Protocol of systematic reviews and meta-analyses of controlled homeopathic studies:

1.) Clinical effects of potentized drugs compared to placebo in 9 pathology-based subgroups

2.) Clinical effects of potentized drugs compared to conventional treatment in 9 pathology-based subgroups

3.) Clinical effects of potentized drugs in preventive use

Protocol of meta-analysis registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 17/08 / 2015 (registration number CRD42015025399) – Version 2.0 comprises the Original Protocol (Version 1.0 and the Amendment to the study Protocol (July 2016); potentized drugs is replaced with homeopathic medicines (HOM), when meaningful

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Contributions
MF is the guarantor. KG and LT drafted the manuscript. All authors contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria. KG, MF and MK developed the search strategy. Search was performed by an assistant and supervised by KG. MK and LT provided statistical expertise and performed the data analyses. MF and KG provided expertise on homeopathy. All authors read, provided feedback and approved the final manuscript.

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INTRODUCTION

Ultra-low doses of active ingredients and highly diluted drugs

Homeopathy is commonly known as a method for the treatment of diseases, in which medicines are applied, that have been successively diluted and shaken or tapped against a surface ('succussion'), resulting in extremely low doses of active ingredients or 'non-molecular' drugs. After the process of succussion the drugs are referred to as "potentised" or "dynamised", the various dilutions (decimal scale, centesimal scale and quintesimal scale) as potencies (X or D, C and Q or LM). This preparation was developed by Samuel Hahnemann (1, §269) and is defined for medical use in the homeopathic pharmacopeia (2). The use of such remedies is summarized under the term "homeopathy" and the remedies themselves are called "homeopathic", respectively. Their mechanism of action is not yet understood. It is assumed that the process of potentization is responsible for treatment effects of homeopathy. As Hahnemann stated, the process reveals "slumbering hidden, dynamic (2, § 11) powers which influence the life principle and change the well-being of animal life (…)". He assumes that only this process develops the "medicinal power" of a homeopathic remedy (2, §269). A molecular dose-effect from a potency above 3C (LD; low 'potencies' from D1 to C3 corresponding to concentrations between 10-1 and 10-7 mol/L) is possible, yet is highly unlikely from a potency beyond 3C. It requires the identification of possible 'non-molecular' or 'meta-molecular' information transfer mechanisms in ultra-low doses of active ingredients (ULD; medium 'potencies' from 4C to 12C corresponding to concentrations between 10^{-8} and 10^{-24} mol/L, i.e., nanomoles to attomoles) and highly diluted drugs (HD; high 'potencies' beyond 12C corresponding to concentrations above 10^{-24} mol/L) (3). Their effect other than placebo is doubted and their use criticized (4, 5). Besides active ingredients, other molecules exist in the respective preparations such as silica, alcohol, and water. However, these "background molecules" are the same in all preparations and therefore are unlikely to exert a specific effect.

Different forms of interventions with homeopathically processed drugs have been developed. To date, basically four types of "homeopathy" can be classified (6): classical or individualized homeopathy (use of only one remedy of different potencies at a time, identified after an extensive anamnesis gathering all symptoms present in the patient), clinical homeopathy (use of one or more remedies of different potencies at a time, chosen from different remedies, which proved effective for a certain disease in previous observations), complex homeopathy (use of various remedies at a time, which proved effective for a certain disease in previous observations), and isopathy (the same substance which caused the disease is potentized and administered in order to heal it).

Contrary to classical and clinical homeopathy, where the symptoms lead to the choice of the remedy, both, complex homeopathy and isopathy are frequently used for preventing diseases or discomfort. This variety of different types of homeopathy biases the scientific debate (7). Therefore, and due to the fact that some complex remedies contain a variety of potencies, we refrain from using the term 'homeopathic remedies', but give preference to 'potentized drugs'.

The homeopathic perspective

The original principle of homeopathy, "like cures like", has been stated by Hahnemann (1, §5-25). He assumed that the organism maintains health by an unknown, so far undetected, and complex power enabling it to respond to any internal or external stimuli by regulating and balancing itself (1, §10). Persistent or strong stimuli, which cannot be coped with, produce a permanent deviation from balance in terms of symptoms, which correspond to certain diseases (1, §11). By experimentation he detected that an input, which is able to produce a response of the organism similar to the imbalanced state of the sick (disease), can cure that original condition ('law of similars'; 1, §22-26). Thus, contrary to the concept in conventional medicine, persistent symptoms in homeopathy are regarded as the signs of this permanent deviation from the healthy state of the organism. When symptoms are addressed by potentized drugs according to the law of similar the organism can rebalance.

Clinical trials in homeopathy

Randomized controlled trials (RCTs) are considered the gold standard to inspect the efficacy of a medical treatment (8). The aim of RCTs is to monitor specific effects of a treatment under rather strictly controlled ideal conditions whereby internal validity is maximized (9). Though it exists a considerable amount of placebo-controlled trials of homeopathic medicines (HOM) (10), the benefit remains unclear due to the mentioned variety of 'homeopathic' interventions (11-13), and due to the limited transferability of daily medical practice into the strict RCTs conditions and vice versa (i.e., restricted external validity). In addition, as the basic concept of homeopathy is different from the one of conventional medicine, it is difficult to test its effects on human organisms with conventional designs of clinical trials (14, 15). A strategic framework to face these problems is currently under development (16).

The conceptual discrepancy might explain the gap between the favorable effects homeopathy produces when compared to conventional treatment and the small or undetectable effects when compared to placebo (17-19). Different authors claim that the real effects of homeopathy can be determined only by testing 'homeopathic care' in practice, as context factors play a significant role and can only be depicted by comparing homeopathic care with standard or alternative care using pragmatic designs (20). Effectiveness of the complex intervention as such has been shown

(21-23). This efficacy-effectiveness dichotomy remains part of the homeopathic debate (16,17). and becomes even more important in respect to the increasing use of homeopathy (24).

Meta-analyses in homeopathy

As RCTs, meta-analyses of the use of HOM face the conflict between fulfilling statistical demands and meeting the homeopathic reality (25). Regarding internal validity, former meta-analyses of placebo-controlled RCTs on the use of homeopathy showed various highly disputed problems (5, 11, 25-27). The main difficulties have been a suspected publication bias, heterogeneity and low quality of existing trials (5, 6, 11, 26).

Publication biases as indicated by asymmetrical funnel plots were identified in meta-analyses though extensive literature searches were performed (5, 11). Walach noted that reviews on peer-reviewed literature normally do not find an outcome different from placebo, contrary to reviews that include all evidence, where a difference from placebo is detected (18).

While the Cochrane Handbook for Systematic Reviews recommends to perform meta-analysis only when participants, interventions and outcomes among trials are sufficiently homogeneous, the heterogeneity index in the meta-analysis of Shang and colleagues (5), for example, was I^2=65%, representing a substantial amount of inconsistency (28). Systematic reviews and meta-analyses of the use of HOM in certain medical conditions reported different outcomes: positive, inconclusive or negative (29-34). Subgrouping of all trials was not performed in the past. Still, distinct evaluations of different medical conditions are needed, as the pooling together of studies in overall meta-analyses does not meet the needs of practitioners.

Almost all meta-analyses assessing trial quality assert low quality of a major proportion of reviewed studies (11, 25, 35). Some evidence has been produced that effect-size between placebo and homeopathy groups decreases, as methodological rigor increases across studies (36-38), a finding reported in conventional clinical research, too.

Taken together, due to these flaws, the results of most former meta-analyses on placebo-controlled RCTs have been considered inconclusive (25). Further, only Mathie met the difficulties evolving out of the different homeopathic concepts mentioned above by restricting his calculations to RCTs and classifying the existing trials as individualized and non-individualized homeopathy (25). However, the use of HOM drugs is not restricted to individualized homeopathy. Therefore, analyses should consider this (16).

Though systematic reviews of homogeneous RCTs are considered the highest level of evidence for a therapeutic treatment (8), the inclusion of non-randomized (e.g. parallel cohort-studies, other prospective controlled-trials such as quasi-randomized controlled trials) studies in systematic reviews has recently received increased attention (39, 40). Although observational

studies are usually considered at higher risk of bias, especially regarding selection bias (i.e., differences in the baseline characteristics of the participants in the different groups; 41), it is emphasized to include them in systematic reviews and meta-analyses as their higher external validity represents more closely the real-world health care conditions (42). Thus, though observational studies are not appropriate to investigate specific effects of HOM, they may disclose whether homeopathic care as a whole exerts beneficial clinical effects in practice, irrespective of its mode of action. This is in line with the reversed epistemological order claimed by Walach and colleagues for testing the efficacy of homeopathy (18) and the Comparative Effectiveness Research Group (42).
Likewise, though several meta-analyses compared homeopathic drugs to placebo, only one systematic review evaluated the homeopathy in relation to conventional treatment. This review has been carried out already 15 years ago (43) and an update is urgently needed as the widespread use of homeopathy calls for its comparison with active treatments.
Prior meta-analyses have evaluated the effects of HOM in prevention of diseases together with its use in treating diseases. As the preventive use of HOM is not consistent with the homeopathic principles, this topic should be considered separately.

A new systematic review and meta-analysis should face these difficulties and add new perspectives. In order to reflect the epidemiological reality and to increase the applicability for practitioners and the benefit for patients, subgrouping of studies into medical conditions was planned. After a preliminary literature search the systematic directory of the international classification for diseases (ICD 10 WHO; 44) was not found suitable for this purpose, due to serious overlapping of subgroups and due to the high number of categories. Thus, a pilot proposal for the subgrouping of studies was developed, taking into account the grade of pathology of the various health problems, as advanced pathologies call for a different and longer treatment than more trivial ones (Table 1). That way we assumed to achieve more homogeneity regarding participants, interventions and outcomes of the studies included in the subgroups. Furthermore, this subgrouping matches the 'homeopathic perspective' better, as one specific ultra- or highly diluted substance is administered for various health problems (e.g. Ipecacuana for vomiting, cough or bleedings). The pathology-based classification also meets the idea that potentized drugs are interacting with the biophysical regulation systems of the target organism (1, §§9-10, 3). Their effect corresponds with the limitations the regulation systems have developed over the time (e.g. acute diseases of limited time in individuals with good regulation and chronic diseases of longer duration in individuals with impaired regulation).

Pilot-classification of diseases for a meta-analysis of clinical studies with ULD and HD drugs						
Grade of pathology	Acute disorders	Chronic disorders	Complex-chronic disorders	Complex-psychiatric disorders	Pediatric disorders	Side-effects from foreign matters
Homeopathic explanation	A healthy and robust defense mechanism can react to external stimuli, such as viruses, bacteria, and traumata with acute diseases or short-term dysfunction which results in a full restore to health.	A weakened defense mechanism, for example by enduring inflammation or genetic deficits, can react to external stimuli with inflammatory or degenerative processes which results in a state of health which is characterized by a persistent disease	A previously compromised defense mechanism such as genetic major illnesses will result in a pathology, which cannot react to external stimuli adequately and produces life-long persistent pathologies	Another deficiency in response of the defense mechanism towards external stimuli and life circumstances results in functional and psychiatric disorders	Children usually have a more flexible immune system and broad spectrum of the defense mechanism to react to external stimuli → **Classifying the use of homeopathy in pediatrics separately**	The defense mechanism is reacting sensitive but adequately to an external stimulus foreign to the organism → **classify the use of homeopathy for side-effects of chemotherapy separately**
Subgroups	Acute inflammatory diseases (e.g. influenza, diarrhea etc.)	Chronic inflammatory diseases (e.g. asthma, Crohn's disease, etc.)	Polygenetic diseases (e.g. hypertension, metabolic disorders, etc.) and cancer	Functional and multifactorial diseases (e.g. migraine, vertigo, etc.)	Pediatric diseases	Side-effects from chemotherapy and chronic poisoning
	Diseases of traumatic origin (e.g. sports trauma, surgery, etc.)	Chronic degenerative diseases (e.g. gonarthrosis, COPD, etc.)		Psychiatric diseases		

Aim

The aim of the planned analyses is to systematically review the literature on homeopathic clinical studies and to evaluate by meta-analytical means whether the clinical effects of potentized drugs are different from control, with special regard to the impact of the various methods and designs used as well as to the differences throughout the various investigated pathologies. Additionally, we aim to identify publication status and quality of trials with special regard to congruence with homeopathic criteria ('model validity') and to investigate whether the effect of using HOM differs with the type of pathology.

In contrast to former meta-analyses, and in order to consider both, internal and external validity, not only RCTs but also controlled observational studies will be taken into account and a separate analysis for the preventive use of homeopathy is planned.

Thus, three systematic reviews and meta-analytical reports will be presented:

1. Evaluation of the clinical effects of potentized drugs in comparison to placebo in nine pathology-based subgroups: 1.) acute inflammatory diseases; 2.) diseases of traumatic origin; 3.) chronic inflammatory diseases; 4.) chronic degenerative diseases; 5.) polygenetic diseases and cancer; 6.) functional and multifactorial diseases; 7.) psychiatric diseases; 8.) pediatric diseases; 9.) side-effects from chemotherapy and chronic poisoning.
2. Evaluation of the clinical effects of potentized drugs in comparison to conventional treatment alone or as an add-on. Pathology-based subgroup analyses will be performed as long as > 1 study per subgroup can be included.
3. Evaluation of the clinical effects of potentized drugs for preventive purposes in comparison to control.

Prior to the analysis, we will pilot the feasibility of the proposed classification.

METHODS

Eligibility criteria

Studies will be selected according to the following criteria:

Study designs: RCTs and controlled observational studies will be included. All other study designs will be excluded.

Participants: Only studies on human organisms will be included. Participants must have exhibited a clinically relevant disease or been healthy and enrolled in a study on disease prevention.

Interventions: We will include studies employing one or more substances, which were homeopathically processed by trituration and succussion. Any Q-potency will be included. Studies analyzing mother tinctures only will not be included.

Comparators: The clinical effects of potentized drugs will be compared 1) to placebo, and 2) to conventional treatments that have shown effectiveness for the respective condition and waiting-list controls, as long as they received standard care. Studies with other types of control (e.g., waiting list without standard care, other complementary medicine methods) will not be included.

Outcomes: Outcomes will be considered as reported, and a primary outcome will be selected according to the prioritization criteria outlined in *Outcomes and prioritization*. Outcomes in all data formats (e.g., dichotomous, continuous) will be considered.

Setting: No restrictions on study settings will apply.
Time frame: No restrictions on time frame of the study will apply.
Years of publication: Research reports from 01.01.1980 to 31.07.2015 will be reviewed. Studies conducted before 1980 will not be 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 will be evaluated by the authors. Any other language will be translated by native speaking assistants.
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 will be eligible for further screening. Book chapters and abstracts will be excluded. Though peer-reviewed, published articles are usually considered as evidence of higher quality (45) we opted to not a priori exclude other types of publication, and instead preferred to determine - as long as sufficient information is reported – the quality of evidence by a thorough assessment of the risk of bias.

Information source

The databases Medline (PubMed interface), Embase (Embase interface), Cochrane Central Register of Controlled Trials (Wiley interface), CORE-Hom and CAM-Quest® (both Carl and Veronica Carstens-Stiftung), SCOPUS (Scopus interface), Science Citation Index (Thompson-Reuters interface), AMED and CINAHL (both EBSCO interface) and LILACS (Biblioteca virtual em salud interface) will be used for the literature search. The internet-based search engine ‚Google Scholar' will be used to complement the search with unpublished studies. The print-library of the Carsten-Stiftung, Essen, Germany and of the faculty of Homeopathy, Glasgow, UK, will supplement the electronic databases. We further aim to identify databases that index master and doctoral theses and conference proceedings or other 'grey' literature (e.g. Master and Dissertation Abstract International over ProQuest, OATD.org, opengrey.org).
The results of the literature search will be compared to and complemented with studies identified by a previous literature review (10). If during the acquisition of full-text literature additional studies are identified, they will be included for further screening. Data records will be managed by means of the citation manager Endnote®.

Search strategy

In 2005 a first literature review of homeopathic studies was conducted and stepwise actualized by graduated medical students of the University of Vienna, most recently 2013. The existing study collection was compared to and complemented with trials identified by a previous literature review (10). 536 studies have been identified for full-text screening. An additional

and preliminary literature search will be performed in August 2015 using the medical subject headings terms (MeSH) 'homeopath*' OR 'homoeopath*. Search limits will be set from 01.01.1980 to 31.12.2015. The search strategy might be adapted, when the database structure implicates it. Additional searches might be added if the studies found would seem limited. Literature search, conducted by an assistant, will be supervised and double-checked by MK and KG.

Study records

Two reviewers (KG and one assistant) will independently screen titles and abstracts of the literature search results for eligibility and exclude all reports that do not concern a clinical study, without an intervention of a homeopathic medicine or without control group as defined above. The full-text will be retrieved for all reports that seem to meet inclusion criteria or where any uncertainty is present. The two reviewers will decide on inclusion independently by screening the full-texts and discrepancies will be resolved by a third reviewer. Records will be entered in Excel®-files for data-handling. They will be allocated to 7 groups: 1) included-therapeutic use, 2) included-preventive use (studies, in which the intervention contains the administration of the potentized product before and after a specific exposure or intervention, will be considered here), 3) excluded-no homeopathy (e.g. phytotherapy, high dilutions without homeopathic processing), 4) excluded-no control (including other study designs like e.g. surveys), 5) excluded-no disease (e.g. muscle soreness, homeopathic proving), 6) excluded-ineligible publication (book chapters, missing full-texts despite comprehensive search and three attempts to contact the author), 7) excluded-duplicates.

Duplicate publications will be identified by comparison of author names, analyzed condition, intervention, or sample size, the most comprehensive report will be considered.

Classification into the pathology-based subgroups will be done according to the following hierarchy:

1) Every study with preventive intervention will be classified to the meta-analysis of preventive studies regardless of the pathology present in the study-subjects.

2) Congenital and psychiatric diseases will be classified accordingly even if the subjects are children. This is justified by the fact that they are advanced pathologies and thus, not comparable to other childhood-diseases.

3) Studies which include either children or subjects in which the homeopathic treatment is applied to counter-act the side-effects of a medical intervention or chronic poisoning will be classified accordingly regardless of the pathology present in the study-subjects, apart from the conditions mentioned under point 2).

4) The different pathologies will be classified according to the protocol

Allocation of the included studies to the pathology-based groups will be double-checked by two trained homeopaths (MF and KG), and discrepancies resolved by discussion. Inter-rater agreement will be calculated.

Data items

Data extraction will be performed utilizing standardized and piloted Excel-files. Two reviewers (KG and LT) will extract the data and will double-check the information independently. The following data will be extracted from the included studies:

- Publication type (substantive research article peer-reviewed; substantive research article non peer-reviewed; minor research article peer-reviewed; thesis; minor research article non peer-reviewed; master thesis; doctoral thesis; conference proceedings)
- Study aim and target population; inclusion and exclusion criteria
- Study design (RCT, controlled cohort study, case-controlled study)
- Intervention details (LD, ULD or HD remedy; potency; type of homeopathy (classical (open; restricted; selective); clinical; complex; isopathic; preventive); placebo or conventional treatment as control; homeopathy as add-on (i.e. homeopathy provided as an addition to conventional medicine as basic therapy) or not; conventional intervention)
- All endpoints and corresponding outcomes (see *'Outcomes and prioritisation'*)
- Number of patients that have participated, and that have been evaluated in each group; attrition rate; intention-to-treat or per-protocol analysis
- Statistical values: measures of central tendency and dispersion for continuous data, number of favorable events for dichotomous data; 95% confidence intervals
- Allocation to the pathology-based subgroups
- Risk of bias indicators (see *'Risk of bias of individuals studies'*)
- External validity indicators (see *'Risk of bias of individuals studies')*
- Homeopathic model validity indicators (see *'Risk of bias of individuals studies')*
- Funding and declared conflicts of interest

Cross-over studies will be included and the adequacy of the wash-out-period will be assessed as an additional risk of bias evaluation. Sensitivity analyses will be carried out.

If in a study with more than two study arms one group could be used for more than one comparison, a penalization will be applied to correct for multiple comparisons. In this case, the variance of the respective group will be enlarged by doubling the group size, so that the SD will be enlarged by the factor $\sqrt{2}$.

Nominal outcomes with more than 2 categories will be dichotomized as appropriate.

Whenever possible, results of an intention-to-treat analysis will be used. Disagreements on data

extraction will be resolved by discussion. If information should be missing, the study authors will be contacted by e-mail (maximum of 3 e-mail attempts).

Outcomes and prioritisation

One outcome per study will be identified. As we expect considerable variety in outcomes, we plan to apply the following approach in order to reduce heterogeneity: Within each pathology-based subgroup, the most often used outcome will be given priority. For the studies without such outcome, 'alternative' outcomes will be chosen with regard to clinical relevance following the approach of Mathie (6, 25) described below.

If the pathology-based subgrouping will not be feasible (≤ 1 study per subgroup), subgrouping will be performed according to similarity of the different outcomes. If outcome-based subgrouping will not be applicable, we will choose the outcomes following the hierarchical ranking approach of (6, 25):

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

Mathie (6, 25) describes this hierarchical ranking as consistent with the International Classification of Functioning, Disability and Health (ICF) of the World Health Organization (WHO; 46). This approach will be followed regardless of the main outcomes chosen in the primary study.

If there should still be multiple outcomes on the same level of hierarchy, an informed decision of the reviewer considering clinical relevance, reliability and validity of the measurement of the outcome measure will determine which outcome to include.

If there should be multiple measurements of the main outcome chosen, the last reported follow-up (measured from the start of the intervention) will be considered as endpoint to include, unless for self-limiting conditions (e.g. common cold) where the most suitable measurement point for the course of disease will be chosen.

Risk of bias of individual studies

The included individual studies were assessed in the following way:

- The internal validity of the RCTs will be evaluated by the Cochrane Collaboration's tool (47) for assessing the risk of bias in randomized trials for the seven following domains: (I) random sequence generation; (II) allocation concealment; (III) blinding of participants and personnel; (IV) blinding of outcome assessment; (V) incomplete outcome data; (VI) selective reporting; (VII) anything else.
- The internal validity of the observational studies will be assessed by the Cochrane risk of bias assessment tool for non-randomized studies of interventions (ACROBAT-NRSI; 48) for the seven following bias domains: (I) confounding; (II) selection of participants into the study; (III) measurement of interventions; (IV) departures from intended interventions; (V) missing data; (VI) measurement of outcomes; (VII) selection of reported results.

  Due to the diversity of the medical conditions in the studies to review, no prespecified confounders and co-interventions (differing between treatment and control group and potentially impacting the outcome) as required by ACROBAT-NRSI can be determined. Instead, before extracting data of the included studies, confounders and potentially biasing co-interventions will be defined for each single study and then compared to the actual ones. General confounding variables for the propensity of use of homeopathy have been shown to be a female sex and a higher education (49). These variables will be considered if applicable.
- The external validity will be assessed by the corresponding scale of the Downs and Black checklist (50) with three items: (I) whether the subjects asked to participate were representative of the entire population from which they were recruited; (II) whether the subjects prepared to participate were representative of the entire population from which they were recruited; (III) whether staff, places, and facilities where the patients were treated were representative of the treatment the majority of the patients receive.
- The homeopathic model validity will be evaluated by the six judgmental domains proposed by Mathie and colleagues (12): (I) rationale for the choice of the particular homeopathic intervention; (II) homeopathic principles reflected in the intervention; (III) extent of homeopathic practitioner input; (IV) nature of the main outcome measure; (V) capability of the main outcome measure to detect change; (VI) length of the follow-up to the endpoint of the study.

Risk of bias will be rated by MK and LT. The homeopathic model validity will be assessed by MF and KG. External validity will be rated by KG, MF, MK, and LT. Disagreements will be solved by discussion. Inter-rater agreement as well as the proportion of unclear judgment will be noted.

Data synthesis

The three systematic reviews of potentized drugs 1) in comparison with placebo, 2) in comparison with active treatment, and 3) in prevention, will each be complemented by a quantitative meta-analysis.

The meta-analytical comparison of potentized drugs with placebo respectively with active treatment will be evaluated once as an overall treatment effect, and once within the nine pathology-oriented subgroups (for each group with >1 study), in order to determine the reduction of heterogeneity due to the new classification.

Different summary tables will be presented:

- Descriptive information of the included studies
- Extracted raw data
- Risk of bias assessment.

In the distinct meta-analyses, treatment effects will be considered as follows: difference between 1) the potentized drug group and the placebo group, 2) the potentized drug group and the active treatment group, 3) the potentized drug group and the control group in the prevention studies.

For dichotomous outcomes, the OR and the 95% CI will be determined. For continuous measures, the standardized mean difference (SMD) and the 95 CI will be calculated. In order to be able to perform pooled analyses of all treatment effects, SMD will be transformed to OR (51). Non-parametric outcomes will be converted into SMD and the CI will be determined.

If not sufficient data to determine the SMD is reported, authors will be contacted. If information cannot be obtained, the SMD will be estimated by imputing relevant other data from the same study (52). If no relevant other data are available for the chosen outcome, an alternative suitable outcome will be elected.

Studies will be excluded from the meta-analysis if data cannot be extracted (i.e. when authors cannot be contacted in case of unclear or non-interpretable data).

For RCTs, unadjusted values (i.e., without adjustment for inter-group differences at baseline) will be considered. If not reported, baseline adjusted values will be employed.

For NRSs, if possible, adjusted estimates will be extracted. If in a primary study multiple adjusted estimates are provided, the model most suitable according to our assessment of the confounders will be chosen.

In order to explore the role of study design, RCTs and NRSs will be evaluated once in separate analyses, and once in a pooled analysis (53).

For cluster-randomized trials we will follow the recommendation of the Cochrane Handbook for Systematic Reviews of Interventions (52).
For each study, the appropriateness of the conventional treatment at the time of the study conduction will be assessed by two raters (MF, KG).
Whenever possible, ITT-data will be considered.
Due to the clinical diversity, a random-effects model with DerSimonian-Laird estimator will be used. Forest plots will be used for the presentation of findings.

Statistical heterogeneity will be assessed by the Q-test (significance level p = .10) and I^2 statistic according to Cochrane handbook (28): 0% - 40%: might not be important; 30% - 60%: may represent moderate heterogeneity; 50% - 90%: may represent substantial heterogeneity; 75% - 100%: considerable heterogeneity.
Subgroup and sensitivity analysis will be performed to explore sources of heterogeneity by employing meta-regression models.
Sensitivity analyses

- Risk of bias: internal validity (overall score and differentiated according to source of bias)
- Risk of bias: external validity
- Risk of bias: model validity
- Substantive peer-review research articles vs. "grey"/other type of literature
- Double-blinded vs. no/single-blinding
- ITT versus per protocol
- Dichotomous vs. continuous outcomes
- Inclusion of imputed SMD
- RCTs versus NRSs
- Cross-over design
- Appropriateness of conventional treatment

Subgroup analyses:

- Type of homeopathy (classical (open; selective; restricted); clinical; complex; isopathy)
- Whether or not the homeopathic treatment was provided as an add-on to standard care
- Within the comparison to conventional treatment: comparison of effects of potentized drugs vs. active control and potentized drugs vs. waiting-list receiving standard care
- Potency (D1-C3, C4-C12; >C12)
- Whether or not sponsor had vested interest

Once the three meta-analyses will be completed according to this protocol, further refined analyses comparing subgroups from these three different study-subsets will be carried out. A protocol will be developed accordingly.

To explore the publication bias, funnel plots, Egger's test, rank correlation test, and the fail-safe number will be used.
Analyses will be performed with the *metafor* module of the statistical software R.

Meta-biases

Meta-biases will be discussed relating to the Cochrane handbook (54).

Confidence in cumulative evidence

Confidence in cumulative evidence will be discussed relating to GRADE (55).

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