#### Item 15: RISK OF BIAS ACROSS STUDIES.

Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).

**Examples.** “For each trial we plotted the effect by the inverse of its standard error. The symmetry of such ‘funnel plots’ was assessed both visually, and formally with Egger's test, to see if the effect decreased with increasing sample size.”

“We assessed the possibility of publication bias by evaluating a funnel plot of the trial mean differences for asymmetry, which can result from the non publication of small trials with negative results…Because graphical evaluation can be subjective, we also conducted an adjusted rank correlation test and a regression asymmetry test as formal statistical tests for publication bias…We acknowledge that other factors, such as differences in trial quality or true study heterogeneity, could produce asymmetry in funnel plots.”

#### Explanation.

Reviewers should explore the possibility that the available data are biased. They may examine results from the available studies for clues that suggest there may be missing studies (publication bias) or missing data from the included studies (selective reporting bias) (see [Box 7](http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000100#pmed-1000100-box007)). Authors should report in detail any methods used to investigate possible bias across studies

It is difficult to assess whether within-study selective reporting is present in a systematic review. If a protocol of an individual study is available, the outcomes in the protocol and the published report can be compared. Even in the absence of a protocol, outcomes listed in the methods section of the published report can be compared with those for which results are presented . In only half of 196 trial reports describing comparisons of two drugs in arthritis were all the effect variables in the methods and results sections the same . In other cases, knowledge of the clinical area may suggest that it is likely that the outcome was measured even if it was not reported. For example, in a particular disease, if one of two linked outcomes is reported but the other is not, then one should question whether the latter has been selectively omitted .

Only 36% (76 of 212) of therapeutic systematic reviews published in November 2004 reported that study publication bias was considered, and only a quarter of those intended to carry out a formal assessment for that bias. Of 60 meta-analyses in 24 articles published in 2005 in which formal assessments were reported, most were based on fewer than ten studies; most displayed statistically significant heterogeneity; and many reviewers misinterpreted the results of the tests employed. A review of trials of antidepressants found that meta-analysis of only the published trials gave effect estimates 32% larger on average than when all trials sent to the drug agency were analyzed.