Guidance document to accompany flowchart to determine the impact of a study/studies with an associated retraction on a Cochrane review

Background

Systematic reviews may include studies that are associated with articles that have been retracted. This may occur due to the inadvertent inclusion of a study with an associated retraction, or due to the retraction of an article following publication of the review [1-4]. Cochrane reviews are generally protected from the inclusion of studies that already have an associated retraction due to their comprehensive search strategies and detailed editorial policies [5,6], but they are still vulnerable to retractions that happen after publication of the review.

The general impact of retracted studies on systematic review conclusions is an active area of research. Some research indicates conclusions of systematic reviews and meta-analyses generally appear to be robust to the effect of the inclusion of studies associated with a retraction [2,7], for example, Fanelli et al. found that pooled estimates calculated without the data from a retracted study were in general similar in magnitude and direction to the original, and that in 96% of cases, they were within the original 95% Confidence Interval [2]. However, other studies indicate that the impact can be greater, for example Xu et al. [8] found that the exclusion of data from retracted studies can meaningfully alter effect estimates, especially in clinical areas where such studies cluster and where repeated publication of manipulated or exaggerated results occurs. Importantly, even when revised relative risks remain within original confidence intervals, changes may still be clinically significant when considered in terms of absolute effects, such as numbers needed to treat, which can change substantially and influence clinical decision-making. Despite this, studies looking at the effect of individual retractions on review findings have identified cases where findings are likely to change meaningfully following the removal of data from the study, or studies, with an associated retraction [2,3,7]. This includes substantial effects that may potentially change the interpretation of the results, such as a change in the direction of an effect [4]. Guidance from the Committee on Publication Ethics (COPE), of which Cochrane is a member, recommends that 'editors should retract a systematic review publication if they no longer have confidence in the results and conclusions due to retracted or corrected included studies' [9].

Please note:
All references to "retractions" of Cochrane reviews in this framework relate to terminology to be introduced under a forthcoming update to Cochrane's current withdrawal policy, which will be revised and renamed as a retraction policy. At the time of publication of this framework, the existing withdrawal policy remains in effect.

Introduction to this guidance document

- This guidance document and the accompanying flowchart ('Flowchart to determine the impact of a study/studies with an associated retraction on a Cochrane review') are for use by authors of Cochrane reviews in cases where it has been identified that a published Cochrane review includes data from one or more studies that are associated with a retracted article.
- The guidance document should be used in conjunction with the accompanying flowchart, and provides further information relating to each step.
- The flowchart and guidance document should only be used in cases where the study with the associated retraction is an *included* study in the Cochrane review. It does not apply where studies have purely been cited in the Introduction or Discussion, or are in 'Awaiting Classification.' In

these cases, when the next Update is conducted, the citation to the retracted article should be removed, along with any associated text. Any study with an associated retraction that is in 'Awaiting Classification' should be moved to 'Excluded Studies.'

- This guidance document is for use with all types of Cochrane review, regardless of whether quantitative analysis has been carried out.
- As soon as it has been identified that a Cochrane review includes a study/studies with an associated retraction, an Editorial Note should be added to the review informing readers of this. The addition of this Editorial Note will be coordinated by the Research Integrity Editor and the note will state that the review includes a study/studies that have retractions associated with them and that an assessment into the impact on the review's findings and conclusions is underway.
- Cochrane review authors should then follow the steps in this guidance document to determine whether they still have confidence in the conclusions of the review, or whether the inclusion of the study/studies with an associated retraction has had a meaningful impact.
- After following the steps in this guidance document, review authors should present their assessment of the impact of the study/studies on the review to the Research Integrity Editor to coordinate with the relevant Editor (email researchintegrity@cochrane.org).
- The Editor will use the information to decide on the appropriate course of action for the published review, depending on the significance of the impact on the conclusions of the review.
- In the early stages of using this guidance document, the Editor may consult the Editorial Board to aid with consistent decision making, and to determine thresholds for future updates to this guidance document.
- The outcomes that the Editor may decide upon include one or more of the following:
    - Addition of a new Editorial Note to the Cochrane review to inform users of the review that the effect of the included study/studies with an associated retraction has been assessed, and it has been determined that the findings of the Cochrane review have not been meaningfully impacted. This note should detail what effects, if any, the removal of the study/studies has.
    - Retraction of the Cochrane review - this may be the outcome in cases where it has been determined that inclusion of the study/studies with an associated retraction(s) has had such a meaningful impact that the editors no longer have confidence in the conclusions of the Cochrane review.
- Cochrane review authors can remove the included study/studies with an associated retraction(s) via an update to their review. Authors should detail the included study/studies with an associated retraction(s) as part of their rationale for the update.

How to use this guidance document

- Cochrane review authors should work through the steps in the guidance document below sequentially to consider different ways in which their review may have been impacted by the inclusion of the study/studies with an associated retraction.
- The guidance document should be used in conjunction with the accompanying flowchart ('Flowchart to determine meaningful impact of a study/studies with an associated retraction on a Cochrane review'), which provides a visual overview. The guidance document provides additional information including questions and points to consider at each stage as well as links and citations to relevant resources and literature. These should be used as a guide only and are not agreed thresholds.
- All steps are applicable in the case of Cochrane reviews of interventions that include meta-analyses. For reviews of interventions that contain synthesis without meta-analyses and for all other review types, not all steps will be applicable. This is indicated at the relevant decision points in the guidance document and flowchart.

- Following completion of all relevant steps, the authors of the Cochrane review should make an assessment as to whether there has been any meaningful impact on the findings and whether or not we still have confidence in the review's conclusions. This will be a subjective assessment as there are currently no agreed numerical cut offs for a 'meaningful' effect on a review, as further research is needed in this area.
- Review authors should consider the answers to all relevant questions in the flowchart and guidance document together, as different factors may interact to increase or decrease the impact. For example, a change in the direction or magnitude of an effect estimate may have little impact when considered in the context of effect estimates on the width of the confidence intervals or certainty of the evidence, whereas a small change in magnitude of the effect may be considered more relevant if a large proportion of the data came from a study associated with a retraction.
- In general, decisions on impacted Cochrane reviews will need to be made individually, on a case-by-case basis.
- As experience is gained in using this flowchart and guidance document, they will be updated. Review authors who identify other relevant literature should inform Cochrane's Research Integrity Team via researchintegrity@cochrane.org.

Step 1: Is the study/studies with an associated retraction an included study in the review?

- The flowchart and accompanying guidance document are only for use when one or more studies with an associated retraction have been included in the review.
- If the retracted study/studies are in "Awaiting Classification", they should be moved to "Excluded studies" when the next update is conducted.
- If the retracted study/studies are cited in the Introduction or Discussion sections, all reference to them should be removed when the next update is conducted.

Step 2: Consider whether any other studies included in the Cochrane review have an associated retraction, expression of concern or editorial note

- **Check whether any other studies included in the Cochrane review have an associated retraction**
    - If any other studies with an associated retraction are identified, all steps and questions in the flowchart and guidance document should be considered in the context of ***all*** included data that comes from studies with an associated retraction. It is not necessary to look at the effect of individual studies.
    - For further guidance on how to identify whether any other studies included in the review have an associated retraction see:
        - Section 4.4.6 Identifying fraudulent studies, other retracted publications, errata and comments in the Cochrane Handbook
        - 4.S1 Technical Supplement to Chapter 4: Searching for and selecting studies in the Cochrane Handbook in the Cochrane Handbook
        - Cochrane policy for managing potentially problematic studies
        - Cochrane policy for managing potentially problematic studies: implementation guidance
        - The Retraction Watch Database
        - Consider checking whether any other studies included in the Cochrane review have associated expressions of concerns or editorial notes.
    - Expressions of concern and editorial notes are harder to identify than retractions (particularly as not all notices will be indexed) but their presence on an article may

help inform the decision on what action to take on the Cochrane review, and avoid the process of assessing the impact of a study/studies associated with a retraction being carried out multiple times. This is because such articles may be in the process of being investigated by the journal for retraction. Review authors may therefore wish to move such studies to 'Awaiting Classification' when updating the Cochrane review). For further information on managing studies with an associated expression of concern, see the Cochrane policy for managing potentially problematic studies: implementation guidance.

- Identifying included studies that have an associated expression of concern or editorial note may be particularly relevant to the decision on the Cochrane review in cases where the included studies that are associated with a retraction are by an author group who have multiple articles with expressions of concern or editorial notes alerting readers that they are being investigated. This may be particularly relevant when a large percentage of the included studies in the Cochrane review are by the same author group.

Step 3: Consider the scale of contribution of the study/studies with an associated retraction to the Cochrane review

- It is important to consider the proportion of the data that the study/studies with an associated retraction contributes to the review.
- There is currently no consensus on a threshold for what proportion of data/participants is sufficient to have a meaningful enough impact on the review to result in no longer having confidence in its conclusions, therefore such decisions must be made on a case-by-case basis.
- Review authors should consider the following when assessing the impact of the scale of the contribution:
  - What proportion of the data comes from the from the study/studies with an associated retraction?
  - What proportion of the data for the main outcomes (those reported in the summary of findings table(s), or those reported in the summary version of reviews that do not have a summary of findings table) comes from the study/studies with an associated retraction?
  - Is/are the study/studies with an associated retraction the only study/studies for any of the main outcomes of the review? Depending on the certainty of the evidence, such cases may have a very meaningful impact on the conclusions of the review.
- Several studies have considered how to define 'meaningful impact' of an individual study on the findings of a systematic review in relation to the percentage of data/participants from a 'problematic' or retracted study. Cochrane review authors may wish to consider these to help inform their assessment:
  - O'Connell et al. (2023) investigated the impact of a group of problematic studies on the result of a specific meta-analysis, and developed an Impact Index. Based on their expert opinion, they determined that if 15% or more of the data came from a problematic study/studies, there was a meaningful impact on the findings.[10]
  - Marrett et al. (2009) considered quantitative review where more than 30% of data came from problematic studies to be at greatest risk of their findings being affected.[7]

Step 4: Consider whether the study/studies with an associated retraction is included in any quantitative synthesis

- If it/they is/are **not** included in quantitative synthesis, continue to Step 5.
- If it/they is/are included in quantitative synthesis, such as meta-analyses, Cochrane review authors should conduct a sensitivity analysis to determine the effect of removal of the study/studies with an associated retraction on the results of the Cochrane review. For more information on conducting sensitivity analyses, see Section 10.14 Sensitivity Analyses of the Cochrane Handbook.
- Following the sensitivity analysis, review authors should consider:
    - Does removal of the study/studies change the direction of the effect estimate for any of the main outcomes (those reported in the summary of findings table(s))?
    - Does removal of the study/studies change the direction of the effect estimate for any of the other outcomes? (N.B. although it is the main outcomes that could impact the conclusions, it is important to look at all outcomes at this stage, as the effect on all outcomes would need to be detailed in an editorial note or retraction notice).
    - Is there a change in any outcome from benefit to harm, or harm to benefit?
    - Does removal of the study/studies change the magnitude of the effect estimate for any of the main outcomes?
    - Does removal of the study/studies change the magnitude of the effect estimate for any of the other outcomes?
    - Are any of the new effect estimates for any of the main outcomes outside of the original confidence intervals?

Step 5: Reassess the certainty or quality of the evidence without the study/studies with an associated retraction.

- Cochrane review authors should reassess the certainty or quality of the evidence in the same way as it was originally assessed for that review.
- For reviews of interventions that used GRADE, this reassessment should be done in line with MECIR conduct standard 74: Use the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of the body of evidence for each outcome, and to draw conclusions about the certainty of evidence within the text of the review [3] (see MECIR Box 14.2.a)
- Following reassessment of the certainty or quality of the evidence, review authors should consider:
    - Does removal of the study/studies with an associated retraction change the level of certainty for any of the main outcomes (those reported in the summary of findings table(s))?

Step 6: Combine the results of all the above questions and assessments to consider the overall impact of the study/studies with an associated retraction

- Cochrane review authors should assess whether, based on all the information above, removal of the data from the study/studies with an associated retraction changes the conclusions of the Cochrane review. When doing so, they should consider whether removal of the data from the study/studies with an associated retraction impacts on the threshold used in that review to draw conclusions from the data.
- The decision on whether the conclusions of a review have been meaningfully impacted by the inclusion of a study/studies with an associated retraction will be influenced by several factors and therefore will need to be made on a case-by-case basis.
- Review authors should consider the results of all assessments and answers to all the question above in the context of one another when making their final assessment for the Editor. Chapter

15: Interpreting results and drawing conclusions of the Cochrane Handbook may help when assessing this.

- Review authors should particularly consider whether removal of the study/studies with an associated retraction leads to any changes to the main outcomes (those included in the summary of findings table(s)). This includes the presentation of any absolute and relative effects for reviews of intervention or prognostic studies.
- Review authors may wish to consult Weeks et al. (2023) when determining the significance and importance of any changes (in particular, Sections 2.4, 3.5 and Appendix 3) [11], and consider:
    - Does this change have implications for practice?
    - Does this change have implications for research?
- Several studies have considered how to define meaningful impact' of an individual study on the findings of systematic review. Review authors may wish to consider the following to help inform their assessment:
    - Avenell et al. (2022) judged the effects of an included study to be meaningful if there was a change in direction of the effect (for example from negative to neutral, or neutral to positive). They defined moderate effects as changes that were within the same effect size, and minor changes as those that did not change the interpretation of the results [4].
    - O'Connell et al. (2023) considered the effect of four domains – scale of contribution, impact on the pooled effect, impact on precision, and impact on inconsistency. For each of these domains they made a judgement on whether they considered the impact substantial, moderate, or low. An overall judgement on the level of impact on the review (low, moderate, or high impact) was determined by combining the results for each domain [10].
- When making their final assessment of impact on the review, authors should consider whether they have answered yes to any of the questions in the steps above.
    - If the answers to all questions above is no, and based on the review authors' assessment, the inclusion of the study/studies with an associated retraction does **not** change the conclusions of the Cochrane review, a recommendation should be made to the Editor that a new editorial notes is added to the review stating that the conclusions of the review are not affected by the inclusion of data from a study/studies with an associated retraction. In their recommendation to the Editor, the review authors should detail whether and how any of the results and findings of the review are affected (see Appendix 1 and Appendix 2 for examples).
    - If the answer to any of the question above is yes, and/or based on the review authors' assessment, the inclusion of data from the study/studies with an associated retraction changes the conclusions of the Cochrane review, details should be provided to the Editor on how the findings and conclusions are affected and, in the review authors' opinion, how meaningful the impact is. Review authors should also indicate their availability and willingness to conduct a full update to the review.

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Appendix 1

Below is a worked example of applying to the flowchart and guidance document to a published Cochrane Review that has included studies with associated retractions, to determine their impact on the findings and conclusions of the Review.

Review title: Antioxidants for female subfertility: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007807.pub4/full

Seven retracted studies:

- Badawy et al. 2006, 10.1016/j.fertnstert.2006.02.097;
- El Refaeey et al. 2014, 10.1016/j.rbmo.2014.03.011;
- El Sharkwy & Abd El Aziz 2019a, https://doi.org/10.1002/ijgo.12902;
- El Sharkwy 2019b https://doi.org/10.1080/09513590.2019.1576622
- Gerli et al. 2007, https://doi.org/10.26355/eurrev_202309_33752, full text: https://europepmc.org/article/MED/18074942;
- Hashemi et al. 2017, https://doi.org/10.1080/14767058.2017.1372413).
- Ismail et al. 2014, http://dx.doi.org/10.1016/j.ejogrb.2014.06.008;

In addition, expressions of concern have been published for two studies

- Jamilian et al. 2018, https://doi.org/10.1007/s12011-017-1236-3;
- Zadeh Modarres 2018, https://doi.org/10.1007/s12011-017-1148-2

Outcome after using the framework: For the summary of findings table 1 on antioxidant(s) compared to placebo or no treatment/standard treatment for female subfertility, the retracted studies and expressions of concern do not have a meaningful impact on the findings. For summary of findings table 2 on head-to-head antioxidants for female subfertility, the retracted studies and expressions of concern have some impact on the findings; El Sharkwy 2019a was the only study to contribute results for two outcomes (clinical pregnancy and miscarriage in the 'N-acetylcysteine versus L-carnitine' comparison), which changes the certainty of the evidence for these outcomes from no evidence of a difference (for clinical pregnancy) and very low certainty (for miscarriage) to no studies measured these outcomes. However, overall, there is no meaningful impact on the findings and we still have confidence in the conclusions. Therefore, in this case, an editorial note on the published Cochrane review would be appropriate.

Assessment of impact of retracted studies

Badawy et al. 2006

- RCT (2 groups), 804 participants.
- N-acetyl-cysteine versus placebo plus clomiphene citrate
- **CONCLUSION:** Removal of this study from three analyses (included SoF table 1) makes little difference to the effect sizes, and no differences to the conclusions.
- In the comparison: ***Antioxidant supplement versus placebo, no treatment/standard treatment***

Analysis 1.5 Clinical pregnancy (subgroup by comparison) – included in **SoF table 1**	63/404 versus 79/400 – OR 0.75 (0.52 to 1.08). This analysis has 37 studies included. Removal of this study only slightly changes overall effect size from 1.65 (1.43 to 1.89) to 1.89 (1.62 to 2.19).
Analysis 1.6 Clinical pregnancy (subgroup by type of antioxidant)	As above (same data as in analysis 1.5).
Analysis 1.7 Clinical pregnancy ('stratified' by indication for subfertility – not combined).	In the group 'Unexplained' (same data as in analysis 1.5). Not explored this one as the different indications aren't given in the SoF table.
Analysis 1.9 Adverse events ('stratified by different events)	'***Miscarriage'*** – included in **SoF table 1** 27/404 versus 29/400 – OR 0.92 (0.53 to 1.58). This analysis includes 25 studies. Removal of this study only slightly changes the overall effect size – OR 1.13 (0.82 to 1.55) to 1.25 (0.85 to 1.86). ***'Multiple pregnancy'*** – included in **SoF table 1** 8/404 versus 12/400 – OR 0.65 (0.26 to 1.62). This analysis includes 9 studies. Removal of this study doesn't have much impact on the overall effect size – OR 1.00 (0.63 to 1.56) to 1.15 (0.68 to 1.94)

El Refaeey et al. 2014

- RCT (2 groups), 110 participants
- CoQ10 + Clomiphene citrate versus Clomiphene citrate
- **CONCLUSION:** Removal of this study from three analyses (included SoF table 1) makes little difference to the effect sizes, and no differences to the conclusions
- In the comparison: ***Antioxidant supplement versus placebo, no treatment/standard treatment***

Analysis 1.5 Clinical pregnancy (subgroup by comparison) – included in **SoF table 1**	19/55 versus 3/55 – OR 9.15 (2.52 to 33.22) This analysis has 37 studies included. Removal of this study changes overall effect size from 1.65 (1.43 to 1.89) to 1.60 (1.39 to 1.84)
Analysis 1.6 Clinical pregnancy (subgroup by type of antioxidant)	As above (same data as in analysis 1.5).
Analysis 1.7 Clinical pregnancy ('stratified' by indication for subfertility – not combined)	In the group 'Polycystic ovary syndrome'. (same data as in analysis 1.5). Not explored this one as the different indications aren't given in the SoF table.
Analysis 1.9 Adverse events ('stratified by different events)	***'Miscarriage'*** – included in **SoF table 1** 2/55 versus 0/55 – OR 5.19 (0.24 to 110.57) This analysis includes 25 studies. Removal of this study – OR 1.13 (0.82 to 1.55) to 1.10 (0.80 to 1.51) ***'Multiple pregnancy'*** – included in **SoF table 1** 1/55 versus 0/55 – OR 3.06 (0.12 to 76.64) This analysis includes 9 studies. Removal of this study – OR 1.00 (0.63 to 1.56) to 0.97 (0.61 to 1.53)

El Sharkwy 2019a

- RCT (2 groups), 164 participants
- N-acetylcysteine versus placebo
- **CONCLUSION:** Excluding this trial from the review would mean:
    - There would be no data on clinical pregnancy for the comparison of N-acetylcysteine versus L-carnitine. This is row 2 of SoF table 2. The conclusion would change from 'Very low-quality evidence shows no evidence of a difference' to 'No studies reported this outcome'.
    - For adverse events – miscarriage: the conclusion of 'Low quality evidence shows no difference in miscarriage' would change to 'No studies reported this outcome'.
- Included in comparison 2 - ***Head-to-head antioxidants***

Analysis 2.4 - Clinical pregnancy ('Stratified' by type of antioxidant – only study in this group) – included in **SoF table 2**	10/82 vs 12/82 – OR 0.81 (0.33 to 2.00)
Analysis 2.5 - Clinical pregnancy ('Stratified' by indications for subfertility – only study in this group)	As above (same data as in analysis 2.4).
Analysis 2.7 - Adverse events ('stratified by different events)	***'Miscarriage'*** - included in **SoF table 2** – three studies included in this meta-analysis, but this is the only study with events (other two studies

	have zero events in both groups). So, only this study contributes to the odds ratio. 6/82 versus 4/82 – OR 1.54 (0.42 to 5.67).

El Sharkwy 2019b

- RCT (two groups), 280 participants
- CC plus metformin and L-carnitine versus CC plus metformin and placebo
- **CONCLUSION:** Removal of this study from two analyses (included SoF table 1) makes little difference to the effect sizes, and no differences to the conclusions.
- In the comparison: ***Antioxidant supplement versus placebo, no treatment/standard treatment***

Analysis 1.5 Clinical pregnancy (subgroup by comparison) – included in **SoF table 1**	39/140 versus 9/140 – OR 5.62 (2.60 to 12.14). This analysis has 37 studies included. Removal of this study changes overall effect size from 1.65 (1.43 to 1.89) to 1.56 (1.36 to 1.80).
Analysis 1.6 Clinical pregnancy (subgroup by type of antioxidant)	As above (same data as in analysis 1.5).
Analysis 1.7 Clinical pregnancy ('stratified' by indication for subfertility – not combined).	In the group 'Polycystic ovary syndrome'. (same data as in analysis 1.5). Not explored this one as the different indications aren't given in the SoF table.
Analysis 1.9 Adverse events ('stratified by different events)	***'Miscarriage'*** – included in **SoF table 1** 7/140 versus 2/140 – OR 3.63 (0.74 to 17.80). This analysis includes 25 studies. Removal of this study – OR 1.13 (0.82 to 1.55) to 1.06 (0.76 to 1.47).

Gerli et al. 2007

- RCT (two groups), 92 participants
- Combination of myo-inositol 2g plus folic acid versus folic acid.
- **CONCLUSION:** Excluding this trial from the review will make no difference to the conclusions.
- From the Results: *"In one trial (Gerli 2007) (see Table 1), only half of the participants declared that they wanted to become pregnant before the study began; we have therefore included this trial, but have not used the data in the meta-analysis (see Characteristics of included studies)."*
- Data given from this study in table 1 – but not included in the Summary of Findings table.

Ismail et al. 2014

- RCT (2 groups), 170 participants
- Oral-carnitine versus placebo
- **CONCLUSION:** Removal of this study from four analyses (included SoF table 1) makes little difference to the effect sizes, and no differences to the conclusions.
- In the comparison: ***Antioxidant supplement versus placebo, no treatment/standard treatment***

Analysis 1.5 Clinical pregnancy (subgroup by comparison) – included in **SoF table 1**	42/85 versus 1/85 – OR 82.05 (10.92 to 616.59). This analysis has 37 studies included. Removal of this study changes overall effect size from 1.65 (1.43 to 1.89) to 1.52 (1.32 to 1.75).

Analysis 1.6 Clinical pregnancy (subgroup by type of antioxidant)	As above (same data as in analysis 1.5).
Analysis 1.7 Clinical pregnancy ('stratified' by indication for subfertility – not combined).	In the group 'Polycystic ovary syndrome'. (same data as in analysis 1.5). Not explored this one as the different indications aren't given in the SoF table.
Analysis 1.9 Adverse events ('stratified by different events)	***'Miscarriage'*** – included in **SoF table 1** 2/85 versus 4/85 – OR 0.49 (0.09 to 2.74). This analysis includes 25 studies. Removal of this study – OR 1.13 (0.82 to 1.55) to OR 1.16 (0.84 to 1.61). ***'Multiple pregnancy'*** – included in **SoF table 1** 5/85 versus 0/85 – OR 11.68 (0.64 to 214.68). This analysis includes 9 studies. Removal of this study – OR 1.00 (0.63 to 1.56) to 0.86 (0.54 to 1.38). ***'Gastrointestinal disturbances'*** – included in **SoF table 1** 4/85 versus 2/85 – OR 2.05 (0.37 to 11.50). This analysis includes 3 studies. Removal of this study – OR 1.55 (0.47 to 5.10) to 1.17 (0.22 to 6.25). ***'Headaches'*** 2/85 versus 1/85 – OR 2.02 (0.18 to 22.75). This analysis includes 2 studies. Removal of this study – OR 0.89 (0.45 to 1.75) to 0.82 (0.40 to 1.68).

Hashemi et al. 2017

- RCT (two groups), 40 participants
- Vitamin E versus placebo
- **CONCLUSION:** Excluding this trial from the review will make no difference to the conclusions.
- No data available to include in a meta-analysis
    - *"We tried to contact authors of all the included studies to obtain further details and clarification, but we could not obtain data for meta-analysis from 24 trials…"*
    - *"Eleven trials did not report any pregnancy outcomes"*

Assessment of impact of expressions of concern

Jamilian 2018

- RCT (two groups), 40 participants
- Chromium versus placebo
- **CONCLUSION:** Excluding this trial from the review will make no difference to the conclusions.
- No data available to include in a meta-analysis
    - *"We tried to contact authors of all the included studies to obtain further details and clarification, but we could not obtain data for meta-analysis from 24 trials…"*
    - *"Eleven trials did not report any pregnancy outcomes"*

Zadeh Modarres 2018

- RCT (two groups), 40 participants
- Selenium versus placebo
- **CONCLUSION:** Excluding this trial from the review will make no difference to the conclusions.
- No data available to include in a meta-analysis
    - *"We tried to contact authors of all the included studies to obtain further details and clarification, but we could not obtain data for meta-analysis from 24 trials…"*
    - *"Eleven trials did not report any pregnancy outcomes"*

Overall comments

SoF table 1

The impact on the meta-analysis outcomes included in **SoF table 1** – removal of the retracted studies makes very little difference to the overall effect sizes and no difference to the conclusions. All these outcomes are of low certainty in the SoF table.

- **Clinical pregnancy:** Analysis 1.5 includes 37 studies. Removal of the four retracted studies (Badawy 2006, El Sharkwy 2019b, Ismail 2014 and El Refaeey 2014) - overall effect size from 1.65 (1.43 to 1.89) to 1.47 (1.18 to 1.82).
- **Adverse events – miscarriage:** Analysis 1.9 includes 25 studies. Removal of the four retracted studies (Badawy 2006, El Sharkwy 2019b, Ismail 2014 and El Refaeey 2014) - overall effect size from 1.13 (0.82 to 1.55) to 1.17 (0.76 to 1.79)
- **Adverse events – Multiple Pregnancy:** Analysis 1.9 includes 9 studies. Removal of the three retracted studies (Badawy 2006, Ismail 2014 and El Refaeey 2014) - overall effect size from 1.00 (0.63 to 1.56) to 0.92 (0.52 to 1.61)
- **Adverse events – Gastrointestinal disturbances:** Analysis 1.9 includes 3 studies. Removal of one retracted study (Ismail 2014) – overall effect size from 1.55 (0.47 to 5.10) to 1.17 (0.22 to 6.25)

SoF table 2

For the meta-analysis outcomes included in **SoF table 2,** the removal of one study (El Sharkwy 2019a):

- **Clinical pregnancy:** only one study in the comparison 'N-acetylcysteine versus L-carnitine'. The conclusion of 'Very low-quality evidence shows no evidence of a difference' would change to 'No studies measured this outcome'.
- **Adverse events – miscarriage:** for the comparison of 'N-acetylcysteine versus L-carnitine' this was the only study included. Removal of this study would change the conclusions from 'Low quality evidence shows no difference in miscarriage' would change to 'No studies measured this outcome'.

Appendix 2

Below is a worked example of applying to this flowchart and guidance document to a published Cochrane Review that has included studies with associated retractions, to determine their impact on the findings and conclusions of the Review.

Review title: Clomiphene and other antioestrogens for ovulation induction in polycystic ovarian syndrome (https://doi.org/10.1002/14651858.CD002249.pub5)

There are four retracted studies included in the review:

- Badaway 2008
- Badaway 2009
- Badaway 2011

- Parsanezhad 2002b

Outcome after using the framework: These retracted studies do not have a meaningful impact on the findings and we still have confidence in the conclusions. Therefore, in this case, an editorial note on the published Cochrane review would be appropriate.

Assessment of impact of retracted studies

Badaway 2008

- 1/28 RCTs; 318 participants/total number not stated
- Included in clomiphene citrate with hMG comparison. This was part of **Comparison 3.** Antioestrogen versus gonadotropin. Included in 3/5 meta-analyses – outcomes are miscarriage, multiple pregnancy and OHSS. Miscarriage is a primary outcome, multiple pregnancy and OHSS are secondary outcomes.
- Not included in an SoF table
- Included in Abstract: 'Limited evidence suggested that compared with a gonadotropin, clomiphene citrate was associated with a reduced chance of a pregnancy, ongoing pregnancy, or live birth, with no clear evidence of a difference in multiple pregnancy rates'. This statement also reflected in PLS.
- The multiple pregnancy outcome is the only one that includes Badaway 2008. If it were removed from the MA, confidence intervals would be even wider: OR 0.26 (0.06, 1.06) would change to OR 0.27 (0.04, 1.71). Summary statement in Abstract would likely stay the same.
- Badaway 2008 also included in miscarriage outcome: if removed from MA, the effect estimate would change from OR 0.84 (0.39, 1.78) to OR 0.68 (0.28, 1.75). Not a meaningful impact.
- Badaway 2008 also included in OHSS outcome: if removed from MA, the effect estimate would change from OR 0.19 (0.02, 1.67) to OR 0.19 (0.01, 4.08). Not a meaningful impact.
- **Overall, no meaningful impact**

Badaway 2009

- 1/28 RCTs; 212 participants/total number not stated
- Included in clomiphene citrate regimen A versus clomiphene citrate regimen B comparison. Not included in any meta-analyses, but included in one single-study forest plot. Outcome: miscarriage, effect estimate OR 1.25 (0.27, 5.70). Miscarriage is a primary outcome.
- Included in SoF table 4. Certainty rated as very low, due to RoB (x1) and imprecision (x2)
- Mentioned in Abstract: 'Data for early versus late regimens of clomiphene citrate were insufficient to be able to make a judgement on differences for pregnancy outcomes'. This statement reflected in the PLS.
- **Overall, not a meaningful impact. If study were removed, there would be no evidence, but now there is only very uncertain evidence.**

Badaway 2011

- 1/28 RCTs; 371 participants/total number not stated

- Included in clomiphene citrate versus tamoxifen comparison. Included in 4/5 meta-analyses – outcomes are miscarriage, clinical pregnancy, multiple pregnancy and OHSS. Miscarriage is primary outcome.
- Included in SoF table 2 for all four of these outcomes.
- Included in Abstract: results from all four outcomes reported.
- Miscarriage outcome: effect estimate from meta-analysis currently OR 1.81 (0.80, 4.12) - favours tamoxifen. Highest weight in meta-analysis – 45.2%. If removed from meta-analysis the effect estimate changes to OR 2.29 (0.80, 6.57). Conclusion now would probably be evidence of benefit, similar to previous analysis. GRADE certainty currently 'low' due to imprecision and risk of bias. This would probably not change.
- Clinical pregnancy rate: effect estimate from meta-analysis currently OR 1.30 (0.92, 1.85) - favours clomiphene. Highest weight in meta-analysis: 29.6%. If removed from the meta-analysis the effect estimate changes to OR: 1.05 (0.68, 1.63). Conclusion now would probably be 'little to no difference'. Authors original conclusion was 'no clear evidence of a difference'. GRADE certainty currently 'low': downgraded for heterogeneity and risk of bias. I2 still high with study removed – 72%. Risk of bias picture broadly unchanged.
- Multiple pregnancy rate: effect estimate from meta-analysis currently OR 2.34 (0.34, 16.04) - favours tamoxifen. Lower weight in meta-analysis: 33.7%. If removed from meta-analysis only one study would contribute data and effect estimate would be OR 1.00 (0.06, 16.44). Conclusion would be 'no difference'. Authors' original conclusion was 'insufficient evidence of a difference'. GRADE certainty currently 'very low': downgraded for risk of bias and imprecision. This would not change.
- OHSS: zero event rates in all three studies in the meta-analysis. Authors' original conclusion 'There were no instances of OHSS in either the clomiphene citrate or the tamoxifen group reported from three studies' This would not change.
- **Overall, probably not a massive difference (given the age of the review the authors have used an older approach to drawing conclusions, focusing more on statistical significance to determine whether there is a difference between treatments, making this judgement less straightforward).**

Parsanezhad 2002b

- 1/28 RCTs; 100 participants/not stated
- Included in Clomiphene citrate plus bromocriptine versus clomiphene citrate comparison. Included in one meta-analysis - clinical pregnancy – not a primary outcome.
- Included in Summary of findings table.
- Briefly mentioned in Abstract, but only in context of an inconclusive body of evidence.
- Clinical pregnancy outcome: effect estimate from meta-analysis currently OR 1.03 (0.48, 2.21). Only two studies in analysis and each contribute roughly half the weight. If removed from the meta-analysis the effect estimate would be OR 1.07 (0.37, 3.11). Conclusion would still be 'no difference'. Authors' original conclusion was 'no evidence of a difference'. GRADE certainty 'low' - downgraded for imprecision and risk of bias. Unlikely to change.
- **Overall, not a meaningful impact**