Systematic review and meta-analysis of randomised, placebo-controlled, trials of non-individualised homeopathic treatment: Study protocol

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INTRODUCTION

Homeopathy is a system of medicine that uses specific preparations of substances whose effects, when administered to healthy subjects, correspond to the manifestations of the disorder (symptoms, clinical signs, pathological states) in the individual patient.\(^a\)

It is believed that the effect is to stimulate a healing response in the patient.\(^1\) Homeopathic medicines are also used in other therapeutic approaches such as anthroposophic medicine\(^b\) and homotoxicology.\(^c\)

There are several distinct forms of homeopathy, the main types being ‘individualised’ homeopathy, ‘clinical’ homeopathy, ‘complex’ homeopathy, and isopathy. In individualised homeopathy – as originally defined by its founder, Samuel Hahnemann – typically a single homeopathic medicine is selected on the basis of the ‘total symptom picture’ of a patient, including his/her mental, general and constitutional type.

In clinical homeopathy, one or more homeopathic medicines are administered for standard clinical situations or conventional diagnoses. In complex homeopathy, several homeopathic medicines are combined in a fixed (‘complex’) formulation. Isopathy is the use of homeopathic dilutions from the causative agent of the disease itself, or from a product of the disease process, to treat the condition;\(^1\) isopathic medicines include organisms and allergens prescribed on a basis different from individualised homeopathic prescribing in the classical sense.

A previous review protocol focused on individualised homeopathy.\(^2\) The current protocol focuses solely on non-individualised homeopathy, which includes all interventions that have involved the same, specified, homeopathic medication being allocated to each and every participant in the clinical trial: clinical homeopathy, complex homeopathy or isopathy.

The nature of the research evidence in homeopathy has long been a matter of scientific debate. Recently, however, the argument has begun to reach the point of impasse. Homeopathy’s advocates tend to deny the worth of placebo-controlled randomised controlled trials (RCTs),\(^e,g,3\) whilst its critics dispute the therapy’s scientific rationale and/or the existence of any positive findings in the research literature.\(^4\) There is a need to temper these divergent opinions by considering the existing evidence based on a complete and objective assessment of the facts, including the nature and the quality of the research evidence, with an additional requirement to reflect the distinction between individualised and non-individualised homeopathy.

The pinnacle of the hierarchy of clinical research publications (‘type I’ evidence) comprises systematic reviews (SRs), of which several have been published on RCTs in homeopathy. Some SRs have focused on specific medical conditions, with conclusions that are variously positive,\(^e,g,5,6,7\) negative\(^e,g,8,9,10\) or non-conclusive.\(^e,g,11,12,13\)

Five ‘global’, or ‘comprehensive’, SRs have examined the RCT research literature on homeopathy as a whole, including the broad spectrum of medical conditions that have been researched, and by all forms of homeopathy. Four of these SRs reached the conclusion that, overall, the homeopathic intervention probably differs from placebo.\(^14,15,16,17\) When Linde and colleagues carried out a sensitivity analysis on the data that informed their 1997 global SR based on trial quality, the observed effects were substantially reduced, though homeopathy remained significantly more effective than placebo until all but the final 5 highest-quality trials out of 89 were excluded from the analysis.\(^18\) Neither of Linde’s reviews found sufficient evidence to draw conclusions about the ‘efficacy of homeopathy’ for any specific medical condition. The SR by Shang et al, published in 2005, concluded that there was “weak...
evidence for a specific effect of homoeopathic remedies…compatible with the notion that the clinical effects of homoeopathy are placebo effects.\textsuperscript{6} Shang’s methods and conclusions have subsequently been criticised.\textsuperscript{20}

One other global SR considered solely RCTs that were controlled by an intervention other than placebo (OTP).\textsuperscript{21}

Previous reviews contain two key limitations:

1. Global SRs have typically assessed the RCT findings of all forms of homoeopathy (individualised, clinical, complex, isopathy) together, as if they are the same intervention. As discussed above, there are marked differences in the nature of the therapeutic interventions, and the distinction between them is important, for it affects the interpretation of the research findings in each case. Placebo-controlled RCTs of a particular homoeopathic medicine (non-individualised homoeopathy) allows conclusions about that medicine’s efficacy for the clinical condition investigated in the cohort of subjects concerned; in a similarly controlled trial of individualised homoeopathy, however, such ‘efficacy’ applies to the range of homoeopathic medicines prescribed to the individuals included in the trial. Moreover, in studies of individualised homoeopathy, ‘efficacy’ is potentially masked by a significant effect of the in-depth homoeopathic consultation that is common to the test group and the control group.\textsuperscript{22,23}

2. Though not systematic reviews, some accounts of homoeopathy research, including our own,\textsuperscript{24} have summarised the findings of RCTs using ‘vote counting’, whereby each trial is designated ‘positive’ or ‘negative’ or ‘non-conclusive’ based on its most important statistical findings. While such an approach has the advantage that it overcomes problems associated with heterogeneous groups of trials and reflects the condition-specific nature of the research evidence, it does not grapple with the key matter of magnitude of treatment effect. Nor does this method reflect a single ‘main outcome measure’ of each trial in a systematic way. There is a need to quantify treatment effects of homoeopathic interventions for given medical conditions, and the use of a systematically and consistently determined ‘main outcome measure’ per RCT would be helpful in focusing on matters of greatest clinical importance.

Four additional matters also need to be addressed:

a. Nearly all SRs to date have examined RCTs of treatment and of prophylaxis indistinguishably. It is not clear, however, whether the homeopathic rationale for each approach is the same: an individual person’s symptoms are the target of homeopathic treatment but other rationales, including anticipated symptoms, provide the basis for homeopathic prophylaxis.

b. The internal validity of a trial (the extent to which the design, conduct and analysis has minimised or avoided biases in its comparison of treatments\textsuperscript{25,26}) reflects the quality of its methods of randomisation, blinding, and a number of other key attributes. Some comprehensive reviews have used a numerical system such as the Jadad score\textsuperscript{27} to assess RCT quality in homoeopathy. More modern systems of assessment, such as that adopted by Shang et al.\textsuperscript{19} do not allocate single overall scores; instead, they adopt qualitative standards against which a trial’s internal validity is judged as having low, uncertain or high risk of bias.\textsuperscript{28} Neither system is intended to enable the identification of finer distinctions in degree of quality.

c. Concerns about research quality in homoeopathy go beyond its internal validity.\textsuperscript{29} Previous SRs of homoeopathy have failed to assess the quality of the homoeopathic intervention itself (i.e. the model validity\textsuperscript{30} of the original RCT). Without such additional assessment, conclusions about trial quality in homoeopathy are severely limited. We have devised a method to assess the model validity of clinical trials of homoeopathic treatment.\textsuperscript{31}

d. Few of the previous SRs in homoeopathy have made the distinction between substantive and minor research articles or between the peer-reviewed and non-peer-reviewed research literature: a research dissertation or an abstract presented at a conference, for example, has usually been given a status equal to that of a paper published in a high-ranking academic journal.\textsuperscript{e.g. 16,19} Peer review is an important, though by no means flawless, surrogate for
research quality: for some, it is “an essential arbiter of scientific quality” and “information about the status of research results is as important as the findings themselves”. SRs in homeopathy need to reflect, *a priori*, the distinction between the substantive peer-reviewed journal literature and other, lesser, categories of research evidence.

**Aim of the study**

The aim of this SR/meta-analysis is to examine the efficacy of the homeopathic medicines that have been used in the context of placebo-controlled trials of non-individualised homeopathic treatment. We include RCTs of adults and/or children, and for each medical condition that has been the subject of such research. A single ‘main outcome measure’ is identified per RCT.

Reflecting matters of study quality (including internal validity and model validity), the present study will focus on the two key issues outlined above: (1) in a global meta-analysis, to ascertain if non-individualised homeopathic treatment can be distinguished from the same form of treatment but using placebo medicines; (2) in condition-specific meta-analyses, to quantify any effect of non-individualised homeopathic treatment for medical conditions in which there is >1 eligible placebo-controlled RCT.

**METHODS**

**Eligibility criteria, information sources, study selection and data collection**

The eligible research literature has been identified, to *PRISMA* standards, in a previous paper by our group. From 489 potentially eligible records found up to and including December 2011, 263 fulfilled the criteria of a substantive, non-repeat, journal paper that reported a randomised and controlled study of homeopathy.

Ninety-six of those records reported a placebo-controlled RCT of non-individualised homeopathic treatment and were published in the peer-reviewed journal literature. **Figure 1** is based on our original *PRISMA* flowchart, in which specific exclusion criteria have been applied, as appropriate, to the 96 records:

- Trials of homeopathic prophylaxis
- Trials with crossover design
- Research using radionically prepared ‘homeopathic’ medicines
- The tested intervention is homeopathy combined with other (complementary or conventional) medicine or therapy. (This study design is distinct from that in which concomitant conventional medication remains ongoing in the subjects of each study group)
- Placebo-controlled trial explicitly designated “single-blinded” (i.e. patient-blinded)
- Other specified reason.

Twenty-nine records met those exclusion criteria, leaving 67 that are eligible for SR/meta-analysis – see Figure 1.

All 67 records in this final group will be included in the formal SR, together with relevant records identified in a supplementary search of the literature up to the end of 2013. Any record whose main outcome measurement is not extractable (see below) will be ineligible for meta-analysis.

Only published data will be eligible for analysis. Because it is recognised that contacting the original authors of RCTs may lead to overly positive answers, the authors of eligible papers will not be approached for clarification on unclear or missing facets of any of their methods or results; however, original authors’ cross-reference to their previously published study methods will be followed up and taken into account as necessary. For trials with more than two study groups, only the data concerning comparisons

\[d\] Prophylaxis: A trial on healthy individuals in which the homeopathic intervention aims to prevent the occurrence of disease *de novo* (i.e. ‘primary prevention’). Studies using a strategy of primary prevention, with subsequent treatment as necessary, are categorised ‘treatment’ trials.

\[e\] In due course, crossover trials will be appraised separately from those of parallel-group design.
between non-individualised homeopathy and placebo will be extracted from the 67 papers.

**Study characteristics and data items**

Two reviewers independently will extract relevant data using a standard data recording approach, in spreadsheet format (Microsoft Excel). The data extracted per trial will include, as appropriate: demographics of participants (gender, age range, medical condition); study setting; potency or potencies of homeopathic medicines; whether a pilot trial; ‘main outcome measure’ (see below) and measured end-point; other outcome measures reported; funding source/s. The statistical items noted will be: whether power calculation carried out; whether intention-to-treat (ITT) analysis; sample size and missing data for each intervention group.

**Identification of ‘main outcome measure’ per RCT:**

For each trial, and for the purposes of risk-of-bias assessment, we shall identify a single ‘main outcome measure’ using a refinement of the approaches adopted by Linde et al. and by Shang et al. Each trial’s ‘main outcome measure’ will be identified based on the following hierarchical ranking order (consistent with the WHO ICF Classification System for Levels of Functioning Linked to Health Condition):[f]

- Mortality
- Morbidity
  - Treatment failure
  - Pathology; symptoms of disease
- Health impairment (loss/abnormality of function, incl. presence of pain)
- Limitation of activity (disability, incl. days off work/school because of ill health)
- Restriction of participation (quality of life)
- Surrogate outcome (e.g. blood test data, bone mineral density).

We shall follow the WHO ICF system regardless of what measure may have been identified by the investigators as their ‘primary outcome’. In cases where, in the judgment of the reviewers, there are two or more outcome measures of equal greatest importance within the WHO ICF rank order, the designated ‘main outcome measure’ will be selected randomly from those two or more options using the toss of coins or dice.

Unless otherwise indicated, the single end-point (measured from the start of the intervention) associated with the designated ‘main outcome measure’ will be taken as the last follow-up at which data are reported for that outcome.

**Risk of bias in individual studies**

Using the standard criteria defined by Cochrane, the extraction of information will enable appraisal of ‘low risk’, ‘uncertain risk’ or ‘high risk’ of bias with respect to: (Domain I) the methods used to generate the random sequence; (Domain II) the method of allocation concealment used to implement the random sequence; (Domain IIIa) the blinding of participants and study personnel; (Domain IIIb) the blinding of outcome assessors;[8] (Domain IV) whether all the randomised patients are accounted for in the analysis; (Domain V) whether there is evidence of selective outcome reporting; (Domain VI) whether there is evidence of other bias.

Two assessors will mutually scrutinise and compare their judgments, with discrepancies between them resolved by consensus discussion. A risk-of-bias summary table will be produced, characterising each of the 67 eligible records. For Domain IV, a trial will automatically be regarded as no better than ‘unclear’ if there is greater than 20% participant attrition rate, irrespective of whether ITT analysis has been carried out. Domain V will automatically be designated ‘high risk of balance’ if its main outcome measure cannot be extracted to enable calculation of ‘treatment effect’ (see below). Assessment of Domain VI will explicitly include appraisal of data imbalance at baseline; the source of any research sponsorship will be taken into account for subgroup analysis (see below), not in risk-of-bias assessment per se.

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[8] Domains are designated IIIa and IIIb to reflect their common focus on matters connected with blinding.
**Rating of trials for risk of bias (internal validity):**

By the standard Cochrane approach, each trial is designated: low risk of bias for all key domains; uncertain risk of bias for one or more key domains; high risk of bias for one or more key domains. This three-tiered rating style will be insufficient to enable meaningful sensitivity analysis of trial quality in meta-analysis (see also below). We therefore propose to adopt a novel method of nomenclature, based on the Cochrane approach, for rating risk-of-bias characteristics across all domains per trial:

\[ A = \text{Low risk of bias in all seven domains.} \]
\[ B_x = \text{Uncertain risk of bias in } x \text{ domains; low risk of bias in all other domains.} \]
\[ C_y.x = \text{High risk of bias in } y \text{ domains; uncertain risk of bias in } x \text{ domains; low risk of bias in all other domains.} \]

This approach yields a total of 36 sub-tiers of risk of bias (see Table 1).

We designate a ‘B1’-rated trial reliable evidence if the sole uncertainty in its risk of bias was for one of domains IV, V or VI (i.e. it was required to be judged free of bias for each of domains I, II, IIIA and IIIB).

**Assessment of model validity**

We shall assess the model validity of eligible RCTs using our criterion-based method of appraisal, which harmonises both with the Cochrane risk-of-bias approach and our quality rating system. The primary model validity findings will be published separately from the paper that reports risk-of-bias assessment and meta-analysis.

**Summary measures for ‘main outcome’**

A ‘summary of findings’ table (containing relevant raw data from the trials) and a summary risk-of-bias table will be prepared.

For the 67 records of non-individualised homeopathy, we shall examine: (1) overall treatment effect; (2) disease-specific treatment effects. In both these categories, ‘treatment effect’ will be taken as the difference between the homeopathy and the placebo groups at our pre-determined end-point of the trial:

- For **dichotomous measures**: odds ratio (OR), with 95% CI;\(^6\)
- For **continuous measures**: standardised mean difference (SMD), calculated using the inverse variance method, with 95% CI.

In trials where the main outcome measure is a continuous variable, and where there are insufficient data presented to identify the mean and/or the SD per group at the defined end-point, the necessary data will be calculated or estimated, if possible, by imputing relevant other data (e.g. SD at baseline) from the same study.\(^5\)

If the original paper does not provide or inform adequate data on the selected ‘main outcome measure’ to enable extraction or calculation of mean and/or SD, we shall describe the selected main outcome as ‘not estimable’: an alternative, estimable, outcome will not be sought.

Consistent with the above, the following studies will be excluded from meta-analysis:

- Those that present non-parametric data only, and where there is no information that enables the data distribution to be assessed;
- Those from which the necessary data cannot be extracted (not provided or uninterpretable).

**Synthesis of results**

1) **Overall ‘treatment effect’ of non-individualised homeopathy**

The ‘main outcome’ data will be synthesised for meta-analysis in two separate sets of studies as appropriate: (1) using the odds ratio (OR) of each trial; (2) using the SMD of each trial.\(^6\) A summary measure of ‘treatment effect’ will be identified across all included studies for each of those two sets. The ‘random effects’ statistical model will be used rather than the ‘fixed effects’ model.\(^5\)

\(^{h}\) If the main outcome is reported as data in more than two categories, these will be dichotomised as appropriate.
Illustration of findings will be by means of forest plot.

Data from the two sets of studies will then also be combined into a single forest plot, re-expressing SMDs by transformation to OR, using an approximation method proposed by Chinn and recommended by Cochrane.

2) Disease-specific treatment effect of non-individualised homeopathy

For each specific medical condition for which there is >1 RCT with extractable main outcome, the data will be synthesised using meta-analysis methods. For each of these particular analyses, a single ‘main outcome measure’ will be designated, if possible, for each medical condition, and reflecting the WHO classification ranking approach (see above). A summary estimate of treatment effect per condition, with 95% CI and P value, will be illustrated by means of forest plot. The ‘random effects’ statistical model will again be used.

3) Measures of consistency:

Asymmetry of each of the above forest plots will be determined from visual inspection of the associated funnel plot graph and by interpretation of the asymmetry (heterogeneity) statistic, $I^2$.

Risk of bias, and other assessments of quality, across studies

An assessment of the overall quality of the evidence (based on the GRADE approach) will take into consideration, with equal weight, the evaluations of risk of bias and of model validity across the range of RCTs concerned.

The ratings obtained for risk of bias and for model validity (see Table 1) may also be used to ascertain the degree of correlation between them (Spearman’s rank correlation coefficient).

This across-study facet of the review work will be the subject of a separate paper from the two that report, respectively, the SR/meta-analysis results and the primary model validity assessments.

Additional analyses on overall ‘treatment effect’ of non-individualised homeopathy (specified prior to data analysis)

Sensitivity analyses:

We shall carry out sensitivity analysis by the trials’ risk-of-bias ratings, and reflecting the extent of reliable evidence.

The sensitivity analysis will address the question: “Do the conclusions of the excluded (lower-quality) papers complement or contradict the results from the meta-analysis?”

Sub-group analyses:

Comparative forest plots are planned as follows:

- Whether or not the study is included in previous comprehensive SR/meta-analysis of homeopathy RCTs;
- Pilot (or ‘preliminary’ or feasibility) study, as defined by the original authors;
- Sample size;
- Potency/potencies of homeopathic medicines used.
- Whether or not the research sponsor is an organisation (e.g. homeopathic pharmacy) that potentially has vested interest in the trial findings.
- Whether the medical condition studied is ‘acute’ or ‘chronic’ (prior duration of symptoms, $\leq$ 3 months).
**FIGURE 1: Details of numbered references as per original PRISMA flowchart**

96 records of non-individualised homeopathy:

<table>
<thead>
<tr>
<th>Prophylaxis:</th>
<th>Single-blinded:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A58: Brydak</td>
<td>A73: Garrett</td>
</tr>
<tr>
<td>A98: Mokkapatti</td>
<td>A99: Mousavi</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Crossover:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A46: Baillargeon</td>
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<tr>
<td>A66: Fisher</td>
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<tr>
<td>A77: Heusser</td>
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<tr>
<td>A90: La Pine</td>
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<tr>
<td>A114: Saruggia</td>
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<tr>
<td>A118: Shipley</td>
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<tr>
<td>A119: Simpson</td>
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<tr>
<td>A121: Smith</td>
</tr>
<tr>
<td>A129: von Hagens</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Lab. experiment:</th>
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</thead>
<tbody>
<tr>
<td>A46: Baillargeon</td>
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<tr>
<td>A66: Fisher</td>
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<tr>
<td>A77: Heusser</td>
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<td>A90: La Pine</td>
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<td>A119: Simpson</td>
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<td>A121: Smith</td>
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<td>A58: Brydak</td>
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<td>A98: Mokkapatti</td>
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</tbody>
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<table>
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<tr>
<th>Other:</th>
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</thead>
<tbody>
<tr>
<td>A45: Adkison</td>
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<tr>
<td>A57: Brinkhaus</td>
</tr>
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<td>A65: Ferrara</td>
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<td>A87: Kneis</td>
</tr>
<tr>
<td>A97: Merklinger</td>
</tr>
<tr>
<td>A102: Pach</td>
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67 records of non-individualised homeopathy:

<table>
<thead>
<tr>
<th>Combined therapy:</th>
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</thead>
<tbody>
<tr>
<td>A54: Bernstein</td>
</tr>
<tr>
<td>A71: Furuta</td>
</tr>
<tr>
<td>A72: Furuta</td>
</tr>
<tr>
<td>A115: Schirmer</td>
</tr>
</tbody>
</table>

| A42: Aabel | A89: Kotlus |
| A43: Aabel | A91: Labrecque |
| A44: Aabel | A92: Leaman |
| A47: Baker | A93: Leaman |
| A48: Balzarini | A94: Lipman |
| A49: Beer | A95: McCutcheon |
| A50: Belon | A100: Oberbaum |
| A51: Belon | A101: Oberbaum |
| A52: Bergmann | A103: Padilha |
| A53: Bernstein | A104: Papp |
| A55: Berrebi | A105: Paris |
| A56: Bignamini | A108: Rahlfs |
| A59: Cialdella | A109: Rahlfs |
| A60: Clark | A110: Ramelet |
| A61: Cornu | A111: Reilly |
| A62: Diefenbach | A112: Reilly |
| A63: Ernst | A113: Robertson |
| A64: Ferley | A116: Schmidt |
| A67: Frass | A117: Seeley |
| A68: Freitas | A120: Singer |
| A69: Friese | A122: Stevinson |
| A70: Friese | A123: Taylor |
| A74: Gerhard | A125: Tveiten |
| A75: GRECHO | A126: Tveiten |
| A76: Hart | A128: Vickers |
| A78: Hitzenberger | A130: Weiser |
| A79: Hofmeyer | A131: Wiesenauer |
| A80: Jacobs | A132: Wiesenauer |
| A81: Jacobs | A133: Wiesenauer |
| A83: Kaziro | A134: Wiesenauer |
| A84: Khuda-Bukhsh | A135: Wiesenauer |
| A85: Khuda-Bukhsh | A136: Wolf |
| A86: Kim | A137: Zabolotnyi |
| A88: Kolia-Adam |
References for Figure 1:


TABLE 1: Extended Cochrane rating for Risk of Bias (RoB)

*A: Low RoB for all domains;*
*B: Uncertain RoB for designated number of domains;*
*C: High RoB for designated number of domains; uncertain RoB for designated number of domains.*

1) A: ‘Low RoB’ in all 7 domains

2) B1: ‘Uncertain RoB’ in any 1 domain, ‘Low RoB’ in others

3) B2: ‘Uncertain RoB’ in any 2 domains, ‘Low RoB’ in others

4) B3: ‘Uncertain RoB’ in any 3 domains, ‘Low RoB’ in others

5) B4: ‘Uncertain RoB’ in any 4 domains, ‘Low RoB’ in others

6) B5: ‘Uncertain RoB’ in any 5 domains, ‘Low RoB’ in others

7) B6: ‘Uncertain RoB’ in any 6 domains, ‘Low RoB’ in other

8) B7: ‘Uncertain RoB’ in all 7 domains

9) C1.0: ‘High RoB’ in any 1 domain, ‘Low RoB’ in all others

10) C1.1: ‘High RoB’ in any 1 domain, ‘Uncertain RoB’ in any 1 domain, ‘Low RoB’ in others

11) C1.2: ‘High RoB’ in any 1 domain, ‘Uncertain RoB’ in any 2 domains, ‘Low RoB’ in others

12) C1.3: ‘High RoB’ in any 1 domain, ‘Uncertain RoB’ in any 3 domains, ‘Low RoB’ in others

13) C1.4: ‘High RoB’ in any 1 domain, ‘Uncertain RoB’ in any 4 domains, ‘Low RoB’ in others

14) C1.5: ‘High RoB’ 1 domain, ‘Uncertain RoB’ in any 5 domains, ‘Low RoB’ in other

15) C1.6: ‘High RoB’ 1 domain, ‘Uncertain RoB’ in all 6 others

16) C2.0: ‘High RoB’ in any 2 domains, ‘Low RoB’ in all others

17) C2.1: ‘High RoB’ in any 2 domains, ‘Uncertain RoB’ in any 1 domain, ‘Low RoB’ in others

18) C2.2: ‘High RoB’ in any 2 domains, ‘Uncertain RoB’ in any 2 domains, ‘Low RoB’ in others

19) C2.3: ‘High RoB’ in any 2 domains, ‘Uncertain RoB’ in any 3 domains, ‘Low RoB’ in others

20) C2.4: ‘High RoB’ in any 2 domains, ‘Uncertain RoB’ in any 4 domains, ‘Low RoB’ in other

21) C2.5: ‘High RoB’ in any 2 domains, ‘Uncertain RoB’ in all 5 others

22) C3.0: ‘High RoB’ in any 3 domains, ‘Low RoB’ in all others

23) C3.1: ‘High RoB’ in any 3 domains, ‘Uncertain RoB’ in any 1 domain, ‘Low RoB’ in others

24) C3.2: ‘High RoB’ in any 3 domains, ‘Uncertain RoB’ in any 2 domains, ‘Low RoB’ in others

25) C3.3: ‘High RoB’ in any 3 domains, ‘Uncertain RoB’ in any 3 domains, ‘Low RoB’ in other

26) C3.4: ‘High RoB’ in any 3 domains, ‘Uncertain RoB’ in all 4 others

27) C4.0: ‘High RoB’ in any 4 domains, ‘Low RoB’ in all others

28) C4.1: ‘High RoB’ in any 4 domains, ‘Uncertain RoB’ in any 1 domain, ‘Low RoB’ in others

29) C4.2: ‘High RoB’ in any 4 domains, ‘Uncertain RoB’ in any 2 domains, ‘Low RoB’ in other

30) C4.3: ‘High RoB’ in any 4 domains, ‘Uncertain RoB’ in all 3 others

31) C5.0: ‘High RoB’ in any 5 domains, ‘Low RoB’ in both others

32) C5.1: ‘High RoB’ in any 5 domains, ‘Uncertain RoB’ in any 1 domain, ‘Low RoB’ in other

33) C5.2: ‘High RoB’ in any 5 domains, ‘Uncertain RoB’ in both others

34) C6.0: ‘High RoB’ in any 6 domains, ‘Low RoB’ in other

35) C6.1: ‘High RoB’ in any 6 domains, ‘Uncertain RoB’ in other

36) C7.0: ‘High RoB’ in all 7 domains.
REFERENCES


