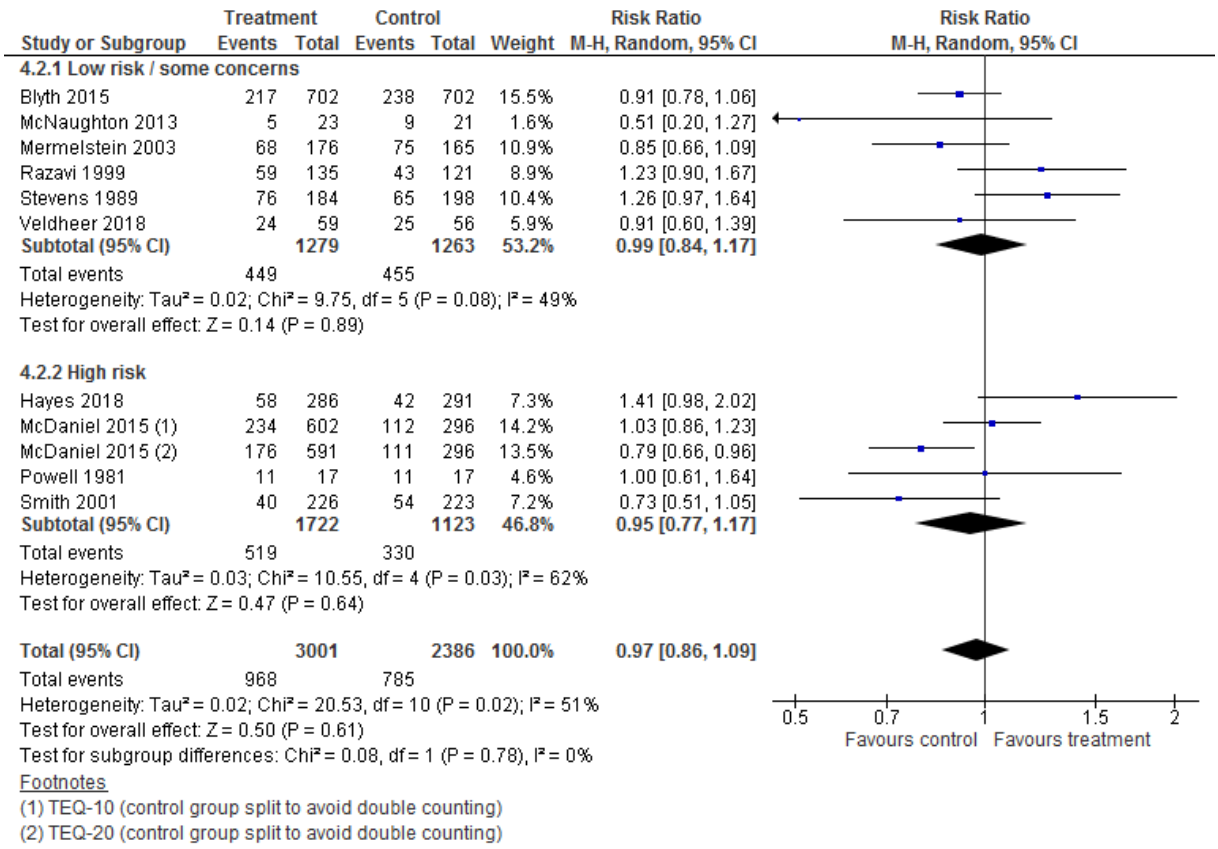


Footnotes

(1) TEQ-10 (control group split to avoid double counting)

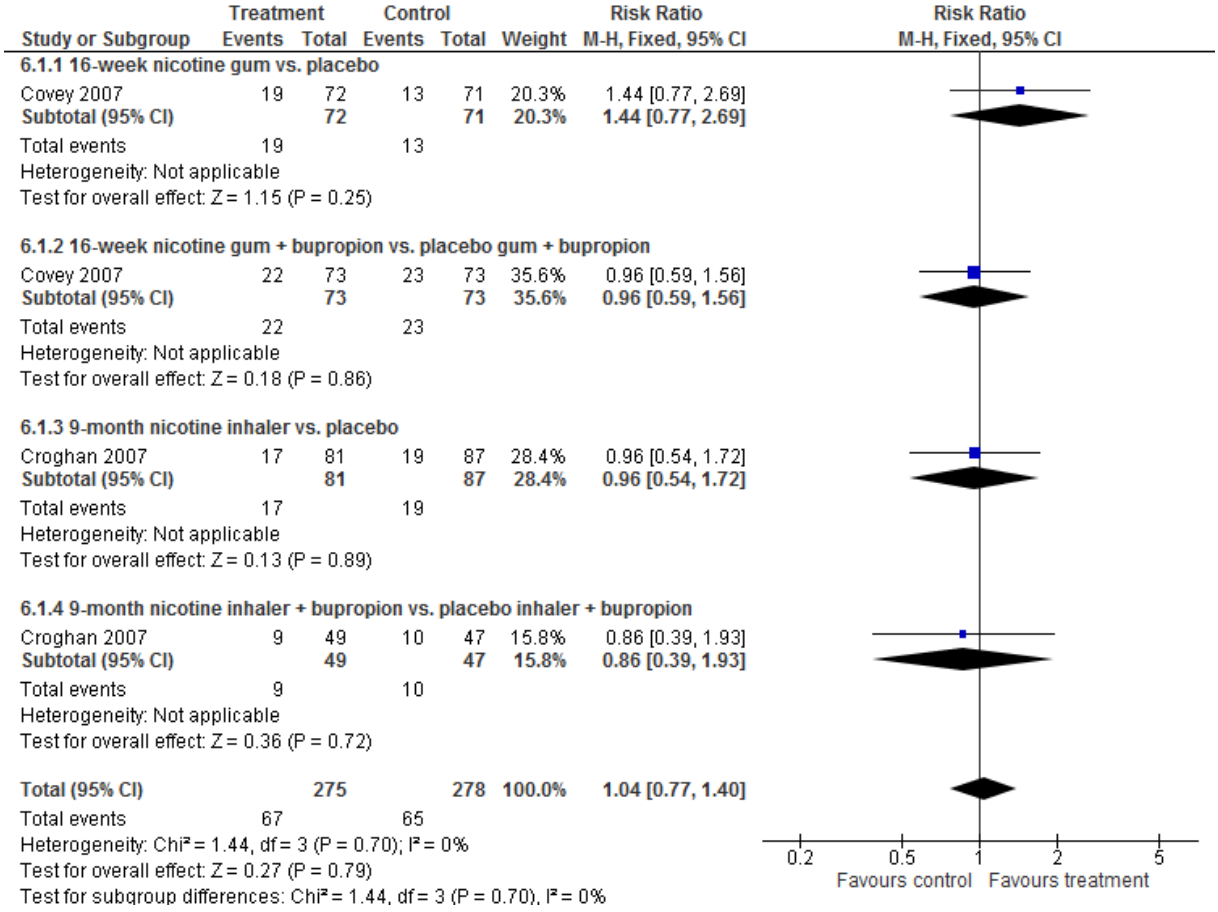
(2) TEQ-20 (control group split to avoid double counting)

Figure 13: Not smoking at longest follow-up – sensitivity analysis by risk of bias



Pharmacotherapy interventions

Figure 14: NRT vs placebo, not smoking 12 + months after quit date by mode



Sensitivity analysis by prior abstinence duration cannot be conducted due to all studies having unclear abstinence durations (but reported as brief by Cochrane TAG).

Figure 15: Bupropion vs placebo, not smoking 12 + months after quit date

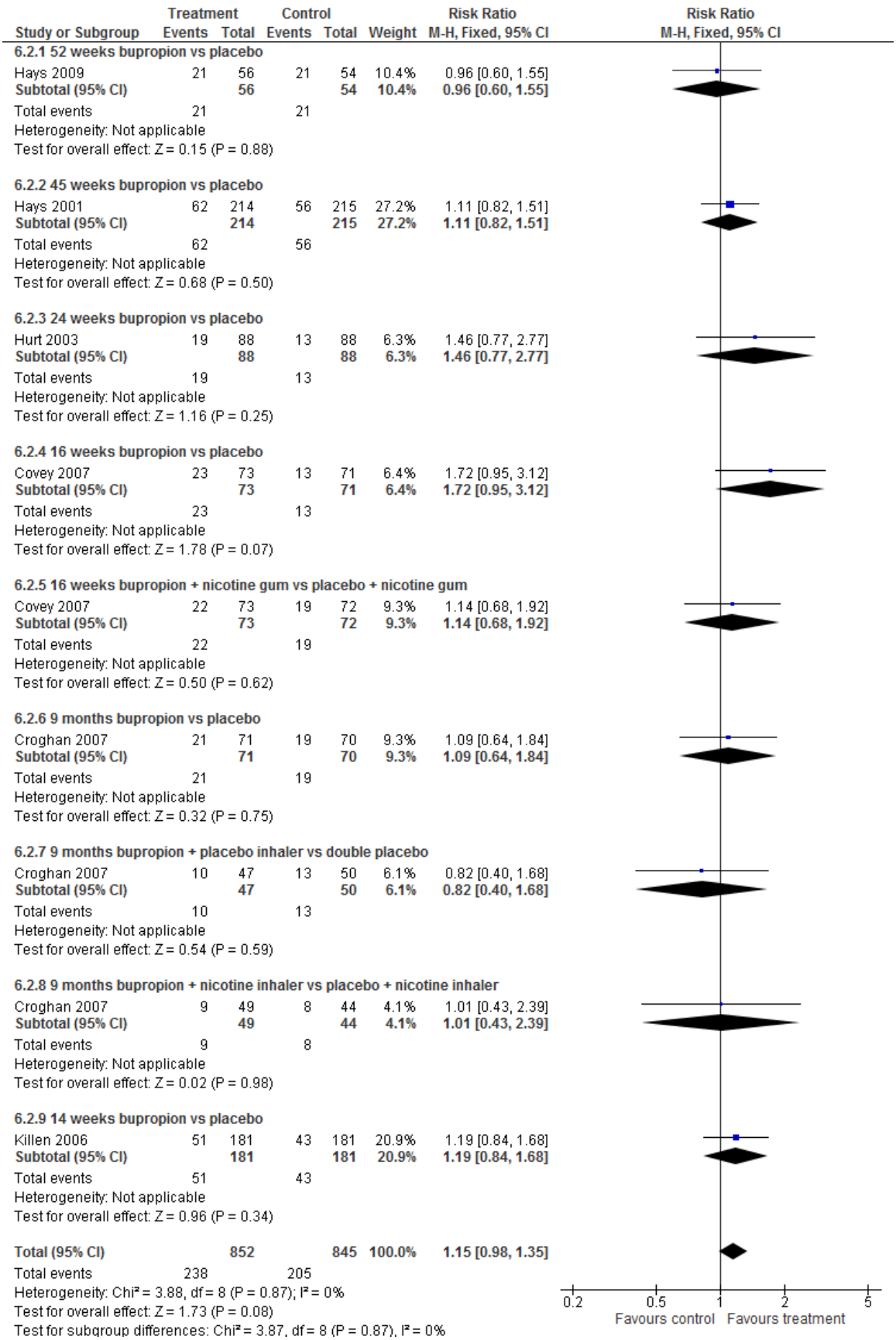


Figure 16: Bupropion vs placebo, not smoking 12 + months after quit date – sensitivity by prior abstinence duration

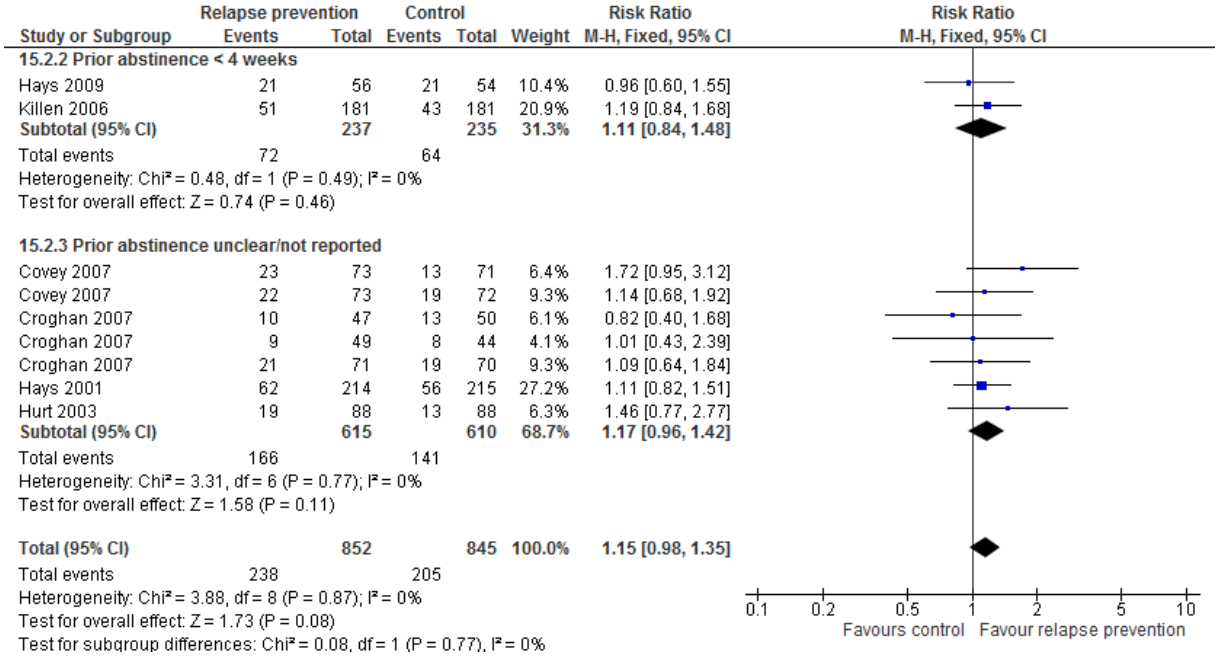
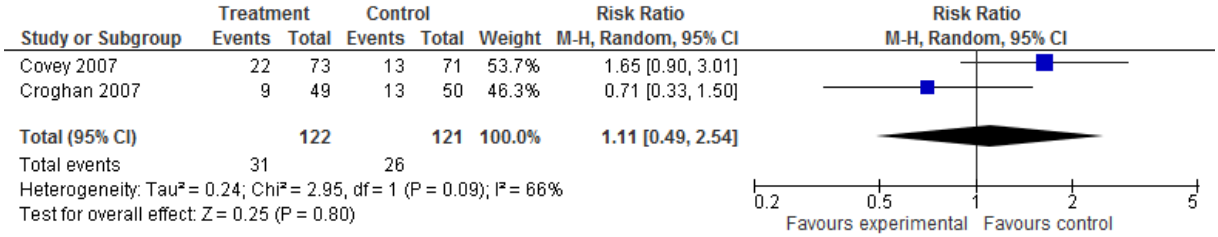


Figure 17: Combination NRT and bupropion vs placebo, not smoking at longest follow-up



Sensitivity analysis by prior abstinence duration cannot be conducted due to all studies having unclear abstinence durations. Sensitivity analysis by risk of bias could not be conducted because both studies are at low risk of bias.

Smokers randomly assigned

Contact time matched (behavioural interventions)

Figure 18: Group/individual therapy format (+/- adjunct pharmacotherapy), cessation at longest follow-up

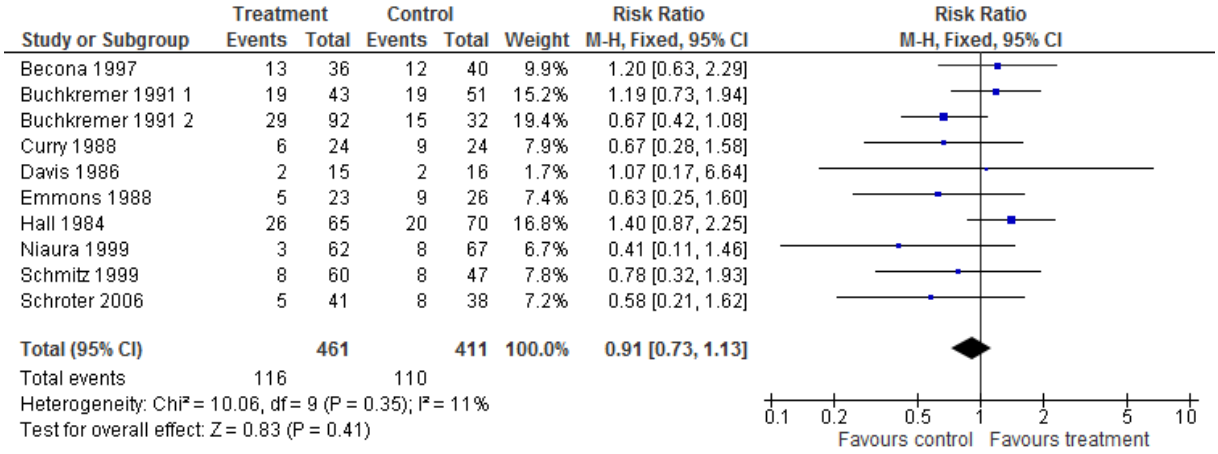
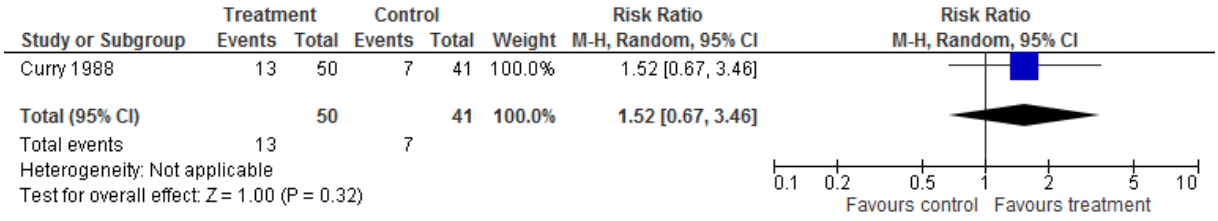


Figure 19: Self-help format, cessation at longest follow-up



Contact time not matched (behavioural interventions)

Figure 20: Face to face interventions: cessation at longest follow-up – by intensity of control group intervention

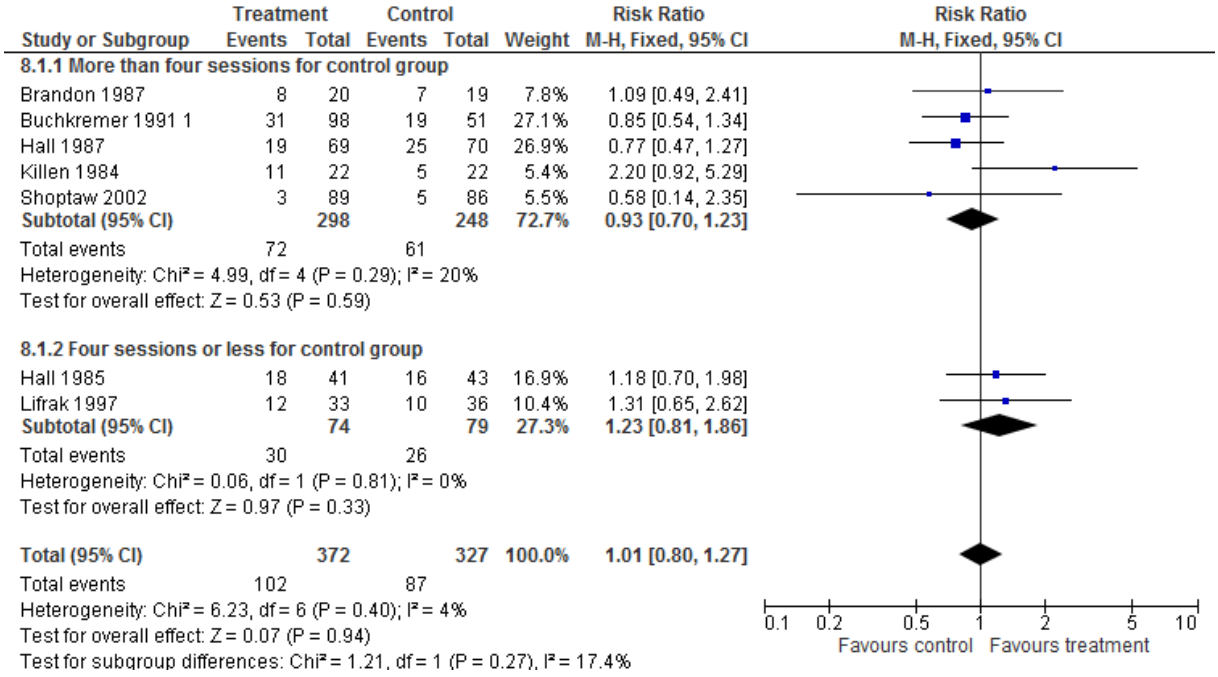
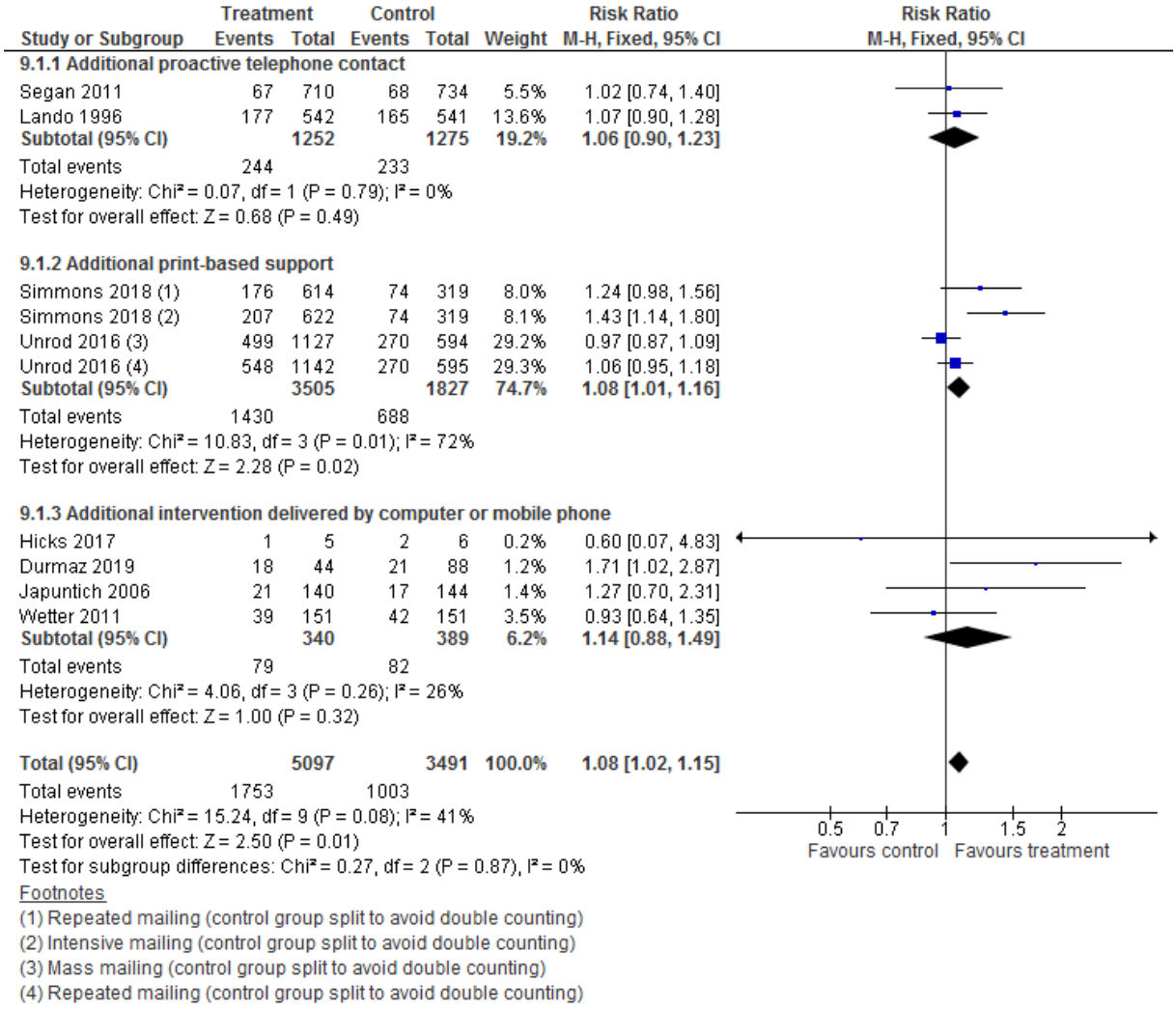
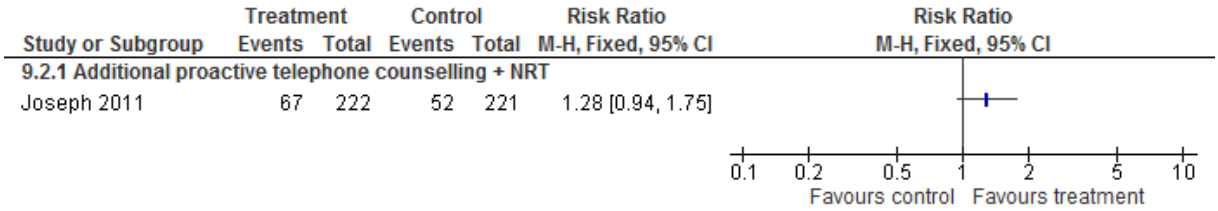


Figure 21: Other modes: cessation at longest follow-up – by mode of additional element



Combined behavioural and pharmacological interventions

Figure 22: Cessation at longest follow-up



Funnel plots for publication bias

Figure 23: Pregnant / postpartum ex-smokers: Not smoking at longest follow-up after delivery

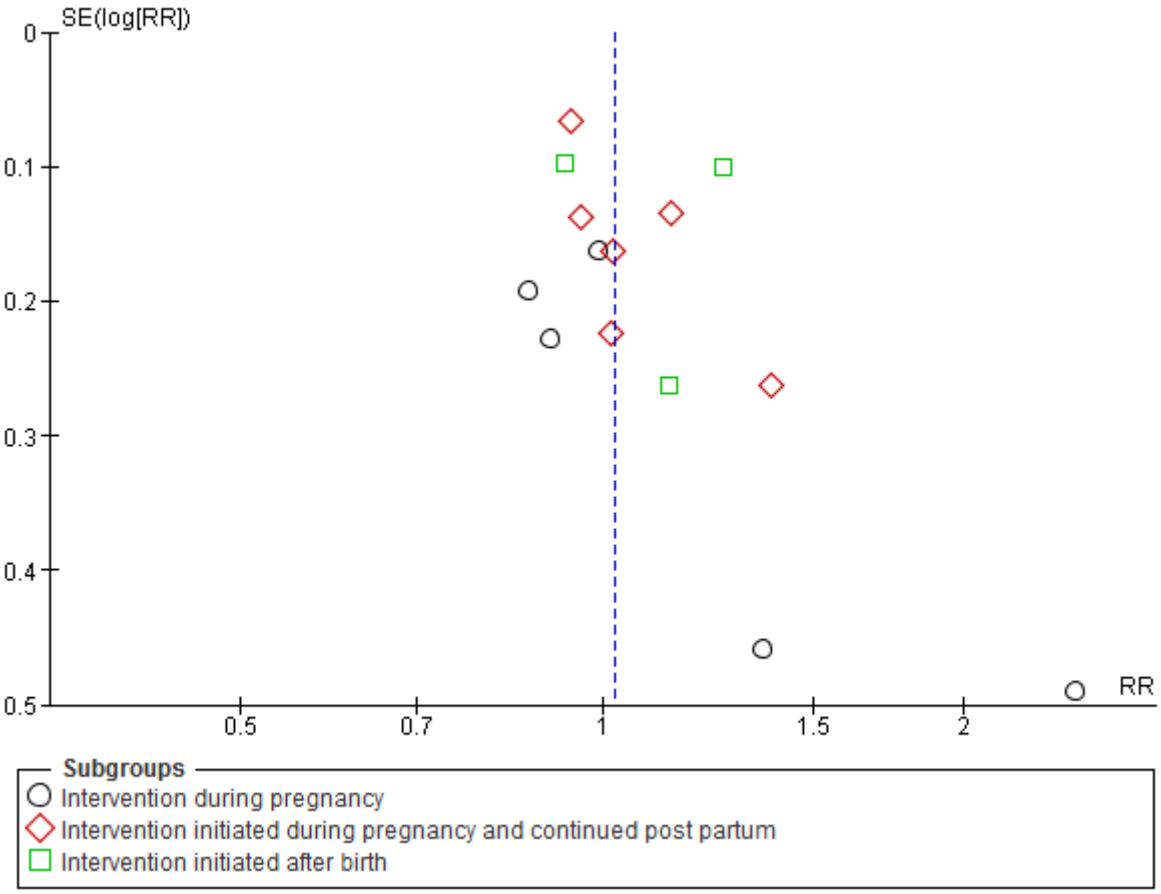
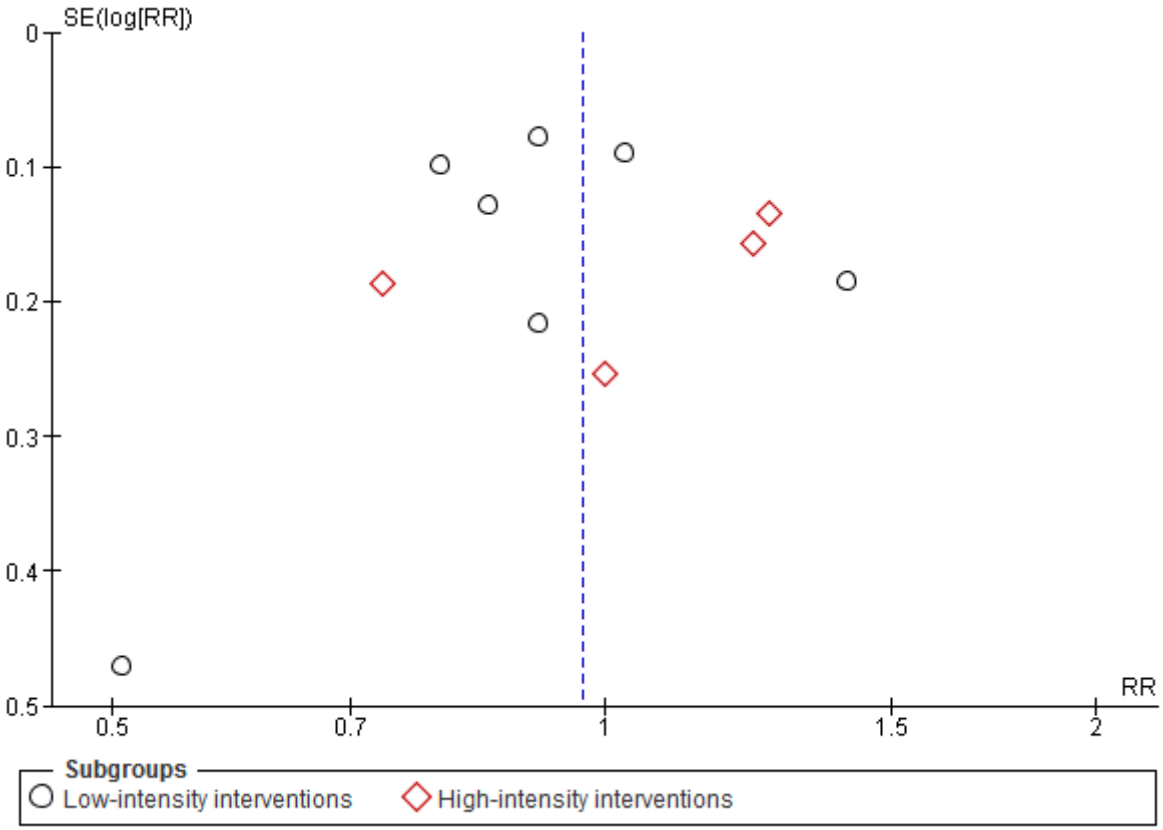


Figure 24: Assisted abstainers: Not smoking at longest follow-up



Appendix F – GRADE tables

Profile 1: Not smoking: pregnant and postpartum ex-smokers (Figure 1-4)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Behavioural interventions for abstinent pregnant/postpartum women	Control	Relative (95% CI)	Absolute	
Not smoking at delivery/last follow-up prior to delivery											
8 (b-g, l, m	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	655/862 (76%)	458/661 (69.3%)	RR 1.04 (0.98 to 1.11)	28 more per 1000 (from 14 fewer to 76 more)	⊕⊕OO LOW
Not smoking at longest follow-up after delivery											
13 (a, c, e-o)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	918/2354 (39%)	738/1948 (37.9%)	RR 1.02 (0.94 to 1.11)	8 more per 1000 (from 23 fewer to 42 more)	⊕OOO VERY LOW

[1] 6/8 studies at high risk of bias due to unclear reporting or poor allocation concealment
[2] CI crosses the MID
[3] 11/13 studies at high risk of bias due to unclear reporting or poor allocation concealment or blinding of outcome assessment

a) Brandon 2012
b) Ershoff 1995
c) Hajek 2001
d) Lowe 1997
e) McBride 1999
f) McBride 2004
g) Morasco 2006
h) Pollack 2016
i) Ratner 2000
j) Reitzel 2010
k) Ruger 2008
l) Secker-Walker 1995
m) Secker-Walker 1998
n) Severson 1997
o) Van't Hof 2000

Profile 2: Not smoking: hospitalised smokers (Figure 5-6)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Interventions for abstinent hospitalised smokers	Control	Relative (95% CI)	Absolute	
Behavioural interventions, not smoking at longest follow-up											
4 (b-e)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	186/660 (28.2%)	189/640 (29.5%)	RR 0.94 (0.8 to 1.11)	18 fewer per 1000 (from 59 fewer to 32 more)	⊕⊕⊕O MODERATE
Pharmacotherapy interventions, not smoking at longest follow-up											
2 (a, b)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	151/701 (21.5%)	63/377 (16.7%)	RR 1.23 (0.94 to 1.6)	38 more per 1000 (from 10 fewer to 100 more)	⊕⊕⊕O MODERATE

[1] CI crosses the MID

a) Brandstein 2012
b) Cummins 2016
c) Hajek 2002
d) Hasuo 2004
e) Schmitz 1999

Profile 3: Not smoking: general population unaided abstainers, behavioural interventions (Figure 7-8)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Behavioural interventions for unaided abstainers	Control	Relative (95% CI)	Absolute	
not smoking at longest follow-up - Low-intensity interventions											
5 (a-e)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	802/2243 (35.8%)	355/1318 (26.9%)	RR 1.08 (0.98 to 1.19)	22 more per 1000 (from 5 fewer to 51 more)	⊕⊕OO LOW

[1] 3/5 studies high risk of bias due to lack of information on randomisation process and allocation concealment. Mixed coverage of blinding.
[2] CI crosses MID

a) Borland 2004
b) Brandon 2000
c) Brandon 2004
d) Fortmann 1995
e) Killen 1990

Profile 4: Not smoking: general population unaided abstainers, pharmacotherapy (Figure 9)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Pharmacotherapy for unaided abstainers	Control	Relative (95% CI)	Absolute	
not smoking 12 months after quit date - Nicotine gum vs placebo after brief unassisted abstinence											
2 (a, b)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	239/1122 (21.3%)	196/1139 (17.2%)	RR 1.24 (1.04 to 1.47)	41 more per 1000 (from 7 more to 81 more)	⊕⊕⊕O MODERATE

[1] 2/2 studies high risk of bias. Randomisation method not stated and unclear allocation concealment.

a) Fortmann 1995
b) Killen 1990

Profile 5: Not smoking: general population assisted abstainers, behavioural interventions (Figure 10-12)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Behavioural interventions for assisted abstainers	Control	Relative (95% CI)	Absolute	
not smoking at longest follow-up											
10 (a-j)	randomised trials	no serious risk of bias[1]	serious[2]	no serious indirectness	serious[3]	none	968/3001 (32.3%)	785/2386 (32.9%)	RR 0.97 (0.86 to 1.09)	10 fewer per 1000 (from 46 fewer to 30 more)	⊕⊕OO LOW

[1] 4/10 studies at high risk of bias but not judged to be widespread enough to downgrade. Sensitivity analysis by risk of bias did not show different effects for high risk of bias studies.
[2] I squared 51%. Splitting by low and high intensity interventions did not resolve heterogeneity.
[3] CI crosses MID

a) Bluth 2015

b) Hayes 2018
c) McDaniel 2015
d) McNaugton 2013
e) Mermelstein 2003
f) Powell 1981
g) Razavi 1999
h) Smooth 2001
i) Stevens 1989
j) Veldheer 2018

Profile 6: Not smoking: general population assisted abstainers, pharmacotherapy (Figure 13-16)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Pharmacotherapy for assisted abstainers	Control	Relative (95% CI)	Absolute	
Nicotine replacement therapy (1 gum, 1 inhaler) versus placebo. not smoking 12 months + after quit date											
2 (a, b)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	67/275 (24.4%)	65/278 (23.4%)	RR 1.04 (0.77 to 1.4)	9 more per 1000 (from 54 fewer to 94 more)	⊕⊕⊕O MODERATE
Bupropion vs. placebo. not smoking 12 months + after quit date											
6 (a, b, d-g)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	238/852 (27.9%)	205/845 (24.3%)	RR 1.15 (0.98 to 1.35)	36 more per 1000 (from 5 fewer to 85 more)	⊕⊕⊕O MODERATE
Combination NRT & bupropion vs placebo. not smoking at longest follow-up											
2 (a, b)	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	very serious[3]	none	31/122 (25.4%)	26/121 (21.5%)	RR 1.11 (0.49 to 2.54)	24 more per 1000 (from 110 fewer to 331 more)	⊕OOO VERY LOW
Varenicline vs placebo. not smoking 12 months + after quit date											
1 (h)	randomised trials	General population: No serious risk of bias	NA[5]	no serious indirectness	General population: No serious	none	General population: 263/603 (43.6%)	General population: 224/607 (37%)	General population: 1.18 (1.03, 1.36)	Not calculable	General population: ⊕⊕⊕⊕ HIGH
Varenicline vs placebo. not smoking 12 months + after quit date											

1 (c)	randomised trials	Severe mental illness (SMI) population: Serious[4]	NA[5]	no serious indirectness	SMI population: No serious	none	SMI population: 18/40 (45%)	SMI population: 7/47 (15%)	SMI population: 3.02 (1.41, 6.49)	Not caluclable	SMI population: ⊕⊕⊕O MODERATE

[1] CI crosses MID
[2] I squared is 66%
[3] CI crosses MID, and <300 participants in total
[4] Study at high risk of bias, high attrition from control group only, unclear reasons, potential for bias.
[5] Studies not combined in meta-analysis due to heterogeneity

a) Covey 2007
b) Croghan 2007
c) Evins 2014
d) Hays 2009
e) Hays 2001
f) Hurt 2003
g) Killen 2006
h) Tonstad 2006

Profile 7: Not smoking: behavioural interventions, time matched (Figure 17-18)

Quality assessment							No of patients		Effect		Confidence
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Behavioural interventions for smokers. RP**	**cessation, matched for programme length**	**Relative (95% CI)**	**Absolute**	
Group or individual format therapy (+/- adjunct pharmacotherapy), not smoking at longest follow-up											
10 (a-j)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	116/461 (25.2%)	110/411 (26.8%)	RR 0.91 (0.73 to 1.13)	24 fewer per 1000 (from 72 fewer to 35 more)	⊕⊕OO LOW
Self-help format, not smoking at longest follow-up											
1 (d)	randomised trials	serious[3]	NA	no serious indirectness	very serious[4]	none	13/50 (26%)	7/41 (17.1%)	RR 1.52 (0.67 to 3.46)	89 more per 1000 (from 56 fewer to 420 more)	⊕OOO VERY LOW

[1] 9/10 studies at high risk of bias, unclear reporting and some risk that allocation was not concealed in some studies,
[2] CI crosses MID
[3] Study at high risk of bias, risk that allocation was not concealed and unclear reporting in other areas
[4] CI crosses MID and <300 participants in total

a) Becona 1997
b) Buchkremer 1991 1
c) Buchkremer 1991 2
d) Curry 1988
e) Davis 1986
f) Emmons 1988
g) Hall 1984
h) Niaura 1999
i) Schmitz 1999
j) Schroter 2006

Profile 8: Not smoking: behavioural interventions face to face, not time matched (Figure 19)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Behavioural interventions for smokers. RP	cessation, different intensity programmes	Relative (95% CI)	Absolute	
Not smoking at longest follow-up											
7 (a-g)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	102/372 (27.4%)	87/327 (26.6%)	RR 1.01 (0.8 to 1.27)	3 more per 1000 (from 53 fewer to 72 more)	⊕⊕OO LOW

[1] 5/7 studies at high risk of bias. Concerns about blinding of outcome assessment in one study, and of participants in another. Some lack of reporting.
[2] CI crosses MID

a) Brandno 1987
b) Buchkremer 1991 1
c) Hall 1985
d) Hall 1987
e) Killen 1984
f) Lifrak 1997
g) Shoptaw 2002

Profile 9: Not smoking: behavioural interventions other modes, not time matched (Figure 20-21)

Quality assessment	No of patients	Effect	Confidence

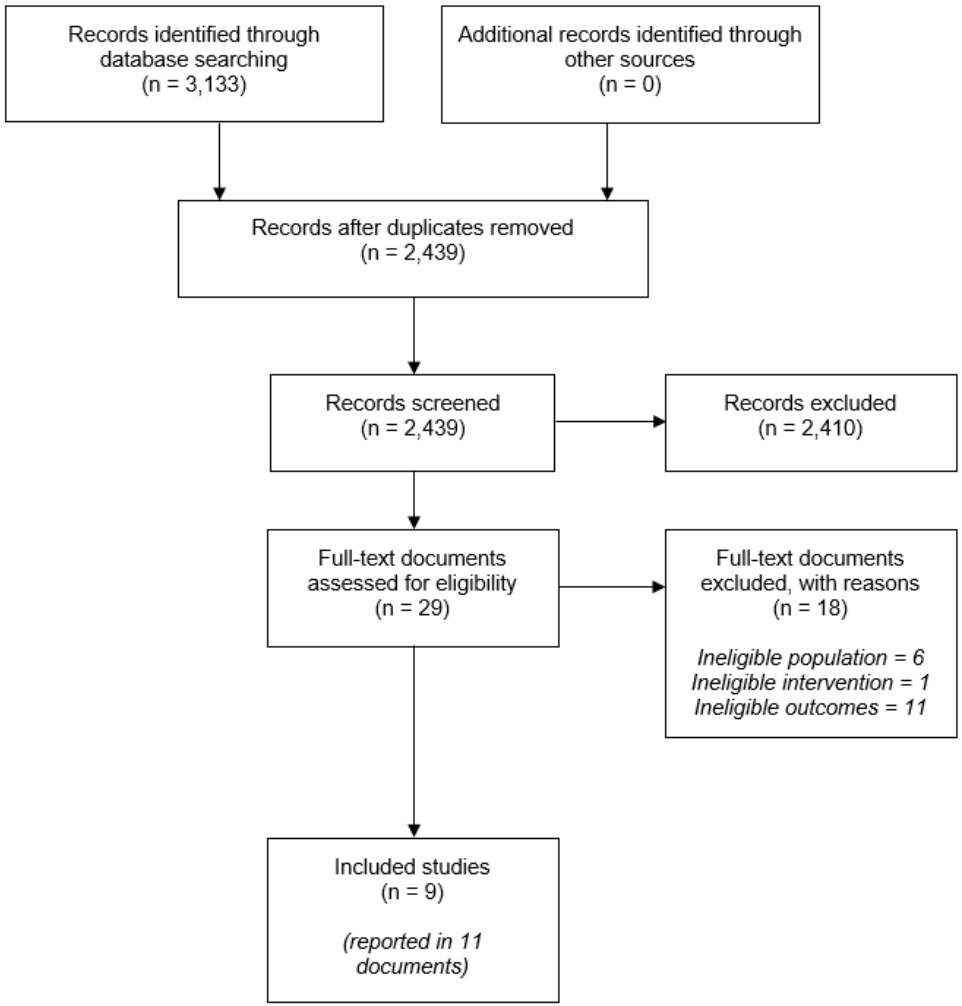
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Interventions for smokers, tests of adjuncts to cessation programmes	Control	Relative (95% CI)	Absolute	
Behavioural interventions (telephone, print, computer, mobile phone), not smoking at longest follow-up											
8 (a-c, e-i)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1753/5097 (34.4%)	1003/3491 (28.7%)	RR 1.08 (1.02 to 1.15)	23 more per 1000 (from 6 more to 43 more)	⊕⊕OO LOW
Combined behavioural and pharma interventions, not smoking at longest follow-up - Additional proactive telephone counselling + NRT											
1 (d)	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[2]	none	67/222 (30.2%)	52/221 (23.5%)	RR 128 (0.94 to 1.75)	66 more per 1000 (from 14 fewer to 176 more)	⊕⊕⊕O MODERATE

[1] 5/8 studies at high risk of bias; study with majority weight at high risk due to lack of blinding or validation.
[2] CI crosses MID

a) Durmaz 2019
b) Hicks 2017
c) Japundich 2006
d) Joseph 2011
e) Lando 1996
f) Segan 2011
g) Simmons 2018
h) Unrod 2016
i) Wetter 2011

Appendix G – Economic evidence study selection

Figure 25: Flow chart of economic evidence study selection


Records identified through database searching (n = 3,133)
Additional records identified through other sources (n = 0)
Records after duplicates removed (n = 2,439)
Records screened (n = 2,439)
Records excluded (n = 2,410)
Full-text documents assessed for eligibility (n = 29)
Full-text documents excluded, with reasons (n = 18)
Ineligible population = 6
Ineligible intervention = 1
Ineligible outcomes = 11
Included studies (n = 9)
(reported in 11 documents)

Appendix H – Economic evidence tables

Health economic evidence profiles of studies included in the economic evidence review for cost-effectiveness of preventing relapse

Study	Blyth 2015 (UK)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: Cost-utility analysis (CUA) **Study design:** Economic evaluation conducted alongside an open, parallel-arm, randomised-controlled trial (RCT). **Approach to analysis:** The primary outcome was carbon monoxide (CO)-verified smoking abstinence between 4 and 12-months. Self-reported abstinence was obtained from telephone call conducted at 3 and 12 months (where a total of no more than 5 cigarettes smoked) [a]. Abstinence was confirmed with CO test of <10 parts per million at 12 months. Resource use was estimated alongside the RCT and	**Population:** CO-verified, 4-week quitters treated in NHS Stop Smoking Clinics **Intervention:** Full pack of eight "Forever Free" booklets. Booklet 1 is a brief summary of all issues relevant to smoking relapse prevention. The remaining seven booklets provide more extensive information on important issues for relapse prevention [b]. **Comparator:** The Leaflet "Learning to Stay Stopped" that contains brief but comprehensive information on issues related to smoking relapse	**Mean cost per participant (12 months):** [c] NHS perspective plus participant medication costs Forever Free booklet: £578.17 Leaflet: £674.87 NHS perspective Forever Free booklet: £553.78 Leaflet: £657.95 Costs of 8 Forever Free Booklets: £20.78 **Cost savings**: None reported **Currency & cost year:** £; 2012/2013 **Cost components incorporated:** ***NHS perspective***: Booklet costs (intellectual property, adaptation, printing and postage), and healthcare	**QALYs (12 months):** Forever Free booklet: 0.753 (standard deviation (SD) 0.204) Leaflet: 0.747 (SD 0.196)	**Cost effectiveness ratios:** [d] A net benefit analysis was conducted. Incremental net benefit for the Forever Free booklet (assuming a QALY value of £20,000) NHS perspective: £74.79 NHS plus participant medication costs: £78.20 **Analysis of uncertainty** A non-parametric bootstrap analysis was conducted to estimate cost-effectiveness acceptability curves (CEACs). The CEAC showed that there is a large uncertainty associated with this result, as the Forever Free booklet intervention has only a 64.4% probability of being cost-effective at a £20,000 per QALY threshold (NHS perspective) and 66.1% using the NHS plus participant medication costs perspective.

Study	Blyth 2015 (UK)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
participants were asked to report how many items they had received during follow-up. The EuroQol 5 dimensions and 3 levels (EQ-5D-3L) questionnaire was administered at baseline, 3- and 12-month follow-up. A net benefit approach was used to estimate potential benefits of the intervention **Perspective:** National Health Service (NHS) plus participants' medication costs **Time horizon:** 12 months **Treatment effect duration:** Up to 1 year **Discounting:** Not relevant (short time-horizon)		resources (NHS Stop Smoking Clinic visits and phone calls, stop smoking aids and materials, GP visits, and hospital admissions). ***Individual medication costs**:* stop smoking aids paid for by individuals.		
Data sources				
Health outcomes: Carbon monoxide-validated, prolonged smoking abstinence from month 4 to 12 was estimated in the RCT. **Quality-of-life weights:** EQ-5D-3L was administered alongside the RCT and York tariffs were used to convert responses into utility scores. **Cost sources:** Intervention and comparator				

Study	Blyth 2015 (UK)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
costs were estimated during the RCT. Other costs were taken from standard UK sources such as NHS reference costs or the Personal and Social Service Unit's unit costs of health and social care report.				
Comments				
Source of funding: National Institute for Health Research (NIHR) **Limitations:** As with practically all behavioural interventions it was not possible to blind participants and investigators to the group allocation. Bias might have been introduced in the measurement process and mediating variables such as participants' reporting that they had read educational materials and in their feedback on the perceived helpfulness of the educational booklets. Costs may have been influenced by an outlier in the control arm. **Other:** All trial participants had received intensive behavioural support from stop smoking advisors before participating in the trial, and most of them (89%) had experience of quitting previously. Therefore, it is very likely that they had received information from stop smoking advisors similar to that in the Forever Free booklets.				
Overall applicability: Directly applicable **Overall quality:** Minor limitations				
Abbreviations: CEA: cost-effectiveness analysis; CEAC: cost-effectiveness acceptability curve; CO: Carbon monoxide; EQ-5D-3L: EuroQol 5 dimensions and 3 levels; NHS: National Health Service; QALYs: Quality-adjusted life-years; RCT: randomised controlled trial				
a) A shopping voucher (£20 value) was offered to each of the participants who attended the CO test at 12 months in both intervention and control arms. Abstinence was measured at 3 months, but rates were applied from 4-months allowing for a 1-month grace period.				
b) The original "Forever Free" booklets were prepared for users in the USA. They were revised and updated in places where it was judged necessary or helpful, to make the material more suitable to British users and the UK NHS. The study states that the booklets were delivered after randomisation but doesn't state whether this was staggered or all eight booklets were delivered at the start. *c)* The major difference in costs was due to increased hospital admissions in the control arm (£221.67 vs. £338.08) where one person in the control group reported spending 98 days in hospital. Use of other healthcare resources was similar across both arms. *d)* The economic analysis used incremental costs and benefits which were adjusted for in seemingly unrelated regression analysis.				

Study	Bolin 2009 (Sweden)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: Cost utility analysis (CUA) **Study design:** Markov model (BENESCO	**Population:** 1,927 smokers were recruited to the first 12-week treatment with varenicline (open-label). Of these, 1,210 who had quit smoking	**Cost** Varenicline (12 weeks): €452 Varenicline (12 + 12 weeks): €705	**Incremental QALYs (all patients, men)** Varenicline (12 + 12 weeks) vs varenicline (12 weeks): 4,185	**Cost effectiveness ratios** Incremental cost per QALY, varenicline (12 + 12 weeks) vs varenicline (12 weeks) Men: €7,066 Women: €7,108 Incremental cost per QALY, varenicline (12 + 12

Study	Bolin 2009 (Sweden)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
model) based on a randomised controlled trial (RCT) **Approach to analysis:** Efficacy was based on a published RCT that estimated the efficacy of 12 weeks of maintenance therapy with varenicline or placebo using a randomised, double-blind approach. Costs of events were derived from the literature as well as utility values associated with health states. **Perspective:** Both health care system and society (indirect effects of production and consumption) **Time horizon:** 50 years **Treatment effect duration:** 1-year quit rates estimated from the RCT and long-term	were randomised to another 12-week double-blind treatment phase of either varenicline or placebo [a]. **Intervention:** 12 weeks of varenicline [b] for smoking cessation plus 12 weeks of varenicline maintenance for quitters. Varenicline was given at a dosage of 1mg twice per day. **Comparator:** 12 weeks of varenicline for smoking cessation plus placebo for quitters	**50-year incremental costs (all patients, men)** Varenicline (12 + 12 weeks) vs varenicline (12 weeks) Intervention costs: €42,733,723 Health care costs: -€13,162,508 **50-year incremental costs (all patients, women)** Varenicline (12 + 12 weeks) vs varenicline (12 weeks) Intervention costs: €52,830,477 Health care costs: -€18,996,258 **Cost savings** None **Currency & cost year:** €; 2003 **Cost components incorporated:** Costs of smoking-related morbidities (lung cancer, stroke, coronary heart disease, chronic obstructive pulmonary disease), costs of interventions, indirect	**Incremental QALYs (all patients, women)** Varenicline (12 + 12 weeks) vs varenicline (12 weeks): 4,760	weeks) vs varenicline (12 weeks), including costs of production and consumption Men: €24,149 Women: €24,436 **Analysis of uncertainty** Both univariate and stochastic sensitivity analyses were conducted. The time-horizon of the analysis was the parameter with the largest impact on results. For example, reducing the time horizon to 10 years resulted in the incremental cost per QALY for varenicline (12 + 12 weeks) increasing to €93,583 for men and €141,197 for women [c]. The stochastic sensitivity analysis showed that at a threshold of €25,000 per QALY the probability for varenicline (12 + 12 weeks) to be cost-effective was over 80% for both men and women (this was only presented graphically)

Study	Bolin 2009 (Sweden)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
benefits estimated with a Markov model **Discounting:** 3% for costs and benefits		costs (production and consumption)[c]		
Data sources				
Health outcomes: 1-year quit rates were taken from a RCT (Tonstad et al, 2006) **Quality-of-life weights:** These were taken from the published literature but were not described **Cost sources:** Costs associated with smoking-related morbidities were taken from diagnosis related group tariffs obtained from a Swedish county. Cost of interventions appear to have been local prices.				
Comments				
Source of funding: This study was sponsored by Pfizer AB, Sweden. **Limitations:** Author-recognised limitations: None. In general there was little information on some features of the analysis. A clearer description of production and consumption costs and a better representation of the model would have been useful. Also only incremental values were reported instead of total costs and QALYs per patient, which would have been more useful. **Other:** None				
Overall applicability: Directly applicable **Overall quality:** No limitations				
Abbreviations: CUA: cost-utility analysis; QALYs: Quality-adjusted life-years; RCT: randomised controlled trial.				

a) Patients were assumed to make only one quit attempt
b) Varenicline was given at a dosage of 1mg twice per day
c) Longer term time horizons apply increased costs, disutility and lifer years lost due to smoking related morbidities when compared with shorter time horizons. Interventions associated with higher quit rates are more cost-effective when time horizons are increased, and less cost-effective when they are decreased.

Study	Brandon 2003 (USA)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: Cost-effectiveness analysis (CEA)	**Population:** Ex-smokers who self-reported abstained for at least 7 days at the time of baseline questionnaire completion.	**Total costs** NR **Cost savings** NR	**Percentage of participants smoking at 12-month follow-up** [d] Subgroup abstinent for less than 3 months at baseline	**Cost effectiveness ratios** Cost (per person) of relapse prevention during the 12-month follow-up, mailings vs no mailings Whole sample: $174 Participants who had been abstinent for less than 3 months at baseline: $126

Study	Brandon 2003 (USA)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Study design: A RCT was carried out using a 2x2 factorial design **Approach to analysis:** The trial was based on a feasibility study that asked respondents who replied to newspaper advertisement to rate their interest in a series of possible modes of relapse prevention **Perspective:** NR **Time horizon:** One year **Treatment effect duration:** Abstinence relapse rates were taken from the RCT **Discounting:** N/A	Final sample: 584 Follow up: 446 **Intervention:** 1) Mailings only [a]: a series of "Stay Quit" booklets sent regularly over a 12-month period 2) Hotline only [b]: access to a toll-free telephone hotline number with trained operators 3) Combination of mailings and hotline **Comparator:** No intervention [c]	**Currency & cost year:** US$; price year not reported **Cost components incorporated:** NR	Mailings: 11.9% No mailings: 35.0% Difference statistically significant (P<0.001) Subgroup abstinent between 3 to 7 months at baseline Mailings: 11.9% No mailings: 8.9% Subgroup abstinent between 7 to 18 months at baseline Mailings: 7.0% No mailings: 4.0% Subgroup abstinent for more than 18 months at baseline Mailings: 4.0% No mailings: 5.1%	**Analysis of uncertainty** Not investigated
Data sources				
Health outcomes: : Health outcomes were estimated from the RCT **Quality-of-life weights:** NR **Cost sources:** NR				
Comments				
Source of funding: The study was funded by grants from the American Cancer Society and (US) National Cancer Institute. **Limitations:** The study was based on an RCT feasibility study and did not report methods or sources of data, thus hindering an assessment of the study quality. **Other:** None				

Study	Brandon 2003 (USA)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
Overall applicability: Partly applicable **Overall quality:** Major limitations				
CEA: cost-effectiveness analysis; N/A: not applicable; NR: not reported; RCT: randomised controlled trial				
a) Participants in the repeated-mailings intervention received a series of "Stay Quit" booklets through the mail. A booklet was mailed immediately after enrolment and at 1, 2, 3, 5, 7, 9, and 12 months thereafter. The first booklet included an introduction to the basic relapse-prevention principles and techniques - similar to the information packet sent to participants in the other two interventions. The remaining seven booklets included more extensive information on a topic related to maintaining abstinence. b) Participants assigned to the hotline intervention received the same relapse-prevention material as participants in the control condition, plus a laminated wallet card with the toll-free telephone hotline number. The card instructed participants to call the number for any of the following reasons: to ask questions about smoking or remaining abstinent; if they were experiencing a smoking-related crisis; if they had "slipped"; or if they just needed to talk to someone. Operators were trained to assess the caller's current situation, provide advice based on relapse-prevention theory and research, and provide social support. Although telephone calls were intended to be initiated by participants, a backup strategy was employed for proactive calls to participants who did not call the hotline over any 3-month period. Participants had access to the hotline for 12 months. c) A minimum contact control condition comprising a single mailing of basic smoking cessation and relapse-prevention advice. d) Smoking status was identified through a self-completed questionnaire at 12 months, which was returned by 76% (446) subjects, with equivalent return rates across trial arms.				

Study	Brandon 2004 & Chirikos 2004 (USA)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
Economic analysis: Cost-utility analysis (CUA) **Study design:** A RCT was carried out using a 2x2 factorial design. **Approach to analysis:** The analysis was based on a cost-utility study that used data from a	**Population:** individuals who had abstained from smoking for at least 1 week, any current smoker who reported planning to quit within the next 6 months and any former smoker who had been abstinent for no more than 6 months.	**Incremental costs** Massed mailing vs MCC: $21.25 Repeated letters vs MCC: $26.00 Repeated mailing vs MCC: $43.94 **Cost savings** NR	**Incremental 24-month abstinence** [c] Massed mailing vs MCC: 11.4% Repeated letters vs MCC: 2.4% Repeated mailing vs MCC: 12.2% **Incremental QALYs** [d]	**Cost effectiveness ratios** Incremental cost per 24-month abstinence Massed mailing vs MCC: $186 Repeated mailing vs MCC: $360 Incremental cost per QALY Massed mailing vs MCC: $83 Repeated mailing vs MCC: $160 **Analysis of uncertainty** NR

Study	Brandon 2004 & Chirikos 2004 (USA)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
RCT study enrolling respondents to a newspaper advertisement. Participants were asked to rate their interest in a series of possible modes of relapse prevention. **Perspective:** Payer **Time horizon:** 24 months **Treatment effect duration:** Abstinence relapse rates were taken from the RCT **Discounting:** 4% for QALYs (no discount for one-year costs)	Sample: 431 participants **Interventions** Massed mailing: participants received eight "Forever Free" booklets (FFB) [a] at study enrolment. There was no further contact until the 12-month follow-up. Repeated letters: Participants received the single FFB followed by seven brief letters sent at the same intervals as the booklets were sent in the repeated-mailings condition: 1, 2, 3, 5, 7, 9, and 12 months. This intervention provided some extended contact and social support, but without the traditional elements of relapse-prevention training, such as coping-skills training [a].	**Currency & cost year:** US$; 2000 **Cost components incorporated:** Materials (booklets), time and-motion estimates of clerical input weighted by the hourly wage rate of US correspondence clerks, an estimate of other overhead expenses, and costs of smoking cessation methods.	Massed mailing vs MCC: 0.2561 Repeated mailing vs MCC: 0.2741 QALYs for repeated letters vs MCC were not calculated as there was no statistically significant difference.	

Study	Brandon 2004 & Chirikos 2004 (USA)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
	Repeated mailings: participants received the series of eight FFBs through the mail. A booklet was mailed immediately after a participant enrolled and at the following times thereafter: 1, 2, 3, 5, 7, 9, and 12 months. **Comparator** Minimum contact comparison (MCC): participants received only the single FFB at the time of enrolment.			
Data sources				
Health outcomes: Health outcomes were estimated from the RCT **Quality-of-life weights:** QALY estimates were based on life-table parameters found in the literature. **Cost sources:** Costs were derived from direct assessment in the RCT, national discount prices, Medicare Fee Schedule amounts for physician time and hourly wage rates.				
Comments				
Source of funding: The study received a (US) National Cancer Institute grant. **Limitations:** Author-recognised limitations: the major limitation of this study concerned the self-selection of participants, who may not be representative of the overall population of ex-smokers; a further limitation of the study was its reliance on self-reported outcomes as only a few participants underwent biochemical validation; the racial and ethnic distribution of the sample (92% Caucasian) represents a possible limitation to the generalizability of the findings. **Other:** Methods and results were mainly taken from the Brandon 2004 study.				
Overall applicability: Partly applicable **Overall quality:** Minor limitations				
Abbreviations: CUA: cost-utility analysis; FFB: Forever Free booklets; MCC: minimum contact comparison; NR: not reported; QALYs: quality-adjusted life-years.				

Study	Brandon 2004 & Chirikos 2004 (USA)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
a) The Forever Free booklets covered topics including (a) an introduction and description of nicotine dependence, (b) the stages of quitting, (c) situations that are high risk for relapse, (d) ways of coping with urges to smoke, (e) suggestions for making lifestyle changes, and (f) the abstinence violation effect and ways to handle initial slip. b) The letters (a) included two short paragraphs of supportive messages (e.g., "Congratulations, and keep up the good work," "Remember that quitting smoking is the single most important health decision that most people can make"), (b) emphasized the importance of continued commitment (e.g., "If you keep trying, you can succeed"), and (c) encouraged another quitting attempt if relapse had occurred (e.g., "Most people require several attempts at quitting, so please don't give up"). c) Abstinence was identified from self-reported questionnaires at 12, 18 and 24 months. d) QALYs were calculated by applying utility weights (obtained from published literature) by smoking status.				

Study	Brandon 2012 (USA)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
Economic analysis: Cost-effectiveness analysis (CEA) **Study design:** The analysis was based on a RCT: participants were assigned to the 2 intervention arms by a computer algorithm using simple randomization at the time of data entry of the telephone screening questionnaire. **Approach to analysis:** The analysis was based	**Population:** Pregnant women in months 4 through to 8 of pregnancy, who had previously smoked at least 10 cigarettes per day for at least 1 year before pregnancy; and who quitted smoking either in anticipation of, or during pregnancy, and had abstained for the past week. Sample: 504 **Intervention:**	**Total costs** The total cost per user of the FFB intervention was $53.60 **Cost savings** NR **Currency & cost year:** US$; 2011 **Cost components incorporated:** Printing and delivery cost of the booklets themselves; labour costs associated with enrolling and tracking	**Abstinence rates** [c] At 8 months post-partum FFB: 69.6% UCC: 58.5% At 12 months post-partum FFB: 66.2% UCC: 58.6%	**Cost effectiveness ratios** Incremental cost per each additional abstinence at 12 months post-partum with FFB vs UCC: $248 **Analysis of uncertainty** NR

Study	Brandon 2012 (USA)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
on a RCT that provided data on health outcomes and resource use patterns to carry out a CEA **Perspective:** NR **Time horizon:** 12 months **Treatment effect duration:** Abstinence relapse rates were taken from the RCT **Discounting:** N/A	10 "Forever Free" booklets (FFB): participants received the series of relapse prevention booklets, mailed until 8 months postpartum. The original FFBs were customized to pregnancy and there was greater emphasis on social support and pregnancy-specific stressors [a]. **Comparator:** Usual care control (UCC): women received 2 high-quality publications, a copy of the National Cancer Institute booklet, "Clearing the Air", and the American Cancer Society pamphlet "Living Smoke-free for You and Your Baby" [b].	users, and mailing the booklets, weighted by the hourly wage rate of correspondence clerks in the USA; postage; and other supplies and overhead.		
Data sources				
Health outcomes: Health outcomes were estimated from the RCT. **Quality-of-life weights:** NR **Cost sources:** Not clearly reported. Personnel costs were based on hourly wage rates in the USA.				
Comments				

Study	Brandon 2012 (USA)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
Source of funding: The study was funded by a (US) National Cancer Institute grant. **Limitations:** Author-recognised limitations: the study has limited generalizability as it was not population-based and thus is not representative of the full population of pregnant ex-smokers; smoking status was determined by self-report with bioverification conducted for only a small subsample, with some inconsistent results; a strong treatment effect was found only in the subgroup of women from low-income households. **Other:** None				
Overall applicability: Partly applicable **Overall quality:** Minor limitations				
Abbreviations: CEA: cost-effectiveness analysis; FFB: Forever Free Booklets; N/A: not applicable; NR: not reported; RCT: randomised controlled trial; UCC: usual care control.				
a) FFBs include information about the nature of tobacco dependence, instruction in the use of cognitive and behavioural skills to deal with urges to smoke, awareness of high-risk "triggers" to smoke, strategies for managing an initial slip or lapse, and specific health information. The series included 2 pregnancy specific booklets: "A Time of Change" delivered shortly before a participant's due date, and "Partner Support" designed to be shared with the participant's partner. 10 Booklets were distributed in a sequence and timing designed to provide timely content over the pregnancy and postpartum period. The full FFB package included 4 booklets (Overview; Smoking Urges; Smoking and Health; A Time of Change) mailed over equal intervals between the date of a participant's enrolment in the study and her expected due date, and 5 booklets (What If You Have a Cigarette? Smoking, Stress and Mood; Lifestyle Balance; Smoking and Weight; Life Without Cigarettes) mailed at 1, 2, 3, 4, 6, and 8 months postpartum. The "Partner Support" booklet was mailed with the first booklet, including instructions to deliver it to the participant's primary partner. b) The National Cancer Institute booklet, "Clearing the Air" is a 36-page, comprehensive guide toward quitting smoking, with 7 pages dedicated to relapse prevention. However, the content is not customized for pregnant or postpartum women. The American Cancer Society pamphlet "Living Smoke-free for You and Your Baby" is a trifold pamphlet that describes the benefits of quitting smoking during pregnancy and staying quit after the baby is born. c) 7 day point-prevalence abstinence – assessed via questionnaire. Carbon monoxide and saliva was confirmed in a sub-sample who reported abstinence at any one of the follow up points and lived with 100 mile radius (22 women), these being 95% consistent with self-reported figures.				

Study	Knight 2010 (US)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
Economic analysis: Cost effectiveness analysis (CEA) and cost utility analysis (CUA)	**Population:** The initial population included 25% US smokers who are assumed to make a quit attempt. The	**Cost of intervention:** Varenicline (12 + 12 weeks): $603.89 Varenicline (12 weeks): $370.96 Bupropion: $264.40	**Lifetime QALYs (1000s)** Varenicline (12 weeks) 174,373 Varenicline (12 + 12 weeks) 174,630	**Cost effectiveness ratios** Incremental cost per QALY, varenicline (12 + 12 weeks) vs varenicline (12 weeks): $972 Varenicline (12 + 12 weeks) dominated all the other interventions.

Study	Knight 2010 (US)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Study design: Markov model (BENESCO model) based on a mixed-treatment comparison of randomised controlled trials (RCTs) **Approach to analysis:** Efficacy was based on a mixed-treatment comparison from three RCTs. One of these, estimated the efficacy of 12 weeks of maintenance therapy with varenicline or placebo using a randomised, double-blind approach. Costs of events and utility values associated with health states were derived from the literature. **Perspective:** Not explicitly stated (probably third-party payer) **Time horizon:** Lifetime	analysis then focused on those that were abstinent after 12 weeks of varenicline treatment. **Intervention [a]:** 12 weeks of varenicline for smoking cessation plus 12 weeks of varenicline maintenance for quitters **Comparator [b]:** 12 weeks of varenicline for smoking cessation plus placebo for quitters 12 weeks of bupropion for smoking cessation 12 weeks of nicotine replacement therapy (NRT) for smoking cessation Unaided cessation	NRT: $405.47 Unaided cessation: $0 **Lifetime costs (millions) based on 11.9 million participants** Varenicline (12 + 12 weeks): $328,528 Varenicline (12 weeks): $328,279 Bupropion: $330,689 NRT: $332,622 Unaided cessation: $333,283 **Cost savings** Not reported **Currency & cost year:** US$; 2005 **Cost components incorporated:** Costs of smoking-related morbidities (lung cancer, stroke, coronary heart disease, chronic obstructive pulmonary disease and asthma), costs of interventions [a]	Bupropion 173,999 NRT 173,970 Unaided cessation 173,413 **1-year quit rates [b]:** Varenicline (12 + 12 weeks): 27.7%% Varenicline (12 weeks): 22.9%% Bupropion 15.9% NRT 15.4% Unaided cessation 5%.	**Analysis of uncertainty** The PSA showed that varenicline (12 + 12 weeks) had a 73% probability of being cost-effective at a willingness to pay threshold of $30,000 per QALY.

Study	Knight 2010 (US)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Treatment effect duration: 1-year quit rates estimated from RCTs and lifetime benefits estimated with a Markov model **Discounting:** 3% for costs and benefits				
Data sources				
Health outcomes: 1-year quit rates were derived from a mixed treatment comparison of 3 RCTs (Tonstad et al 2006; Gonzales et al, 2006; Jorenby et al, 2006) and for NRT were taken from a meta-analysis by Silagy, 2004. **Quality-of-life weights:** These were taken from published literature but were not described **Cost sources:** Costs associated with smoking-related morbidities were taken from the published literature but were not described. Costs of interventions were taken from the US Red Book.				
Comments				
Source of funding: Financial support from Pfizer, Inc. **Limitations:** Author-recognised limitations: a full update to the BENESCO model, updating all input data in line with analysis of the latest available information, including updated meta-analyses of all efficacy figures, would provide valuable further insight. Only direct costs were considered and other wider economic impacts of smoking-related diseases was not included. **Other:** None				
Overall applicability: Directly applicable **Overall quality:** No limitations				
Abbreviations: NRT: nicotine replacement therapy; PSA: probabilistic sensitivity analysis; RCT: randomised controlled trial.				

a) All Varenicline doses were 1mg twice daily.
b) All comparators 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.
c) All treatment costs for smoking related morbidities are drawn from the literature. Differences in lifetime costs are driven by differences in quitting strategy which impact on the ratio of smokers/non-smokers throughout the model. No indirect costs were included e.g. increased productivity, second hand smoke effects etc.
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.

Study	Ruger 2008 (USA)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: Cost-effectiveness analysis (CEA) and cost utility analysis (CUA) **Study design:** Randomised controlled trial (RCT) with results used in a lifetime Markov model **Approach to analysis:** The findings of a RCT enrolling low-income pregnant women, recruited from multiple obstetric sites in the Boston (USA) metropolitan area were used to estimate the costs, benefits, and cost-effectiveness of the intervention, incorporating published quality-adjusted life year (QALY) and life year (LY) estimates. **Perspective:** Societal **Time horizon:** Lifetime	**Population:** Low-income pregnant women (less than 28 weeks gestation), receiving prenatal care. Sample size (baseline non-smoker): 57 **Intervention:** Individually tailored motivational interviewing (MI), which public health nurses delivered to low-income women who received an average of three home visits. The MI components were tailored to each participant's stage of readiness and MI sessions lasted 1 hour on average. MI participants also received a self-help smoking cessation manual [a]. **Comparator:** Usual care (UC): standard prenatal care from participants'	**Total cost of the intervention (per patient)** MI: $309.20 UC: $4.85 **Cost savings** Cost savings for maternal and neonatal outcomes were included. **Currency & cost year:** US$; 1997 **Cost components incorporated:** Intervention costs (staff time related to intervention delivery; costs of analysing environmental nicotine used in MI; cost of training nurses; costs of producing self-help materials); cost savings for neonatal intensive care, chronic medical conditions, and acute conditions during the first year of life; cost savings for maternal health care (cardiovascular and lung diseases).	**Total relapse prevention rate (per patient)** [c] MI: 0.43 (9/21) UC: 0.18 (5/28) **Total LYs (per patient)** [d] MI: 0.61 UC: 0.26 **Total QALYs (per patient)** MI: 0.83 UC: 0.35 **Incremental effects** Additional relapse prevented MI vs UC: 0.25 **Incremental life-years** MI vs UC: 0.36 **Incremental QALYs** MI vs UC: 0.49	**Cost-effectiveness** Incremental cost per relapse prevented MI vs UC: $1,217 Incremental cost per LY saved MI vs UC: $851 Incremental cost per QALY gained MI vs UC: $628 **Analysis of uncertainty** Univariate and multivariate sensitivity analyses were carried out on selected inputs. Including assumption of maternal medical cost savings for MI (=$6000 per participant) resulted in MI dominating usual care for relapse prevention. Including assumption of $1000 neonatal cost savings during the first year of life resulted in the MI intervention dominating usual care for relapse prevention. Increasing MI's effectiveness by around 15% resulted in an approximately 36% decrease in the incremental cost per QALY ratio. In two-way sensitivity analyses, MI was still relatively cost-effective for relapse prevention ($17,300/QALY saved) even if it cost as much as $2,000/participant and was less effective.

Study	Ruger 2008 (USA)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Treatment effect duration: Relapse rates were taken at 6 months postpartum **Discounting:** 3% for costs and benefits	health-care provider at the clinic site [b].			
Data sources				
Health outcomes: Health outcomes were estimated from the RCT (within trial analysis). **Quality-of-life weights:** Utility weights were taken from the published literature. **Cost sources:** Costs data were taken directly from the trial and from various published sources.				
Comments				
Source of funding: A grant from the (US) National Cancer Institute. **Limitations:** Author-recognised limitations: the study had a very restricted patient population (low-income), only one geographic location, uncertainty around the data on long-term morbidity and mortality data for children related to smoking-related illnesses, small sample size; some non-smoking related costs and benefits of MI were not measured. **Other:** None				
Overall applicability: Partly applicable **Overall quality:** Minor limitations				
Abbreviations: CEA: cost-effectiveness analysis; MI: motivational interviewing; RCT: randomised controlled trial; UC: usual care.				

a) The MI sessions: 1) educated clients about the impact of smoking on mothers, foetuses, and new-borns; 2) helped clients evaluate their smoking behaviour; 3) helped increase self-efficacy for smoking cessation and abstinence; 4) provided information on reducing exposure to environmental tobacco smoke and set goals on changes in smoking; and 5) provided feedback about household nicotine levels.
b) An up-to-5-minute intervention outlined the harmful effects of smoking during and after pregnancy. Self-help materials were also provided.
c) Self-reported abstinence over in the last 30 days ("not even a puff").
d) Quit rates were converted into Life Years and QALYs using data from published literature (American Cancer Society's Cancer Prevention Study. Separate estimates were obtained for female former smokers by age group and duration of quitting. These were calculated using a Markov model which allowed for a 35% probability of relapse after 1 year.

Study	Taylor 2011 & Coleman 2010 (UK)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: Cost-utility analysis (CUA)	**Population:** A hypothetical cohort of 1000 smokers who	**Total costs (per patient)** Bupropion: £6,755 No intervention: £6,822	**QALYs (per patient)** [b] Bupropion: 12.76 No intervention: 12.69	**Cost effectiveness ratios** [c] Incremental cost per QALY

Study	Taylor 2011 & Coleman 2010 (UK)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Study design: RCTs were used to derive data on the efficacy of treatments: 4 trials for bupropion (two used factorial designs, 1 used computer-generated randomisation, and in the last one randomization was by dynamic allocation), 4 trials for nicotine replacement therapy (NRT) (two used factorial designs, one was a 2 × 2 factorial design and the other a 4 × 3 crossed factorial design), and 1 trial for varenicline (multiple country, computer-generated randomisation sequence, stratified by centre). No intervention: the comparison used abstinence rates from control groups in relevant drug trials. **Approach to analysis:** A deterministic cohort simulation model was	had recently initiated quit attempts ('recent quitters'). **Interventions:** • Bupropion: one daily tablet for 6 days followed by 2 daily tablets for a 7 week period • NRT: 12 weeks of daily nicotine patches [a] • Varenicline: 2 tablets daily for 77 days **Comparator:** No intervention	NRT: £7,050 No intervention: £7,039 Varenicline: £6,794 No intervention: £6,704 **Cost savings from reduction to comorbidities:** NR **Currency & cost year:** GBP £; 2008 **Cost components incorporated:** Costs of the interventions & smoking-related morbidity costs (lung cancer, stroke, coronary heart disease, myocardial infarction, COPD).	NRT: 12.63 No intervention: 12.58 Varenicline: 12.79 No intervention: 12.75 **Quit rates:** Bupropion: 37% No intervention: 29% NRT: 23% No intervention: 18% Varenicline: 41% No intervention: 36%	Bupropion dominated no intervention (bupropion was more effective and less expensive) NRT vs no intervention: £265 Varenicline vs no intervention: £2106 **Analysis of uncertainty** All model inputs were varied across reasonable and published ranges of values. Base case results were robust to wide ranges of variations. Cost-effectiveness ratios only exceeded the UK National Institute of Health and Care Excellence (NICE) benchmark of £20,000 per QALY when drug treatment effects were postulated to last for no longer than 1 year; or, for NRT and varenicline, efficacy was reduced to 10% of that observed in clinical trials.

Study	Taylor 2011 & Coleman 2010 (UK)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
used to determine the lifetime economic and health impact of three smoking relapse prevention interventions. The model used UK population-based studies, data from RCTs, and other published studies. **Perspective:** UK National Health Service (NHS) **Time horizon:** Lifetime **Treatment effect duration**: Information on intervention efficacy was taken from a systematic review of trials of drugs used for relapse prevention **Discounting:** 3.5% for costs and benefits				
Data sources				
Health outcomes: Data on treatment efficacy were taken from a systematic review of published RCTs. **Quality-of-life weights:** Utility estimates were derived from a review of published sources, including a review, a clinical trial, and a Scottish, community-based survey. **Cost sources:** Drug costs were taken from the British National Formulary; costs of comorbidities were derived from official guidelines and audits.				
Comments				
Source of funding: The study was funded by the NIHR Health Technology Assessment Programme. Funding was also received from the British Heart Foundation, Cancer Research UK, the Economic and Social Research Council, the Medical Research Council and the Department of Health, under the				

Study	Taylor 2011 & Coleman 2010 (UK)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
auspices of the UK Clinical Research Collaboration. **Limitations**: Author-recognised limitations: Assumptions within the health economic model were generally conservative, resulting in a tendency to underestimate and not overestimate cost effectiveness **Other:** The study came from a Health Technology Assessment (2010; Vol. 14: No. 49).				
Overall applicability: Directly applicable **Overall quality:** No limitations				
Abbreviations: CUA: cost-utility analysis; HTA: health technology assessment; NHS: National Health Service; NRT: nicotine replacement therapy; RCT: randomised controlled trial; UK: United Kingdom.				

a) It was recommended that 15mg patches were used daily for 8 weeks, followed by 10mg patches used daily for 2 weeks, then 5mg patches used daily for 2 weeks. It was assumed unlikely that the full recommended course would be used therefore an average patch use of 60.48% was assumed for costings.
b) QALYs included disutility applied to smoking related comorbidities (lung cancer, stroke, coronary heart disease, myocardial infarction, COPD) and life years estimated using age-specific mortality rates for smokers and non-smokers.
c) Differences in incremental costs and QALYs driven by lower efficacy rates resulting in fewer smokers and smoking related comorbidities/deaths.

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	**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	**Lifetime costs (millions) – Payer perspective:** Varenicline (12 weeks): Can$25,369 Varenicline (12 + 12 weeks): Can$25,426 Bupropion: Can$25,510 NRT: Can$25,705 Unaided cessation: Can$25,746 **Lifetime costs (millions) – Societal perspective:** Varenicline (12 weeks): Can$98,739	**Lifetime QALYs (1000s):** Varenicline (12 weeks) 15,398 Varenicline (12 + 12 weeks) 15,413 Bupropion 15,376 NRT 15,374 Unaided cessation 15,342 **1-year quit rates [d]:** Varenicline (12+12 weeks) 27.7% Varenicline (12 weeks) 22.9%, Bupropion	**Cost effectiveness ratios [e]** From the payer perspective, the incremental cost per QALY, varenicline (12 + 12 weeks) vs varenicline (12 weeks) was Can$3,758 Varenicline (12 + 12 weeks) dominated all the other interventions. From the societal perspective varenicline (12 + 12 weeks) was dominant compared with all the other options. **Analysis of uncertainty** Probabilistic sensitivity analysis (PSA) showed that varenicline (12 + 12 weeks) had a 95% probability of being cost-effective at a

Study	von Wartburg 2014 Canada)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
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. **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 and benefits	**Comparator [b]:** Varenicline for smoking cessation plus additional 12 weeks of placebo for quitters Bupropion for smoking cessation Nicotine replacement therapy (NRT) for smoking cessation Unaided cessation: no further description was provided	Varenicline (12 + 12 weeks): Can$98,902 Bupropion: Can$99,902 NRT: Can$100,177 Unaided cessation: Can$101,730 **Cost savings**: Not reported **Currency & cost year:** Can$; 2009 **Cost components incorporated:** Costs of smoking-related morbidities (lung cancer, stroke, coronary heart disease, chronic obstructive pulmonary disease and asthma), costs of interventions, indirect costs [c]	15.9%, NRT 15.4%, Unaided cessation 5%.	willingness to pay threshold of Can$30,000 per QALY compared with varenicline (12 weeks) and 100% compared with the other interventions (from the payer perspective).
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				

Study	von Wartburg 2014 Canada)			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
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 participant'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.
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.

Appendix I – Health economic evidence profiles

See Appendix H

Appendix J – Health economic analysis

A detailed description of the model with full results and sensitivity analyses is provided in a separate economic modelling report (evidence review XX).

Appendix K – Excluded studies

Public health studies

The studies in the table below are those excluded at full text stage for all versions of the Cochrane review combined. The PRISMA diagram in Appendix C shows 32 full-text articles excluded, which includes only those excluded for this 2019 update of the Cochrane review.

Table 7: Excluded studies (n=51)

Study citation	Exclusion reason
ACTRN12618000408280 ACTRN12618000408280. Cessation and Relapse Prevention (CARP) Trial: nicotine vaporisers compared to standard nicotine replacement therapy for smoking cessation among people with co-morbidities. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ACTRN12618000408280 (first received 21 March 2018).	No appropriate comparator
Adams 2011 **[CRSSTD: 2963247]** Adams KK, Merritt TA. Prevention of postpartum smoking relapse in mothers to prevent infant exposure to second-hand smoke. Journal of Investigative Medicine 2011;59:102. [CRSREF: 2963248]	Only 2 months follow up
Allen 2007 **[CRSSTD: 2963249]** Allen S, Bade T, Hatsukami D. Smoking relapse in women: effect of menstrual phase. In: SYM 10B Society for Research on Nicotine and Tobacco 13th Annual Meeting; 2007 February 21-24; Austin, TX. 2007. [CRSREF: 2963250]	Only 12 weeks follow up
Alterman 2001 **[CRSSTD: 2963251]** Alterman AI, Gariti P, Mulvaney F. Short- and long-term smoking cessation for three levels of intensity of behavioral treatment. Psychology of Addictive Behaviors 2001;15(3):261-4. [CRSREF: 2963252]	Considered for inclusion because comparison of different intensity interventions. No mention of relapse prevention
Berndt 2012 **[CRSSTD: 9969643]** Berndt N, Bolman C, Lechner L, Mudde A, Verheugt FW, De Vries H. Effectiveness of two intensive treatment methods for smoking cessation and relapse prevention in patients with coronary heart disease: study protocol and baseline description. BMC Cardiovascular Disorders 2012;12:33. [CRSREF: 9969644]	Content of intervention did not involve relapse prevention
Bottausci 1995 **[CRSSTD: 2963253]** Bottausci AJ. An experimental study of cue exposure as a relapse prevention technique in smoking cessation maintenance. Masters Abstracts International 1995;32(3):1063. [CRSREF: 2963254]	Small trial, < 10 participants per condition
Brown 2001 **[CRSSTD: 2963255]** Brown RA, Kahler CW, Niaura R, Abrams DB, Sales SD, Ramsey SE, et al. Cognitive-behavioral treatment for	Considered for inclusion because comparison of different intensity interventions. Intervention focus was on use of CBT for treatment of

Study citation	Exclusion reason
depression in smoking cessation. Journal of Consulting and Clinical Psychology 2001;69:471-80. [CRSREF: 2963256]	depression. Relapse mentioned only in text
Carmody 1988 **[CRSSTD: 2963257]** Carmody TP, Loew DE, Hall RG, Breckenridge JS. Nicotine polacrilex: clinic-based strategies with chronically ill smokers. Special Issue. Pharmacological adjuncts and nutritional supplements in the treatment of drug dependence. Journal of Psychoactive Drugs 1988;20(3):269-74. [CRSREF: 2963258]	Only 3 months follow-up reported. No significant differences at this point
Carmody 2017 **[CRSSTD: 9969645]** Carmody TP, Duncan CL, Solkowitz SN, Huggins J, Simon JA. Hypnosis for smoking relapse prevention: a randomized trial. American Journal of Clinical Hypnosis 2017;60(2):159-71. [CRSREF: 9969646]	Wrong comparator as both groups had the same amount of contact
Cather 2013 **[CRSSTD: 9969647]** Cather C, Dyer MA, Burrell HA, Hoeppner B, Goff DC, Evins AE. An open trial of relapse prevention therapy for smokers with schizophrenia. Journal of Dual Diagnosis 2013;9(1):87-93. [CRSREF: 9969648]	All participants received the same intervention
Cinciripini 2000 **[CRSSTD: 2963259]** Cinciripini PM, McClure JB, Wetter DW, Perry J, Blalock JA, Cinciripini LG, et al. An evaluation of videotaped vignettes for smoking cessation and relapse prevention during pregnancy: the very important pregnant smokers (VIPS) program. Tobacco Control 2000;9 Suppl:III, 61-3. [CRSREF: 2963260]	Not possible to distinguish relapse prevention from cessation components
Copeland 2006 **[CRSSTD: 2963261]** Copeland AL, Martin PD, Geiselman PJ, Rash CJ, Kendzor DE. Smoking cessation for weight-concerned women: group vs. individually tailored, dietary, and weight-control follow-up sessions. Addictive Behaviors 2006;31(1):115-27. [CRSREF: 2963262]	Evaluated a weight management programme for preventing relapse; see separate Cochrane review
Davis 1995 **[CRSSTD: 2963263]** Davis MJ, Baker LJV. Smoking cessation: the use of a choice of strategies to aid cessation and maintenance. Irish Journal of Psychology 1995;16(2):150-61. [CRSREF: 2963264]	Short follow-up
DiSantis 2010 **[CRSSTD: 2963265]** DiSantis KI, Collins BN, McCoy AC. Associations among breastfeeding, smoking relapse, and prenatal factors in a brief postpartum smoking intervention. Acta Obstetricia Et Gynecologica Scandinavica 2010;89(4):582-6. [CRSREF: 2963266]	Pilot study with only 1-month follow-up
Dooley 1992 **[CRSSTD: 2963267]** Dooley RT, Halford WK. A comparison of relapse prevention with nicotine gum or nicotine fading in modification of smoking. Australian Psychology 1992;27(3):186-91. [CRSREF: 2963268]	Only 3 months follow-up reported. No significant differences at this point

Study citation	Exclusion reason
Dubren 1977 **[CRSSTD: 2963269]** Dubren R. Self-reinforcement by recorded telephone messages to maintain non-smoking behavior. Journal of Consulting and Clinical Psychology 1977;45:358-60. [CRSREF: 2963270]	Only 1-month follow-up reported
Dunphy 2000 **[CRSSTD: 2963271]** Dunphy PM. Using an Empowerment and Education Intervention to Prevent Smoking Relapse in the Early Postpartum Period [dissertation]. Philadelphia: University of Pennsylvania, 2000. [CRSREF: 2963272]	Only 4 to 8 weeks follow-up after delivery and intervention
Elfeddali 2012 **[CRSSTD: 2963273]** Elfeddali I, Bolman C, Candel MJ, Wiers RW, De Vries H. Preventing smoking relapse via web-based computer-tailored feedback: a randomized controlled trial. Journal of Medical Internet Research 2012;14(4):e109. [CRSREF: 2963274]	Participants randomly assigned before quitting, no cessation intervention provided to controls, so test of an Internet cessation programme. Not relapse prevention
Evins 2011 **[CRSSTD: 2963275]** Evins AE, Pachas G, Mischoulon D, Urbanoski K, Carlini S, Sousa J, et al. A double-blind, placebo-controlled trial of the NMDA glycine site antagonist, GW468816, for prevention of relapse to smoking in females. Journal of Clinical Psychopharmacology 2011;31(5):597-602. [CRSREF: 2963276]	Only 60-day follow-up
Feeney 2001 **[CRSSTD: 2963277]** Feeney GF, McPherson A, Connor JP, McAlister A, Young MR, Garrahy P. Randomized controlled trial of two cigarette quit programmes in coronary care patients after acute myocardial infarction. Internal Medicine Journal 2001;31(8):470-5. [CRSREF: 2963278]	Not explicitly described as a relapse prevention intervention, and the control condition had low implementation of the basic cessation programme
French 2007 **[CRSSTD: 2963279]** French GM, Groner JA, Wewers ME, Ahijevych K. Staying smoke free: an intervention to prevent postpartum relapse. Nicotine & Tobacco Research 2007;9(6):663-70. [CRSREF: 2963280]	Not randomised
French 2018 French KM, Gonzalez SZ, Sherman SE, Link AR, Malik SZ, Tseng C-H, et al. Financial IncEntives for Smoking TreAtment: protocol of the FIESTA trial and FIESTA Oral Microbiome Substudy. Trials 2018;19(1):646.	Study of incentives
Froelicher 2000 **[CRSSTD: 2963281]** Froelicher ES, Christopherson DJ. Women's Initiative for Nonsmoking (WINS) I: design and methods. Heart & Lung 2000;29(6):429-37. [CRSREF: 2963282]	Described a trial in progress, no intervention results
Garvey 2012 **[CRSSTD: 2963283]**	Considered for inclusion because of front-loading of counselling

Study citation	Exclusion reason
Garvey AJ, Kalman D, Hoskinson RA Jr, Kinnunen T, Wadler BM, Thomson CC, et al. Front-loaded versus weekly counseling for treatment of tobacco addiction. Nicotine & Tobacco Research 2012;14(5):578-85. [CRSREF: 2963284]	sessions in one group. No mention of relapse prevention
George 2000 **[CRSSTD: 2963285]** George TP, Ziedonis DM, Feingold A, Pepper WT, Satterburg CA, Winkel J, et al. Nicotine transdermal patch and atypical antipsychotic medications for smoking cessation in schizophrenia. American Journal of Psychiatry 2000;157(11):1835-42. [CRSREF: 2963286]	Tested a specialised group therapy intervention for people with schizophrenia compared with a standard programme. Included other components in addition to relapse prevention
Goldstein 1989 **[CRSSTD: 2963287]** * Goldstein MG, Niaura R, Follick MJ, Abrams DB. Effects of behavioral skills training and schedule of nicotine gum administration on smoking cessation. American Journal of Psychiatry 1989;146:56-60. [CRSREF: 2963288]	Considered for inclusion because comparison of different intensity interventions. No mention of relapse prevention
Gruder 1993 **[CRSSTD: 2963289]** * Gruder CL, Mermelstein RJ, Kirkendol S, Hedeker D, Wong SC, Schreckengost J, et al. Effects of social support and relapse prevention training as adjuncts to a televised smoking-cessation intervention. Journal of Consulting and Clinical Psychology 1993;61(1):113-20. [CRSREF: 2963290] Warnecke RB, Flay BR, Kviz FJ, Gruder CL, Langenberg P, Crittenden KS, et al. Characteristics of participants in a televised smoking cessation intervention. Preventive Medicine 1991;20:389-403. [CRSREF: 2963291]	Not possible to distinguish between relapse prevention and cessation components
Hall 1994 **[CRSSTD: 2963292]** Hall SM, Munoz RF, Reus VI. Cognitive-behavioral intervention increases abstinence rates for depressive-history smokers. Journal of Consulting and Clinical Psychology 1994;62(1):141-6. [CRSREF: 2963293]	Considered for inclusion because comparison of different intensity interventions. Primary focus was on CBT for depression as adjunct to cessation intervention. No mention of relapse prevention
Hall 1996 **[CRSSTD: 2963294]** * Hall SM, Munoz RF, Reus VI, Sees KL, Duncan C, Humfleet GL, et al. Mood management and nicotine gum in smoking treatment - a therapeutic contact and placebo-controlled study. Journal of Consulting and Clinical Psychology 1996;64:1003-9. [CRSREF: 2963295]	Considered for inclusion because comparison of different intensity interventions. Primary focus was on mood management as adjunct to cessation intervention. No mention of relapse prevention
Hall 1998 **[CRSSTD: 2963296]** * Hall SM, Reus VI, Munoz RF, Sees KL, Humfleet G, Hartz DT, et al. Nortriptyline and cognitive-behavioral therapy in the treatment of cigarette smoking. Archives of General Psychiatry 1998;55:683-90. [CRSREF: 2963297] Hall SM, Reus VI, Munoz RF, Sees KL, Humfleet GL, Frederick S. Nortriptyline and cognitive-behavioral treatment of cigarette smoking. In: Proceedings of the CPDD Annual Meeting; San Juan, Puerto Rico. Vol. 52. 1996. [CRSREF: 2963298]	Considered for inclusion because comparison of different intensity interventions. No mention of relapse prevention

Study citation	Exclusion reason
Hall 2011 **[CRSSTD: 2963299]** * Hall SM, Humfleet GL, Muñoz RF, Reus VI, Prochaska JJ, Robbins JA. Using extended cognitive behavioral treatment and medication to treat dependent smokers. American Journal of Public Health 2011;101(12):2349-56. [CRSREF: 2963300] Prochaska JJ, Hall SM, Humfleet G, Munoz RF, Reus V, Gorecki J, et al. Physical activity as a strategy for maintaining tobacco abstinence: a randomized trial. Preventive Medicine 2008;47(2):215-20. [CRSREF: 2963301]	Considered for inclusion because study evaluated extended therapy. Not relapse prevention
Hassandra 2017 **[CRSSTD: 9969649]** * Hassandra M, Lintunen T, Hagger MS, Heikkinen R, Vanhala M, Kettunen T. An mHealth app for supporting quitters to manage cigarette cravings with short bouts of physical activity: a randomized pilot feasibility and acceptability study. JMIR mHealth and uHealth 2017;5(5):e74. [CRSREF: 9969650] Hassandra M, Lintunen T, Kettunen T, Vanhala M, Toivonen HM, Kinnunen K, et al. Effectiveness of a mobile phone app for adults that uses physical activity as a tool to manage cigarette craving after smoking cessation: a study protocol for a randomized controlled trial. JMIR Research Protocols 2015;4(4):e125. [CRSREF: 9969651]	Wrong intervention. Relapse-prevention but exercise-based
Juliano 2006 **[CRSSTD: 2963161]** Juliano LM, Houtsmuller EJ, Stitzer ML. A preliminary investigation of rapid smoking as a lapse-responsive treatment for tobacco dependence. Experimental & Clinical Psychopharmacology 2006;14:429-38. [CRSREF: 2963162]	Previously included study. Excluded from 2018 update because included relapsed smokers rather than abstainers
Klesges 1987 **[CRSSTD: 2963302]** Klesges R, Glasgow RE, Klesges L, Morray K, Quale R. Competition and relapse prevention training in worksite smoking modification. Health Education Research 1987;2:5-14. [CRSREF: 2963303]	Randomisation and analysis by worksite, number of individuals in each treatment condition not given. A non-significant difference favoured relapse prevention
Lando 1997 **[CRSSTD: 2963304]** * Lando HA, Rolnick S, Klevan D, Roski J, Cherney L, Lauger G. Telephone support as an adjunct to transdermal nicotine in smoking cessation. American Journal of Public Health 1997;87:1670-4. [CRSREF: 2963305] Rolnick SJ, Klevan D, Cherney L, Lando HA. Nicotine replacement therapy in a group model HMO. HMO Practice 1997;11:34-7. [CRSREF: 2963306]	Considered for inclusion because comparison of different intensity interventions. No mention of relapse prevention
Laude 2017 **[CRSSTD: 9969652]** Laude JR, Bailey SR, Crew E, Varady A, Lembke A, McFall D, et al. Extended treatment for cigarette smoking cessation: a randomized control trial. Addiction 2017;112(8):1451-9. [CRSREF: 9969653]	Not relapse prevention
Macleod 2003 **[CRSSTD: 2963307]**	Considered for inclusion because comparison of different intensity

Study citation	Exclusion reason
Macleod ZR, Charles MA, Arnaldi VC, Adams IM. Telephone counselling as an adjunct to nicotine patches in smoking cessation: a randomised controlled trial. Medical Journal of Australia 2003;179:349-52. [CRSREF: 2963308]	interventions. No mention of relapse prevention
Miller 1997 **[CRSSTD: 2963309]** * Miller NH, Smith PM, DeBusk RF, Sobel DS, Taylor CB. Smoking cessation in hospitalized patients - results of a randomized trial. Archives of Internal Medicine 1997;157:409-15. [CRSREF: 2963310] Taylor CB, Miller NH, Herman S, Smith PM, Sobel D, Fisher L, et al. A nurse-managed smoking cessation program for hospitalized smokers. American Journal of Public Health 1996;86:1557-60. [CRSREF: 2963311]	Hospital intervention included relapse prevention components but excluded because no information on smoking status of participants, and intervention similar in other respects to other inpatient trials. Also compared 2 intensities of telephone follow-up but these were not described as relapse prevention
NCT00218465 **[CRSSTD: 9969654]** NCT00218465. Effectiveness of GW468816, an NMDA glycine site antagonist, for prevention of relapse to smoking. clinicaltrials.gov/show/NCT00218465 (date first received: 2010). [CRSREF: 9969655]	Only 5-week follow-up
NCT00621777 **[CRSSTD: 9969656]** NCT00621777. A study of varenicline for prevention of relapse to smoking in patients with schizophrenia. clinicaltrials.gov/ct2/show/nct00621777 (date first received: 2015). [CRSREF: 9969657]	Only 3 month follow-up
NCT01131156 **[CRSSTD: 9969658]** NCT01131156. Prevention of postpartum smoking relapse in mothers of infants in the neonatal intensive care unit (NICU). clinicaltrials.gov/ct2/show/NCT01131156 (date first received: 2010). [CRSREF: 9969659]	Only 8-week follow-up
NCT02888444 **[CRSSTD: 9969660]** NCT02888444. Smoking relapse prevention among COPD ex-smokers. clinicaltrials.gov/show/NCT02888444 (date first received: 2016). [CRSREF: 9969661]	Only 24-week follow-up
NCT02968095 **[CRSSTD: 9969662]** NCT02968095. Text message support to prevent smoking relapse. clinicaltrials.gov/show/NCT02968095 (date first received: 2016). [CRSREF: 9969663]	Only 6-week follow-up
NCT03113370 NCT03113370. Preventing tobacco relapse with omega-3s trial. clinicaltrials.gov/show/NCT03113370 (first received 13 April 2017).	Only 12-week follow-up
NCT03262662 NCT03262662. EVarQuit: extended pre-quit varenicline to assist in quitting smoking. clinicaltrials.gov/show/NCT03262662 (first received 25 August 2017).	Not relapse prevention
NCT03690596	Only 12-week follow-up

Study citation	Exclusion reason
NCT03690596. Smoking relapse prevention via just-in-time-adaptive interventions. clinicaltrials.gov/show/NCT03690596 (first received 1 October 2018).	
NCT03930329 NCT03930329. Mindfulness-based treatment to prevent smoking relapse. clinicaltrials.gov/show/NCT03930329 (first received 29 April 2019).	Only 8-week follow-up
Phillips 2012 **[CRSSTD: 2963312]** Phillips RM, Merritt TA, Goldstein MR, Deming DD, Slater LE, Angeles DM. Supporting mother-infant bonding increases the duration of breastfeeding in mothers with newborns in the neonatal intensive care unit. Breastfeeding Medicine 2011;6:S4. [CRSREF: 2963313] * Phillips RM, Merritt TA, Goldstein MR, Deming DD, Slater LE, Angeles DM. Prevention of postpartum smoking relapse in mothers of infants in the neonatal intensive care unit. Journal of Perinatology 2012;32(5):374-80. [CRSREF: 2963314]	Only 8-week follow-up
Reid 1999 **[CRSSTD: 2963315]** Reid RD, Pipe A, Dafoe WA. Is telephone counselling a useful addition to physician advice and nicotine replacement therapy in helping patients to stop smoking? A randomized controlled trial. Canadian Medical Association Journal 1999;160:1577-81. [CRSREF: 2963316]	Considered for inclusion because comparison of different intensity interventions. No mention of relapse prevention
Schlam 2016 Schlam TR, Fiore MC, Smith SS, Fraser D, Bolt DM, Collins LM, et al. Comparative effectiveness of intervention components for producing long-term abstinence from smoking: a factorial screening experiment. Addiction 2016;111(1):142-55. [DOI: 10.1111/add.13153]	Study of extended NRT in smokers: covered in Lindson 2019
Schnoll **2015** **[CRSSTD: 9969639]** Schnoll RA, Goelz PM, Veluz-Wilkins A, Blazekovic S, Powers L, Leone FT, et al. Long-term nicotine replacement therapy: a randomized clinical trial. JAMA Internal Medicine 2015;175(4):504-11. [CRSREF: 9969640]	Previously included study. Excluded in 2019 update as extended NRT is covered in Lindson 2019
Snuggs 2012 **[CRSSTD: 9969664]** Snuggs S, McRobbie H, Myers K, Schmocker F, Goddard J, Hajek P. Using text messaging to prevent relapse to smoking: intervention development, practicability and client reactions. Addiction 2012;107(Suppl 2):39-44. [CRSREF: 9969665]	Wrong design, all participants received text messages
Solomon 2000 **[CRSSTD: 2963317]** Solomon LJ, Scharoun GM, Flynn BS, Secker-Walker RH, Sepinwall D. Free nicotine patches plus proactive telephone peer support to help low-income women stop smoking. Preventive Medicine 2000;31:68-74. [CRSREF: 2963318]	Considered for inclusion because comparison of different intensity interventions. No mention of relapse prevention

Study citation	Exclusion reason
Storro 2008 **[CRSSTD: 2963319]** Storro O, Oien T, Johnsen R. Preventing relapse of smoking among postnatal women and their partners in primary care: a controlled birth cohort intervention study. Allergy 2008;63(Suppl 88):483. [CRSREF: 2963320]	Controlled cohort study of postpartum intervention, not randomised
Tonstad 2013 **[CRSSTD: 2963321]** Tonstad S, Heggen E, Giljam H, Lagerbäck PA, Tønnesen P, Wikingsson LD, et al. Niccine®, a nicotine vaccine for relapse prevention: a phase II, randomized, placebo-controlled, multicenter clinical trial. Nicotine & Tobacco Research 2013 [Epub ahead of print]. [CRSREF: 2963322]	Test of vaccine versus placebo. Effect of pharmacotherapy post-quit confounded with pharmacotherapy before quitting
Yoon 2009 **[CRSSTD: 2963323]** Yoon JH, Higgins ST, Bradstreet MP, Badger GJ, Thomas CS. Changes in the relative reinforcing effects of cigarette smoking as a function of initial abstinence. Psychopharmacology 2009;205(2):305-18. [CRSREF: 2963324]	Only 2-week follow-up
Zelman 1992 **[CRSSTD: 2963325]** Zelman DC, Brandon TH, Jorenby DE, Baker TB. Measures of affect and nicotine dependence predict differential response to smoking cessation treatments. Journal of Consulting and Clinical Psychology 1992;60:943-52. [CRSREF: 2963326]	Considered for inclusion because comparison of different intensity interventions. No mention of relapse prevention

Table 8: Excluded studies included in the Cochrane review (n=7)

Study citation	Exclusion reason
Blebil 2014 Blebil AQ, Sulaiman SA, Hassali MA, Dujaili JA, Zin AM. Impact of additional counselling sessions through phone calls on smoking cessation outcomes among smokers in Penang State, Malaysia. BMC Public Health 2014;14:460. [CRSREF: 9969604]	Exclude on setting: Malaysia, non-OECD country
Campos 2018 Campos ACF, Nani ASF, Fonseca VADS, Silva EN, Castro MCS, Martins WA. Comparison of two smoking cessation interventions for inpatients. Jornal Brasileiro de Pneumologia 2018;44(3):195-201.	Exclude on setting: Brazil, non OECD country
Cheung 2015 Cheung YT, Chan CH, Lai CK, Chan WF, Wang MP, Li HC, et al. Using WhatsApp and Facebook online social groups for smoking relapse prevention for recent quitters: a pilot pragmatic cluster randomized controlled trial. Journal of Medical Internet Research 2015;17(10):e238. [CRSREF: 9969614]	Exclude on setting: China, non OECD country
Hannöver 2009 * Hannöver W, Thyrian JR, Roske K, Grempler J, Rumpf HJ, John U, et al. Smoking cessation and relapse prevention for postpartum women: results from a randomized controlled trial	Exclude on study design: quasi randomised

Study citation	Exclusion reason
at 6, 12, 18 and 24 months. Addictive Behaviors 2009;34:1-8. [CRSREF: 2963140; DOI: 10.1016/j.addbeh.2008.07.021] Roske K, Schumann A, Hannöver W, Grempler J, Thyrian JR, Rumpf HJ, et al. Postpartum smoking cessation and relapse prevention intervention: a structural equation modeling application to behavioral and non-behavioral outcomes of a randomized controlled trial. Journal of Health Psychology 2008;13:556-68. [CRSREF: 2963141] Thyrian JR, Freyer-Adam J, Hannöver W, Roske K, Mentzel F, Kufeld C, et al. Adherence to the principles of motivational interviewing, clients' characteristics and behavior outcome in a smoking cessation and relapse prevention trial in women postpartum. Addictive Behaviors 2007;32:2297-303. [CRSREF: 2963142]	
Sheffer 2010 Sheffer CE, Stitzer M, Brandon T, Bursac Z. Effectiveness of adding relapse prevention materials to telephone counselling. Journal of Substance Abuse Treatment 2010;39:71-7. [CRSREF: 2963222]	Exclude on study design: quasi randomised
STRATUS-WW 2006 * Niaura R. Long-term maintenance of abstinence from smoking with rimonabant: results from the STRATUS Worldwide trial. 1-year efficacy/safety results. American Thoracic Society Conference. 2005. [CRSREF: 2963230; Other: clinical trials.gov ID NCT00459173] Niaura R. Long-term maintenance of abstinence from smoking with rimonabant: results from the STRATUS Worldwide trial. 6-month efficacy/safety results. In: American Thoracic Society Conference. 2004:POS1-054. [CRSREF: 2963231] Sanofi Aventis. Information meeting. en.sanofi-aventis.com/Images/en_050301_up_2004_Full_Year_Results_Analysts_Investors_meeting_in_Paris_presentation_tcm24-3612.pdf (accessed 23 November 2006). [CRSREF: 2963232]	Exclude on intervention: rimonabant excluded
Van Osch 2008 Van Osch L, Lechner L, Reubsaet A, Wigger S, De Vries H. Relapse prevention in a national smoking cessation contest: effects of coping planning. British Journal of Health Psychology 13;2008:525-35. [CRSREF: 2963244]	Exclude on study design: quasi randomised

Economic studies

Table 9: Excluded health economics studies

Study citation	Exclusion reason
Annemans L, Marbaix S, Nackaerts K, Bartsch P. Cost-effectiveness of retreatment with varenicline after failure with or relapse after initial treatment for smoking cessation. Prev Med Rep. 2015;2:189-95.	Ineligible population
Chen YF, Madan J, Welton N, Yahaya I, Aveyard P, Bauld L, et al. Effectiveness and cost-effectiveness of computer and other electronic aids for smoking cessation: A systematic	Ineligible population

Study citation	Exclusion reason
review and network meta-analysis. Health Technol Assess. 2012;16(38):hta16380.	
Coyle K, Coyle D, Lester-George A, West R, Nemeth B, Hiligsmann M, et al. Development and application of an economic model (EQUIPTMOD) to assess the impact of smoking cessation. Addiction. 2018;113(Suppl 1):7-18.	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 population
Diaz DB, Brandon TH, Sutton SK, Meltzer LR, Hoehn HJ, Meade CD, et al. Smoking relapse-prevention intervention for cancer patients: Study design and baseline data from the surviving SmokeFree randomized controlled trial. Contemp Clin Trials. 2016;50:84-89.	Ineligible outcomes
French GM, Groner JA, Wewers ME, Ahijevych K. Staying smoke free: An intervention to prevent postpartum relapse. Nicotine Tob Res. 2007;9(6):663-70.	Ineligible outcomes
Kautiainen K, Ekroos H, Puhakka M, Liira H, Laine J, Linden K, et al. Re-treatment with varenicline is a cost-effective aid for smoking cessation. J Med Econ. 2017;20(3):246-52.	Ineligible population
Keating GM, Lyseng-Williamson KA. Varenicline: A pharmacoeconomic review of its use as an aid to smoking cessation. Pharmacoeconomics. 2010;28(3):231-54.	Ineligible outcomes
Meltzer LR, Meade CD, Diaz DB, Carrington MS, Brandon TH, Jacobsen PB, et al. Development of a targeted smoking relapse-prevention intervention for cancer patients. J Cancer Educ. 2018;33(2):440-47.	Ineligible outcomes
Ockene JK, Emmons KM, Mermelstein RJ, Perkins KA, Bonollo DS, Voorhees CC, et al. Relapse and maintenance issues for smoking cessation. Health Psychol. 2000;19(1S):17-31.	Ineligible outcomes
Rasch A, Grelner W. Efficacy and cost-effectiveness of smoking cessation courses in the statutory health insurance: A review. Gesundheitswesen. 2009;71(11):732-38.	Ineligible outcomes
Ruger JP, Emmons KM. Economic evaluations of smoking cessation and relapse prevention programs for pregnant women: A systematic review. Value Health. 2008;11(2):180-90.	Ineligible outcomes
Ruger JP, Emmons KM, Kearney MH, Weinstein MC. Measuring the costs of outreach motivational interviewing for smoking cessation and relapse prevention among low-income pregnant women. BMC Pregnancy Childbirth. 2009;9:46.	Ineligible outcomes
Severson HH, Andrews JA, Lichtenstein E, Wall M, Akers L. Reducing maternal smoking and relapse: Long-term evaluation of a pediatric intervention. Prev Med. 1997;26(1):120-30.	Ineligible outcomes
Snuggs S, McRobbie H, Myers K, Schmocker F, Goddard J, Hajek P. Using text messaging to prevent relapse to smoking: Intervention development, practicability and client reactions. Addiction. 2012;107(Suppl 2):39-44.	Ineligible outcomes
Soini E, Hallinen T, Brignone M, Campbell R, Diamand F, Cure S, et al. Cost-utility analysis of vortioxetine versus agomelatine, bupropion SR, sertraline and venlafaxine XR	Ineligible population

Study citation	Exclusion reason
after treatment switch in major depressive disorder in Finland. Expert Rev Pharmacoecon Outcomes Res. 2017;17(3):293-302.	
Sung HY, Penko J, Cummins SE, Max W, Zhu SH, 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 population
Turner J, McNeill A, Coleman T, Bee JL, Agboola S. Feasibility of offering nicotine replacement therapy as a relapse prevention treatment in routine smoking cessation services. BMC Health Serv Res. 2013;13:38.	Ineligible outcomes

Appendix L – Research recommendations

Research recommendation 11

Are nicotine replacement therapy or nicotine-containing e-cigarettes effective for preventing relapse after a successful quit attempt?

Why this is important

Strategies to avoid relapsing are an important part of stop smoking advice and support. No evidence on e-cigarettes for relapse prevention was identified and evidence about NRT for preventing relapse was mixed. It is therefore important to determine what nicotine-containing products or combination of products are best at preventing relapse after a successful quit attempt.

Rationale for research recommendation

Importance to 'patients' or the population	Relapse to smoking is common and it can take multiple attempts to stop smoking permanently. Various nicotine containing products are available and so it is important for people to have information about which products or combinations of products are most likely to help them avoid relapsing to smoking after a successful quit attempt.
Relevance to NICE guidance	It is important to understand which products or combinations of products are effective for preventing relapse, in particular over the long term in people who have successfully stopped smoking.
Relevance to the NHS	Strategies to avoid relapsing are an important part of stop smoking advice and support. It is important to determine which nicotine-containing products or combination of products are best at preventing relapse after a successful quit attempt, in order that stop-smoking advisers can provide people with this information.
National priorities	Relapse is common and the extensive harms of smoking are well known. It is important to identify which products or combination of products can support people to stop smoking permanently.
Current evidence base	No evidence was identified on e-cigarettes for relapse prevention. Although there was evidence that using a single type of fast-acting NRT in people who had recently quit may be effective, this did not reduce relapse with any certainty when people had stopped smoking for longer. More evidence is needed on preventing relapse over the long term in people who have successfully quit, as opposed to having just

	started a quit attempt, to provide conclusive results.
Equality considerations	Encouraging people to keep trying to quit is important, particularly for those who are finding quitting very difficult. The committee noted that acknowledging individual choice and discussing the various options is an important part of supporting people to quit successfully. Being able to provide information on which products or combinations of products are likely to be effective, will help to support people in their attempts to quit.

Modified PICO table

Population	People who have stopped smoking.
Intervention	Use of nicotine replacement therapy products or nicotine containing e-cigarettes for preventing relapse to smoking.
Comparator	No intervention or placebo Usual care A shorter intervention or intervention not specifically to prevent relapse
Outcome	Abstinence from smoking

Research recommendation 12

How can people who have recently stopped or temporarily abstained from smoking in a smoke-free in-patient or treatment environment be best supported after discharge to prevent relapse or to stop permanently?

Why this is important

There are clear benefits for preventing a relapse to smoking among those who have stopped smoking in the short term or who have been able to temporarily abstain from smoking while in a smoke-free inpatient or treatment environment. However the committee noted that there is risk of relapse at the point of discharge, particularly if people are unable to access treatments for long enough to consolidate a quit or if the support they have received as an inpatient is not continued after discharge into the community.

Rationale for research recommendation

Importance to ‘patients’ or the population	It can take multiple attempts to stop smoking permanently. It is important that people who have recently stopped smoking or who have abstained temporarily while in a smoke-free treatment environment, are encouraged and supported to continue with this, after they are discharged.
Relevance to NICE guidance	Determining how best to support people to prevent them relapsing when they are discharged from a smoke-free treatment environment, would complement the existing recommendations.
Relevance to the NHS	Relapse in smoking cessation is common and multiple attempts may be needed. While people are in a smoke-free inpatient or treatment environment there is the opportunity to deliver interventions to support and encourage smokers to quit smoking or abstain temporarily. However, it is important that the support and encouragement continues after they are discharged in order to build on these gains and prevent relapse.
National priorities	The NHS Long Term Plan notes that by 2023/24 all people admitted to hospital who smoke will be offered NHS funded tobacco treatment services.
Current evidence base	Expert testimony highlighted the risk of relapse when people who have recently stopped smoking or temporarily abstained while in a smoke-free environment are discharged into the community. Contributary factors may include being unable to access treatments for long enough to consolidate a quit, or discontinuation of the support they received as an inpatient. It is therefore important to determine how best to provide that ongoing support in order to build on any health gains achieved.
Equality considerations	Expert testimony was provided to the committee in relation to people who had recently stopped smoking or temporarily abstained while in mental health care settings. While smoking prevalence is higher among people with mental health conditions than among the general population, this research recommendation applies to a range of smoke-free inpatient and treatment environments.

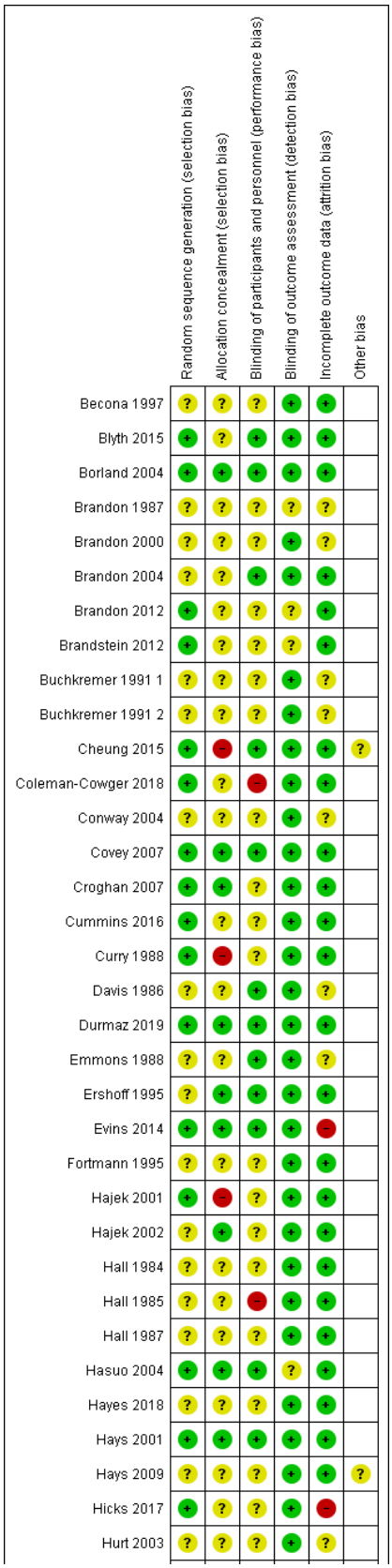
Modified PICO table

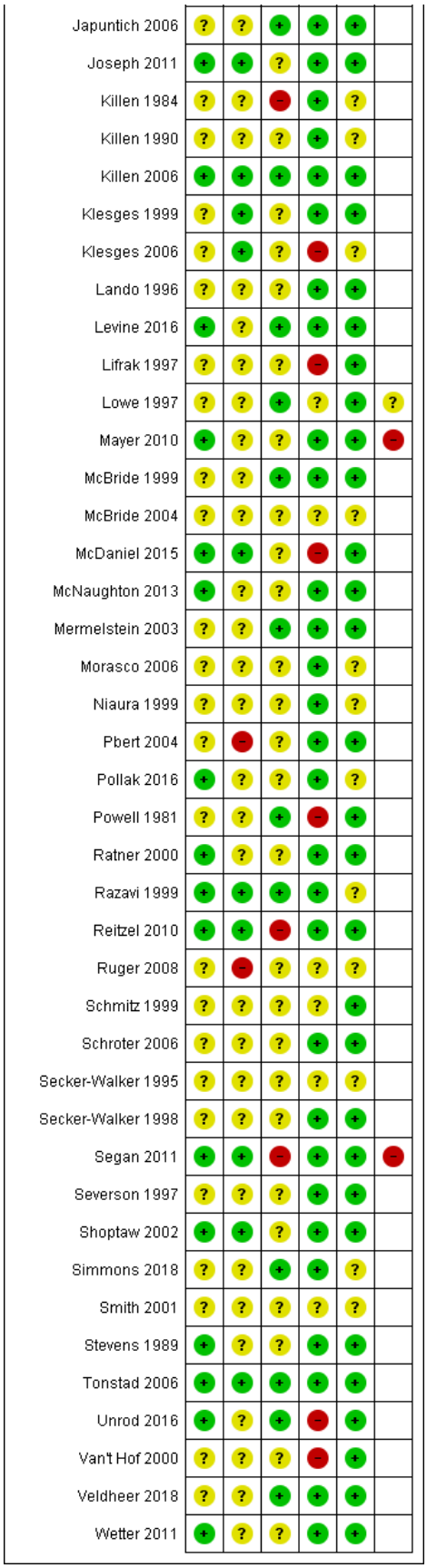
Population	People who have recently stopped smoking or temporarily abstained while in a smoke-free inpatient or treatment environment and who are being discharged to the community.

Intervention	Smoking cessation interventions Interventions that aim to prevent relapse
Comparator	Other intervention No intervention
Outcome	Abstinence from smoking Uptake of stop smoking support in people who have been discharged from smoke-free inpatient or treatment environments.

Appendix M

Risk of bias by domain




Japuntich 2006
Joseph 2011
Killen 1984
Killen 1990
Killen 2006
Klesges 1999
Klesges 2006
Lando 1996
Levine 2016
Lifrak 1997
Lowe 1997
Mayer 2010
McBride 1999
McBride 2004
McDaniel 2015
McNaughton 2013
Mermelstein 2003
Morasco 2006
Niaura 1999
Pbert 2004
Pollak 2016
Powell 1981
Ratner 2000
Razavi 1999
Reitzel 2010
Ruger 2008
Schmitz 1999
Schroter 2006
Secker-Walker 1995
Secker-Walker 1998
Segan 2011
Severson 1997
Shoptaw 2002
Simmons 2018
Smith 2001
Stevens 1989
Tonstad 2006
Unrod 2016
Van't Hof 2000
Veldheer 2018
Wetter 2011

Health economic quality assessment

Study identification **Blyth A, Maskrey V, Notley C, Barton GR, Brown TJ, Aveyard P, et al. Effectiveness and economic evaluation of self-help educational materials for the prevention of smoking relapse: Randomised controlled trial. Health Technol Assess. 2015;19(59):hta19590.**		
Guidance topic: Preventing relapse		**Relapse prevention**
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	4-week quitters
1.2 Are the interventions appropriate for the review question?	Yes	Booklets for smoking relapse prevention
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	UK study
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	National Health Service (NHS) (plus participant costs)
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Partly	Only quit-rates were calculated
1.6 Are all future costs and outcomes discounted appropriately?	NA	1-year time-horizon
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	Quality-adjusted life-years (QALYs) were used based on EuroQol 5 dimensions 3 levels (EQ-5D-3L) responses from a randomised controlled trial (RCT) and York tariffs for utilities
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	No	Costs and benefits from other sectors were 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?	No	No model was used
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	12 months
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	Based on UK quitters from NHS clinics

2.5 Are the estimates of relative intervention effects from the best available source?	Yes	Taken from the RCT
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?	Yes	Taken from the RCT
2.8 Are the unit costs of resources from the best available source?	Yes	Unit costs were taken from standard UK sources
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	A net benefit analysis was conducted
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	A non-parametric bootstrap analysis was conducted
2.11 Is there any potential conflict of interest?	None	
2.12 Overall assessment: Minor limitations		
Other comments: None		
Abbreviations: EQ-5D-3L: EuroQol 5 dimensions 3 levels; NHS: National Health Service; QALY: quality-adjusted life-year; RCT: randomised controlled trial		