Reviewer’s report

Title: Randomized clinical trials with inadequate blinding report enhanced placebo effects for intervention groups and nocebo effects for placebo groups: a protocol for a meta-epidemiological study of PDE-5 inhibitors

Version: 1 Date: 23 August 2012

Reviewer: Levente Kriston

Reviewer’s report:

The authors should be appreciated for investigating the interesting question of consequences of inadequate blinding in randomized controlled trials. The protocol follows established standards (PRISMA) and documents the rationale, hypotheses, design, and planned statistical analysis in detail. I have only one major and a few minor comments that may contribute to improving the study protocol.

Major compulsory revision:

The primary analysis seems to be a comparison of within-group improvement (IIEF-EF change scores) of intervention and placebo groups, respectively, between studies with low and high/unclear risk of bias. It should be noted that this comparison is observational and risk of bias is likely to be associated with several variables that also influence within-group effects. Consequently, the comparison is likely to be confounded. For example, assume that within-group improvement in intervention groups in unblinded studies is larger than in blinded studies (this corresponds to the enhanced placebo effects hypothesis), but unblinded studies are also older, indicate other sources of bias, and include patients with more severe disease than the blinded studies.

How would such a result be interpreted? Is it the blinding or some of the other factors that is associated with the increased within-group effect? The authors are advised to address this point conceptually and frame some strategies to deal with possible confounding (e.g., testing whether confounding is present, adjustment through multivariable meta-regression if needed and possible, etc.). Correspondingly, phrases like “This review will test the hypothesis that unblinding in RCTS causes enhanced placebo effects...” (p. 5.) should be formulated more carefully, as causality cannot easily be shown in observational studies.

Minor essential revisions:

The title seems to be reporting a result that can be known only after the study was performed. A more neutral wording may be more appropriate.

Sources of funding and possible conflict of interest should be reported.

Discretionary revision:

The conceptual clarity of the protocol could be improved by carefully defining
terms like "placebo effect", "non-specific effects", etc. For example, on p. 13 it seems that the term "placebo effect" is used to describe response/improvement in the placebo group. However, improvement in placebo groups can only partly be attributed to receiving a placebo (placebo effect); other factors like spontaneous improvement may also be part of the placebo response. It is clear that the terminology in somewhat inconsistent in this research field, but readers would considerably profit from a definition of the essential terms.

**Declaration of competing interests:**

Reviewer conflict of interest: none.