# Outcome reporting bias in trials: a methodological approach for the assessment and adjustment in a systematic review

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**Summary Points Box**

* Outcome reporting bias (ORB) occurs when the selection for publication of a subset of the original recorded outcomes is based on knowledge of the results. ORB is a threat to evidence based medicine and contributes to waste in research.
* Empirical evidence suggests that statistically significant outcomes had higher odds of being fully reported compared to non-significant outcomes (range of odds ratios: 2.2 to 4.7).
* The ORBIT (Outcome Reporting Bias in Trials) research programme offers tools for systematic reviewers to identify missing outcome data, and assess and adjust for ORB. A tutorial is provided to illustrate how these tools could be used within a systematic review.

## Standfirst

*“Trials that presented findings that were not significant (P≥0.05) for the protocol-defined primary outcome in the internal documents either were not reported in full or were reported with a changed primary outcome”* [1].

Systematic reviews of clinical trials aim to include all relevant studies conducted on a particular topic and to provide an unbiased summary of their results, producing the best evidence about the benefits and harms of medical treatments. However, relevant studies may not provide the results for all outcomes that were measured or may selectively report only some of the analyses undertaken, leading to unnecessary waste in the production and reporting of research, and potentially biasing the conclusions to systematic reviews. In this article, Kirkham and colleagues provide a methodological approach, with an example, of how to identify missing outcome data and to assess and adjust for outcome reporting bias in systematic reviews.

## Introduction

Selective reporting of outcome data creates a missing data problem. Bias arises when trialists select outcome results for publication based on knowledge of the results. Hutton and Williamson first defined outcome reporting bias (sometimes termed selective reporting bias) in 2000:

*“the selection on the basis of the results of a subset of the original variables recorded for inclusion in a publication”*[2].

Empirical research provides strong evidence that outcomes that are statistically significant have higher odds of being fully reported compared to non-significant outcomes (range of odds ratios: 2.2 to 4.7) [3, 4]. In the ORBIT (Outcome Reporting Bias In Trials) study, ORB was suspected in at least one trial in more than a third (96/283; 34%) of Cochrane systematic reviews [5]. In the subsequent follow-up study looking at the same problem in a review of harm outcomes, review primary harm outcome data was missing from at least one eligible study in over 75% of systematic reviews [6].

The aim of this educational paper is to demonstrate, with an example, the steps that systematic reviewers dealing with healthcare interventions could take to minimise the amount of missing data within their reviews, and how reviewers could detect and classify the suspicion of outcome reporting bias (ORB) within included studies for both benefit and harm outcomes using ORBIT methodology. We also provide details on a statistical approach to assess the robustness of meta-analysis conclusions to this potential source of bias that non-methodologists could implement on a web-based platform.

*Selecting the most appropriate review outcomes*

One way to streamline and to help reduce ORB in the systematic review process is for reviewers to consider outcomes that have been deemed to be ‘core’ for all trials in a particular topic area, and for these outcomes to be used in the review [7]. The use of core outcome sets will ensure that every included trial could contribute data to the review analyses on the key outcomes. An example is a set of core outcomes that have been developed for skin conditions which have now been endorsed by the **C**ochrane **S**kin **G**roup - **Co**re **Ou**tcome **S**et **In**itiative (CSG-COUSIN) [8].

We recommend that systematic reviewers should consider core outcome sets when registering their topics with Cochrane Review Groups or in PROSPERO (International prospective register of systematic reviews). Systematic reviewers can identify if relevant core outcome sets exist for their review area by searching the publically accessible COMET (Core Outcome Measures in Effectiveness Trials) database [9].

*Inclusion/exclusion criteria*

Reviewers should not exclude studies from their review on the basis of not reporting the review outcomes of interest, as non-reporting does not necessarily mean that the outcome was not measured [5]. This recommendation also forms part of the mandatory methodological standards (item C40) for the conduct of new Cochrane intervention reviews (MECIR) [10]. Despite these recommendations and recent screening initiatives introduced by the Cochrane Editorial Unit, a quarter of Cochrane reviews are still excluding studies due to no relevant outcome data [11].

We strongly encourage that systematic reviewers include relevant studies in their review irrespective of whether they reported any of the review outcomes of interest, and assess those studies in accordance to the methods described below.

*Identifying missing outcome data within reviews*

An outcome matrix was proposed [5] to help detect missing study outcome data. Reviewers can construct the matrix with the outcomes of interest in the review and those reported in the trial reports listed in the columns, with the different studies listed in the rows. An example of an outcome matrix for a Cochrane systematic review ‘Topiramate add-on for drug-resistant partial epilepsy’ [12] is presented in Figure 1. At the time this review was undertaken there was no core outcome set that covered the scope of the review and therefore the outcome choices were left to the review authors’ discretion. The review aim was to evaluate the efficacy and tolerability of topiramate when used as an add-on treatment for people with drug resistant partial epilepsy. The review considered two benefit and 12 harm outcomes. Eleven studies were included, whilst the review authors excluded one further study due to there being ‘no relevant outcome data’. As per our earlier recommendation, the review authors should not have excluded this study (‘Coles 1999’) from the review, however, we include this study in the example in order to provide a retrospective assessment of the impact of outcome reporting bias in this review. The outcome matrix, like the one presented in Figure 1, provides a transparent way for systematic reviewers to display which review outcomes were reported for each trial included in the review, and which were missing or partially reported. Partial reporting of outcome data are those that are inadequately reported for inclusion in a review meta-analysis (for example, an effect size was presented with no measure of precision or exact p-value).

For trials that do not or partially report on outcomes, the matrix also allows reviewers to assess the risk of ORB according to the ORBIT classification system (see next section). In the epilepsy example, we can see from the matrix that all studies (accept the excluded Cole 1999 study) reported data on 50% reduction in seizure frequency but only six of the studies fully reported data on seizure freedom. These are structurally related outcomes such that if a trial author reports on one of these outcomes, this suggests that the trialist must have also measured the other outcome.

We strongly encourage systematic reviewers to include an outcome matrix within their reviews. The ORBIT matrix generator, available on the ORBIT website [13] is a tool that researchers can easily use to construct an ORBIT outcome matrix, which researchers can also export for inclusion into a systematic review manuscript.

*Obtaining unpublished information*

Sources for obtaining unpublished information on clinical trials for use in systematic reviews have previously been described [14]. These sources (for example, trial registry and regulatory agency databases, trialist and sponsor contact, litigation documents, conference abstracts and internet searches) can help identify the existence of unreported outcomes within published trials. To minimise the amount of missing data within reviews, we recommend that reviewers should attempt to obtain as much missing outcome data from their reviews as possible. Reviewers can then update the outcome matrix to reflect information obtained from unpublished sources.

*Detecting outcome reporting bias*

In the absence of obtaining any usable missing outcome data from these sources, the ORBIT researchers developed classification systems to help systematic reviewers detect ORB within reviews. The method relies only on information within the published trial report (e.g. inconsistency between sections such as the abstract, [methods](http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001666#s3), and [results](http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001666#s4)), expert clinical judgment and a review of which outcomes researchers usually report across a set of trials in a review [5]. The ORBIT researchers have demonstrated that the classification systems are able to detect bias with high sensitivity even without access to other source documents to help aid the assessment, such as trial registry entries and study protocols [5]. The classifications can also help reviewers judge the level of risk of bias within the ‘selective reporting outcome’ domain using the risk of bias tool currently used by the Cochrane Collaboration [15]. Trials either not reporting or partially reporting a review outcome should be labelled high risk, low risk or no risk according to ORBIT terminology for benefit outcomes [Table 1], or for harm outcomes [Table 2]. The two classification systems identify whether there is evidence that the trialist measured and analysed (or compared) the outcomes, whether the trialist measured but did not necessarily analyse (or compare) outcomes, whether it was unclear that the trialist measured the outcomes, or if it is clear the trialist did not measure the outcomes.

For the epilepsy review, the classifications awarded for each outcome with missing or partially reported outcome data are presented in the outcome matrix [Figure 1], with a full justification of each classification listed in [Supplementary Table 1], using where appropriate verbatim text taken from the trial report. These justifications can also be included in systematic reviews to support the risk of bias assessment. For example, in Cochrane reviews, authors are encouraged to provide ‘support for judgment’ on each risk of bias judgement made.

In order to assess the risk of bias due to selective reporting, we recommend that the ORBIT classification system is used by systematic reviewers as a framework to determine whether there is a high or low risk of ORB when there is missing or partially reported review outcome data. We also recommend that the assessment is completed by at least two independent researchers and differences discussed to agree on an overall classification (in the epilepsy review, assessments were completed by two methodologists and a clinical neurologist).

*Adjusting for outcome reporting bias in systematic reviews*

Copas and colleagues have developed new statistical sensitivity approaches for assessing the robustness of review meta-analysis conclusions when ORB is suspected [16]. The Copas approach takes into account the relative sample size of the studies with missing outcome data and models directly the ORB mechanism for both benefit and harm outcomes. The Copas method is particularly attractive as it utilises the high and low risk of bias classifications already assigned using the ORBIT classification systems.

As an example, we return to the epilepsy example mentioned earlier, for which the outcome matrix of ORBIT classifications is shown in Figure 1. The Copas method is currently implementable on a user-friendly platform for fixed effects meta-analyses for binary data via the ORBIT website [17]. Full instructions on how to set up the data frame and implement this method are available in ten simple steps on the website [17]. The data frame for the epilepsy example is also downloadable from this website. The method can be applied to other data types and random effects meta-analyses - the study team are currently working on implementing this on the same user-friendly platform. However, further support on the implementation and interpretation of the Copas method can be made through the ‘Contact’ page of our website.

After applying the Copas bias adjustments for partially reported or unreported outcomes [Table 3], the review had overestimated the benefits and underestimated the harms of the test treatment [16]. The adjustment was greater for the harm outcomes, for which fewer studies reported the outcomes of interest, and less concerning for the benefit outcomes where there were fewer missing outcomes. As an example, considering the harm outcome nausea and vomiting, the unadjusted estimate (Relative Risk 1.5, 95% confidence interval 0.71 to 3.15) reported in the review suggested that there was no statistically significant difference between treatments. However, the Copas ORB adjusted estimate (Relative Risk 1.9, 95% confidence interval 1.08 to 3.59) suggested there was statistically significantly more harm in the treatment arm.

In the presence of suspected ORB, we recommend that the quality of evidence is lowered in relation to the standard GRADE (Grades of Recommendation, Assessment, Development and Evaluation) assessment applied in reviews. Also, we recommend that sensitivity analyses are performed for important outcomes to assess the robustness of conclusions to ORB [16].

## Conclusions

Empirical evidence has suggested that ORB is a threat to the validity of the evidence base and contributes to research waste, and here we have highlighted up-to-date approaches and recommendations for detecting and adjusting for this problem as part of a sensitivity analysis within systematic reviews. We anticipate applications of, and continued methodological research into the assessment and adjustment of ORB to continue into the next decades. The ORBIT website is a useful resource, providing researchers with tools for ORB detection and methods for sensitivity analysis as well as being a repository for important publications in this field.

**Contributors and sources:** The authors include statisticians and a clinical epidemiologist with expertise in outcome reporting bias and a particular interest in methods and initiatives for reducing waste in research. All authors contributed to the planning, writing and editing of this paper. JJK provided the illustrative example and is the guarantor.

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| --- |
| **Table 1: The ORBIT classification system for missing or complete outcome reporting in benefit outcomes [5]** |
| **Classification** | **Description** | **Level of reporting** | **Risk of bias\*** |
| ***Clear that the outcome was measured and analysed*** |
| **A** | Trial report states that outcome was analysed but only reports that result was not significant (typically stating p-value>0.05). | Partial | High Risk |
| **B** | Trial report states that outcome was analysed but only reports that result was significant (typically stating p-value<0.05). | Partial | No Risk |
| **C** | Trial report states that outcome was analysed but insufficient data were presented for the trial to be included in meta-analysis or to be considered to be fully tabulated. | Partial | Low Risk |
| **D** | Trial report states that outcome was analysed but no results reported. | None | High Risk |
| ***Clear that the outcome was measured*** |
| **E** | Clear that the outcome was measured. Judgment says outcome ***likely*** to have been analysed but not reported because of non-significant results. | None | High Risk |
| **F** | Clear that the outcome was measured. Judgment says outcome ***unlikely*** to have been analysed. | None | Low Risk |
| ***Unclear whether the outcome was measured*** |
| **G** | Not mentioned but clinical judgment says likely to have been measured and analysed but not reported on the basis of non-significant results. | None | High Risk |
| **H** | Not mentioned but clinical judgment says unlikely to have been measured at all. | None | Low Risk |
| ***Clear that the outcome was not measured*** |
| **I** | Clear that the outcome was not measured. | NA | No Risk |

\*Risk of bias arising from the lack of inclusion of non-significant results when a trial was excluded from a meta-analysis or not fully reported in a review because the data were unavailable.

|  |  |
| --- | --- |
| **Table 2: The ORBIT II classification system for missing or complete outcome reporting in harm outcomes [6]** |  |
| **Classification** | **Description** | **Level of reporting** | **Risk of bias\*** |
| **Explicit specific harm outcome: measured and compared across treatment****groups** |  |  |
| **P1** | States outcome analysed but reported only that p-value>0.05. | Partial | High Risk |
| **P2** | States outcome analysed but reported only that p-value<0.05. | Partial | High Risk |
| **P3** | Insufficient reporting for meta-analysis or full tabulation. | Partial | Low Risk |
| **Explicit specific harm outcome: measured but not compared across****treatment groups** |  |  |
| **Q** | Clear that outcome was measured and clear outcome was not compared. | NA | No risk |
| **Explicit specific harm outcome: measured, not clear whether compared or****not across treatment groups** |  |  |
| **R1** | Clear that outcome was measured but no results reported. | None | High Risk |
| **R2** | Result reported globally across all groups. | None | High Risk |
| **R3** | Result reported from some groups only. | None | High Risk |
| **Specific harm outcome not explicitly mentioned: clinical judgment says likely measured and likely compared across treatment groups** |  |  |
| **S1** | Only pooled adverse events reported (could include specific harm outcome). | None | High Risk |
| **S2** | No harms mentioned or reported.  | None | High Risk |
| **Specific harm outcome not explicitly mentioned: clinical judgment says likely measured but no events** |  |  |
| **T1** | Specific harm not mentioned but all other specific harms fully reported. | None | Low Risk |
| **T2** | No description of specific harms. | None | Low Risk |
| **Specific harm outcome not explicitly mentioned, clinical judgment says unlikely measured** |  |  |
| **U** | No harms mentioned or reported. | None | Low Risk |
| **Explicit the specific harm outcome was not measured** |  |  |
| **V** | Report clearly specifies that data on the specific harm of interest was not measured. | NA | No Risk |

\*Bias would occur if specific harm had been measured, but data were presented or suppressed in a way that would mask the harm profile of particular interventions.

**Table 3:** Unadjusted and ORB-adjusted (using Copas method) Mantel-Haenszel estimates and confidence intervals [16]

|  |  |  |
| --- | --- | --- |
|  | Unadjusted | Copas adjustment |
|  | Pooled estimate (Relative Risk) | Lower 95% confidence interval | Upper 95% confidence interval | Pooled estimate (Relative Risk) | Lower 95% confidence interval | Upper 95% confidence interval |
| *Benefits* |  |  |  |  |  |  |
| 50% seizure reduction | 2.97 | 2.38 | 3.72 | 2.87 | 2.31 | 3.57 |
| Seizure freedom | 3.41 | 1.37 | 8.51 | 2.66 | 1.19 | 5.78 |
| *Harms* | Pooled estimate (Relative Risk) | Lower 99% confidence interval | Upper 99% confidence interval | Pooled estimate (Relative Risk) | Lower 99% confidence interval | Upper 99% confidence interval |
| Treatment withdrawal | 2.44 | 1.45 | 4.10 | 2.47 | 1.48 | 4.13 |
| Dizziness | 1.54 | 1.07 | 2.22 | 1.64 | 1.16 | 2.32 |
| Headache | 0.99 | 0.67 | 1.44 | 1.14 | 0.83 | 1.58 |
| Nausea/vomiting | 1.50 | 0.71 | 3.15 | 1.90 | 1.08 | 3.59 |
| Paraesthesias | 3.91 | 1.51 | 10.12 | 4.40 | 1.87 | 10.83 |
| Weight loss | 3.47 | 1.55 | 7.79 | 3.60 | 1.69 | 7.92 |
| Fatigue | 2.19 | 1.42 | 3.40 | 2.22 | 1.46 | 3.42 |
| Somnolence | 2.29 | 1.49 | 3.51 | 2.35 | 1.55 | 3.57 |
| Concentration impairment | 7.81 | 2.08 | 29.29 | 8.25 | 2.45 | 29.89 |
| Speech difficulty | 3.37 | 0.80 | 14.13 | 4.48 | 1.55 | 16.01 |
| Thinking abnormality | 5.70 | 2.26 | 14.38 | 6.02 | 2.54 | 14.79 |
| Ataxia | 2.29 | 1.10 | 4.77 | 2.61 | 1.36 | 5.16 |

**Figure 1: Outcome matrix for epilepsy review with ORBIT classifications**

| Study ID(author, date of publication) |  |  | Review primary benefit outcome | Review secondary outcomes | Review harm outcomes |
| --- | --- | --- | --- | --- | --- |
| Sample size (Topiramate)  | Sample Size (Placebo)  | 50% reduction in seizure frequency | Seizure freedom | Treatment withdrawal\* | Dizziness | Headache | Nausea/vomiting | Paraesthesias | Weight loss | Fatigue | Somnolence | Concentration impairment | Speech difficulty | Thinking abnormally | Ataxia |
| Ben-Menachem 1996 | 28 | 28 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngE | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 |
| Elterman 1999 | 41 | 45 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.png R1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.png R1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.png R1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.png R1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.png R1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.png R1 |
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| Guberman 2002 | 171 | 92 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 |
| Korean 1999 | 91 | 86 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png |
| Privitera 1996 | 143 | 47 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngE | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngQ | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png |
| Rosenfeld 1996 | 167 | 42 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/circle.pngC | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png |
| Sharief 1996 | 23 | 24 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 |
| Tassinari 1996 | 30 | 30 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngR1 |
| Yen 2000 | 23 | 23 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngE | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngS1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngT1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngS1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngT1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngT1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngT1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngT1 |
| Zhang 2011 | 46 | 40 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngS1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngT1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngT1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngT1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/tick.png | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngT1 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngT1 |
| Excluded Study: Reason for exclusion “did not look at the outcome of interest: 50% or greater reduction in seizure frequency, treatment withdrawal or side effects.” |
| Coles 1999 | 52 | 51 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngE | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngE | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngG | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngS2 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngS2 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngS2 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngS2 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngS2 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngS2 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngS2 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngS2 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngS2 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngS2 | http://ctrc.liv.ac.uk/orbit/assets/images/icons/cross.pngS2 |

\* In epilepsy, treatment withdrawal reflects both benefit/harm, i.e. withdrawal from treatment due to recurrent seizures on treatment (lack of benefit) and/or withdrawal due to adverse events (harm).

 indicates full reporting  indicates not reported – not clear whether measured or not  indicates partial reporting  not measured