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Systematic reviews and meta-analyses in Homeopathy: Recommendations for summarising evidence from homeopathic intervention studies (Sum-HomIS recommendations)

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ABSTRACT

Background: Mainly due to the use of different inclusion criteria and quality assessments, systematic reviews (SRs) and meta-analyses (MAs) with homeopathic intervention studies (HOMIS) have shown inconsistent results. We aimed to build recommendations for "Summarizing evidence from Homeopathic Intervention Studies" (Sum-HomIS recommendations) in order to approach standardization.

Methods: Against the background of a framework-project to update the evidence from homeopathic intervention studies, we launched an expert panel on how to assess the quality of HOMIS and how to summarize evidence from HOMIS. The results of a literature review and the expert communications in advance of the panel as well as the consensus from the discussions are presented here. We added specific considerations for homeopathic veterinary research.

Results: On top of the general guidelines when planning a review we report five basic Sum-HomIS recommendations. These are: 1) A broad literature search including special archives and consideration of so-called grey-literature; 2) The inclusion of controlled observational studies alongside randomized controlled trials; 3) The choice of a clear clinical research question in the terms that, if possible, the review project includes studies with predominantly homogeneous populations, interventions, comparators and outcomes (PICOs); 4) The use of a global quality assessment including the assessment of external, model and internal validity; 5) A summary of evidence using the GRADE-approach if the body of evidence is sufficiently large and homogenous or a descriptive summary if it is not so.

Conclusions: We present recommendations for designing, conducting, and reporting SRs and MAs with HOMIS.

1. Introduction

Systematic Reviews (SRs) and meta-analyses (MAs) of homeopathic intervention studies (HOMIS) face the conflict between fulfilling statistical demands and meeting the reality of daily homeopathic practice.[1–4] It is often stated that HOMIS, regardless of positive or negative outcomes, are unlikely to reflect usual practice[1,3,5,6] or are lacking in rigor to conclude that homeopathic interventions are effective when compared to placebo.[7–9] In the most recent SR of HOMIS, poor methodological quality (internal validity) was successfully addressed by proper quality assessments.[10–13] Still unaddressed problems of SRs of HOMIS are the heterogeneity of studies regarding populations, interventions, comparators and outcomes (PICOs),[4,14,15] the uncertainty whether the results are based on care as usual,[1,3] and the question whether the interventions used reflect 'good homeopathic practice'.[16,17] Besides heterogeneity, study quality and transferability of results into

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homeopathic practice, publication bias,[3,8,18] the problem of placebo-controls for complex interventions,[19–21] and the choice of included studies may have an impact on the validity of the results of SRs and MAs with HOMIS.[22] Altogether, earlier SRs and MAs of HOMIS were inconclusive regarding effectiveness in specific clinical indications.[2–6,8,10,11,13,23,25]

Generally it is recommended to include only the best available evidence, namely randomized controlled trials (RCTs), into SRs and MAs,[26] because the results of such RCTs are the least prone to bias and the strongest evidence for efficacy of any intervention. Still placebo-controlled trials maximize internal validity and, as a rule, neglect external validity.[27,28] The inclusion of controlled observational studies (COS), such as cohort or case-control studies, or pragmatic randomized studies (vs placebo as well as other than placebo controls) would balance the results of pooled evidence to a certain degree.[29] Therefore, guideline-makers encourage to broaden the eligibility criteria and include COS as well as different comparators. Some authors suggest for instance a comparison with gold standard treatments instead of placebo, as this facilitates the assessment whether a certain intervention is transferable into the conditions of therapeutic practice. These head-to-head trials are not placebo-controlled, usually not blinded and rarely randomized,[30,31] but their results provide important supplementary evidence.

When reviewing HOMIS it is especially important to include COS and pragmatic trials, because there exist only few placebo controlled RCTs per defined PICOs.[32] Furthermore, accurate planning and reliable quality assessment tools, in addition to the already existing conventional ones, are needed when undertaking future summaries of evidence of HOMIS: Homeopathy is a complete medical system,[16,20,33] which consists in individualizing the homeopathic medicine (HMP) for the patient. The inherent consequences for homeopathy research in terms of, for example, study designs and the choice of outcomes are multiple and discussed in detail in a related paper of our research group.[34] In the recommendations in the design and conduction of randomized controlled trials in homeopathic medicine[34] the wide range of implied problems in homeopathic research and the possible resulting study designs are presented there. It is logical that this variety of designs leads to a high level of heterogeneity in the existing pool of evidence from HOMIS. Keeping this in mind, we are aiming with this study to help untangle the confusion concerning the divergent results by establishing recommendations for designing, conducting, and reporting SRs and MAs with HOMIS.

2. Methods

The present recommendations were developed based on two complementary pillars.

First, the researchers' experience. We write against the background of a program to update the evidence from HOMIS.[35] The program includes an overview of controlled HOMIS,[32] a corresponding database (Link)[36] and several SRs and MAs of homeopathic interventions according to diagnostic groups, as well as a quality assessment instrument, that, for the first time, simultaneously estimates methodological rigor, interventional validity, and practical applicability of a specific homeopathic therapeutic method https://zenodo.org/records/5813499#.YwDFbi0RqT-.[38] The second pillar of the present recommendations is the result of an expert panel during which two important issues concerning SRs and MAs with HOMIS were discussed. Namely, how to assess the study quality of HOMIS and, how summarize data of RCTs and COS conjointly. Finally, it needs to be decided how and when pooling of data shall be performed.

The panel of 36 people was convened for a 2-day workshop, and a consensus discussion was moderated by the first author (KG) who also summarized the results of the panel from detailed minutes. Experts for the panel were identified by literature search and word of mouth. We counted as experts, 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 SR with or without MA (list of participants see supplement 1). For the preparation of the panel, we reviewed conventional standards and guidelines, mainly the Cochrane Handbook for the conduction of SRs[26] and the PRISMA guidelines.[39,40] Additionally, we searched specifically for guidelines regarding SRs, which include evidence from randomized-controlled trials (RCTs) as well as from COS, such as AMSTAR 2.[41] None of the experts approached refused to cooperate. Upfront, we sent a questionnaire to the experts and summarized their answers for the panel discussion. Three aims were defined for the panel: 1) to agree on one or two instrument(s) to assess the risk of bias of RCTs and COS, 2) to define, what aspects need to be considered for the summary evidence regarding a statement of confidence in the results, and 3) to agree on a meaningful format for the evidence summary. These aspects were discussed during the panel and the decisions or definitions were made at place.

Last, but not the least, we asked experts of veterinary research in the field of homeopathy who participated at the expert panel to contribute a paragraph to this manuscript with special considerations for their research area.

3. Results

3.1. Literature review and expert communications

From our experience, the literature review, and the expert communications, we recommend the following:

Researchers planning a review of HOMIS should follow the existing guidelines and general recommendations on how to conduct SRs and MAs. Thus, the researchers should:

1) Consult PubMed and the *International prospective register of systematic reviews – PROSPERO*, https://www.crd.york.ac.uk/prospero/, to find out, whether other review authors have the same research intention and have already published either articles or protocols concerning the topic of interest and in order to gain an impression of the specific pool of evidence. Additionally, consult the newly built database of HOMIS (https://www.ikim.unibe.ch/forschung/fachbereiche/klassische_homoeopathie__potenzierte_substanzen/homeopathy_clinical_trials/index_ger.html) [32,36] in order to check whether there are sufficient adequate studies on the topic of interest.
2) Consult the *Cochrane Handbook for Systematic Reviews of Interventions,* fully available online http://www.training.cochrane.org/handbook, and the reporting guidelines for SRs and MAs, viz PRISMA, available either via the equator network https://www.equator-network.org/ or via the PRISMA-website http://www.prisma-statement.org
3) Write a protocol, again following the respective guidelines http://www.prisma-statement.org/Extensions/Protocols [40] and register the protocol in a public database, e.g. PROSPERO. In this protocol all methodological aspects, such as the eligibility criteria, the choice of outcomes, when to pool or not to pool data, and how you plan to summarize the evidence from the included studies, should be defined.

It may be advisable to choose a scoping review if preliminary searches depict a small and heterogeneous study pool or to choose a narrative review, if the study pool seems substantially large but the outcomes are still heterogeneous.

3.2. Consensus of the expert panel

Additionally, we defined recommendations for reviewers of HOMIS against the background of the common pitfalls within previous reviews of HOMIS, which were identified from literature and discussed with experts. The provided solutions have been formulated during the expert panel and are shown as guidance in Table 1.

Table 1
Recommendations.

Aspect of reviews	Recommendation
1. The literature search	Extend from conventional databases to archives and other sources (e.g. websites of journals, author contacts, non-english language) in order to allow broadening the evidence base for HOMIS. Check the HOMIS database.
2. The selection of study-designs	Is preferably expanded to COS and studies using other-than-placebo controls to allow an estimate of the clinical effectiveness and clinical relevance of the results.
3. Populations, Interventions, controls and outcomes	Preferably homogenous PICOs to allow a statement to be made on specific effectiveness of particular homeopathic interventions in explicit medical indications.
4. The study quality	Include the evaluation of external and model validity alongside methodical risk-of-bias assessments. Check whether CATHIS is applicable.
5. The summary of evidence	Stick to descriptive statistics and narrative results, unless the body of evidence is sufficiently large and homogenous[a]. If so, consider meta-analysis and using the GRADE methodology.

Table 1:Sum-HomIS Recommendations in short: HOMIS=homeopathic intervention studies; COS= controlled observational studies; PICOs=Population, Intervention(s), Comparator(s) and Outcome(s); CATHIS=critical appraisal tool for homeopathic intervention studies; GRADE= Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading evidence.

[a] 'sufficiently large' depends on the size and power of the individual studies. In case of doubt, get an experts' advise.

In the following we elaborate the background behind the expert recommendations.

Literature search: establish a process to identify unpublished studies, e.g., searching so-called grey literature, such as dissertation and theses abstracts, or national databases as well as archives in order to avoid publication bias and broaden the evidence base for the review. Publication bias is defined as the phenomenon that studies published in peer-reviewed journals are much more likely to report statistically significant than non-significant results. Reversely, negative results or statistically insignificant results are often either not published at all or hidden in conference abstracts, in grey literature, or in non-English language journals. Publication bias leads to the assumption that the published studies included in SRs may not represent all studies.[42] The publication bias was explicitly and diversely discussed by two authors of previous MAs with HOMIS[3,8] and may be true for HOMIS in particular, because some original studies have been published in journals which are not indexed in data-bases for conventional medicine.[43] Therefore, some homeopathic evidence is likely to regularly remain undetected by literature searches.

There exists a new database of controlled HOMIS of various study designs, which is based on a continuously updated literature search (lastly in March 2021, next update ongoing) in more than 20 databases and archives. It includes grey literature and is sorted by medical conditions (https://www.ikim.unibe.ch/forschung/fachbereiche/klassische_homoeopathie__potenzierte_substanzen/homeopathy_clinical_trials/index_ger.html). [32,36] It may be used for preliminary searches and orientation. Literature search should be updated based on the question or condition of interest.

Eligibility criteria (selection of study designs and PICOs): it is advisable to include other study designs, such as COS and studies using other-than-placebo controls in order to increase external validity. This is recommended since populations, treatment, and outcomes investigated in placebo controlled RCTs so far, may not reflect homeopathic routine care.[1,3,44–47] Furthermore, there exists a large but very heterogenous body of evidence from HOMIS over many medical conditions and homeopathic interventions,[32,36] but only few conditions have been reviewed with regard to homogenous PICOS.[4,32] In line with the Cochrane Handbook, Chapter 3, we recommend choosing eligibility criteria as homogeneous as possible. However, PICOs and study designs in the pool of homeopathic evidence may be quite heterogenous. Thus, it is very important to have a sound explanation at protocol stage as to why the specific eligibility criteria may have been broadened.

The study quality: assess the studies' quality for external and model validity alongside methodical Risk of bias (RoB)-assessments. As the result of the quality assessment is mostly an important inclusion criterion for final analyses and conclusions of SRs and MAs, the choice of the quality assessment tool and the evaluation of different quality aspects is a crucial point to consider when planning a review project with HOMIS. Because There is a need to assess to what extent HOMIS represent both 'good homeopathic practice' and routine care and methodological high-quality research. While there exist some tools for each single quality aspect (external and model validity and methodical risk of bias assessment),[17,48–51] only one global tool, encompassing all three aspects, has been developed for HOMIS (Critical Appraisal Tool for Homeopathic Intervention Studies – https://zenodo.org/records/5813499#.YwDFbi0RqT-CATHIS).[38] We recommend using the CATHIS tool for future reviews with HOMIS. It is available online: CATHIS 2.0 template | Zenodo.[38]

The summary of evidence: as stated in the Cochrane handbook, we also recommend including studies with homogeneous PICOS in the reviews and pooling the data only if the body of evidence is homogeneous. However, as we already mentioned this is rarely the case with the existing pool of HOMIS.

We still want to emphasize the importance of a thorough summary of evidence as many reviews of HOMIS to date have been flawed by author bias that led to sub-optimal practice of summarizing the evidence. A case for debate is for example the analysis of Shang et al.[52] or the health technology assessment on homeopathy by the Australian government (National Health and Medical Research Council (NHMRC) report)[28,53,54] where among others selection bias took place. The authors of both evaluations regarding the effectiveness of homeopathy included only a small set of trials in the final analyses. In the selection of the studies they did not adhere to the Cochrane Handbook for Systematic Reviews of Interventions or best established practice, which would have demanded using all the evidence or robustly justifying their selections in advance.[7,8] Re-analyses by other authors led to different effect sizes and opposite conclusions, if different quality criteria were applied or a different cut-off value for the sample size of included studies were assumed.[22] As different types of homeopathy may have different effectiveness, these previous attempts to summarize the evidence from all types of HOMIS are problematic. Mathie and colleagues have analyzed HOMIS per type of homeopathic intervention (individualized or not) and comparator (placebo or not),[10,11,13,25] which is interesting but still not sufficient for assessing the evidence of specific homeopathic interventions in specific medical problems in order to formulate practice recommendations.

Another important issue concerning the summary of evidence from HOMIS is the choice of study outcomes: these may be heterogeneous, even in the presence of a uniform population, intervention, and comparator of the HOMIS to be included in the review project. Together, the selection of studies and outcomes for the data-pooling and the summary of evidence of the review project have the biggest impact on the results.

In view of this, the expert panel concluded the importance of more homogeneity of PICOs for future reviews.

In short, we recommend MA of data, if the body of evidence is sufficiently large and either defining one homogeneous outcome of clinical relevance or averaging outcomes within studies and meta-analyzing the averaged outcome across studies, as it is established best practice.[55] In addition, we recommend an overall analysis (including RCTs and COS such as cohort or case-control studies, or pragmatic randomized studies)

and enough sensitivity analyses in order to be able to discuss the results accurately. It should be kept in mind that all planned analyses must be predefined in the protocol.

A way to estimate the confidence in the results of the MA or the review, especially if one included evidence from RCTs and other study designs, is the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[56–58] system. Using this system for HOMIS was discussed diversely during the panel. It was generally agreed that GRADE needs a lot of experience and is only suitable, if the body of evidence is sufficiently large, e.g., five or more studies, and if similar outcomes are used across the investigated studies. In line with the Cochrane Consumers Communication paper, it appeared to many of the panel that GRADE downgrades evidence, if the pool is not sufficiently large or mainly contains RCT's.[59] Therefore, it may be more advisable to remain descriptive if there are only few studies for specific PICOs. This being decided, although advocates of GRADE recommend using the system also for narrative reviews.[60]

4. Discussion

We collected information on how to conduct and report SRs and MAs of HOMIS and formulated analogous recommendations for summarizing the related evidence (Sum-HomIS Recommendations) based on literature guidelines, expert interviews, and consensus. Five recommendations on *study eligibility, selection of study-designs, PICOs, quality assessments* and the *summary of evidence* have been formulated (Table 1). The present recommendations can be used for human and veterinary medicine likewise, because HMPs are selected for treatment based upon the most relevant symptoms and signs of the individual patient rather than common features of the pathological process as defined by diagnoses. Hence, HMPs are identical with regard to production, quality, safety, and principles of application, regardless of whether they are used in animals or humans.[61]

4.1. Findings in context of other evidence

Up until 2013, when Mathie et al. launched their 'best homeopathic evidence' project,[14] most summaries of HOMIS did not allow a differentiated debate on the most probably distinct effects of particular homeopathic intervention types, e.g. individualized, routine, complex.[16,33] The results of were therefore inconsistent [2] and flawed.[52,62] Mathie and colleagues analyzed HOMIS per type of homeopathic intervention (individualized or not) and comparator (placebo or not).[10,11,13,25] The Sum-HomIS Recommendations focus on the improvement of summarized evidence from HOMIS. For review purposes one would preferably include a set of HOMIS with homogenous PICOs[63] which was investigated with placebo controlled RCTs and pragmatic study designs (such as RCT with standard of care controls or COS). Even if such a pool of homeopathy studies only exists for few conditions [32] so far, this approach was considered as the most suitable from the expert panel. This way, a clear-cut statistical approach to the study set can be defined upfront and reviews will contribute to interesting clinical discussions or find robust results. For example, a tendency for an effect of arnica over placebo was found ($p = 0.06$), when used as a routine in the peri-operative setting.[64]

The recommendation to review a set of HOMIS which is as homogeneous as possible, underscores of course the need to repeat those high quality homeopathy RCTs that have already been conducted.[34]

4.2. Limitations

The SumHomIS recommendations are the consensus of our working group and have as such no claim to objectivity or completeness. In fact, the central recommendation to strive for more HOMIS reviews with homogenous PICOS was controversial when discussed between the authors. However, SumHomIS are what a group of homeopathy and integrative medicine review experts agreed would be best standard. The downside of this recommendation is that for most medical conditions the evidence from HOMIS is not sufficient to answer the question whether the particular homeopathic method used in the studies has a specific effect and/ or is efficient over placebo in certain clinical indications. This aspect could only be answered by sufficiently large and rigorous placebo-controlled or pragmatic RCTs, which evidently do not exist so far. More high-quality research is urgently needed. So we hope that this paper is also a call for university-based institutions with the availability of public, independent research funds[54] to engage in homeopathic research.

4.3. Impact

As the debate on the effectiveness of homeopathic interventions is still ongoing, we believe that the application of the five consensus recommendations collected above will gradually clarify the question of the clinical effectiveness of specific homeopathic interventions with regards to certain medical indications. The SumHomIS recommendations focus on real-world clinical effectiveness. This comes along with an ongoing discussion in medicine,[30,45–47,56,65,66] that evidence from clinical studies needs to be viewed alongside its transferability and applicability in practice. The fact that reviews with only double-blind placebo-controlled RCTs have brought few answers is supported by a recent review of a third of all Cochrane reviews conducted since 2008, when GRADE became widely applicable. It summarized that only 5,6% of all Cochrane reviews concluded that there exists robust positive evidence supporting the medical intervention in question.[66] In response, it is now widely supported to evaluate different treatment options by including a more heterogeneous patient sample, using real-world treatment protocols focusing on patient-centered outcomes and using a pragmatic study design.[45–47]

In this line, we want to emphasize, that homeopathy, when used individualized as per its treatment principle to treat "likes by likes" is a therapeutic approach based on an individual not on a specific clinical indication and hence, is as a method either effective or not. As there exist rigorous studies with good model validity,[67] we hypothesize that these results are transferable into other medical indications, under the premise that the treatment principles and strategies are correctly applied.[54] The consistent use of the newly developed quality assessment tool and, thus, the consistent evaluation of external and model validity alongside methodical RoB-assessments will further enhance the awareness of the importance of these aspects on the evidence base of the respective homeopathic intervention.

5. Conclusion

The Sum-HomIS Recommendations focus on the improvement of summarized evidence from HOMIS. Five consensus recommendations on literature search, selection of studies, PICO, study quality assessment and summary of evidence in SRs and MAs on HOMIS have been formulated. Their implication may clarify the debate on the efficiency, efficacy and effectiveness of homeopathy.

Author contributions

Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work was performed by all authors. Drafting the article or revising it critically for important intellectual content was performed by all authors. Final approval of the version to be published was given by all authors. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved was given by all authors.

Submission

This research has not been published previously and it is not under consideration for publication elsewhere.

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Credit authorship contribution statement

KG organized the expert communications and the panel, summarized the consensus and drafted the manuscript. HW advised the project and contributed to the design and the manuscript. SUZ coordinated the project and contributed to the expert panel and the manuscript. MF and SB contributed to the expert panel and the manuscript. PW is the corresponding author and contributed to the expert panel and the manuscript.

Conflict of interest

Some of the authors are homeopathic doctors respectively veterinarians (KG, MF, PW). Three authors are members of the board of the Scientific Society for Homeopathy (WissHom, Koethen, Germany; MF, PW, SUZ). They and all other authors have no conflict to declare.

Declaration of Competing Interest

Authors declare none.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ctim.2023.102999.

References

1 Dean ME. *The trials of homeopathy*. Essen: KVC-Verlag; 2004.
2 Hahn RG. Homeopathy: meta-analyses of pooled clinical data. *Forsch Komplementmed*. 2013;20(5):376–381.
3 Linde K, Clausius N, Ramirez G, et al. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. *Lancet*. 1997;350(9081):834–843.
4 Mathie RT, Hacke D, Clausen J, et al. Randomised controlled trials of homeopathy in humans: characterising the research journal literature for systematic review. *Homeopathy*. 2013;102(1):3–24.
5 Kleijnen J, Knipschild P, ter Riet G. Clinical trials of homoeopathy. *BMJ*. 1991;302(6772):316–323.
6 Cucherat M, Haugh MC, Gooch M, et al. Evidence of clinical efficacy of homeopathy. A meta-analysis of clinical trials. HMRAG. Homeopathic Medicines Research Advisory Group. *Eur J Clin Pharm*. 2000;56(1):27–33.
7 National Health and Medical Research Council; Australia. Australian Health and Medical Research Council (NHMRC) Information Paper: Evidence on the effectiveness of homeopathy for treating health conditions; 2015. https://www.nhmrc.gov.au/file/14826/download?token=CwhjCeTl; Accessed 11.07.2022.
8 Shang A, Huwiler-Müntener K, Nartey L, et al. Are the clinical effects of homoeopathy placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy. *Lancet*. 2005;366(9487):726–732.
9 EASAC, European Academies Science Advisory Council. Homeopathic products and practices: assessing the evidence and ensuring consistency in regulating medical claims in the EU; 2017. https://easac.eu/fileadmin/PDF_s/reports_statements/EASAC_Homepathy_statement_web_final.pdf; Accessed 11.07.2022.
10 Mathie RT, Lloyd SM, Legg LA, et al. Randomised placebo-controlled trials of individualised homeopathic treatment: systematic review and meta-analysis. *Syst Rev*. 2014;3, 142.
11 Mathie RT, Ramparsad N, Legg LA, et al. Randomised, double-blind, placebo-controlled trials of non-individualised homeopathic treatment: systematic review and meta-analysis. *Syst Rev*. 2017;6(1), 63.
12 Mathie RT, Ulbrich-Zurni S, Viksveen P, et al. Systematic review and meta-analysis of randomised, other-than-placebo controlled, trials of individualised homeopathic treatment. *Homeopathy*. 2018.
13 Mathie RT, Fok YYY, Viksveen P, et al. Systematic review and meta-analysis of randomised, other-than-placebo controlled, trials of non-individualised homeopathic treatment. *Homeopathy*. 2019;108(2):88–101.
14 Mathie R.T. , Legg L.A. , Clausen J., et al., 2013. Systematic review and meta-analysis of randomised, placebo-controlled, trials of individualised homeopathic treatment: study protocol. Version 1.0; 2013. ⟨http://www.britishhomeopathic.org/wp-content/uploads/2013/05/Study_protocol_for_systematic_review.pdf⟩). Accessed 7th June 2019.
15 Khan KS, Kunz R, Kleijnen J, et al. Five steps to conducting a systematic review. *J R Soc Med*. 2003;96(3):118–121.
16 Vithoulkas G. Serious mistakes in meta-analysis of homeopathic research. *J Med Life*. 2017;10(1):47–49.
17 Mathie RT, Roniger H, Van Wassenhoven M, et al. Method for appraising model validity of randomised controlled trials of homeopathic treatment: multi-rater concordance study. *BMC Med Res Method*. 2012;12, 49.
18 Gartlehner G, Emprechtinger R, Hackl M, et al. Assessing the magnitude of reporting bias in trials of homeopathy: a cross-sectional study and meta-analysis. *BMJ Evid Based Med*. 2022.
19 Walach H. The efficacy paradox in randomized controlled trials of CAM and elsewhere: beware of the placebo trap. *J Alter Complement Med*. 2001;7(3):213–218.
20 Walach H, Jonas WB, Ives J, et al. Research on homeopathy: state of the art. *J Alter Complement Med*. 2005;11(5):813–829.
21 Walach H., Jonas W.B., Lewith G. , 2002. The role of outcomes research in evaluating complementary and alternative medicine. 2002: 29–45.
22 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):1197–1204.
23 Linde K, Scholz M, Ramirez G, et al. Impact of study quality on outcome in placebo-controlled trials of homeopathy. *J Clin Epidemiol*. 1999;52(7):631–636.
25 Mathie RT, Ulbrich-Zürni S, Viksveen P, et al. Systematic review and meta-analysis of randomised, other-than-placebo controlled, trials of individualised homeopathic treatment. *Homeopathy*. 2018;107(4):229–243.
26 Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook. Accessed 24.8.2022.
27 Thorpe KE, Zwarenstein M, Oxman AD. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *CMAJ*. 2009;180(10).
28 Loudon K, Treweek S, Sullivan F, et al. The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ*. 2015;350:h2147.
29 Walach H, Loef M. Using a matrix-analytical approach to synthesizing evidence solved incompatibility problem in the hierarchy of evidence. *J Clin Epidemiol*. 2015;68(11):1251–1260.
30 Luce BR, Kramer JM, Goodman SN, et al. Rethinking randomized clinical trials for comparative effectiveness research: the need for transformational change. *Ann Intern Med*. 2009;151(3):206–209.
31 Tunis SR, Benner J, McClellan M. Comparative effectiveness research: policy context, methods development and research infrastructure. *Stat Med*. 2010;29(19):1963–1976.
32 Gaertner K, Loef M, Frass M, et al. Bibliography of Homeopathic Intervention Studies (HOMIS) in human diseases. *J Integr Complement Med*. 2023;29(1):14–21.
33 Oberbaum M, Vithoulkas G, Van Haselen R. Clinical trials of classical homeopathy: reflections on appropriate research designs. *J Alter Complement Med*. 2003;9(1):105–111.
34 Gaertner K, von Ammon K, Fibert P, et al. Recommendations in the design and conduction of randomised controlled trials in human and veterinary homeopathic medicine. *Complement Ther Med*. 2023;76, 102961.
35 Gaertner K. , Walach H. , Baumgartner S., et al., 2020. Update of empirical evidence: frame-work protocol for the systematic evaluation of homeopathic intervention studies (HOMIS) in humans. Version 1.0. Internet: Zenodo; 2020.
36 Institut für Komplementäre und Integrative Medizin. Homeopathy Clinical Trials; 2023. ⟨https://www.ikim.unibe.ch/forschung/fachbereiche/klassische_homoeopathie__potenzierte_substanzen/homeopathy_clinical_trials/index_ger.html⟩). Accessed 29.04.2023.
38 Gaertner K. , Hahn, R. , Razlog, R. ,et al., 2022. CATHIS 2.0 template (2.0); 2022. ⟨https://doi.org/10.5281/zenodo.5813499⟩. Accessed July 12, 2022.
39 Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
40 Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4(1).
41 Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358:j4008.
42 Sun J, Freeman BD, Natanson C. Chapter 22 - meta-analysis of clinical trials. In: Gallin JI, Ognibene FP, Johnson LL, eds. *Principles and practice of clinical research*. Fourth ed. Boston: Academic Press; 2018:317–327.
43 Caulfield T, DeBow S. A systematic review of how homeopathy is represented in conventional and CAM peer reviewed journals. *BMC Complement Alter Med*. 2005;5, 12.
44 Porzsolt F, Rocha NG, Toledo-Arruda AC, et al. Efficacy and effectiveness trials have different goals, use different tools, and generate different messages. *Pragmat Obs Res*. 2015;6:47–54.
45 Raad Volksgezondheid & Samenleving. No evidence without context. About the illusion of evidence-based practice in healthcare.; 2017. ⟨https://www.raadrvs.nl/documenten/publications/2017/6/19/no-evidence-without-context.-about-the-illusion-of-evidence%E2%80%90based-practice-in-healthcare⟩. Accessed 05.07.2022.

46 Schlegl E, Ducournau P, Ruof J. Different weights of the evidence-based medicine triad in regulatory, health technology assessment, and clinical decision making. *Pharm Med*. 2017;31(4):213–216.
47 Wieringa S, Engebretsen E, Heggen K, et al. Has evidence-based medicine ever been modern? A Latour-inspired understanding of a changing EBM. *J Eval Clin Pr*. 2017;23 (5):964–970.
48 Saha S, Koley M, Ganguly S, et al. Developing the criteria for evaluating quality of individualization in homeopathic clinical trial reporting: a preliminary study. *J Integr Med*. 2014;12(1):13–19.
49 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 Altern Med*. 2014;2014, 694804.
50 Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919.
51 Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *Bmj*. 2019;366:l4898.
52 Frass M, Schuster E, Muchitsch I, et al. Asymmetry in the lancet meta-analysis. *Homeopathy*. 2006;95(1):52–53.
53 Roberts R., Tournier A. Response by the Homeopathy Research Institute to 'the Australian report'; 2016. ⟨https://www.hri-research.org/wp-content/uploads/2016 /02/HRI-Response-to-NHMRC-Information-Paper.pdf⟩.
54 Weiermayer P, Frass M, Peinbauer T, et al. Evidence-based homeopathy and veterinary homeopathy, and its potential to help overcome the antimicrobial resistance problem - an overview. *Schweiz Arch Tierheilkd*. 2020;162(10):597–615.
55 Cooper H, Hedges LV, Valentine JC. *The handbook of research synthesis and meta-analysis*. Russell Sage Foundation; 2019.
56 Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650): 924–926.
57 Schünemann H. , Brozek J. , Guyatt G.H. , et al., 2013. GRADE Handbook: Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach; 2013. ⟨http://gdt.guidelinedevelopment.org/app/handbook/ha ndbook.html#h.buaodtl66dyx⟩.
58 Schünemann H.J.H.J. , Vist G.E. , Glasziou P. ,et al., 2021. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins J. P.T. TJ, Chandler J. , Cumpston M. , Li T. , Page M.J. , Welch V.A. (editors), ed. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane; 2021.
59 Ryan R., Hill S. How to GRADE the quality of the evidence. *Cochrane Consumers and Communication La Trobe University*. 2018;⟨http://cccrg.cochrane.org/author-resource s⟩.
60 Murad MH, Mustafa RA, Schünemann HJ, et al. Rating the certainty in evidence in the absence of a single estimate of effect. *Evid Based Med*. 2017;22(3):85–87.
61 European Parliament and Council. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to Medicinal Products for Human Use; 2001. ⟨https://www.ema.europa.eu/en/ documents/regulatory-procedural-guideline/directive-2001/83/ec-european-parli ament-council-6-november-2001-community-code-relating-medicinal-products-hum an-use_en.pdf⟩. Accessed 18.4.2022.
62 Rutten AL, Stolper CF. The 2005 meta-analysis of homeopathy: the importance of post-publication data. *Homeopathy*. 2008;97(4):169–177.
63 McKenzie J.E. BS, Ryan RE, Thomson HJ, et al. Defining the criteria for including studies and how they will be grouped for the synthesis. In: Higgins J.P.T. TJ, Chandler J., Cumpston M., Li T., Page M.J., Welch V.A., ed. *Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022)*.
64 Gaertner K, Baumgartner S, Walach H. Is homeopathic arnica effective for postoperative recovery? A meta-analysis of placebo-controlled and active comparator trials. *Front Surg*. 2021;8, 680930.
65 IOM. (Institute of Medicine). Clinical Practice Guidelines we can trust; 2011. ⟨htt ps://www.awmf.org/fileadmin/user_upload/Leitlinien/International/IOMCPGlan g2011.pdf⟩. Accessed 15.04.2022.
66 Howick J, Koletsi D, Ioannidis JPA, et al. Most healthcare interventions tested in Cochrane reviews are not effective according to high quality evidence: a systematic review and meta-analysis. *J Clin Epidemiol*. 2022;148:160–169.
67 Mathie RT, Van Wassenhoven M, Jacobs J, et al. Model validity and risk of bias in randomised placebo-controlled trials of individualised homeopathic treatment. *Complement Ther Med*. 2016;25:120–125.