Understanding the impact of outcome reporting bias in trials (the ORBIT study)

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1.INTRODUCTION:

Randomised controlled trials (RCTs) represent the gold standard methodological design to evaluate the effectiveness of a treatment in humans but the reporting of these is subject to bias, including study publication bias and outcome reporting bias (ORB). National and international organisations and charities give recommendations for good research practice in relation to RCTs but to date no review of these guidelines has been undertaken with respect to reporting.

A previous study demonstrated that the selective non-reporting of outcomes within a study can have a substantial effect on meta-analysis when the amount of missing data is large, however in four of the five meta-analyses examined, the impact on conclusions was minimal due to the small amount of missing data [1].

2. AIMS AND OBJECTIVES:

To estimate the impact of ORB on the meta-analysis of the primary outcome in an unselected cohort of Cochrane reviews and to assess the guidelines issued by organisations and charities that fund clinical trials.

3. METHODS:

Assessment of impact
Reviews were eligible if any of the studies included in the review did not report on the primary outcome of the review or if studies were excluded due to no relevant outcome data. Eligible studies were then classified for suspicion of ORB. Reviewers were contacted to find out if eligible studies not reporting the outcome of interest would be included in the reviews' meta-analysis of the primary outcome. The maximum bias bound approach [2,3] was used to assess the impact of ORB so results were comparable across reviews.

Guidelines
National and International organisations and charities were contacted to establish whether they fund clinical trials and if they issued guidelines to researchers. These guidelines were assessed to see what guidance was given regarding publication. Issues relating to publication bias and ORB were reviewed, including trial registration and protocol adherence [4].

5. RESULTS:

Assessment of impact
To date; only 23% (34/151) of reviews had one meta-analysis of the primary outcome, 23% (35/151) involved no meta-analysis and 54% (82/151) included more than one meta-analysis related to the primary outcome.

The robustness of the conclusions of the original analyses were assessed with a sensitivity analysis (Figure 1). This is an example as the work is ongoing. It was found that a median of 51% (range 6% and 99%) of data may be missing from the meta-analysis from studies that were eligible for the reviews and a median of 17% (range 0 to 97%) had a high suspicion of ORB.

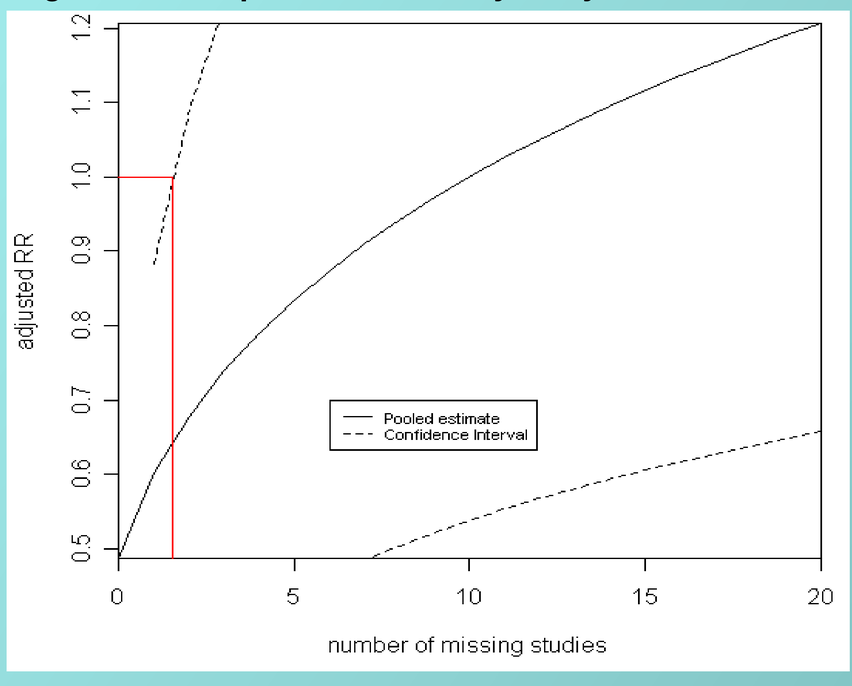
Guidelines
Seventeen organisations and 56 charities were eligible of 140 surveyed for this review, although there was no response from 11 (Table 1). Trial registration, protocol adherence, trial publication and monitoring against the guidelines were often explicitly discussed or implicitly referred too. However, only eleven of these organisations or charities mention the publication of negative as well as positive outcomes and just three of the organisations specifically state that the statistical analysis plan should be strictly adhered to and all changes should be reported.

6. CONCLUSIONS:

Assessment of impact
Reviewers should scrutinise trials with missing outcome data and ensure that an attempt to contact trialists is made if the study does not report results. Trials should then be assessed for suspicion of outcome reporting bias. The lack of reporting of specified outcome(s) should not be an automatic reason for exclusion of studies.

Guidelines
There is a need to provide more detailed guidance for those conducting and reporting clinical trials to help prevent the selective reporting of outcomes. Current guidelines need to be updated, many include statements regarding the publication of 'negative' studies to prevent publication bias but do not go as far as mentioning ORB.

Figure 1: Example of a sensitivity analysis for a review from ORBIT



Number of studies included in the meta-analysis = 4 (3698 participants)

Number of eligible studies that did not report outcome of interest = 5 (710 participants)

There was high suspicion of ORB in one study and it would take two studies to overturn the conclusion of the review.

Table 1 Summary of response from organisations and charities

Action	Number of organisations (percentage)	Number of charities (percentage)	Total (percentage)
Contacted	25	115	140
Eligibility			
Eligible	17 (68%)	56 (49%)	73 (52%)
Not eligible	8 (32%)	48 (42%)	56 (40%)
No reply	0 (0%)	11 (9%)	11 (8%)
Guidelines (n=73)			
Guidelines/terms and conditions received	14 (82%)	52 (93%)	66 (90%)
Limited contact	2 (12%)	1 (2%)	3 (4%)
No guidelines	1 (6%)	1 (2%)	2 (3%)
Could not send due to confidentiality	0 (0%)	2 (3%)	2 (3%)
Not referred to other guidelines	3 (18%)	14 (25%)	17 (23%)
Referred to other guidelines:[1]	14 (82%)	42 (75%)	56 (77%)
Reference in guidelines/through contact (n=73) to:			
Trial registration explicitly	12 (71%)	7 (13%)	19 (26%)
Trial registration implicitly	0 (0%)	29 (52%)	29 (40%)
Protocol adherence/amendment explicitly	12 (71%)	20 (36%)	32 (44%)
Protocol adherence/amendment implicitly	2 (12%)	24 (43%)	26 (36%)
Trial publication explicitly	14 (82%)	35 (63%)	49 (67%)
Trial publication implicitly	1 (6%)	13 (23%)	14 (19%)
Monitoring against guidelines explicitly	11 (65%)	36 (64%)	47 (64%)
Monitoring against guidelines implicitly	1 (6%)	11 (20%)	12 (16%)
Publication of negative studies explicitly	6 (35%)	5 (9%)	11 (15%)
Publication of negative studies implicitly	3 (18%)	24 (43%)	27 (37%)
Publication of negative outcomes explicitly	6 (35%)	5 (9%)	11 (15%)
Publication of negative outcomes implicitly	3 (18%)	24 (43%)	27 (37%)

1. Each charity/organisation may refer to one or more other guidelines
2. Limited contact meant that there was initial contact with the organisation/ charity to confirm that they did fund clinical trials and the maximum grant available was, but then no further information was forthcoming.
3. Explicitly means that the charities/organisations guidelines referred to one of the guideline domains (trial registration, protocol adherence, publication, or monitoring) within their guidelines.
4. Implicitly means that the charities/organisations guidelines referred to other guidelines such as CONSORT, ICH E6 guidelines etc which referred to the guideline domains.

REFERENCES:

1. Williamson PR and Gamble C. Identification and impact of outcome selection bias in meta-analysis. *Stat Med* 2005, 24: 1547-1561.
2.Copas J, Jackson D. A bound for publication bias based on the fraction of unpublished studies. Biometrics 2004; 60; 146-153.
3. Williamson PR and C Gamble. Application and investigation of a bound for outcome reporting bias. Trials 2007,8:9.
4 Dwan K, Gamble C, Williamson PR, Altman DG. Reporting of clinical trials: a review of funder's guidelines. Trials (submitted)