Efficacy of homeopathic treatment: Systematic review of meta-analyses of randomised placebo-controlled homeopathy trials for any indication (SMAP-HOM): Protocol

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Table of content

ADMINISTRATIVE INFORMATION

The structure of this protocol corresponds to the structure of the PRISMA-P checklist (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) (1).

1. Title

1.1 Identification

This is a protocol for a systematic review

1.2 Update

Not applicable, this is not an update

1.3 Name of the systematic review

Efficacy of homeopathic treatment: systematic review of meta-analyses of randomised placebo-controlled homeopathy trials for any indication (SMAP-HOM).

1.4 Date of this document

25 November 2020

2. Registration

The protocol record was submitted for registration in the PROSPERO registry (International prospective register of systematic reviews; https://www.crd.york.ac.uk/prospero/), on 25 November 2020, ID#209661.

3. Authors

3.1 Contact information

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3.2 Author contributions

3.2.A General information

The protocol for this systematic review was conceived and drafted by HJH and HK at IFAEMM. Two authors from other institutions (KvA, DSR) were invited to participate in the project, in order to provide subject-specific expertise in homeopathy (theory, clinical use, empirical assessment), which was not available at IFAEMM.

3.2.B Contributions from each author

HJH: protocol drafting and revision, literature screening, eligibility assessment of full text reports, data extraction, assessment of risk of bias in the meta-analyses, data synthesis, interpretation of results, manuscript drafting, guarantor

AG: protocol revision, literature screening, data extraction, data management and analyses, data synthesis, manuscript drafting

KvA: protocol revision, interpretation of results, manuscript drafting

DSR: protocol revision, interpretation of results, manuscript drafting,

GSK: protocol revision, eligibility assessment of full text reports, assessment of risk of bias in the meta-analyses, interpretation of results, manuscript drafting

HK: protocol drafting and revision, eligibility assessment of full text reports, assessment of risk of bias in the meta-analyses, interpretation of results, manuscript drafting

4. Amendments

Not applicable, this is not an update.

5. Financial support

5.1 Sources

Three foundations provide funding specifically for this systematic review:

- Christophorus-Stiftung, Kernerplatz 2, 70182 Stuttgart, Germany (grant # 393 CST, date 22 May 2020)
- Stiftung Marion Meyenburg, Heilwigstr. 35, 20249 Hamburg, Germany (date 24 Sep 2020)
- Dr. Hauschka-Stiftung, Bosslerweg 2, 73087 Bad Boll/Eckwälden, Germany (date 16 Nov 2020)

One foundation provides general funding for IFAEMM (cf. section 3.1A) in the period 2020-2022:

- Software-AG Stiftung, Am Eichwäldchen 6, 64297 Darmstadt, Germany (grant # SE-P 13544, date 9 Dec 2019).

5.2 Sponsors

Not applicable. See 5.1

5.3 Role of sponsor or funder

The funders had no influence on the writing of this protocol and will have no influence on the planning, conduct and publication of this systematic review.

INTRODUCTION

6. Background and Rationale

Homeopathy is a therapy system widely used in Europe, India and other countries (2). Core features of homeopathy include *drug provings* (observation of symptoms occurring in healthy persons exposed to substances of mineral, botanical or zoological origin), *simile principle* (similarity between symptom patterns in drug provings and the symptoms to be treated with the same substance), and *potentization* (successive dilution of the homeopathic substance, with each dilution step involving repeated shaking of liquids or grinding of solids into lactose, respectively) (3).

Clinical effects of homeopathic treatment have been investigated in several hundred randomised controlled trials (4) and in systematic reviews thereof. Among the systematic reviews, two contrasting approaches can be discerned:

One approach is to focus on a specific indication (e.g. depression (5), acute respiratory tract infections in children (6)), while often including open-label trials and observational studies, with data synthesis grouped by design, yielding information about homeopathy in patient care.

Another, opposite approach is to include all indications, while restricting study designs to placebo-controlled trials, and aggregating results in a meta-analysis, yielding information about specific effects of "homeopathy" as such (i.e. pooling trials of all homeopathic remedies, e.g. (7)) or of major homeopathy types (e.g. all trials of individualised homeopathy (8)) beyond placebo. In the period 1997-2017, at least six meta-analyses of placebo controlled homeopathy trials for any condition have been published (7-12). These analyses have differed in their methods for trial inclusion, data synthesis and assessment of risk of bias, as well as their results and conclusions. During this period, there have been substantial developments of methodology and quality standards for meta-analyses and other systematic reviews (13-16), including systematic reviews of systematic reviews, also called overviews or umbrella reviews (17-19). To our knowledge, a formal systematic review of meta-analyses of randomised placebo-controlled homeopathy trials for any condition has not been performed. This is a protocol for such a review.

7. Objectives

7.1 Research questions

<u>7.1A Efficacy of homeopathy beyond placebo</u>

Does homeopathic treatment have positive effects beyond placebo in meta-analyses of randomised placebo-controlled trials for any condition?

<u>7.1B Common effect</u>

Do the findings from these meta-analyses support the notion of a common effect (or absence thereof) across different types of homeopathic treatments (e.g. individualised/classical homeopathy, complex homeopathy) and across different types of indications (e.g. acute, chronic)…

7.1B1: …in the main analysis?

7.1B2: …in subgroup analyses of the respective meta-analysis or meta-analysis program?

7.2 PICO

<u>Participants</u>: Any type of patients with any type of existing symptoms or diseases

<u>Interventions</u>: Prevention or treatment with homeopathic medicinal products, optional homeopathic case-taking

Comparators: Prevention or treatment with placebos, optional homeopathic case-taking.

Outcomes: Overall effect estimate from major outcomes extracted from the original trials, such as odds ratios or standardised mean difference, with 95% confidence interval and p-value

METHODS

8. Eligibility criteria for meta-analyses

This section presents eligibility criteria for the meta-analyses (not for the individual trials included in them).

8.1 Design

Include: Meta-analyses of randomised controlled trials, including secondary analyses thereof

Exclude: Narrative reviews; systematic reviews without a quantitative synthesis of treatment effect estimates, meta-analyses not based on randomised controlled trials

8.2 Patients and settings

Include: Humans, no age restriction, any country, any setting

Exclude: Veterinary trials, meta-analyses restricted to specific age or gender groups

8.3 Indications

Include: Meta-analyses covering any indication, disease or symptom

Exclude: Meta-analyses restricted to specific indications, indication groups or clinical domains

8.4 Interventions

Include: Homeopathy, defined as

- Prevention or treatment with homeopathic medicinal products, i.e. products manufactured by a method described in a homeopathic pharmacopoeia (mandatory)
- Homeopathic case-taking (optional) (20)

Exclude:

- Any other new intervention (but continuation of ongoing therapy does not lead to exclusion)
- Homeopathic case taking without use of homeopathic medicinal products
- Meta-analyses restricted to specific homeopathic products or product groups

8.5 Comparators

Include: Placebo

Exclude: Meta-analyses not including placebo-controlled trials

8.6 Outcomes

Include: Meta-analyses of therapeutic benefit, measured by any clinically relevant outcome

Exclude: Meta-analyses not including therapeutic benefit (e.g. including use or safety only)

8.7 Report time frame

Include: Meta-analysis publications from 1 January 1990 up to 31 October 2020

8.8 Report language

Include: Any language

8.9 Type of publication

Include: all three criteria (a-c) must be fulfilled:

(a) written and dated reports with identifiable authors
(b) which are or have been in the public domain OR have been submitted to a third party
(c) with presentation of methods and results in sufficient detail, allowing for assessment of the research questions (cf. section 7.1) in a meaningful way

8.10 Type of meta-analysis publication

Include:

1. Primary publication of a meta-analysis

2. Additional analyses: all four criteria (a-d) must be fulfilled:

(a) pertaining to a meta-analysis included in this systematic review
(b) presenting results not included the primary meta-analysis publication
(c) contributing to the assessment of the research questions (cf. section 7.1) in a meaningful way
(d) fulfilling the "type of publication" critera (section 8.9)

9. Information sources

9.1 Databases

We will search nine online databases, thereof four (A-D) largely or totally restricted to systematic reviews, three (E-G) generic and two (H-I) focused on complementary or alternative therapies. In addition, one private database (author HJH) will be searched. Planned dates of coverage are 1 January 1990 to 31 October 2020 (cf. section 8.7).

A. Cochrane Database of Systematic Reviews

URL: https://www.cochranelibrary.com/cdsr/about-cdsr

SEARCH: MeSH DESCRIPTOR Homeopathy EXPLODE ALL TREES

B. Database of Abstracts of Reviews of Effects (DARE)

URL: https://www.crd.york.ac.uk/CRDWeb/

SEARCH: MeSH DESCRIPTOR Homeopathy EXPLODE ALL TREES

C. International Prospective Register of Systematic Reviews (PROSPERO)

URL: https://www.crd.york.ac.uk/prospero/

SEARCH: MeSH DESCRIPTOR Homeopathy EXPLODE ALL TREES

D. Joanna Briggs Institute Systematic Review Register

URL: https://joannabriggs.org/systematic-review-register

SEARCH: homeopathy OR homoeopathy OR Homöopathie OR homeopathic OR homoeopathic OR homöopathisch

E. Embase

URL: https://www.embase.com/login

SEARCH: Will be determined

F. PubMed

URL: https://pubmed.ncbi.nlm.nih.gov/

SEARCH: ("meta-analysis"[Publication Type] OR "systematic review"[Publication Type]) AND "homeopathy"[MeSH Terms]) AND "humans"[MeSH Terms])

G. Latin American and Caribbean Health Sciences Literature (LILACS)

URL: https://lilacs.bvsalud.org/en/

SEARCH: Filters applied (Main subject: Homeopathy; Type of study: Systematic reviews)

H. Allied and Complementary Medicine Database (AMED)

URL: https://health.ebsco.com/products/amed-the-allied-and-complementary-medicine-database/complementary-alternative-medicine

SEARCH: KW (homeopathy OR homoeopathy) AND TI (meta-analysis OR review OR placebo-controlled) NOT (veterinary OR animal) UND Filter: "Academic Journals"

I. CAMbase

URL: http://cambase.dmz.uni-wh.de/CiXbase/camdb/

SEARCH: Keyword: (Homeopathy OR homeopathic OR homoeopathy OR homoeopathic) AND (systematic review OR meta-analysis)

9.2 Other sources

We will send a list of included meta-analyses (cf. section 11.2B) to experts in the field, in order to identify any missing eligible publications (cf. section 8.9) including additional analyses (cf. section 8.10).

10. Search strategy

Search strategies for online databases are presented in section 9.1.

11. Records of meta-analyses

11.1 Data management

Literature search results will be entered into EndNote X8 literature software. The search process will be documented in MS Excel, using a piloted search documentation form.

11.2 Selection process

11.2A Screening

Two reviewers (HJH, AG) will independently search the literature databases, screening titles and abstracts for identification of potentially eligible meta-analysis records. The results of the two screening procedures will be compared, discrepancies will be resolved by discussion (HJH, AG).

11.2B Eligibility

For the potentially eligible meta-analysis records, full text reports will be obtained. Two reviewers (HJH + either HK or GSK) will independently read the full texts and assess eligibility, checking against the eligibility criteria listed in section 8. The results of the two eligibility assessments will be compared, discrepancies will be resolved by discussion (HJH + HK and/or GSK).

11.2C Reasons for exclusion

Reasons for exclusions at the Eligibility stage will be documented and summarised.

11.3 Data collection process

Two reviewers (HJH, AG) will independently extract data from the full-text reports into Excel files, using a piloted data extraction form. One reviewer (AG) will compare the two sets of extracted data. Discrepancies will be resolved by discussion (HJH, AG; if necessary also HK).

We will not contact authors for additional, unpublished information on included meta-analyses. With the long report time frame (cf. section 8.7) this could introduce bias in the availability of such information. Notably, this is distinct from contacting authors for published reports (cf. sections 8.9, 8.10 and 10.2).

12. Data items

The following data items will be extracted from the full-text reports of the included meta-analyses (data from individual trial publications will not be used):

12.0 Type of meta-analysis publication

With respect to eligibility criterion 8.10, each included meta-analysis publication will be categorised as:

12.0A: Primary publication of a meta-analysis

12.0B: Additional analyses pertaining to 12.0A, authors include first author or last author or corresponding author for 12.0A

12.0C: Additional analyses pertaining to 12.0A, authors do not include first author nor last author nor corresponding author for 12.0A

12.1 Eligibility criteria for trials in the meta-analyses

Design: Blinding? Parallel group? Crossover trials?

Publication types: Language restriction? Publication type restrictions?

Patients: Restrictions regarding age / gender / indications?

Interventions:

- Prevention? Treatment of existing symptoms/disease?
- Definition of homeopathy
- Type of homeopathic treatment included (categories described in section 12.7)

12.2 Research questions, protocol

Research questions of the meta-analysis.

Protocol mentioned in publication? Stated as predefined? Pre-published?

12.3 Literature searches

End search (YYYY-MM-DD), Manuscript submitted (YYYY-MM-DD)

Electronic databases searched: Number and names of databases.

Previous meta-analyses or systematic reviews consulted? Other searches, e.g. grey literature, hand searches? Contact with experts ? Contact with pharmaceutical companies?

12.4 Quality of trial data handling

Screening of titles and abstracts, assessment of full text for inclusion, data extraction, assessment of trial quality/risk of bias (for each item: performed by one person / by two persons, one checking the other / by two persons, independently / other)

12.5 Trial characteristics

12.5A Excluded trials

List of excluded trials?

Reason for exclusion of each trial provided?

12.5B Included trials

N trials [or comparisons] eligible, including trials without sufficient data for meta-analysis / included for meta-analysis

Year range for trial publication,

Data on individual studies presented (name of each item)

Sample size, country and language of trial publications

N trials with continuous or rank-ordered outcomes / with binary outcomes

Funding source of trials

12.6 Patient characteristics

Age, gender, indications

12.7 Homeopathic treatment

Individualized OR Classical / Non-individualized (Clinical OR Single remedy, Isopathy, Complex OR Fixed, Unclear).

Potency/dilution: classification and criteria (e.g. “low potency: < Cx” , “high dilution: ≥ Cy”), N trials with high potencies

12.8 Assessment of risk of bias / methodological quality of trials

Name of risk of bias instruments used in the meta-analysis

Assessment of each of the following quality components (Yes/No): Generation of allocation sequence, Randomisation concealment, Double-blinding [OR: Blinding of patients, Blinding of evaluators], Baseline comparability, Dropout/withdrawals, Statistical analysis, Outcome reporting, Medline-indexed, Other. Total number of descriptors

„High-quality studies“: Criteria, described as predefined?

Association between quality components and effect estimates (cf. section 12.11), meta-regression

12.9 Heterogeneity, meta-bias

Statistical heterogeneity test findings

Funnel plot inspection findings, asymmetry coefficient, other tests for possible small study effects / publication bias (name and result of test)

Assessment of outcome reporting bias

12.10 Results of individual trials, categorised

N trials with HOM>PLAC significant ($p<0.05$) / HOM>PLAC not significant / PLAC>HOM not significant / PLAC>HOM significant ($p<0.05$)

12.11 Meta-analysis results

Unless otherwise stated, the unit of analysis result is the effect estimate (12.11A), which will be classified according to the statistical method used (12.11B) and the type of analysis (12.11C).

12.11A. Effect estimate

Metric for each result (e.g. odds ratio, standardised mean difference), value, 95% for value, p-value

12.11B. Statistical method

Random-effects / fixed-effects / other

12.11C. Type of analysis

1. All included trials

2A. Sensitivity analysis with sample restriction to:

- higher-quality trials (one category for each meta-analysis)
- trials fulfilling one specific quality criterion
- trials with a minimum sample size / N largest trials within a set of trials
- trials with dropout rate below a specified threshold
- other criterion

2B. Cumulative meta-analysis, with

- rank-ordered categories of trial quality (e.g. high / low / very low)
- incremental steps on a specified scale

3. Adjustment for possible small study effects / publication bias (including results other than effect estimates)

4. Subgroup analysis:

- Homeopathy type: individualised or classical / non-individualised (clinical homeopathy / complex homeopathy / isopathy)
- Homeopathic potency range: low / high / mixed
- Age groups: children, adults, elderly
- Acute vs chronic indications
- Type of outcome extracted from trial: binary / continuous or rank-ordered

13. Outcomes and prioritization

13.0. Characteristics of meta-analyses and trials

All listed items refer to items reported in the meta-analyses

13.0A Features of meta-analyses

1. Eligibility criteria for trials: design, publication type, patients, interventions, comparators, outcomes, other
2. Analysis protocol, procedures for literature search, quality of trial data handling
3. Assessment of methodological quality / risk of bias of trials: instruments, criteria, number and type of quality components

13.0B. Characteristics of trials

1. Year and language of publication, countries, setting, sample size,
2. Patient characteristics: age, gender, indications
3. Intervention: type of homeopathy, homeopathic potency range
4. Metric of clinical outcome extracted from the trial: binary / continuous
5. Overlap of trials between earlier and later meta-analyses
6. Methodological quality / risk of bias of trials

13.0C. Heterogeneity, Meta-bias

1. Statistical homogeneity/heterogeneity test results
2. Associations between methodological quality (risk of bias) and effect estimates
3. Funnel plot symmetry/asymmetry, statistical tests for possible small study effects / publication bias
4. Assessment of outcome reporting bias

13.1. Primary clinical outcome of this systematic review

The primary clinical outcome of this systematic review will be the combined effect estimate for the main/primary clinical outcome reported in each meta-analysis, under two different conditions:

13.1A All trials

Effect estimate in the analysis of all included trials in each meta-analysis.

13.1B Trials of higher methodological quality

Effect estimate in one analysis with the trial sample restricted according to the following criteria, all of which must be fulfilled:

1. trials of higher methodological quality (or lower risk of bias), as stated and defined by the authors of the meta-analysis
2. maximum one single high-quality category defined for the respective meta-analysis
3. based on an assessment of at least three specified components of methodological quality (e.g. concealment of allocation sequence, blinding of outcome assessors)

Rationale for primary outcomes: The effect estimate 13.1A is based on the most comprehensive sample of trials fulfilling the eligibility criteria for the respective meta-analysis, while the estimate 13.1B is based on one single subcategory of trials with higher methodological quality, allowing for summarizing into one result. All other “higher-quality” analyses will be addressed in section 13.2, below.

In case of meta-analyses comprising more than one main clinical outcome, all clinical outcomes will be included in this systematic review.

13.2. Secondary outcomes of this systematic review

All following descriptions refer to the main clinical outcome analysis reported in each meta-analysis.

13.2A Sensitivity analyses: methodological quality (risk of bias) of individual trials

Effect estimate in sensitivity analyses with sample restriction of analysed trials according to the methodological quality (risk of bias) of individual trials, as assessed by:

1. individual quality components such as concealment of allocation sequence, double blinding [blinding of participants, study personnel and outcome assessors], peer-reviewed trial publication,
2. the criterion “high-quality trials” (as in item 13.1B above) + one or several additional quality components
3. stepwise removal of trials by risk-of-bias ratings, conceptualised in a hierarchical order by the authors of the respective meta-analysis: incremental (e.g. ascending numbers in a numeric scale) / rank-ordered Likert scale (e.g. poor - fair - good)
4. other combination of quality components, grouped by total number of components in the respective analysis: 2-4 / ≥5

13.2B Supplementary analyses: risk of bias across trials (meta-bias)

Supplementary analyses based on assumed risk of bias across trials (meta-bias):

1. Statistical adjustment for possible publication bias or other small trial effects
2. Sensitivity analyses with sample restriction to trials according to sample size
3. Analyses addressing possible outcome reporting bias

13.2C Combined analyses

Effect estimate in analyses combining features of 13.2A and 13.2B.

13.3. Subgroup analyses

With regard to research question 7.1B2, four types of subgroups (A.1-4) will be analysed, with four types of results (B.1-4), grouped by the timing of the analysis (C.1-2):

A. Subgroup types

1. Homeopathy type:
    a. individualised or classical homeopathy
    b. clinical homeopathy
    c. complex homeopathy
    d. isopathy
    e. non-individualised homeopathy = b+c+d
2. Homeopathic potency range: low / high
3. Age groups: children, adults, elderly
4. Type of outcome extracted from trial
    a. binary
    b. continuous or rank-ordered

B. Analysis results

1. Effect estimate in subgroup
2. Tests for interactions between subgroups
3. Statistical homogeneity/heterogeneity
4. Funnel plot symmetry/asymmetry and related statistical tests

C. Timing of subgroup analysis

1. Pre-specified (specified in pre-published protocol OR explicitly stated to be pre-specified)
2. Post-hoc OR no information

Comment: Effect estimates for homeopathy vs placebo in diagnostic subgroups does not fall into the scope of this systematic review (cf. research question 7.1A and eligibility criterion 8.3).

14. Risk of bias

14.1 Risk of bias in trials included in each meta-analysis

Instruments and criteria used for risk-of-bias assessment in each meta-analysis are described in section 13.0.A3. Ratings of risk of bias of trials in each meta-analysis are described in section 13.0B.6

14.1 Risk of bias in the meta-analyses included in this systematic review

14.1A Risk of bias tools used

Risk of bias / methodological quality of the meta-analyses will be assessed using the ROBIS tool (Risk of Bias in Systematic Reviews) (14), supplemented with items 7, 10 and 16 from the AMSTAR-2 tool (A MeaSurement Tool to Assess systematic Reviews) (15), which are not addressed in ROBIS.

14.1B Risk of bias assessment of supplementary analysis publications

With regard to the types of meta-analysis publication (sections 8.10 and 12.0) the risk of bias assessment of each meta-analysis will comprise the data items extracted from the publication types 12.0A as well as 12.0B. The reason is, these data will essentially come from the same author group; hence, for the purpose of the present systematic review they can be assessed as a single "meta-analysis unit".

Publication types 12.0C will not be subject to full risk-of-bias assessment (section 14.1A), although individual ROBIS Domains and AMSTAR-2 items way be used for assessment of risk of bias of these publications, depending on their scope and content.

14.1C Use of risk of bias assessments

Results of the 5 ROBIS summary assessments (Concerns regarding Domains 1-4, Risk of bias in the review) and the 3 AMSTAR-2 items will be presented for each meta-analysis. In addition, the ROBIS assessments of Risk of bias in the Review will be used in additional analyses 15.3.2

15. Data synthesis

15.1 Criteria under which study data will be quantitatively synthesized

For each included meta-analysis (comprising the publication types 12.0A, 12.0B and 12.0C), descriptive data (listed in section 13.0) and results (13.1-3) will be summarised, preferably in table format. Indications in trials, listed in the meta-analyses, will be coded according to the International Classification of Diseases 10th Revision (ICD-10) and aggregated into diagnosis blocks and diagnosis chapters, as appropriate.

Tables of meta-analysis results will include the following items:

A. First author and year of meta-analysis publication,
B. Criterion for trial selection or the choice of supplementary statistical analysis, respectively
C. N trials analysed
D. Effect estimate with p-value.
E. Other, supplementary statistical test result, if applicable

"Effect estimate" (item 15.1D) refers to

- the comparison homeopathy vs placebo
- for the main clinical outcome extracted from the trials
- among all included and analysable trials or in defined subgroups thereof,
- measured by odds ratios, standardised mean difference or other estimate, with 95% confidence interval and p-value.

15.2 Planned summary measures

This being a systematic review of meta-analyses, the quantitative synthesis will be restricted to descriptive/summary statistics for the extracted variables

With respect to research question 7.1A ("does homeopathic treatment have positive effects beyond placebo"?), all effect estimates (15.1D) will be classified as

0. "No significant difference": The 95% confidence interval for the effect estimate crosses the boundary between "favouring homeopathy" and "favouring placebo", as defined in the respective meta-analysis OR (if 95% confidence interval not reported) p-value ≥ 0.05
1. "Positive effect": Effect estimate favouring the homeopathy group with the 95% confidence interval not crossing the boundary between "favouring homeopathy" and "favouring

placebo", as defined in the respective meta-analysis OR (if 95% confidence interval not reported) p-value < 0.05

2. "Negative effect": As 1, except effect estimate favouring the placebo group

If several meta-analytic techniques including random-effects models are published for the same analysis (cf. section 12.11), results from random-effects models will be used for the data synthesis.

15.3 Additional analyses

15.3.1. Additional analyses reported in the meta-analyses

Additional analyses reported in the meta-analyses and their use are presented in sections 13.1B, 13.2 and 13.3

15.3.2. Additional analyses to be performed in this systematic review

When summarizing the outcome analyses (section 13), the effect estimates will be restricted to meta-analyses for which risk of bias in the meta-analysis (Low/Unclear/High, according to ROBIS (14)) was rated as Low.

16. Meta-bias

Reported assessments of possible meta-bias in the meta-analytic datasets are described in section 13.0C. Reported analyses to correct for possible meta-bias are described in section 13.2B-C

17. Confidence in cumulative evidence

Confidence in cumulative evidence for the two research questions (section 7.1) will be summarized, using the conceptual framework of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) group (21).

We will specifically assess the following seven items, with special regard to six of the GRADE publications in the Journal of Clinical Epidemiology (2011-2019):

A. study limitations (risk of bias) (GRADE publication #4 (22), cf. sections 13.0C2; 13.1B, 13.2A)
B. risk of publication bias and outcome reporting bias (GRADE #5 (23), sections 13.0C.3-4; 13.2B-C)
C. imprecision (GRADE #6 (24))
D. magnitude of effects (GRADE #9 (25), sections 13.1-2)
E. inconsistency/heterogeneity (GRADE #7 (26), section 13.0C1)
F. indirectness (GRADE #8 (27))
G. findings of the subgroup analyses (section 13.3)

In addition, other issues discussed in the GRADE publications may also be included in the assessment, dependent on the findings.

Comment: We expect some features of the GRADE approach to be less relevant for this systematic review, e.g. GRADE assessments cover a range of outcomes for one specific condition, while the meta-analyses assessed in this review are expected to use only one outcome extracted from a range of conditions; GRADE has a focus on comparative trials of different interventions, while this review is restricted to placebo-controlled trials of one type of interventions.

OTHER INFORMATION

18. Previous work of the authors on the subject of this systematic review

HJH and HK have commented on six meta-analyses relevant for this SR: Hamre HJ, Kiene H. Scientific assessment of the motion V-01, 8 Nov 2019. URL: http://www.ifaemm.de/F11_homeo.htm

19. Conflict of interests

In the past 3 years, HJH has received research grants from two manufacturers of anthroposophic medicinal products (Wala Heilmittel GmbH, Bad Boll/Eckwälden, Germany; Weleda AG, Arlesheim Switzerland). Anthroposophic medicine is not based on the homeopathic simile principle nor on drug provings, but some anthroposophic medicinal products are potentized. The two manufacturers had no involvement with the present systematic review. DSR has received a development grant from Heel GmbH for online training in case report writing. GSK has received honoraria from Heel GmbH for consulting on award competitions. AG, KvA and HK have nothing to declare.

20. Dissemination plans

The results of this systematic review will be published in a peer-review journal.

LIST OF ABBREVIATIONS

AMSTAR-2	A MeaSurement Tool to Assess systematic Reviews, Version 2
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IFAEMM	Institute for Applied Epistemology and Medical Methodology at the Witten/Herdecke University
ROBIS	Risk of Bias in Systematic Reviews
SMAP-HOM	Systematic review of Meta-Analyses of randomised Placebo-controlled HOMeopathy trials for any indication [this systematic review]

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