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[Intervention Protocol]

# Pharmacological and electronic cigarette interventions for smoking cessation in adults: component network meta-analyses

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## ABSTRACT

### Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To conduct component network meta-analyses (cNMAs) to investigate the comparative effectiveness, safety and tolerability of different smoking cessation pharmacotherapies and electronic cigarettes (EC), singly and combined, when helping people to stop smoking tobacco.

To investigate:

- how the different characteristics of smoking cessation pharmacotherapies and EC interventions (e.g. intervention subtype, dose, length of intervention, whether the intervention is used prequit as well as from quit date or from quit date only) influence efficacy, safety and tolerability;
- whether identifiable participant characteristics and behavioural support suggest different optimal intervention strategies.

## BACKGROUND

### Description of the condition

Globally, tobacco smoking is a leading cause of preventable death and disease ([WHO 2021](#)). It is also a key driver of health inequalities, disproportionately affecting vulnerable populations, for example, people with low incomes and mental health conditions ([ASH 2019](#)). However, cessation is effective at reducing much of the harm caused, even after many years of smoking ([Pirie 2013](#)). Smoking cessation interventions are among the most cost-effective in medicine, with many estimates suggesting such interventions reduce health service costs overall ([Hoogendoorn 2010](#)). Many people who smoke would like to stop; however, typically it takes many attempts to quit before achieving success ([Chaiton 2016](#)). This is partly because none of the treatments available to treat tobacco dependence have particularly high success rates, and few people use these treatments optimally ([Raupach 2014](#)).

### Description of the intervention

Evidence suggests that the most effective way to stop smoking is to use a combination of behavioural and pharmacological support ([Hartmann-Boyce 2019](#)). Five pharmacotherapies for quitting smoking are licensed in at least some parts of the world: nicotine replacement therapy (NRT), bupropion, varenicline, cytisine and nortriptyline ([WHO 2019](#)). Electronic cigarettes (EC) are also increasingly used, and in some countries guidelines support their recommendation by health providers to support a quit attempt ([ASH 2021](#); [RCP 2016](#)). Standard Cochrane intervention reviews provide evidence that all of these interventions are effective smoking cessation aids ([Cahill 2016](#); [Hartmann-Boyce 2018](#); [Hartmann-Boyce 2021b](#); [Howes 2020](#)), and they are all traditionally viewed as competing approaches to smoking cessation, though in some cases they may be used in combination.

### How the intervention might work

NRT is a medication formulated for absorption through the oral mucosa (chewing gum, lozenges, sublingual tablets, inhaler/inhalator, mouth spray, strips), nasal mucosa (spray), or skin (transdermal patches) ([Hartmann-Boyce 2018](#)). Nicotine transdermal patches are worn on the body and deliver a nicotine dose slowly and passively through the skin. In contrast, other types of NRT (e.g. gum or lozenge), deliver nicotine faster.

Nicotine is one of the vehicles of tobacco addiction and neuroadaptations in response to repeated ingestion mean that when a person stops smoking tobacco, they experience withdrawal symptoms. The aim of NRT is to replace the nicotine that the smoker would have been receiving, ameliorating withdrawal, which manifests as urges to smoke and aversive mood and physical symptoms. Inability to tolerate withdrawal accounts for most cases of early relapse to smoking. After some weeks, the urges to smoke abate, and nicotine can be stopped without precipitating withdrawal in most people. NRT is available worldwide and the World Health Organization (WHO) deems it an essential medicine ([Kishore 2010](#)).

Varenicline and cytisine are both nicotine receptor partial agonists ([Cahill 2016](#)). They activate the nicotinic receptors usually activated by nicotine to release dopamine, and prevent nicotine from further activating these receptors. This appears to relieve withdrawal symptoms and reduce the rewarding effects of tobacco smoking.

Current evidence suggests that both cytisine and varenicline are efficacious cessation treatments ([Cahill 2016](#)); however, varenicline is used more extensively worldwide. Cytisine is only available in some European and Asian countries. However, it has been identified as a potentially attractive treatment option due to its lower cost relative to other smoking cessation treatments. It is currently undergoing trials with a view to obtaining licences for worldwide use ([Courtney 2021](#); [NCT03709823](#); [Nides 2021](#)).

Bupropion and nortriptyline are antidepressant treatments that have also been used for smoking cessation ([Howes 2020](#)). It is not entirely clear why these two antidepressants can help people to stop smoking. Not all antidepressants are effective cessation aids, suggesting that the mechanism of action is separate from their antidepressant actions. Some antidepressants may have a specific effect on neural pathways or receptors that underlie nicotine addiction. Many countries have licensed bupropion as a smoking cessation aid; whereas nortriptyline is licensed for this purpose in New Zealand only.

EC appeared on the market in 2006, and are electronic devices that heat a liquid into an aerosol for inhalation, termed vaping ([Hartmann-Boyce 2021b](#)). The liquid usually comprises propylene glycol and glycerol, with or without nicotine and flavours, and is stored in disposable or refillable cartridges or a reservoir. Although EC are banned in some countries, vaping is currently legal in the UK, the EU, the USA, Canada, and New Zealand (among other countries). As many EC contain nicotine, they could function as a form of NRT. Indeed, there is evidence that they are effective cessation aids and they may be more effective than traditional NRT ([Hajek 2019](#)). In some countries, EC are classed as a tobacco product; however, as they do not contain tobacco leaf and licensed products can be promoted as a tobacco cessation aid in some countries, we do not consider them as such here.

Due to the number of people who do not manage to quit smoking, or who relapse to smoking despite using these interventions, as well as providing these interventions in isolation there has been an interest in combining them. This could capitalise on the different mechanisms of action to combat tobacco addiction from multiple angles ([Ebbert 2010](#)).

### Why it is important to do this review

Against a backdrop of finite resource, and when dealing with a health behaviour so resistant to change, it is particularly important to pinpoint the treatment strategies that work best, focus available efforts and funds on these approaches, and promote them to the general public. This requires data on comparative effectiveness. Additionally, it is important to consider success rates alongside the safety and tolerability of available interventions. Tolerability has an impact on adherence to pharmacological treatment ([Balmford 2010](#); [de Dios 2012](#)), which in turn effects quitting success ([Raupach 2014](#)). Although there is evidence that NRT is a safe and effective medication for smoking cessation ([Hartmann-Boyce 2018](#)), adverse effects such as skin irritation when using patches or irritation of the nose, throat or eyes when using a nasal spray, can lead smokers to discontinue treatment ([Raupach 2014](#)). Equally, a highly efficacious treatment may not be the best approach if it results in serious health problems. Questions remain around the safety of some licensed cessation pharmacotherapies; for example, there have been concerns regarding the mental health effects of varenicline and the effects of bupropion on the risk of seizure ([Howes 2020](#);

Moore 2011; Pesola 2002). As EC are a relatively new approach to quitting smoking the evidence is still accumulating on safety, and there is substantial debate over their potential effects on health (Hartmann-Boyce 2021b).

Two network meta-analyses (NMAs) investigating the comparative effectiveness of pharmacological smoking cessation treatments in the general population have previously been carried out; one published in 2013 (Cahill 2013) and the other with searches conducted up to February 2019 (Thomas 2021). The former NMA did not include EC and the latter did not include cytisine or nortriptyline as competing treatment options. This present review will strengthen the evidence base by including all approved intervention options currently available across the world. It will also incorporate studies completed and published since the previous searches were carried out, which is particularly important when incorporating the fast-moving literature on EC. We will use component network meta-analysis (cNMA) to explore additional questions beyond just comparing different medicine types. cNMA will allow us to split our interventions of interests into components, allowing comparison between all of their separate parts (Freeman 2018). We will investigate differences in effects by intervention subtype (e.g. gum, patch, etc.), dosage, timing of intervention (i.e. prequit through to postquit/from quit date only) and interactions between interventions that are used concurrently (it is common for people to use two stop-smoking medications simultaneously). We also plan to investigate moderators of the effects of smoking cessation pharmacotherapies and EC, including population characteristics and the behavioural support offered alongside pharmacotherapies. Having more detailed information on how to use and provide smoking cessation medications and EC to maximise their effectiveness, tolerability and safety will allow us to pinpoint the most and least effective elements of these interventions, as well as identifying which intervention types may suit certain people best. This will allow for more tailored and effective medication strategies for people who would like to stop smoking. This, in turn, has the potential to reduce healthcare costs, the burden on practitioners and patients, and the burden of disease and death associated with smoking in the general population. These are key drivers of health inequalities, and have a considerable negative impact on individuals, health services and economies.

## OBJECTIVES

To conduct component network meta-analyses (cNMAs) to investigate the comparative effectiveness, safety and tolerability of different smoking cessation pharmacotherapies and electronic cigarettes (EC), singly and combined, when helping people to stop smoking tobacco.

To investigate:

- how the different characteristics of smoking cessation pharmacotherapies and EC interventions (e.g. intervention subtype, dose, length of intervention, whether the intervention is used prequit as well as from quit date or from quit date only) influence efficacy, safety and tolerability;
- whether identifiable participant characteristics and behavioural support suggest different optimal intervention strategies.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials (RCTs) and cluster RCTs (cRCTs). Well-conducted RCTs give the strongest evidence on the effectiveness and safety of treatment. We will exclude crossover RCTs as it is impossible to assess the effects of a particular smoking cessation intervention on abstinence in the long-term using these studies. As there are numerous trials of smoking cessation pharmacotherapies, we will exclude non-randomised studies (including quasi-RCTs). We will include studies regardless of language or publication type.

#### Types of participants

Adults (aged 18 years or older) who smoke cigarettes. People who use more than one type of tobacco will be included as long as cigarette smoking is an inclusion criteria and the trial meets the rest of our eligibility criteria. However, we will exclude studies that solely recruited pregnant women, as some of the interventions being assessed are unlikely to be offered to this population. Similarly, the reason for excluding young people (under the age of 18 years) is that some interventions of interest in this review are not available to, or licensed for, young people, and young people metabolise nicotine differently. Excluding these two populations will ensure that all participants included in our analyses are jointly randomisable (Higgins 2021).

#### Types of interventions

Any approved pharmacotherapies and technologies used for tobacco smoking cessation worldwide (i.e. any forms of NRT, EC, varenicline, cytisine, bupropion or nortriptyline use), including combination use of more than one of these intervention types. Although some countries allow the use of smokeless or heated tobacco products as harm reduction products, they will be excluded from this review as they are not typically used to quit smoking and they contain tobacco leaf. In addition, we will only include interventions that describe themselves as 'relapse prevention' when they were delivered to people who were still smoking tobacco at study enrolment.

Studies will not be eligible if one of the study arms receives an additional intervention component whose effects cannot be separated from the pharmacotherapy or EC interventions of interest (e.g. where behavioural counselling or a financial incentive is only provided in one study arm). However, studies that provide an additional component (e.g. behavioural support) equally to all included study arms will be eligible. We will exclude trials that asked participants to reduce the amount they smoked, where complete quitting was not a goal of the study intervention.

We will evaluate the comparative effects of the following component types in our cNMA:

- intervention type;
- intervention delivery mode;
- dose;
- intended duration of use;
- tapering of dose;

- timing of intervention (in relation to quit day; i.e. prequit as well as from quit date or from quit date only), and whether any prequit pharmacotherapy is used while reducing to quit or while smoking as usual.

For a full list of components, see [Appendix 1](#).

Relevant comparators will include:

- no pharmacotherapy and no EC intervention;
- placebo pharmacotherapy;
- non-nicotine EC
- another eligible intervention type (e.g. a study comparing NRT with varenicline);
- the same intervention type as provided in the intervention arm, but with a varying component or components (e.g. nicotine 21 mg patch versus nicotine 14 mg patch).

However, studies with a 'no pharmacotherapy and no EC intervention' comparator will not be used to assess our tolerability outcome (below), as it is not possible to assess this in participants who have received no pharmacotherapy or EC intervention.

### Types of outcome measures

Studies must assess smoking abstinence at least six months following baseline to be eligible for inclusion. This is in line with the standard methods of Cochrane Tobacco Addiction Group (TAG).

### Primary outcomes

Primary efficacy outcome:

- long-term smoking cessation (i.e. for six months or longer). The preferred outcome will be biochemically validated continuous or prolonged abstinence at the longest reported time point, including all participants randomised in their original groups. We will assume that any participants lost to follow-up are smoking, as is standard in the field ([West 2005](#)), and in line with standard Cochrane TAG methods.

Primary safety outcome:

- number of participants reporting serious adverse events (SAEs) between baseline and follow-up, analysed on a complete case basis, as close to the six-month follow-up as possible. Alternatively, if interventions extend beyond the six-month follow-up then this outcome will refer to the follow-up time measured as close to intervention end as possible. SAEs are defined as events that result in death, are life-threatening, require hospitalisation or prolongation of existing hospitalisation, result in persistent or significant disability or incapacity, result in congenital anomaly or birth defect, or a combination of these. Examples of SAEs are seizures, potentially fatal overdoses or suicide attempts and deaths.

We will not measure adverse events (AEs) as an outcome as these are typically poorly reported, and are most relevant when assessing the tolerability of an intervention. This will be better assessed using our secondary outcome (withdrawal due to intervention), described below.

### Secondary outcomes

Secondary tolerability of interventions outcome:

- number of participants who withdrew from the trial due to pharmacological or EC interventions, measured on an intention-to-treat basis, as close to the six-month follow-up as possible. Alternatively, if interventions extend beyond the six-month follow-up then measured as close to intervention end as possible.

## Search methods for identification of studies

### Electronic searches

We will identify all listed included and excluded studies in the most recent updates of relevant Cochrane Reviews. These reviews cover all the interventions relevant to this review (i.e. varenicline and cytisine ([Cahill 2016](#)); NRT ([Hartmann-Boyce 2018](#); [Lindson 2019](#)); bupropion and nortriptyline ([Howes 2020](#)); and EC ([Hartmann-Boyce 2021b](#)). We will also update the searches for each of these reviews by searching Cochrane TAG's specialised register using the search strategies specified in [Appendix 2](#). The register includes any outputs of tobacco-related RCTs found within the following databases since their inception, and Cochrane TAG's information specialists maintain it with monthly updates:

- Cochrane's Central Register of Controlled trials (CENTRAL);
- MEDLINE (via Ovid);
- Embase (via Ovid);
- PsycINFO (via Ovid);
- U.S. National Library of Medicine's [clinicaltrials.gov](https://clinicaltrials.gov) trial registry, via CENTRAL;
- WHO International Clinical Trials Registry Platform (ICTRP; [www.who.int/ictip/](http://www.who.int/ictip/)), via CENTRAL.

For further details of the searches used to populate Cochrane TAG's register, see Cochrane TAG's website ([tobacco.cochrane.org/resources/cochrane-tag-specialised-register](https://tobacco.cochrane.org/resources/cochrane-tag-specialised-register)).

For the living systematic review of '*Electronic cigarettes for smoking cessation*' ([Hartmann-Boyce 2021b](#)), we will additionally search MEDLINE, Embase and PsycINFO via Ovid, in line with the review search strategy. As a living systematic review with monthly searches, searching multiple databases as well as the register increases the chances of finding the most recent studies for review updates.

There will be no restrictions on searching other than the search dates of the previous versions of relevant reviews.

### Searching other resources

We will contact investigators of trials that we know to be ongoing or where we have insufficient information to make an eligibility judgement.

## Data collection and analysis

### Selection of studies

We will upload the results of our searches of the existing reviews and of Cochrane TAG's specialised register into [Covidence](#), which will remove most duplicate records. Two review authors will independently screen each reference to establish eligibility. We will screen references in two stages; first screening titles and abstracts. For those that appear to be eligible, or where after discussion within the team eligibility is still unclear, we will retrieve full-text reports.



Two review authors will then independently screen each full-text for eligibility (second stage). Where there are any disagreements between authors, a third review author will screen the studies.

### Data extraction and management

We will extract the following data from each eligible study using an extraction form designed and piloted by the author team.

- **Study characteristics:** relevant references, study registration details, country, funder, author conflicts of interest, design and unit of randomisation, if a cRCT we will also extract number of clusters allocated to the intervention and comparator, mean cluster size, and intracluster correlation coefficient (ICC) where reported.
- **Recruitment:** recruitment method, setting, eligibility criteria.
- **Participant characteristics:** number randomised, gender, age, proportion pregnant, proportion with pre-existing conditions or hospitalised, motivation to quit, number of cigarettes per day (as a proxy of cigarette dependence).
- **Intervention and comparator details:** pharmacotherapy (or EC) type and subtype, dose, length of use, method of delivery, other details.
- **Common behavioural support/co-intervention:** type (self-help only; interactive behavioural support), mode of delivery, overall duration of support (total time in hours).
- **Smoking abstinence outcome:** definition of abstinence, definition of biochemical validation where relevant, number abstinent per arm, follow-up point, number of participants followed up at this time point.
- **Safety and tolerability outcomes:** follow-up point, number of participants reporting SAEs in each arm, number of withdrawals due to intervention in each arm, number of participants followed up at this time point.
- **Risk of bias:** information related to any of the risk of bias domains outlined below, information related to any other potential biases identified.

In line with guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021), one review author will extract data on study characteristics, methodology and participant characteristics. However, two review authors will independently extract component and covariate data, outcome data and information for risk of bias assessments, with any discrepancies discussed between them. Where we cannot reach a consensus, we will discuss the discrepancy more widely within the review author team until the issue is resolved. Where necessary, we will contact study authors for clarifying information.

Where data have already been extracted in duplicate and risk of bias has already been assessed for eligible studies (because they are already included in a relevant Cochrane Review; Cahill 2016; Hartmann-Boyce 2018; Hartmann-Boyce 2021b; Howes 2020; Lindson 2019), we will check that this has been performed consistently and in accordance with the most up-to-date *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021) and Cochrane TAG guidance. Where this has been done, we will use these data and assessments rather than re-evaluate these. Where it appears that insufficient data have been extracted, risk of bias guidance has not been consistently applied or where specific domains have not been evaluated for specific reviews, review authors will extract the required data as described in the previous

paragraph. We will present extracted data in 'Characteristics of included studies' and risk of bias tables.

### Assessment of risk of bias in included studies

We will assess risk of bias for each included study using the Cochrane RoB 1 tool, assessing the following domains:

- sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding (performance and detection bias);
- incomplete outcome data (attrition bias);
- other sources of bias (where appropriate; if the bias detected in the study reports does not appear to be associated with one of the other domains).

For cRCTs only, we will also assess the following domains:

- recruitment bias due to recruitment of participants to clusters after allocation;
- unbalanced baseline characteristics;
- whether statistical adjustment had been made to the analysis to account for the potential correlation of effects within clusters.

Each domain will be assessed as being at low, unclear or high risk of bias.

Following standard Cochrane TAG methods, we will assess blinding as follows.

- Studies that report sufficient blinding procedure, as well as who was blinded will be assessed at low risk of bias.
- Where sufficient blinding has not been carried out, we will judge studies at low risk of bias if smoking status was measured objectively (i.e. biochemical validation).
- We will judge studies at high risk of bias if sufficient blinding did not take place and smoking status was measured by self-report only. In this case, results may be prone to differential misreport.

In addition, we will assess attrition bias as follows.

- We will judge studies at low risk of bias when the following conditions are all met: numbers lost to follow-up at the longest time point are clearly reported for each group (not just overall, unless the overall percentage lost is less than 10%); the overall number of participants lost at the longest time point is not greater than 50%; and the difference in percentage followed up between groups at longest time point is not greater than 20%. We will also consider results at low risk of attrition bias if the authors report a sensitivity analysis that indicates the overall direction of effect was not sensitive to different imputation methods for loss to follow-up.
- We will judge studies at high risk of bias when the above thresholds are not met, or in the case of cRCTs, where entire clusters are not followed up.
- We will judge studies at unclear risk when the number lost to follow-up in each group is unclear, and authors do not report a sensitivity analysis based on loss to follow-up.

Each study will be given an overall risk of bias where studies with at least one domain rated at high risk will be deemed to be at overall high risk, studies with all domains rated as low risk will be given an

overall rating of low risk and all the remaining studies will be rated as at unclear overall risk of bias.

### Measures of treatment effect

In the cNMAs, we will report pooled results as odds ratios (OR) with 95% credibility intervals (CrIs) as the statistical model described in [Data synthesis](#) is conducted on the log-OR scale. However, we will also consider the absolute effect sizes implied by these pooled estimates and report these in our summary of findings tables. Using the posterior distribution of the 'no intervention' baseline quit rate, we will obtain the weighted mean quit rate in the 'no intervention' arms (i.e. the proportion quitting out of those allocated to the 'no intervention' arms). This will then be used to estimate the likely quit rate among those with the component of interest using the component effect sizes.

### Unit of analysis issues

For cRCTs, where possible, we will use the effect size reported in the relevant systematic review ([Cahill 2016](#); [Hartmann-Boyce 2018](#); [Hartmann-Boyce 2021b](#); [Howes 2020](#); [Lindson 2019](#)), where adjustments will have been made for clustering (or if not available, in the original trial paper, making our own adjustments for clustering as necessary). We will ensure that these are either extracted as, or converted to, ORs and standard errors and take these into account using multiple likelihood shared parameter model.

### Dealing with missing data

Any participants lost to follow-up will be assumed smoking as is standard in the field ([West 2005](#)), and is standard across reviews produced by Cochrane TAG. In the risk of bias tables, we will note the proportion of participants for whom the outcome was imputed in this way, and whether there was either high or differential loss to follow-up. The assumption that 'missing = smoking' provides conservative absolute quit rates, and makes little difference to the OR unless dropout rates differ substantially between groups.

For our tolerability outcome (withdrawals due to treatment), participants who are not specifically recorded as withdrawn will be not be deemed to have withdrawn due to treatment. Therefore, we will use the number randomised as our denominator.

In contrast, our safety outcome (SAE) will be assessed as complete case, and therefore those lost to follow-up will not be included in our analysis. Assuming those lost to follow-up had not experienced an SAE is not a valid assumption. In fact, participants may be lost to follow-up because they have experienced an SAE. Therefore, this is the most conservative approach to assessing safety.

### Assessment of heterogeneity

We will conduct a separate cNMA for each of the three specified outcomes, provided data are sufficient to fit the cNMA model. We will consider whether any of the eligible studies are too clinically heterogeneous to include in the relevant cNMAs without violating the transitivity assumption (i.e. whether there are studies that are not jointly randomisable). We will consider heterogeneity and model fit for our cNMAs using the CrIs for individual components, and the between-study standard deviation (SD) and deviance information criterion (DIC) for overall models. When testing potential moderators of component effects, we will add variables into the overall model with all components and consider the impact

they have on SD and DIC. We will consider a reduction of three or more as meaningful with regards to DIC.

### Assessment of reporting biases

There is no established way of assessing reporting bias within cNMAs. However, we will adapt existing methods for assessing publication bias in standard systematic reviews by generating a funnel plot for each of the pharmacotherapies of interest (NRT, EC, varenicline, cytisine, nortriptyline, bupropion) versus placebo, and overlaying these plots on top of one another, while aligning the reference lines (representing the overall component effect). We will assess whether studies are distributed asymmetrically as potential evidence of publication bias. We will create a funnel plot for each of the outcomes (smoking cessation, SAEs, withdrawal due to intervention).

### Data synthesis

We will use Bayesian cNMA and component network meta-regression (cNMR) random-effects models, with adjustment for multi-arm studies, to evaluate the effectiveness of the components identified above versus placebo or no relevant intervention, and versus one another (see [Types of interventions](#)). We will draw conclusions about which components are most strongly associated with smoking cessation, safety and tolerability ([Freeman 2018](#)). We will carry out a cNMA for each of the three specified outcomes (smoking cessation, SAEs, and withdrawal due to intervention) using [WinBUGS](#) and [R](#), through the [R2WinBUGS](#) package ([Sturtz 2005](#)). As noted previously, we will report pooled results as ORs with 95% CrIs and present these findings in forest plots. However, we will also consider the absolute effect sizes implied by these pooled estimates. Models will be constructed similarly to those used by [Freeman 2018](#) and adapted to include a binomial likelihood with logit link for binary outcome. For each cNMA and cNMR model, we will run three different Markov chains with different initial values, each with at least 30,000 iterations, discarding the first 15,000 iterations and with the default thinning interval (equal to 3) set by the [R2WinBUGS](#) package ([Sturtz 2005](#)) to compute summary estimates. Trace plots will be used to evaluate convergence for each chain for all component effects and all tested interactions between components. Minimally informative (non-Jeffrey's) prior distributions for the trials' baseline risks (defined as quit rates in control arms), component and interaction effects, and between-trial (heterogeneity) SD (measured on the log-odds scale) will be used, as in [Freeman 2018](#). A single between-trial SD parameter will be estimated.

We will investigate interactions between and within pharmacotherapy types and modes of delivery that are, or could be, combined in practice. We will also investigate interactions between pharmacotherapy type and timing of intervention (i.e. prequit as well as from quit date or from quit date only). When investigating interactions between different types of NRT, we will collapse all types of fast-acting NRT into one node. Interactions will need to be present in 20 or more study arms in order for us to conduct analyses, in line with the methods of our previous cNMA of behavioural smoking cessation treatments ([Hartmann-Boyce 2022](#)).

### Meta-regression

We will extend the main Bayesian cNMA model to several cNMR models; each of which will include the following covariates separately:



- participants selected based on pre-existing condition or hospitalisation;
- study level motivation to quit;
- length of follow-up;
- behavioural support (i.e. no behavioural support; self-help only; interactive behavioural support);
- funded by industry (pharmaceutical, tobacco or independent EC);
- quit rates in control arms (i.e. baseline risk);
- year of publication.

We will assume a common interaction between each covariate and the components, except for 'funded by industry', for which different interaction terms will be fitted to each component.

### Sensitivity analysis

We will test whether the findings from our models are sensitive to the exclusion of the following sets of studies:

- those that solely recruited participants who were hospitalised or recruited participants on the basis of a pre-existing condition;
- those that we judge at high overall risk of bias;
- those that have a larger contribution to the DIC than expected (i.e. DIC greater than 3).

### Summary of findings and assessment of the certainty of the evidence

There is no agreed best method for evaluating the certainty of cNMA evidence. Therefore, we will use the approach used in our cNMA of behavioural interventions for smoking cessation ([Hartmann-Boyce 2021a](#)), after consulting with methodological experts, including the Cochrane Editorial and Methods Department. We will evaluate certainty for our component effect estimates by drawing upon the principles set forward for GRADE evaluations for NMA ([Puhan 2014](#)), with adaptations to some domains to better suit cNMA.

We will present modified summary of findings tables presenting effect estimates and GRADE evaluations for each component of the primary efficacy outcome analysis and the primary SAE outcome analysis. We will use an adapted version of an approach proposed by [Yepes-Nunez 2019](#). The key principles of this are outlined below.

- **Risk of bias** assessed by evaluating whether the sensitivity analysis removing studies at high risk of bias meaningfully alters the effect estimate.
- **Imprecision** assessed using the CIs for individual components and the number of events in studies including that component.
- **Inconsistency** assessed by considering data from both pairwise comparisons (as per the most recent standard versions of the Cochrane Reviews investigating the individual pharmacotherapies/EC) and the cNMA.
- **Indirectness** assessed by considering data from both pairwise comparisons (as per the reviews investigating the individual pharmacotherapies/EC) and the cNMA, as well as considering the impact of covariates on component effect estimates.
- **Publication bias** assessed using comparison adjusted funnel plots, as described in [Assessment of reporting biases](#).

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## APPENDICES

### Appendix 1. List of components

#### Intervention type

- Nicotine
- Varenicline
- Cytisine
- Bupropion
- Nortriptyline
- Placebo

#### Delivery mode

- Tablet
- EC
- Patch
- Gum
- Lozenge
- Microtabs
- Nasal spray
- Mouth spray
- Oral strips
- Inhalator

#### Dose

- Lower than standard
- Standard (nicotine patch: 21/25 mg; nicotine gum: 4 mg; nicotine lozenge: 2 mg; nicotine nasal spray: 10 mg; nicotine inhalator: 15 mg/mL; nicotine microtab: 2 mg; nicotine mouth spray: 1 mg; nicotine oral strips: 2.5 mg; varenicline 2 mg per day; cytisine: 1.5-mg/tablet 25-day downward titration schedule; bupropion: 300 mg per day; nortriptyline: 75 mg to 100 mg; EC: 10 mg/mL to 20 mg/mL).
- Higher than standard
- n/a (placebo)

#### Intended duration of use

- Shorter than standard (less than 12 weeks)
- Standard (12 weeks)
- Extended (greater than 12 weeks)

#### Tapering

- Yes
- No

#### Timing of intervention (in relation to quit date)

- Prequit, while reducing smoking (as well as from quit date)
- Prequit, without smoking reduction (as well as from quit date)
- From quit day only

### Appendix 2. Search strategies of included reviews

#### Nicotine replacement therapy versus control for smoking cessation ( [Hartmann-Boyce 2018](#) )

*Last searched: 6 July 2017*

#1 NRT: TI,AB,KY,XKY,MH,EMT

#2 (nicotine NEAR2 patch\*):TI,AB,KY,XKY,MH,EMT

#3 (nicotine NEAR2 gum):TI,AB,KY,XKY,MH,EMT

#4 (nicotine NEAR2 nasal spray):TI,AB,KY,XKY,MH,EMT

#5 (nicotine NEAR2 lozenge\*):TI,AB,KY,XKY,MH,EMT

#6 (nicotine NEAR2 tablet\*):TI,AB,KY,XKY,MH,EMT

#7 (nicotine NEAR2 sublingual):TI,AB,KY,XKY,MH,EMT

#8 (nicotine NEAR2 inhal\*):TI,AB,KY,XKY,MH,EMT

#9 (nicotine NEAR2 replacement):TI,AB,KY,XKY,MH,EMT

#10 (nicotine NEAR3 therap\*):TI,AB,KY,XKY,MH,EMT

#11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

#### **Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation ( [Lindson 2019](#) )**

*Last searched: 30 April 2018*

#1 NRT: TI,AB,KY,XKY,MH,EMT

#2 (nicotine NEAR2 patch\*):TI,AB,KY,XKY,MH,EMT

#3 (nicotine NEAR2 gum):TI,AB,KY,XKY,MH,EMT

#4 (nicotine NEAR2 spray\*):TI,AB,KY,XKY,MH,EMT

#5 (nicotine NEAR2 lozenge\*):TI,AB,KY,XKY,MH,EMT

#6 (nicotine NEAR2 tablet\*):TI,AB,KY,XKY,MH,EMT

#7 (nicotine NEAR2 sublingual):TI,AB,KY,XKY,MH,EMT

#8 (nicotine NEAR2 inhal\*):TI,AB,KY,XKY,MH,EMT

#9 (nicotine NEAR2 strip\*):TI,AB,KY,XKY,MH,EMT

#10 (nicotine NEAR2 microtab\*):TI,AB,KY,XKY,MH,EMT

#11 (nicotine NEAR2 replacement):TI,AB,KY,XKY,MH,EMT

#12 (nicotine NEAR3 therap\*):TI,AB,KY,XKY,MH,EMT

#13 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR 11 OR 12

#### **Antidepressants for smoking cessation ( [Howes 2020](#) )**

*Last searched: 10 May 2019*

#1 (bupropion or zyban):TI,AB,MH,EMT,KY,XKY

#2 nortriptyline:TI,AB,MH,EMT,KY,XKY

#3 (monoamine oxidase inhib\*):TI,AB,MH,EMT,KY,XKY

#4 (moclobemide or selegiline or lazabemide):TI,AB,MH,EMT,KY,XKY

#5 (SSRI\* or ((selective serotonin re-uptake inhibitor\*) or (selective serotonin reuptake inhibitor\*))) :TI,AB,MH,EMT,KY,XKY

#6 (fluoxetine or sertraline or paroxetine or zimelidine):TI,AB,MH,EMT,KY,XKY

#7 (doxepin or imipramine or tryptophan or venlafaxine):TI,AB,MH,EMT,KY,XKY

#8 ((john\* wort) or hypericum):TI,AB,MH,EMT,KY,XKY

#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

#### **Nicotine receptor partial agonists for smoking cessation ( [Cahill 2016](#) )**

**Pharmacological and electronic cigarette interventions for smoking cessation in adults: component network meta-analyses (Protocol)**

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*Last searched: 12 May 2015*

(cytisine or Tabex or dianicline or varenicline or Champix or Chantix):TI,AB,MH,EMT,XKY,KY,KW

MeSH DESCRIPTOR Nicotine WITH AG AI

MeSH DESCRIPTOR Nicotinic Agonists

MeSH DESCRIPTOR Nicotinic Antagonists

nicotinic agonist\*:TI,AB,MH,EMT,XKY,KY,KW

nicotinic antagonist\*:TI,AB,MH,EMT,XKY,KY,KW

nicotin\* NEAR2 partial:TI,AB,MH,EMT,XKY,KY,KW

#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

### **Electronic cigarettes for smoking cessation ( [Hartmann-Boyce 2021b](#) )**

*Last searched: 1 October 2021*

#1 exp case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy\$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw.

#2 (e-cig\* or ecig\* or electr\* cigar\* or electronic nicotine).mp. or (vape or vapes or vaporizer or vapourizer or vaporiser or vapouriser or vaper or vapers or vaping).ti,ab. or exp Electronic Nicotine Delivery Systems/

#3 (randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.

#4 exp animals/ not humans.sh.

#5 3 not 4

#6. 2 and 5

#7 1 and 2

#8 6 or 7

#9. smoking cessation.mp. or exp Smoking Cessation/

#10 tobacco cessation.mp. or "Tobacco-Use-Cessation"/

#11 (nicotine dependence or tobacco dependence).mp.

#12 exp Smoking/th

#13 "Tobacco-Use-Disorder"/

#14 Smoking reduction/ or Smoking reduction.mp.

#15 exp Pipe smoking/ or exp Tobacco smoking/ or exp Tobacco Products/

#16 ((quit\* or stop\* or ceas\* or giv\* or abstain\* or abstinen\*) adj5 (smoking or smoke\* or tobacco)).ti,ab.

#17 exp Tobacco/ or exp Nicotine/

#18 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

#19 8 and 18

### **CONTRIBUTIONS OF AUTHORS**

NL drafted the protocol.

All other authors commented and contributed to the final version.



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NL: none.

AT: none.

JLB: none.

PA: none.

TRF: none.

JMOM: none.

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SCF: none.

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