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METHODS AND TECHNIQUES

ADDICTION SSA

Assessing and minimizing risk of bias in randomized controlled trials of tobacco cessation interventions: Guidance from the Cochrane Tobacco Addiction Group

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Abstract

The Cochrane Tobacco Addiction Group has created risk of bias tools, which are topic-agnostic. In 2012 the Cochrane Tobacco Addiction Group created guidance specific to considerations for reviews of randomized controlled trials of tobacco cessation interventions, building on existing Cochrane tools. The guidance covers issues relating to selection bias, performance bias, detection bias, attrition bias and selective reporting. In this paper, we set out to make this guidance publicly available, so that others can use and cite it. We provide advice for using this tool to appraise trials critically as a systematic reviewer. We also provide guidance for triallists on ways to use this tool to improve trial design and reporting.

KEYWORDS
cessation, critical appraisal, randomized controlled trial, risk of bias, systematic review, tobacco

INTRODUCTION

The Cochrane Tobacco Addiction Group has existed for more than 25 years, publishing high-quality, robust systematic reviews evaluating the benefits and harms of tobacco control interventions [1–3]. We follow the risk of bias guidance set by Cochrane, which has evolved with subsequent versions of the Cochrane Handbook, most recently updated in 2022 [4]. However, we have also augmented this with specific considerations for randomized controlled trials of tobacco cessation interventions, documented since 2012. This guidance has been available off-line to Cochrane Tobacco Addiction Group authors and has been used in other systematic reviews of tobacco control interventions, as well as Cochrane [5, 6].

In this paper, we set out to make this guidance publicly available so that others can use and cite it. We provide advice for using this tool as a reviewer, and also encourage the use of this tool for people designing trials in this area. Minimizing bias in trials not only contributes to the validity of the primary research but also to the certainty of the conclusions that can be drawn from evidence syntheses containing those trials. By not only carrying out research, but designing and conducting it well, tobacco control researchers can increase the chances of our research being usefully implemented into policy and practice and ultimately aiding as many people as possible to quit combustible tobacco use.

IMPORTANT CONSIDERATIONS WHEN APPLYING THE BELOW GUIDANCE

We ask readers to note that this is intended as a guide only, in recognition that different reviewers and triallists will have different needs with reference to assessing risk of bias and designing trials, depending upon study type(s). This document currently only covers randomized controlled trials, quasi-randomized controlled trials and cluster-randomized controlled trials. It is most relevant to trials of tobacco cessation interventions.

The Cochrane Handbook sets out detailed instructions for assessing risk of bias [4]. The guidance we provide here is intended to supplement rather than replace the guidance in the Cochrane Handbook, by exploring some considerations specific to studies of tobacco

cessation interventions. There have been a number of iterations of Cochrane's tool for assessing risk of bias in randomized controlled trials. 'Risk of bias 1' was detailed in the Cochrane Handbook published in 2011, and the newer 'Risk of bias 2' tool is detailed in the current Handbook, first published in 2019 [4, 7]. We structure our guidance here in line with the domains of 'Risk of bias 1', as it is the most familiar and simple of the tools. However, the points we focus upon are relevant across both tools. In the process of writing this paper, we reviewed the domains and signalling questions that make up 'Risk of bias 2' and did not identify any additional tobacco cessation-specific considerations that should be accounted for if using that tool rather than 'Risk of bias 1'. This is to be expected, as 'Risk of bias 1' and 'Risk of bias 2' account for the same underlying sources of bias. As well as detailing how randomized controlled trials should be assessed by reviewers according to each domain, we also outline the connotations of these potential risks for those designing and reporting on randomized controlled trials.

However, assessments of risk of bias are subjective, and may vary based on reviewer. The guidelines below may not apply to all reviews or trials, and the most important thing is not consistency across reviews, but transparency and consistency within reviews: if systematic reviewers are clear about why they have made their risk of bias judgements, readers are then empowered to also make their own judgements. Similarly, if triallists need to deviate from the recommendations below, they should be clear about their reasons and the methods taken to minimize bias.

We would generally recommend assessing risk of bias based on the information provided in the published report and/or protocol of a trial and would not, as a matter of course, e-mail authors in cases of uncertainty for information relating to risk of bias in their studies. This highlights the importance of thorough reporting of randomized controlled trials to ensure that reviewers have the information needed to make their judgements as informed as possible. Use of the Consolidated Standards of Reporting Trials (CONSORT) statement by triallists to guide the reporting of randomized controlled trials can mitigate the exclusion of key information [8, 9].

Further risk-of-bias domains apply to cluster and cross-over randomized trials; however, we reviewed these and did not believe there to be any additional topic-specific considerations. As a result, we do not cover them here. Additionally, publication bias is assessed across rather than within trials, and hence does not fall within the scope of this guidance. However, its assessment is critical in systematic reviewing. We refer readers to the Cochrane Handbook for the most up-to-date information on assessing risk of bias in cluster and cross-over trials, as well as publication bias, and for guidance on how risk of bias should be taken into account when assessing certainty of an overall body of evidence [4].

KEY RISKS OF BIAS

Risk-of-bias considerations for assessing, designing and reporting randomized controlled trials are summarized by 'Risk of bias 1' domain in Table 1. For issues not specific to tobacco cessation trials, further information on assessing domains can be found in the Cochrane Handbook [4]. Considerations more specific to tobacco cessation trials are described in more detail in the following sections.

ASSESSING BLINDING IN TOBACCO CESSATION TRIALS

There are two types of bias that can be introduced by lack of blinding: performance bias is when a participant or person delivering a treatment may perform better (or worse) because they know which condition they are assigned to, and detection bias is when, even if performance is the same, the outcome is subject to biased reporting because the person assessing the outcome is not blind to treatment allocation.

Risk-of-bias assessments for blinding will depend upon the type of intervention being evaluated. Although not specific only to trials of tobacco cessation, it is common for systematic reviews in this area to include trials testing both pharmaceutical interventions and purely behavioural interventions. In behavioural interventions blinding of participants and personnel is often not possible, whereas in pharmaceutical interventions it is expected. We provide further details of how the Cochrane Tobacco Addiction Group have dealt with this issue here.

Assessing blinding-related risk of bias in randomized controlled testing the effects of pharmaceutical interventions is much more straightforward than in studies of behavioural interventions and should follow general guidelines set out by Cochrane, i.e. assessment of both performance and detection bias [4, 7].

For systematic reviews of purely behavioural interventions reviewers may choose not to evaluate performance bias (e.g. [11, 12]). The reasoning behind this is that assessing performance bias would leave all studies at high risk, making it difficult to differentiate between higher- and lower-quality trials. For instance, it would make it impossible to carry out a sensitivity analysis testing the impact of removing lower-quality trials from a meta-analysis. It also holds trials to an unrealistic standard, and devalues research that has taken all available precautions to mitigate bias. However, if performance bias is not assessed as part of the risk-of-bias assessment for each individual trial it is still important to take into account the limitations that a lack of participant blinding has for the evidence overall.*

For systematic reviews testing a mix of behavioural interventions and pharmaceutical interventions, reviewers may choose only to assess performance bias for the pharmaceutical studies (e.g. [13, 14]). If a reviewer chooses to assess performance bias in studies of behavioural interventions, where true blinding is not possible, the following considerations should be taken into account:

- *If participants received similar amounts of face-to-face contact across all arms included in the review*. For example, a study comparing a stage of change intervention with a comparable counselling

*A drawback of this approach is that pharmaceutical studies are evaluated against a different set of criteria than studies of behavioural interventions.

TABLE 1 Key types of bias.

Type of bias	Considerations for trial design	Considerations for trial reporting	Considerations for risk of bias assessment
Random sequence generation (selection bias)	Use a method that is truly random, e.g. random number generator, computer-based randomization systems	Ensure the programme or method used for random sequence generation is reported in full	Do the authors report using a method considered truly random? (See Cochrane risk of bias tools for further guidance; no tobacco specific considerations) [4]
Allocation concealment (selection bias)[a]	Use a method in which neither the participant nor study staff are aware of the group to which the participant has been assigned until allocation is complete, e.g. central computerized randomization; sequentially numbered, opaque, sealed envelopes; sequentially numbered drug containers prepared by an independent pharmacy	Report details in full; e.g. if computerized randomization is used, be clear that allocation is also automated via the computerized system; if using envelopes, specify that they are opaque	Are participants and study staff unaware of the group to which the participant has been assigned until allocation is complete? (see Cochrane risk of bias tools for further guidance; no tobacco specific considerations) [4]
Blinding (performance bias)	*For pharmaceutical interventions and e-cigarettes*: use of a matched-modality placebo, or an active intervention where the possibility of similar efficacy exists. Participants and study staff blinded to treatment allocation where possible	*For pharmaceutical interventions and e-cigarettes*: be clear about modality of placebo and/or active treatment. Define who was blinded rather than simply using terms such as 'double-blinded'. Indicate whether participants guessed treatment assignment	*For pharmaceutical interventions and e-cigarettes*: is it clear that both study staff and participants were unaware of treatment assignment? If not (e.g. head-to-head comparisons of two active interventions), are the interventions of similar intensity (e.g. similar length, similar amount of behavioural support)? (See Cochrane risk of bias tools for further guidance; no tobacco-specific considerations)
	For behavioural interventions: where possible, ensure similar amounts of contact are provided between arms (e.g. use of a comparator arm of the same modality but with content on safe sex or healthy eating practices). If possible, minimize knowledge of what the other group(s) receive. Avoid use of waiting-list controls	*For behavioural interventions*: report content and intensity of comparator arm(s) in same detail as intervention arm(s), e.g. not just 'usual care'. If participants receive unequal amounts of support, report whether participants were aware of what other group(s) received. If waiting-list controls are used, report whether participants were aware of this at study start	*For behavioural interventions*: did participants receive similar amounts of face-to-face contact across all arms included in the review? Were participants aware of what the other group was receiving? Were some participants randomized to a waiting-list control where they may have delayed quitting in anticipation of receiving the intervention?
Blinding (detection bias)	Where possible, biochemically validate cessation at 6 months or longer using an appropriate method (e.g. where intervention involves nicotine delivery, do not use a nicotine metabolite such as cotinine for biochemical validation)	Report whether cessation was biochemically validated or self-reported. If only self-reported rates are reported justify the reasons for this. Report methods and timings of biochemical validation in full, including cut-offs	Is tobacco use status biochemically validated at the time-point of interest? How are safety measures collected? If subjective measurements are used, did intervention and control arms receive similar amounts of face-to-face contact?
Incomplete outcome data (attrition bias)	Pre-plan and resource for following-up as many participants as possible at 6 months or longer with regard to primary outcomes (e.g. tobacco cessation; safety). Endeavour to have similar follow-up rates between arms.	Report how many participants were followed-up at each time-point in each arm for each outcome. Include follow-up targets and processes in initial protocol. Be clear about any assumptions made when calculating follow-up	For each of your main outcomes of interest: how many participants were followed-up overall? Did proportion followed-up vary by group? Were conclusions affected by assumptions

(Continues)

TABLE 1 (Continued)

Type of bias	Considerations for trial design	Considerations for trial reporting	Considerations for risk of bias assessment
	Test sensitivity of results to different assumptions about participants lost to follow-up (e.g. whether interpretation of results is the same when using complete case analyses as when assuming missing = smoking). (Note, assuming people lost to follow-up are continuing smokers is the preferred model for primary analyses according to the Russell Standard) [10]	rates (e.g. missing = smoking). Report results from sensitivity analyses testing different assumptions about loss to follow-up	regarding status of participants lost to follow-up?
Selective reporting	Prior to study start, specify all outcomes that will be measured, and how and when they will be measured, on a publicly accessible site. If an outcome will be assessed in more than one way or at more than one time-point, clarify which will be the primary measurement for analyses	When reporting study results, ensure all outcome measures specified in the protocol/statistical analysis plan are fully available to readers. If deviations from protocol have occurred, explain these and justify them. Statistical significance and/or direction of effect should not determine how results are reported or the level of detail given	Were outcomes registered before enrolment of first participant, and was the instrument, time-point and method of analysis pre-specified? Are all expected outcome measurements reported? If not, are justifiable reasons given for their absence?[b]

[a]A note on baseline differences: some risk of bias tools suggest reviewers should evaluate baseline differences to judge whether selection bias is likely to be present. We advise against this: in small studies which report multiple baseline characteristics, it is quite possible that baseline differences will occur by chance alone, which is not in itself a risk of bias.

[b]Guidance is generally unclear on exactly what counts as a 'justifiable reason' for deviating from planned outcomes. For example, 'justifiable reasons' could include study stopping before the primary outcome could be measured (e.g. due to safety concerns or because of supply issues) or pragmatic issues with biochemically validating smoking cessation (e.g. in-person collection planned but not carried out due to COVID-19 pandemic restrictions). Conversely, less justifiable reasons may include low return rate of biochemical validation (this is typically not a valid reason to prefer self-report over biochemically validated quit rates) or only reporting outcomes in full where a statistically significant difference was detected.

intervention not based on stage of change, matched in contact time, may be less subject to performance bias than a study comparing a multi-session counselling intervention with one-off advice.

- *Whether participants were aware of what the other group was receiving*. If control group participants do not know that the intervention group is receiving a more intensive intervention, this may decrease the risk of performance bias. This is especially important in trials using waiting-list controls because participants may delay any attempts to quit tobacco use, as they know they will be receiving the intervention on completion of the trial. This can lead to artificially low quit rates in the control arm.

For all randomized controlled trials investigating tobacco cessation interventions, including behavioural studies where blinding of participants is not possible, we recommend that detection bias is assessed in the following way:

- Studies be judged at *low risk of bias* if tobacco use is measured objectively (i.e. biochemical validation).
- Studies be judged at *low risk of bias* if tobacco use is measured by self-report but the intervention and control arms received similar amounts of face-to-face contact (or none).
- Studies be judged at *high risk of bias* if tobacco use is measured by self-report and there is a differential amount of person contact between the trial arms of interest. This is because results may be prone to differential misreport.
- As with all other domains, studies should be judged at *unclear risk of bias* if there is insufficient information available to make a judgement when using 'Risk of bias 1' [7].

Where any outcome is self-reported, the blinding of the researcher does not have an impact on the risk of detection bias. Even if the person collecting the self-report data is blind to treatment allocation, the true outcome assessors in these instances are the participants themselves.

ASSESSING INCOMPLETE OUTCOME DATA IN TOBACCO CESSATION TRIALS

Incomplete outcome data refers to the risk of attrition bias—namely, that the proportion of participants not followed-up may have impacted upon the observed results. Dropout is often high in studies of tobacco cessation, with participants who have not quit or have

relapsed less likely to attend follow-up visits [10]. Any threshold for follow-up is, by its nature, arbitrary, and therefore it is difficult to give firm guidelines on assessment for this domain. We give the thresholds used by the Cochrane Tobacco Addiction Group below, but ideally what reviewers should be looking for are sensitivity analyses qualifying the level of uncertainty introduced by attrition. We recommend the following:

- Studies be judged to be at *low risk of bias* where numbers of participants lost to follow-up are clearly reported for each group (not just overall, unless the overall percentage lost is less than 10%); *and* the overall proportion of participants lost is not greater than 50%; *and* the difference in percentage followed-up between groups is not greater than 20%; *and/or* the authors report sensitivity analyses which indicate the overall direction of effect is not sensitive to different imputation methods for loss to follow-up.
- Studies be judged to be at *high risk of bias* where the above thresholds were not met, *or* where the authors report that assumptions regarding loss to follow-up alter the overall direction of the effect.
- Studies be judged at *unclear risk of bias* where the proportion of participants lost to follow-up in each group is not clear *and* authors do not report sensitivity analyses based on loss to follow-up, when using 'Risk of bias 1' [7].

Judgements of the impact of incomplete outcome data should be made based on the period of follow-up used in the main analysis of the review (e.g. if a study has 1- and 5-year follow-up, and the 1-year follow-up is used in the review, the percentage of participants followed-up should be described based on 1-year data as opposed to 5-year data).

OVERALL RISK OF BIAS

Sometimes, systematic reviewers will want to calculate an overall risk of bias for a study (e.g. to decide which studies to remove from a meta-analysis in a sensitivity analyses). We recommend the following: a study be judged to be at high risk of bias overall if judged to be at high risk in at least one domain; a study be judged to be at low risk of bias overall if judged to be low risk in every domain assessed; all other studies be judged at unclear risk (e.g. those with a mix of low and unclear judgements, or all unclear judgements). This is consistent with guidance from Risk of bias 2 [4].

CONCLUSION

Evidence-based policy and practice is only as good as the evidence that underlies it. Bodies of evidence benefit from well-conducted and well-reported trials, and from systematic reviews with rigorous and transparent methods for assessing risk of bias. Further work is needed to agree on the best ways to assess risk of bias in non-randomized trials of tobacco control interventions. We hope the above guidance will help reviewers and triallists of the future in conducting the best possible trials and reviews to combat tobacco addiction, and save lives worldwide.

AUTHOR CONTRIBUTIONS

Jamie Hartmann-Boyce: Conceptualization (equal); methodology (equal); writing—original draft (equal); writing—review and editing (equal). **Nicola Lindson:** Conceptualization (equal); methodology (equal); writing—original draft (equal); writing—review and editing (equal).

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DECLARATION OF INTERESTS

None.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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