Update of empirical evidence: frame-work protocol for the systematic evaluation of homeopathic intervention studies (HOMIS) in humans

1.) Scoping review: bibliography and bibliometric analysis

2.) Quality assessment: Critical Appraisal Tool for Homeopathic Intervention Studies – CATHIS

3.) Systematic Reviews and meta-analyses: step-by-step evaluation of pooled effects of HOMIS in specific conditions

This framework protocol defines the research strategy for a stepwise evaluation of the evidence body of homeopathic intervention studies (HOMIS) in human diseases. It is a further development of the research protocol previously registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 17/08/2015 (registration number CRD42015025399). The original project was discontinued and this protocol defines the adapted approach.

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Contributions

KG drafted the manuscript. All authors contributed to the development of strategy and approved the final manuscript.

Support

The Tiedemann Foundation for Classical Homeopathy, the Homeopathy Foundation of the Association of Homeopathic Doctors in Germany (DZVhÄ) and the Pierre Schmidt Foundation in Switzerland provided project-development funding, but did not have any role in the design and conduct of the project.

October 5, 2020

SUMMARY

Background

Evidence regarding therapeutic effectiveness of homeopathic interventions in human diseases is inconclusive. The great variety of interventions, inadequate quality assessments and the gap between positive results from effectiveness research and divergent results from efficacy studies call for a strategic framework to adequately assess the clinical effects of homeopathic interventions.

Objective

We aim to outline a strategy for the evaluation of the body of evidence from homeopathic intervention studies (HOMIS) in humans.

Methods

Based on the strategy of a previously published protocol (PROSPERO) systematic literature searches in over 18 databases and other sources have been conducted first in 2015. The resulting records have been screened and all studies investigating homeopathic interventions in humans by comparing them either to placebo, standard of care interventions or no interventions have been included in a database. In 2016, the original protocol was amended and the included studies have been allocated into ICD-10 and ICF categories. When the initial approach yielded feasibility, a new strategy with three key elements was defined by the end of 2017:

1. In a scoping review, a comprehensive bibliography and bibliometric analysis is to be conducted
2. A quality assessment tool (Critical Appraisal Tool for Homeopathic Intervention Studies – CATHIS) is to be developed
3. Various systematic reviews and meta-analyses to identify effects of HOMIS in specific conditions are to be conducted.

The literature search and the database were continuously updated and the resulting data was organized in tables and charts for the scoping review and the bibliography as

defined in the initial protocol. An international experts committee was gathered for the development of a consensus-instrument to assess internal, external and model validity of HOMIS likewise (CATHIS). On the base of the comprehensive bibliography of HOMIS and the CATHIS tool, systematic reviews and meta-analyses will be performed progressively to adequately assess effects of HOMIS for those conditions with sufficient homogeneous data available per ICD-10 category.

Conclusion

A stepwise evaluation of particular homeopathic interventions in specific ICD-10 categories has been developed. Systematic reviews and meta-analyses of the respective HOMIS will allow an evidence-based assessment of clinical efficacy and effectiveness, based on this framework-protocol.

INTRODUCTION

Evidence from homeopathic intervention studies

Homeopathic intervention studies (HOMIS) is the term used to describe any clinical study investigating therapeutic or preventive interventions with homeopathic medicinal products (HMPs). Though a considerable amount of HOMIS exist (1, 2), several attempts to summarize the evidence from HOMIS failed to result in a conclusion (3-8) whether HMPs are effective in treating and/or preventing human diseases. The topic is discussed highly controversial. The following aspects contribute to the complexity of the discussion:

1.) There exist different homeopathic approaches or therapeutic strategies to apply HMPs. In practice, there exists a great variety of strategies, but four main types have been defined for research purposes (1-3):

- Individualised (or classical) homeopathy is characterised by a consultation followed by the prescription of a single homeopathic medicine individually selected for the patients' symptoms according to the homeopathic law of similars
- Routine homeopathic prescriptions (or clinical homeopathy), characterised by the use of a single HMP for a clinical condition (e.g. *Arnica montana* for physical trauma or *Nux vomica* for gastritis)
- Multi-constituent homeopathic prescription (or complex homeopathy), characterized by the use of HMPs which are given either in a fixed combination or concurrently
- Isopathy, characterized by the prescription of HMPs, which have been prepared from the substance which caused the disease (e.g. grass pollen for hay fever or arsenic for chronic arsenic poisoning)

We hypothesize that the therapeutic effect differs between the particular homeopathic strategies used. Therefore, combining data from all investigated homeopathic interventions does not seem reasonable, especially if also multiple medical conditions are pooled into meta-analyses. In order to reduce the heterogeneity of studies in meta-analyses, distinct sub-sets of trials were selected by reviewers of HOMIS in the past.

This led, in turn, to divergent pooled estimates for the effect of homeopathic interventions (9).

2.) HMPs are medicines that are prepared by successive dilution and shaking ('succussion'). This often results in extremely low doses of active ingredients or 'non-molecular' drugs. From a skeptical viewpoint, an effect of HMPs is therefore not plausible and all detected clinical effects are mainly due to placebo-effects or regression to the mean (4). In this line, meta-analyses including exclusively placebo-controlled HOMIS brought about merely small effects, which were not robust to sensitivity analyses (3, 4). From a different viewpoint, however, treatment received by a trained homeopathic practitioner (often termed as *homeopathic care* (10)) may include beneficial effects, which are not specific to the HMP itself but are induced by multiple factors, such as attitudes of the patient and the practitioner, the extended anamnesis during a homeopathic consultation and the setting (11, 12). Interestingly, considerable and clinically relevant effects of homeopathic interventions, i.e. effects comparable with conventional standard care, were detected in effectiveness-studies (13-16).

Further contributing to this efficacy-effectiveness dichotomy is the fact that homeopathic interventions are supposed to regulate the organisms based on neuro-endocrinological, neuro-hormonal and neuro-immunological feed-back mechanisms, and the resulting effect is expected to be observed in different functional levels of the organism, i.e. mental, emotional and physical symptoms may be affected simultaneously (17-20). In this case, the chosen endpoints in a clinical investigation need to include outcomes able to detect these complex changes which may result from treatment with HMPs (21), e.g. patient-reported outcome measures (PROMs).

3.) Low methodological quality attributed to a major proportion of HOMIS preclude conclusive effect estimations in overall analyses (3, 5-7, 22, 23). Additionally, other conceptual flaws of HOMIS, such as missing coherence with the homeopathic intervention as it is done in practice (i.e. low model and external validity) may further bias the results (21, 24).

The debate whether homeopathic interventions cause beneficial effects in the course of human diseases and can consequently add to conventional medical care remains active

(25, 26) and homeopathic care is sought by a major part of the population in many countries (27-30). Therefore, a strategic framework to critically assess the evidence body of HOMIS is warranted. In 2015, we designed a new approach for such a project. The protocol was published with the International Prospective Register of Systematic Reviews (PROSPERO) (31). However, the original strategy was discontinued because the amount of HOMIS detected in the literature search, the heterogeneity of HOMIS resulting from the bibliographic evaluation and the lack of a comprehensive quality-assessment tool made a meaningful overall summary of evidence impossible.

Therefore, the strategic concept and the timed coordination of the project were changed and this framework protocol states objectives and methods of the adapted research project.

AIMS AND OBJECTIVES

Considering the above, the necessary starting point for a meaningful synthesis of the results of HOMIS is a systematic overview of literature, where the studies are arranged according to specific populations (with medical conditions), homeopathic interventions, respective comparators and outcomes (PICOS). Taking the described efficacy-effectiveness gap into account, such an overview should include placebo-controlled studies as well as studies with active comparators (e.g. pragmatic study designs)(32, 33). Further in this line, a comprehensive instrument to assess quality of HOMIS regarding coherence with and transferability into clinical practice is needed in order to adequately assess clinical effects of homeopathic interventions (34, 35). Once both, the literature overview and a reasonable quality assessment instrument are available, selected HOMIS with homogenous PICOS can be evaluated in systematic reviews and meta-analyses.

Hence, we anticipate a stepwise assessment of the empirical evidence from HOMIS according to the strategy just outlined. The following steps are to be accomplished:

1. A scoping review of HOMIS in human diseases and a systematic, bibliographic elaboration with the help of international classifications (ICD-10 & ICF; (36, 37))
2. The development of a comprehensive instrument to assess the quality of HOMIS
3. Several systematic reviews and meta-analyses, each one of particular homeopathic interventions in medical conditions, where sufficient homogeneous data is available

To date (September 2020), the scoping review is almost completed and the quality assessment tool is in the phase of the face-validity check.

METHODS

1. Scoping review

Following the previously defined eligibility criteria and data-extraction methods (31), the relevant studies for the scoping review were identified. The detailed search strategy and information sources are available as a supplement to this protocol (last update January 31st 2020).

Eligibility criteria

Studies were eligible as stated in the protocol (31):
Study designs: RCTs and controlled observational studies. All other study designs are excluded.
Participants: Studies on humans. Participants must have exhibited a clinically relevant disease or been healthy and enrolled in a study on disease prevention.
Interventions: All studies employing one or more substances, which were homeopathically prepared (processed by trituration and succussion). Studies analyzing mother tinctures only are not included.
Comparators: Studies investigating clinical effects of HMPs compared to placebo, to conventional treatments that have shown effectiveness for the respective condition as

well as compared to no intervention, as long as they received standard care. Studies with other types of control (e.g. no intervention without standard care, other complementary medicine methods) are excluded.

Outcomes: Outcomes are considered as reported in all data formats (e.g., dichotomous, continuous).

Setting: No restrictions on study settings apply.

Time frame: No restrictions on time frame of the study apply.

Years of publication: Research reports from 01.01.1980 to 31.01.2020 are reviewed. Studies conducted before 1980 are not considered, as incompleteness due to different journal policies (i.e., listing of older studies only in some journals) may bias the search result.

Languages of publication: Publications in English, German, Spanish, French, and Italian are evaluated by the research group. Studies published in other languages are translated with the help of google translate and/or native speakers.

Publication status: Substantive research articles (either peer-reviewed or not) as well as conference proceedings, minor articles (below 500 words) and master and doctoral theses were eligible for further screening. Book chapters and abstracts were excluded. Though peer-reviewed articles are usually considered as evidence of higher quality (38) other types of publications are not excluded a priori, but the quality of evidence is determined - as long as sufficient information is reported –by a thorough assessment from the research team.

Study records, data-items and coding

Records are screened and extracted independently by two reviewers, following the predefined methodology (31) by using Endnote citation manager and Excel. Data is organized in two different tables: one for preventive interventions (interventions before any of the symptoms or complaints were apparent (e.g. pre-operative administration of HMPs, intake of HMPs in order to prevent common colds, muscle strain) and one for therapeutic interventions. The following study identifiers are extracted and coded: author(s), title, year of publication, journal and/or digital object identifiers (39) or place of publication (reports and theses), peer-review status, study

design, setting, intervention design (interventions administered as add-on to standard therapy or alone), number of treatment arms, language, objective(s), target population, homeopathic intervention(s), type of homeopathy, comparator(s) and (if active comparator) type of active treatment, sample size, number of participants per group, attrition rate and endpoints.

During this process, the studies are screened and coded as included (therapeutic or preventive) or excluded (with reason). Reasons for exclusion are: 1.) intervention without HMPs, 2.) no comparator, 3.) participants are not humans or the investigation is a laboratory experiment, 4.) manuscript or report do not provide sufficient information, 5.) reprints or duplicate publications.

According to the amendment of the initial protocol (40), studies are additionally allocated to the investigated diseases as sort by the International Classification of Diseases (ICD-10, version 2016; (36)), as well as ciphered and grouped according to the checklist for International Classification of Functioning, Disability and Health (ICF Checklist, version 2.1a clinical form; (37)). For the allocation into ICF checklist-categories the main outcome of the concerned study is considered as defined by the authors or, if no primary outcome is defined, as the one appearing to be the most clinically relevant according to the hierarchical ranking approach of Mathie et al. 2013 (41). If more than three studies of the same condition are found, the most common outcome is used for the assignation. Outcomes are allocated either to the organ-specific category of ICF or, for unspecific outcomes such as symptom scores, the most suitable category is chosen (e.g., studies on acute viral infections tested by a symptom score including fever, body-aches as well as organ-specific symptoms and more are assigned to immunological functions). For the classification into the ICD-10 code, the condition of study population and the main endpoint of the study are used. For example, if a study has investigated a specific population, but no corresponding clinical outcome has been tested, the outcome itself determines the code (e.g. change in depression scores (outcome) in menopausal woman (study population) is coded as depression). Further, the most specific category is chosen, e.g. for a study investigating a specific condition (e.g., sinusitis) the corresponding cipher is assigned, but for a study investigating a range of conditions (e.g. upper respiratory tract infections (URTI)), superordinate

cipher is designated. If for a clinical condition no common outcome is detectable, the conditions are grouped separately.

Data synthesis

Data is summarized and edited with the help of Excel® (Microsoft Corporation).

From the original data-sheet, the important study characteristics (design, peer-review status, intervention, comparator, sample size, and peer-review status) are transferred into a summary table, which is arranged according to the ICF and ICD-10 coding.

From this table, the ICD-10 categories, which include more than one study with the same homeopathic intervention per code, are deducted into a second overview table. Corresponding macros were created for the deduction rules in order to allow continuous updates of the content.

For bibliographic analyses, descriptive statistics will be used and the results will be presented with total numbers, percentages and, if applicable, means and interquartile ranges.

2. Quality assessment tool for homeopathic intervention studies

An adapted Delphi-process is used for the development of a global instrument to critically appraise overall study quality of HOMIS. The following outlines the procedural minutes:

1. *A literature scan and discussion with experts aiming to identify available scales and instruments for the assessment of model and external validity*
   The following scales and tools were identified, critically reviewed and used for steps 3-8: the criteria for “Reporting data on homeopathic treatments (RedHot)” (42), published as a supplement to the CONSORT-statement (43); the “Checklist

for the qualitative evaluation of clinical studies with particular focus on external validity and model validity" (34); the "model validity of randomised controlled trials of homeopathic treatment (MVHT)" tool (24); the "external validity assessment tool (EVAT)" (35); the "pragmatic-explanatory continuum indicator summary (PRECIS)" tool, version 1 and 2 (44, 45) and the assessment items for the "Rating of Included Trials on the Efficacy-Effectiveness Spectrum – RITES" (46)

2. *Identification of suitable experts for the Delphi-process*
   Experts were identified by literature search and word of mouth. We counted as expert individuals who had contributed to both the original literature of HOMIS, having conducted at least one clinical and/or experimental study, and at least one systematic review with or without meta-analysis.

3. *Survey of experts*
   A questionnaire containing questions regarding the definition of homeopathic principles, external validity and personal experience with the previously identified assessment tools was sent out to the experts. Eighteen experts responded to the questionnaire.

4. *First draft of the global assessment tool for HOMIS*
   Based on the aspect, identified through steps 1 and 3, one of the authors (47) drafted a first domain-based assessment instrument.

5. *Panel discussion of the first draft*
   A consensus panel was launched to discuss the first draft and to identify any missing items. Twenty-eight experts participated.

6. *Minutes of results, corrections and amends to the first draft*
   KG summarized the results and amended the draft

7. *Feed-back round to the amended draft*

   The draft was again sent for cross-check and further comments to all experts who agreed to participate in the further development of the assessment tool (n=22). Eight responses were received.

8. *Critical appraisal tool of homeopathic intervention studies – CATHIS*

   The draft was again condensed and terminology was refined by KG. A first version of the global assessment instrument with the working title 'Critical appraisal tool of homeopathic intervention studies – CATHIS' was approved by the eight experts who responded to the amended draft.

9. *Face-validity assessment of CATHIS*

   Five suitable reviewers were recruited for face validation. Those were experienced researchers in different specialities of medicine. Most of them had a background in complementary and alternative medicine research. For the validity-assessment, 5 HOMIS were randomly selected of pool of studies included in the literature overview and sent to the reviewers along with the CATHIS-template.

10. *Summary of results and publication of CATHIS*

    Currently, the project is in the second phase of the face-validity assessment. The detailed description of the Delphi-process and the concordance study will be subject to a separate publication.

11. *Validation of CATHIS*

    When the face-validity assessments reach good interrater reliability, it is foreseen to validate the instrument by using it along with some of the existing instruments (e.g. MVHT (24), EVAT (35) or RITES (46) and to compare the results.

3. Systematic Review and meta-analyses

In this third step of the strategic framework, we aim to quantify clinical effects resulting

from particular homeopathic interventions in specific medical conditions (defined per ICD-10 code). The overview tables from the scoping review will serve to identify the relevant clinical conditions.

Protocols and selection of review conditions

Several condition-specific systematic reviews and meta-analyses will be conducted one-by-one. For each analysis a separate, detailed protocol will be published before any quantitative data-analysis is carried out. As we foresee the collaboration with different specialists and investigators, the selection of the conditions depends on the interest and availability of collaborators as well as the possibility of financing the individual projects.

Quality assessments

The newly developed comprehensive assessment tool for the quality ratings will be used, if the face validity shows sufficiently inter-rater reliability. Until the validation of the instrument, one of the existing rating tools (e.g. the Cochrane risk-of-bias tool) will be used and missing quality aspects will be subject to the discussion section.

Statistical methods and summary of results

All methodological features, such as the choice of outcomes and details of the data synthesis and discussion of meta-biases will be subject to the separate research protocols for the respective individual review projects.

REFERENCES

1. Mathie RT, Hacke D, Clausen J, Nicolai T, Riley DS, Fisher P. Randomised controlled trials of homeopathy in humans: characterising the research journal literature for systematic review. Homeopathy. 2013;102(1):3-24.

2. Dean ME. The Trials of Homeopathy. Essen: KVC-Verlag; 2004.

3. Linde K, Clausius N, Ramirez G, Melchart D, Eitel F, Hedges LV, et al. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. Lancet. 1997;350(9081):834-43.

4. Shang A, Huwiler-Müntener K, Nartey L, Jüni P, Dörig S, Sterne JAC, et al. Are the clinical effects of homoeopathy placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy. The Lancet. 2005;366(9487):726-32.

5. Mathie RT, Lloyd SM, Legg LA, Clausen J, Moss S, Davidson JR, et al. Randomised placebo-controlled trials of individualised homeopathic treatment: systematic review and meta-analysis. Syst Rev. 2014;3:142.

6. Mathie RT, Ramparsad N, Legg LA, Clausen J, Moss S, Davidson JR, et al. Randomised, double-blind, placebo-controlled trials of non-individualised homeopathic treatment: systematic review and meta-analysis. Syst Rev. 2017;6(1):63.

7. Mathie RT, Ulbrich-Zurni S, Viksveen P, Roberts ER, Baitson ES, Legg LA, et al. Systematic Review and Meta-Analysis of Randomised, Other-than-Placebo Controlled, Trials of Individualised Homeopathic Treatment. Homeopathy. 2018.

8. Bornhoft G, Wolf U, von Ammon K, Righetti M, Maxion-Bergemann S, Baumgartner S, et al. Effectiveness, safety and cost-effectiveness of homeopathy in general practice - summarized health technology assessment. Forsch Komplementmed. 2006;13 Suppl 2:19-29.

9. Ludtke R, Rutten AL. The conclusions on the effectiveness of homeopathy highly depend on the set of analyzed trials. J Clin Epidemiol. 2008;61(12):1197-204.

10. Relton C, O'Cathain A, Thomas KJ. 'Homeopathy': untangling the debate. Homeopathy. 2008;97(3):152-5.

11. Walach H, Jonas WB, Ives J, van Wijk R, Weingartner O. Research on homeopathy: state of the art. J Altern Complement Med. 2005;11(5):813-29.

12. Fonnebo V, Grimsgaard S, Walach H, Ritenbaugh C, Norheim AJ, MacPherson H, et al. Researching complementary and alternative treatments--the gatekeepers are not at home. BMC Med Res Methodol. 2007;7:7.

13. Spence DS, Thompson EA, Barron SJ. Homeopathic treatment for chronic disease: a 6-year, university-hospital outpatient observational study. J Altern Complement Med. 2005;11(5):793-8.

14. Rossi E, Endrizzi C, Panozzo MA, Bianchi A, Da Fre M. Homeopathy in the public health system: a seven-year observational study at Lucca Hospital (Italy). Homeopathy. 2009;98(3):142-8.

15. Witt C, Keil T, Selim D, Roll S, Vance W, Wegscheider K, et al. Outcome and costs of homoeopathic and conventional treatment strategies: a comparative cohort study in patients with chronic disorders. Complement Ther Med. 2005;13(2):79-86.

16. Witt CM, Ludtke R, Baur R, Willich SN. Homeopathic medical practice: long-term results of a cohort study with 3981 patients. BMC Public Health. 2005;5:115.

17. Hahnemann S. Organon der Heilkunst. Standard edition of 6th ed. Schmidt JM, editor. Heidelberg: Haug; 1996/1999. 388 p.

18. Vithoulkas G. Levels of Health - Second volume of the Science of Homeopathy. 3 ed. Homeopathy IAoC, editor. Alonissos: International Academy of Classical Homeopathy; 2019.

19. Vithoulkas G. The Science of Homeopathy. 1 ed. New York, NY, United States of America: Grove Press; 1980.

20. Vithoulkas G, Carlino S. The “continuum” of a unified theory of diseases. Med Sci Monit. 2010;16(2):SR7-15.

21. Oberbaum M, Vithoulkas G, Van Haselen R. Clinical trials of classical homeopathy: reflections on appropriate research designs. J Altern Complement Med. 2003;9(1):105-11.

22. Linde K. [Are there proven therapies in homeopathy?]. Internist (Berl). 1999;40(12):1271-4.

23. Mathie RT, Fok YYY, Viksveen P, To AKL, Davidson JRT. Systematic Review and Meta-Analysis of Randomised, Other-than-Placebo Controlled, Trials of Non-Individualised Homeopathic Treatment. Homeopathy. 2019;108(2):88-101.

24. Mathie RT, Roniger H, Van Wassenhoven M, Frye J, Jacobs J, Oberbaum M, et al. Method for appraising model validity of randomised controlled trials of homeopathic treatment: multi-rater concordance study. BMC Med Res Methodol. 2012;12:49.

25. Australia. Australian Health and Medical Research Council (NHMRC) Information Paper: Evidence on the effectiveness of homeopathy for treating health conditions. www.nhmrc.gov.au/guidelines-publications/cam02: National Health and Medical Research Council; 2015.

26. Roberts R, Tournier A. Response by the Homeopathy Research Institute to ‘the Australian report’ Internet, 2016 [Available from: https://www.hri-research.org/wp-content/uploads/2016/02/HRI-Response-to-NHMRC-Information-Paper.pdf.

27. Homöopathische Arzneimittel 2014 [press release]. Bonn, ifD Allensbach2014.

28. Klein SD, Torchetti L, Frei-Erb M, Wolf U. Usage of Complementary Medicine in Switzerland: Results of the Swiss Health Survey 2012 and Development Since 2007. PLoS One. 2015;10(10):e0141985.

29. Eardley S, Bishop FL, Prescott P, Cardini F, Brinkhaus B, Santos-Rey K, et al. A systematic literature review of complementary and alternative medicine prevalence in EU. Forsch Komplementmed. 2012;19 Suppl 2:18-28.

30. Relton C, Cooper K, Viksveen P, Fibert P, Thomas K. Prevalence of homeopathy use by the general population worldwide: a systematic review. Homeopathy. 2017.

31. Gaertner K, Torchetti L, Frei-Erb M, Frass M, Kundi M. Protocol of systematic reviews and meta-analyses of controlled homeopathic studies. Internet: International Prospective Register of Systematic Reviews (PROSPERO): Registration number CRD42015025399; 2015 [updated 16. September 2016, cited 15. August 2018]. Available from: https://www.crd.york.ac.uk/PROSPEROFILES/25399_PROTOCOL_20181201.pdf.

32. Graham R, Mancher M, Miller Wolman D, Greenfield S, Steinberg E. IOM (Institute of Medicine). Clinical Practice Guidelines we can trust. Washington, D.C.: The National Academies Press; 2011.

33. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.

34. Bornhoft G, Maxion-Bergemann S, Wolf U, Kienle GS, Michalsen A, Vollmar HC, et al. Checklist for the qualitative evaluation of clinical studies with particular focus on external validity and model validity. BMC Med Res Methodol. 2006;6:56.

35. Khorsan R, Crawford C. How to assess the external validity and model validity of therapeutic trials: a conceptual approach to systematic review methodology. Evid Based Complement Alternat Med. 2014;2014:694804.

36. ICD-10 International Statistical Classification of Diseases and Related Health Problems 10th Revision, (2016).

37. ICF Checklist for International Classification of Functioning, Disability and Health, Version 2.1a, Clinician Form (2003).

38. CIBER. Trust and Authority in Scholarly Communications in the Light of the Digital Transition. Final report. Tennessee: University of Tennessee & CIBER Research Ltd; 2013.

39. Stone J, Gurunathan U, Glass K, Munn Z, Tugwell P, Doi SAR. Stratification by quality induced selection bias in a meta-analysis of clinical trials. J Clin Epidemiol. 2019;107:51-9.

40. Gaertner K, Torchetti L, Kundi M, Frass M. Amendment to protocol of systematic reviews and meta-analyses of controlled homeopathic studies. International Prospective Register of Systematic Reviews (PROSPERO): Registration number CRD42016048366; 2016 [updated 27 September 2016, cited August 2018]. Available from: https://www.crd.york.ac.uk/PROSPEROFILES/48366_PROTOCOL_20160827.pdf.

41. Mathie RT, Legg LA, Clausen J, Davidson JRT, Lloyd SM, Ford I. Systematic review and meta-analysis of randomised, placebo-controlled, trials of individualised homeopathic treatment: study protocol. Version 1.0 2013 [7th June 2019]. Available from: http://www.britishhomeopathic.org/wp-content/uploads/2013/05/Study_protocol_for_systematic_review.pdf].

42. Dean ME, Coulter MK, Fisher P, Jobst K, Walach H. Reporting data on homeopathic treatments (RedHot): a supplement to CONSORT. Homeopathy. 2007;96(1):42-5.

43. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c332.

44. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ. 2015;350:h2147.

45. Thorpe KE, Zwarenstein M, Oxman AD. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. CMAJ. 2009;180:10.

46. Wieland LS, Berman BM, Altman DG, Barth J, Bouter LM, D'Adamo CR, et al. Rating of Included Trials on the Efficacy-Effectiveness Spectrum: development of a new tool for systematic reviews. J Clin Epidemiol. 2017;84:95-104.

47. des AI, (KKG) KfrFdKiG. ICD-10-GM deutsch, Version 2015. In: (DIMDI) DIfrMDuI, editor. Bundesministeriums für Gesundheit2014.

SUPPLEMENT – LITERATURE SEARCH STRATEGY

For all databases the following time limits were set:

- Search performed in April 2015: January 1st, 1980 to December 31st, 2015
- Search performed in August 2017: January 1st 2016 to June 30th 2017
- Search performed in February 2019: July 1st 2017 to January 31st 2019
- Search performed in January 2020: February 1st 2019 to January 25th 2020

1. Searches in online-databases

Free-text searches

1a. *Websites for master- and doctoral theses (for databases see 4.1-4.24):* search with the terms 'homeopat* OR homoeopat* OR omeopat* OR homéopat* OR homeopát* OR hoomeopat* OR homöopat*'

1b. *All other online databases*: The search string of 1a was complemented with BOOLEANS, i.e. 'AND (observation* OR control* OR group*) AND (study OR trial)'. For LILACS the corresponding Spanish BOOLEANS were used. Interfaces and search fields were used as follows:

- *Pubmed: advanced search interface (ab/ti)*[1]
- *Embase: advanced search interface (ab/ti)*
- *Cinahl: advanced search interface (ab, ti and su)*[2]
- *Cochrane: advanced search builder (all fields)*
- *Science citation index expanded (SCIE) & Scientific Electronic Library Online (SciELO): web of science basic search interface (Topic)*[3]
- *Scopus: advanced search interface (ABS-TI-KEY)*[4]
- *AMED (first search only): multifield search interface (all fields)*

[1] Search performed in abstract and title
[2] Search performed in abstract, title and subject (keywords) seperately
[3] Search performed in abstract, title and keywords
[4] Search performed in abstract, title and keywords

- *LILACS: Portuguese advanced search interface (title, abstract, subject) with the truncation '$'* (i.e. homeopat$ OR homoeopath$ OR omeopat* OR homéopat$ OR homeopát$ OR hoomeopat$ OR homöopat$) AND (observation$ OR control$ OR grup$ OR observacion$) AND (study OR trial OR estud$ OR ensaio OR ensayo)

Additional subject headings search (listed databases only):

Pubmed (advanced search): (homeopathy[MeSH Terms]) OR homeopathic remedies[MeSH Terms]) AND (clinical study[Publication Type] OR comparative study[Publication Type] OR multicenter study [Publication Type]) NOT (animals[MeSH Terms] NOT humans[MeSH Terms]).

Embase (advanced search: ab/ti): (homeopathy[Emtree]) OR homeopathic agents[Emtree]) AND (controlled study[Emtree/exp] OR comparative effectiveness[Emtree/exp] OR observational study[Emtree/exp] OR (clinical study[Emtree/exp] NOT (case report OR case study)))

CINAHL (advanced search): (homeopathy[Heading]) OR homeopathic agents[Heading]) AND (experimental studies[Heading] OR non-experimental studies[Heading])

Cochrane (advanced search builder): (homeopathy[MeSH]) OR homeopathic remedies[MeSH]) AND (clinical study[MeSH])

Web of Science (basic search): No subject heading 'Homeopathy' provided. Additionally to the freetext search, the following limits were added to free text-string 'homeopat* OR homoeopat* OR omeopat* OR homéopat* OR homeopát* OR hoomeopat* OR homöopat*'. LIMIT: Document type (article, meeting abstract, proceedings paper), "Clinical Web of science Categories", such as internal medicine, surgery, etc. and 'integrative Medicine.

SCOPUS (advanced search): (Homeopathy[authorkey] OR Homeopathy[indexwords] OR

Homeopathy[Emtree]) AND ((LIMITS: Controlled Study, Major Clinical Study, Clinical Trial, Controlled Clinical Trial, Randomized Controlled Trial, Clinical Article, Comparative Study, Prospective Studies, Multicenter Study, Prospective Study, Cross-Sectional Studies, Medical Practice, Cross-sectional Study, Clinical Practice, Observational Study, Outcomes Research) AND (LIMIT document type (article, conference proceedings)))

AMED (multifield search): Homeopathy exp[sh] AND (Clinical trial exp[sh] OR Comparative study[sh] OR Random allocation[sh] OR double blind method[sh] OR research design[sh])

LILACS *(advanced search):* Error message for the use of the subject descriptor. Additionally to the freetext search, the following limits were added to free text-string 'homeopat$ OR homoeopath$ OR omeopat* OR homéopat$ OR homeopát$ OR hoomeopat$ OR homöopat$'. LIMIT: Publication type (article, thesis, congress and conference).

2. Manual literature searches

Core-Hom database: A list of all references listed between 1980 and 2019 was exported as a pdf-file and transferred via txt-file into endnote for the duplicate-check with the other databases.

HOMINFORM database: A list of all references was provided by the librarian in an excel-file. The file was screened for the terms: 'study', 'trial', 'observation', 'control' and 'group'.

Website of the Indian Journal for Research in Homeopathy: The interface was screened for the keywords 'controlled study', 'controlled trial', 'observational study' and 'observational trial' in all fields.

3. Searches by librarians

CAM-Quest database: The search string was provided by the librarian. The search was performed in all fields as follows: klinische Forschung (clinical research), NOT Veterinärmedizin (veterinary), NOT Arzneimittelprüfung (homeopathic proving), NOT Erfahrungsbericht (case report).

AYUSH RESEARCH PORTAL Website: A list of studies, but no search string was provided. The duplicate-check with the other databases did not reveal further studies.

4. Websites for master- and doctoral theses

4.1 OATD (https://oatd.org)

4.2 Proquest (https://www.proquest.com)

4.3 Openthesis (www.openthesis.org)

4.4 Global ETD-search (http://search.ndltd.org)

4.5 Opengrey (http://www.opengrey.eu)

4.6 DART (http://www.dart-europe.eu/basic-search.php)

4.7 Havard Library (https://library.harvard.edu)

4.8 Österreichische Dissertationsdatenbank (https://www.obvsg.at/services/dissertationsdatenbank/)

4.9 Swissbib (https://www.swissbib.ch)

4.10 RCAAP (https://www.rcaap.pt)

4.11 Dissonline (http://www.dnb.de/DE/Wir/Kooperation/dissonline/dissonline_node.html)

4.12 Theses (http://theses.fr)

4.13 Narcis (https://www.narcis.nl)

4.14 Erudit (https://www.erudit.org/en/theses/)

4.15 HAL (https://hal.archives-ouvertes.fr)

4.16 Tezmerkezi (https://tez.yok.gov.tr/UlusalTezMerkezi/)

4.17 NDTLD Taiwan (https://ndltd.ncl.edu.tw/)

4.18 JAIRO (http://jairo.nii.ac.jp/)

4.19 RIAN (http://rian.ie)

4.20 Ohio LINK (https://www.ohiolink.edu)

4.21 ETHOS (http://ethos.bl.uk/)

4.22 DSPACE (https://www.era.lib.ed.ac.uk)

4.23 AMICUS (http://amicus.collectionscanada.gc.ca/)

4.24 Am Doctoral Diss (https://biblioboard.com/opendissertations/)