II. DETAILS OF PROPOSED RESEARCH

Detailed outline of proposed research (see attached notes for guidance).

Title:

RM05/JH29: Dissemination bias in medical and health related research - an updated synthesis of empirical evidence and a critical assessment of available methods

Background

Synthesis of published research is becoming increasingly important in providing relevant and valid research evidence to clinical and health policy decision making. However, the validity of research synthesis based on published literature will be threatened if published studies comprise a biased selection of all studies that have been conducted.

A previous HTA monograph published in 2000 systematically reviewed studies that provided empirical evidence on publication and related biases, and studies that developed or tested methods for preventing, reducing, or detecting publication and related biases.[1] The review found evidence indicating that studies with significant or favourable results were more likely to be published, or were likely to be published earlier than those with non-significant results. There was limited and indirect evidence indicating the possibility of full publication bias, outcome reporting bias, duplicate publication bias, and language bias. The review identified little empirical evidence relating to the impact of publication and related biases on health policy, clinical decision making and the outcome of patient management. Considering that the spectrum of the accessibility of research results (dissemination profile) ranges from completely inaccessible to easily accessible, it was suggested that a single term “dissemination bias” could be used to denote all types of publication and related biases.[1]

In the previous HTA report, the available methods for dealing with dissemination biases were classified according to measures that could be taken before, during or after a literature review: to prevent publication bias before a literature review (eg, prospective registration of trials), to reduce or detect publication and related biases during a literature review (eg, locating grey literature or unpublished studies, and funnel plot related methods), and to minimise the impact of publication bias after a literature review (eg, confirmatory large scale trials, updating systematic reviews).[1] It was concluded that the ideal solution to publication bias is the prospective, universal registration of all studies at their inception. It was concluded, although debatable, that available statistical methods for detecting and adjusting publication bias should be mainly used for the purpose of sensitivity analysis.

Since the publication of the HTA review of publication and related biases, many new studies on publication and related biases have been published. For example, Egger et al (2003) provided further empirical evidence on publication bias, language bias, grey literature bias, and MEDLINE index bias,[2] and Moher et al (2003) evaluated language bias in meta-analyses of randomised controlled trials.[3] Recently, more convincing evidence on outcome reporting bias has been published.[4,5] The new empirical evidence may contradict or strengthen the empirical evidence included in the previous HTA report. Funnel plot and related statistical methods have been applied in new studies to collections of meta-analyses to estimate possible publication bias in systematic reviews.[6-8] There are also new published studies that investigated methods for dealing with publication bias (for example[9-11]).

Dubben and Beck-Bornholdt (2005) used the funnel plot approach, and found no evidence of publication bias in studies of publication bias.[12] They acknowledged that the analysis was handicapped by insufficient power (with only 26 included studies) and also by the diverse definitions of publication bias in the primary studies. However, Song et al pointed out that the study had other, more important, limitations so that dissemination bias of studies on publication bias could not be safely excluded.[13]

Purpose (aims, objectives)

1. To identify all relevant empirical studies published since 1998. Empirical studies are defined as those that provide empirical evidence on the existence, consequences, causes and/or risk factors of dissemination bias.

2. To identify all relevant methodological studies published since 1998. Methodological studies are those that have developed or investigated methods for preventing, reducing or detecting dissemination bias.

3. To categorise empirical and methodological studies identified according to a conceptual framework of dissemination profile, and to critically appraise studies that provided direct empirical evidence.

4. To synthesise findings from newly identified and previously included studies to enable us to assess whether each type of dissemination bias does exist, and if so the extent of the effect that it may have on results of systematic reviews and hence decision making.

5. To assess the possibility of dissemination bias of studies that provide empirical evidences on dissemination bias.

6. To assess the usefulness and limitations of available methods, and resources required to use these methods to combat each type of dissemination bias, through synthesis of the methodological studies.

7. To examine measures taken in a representative sample of published systematic reviews to prevent, reduce and detect different types of dissemination bias. We will include both narrative and quantitative (meta-analytic) systematic reviews that evaluated effect of healthcare interventions, systematic reviews that evaluated the accuracy of diagnostic tests, and systematic reviews of epidemiological studies that evaluated association of risk factors and health outcomes.

8. To bring together current evidence on the existence and scale of each type of dissemination bias, effects and costs of methods to combat these biases, and current use of these methods to create recommendations for reviewers, policy makers, health professionals and service users, and to disseminate these recommendations.

Investigation methods

The review contains three parts: (1) review of empirical and methodological studies; (2) an assessment of published systematic reviews; (3) synthesising all findings, providing and disseminating recommendations.

Part 1. Review of empirical and methodological studies

Methods used in the previous HTA report will be modified to identify and categorise relevant studies. We will adopt a new framework to categorise relevant studies, and important studies will be assessed using a more critical and structured approach. Details of the review methods are described below and in the Figure.

Criteria for inclusion and literature search strategies

A preliminary literature search indicated that there are a large number of potentially relevant studies in fields of medical and health related research, and searches in the area of social sciences produced few studies in the initial review, so we plan to focus on dissemination bias in health and related research. We will include studies that provide empirical evidence on the existence, consequences, causes, and/or risk factors of types of dissemination bias; and studies that develop or evaluate methods for preventing, reducing or detecting dissemination bias.

Literature searches for methodological studies are often difficult because of ill-defined boundaries and inappropriate indexing in commonly used bibliographic databases.[14] Our previous experience and initial searching suggests that the most productive and efficient methods include searching the Cochrane Methodology Register, references of retrieved articles and citation search of key studies.

We will search the **Cochrane Methodology Register** (CRM) and **MEDLINE** for relevant empirical and methodological studies published since 1998. We will compare studies identified from the MEDLINE and those identified from the Cochrane Methodology Register, to check the completeness and usefulness of the two bibliographic databases for methodological reviews. Key words used in the search of electronic databases will include: publication bias, dissemination bias, language bias, national bias, country bias, reporting bias, grey literature bias, conference/abstract bias, full publication bias, citation bias, time lag/delay bias, reference bias, selection bias, location bias, duplication or multiple publication bias, database bias, index bias, and file drawer. References (titles with or without abstracts) gathered by searching the CMR and MEDLINE will be assessed independently by two reviewers for inclusion or exclusion. Any disagreement will be discussed.

We will also search **EMBASE** (from 2005 to 2007, as EMBASE is searched for the Methodology Register, but we will ensure that we have included the most recent references), **Ahmed** (1998-2007), **Cinahl** (1998-2007), **PsychInfo** (1998-2007), **SIGLE** (1998-2007) and **Dissertation Abstracts** (1998-2007) for any additional relevant studies. Searching of EMBASE, Ahmed, Cinahl, PsychInfor, SIGLE, and Dissertation Abstracts will be conducted by one reviewer. **References of retrieved reviews and studies** will be examined by one reviewer to identify additional relevant studies, including any relevant studies published before 1998 but

missed in the previous HTA report. **Citations of the key studies** will also be searched. The literature search will not be restricted by publication language.

We have conducted a preliminary search of the Cochrane Methodology Register for relevant studies that published since 1998. According to titles (with or without abstracts) of identified references, there are a large number of possibly relevant studies (300-400, after excluding obvious duplicates). More than 200 references were empirical studies, including publication bias (n=26), publication of conference abstracts (n=66), outcome reporting bias (n=26), country or language bias (n=39), grey literature (n=13), time lag bias (n=15), causes of publication bias (n=16), citation bias (n=16). We found 58 studies of methods for dealing with publication bias, including 30 studies of statistical methods, 17 studies of literature search methods, and 11 studies of other methods (eg, trial registration or large scale confirmation trials).

Classification of identified studies

According to findings from our preliminary literature search, relevant studies are numerous in quantity and substantially diverse in quality. It is crucial to classify identified studies using a pre-specified structure to facilitate subsequent assessment and synthesis (Figure).

First , one reviewer will classify identified studies as (1) evidence studies or (2) methodological studies. Evidence studies are defined as studies that provide empirical evidence on the existence, extent, consequences, causes or risk factors of dissemination bias. Methodological studies are defined as those that develop or investigate methods for preventing, reducing or detecting dissemination bias. Some studies may be classified as both an evidence and a methods study.

Review of evidence studies

Evidence studies will be categorised into various types of dissemination bias, according to a framework of dissemination profile (that is, accessibility of research results): non-publication (never, or delayed); incomplete publication (e.g. biased outcome reporting, data dredged subgroup effects, biased full publication of conference abstracts); published but difficult to access (e.g. grey literature, language bias, database bias); other biased dissemination activities (e.g. citation bias, duplicate bias). It is possible that some studies may be included in more than one category.

Then evidence studies will be further separated into two groups: studies that provided direct evidence, and studies that provided indirect evidence. Direct evidence refers to data or observations that could be used to directly indicate dissemination bias, including admissions of bias on the part of those involved in the publication process, comparison of the results of published and unpublished studies, and the prospective or retrospective follow-up of dissemination profile of cohorts of studies. Indirect evidence refers to observations that could be explained indirectly by dissemination bias but other alternative explanations could not be excluded. For instance, a disproportionately high proportion of positive findings in the published literature might provide indirect evidence, as might larger effect sizes in smaller studies compared with larger studies.

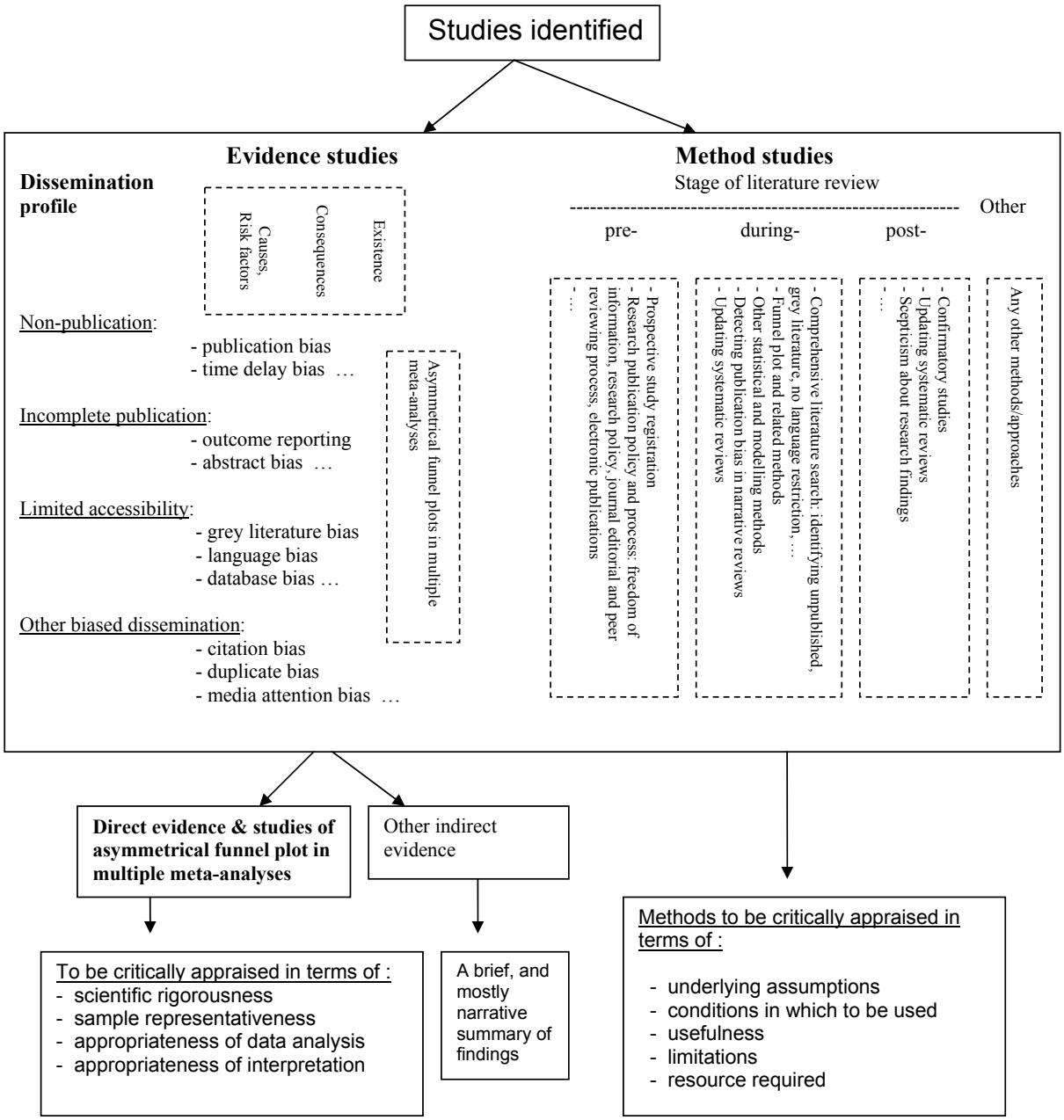
We will apply a checklist of quality assessment to critically appraise studies that provided direct empirical evidence and studies that assessed association between sample size and effects in multiple meta-analyses, with regard to scientific rigorousness, the sample's representativeness, and appropriateness of data analyses and interpretation. Topic specific items will be considered if judged appropriate for different types of bias. More details about the proposed quality assessment are described below.

- ***Scientific rigorousness***: We aim to detect potential threats to the validity of study results. For example, prospective studies are more valid than retrospective studies. Selection and inclusion of samples may be more or less biased, and whether assessments and judgements were independently duplicated.
- ***Generalisability***: It is important to consider whether results of studies could be generalisable to different fields of research, settings, and designs. For example, dissemination bias in randomised trials may not be similar to that in epidemiological studies.
- ***Appropriateness of data analysis***: We will assess whether the data analysis method is appropriate to address the objectives of the study.
- ***Appropriateness of interpretation***: Limitations of the study should be considered when results of a study were interpreted.

Relevant studies included in the previous HTA report[1] will also be critically appraised using the same checklist.

Using a standardised appraisal form (Appendix 1), categorisation of all evidence studies and critical appraisal of selected studies will be independently carried out by two reviewers. Disagreements will be resolved by discussion.

Figure. Classification of identified relevant studies



Assessment of dissemination bias in empirical evidence studies

In this review, we will assess whether dissemination bias is also a problem for studies that provide empirical evidence on dissemination bias. Results of included empirical evidence studies will be independently categorised by two reviewers as positive (significant dissemination bias), non-significant (no clear dissemination bias), or can't tell (see Appendix 1). Then we will examine the association of the results of empirical studies and studies' quality and dissemination profile (including time of publication, journal impact factor, number of citations after a given period of publication, and study's impact on guidelines/recommendations for systematic reviews).

Review of methodological studies

There may be multiple studies investigating the same method. Method studies will be categorised according to methods they investigated, to generate a list of available methods and corresponding studies identified. Then each method will be cross-classified from two aspects: (1) type of dissemination bias and (2) stage of literature review (see Figure). It is possible that the same method may be relevant to different types of dissemination bias or applicable to the different stage of a literature review. Using a standardised method classification sheet (Appendix 2), the review of method studies will be conducted by one reviewer and checked by a second reviewer. Disagreements will be resolved by discussion.

Based on findings of included studies, available methods will be critically appraised in terms of underlying assumptions, conditions under which the method could be used, usefulness, limitations, and resource required.

Presentation and summary of literature review findings

Data extracted from the included studies and results of critically appraisal will be presented in tables and described narratively. If appropriate, results from individual studies will be quantitatively pooled (for example, pooled odds ratio of full publication of conference abstracts with statistically significant results versus those with statistically non-significant results). Results of critical appraisal will be taken into consideration to interpret and explain findings from empirical and methodological studies. We will highlight whether findings from studies newly identified contradict or strengthen findings from studies included in the previous HTA report.

Part 2. Assessment of a sample of published systematic reviews

In the previous HTA report, 193 systematic reviews taken from the Database of Abstract of Reviews of Effectiveness (Centre for Reviews and Dissemination, University of York) were used to identify further evidence of dissemination bias and to illustrate the methods used in systematic reviews for dealing with publication bias. However, there are several shortcomings in the previous assessment. First, systematic reviews included in the DARE database might on average have better quality than those from the general bibliographic databases (such as MEDLINE) so that the representativeness of systematic reviews assessed in the previous HTA report may be questionable. Secondly, 91% of systematic reviews that evaluated the effectiveness of healthcare interventions and 9% that evaluated the accuracy of diagnostic technologies were not separately assessed. The problem of dissemination bias might be different between the two types of systematic reviews. Thirdly, systematic reviews of epidemiological studies of association between risk factors and health outcomes were not included in the previous HTA report.

To overcome these shortcomings, we plan to obtain a representative sample of systematic reviews from the general bibliographic database MEDLINE, including (1) systematic reviews of studies on effects of healthcare interventions, (2) systematic reviews of studies on accuracy of diagnostic tests, and (3) systematic reviews of epidemiological studies on association between risk factors and health outcomes.

> A preliminary search of MEDLINE using "systematic review" or "meta-analysis" (in titles or in abstracts) identified 2779 English-language references published in 2005. We examined the first 300 of the 2779 references and identified 109 systematic reviews that evaluated effects of healthcare interventions (including preventive interventions), 13 systematic reviews of studies of diagnostic tests, and 53 systematic reviews of epidemiological studies (including 18 systematic reviews of genetic studies). This preliminary exercise indicates that there are about 1009 systematic review of effects of health interventions, about 120 systematic reviews of diagnostic tests, and about 490 systematic reviews of epidemiological studies. The following approach is based on findings from this preliminary work.

Identifying and sampling systematic reviews

First, we will search MEDLINE for systematic reviews published in 2005. References identified from MEDLINE will be examined by one reviewer and categorised as systematic reviews of effects of healthcare interventions, systematic reviews of accuracy of diagnostic tests, or systematic reviews of epidemiological studies (genetic epidemiology or not). Then we will use computer-generated random numbers to obtain a random sample of 100 systematic reviews of effects of healthcare interventions, 50 systematic reviews of accuracy of diagnostic tests, and 100 systematic reviews of epidemiological studies (of which 50 will be reviews of genetic epidemiology studies) from all identified systematic reviews.

Extracting data from included systematic reviews

The data extraction from included systematic reviews will be independently conducted by two reviewers to collect the following information (see preliminary data extraction sheet in Appendix 3): type of review (effect, diagnostic, epidemiological), method of data synthesis (narrative or quantitative), whether the issue of publication bias was considered, whether unpublished studies or those published in non-English languages were searched for and included; methods used for dealing with publication bias; any evidence on the existence, extent and consequence of publication bias.

A checklist will also be applied independently by two reviewers to assess the overall quality of included systematic reviews (see Appendix 3). Any disagreements between the two reviewers will be resolved by discussion.

Analysing data from included systematic reviews

Data extracted from systematic reviews of effects of healthcare interventions, systematic reviews of accuracy of diagnostic test, and systematic reviews of epidemiological studies will be separately presented and compared. We will also examine the subgroup of genetic epidemiology reviews separately. We will compare findings from narrative systematic reviews and quantitative systematic reviews (meta-analyses). Systematic reviews of effects of healthcare interventions and systematic reviews of diagnostic accuracy published in 2005 will be compared with those included in the previous HTA report to examine whether the reporting and treatment of dissemination bias has improved over time.

Part 3. Synthesising findings from Part 1 and Part 2

Findings from Part 1 will illuminate the existence or otherwise, extent and potential impact on policy of different types of dissemination bias, and suggest a range of methods for dealing with such biases. Part 2 will provide findings about what actually happens in the practice of systematic reviews. Part 3 aims to compare findings from Part 1 and Part 2, and to identify gaps between empirical and methodological research on dissemination bias, and actual practice of systematic reviews (see the proposed summary table below). For example, considerable resource might be wasted in systematic reviews identifying, translating, and assessing studies published in languages other than English if evidence suggests that language bias is not a problem. Some statistical methods developed may have rarely been used in practice for various reasons (eg, too complicated or no additional advantages as compared with simple methods).

Bias category	Evidence of existence	Methods to combat this bias	Usefulness and limitations of the method	Resources required to use the method
Type of dissemination bias	Based on literature review	Based on literature review	Effect of the methods, as well as limitations, based on literature review and a sample of systematic reviews	Including time, staff, and costs. Based on literature review and experience

Main references

1. Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ. Publication and related biases. *Health Technol Assess* 2000;**4**:1-115.
2. Egger M, Juni P, Bartlett C, Holenstein F, Sterne J. How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study. *Health Technol Assess.* 2003;**7**:1-76.
3. Moher D, Pham B, Lawson ML, Klassen TP. The inclusion of reports of randomised trials published in languages other than English in systematic reviews. *Health Technology Assessment* 2003;**7**:1-90.
4. Chan AW, Hrobjartsson A, Haahr MT, Gotzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *Jama* 2004;**291**:2457-65.
5. Chan AW,.Altman DG. Identifying outcome reporting bias in randomised trials on PubMed: review of publications and survey of authors. *BMJ* 2005;**330**:753.
6. Song F, Khan KS, Dinnes J, Sutton AJ. Asymmetric funnel plots and publication bias in meta-analyses of diagnostic accuracy. *Int J Epidemiol* 2002;**31**:88-95.
7. Sterne J, Jüni P, Schulz K, Altman D, Bartlett C, Egger M. Statistical methods for assessing the influence of study characteristics on treatment effects in 'meta-epidemiological' research. *Statistics in Medicine* 2002;**21**:1513-24.
8. Sutton AJ, Duval SJ, Tweedie RL, Abrams KR, Jones DR. Empirical assessment of effect of publication bias on meta-analyses. *BMJ* 2000;**320**:1574-7.
9. Terrin N, Schmid CH, Lau J, Olkin I. Adjusting for publication bias in the presence of heterogeneity. *Stat.Med* 2003;**22**:2113-26.
10. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. *J Clin Epidemiol* 2005;**58**:882-93.
11. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of Two Methods to Detect Publication Bias in Meta-analysis. *JAMA: The Journal of the American Medical Association* 2006;**295**:676-80.
12. Dubben HH,.Beck-Bornholdt HP. Systematic review of publication bias in studies on publication bias. *BMJ* 2005.
13. Song F. Review of publication bias in studies on publication bias: studies on publication bias are probably susceptible to the bias they study. *BMJ* 2005;**331**:637-8.
14. Edwards S, Lilford RJ, Kiauka S. Different types of systematic review in health services research. In Black N, Brazier J, Fitzpatrick R, Reeves B, eds. *Health services research methods: a guide to best practice*, pp 255-9. London: BMJ Books, 1998.

Appendix 1. Data Extraction Sheet - Empirical Evidence Studies

Preliminary sheet, will be modified by pilot testing

Author (year): _____ Source: _____
Title: _____ Reviewer: _____

Study design & objectives:

Issues:

- ☐ Existence/identifying
- ☐ Causes/risk factors
- ☐ Consequence
- ☐ Other: _____

Categories:

- ☐ Non-publication
- ☐ Incomplete publication
- ☐ Limited accessibility
- ☐ Other: _____

Specific bias:

- ☐ Publication bias
- ☐ Grey literature bias
- ☐ Language bias
- ☐ Reporting bia
- ☐ Abstract bias
- ☐ Time delay bias
- ☐ Database index bias
- ☐ Citation bias
- ☐ Duplicate bias
- ☐ Media attention bias
- ☐ Other: _____

Areas:

- ☐ general health
- ☐ specific health (eg, obesity):
- ☐ other: _____

Study results: ☐ Significant/important bias ☐ Non-significant ☐ Can't tell
Details:

Original authors' conclusions:

Evidence: ☐ Direct ☐ Indirect
For indirect evidence, stop. For studies with direct evidence, continue:

Scientific rigorousness (hints: prospective or retrospective, sample selection bias)

Sample representativeness (hints: research field, participants, outcomes, interventions; study designs)

Appropriateness of data analysis (hints: consider objectives, available data and methods of data analysis)

Appropriateness of interpretations (hints: limitations of the study should be taken into consideration)

Overall study quality:

- ☐ High (hint: without considerable concern on study validity)
- ☐ Moderate (hint: with some concern on study validity)
- ☐ Low (hint: with considerable concern on study validity)
- ☐ Can't tell

Any other comments:

Appendix 2. Data Extraction Sheet – Methodological Studies

Preliminary sheet, will be modified by pilot testing

Author (year): _____ Source: _____ Reviewer: _____
Title: _____

Study design:

Study objectives:

☐ New method, ☐ Established method, ☐ Evidence of usefulness/limitations

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Methods:

- ☐ Study registration
- ☐ Funnel plot
- ☐ Updating reviews
- ☐ Research ethics/policy
- ☐ other: _____
- ☐ Literature search
- ☐ Statistical/modelling
- ☐ Publication process
- ☐ Confirmatory studies

Purpose:

☐ Preventing bias ☐ Reducing bias, ☐ Detecting bias, ☐ Adjusting bias,
☐ other: _____

Stage of literature review:

☐ Before literature review, ☐ In literature review, ☐ After literature review

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What dissemination bias the method is relevant:

- ☐ Publication bias
- ☐ Language bias
- ☐ Abstract bias
- ☐ Database index bias
- ☐ Duplicate bias
- ☐ Other: _____
- ☐ Grey literature bias
- ☐ Reporting bias
- ☐ Time delay bias
- ☐ Citation bias
- ☐ Media attention bias

Main findings and conclusions:

Resources required to use the method:

Reviewer's commentary (study's validity, scientific rigorousness, method's usefulness and limitations, any empirical evidence provided):

Appendix 3. Data Extraction Sheet – Systematic reviews

Preliminary sheet, will be modified by pilot testing

Author (year): _____ **Source:** _____ Reviewer:_____

Objectives: _____ ☐ Effectiveness/adverse effects ☐. Diagnostic ☐. Genetic epidemiology ☐. Other epidemiology

Type of reviews: ☐. Narrative ☐. Meta-analysis

Designs of included studies:
- ☐ RCTs/CCTs (Study= ; patients=)
- ☐ Diagnostic accuracy studies (Study= ; patients=)
- ☐ Epidemiological studies (Study= ; patients=)
- ☐ Other_____ (Study= ; patients=)

How were differences between studies investigated?

☐ NA ☐ Narrative ☐ Statistical ☐ Meta-regression ☐ Sensitivity/subgrouup ☐ Other

Authors' conclusion:

☐ Significant/positive: At least one intervention recommended; or sig. difference found between interventions.
☐ Non-sig./not important: No intervention is recommended, or no sig. differences found among interventions.
☐ Unclear: No able to judge; neither positive nor negative; lack of evidence.

Sources searched to identify studies:

☐ Not stated
☐ MEDLINE ☐ EMBASE ☐ Psychlit ☐ Cochrane ☐ Bibliographies
☐ Handsearch ☐ Experts/authors ☐ Company ☐ Proceedings
☐ Other: _____

Non-English language studies:

☐ Unclear
☐ Searched Yes No If yes, search methods:
☐ Identified Yes No How many?
☐ Included Yes No If included, a). for main analysis b). for sensitivity analysis?

Unpublished studies:

☐ Unclear
☐ Searched Yes No If yes, search methods:
☐ Identified Yes No How many?
☐ Included Yes No If included, a). for main analysis b). for sensitivity analysis?

Issue of publication bias discussed? ☐ No ☐ Yes

Methods used for dealing with publication bias:

- ☐ Not used
- ☐ Prospective register
- ☐ Funnel plot
- ☐ Egger's method
- ☐ Modelling
- ☐ Identify unpublished studies
- ☐ Fail-safe N
- ☐ Rank correlation
- ☐ Large scale trials
- ☐ Other: _____

Details:

Evidence on publication bias ☐ Not available ☐ Available, If available, details
(such as, results of published trials versus unpublished trials; or shape of Funnel plot or related methods)

Systematic review's overall quality:

1. Well defined review question	☐ Yes	☐ Partially	☐ No	☐ Can't tell
2. Identification of all relevant studies	☐ Yes	☐ Partially	☐ No	☐ Can't tell
3. Appropriate assessment of study quality	☐ Yes	☐ Partially	☐ No	☐ Can't tell
4. Reliable and accurate data extraction	☐ Yes	☐ Partially	☐ No	☐ Can't tell
5. Appropriate investigation of heterogeneity	☐ Yes	☐ Partially	☐ No	☐ Can't tell
6. Appropriate data synthesis	☐ Yes	☐ Partially	☐ No	☐ Can't tell
7. Appropriate interpretation of results	☐ Yes	☐ Partially	☐ No	☐ Can't tell