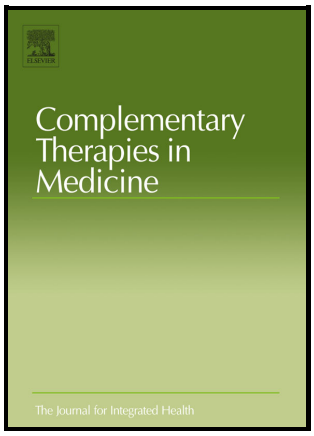

Recommendations in the design and conduction of randomised controlled trials in human and veterinary homeopathic medicineShort title: Recommendations for RCTs in human and veterinary *homeopathy*

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Recommendations in the design and conduction of randomised controlled trials in human and veterinary homeopathic medicine

Short title: Recommendations for RCTs in human and veterinary homeopathy

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Abstract

Background:

Randomised controlled trials (RCTs) are an established research method to investigate the effects of an intervention. Several recent systematic reviews and meta-analyses of RCTs with homeopathic interventions have identified shortcomings in design, conduct, analysis, and reporting of trials. Guidelines for RCTs in homeopathic medicine are lacking.

Objectives:

This paper aims to fill this gap in order to enhance the quality of RCTs in the field of homeopathy.

Methods:

Identification of the homeopathy-specific requirements for RCTs by reviewing literature and experts' communications. Systematization of the findings using a suitable checklist for planning, conducting, and reporting RCTs, namely the SPIRIT statement, and high-quality homeopathy RCTs as examples. Cross-checking of the created checklist with the RedHot-criteria, the PRECIS criteria, and a qualitative evaluation checklist. Consideration of the REFLECT statement and the ARRIVE Guidelines 2.0 for veterinary homeopathy.

Results:

Recommendations for future implementation of RCTs in homeopathy are summarized in a checklist. Alongside, identified useful solutions to the issues encountered when designing and conducting homeopathy RCTs are presented.

Conclusions:

The formulated recommendations present guidelines additional to those in the SPIRIT checklist, on how to better plan, design, conduct, and report RCTs in homeopathy.

Keywords:

randomised controlled trial, RCT, homeopathy, veterinary homeopathy, recommendations, guidelines

Introduction

The randomised controlled clinical trial (RCTs) is an established research method used to investigate the effects of a clinical intervention in a particular setting, within a sample from a specified population and with a specific research question. Studies are classified as either "more explanatory" (focus on specific effects in "ideal" situations) or "more pragmatic" (effectiveness in routine care), depending on where the study is situated on the pragmatic-explanatory continuum of intervention studies (which can be assessed using the **Pr**agmatic-**E**xplanatory **C**ontinuum **I**ndicator **S**ummary tool, PRECIS) [1]. In explanatory trials, the intervention under examination is usually compared with a placebo. The research question under investigation is *if and how an intervention works under the experimental conditions of the trial*. Pragmatic trials, on the other hand, are designed to evaluate interventions in the full spectrum of everyday clinical settings in order to maximize their applicability and generalizability. The research question under these investigations is *whether an intervention actually works in real life* [2]. For implementation of research outcomes into clinical guidelines, both research questions need to be answered, and therefore both types of research are required [3]. It is challenging in the extreme to design a single RCT that combines methodological rigor (internal validity), practical clinical relevance (external validity), and fidelity to the intervention as it is intended (model validity) [4-6]. Furthermore, large parts of the existing evidence from RCTs are insufficient for practice recommendations with regard to medicines and procedures [7].

These shortcomings emerge especially in complementary and integrative medicine (CIM) because CIM largely consists of complex interventions that are particular to the therapeutic approach and are more challenging to test with blinded, placebo controlled RCTs [8-10]. They

are, however, applicable to complex interventions in conventional medicine. Therefore, CIM scientists have developed pragmatic RCTs, comparative effectiveness studies, as inventive adaptations to the classic RCT design [11-13].

For individualized homeopathic interventions, the following particular factors are inherent to the therapeutic approach [14] and have to be taken into account when planning an RCT:

1) Individualization: a homeopathic medicinal product (HMP) is selected for a given individual based on his/her individual symptoms. Thus, the study intervention in the trial may consist of many different HMPs. A consultation with an expert in homeopathy is required to identify the individualised HMP.
2) Case-taking: the case-taking differs from most settings of conventional medical practice. It is often more detailed and not only symptoms that belong to the disease, but also other symptoms and characteristic signs of the individual are collected and taken into consideration for the homeopathic treatment (similar to the bio-psycho-social approach).
3) Outcome and flexibility. Homeopathic treatment is considered to be an iterative process whereby HMPs, potency, dose (repetition), and application may be changed. For example, after taking the first HMP, the symptoms may change and thereby lead to a more suitable subsequent prescription.
4) Outcome and follow-up: intervals and prescriptions are tailored to the individual course of the disease and the individual's general health status after the intervention.

To limit some of these variables, some authors have therefore used more easily reproducible HMP selection strategies, such as symptom cluster or other semi-individualized approaches, some within an explanatory trial design [15-18]. Others have adopted a pragmatic study approach to test the effectiveness of individualized homeopathy as experienced in clinical practice, compared to usual care, using randomized designs such as comparative effectiveness research (CER) [18-20], trials with an observational run-in-phase [21], and trials within cohorts (TwiCs) [13,

[22, 23], as well as non-randomized cohort designs [24]. Other researchers have decided to investigate non-individualized homeopathic treatment compared to placebo instead [25]. Still, RCTs with placebo control are seen as „gold standard“ for evidence of efficacy of medical interventions [26, 27]. Of course, testing homeopathy with this design is also important [11], but many RCTs may not reflect usual homeopathic care. Therefore, researchers developed a method to appraise the model validity of homeopathic treatment in randomised controlled trials in humans, and used this method in subsequent reviews of the homeopathic literature [4, 5, 25, 28-30].

Added to this, recent systematic reviews and meta-analyses have identified some shortcomings in the conduct, analysis, and reporting of homeopathy RCTs in human and veterinary medicine [31-38]. These deficits are found in placebo-controlled as well as other-than-placebo-controlled trials, and with individualized as well as non-individualized homeopathy [31-34].

In addition to the difficulties in the design and high costs of RCTs in general, in many countries in Europe, there is no university-based research infrastructure for CIM, including homeopathy. Ten years ago it was found that: ‘There is almost no significant investment in any EU country in a [complementary and alternative medicine] CAM research structure or strategy’ [39]. This situation has not changed. It also implies that, in the field of homeopathy, there are not many researchers within the EU with a full methodological education and experience in conducting RCTs.

1. Aim and objective

This paper aims to enhance knowledge about the issues concerning the quality and applicability of RCTs in homeopathy, giving recommendations for their design, planning, conduct, and reporting. It highlights the challenges of RCTs when respecting the specific

requirements of studies on individualized or non-individualized homeopathy. Furthermore, it describes differences in methodological issues between trials in human and veterinary homeopathy. It hopes to inspire and encourage researchers to formulate precise research questions and presents guidelines for future homeopathy RCTs based on

1) existing guidelines for the planning [6, 38, 40, 41] and reporting of clinical trials, especially RCTs [42-44],
2) the RedHot-criteria, i.e. the supplemental CONSORT statement for reporting data on homeopathic interventions [45], and
3) literature on existing innovative trial designs for researching homeopathic treatment [13, 15-18, 21-23].

2. Material and method

In the first step the features of RCTs and homeopathy-specific requirements were identified from the literature and from experts' communications. As a basis for discussion, the overview of homeopathy trials by Mathie et al., 2013, was used during the HRI conference 2019 at a workshop on *"Recommendations of high-quality research in homeopathy"* [46]. The participating experts were invited to contribute to the project. Furthermore, KvA and KG invited the researchers who conducted homeopathy trials with innovative designs to contribute their expertise. Also upfront, one of the authors (KvA) screened guidelines and checklists for planning, conducting and reporting RCTs and discussed his findings with the other authors (MFE and KG) and during the workshop. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement by Chan et al. [41] was found the most eluted checklist and was taken as a basis for the present homeopathy trials guidance. This template was supplemented with detailed considerations for homeopathy, from the collected experts' experiences. The experiences were then systematized using an adapted Delphi process by e-mail rounds and calls, if needed. In this way, a research pathway towards

diverse types of RCTs with homeopathy-specific additions was outlined and practical guidelines were formulated.

Finally, the checklist was cross-checked with the RedHot-criteria for reporting [45], PRECIS [1, 47] and the checklist of Bornhöft et al. [6] for additional consideration of external validity. For reporting of RCTs in veterinary homeopathy, for farm animals the REFLECT statement and for experimental animal research the ARRIVE Guidelines 2.0 as well as more disease specific guidelines were consulted [43, 44, 48].

3. Results

3.1. Key features of RCTs as an explanatory trial design according to Kendall et al. [40]

1) The study addresses a focused research question in terms of PICO (population studied, intervention given, comparator chosen, outcomes measured).
2) The sample to be studied should be appropriate to the hypothesis being assessed so that any results are correctly generalizable – as far as possible. The study should recruit sufficient patients to allow a high probability of detecting a clinically relevant and statistically significant difference between treatments if a difference truly exists.
3) There should be effective (concealed) randomization of the subjects to the intervention/control groups (to eliminate selection bias and minimise confounding variables).
4) Groups should be similar at the baseline and treated identically in all aspects, except for the intervention being evaluated. This aim is maximised via randomisation.
5) Trial participants, clinical investigators, and statisticians should be blinded to which group an individual is assigned.

6) Patients should be analysed within the group to which they were allocated, irrespective of whether they experienced the intended intervention (analysis by intention to treat, ITT).
7) The analysis should focus on assessing the research question that initially led to the trial (that is, according to the a priori hypothesis being assessed), rather than "trawling" to find a significant difference. Outcome measures will be state-of-the-art and representative, statistical methods will be rigorous.
8) The study protocol and summary should be submitted to a clinical trials registry or to an equivalent trial platform – and before the trial has commenced.

The features should comply as far as possible with the risk of bias assessment in a randomized trial as recommended by Cochrane [49], or by SYRCLE (adapted for animal research only [50]). They are commonly used to determine a trial's quality.

S*ampling* should follow CONSORT guidelines [42]. A representative study sample should be selected and inclusion and exclusion criteria clear. Usually, the sampling strategy is consecutive sampling, though stratified sampling may be required. A sample size calculation is ideally based on preliminary results of previous (pilot) studies to allow appropriate planning. The importance of a pilot study is to be emphasized not only for power calculation, but also to try out the feasibility of the study design, setting, recruitment, intervention, outcome measurement etc. Submission for ethical approval for an extension in the case of a larger study to follow must be considered in the study protocol (termed an internal pilot), as compared to a standalone pilot study (termed an external pilot).

Randomization should be concealed from the investigator. This minimises confounding variables and is the basis for establishing a causal interpretation for an intervention. It should be stratified (to ensure equal distribution of potentially confounding variables such as study centre/s, gender, age, severity of the disease-condition, time of entry, or others; and to enable proper subgroup analyses) and may be blocked (appropriate for smaller samples). The method

of randomization should be predetermined in a statistical analysis plan, which allows demonstration of the robustness of the results, and included in a (published) study protocol and/or Clinical Trials registry. If possible, a computerized randomization program should be used. All randomization procedures should also be reported in the trial write-up.

Allocation concealment should be used to prevent selection bias when assigning participants to intervention groups. Actual and future allocation to intervention groups is concealed e.g. by allocation per patient in consecutive opaque envelopes to patients, practitioners and researchers and is only revealed after termination of the study and analysis of the results. [49]

Blinding should be done at the stage of applying the intervention, if possible (verum and placebo will be indistinguishable to the patient and to the investigator = double-blind), when measuring the outcome (blinding of outcome assessor), and ideally when analysing the results (blinding of statisticians). This is essential to avoid performance and ascertainment bias. The intervention and the control should be handled similarly in every respect.

ITT analysis allows unbiased comparison of the groups by including all randomised participants (including drop out) and measurement of all intended outcome measures. Thereby, attrition bias is avoided.

Per-protocol-analysis consists of those participants who adhered to the protocol completely in every respect. The results show treatment effects under optimal conditions, but violate randomization rules, with the consequence of overestimating treatment effects.

Furthermore, *incomplete outcome data* as well as *selective outcome reporting* should be avoided: all collected and completed data should be considered for statistical evaluation.

The *method of measuring the outcome* should be appropriate, in accordance with a pre-specified analysis plan (study protocol), finalized before unblinded outcome data were available for analysis and any difference between intervention groups should be avoided.

There are ethical and practical limitations for the use of an RCT design to answer clinical research questions; clinical equipoise (the equality regarding probability of benefit and harm

that must exist between two or more groups being compared in a study) must be taken into consideration [51]. For example, it is unethical to expose patients to an intervention that is believed to be inferior to current treatment, to use possibly harmful treatments or to randomly allocate patients to placebo and withhold a possibly effective treatment. For a short period of time, if there is no life-threatening disease and if the patient (or the animal owner in the case of veterinary research) consents, that may be a question of debate. Practically limiting factors may be lack of resources, or the fact that new interventions are of unknown effectiveness and may be dependent on innovative clinicians' skills.

Therefore, RCTs should be considered only if there is enough preliminary evidence that the intervention is likely to be beneficial (e.g., from observational studies), including some estimation of the size of the likely treatment effect and that presumed costs are justified by the expected benefit.

3.2. Implications for RCTs in homeopathy

Literature dealing with the abovementioned issues was found to be scarce. During expert panel and the following Delphi process the following factors were identified to need special consideration depending on the research question of the respective trial [38, 40]:

3.2.1. *Representativeness and sufficiently large sample size and resources* (corresponds to item 2 of the key features of RCTs as an explanatory trial design according to Kendall et al. [40])

- Patients' affinity to homeopathy could lead to selection bias.
- Patients' preferences could lead to under-recruitment, as is the case for every RCT. E.g., a request for receiving the intervention under investigation could result in patients' unwillingness to receive the control intervention [52].
- There may not be preliminary data available for sample-size calculations.

- Lack of financial resources and staff could lead to difficulties in recruitment (e.g., in single-centre studies) as in RCTs in conventional medicine. In general, there is a lack of financial resources and infrastructure at universities for homeopathy research [39].

3.2.2. *Type of intervention and comparator* (corresponds to item 1 [40])

- The homeopathic intervention is often not standardized and, due to individualization, different knowledge and skills of the homeopathic doctors or veterinarians can have a major influence on the result. Hence, the education and experience of the homeopathic practitioner(s) needs to be described. Also, the method of medicine-selection needs to be described in detail, to enable replication of the treatment.

- Without meticulous adjustments, placebo HMPs are often regarded as unsuitable comparators, because they do not depict the non-specific, multi-dimensional nature of the homeopathic process. The same is true for complex interventions within conventional medicine [8]. In these cases 'Best usual care' may be considered as a comparator to homeopathic treatment using more pragmatic designs. Whether a researcher chooses a placebo-controlled trial, or a pragmatic trial depends on the research question.

3.2.3. *Blinding* (corresponds to item 5 [40])

In placebo-controlled trials with individualized prescription, blinding could cause confusion for the investigator during follow-up assessments. If symptoms are still present or even worse during the follow-ups, the investigator might think that the patient has got an unsuitable HMP or may wonder whether the potency, dose and application have been appropriate [53]. Even though the assessor will be uncertain whether the patient has received placebo or verum, he/she should follow his/her usual procedure. In pragmatic trial designs, blinding of participants or homeopaths

is not possible, e.g., with 'usual care' or 'standard treatment' as a comparator. However, any possibility for blinding needs to be considered and used (for example the double-dummy method, blinding of statisticians and/or assessors).

3.2.4. *Outcome analyses* (corresponds to item 6 and 7 [40])

Suitable outcome measures for the specific problem under investigation need to be chosen. Ideally these should be piloted to assess whether they are appropriate to capture the non-specific changes that occur during the homeopathic process. Alongside disease-specific outcome parameters, detection of non-specific effects such as changes in the general health and well-being status of participants may serve as secondary or tertiary outcome parameters. All outcome parameters need to be suitably objectified (e.g., by using validated scales and questionnaires where applicable). In chronic complaints changes of symptoms develop over a lengthy period. A flexible, appropriate long-term follow-up (e.g., 2 or more years) as trial endpoint may be needed to detect these changes, raising costs. Therefore, short-term diseases might be preferred for RCTs. However, it may be worth it to capture the potential of homeopathic treatment to address long-term chronic disease.

3.2.5. *Ethical and legal implications* (corresponds to item 8 [40])

Previous research that informs a pre-trial calculation of probability or effect size is often not available for homeopathic interventions. In this case or in clinical problems with insufficient treatment effects from conventional therapeutic options, RCTs are recommended to be designed as add-on trials.

Laws concerning research with HMPs may be different in different countries, even within the EU [24]. Nevertheless, approval by an ethical committee is mandatory in any medical research project in humans or animals. Prospective trial registration of human and veterinary clinical trials in a public registry such as ClinicalTrials.gov respectively the Veterinary Clinical Trials Network [54] is needed.

3.3. Special considerations for RCTs in veterinary homeopathy

1) RCTs in veterinary homeopathy may be more cost-efficient as in most cases insurance is not needed for study participants and large numbers of farm animals can be treated under standardised circumstances more easily. For epidemiological diseases in farm animals, for example, the same HMP can be used for the whole herd which can be treated as one individual [55]. Yet, independent replications of high-quality RCTs in veterinary homeopathy are recommended. Furthermore, special consideration of potential confounding factors like management and environmental changes and non-independency of animals within a farm may be needed.
2) HMPs in farm animal practice are often administered via drinking water. Therefore, the person administering the medicine does not come into direct contact with the investigated animals; consequently placebo effects can be excluded [56].
3) Further to this, HMPs without indication are similarly used in animals and humans and, thus, the basic considerations for veterinary homeopathy trials do not differ from the ones presented above [56].

4.4. Questions to be asked and detailed guidance for homeopathy RCTs

4.4.1. Representative and sufficiently large sample size and resources

Is the *study sample* representative of the relevant population? For a *representative and sufficiently large sample size*, the way of recruitment needs to be chosen thoughtfully and data of previous epidemiological studies may be considered. Pre-trial observational studies and feasibility trials are recommended [5, 13, 15, 17, 42, 57-59]. For homeopathy, this has brought valuable information for the conduct of upcoming larger trials [13, 15-18] and allows realistic estimation of necessary resources and sample size.

4.4.2. Costs

What is the *cost* of the study? In the UK, it is estimated that a pragmatic RCT using the TwiCs design [13, 60] costs £50,000 for 100 participants (PF; personal communication). Commonly for RCTs with about 100 participants and five visits, € 5.000 up to € 10.000 per participant should be calculated in Switzerland (Clinical Trial Unit, University of Bern; personal communication). In a systematic review of RCT costs, the total cost per patient is reported to be $43 to $103,325 [61]. Multi-centre studies should be considered but will increase complexity and costs. It may be suitable to consider a "responder-only" design in order to reduce the number of participants, as done by Frei et al. [21]. However, in this design the study results must be interpreted with caution, since pre-treatment with the fitting HMP(s) might limit the magnitude of the response during the RCT part of the study.

RCTs in veterinary medicine are considered to be less expensive in general as no insurance is needed. At least € 50.000 needs to be calculated for a feasibility or pilot veterinary study in hundreds (e.g. pigs) or even thousands (e.g. turkeys) of animals. These estimations have to be adapted according to the conditions in the respective country.

4.4.3. Type of intervention and comparator

Which *type of intervention* should be chosen? Individualized homeopathic treatment comprising a series of fact-finding consultations and individually tailored HMPs which can be changed over time. Semi-individualized HMPs (e.g., the HMP is chosen out of a list, using a questionnaire); non-individualized (every participant is given the same HMP); or complex non-individualised homeopathic prescription (every participant is given the same multi-medicine HMP)?

The effect of the *individualized approach* may be influenced by the prescriber and, as such difficult to reproduce. In single-prescriber trials, it is therefore appropriate to report the prescription method in detail (e.g. software and analysis approach used). In the case of multiple prescribers, stratification or randomization of the prescriber might be considered. Another solution might be to use consensus of at least two experienced homeopathic doctors/veterinarians for selection of the HMP in individualized homeopathic therapy. In a semi-individualised approach the treatment can be reproduced but is influenced by strictness of the prescription criteria used for the HMP selection, and runs the risk of inappropriate prescription. Non-individualised approaches are easiest to reproduce but run a substantial risk of inappropriate application.

4.4.4. Timing of baseline assessment and randomization using an individualized approach

The baseline-assessment should be carried out before case-taking if it is intended to test the effect of HMPs, because the homeopathic case taking may have a therapeutic effect by itself and lead to a false baseline.

For the latter reason, in a *placebo-controlled trial*, randomization should happen *after* the homeopathic case-taking. This was successfully implemented in exemplar trials [15, 16].

In *pragmatic designs*, in which the control group receives usual care and (semi-)individualized homeopathic care provided as an add-on, randomization should be performed *before* the homeopathic case-taking, because the intention is to test the homeopathic approach as a whole, including the case-taking *and* the prescribed HMPs [18].

If the intended intervention is a *standard single or complex HMP* that is the same for all subjects, randomization can be performed *before or after* the baseline-assessment (depending on the facilities present).

4.4.5. Co-interventions

How to deal with *Co-interventions*? Co-interventions may be a component of usual care. Therefore, whether co-interventions are or are not permitted requires consideration. If permitted, they should be described in detail, be equal for both/all treatment groups to avoid confounding. Add-on designs are particularly suitable where co-interventions are allowed.

4.4.6. Consideration of the multi-dimensional, non-specific nature of the homeopathic intervention

How to deal with the *multi-dimensional, non-specific nature of the homeopathic intervention*? Consideration needs to be made of the components of the homeopathic intervention: the HMP; the application of homeopathic principles; and the homeopathic consultation [4]. Therefore, from a clinical perspective, the most meaningful intervention might be 'treatment by a homeopath', and the most useful comparator may be "standard medical treatment / usual care / best practice). But from a scientific perspective, interest has always been on differentiating between placebo and verum HMPs.

To investigate the multi-dimensional components of homeopathy, when HMPs are compared, a three arm RCT might be considered: group 1 (HMP); group 2 (placebo HMP); group 3 (usual care). Or third group with no homeopathic consultation might be added as comparator [42], as done by Frass et al. [62].

In explanatory placebo controlled RCTs of HMPs, participants in both groups should receive the same number of consultations within the same time frame.

4.4.7. Blinding

Does adequate *blinding* remain a problem for individualized studies? Blinding of the homeopathic prescriber may bias the result (see above, *4.2.3.*), as individualized homeopathic therapy methodically implies adaption of the HMP and dosage during the course of treatment [53]. Potential changes (like worsening of all/some symptoms, amelioration of all/some symptoms, combinations of worsening/amelioration of some symptoms, appearance of new symptoms, no change in symptoms) and how to deal with them need to be described in the protocol in advance. Known reactions to HMPs (e.g. 'initial aggravation', 'drug proving symptoms') [45] may effectively unblind the homeopathic prescriber during follow-up. Potential "unblinding" occurs in conventional trials, too.

. Sufficient experience and resources need to be arranged for the preparation of either a placebo of the HMP and/or the conventional medicine. Both should be delivered by the same administrator, who should be the only person apart from the randomiser, to know group allocation. Depending on the availability of resources, double-dummy-studies may be considered [63].

4.4.8. Outcome analyses

Which *outcome measures, measurement-tools, and adequate analyses* are suitable for planning and conducting a homeopathy RCT? In general, resources are needed for a blinded outcome assessor, multiple outcome-measurements and to keep participants in the trial for outcome-assessments, even if they "dropped-out" from the intervention (= ITT analysis). Besides changes in the specific condition examined, treatment effects may be non-specific, influencing general well-being, and overall health. Specific facets of homeopathic treatment which may need consideration are: direction of cure, symptom-shift, minor symptoms. These may be considered in the protocol [8]. Therefore, it is desirable to have several outcome measures evaluating different aspects of the results of the intervention (e.g.

objective biomarkers, subjective patient reported outcome-measures (PROMs) and outcome measures with validated and reliable scales), as in Macías-Cortés et al. 2017 [63]. Therefore, data handling in RCTs on homeopathy can be more complex than in RCTs on conventional medicine. Additionally, possible adverse events and reactions towards HMPs (e.g., initial aggravation and proving symptoms) need to be measured and reported [64].

4.4.9. Safety

How about the *safety* of homeopathy? The safety of homeopathy is one of its acknowledged features and should always be documented. This is done by evaluating the incidence of adverse clinical events and pathologic laboratory results, graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events [65] as well as the European Medical Agency (EMA) glossary and updated versions of ICH-GCP-guidelines. An adverse effect is an inadvertent harmful event resulting from a medication or other medical intervention. In homeopathic trials, distinction must be is made between an adverse event and a homeopathic aggravation [64].

4.4.10. Ethical and legal implications

Are *ethical and legal issues* tackled? Prior approval by an ethical committee is mandatory. Ethical issues need to be managed when working out the dosage of the study intervention and the choice of the comparator. Clinical equipoise needs to be considered [51]. Not depriving patients from a possibly effective treatment is another consideration.

4.5. Examples of innovative designs for homeopathic RCTs

In systematic reviews assessing also model-validity [28, 29], four homeopathic RCTs with individualized strategy [66-69] and one with a complex HMP [70] have been found to be of low risk

of bias along with good homeopathic model validity. However, these systematic reviews considered only trials with placebo-control and parallel-group RCTs.

RCTs with other designs and/or comparators are yet to be summarised in systematic reviews: thus, some innovative homeopathy RCTs are presented here. They include features to fit the requirements of both, conventional medicine, and homeopathy:

4.5.1. The *responder-only design*

This is an RCT with a preceding observational study with classical (= individualized) homeopathic analysis and HMP prescription, and an ensuing phase, with randomization and allocation into two groups, of only those participants who reached a pre-determined threshold of success in the observational phase. This design was implemented in a Swiss trial in children with Attention Deficit Hyperactivity Disorder (ADHD) [21]. This crossover design RCT was nested in a prospective observational study and consisted of three phases: A screening phase started with classical HMP finding, until improvement of at least 50% or 9 points of Conners' Global Index (CGI, max. 30 points) was reached. Then the child and family were asked for participation in a double-blind crossover RCT phase of two crossover periods of six weeks duration each with verum or placebo treatment. The third phase was an open-label follow-up of 18 months with possibilities to change HMPs, if needed. Outcome parameter were CGI values after screening, during the RCT and open-label phases, a qualitative assessment of the child's behaviour and a performance cost evaluation at the end of study [71]. Disadvantages of a crossover study are the longer duration compared to parallel studies, different baselines at the beginning of period 1 and 2, and possible carry-over effects.

4.5.2. Semi-individualized trials

Trials with semi-individualized or semi-standardised HMP-selection are

designed to make replication of treatment easier. They allow individualized homeopathic treatment with a limited number of HMPs and use strict criteria for HMP selection (independent of the homeopath). The HMP selection is based on a questionnaire, with 'symptom clusters' indicating specific HMPs [15, 16] or with processing of the questionnaire outcomes by a computerised algorithm [17, 18]. The disadvantage of a limited number of HMPs is that only a proportion of the patients with the medical condition under investigation would benefit (see: 4.5.2.1.). Allowing free HMP prescription at follow-up could partly solve this problem (see: 4.5.2.2.), but this renders blinding of the physician impossible.

4.5.2.1. An example of an *explanatory, placebo-controlled semi-individualized trial* is a project with a 'symptom cluster approach' in women with premenstrual syndrome (PMS) [15, 16]. All eligible women consulted the study homeopath. Women, whose symptoms matched one of the 5 (in the pilot study) or 14 (in the larger study) pre-selected HMPs, were randomized to one of the treatment groups, homeopathy, or placebo. Those, whose symptoms did not match one of the pre-selected HMPs were not included in the RCT but were allocated to a parallel trial.

4.5.2.2. An example of a *pragmatic semi-individualized trial* is an international trial, also in women with PMS, with 11 pre-selected HMPs for the homeopathic add-on treatment and 'usual care only' for the control group [17, 18]. Women in both groups continued the usual care they were having before the study. After randomization, women in the homeopathy group additionally consulted a homeopathic doctor and received one of 11 pre-selected HMPs, as indicated by an electronic algorithm. At follow-up, change of the HMP was allowed. Women in the usual care group were

advised to consult their general practitioner (GP), if they had not done so before. Otherwise, they continued their usual care.

4.5.2.3. *prognostic factor analysis* (PFA). In successfully treated patients, the selected symptoms that indicate a specific HMP can be either confirmed, validated, or their value can be questioned. Thus, the outcomes of the study can be used to make the specific treatment more accurate. PFA was performed with data of the previously mentioned pragmatic PMS trial [72].

4.5.3. Cohort multiple randomised controlled trials, or Trials within Cohorts (TwiCs) as it was re-named, are specific versions of pragmatic design, suitable for testing multiple interventions. The TwiCs design is a pragmatic approach to randomised trials in which trial participants are randomly selected from an existing cohort. The design has multiple potential benefits, including the option of conducting multiple trials within the same cohort whereby all tested interventions are subject to the same biases:

4.5.3.1. A cohort of 144 children with ADHD was recruited, and a three-armed RCT conducted whereby 83 randomly selected patients were offered treatment by homoeopaths or nutritional therapists, 72 accepted, and outcomes of 50 with more than one appointment were collected from carers and teachers. Their outcomes, measured by Conners Global ADHD Index were compared with those not offered interventions [6, 13].

4.5.3.2. The effectiveness of adjunctive treatment by homeopaths compared to usual care alone was tested over a period of 12 months in patients with self-reported depression. One third of 566 patients were randomly selected for an offer of treatment provided by a homeopath from a pre-existing cohort [23]. The unequal randomization enabled a large-scale cost-effective study.

The main limitation of this approach is the lack of blinding. Also, this design is only suitable for testing whether additional homeopathic care has an additional effect to usual care.

4.5.4. Hybrid (explanatory and pragmatic) 3 armed design (verum, placebo, and usual care) [62, 63]: A hybrid approach was used in a recent randomized prospective, placebo-controlled, double-blind, three-armed multicentre controlled evaluation of survival as well as of Quality of Life (QoL) by questionnaires in patients with advanced non-small cell lung cancer (NSCLC) [62]. The authors planned to compare the treatment outcome, receiving verum or placebo homeopathic treatment in a conventional double-blind design. A third group without any homeopathic intervention was observed regarding survival and served as non-interventional control group. The third group consisted of patients declining to participate in the double-blind part of the study. Those patients underwent standard care alone without homeopathic intervention/treatment (neither verum nor placebo). This third arm was necessary to answer the question about the difference between medication and the homeopathic intervention itself [73]. Otherwise, one could hypothesize that the act of homeopathic intervention itself might have a significant effect which could be valuable to these terminal patients, yet the study design ruled out such a scenario. The limitation of such an approach is usually the lack of sufficient resources.

4.5.5. The *"selected condition – selected HMP" design*.

In some clinical conditions only one or few suitable HMPs are indicated and prescribed, e.g., so-called *clinical* or *routine prescriptions* and prescriptions in endemic situations (*genus epidemicus*).

This approach was implemented in patients who have been intubated and could not be weaned from the respirator due to copious and very viscid bronchial secretions. The HMP potassium dichromate 'Kalium bichromicum' fits to this clinical condition and was assessed in a placebo-controlled RCT. Possibly, the limitation of this approach is the limited number of eligible patients.

4.5.6. Another example, from veterinary medicine, is an RCT for the prophylaxis of diarrhoea in piglets caused by the bacterium Escherichia coli (E. coli). Mother sows were given either the HMP or placebo as prophylaxis. E. coli diarrhoea in piglets is in principle a well suited and comparatively simple model to investigate the efficacy of one HMP in a RCT in a large number of animals under standardised conditions [55]. Thus, for studies in veterinary homeopathy, however, this is a very suitable design.

Add-on studies are a means of evaluating the effectiveness of the homeopathic method in general. This design may be suitable for various conditions and some RCTs have been conducted successfully with this add-on design, for example in patients with cancer [62, 74-76]. However, if efficacy of a special HMP should be proven, a placebo RCT is needed, but features of individualized homeopathy are, then, often neglected.

Another possibility for the control treatment in a pragmatic trial is an active waiting list (with promise of treatment), as was successfully demonstrated in a study on children with upper respiratory tract infections [77].

4.6. Expert opinion

Taken together the discussion of these examples of innovative designs, many special considerations are needed to properly design, plan, conduct and report RCTs in homeopathy. These efforts suggest the need for support by experts in homeopathic research for future RCTs in the field.

The following detailed guidelines, including a step-by-step checklist for planning an RCT in homeopathy, summarise the consensus met by our research group. They may, however, not be complete, as each clinical condition and consecutive homeopathic research question has its own particular implications, which might not be specifically mentioned in the overview or not be covered by the checklist.

4.7. Checklist for planning, conducting, and reporting RCTs in homeopathy

All RCTs require a protocol describing the rationale, methods, data management and statistical analysis plan as well as regulatory details from trial inception to reporting of results. As every study protocol is the base for successful conduct and robustness of a study, a comprehensible protocol checklist is supposed for summarising recommendations for RCTs in homeopathy. The available protocol guidelines and checklists for RCTs are in general not consistent for use in homeopathy [78]. However, after a literature-review, the most suitable template that we have identified for our purpose is a checklist of protocol items for clinical trials (SPIRIT) by Chan et al. [41]. The structure of this checklist allows a stepwise consideration of the following items: Administrative information, Introduction (rationale, objectives, and design), Methods (participants, interventions, outcome measures, blinding, randomization, data-handling, and monitoring), and, lastly, Ethics & Dissemination.

The checklist of items for the REFLECT statement as well as ARRIVE Essential 10 / ARRIVE Recommended Set were considered especially for veterinary homeopathy in farm animals respectively in experimental animal research [43, 44].

By discussion, the SPIRIT checklist was adapted so that it may serve as a standardized base for future conduct of homeopathy RCTs. To reach this, for each item of the checklist, we included the previously collected recommendations and above elaborated "Questions to be asked and detailed Guidelines" for RCTs in homeopathy and added more detailed information regarding formulation of the research question, compilation of the research-team, budgeting, the choice of design and comparator, cohort biometric planning, quality control, and the necessary regulatory aspects.

The summary of our findings is depicted in Table 1, an adapted version of the SPIRIT checklist whose right-hand column reflects homeopathy-specific considerations.

Table 1: Adapted SPIRIT-Checklist to address homeopathy RCT requirements

Adapted SPIRIT-Checklist to address homeopathy RCT requirements with new/added column 4[1]			
Section / item	Item number	Description	Recommendations and considerations ***(adapted, specific to homeopathy in italics and bold, for further explanation see: Supplement 1 Guidance for homeopathy RCT)***
Administrative Planning			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Preliminary formulation of the research question and a working title. The final title may slightly change depending on the choice of study design, population, interventions.
Trial registration	2	Trial identifier and registry name	Examples for human medicine: https://clinicaltrials.gov EudraCT: https://eudract.ema.europa.eu Example for veterinary medicine: https://ebusiness.avma.org/aahsd/study_search.aspx and IACUC [54]
Protocol version	3	Date and version identifier	As protocol amendments may be necessary during the conduct of the trial, this is important for credibility of the research project. Independent from trial registration, the protocol should be published prior to the start of the trial.
Funding	4	Sources and types of financial, material, and other support	All financial sources of the trial are disclosed. For budgeting, local clinical trial units (CTUs), e.g., at universities, can be consulted for help.
Roles and responsibilities	5	5a Names, affiliations, and roles of protocol contributors	Commonly needed: sponsor, principal investigator, coordinator, biometrician, data-manager, monitor, data-safety board.

		5b Contact information for the trial sponsor 5c[2] Role of study sponsor and funders 5d[3] Composition, roles, and responsibilities	Additionally, advisory boards should be implemented. ***Important point for homeopathy trials and to be followed even if resources are scarce.***
Introduction			
Background and rationale	6	6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention 6b Explanation for choice of comparators	Description of the evidence gap, relevance e.g., prevalence, disease burden, economic burden, and the rationale for the choice of design, and comparator. ***Statement concerning the choice of the homeopathic method and parameters, see "Guidance for homeopathy RCT" digit 1a, 4c i.*** ***Statement concerning the choice of comparators, see "Guidance for homeopathy RCT" digit 1b.***
Objectives	7	Specific objectives and hypotheses	Primary and secondary objective(s) and hypotheses are stated. Note: they depend on the comparator and outcome chosen. For example: Primary objective: To investigate whether ***HMPs*** (RCT) / treatment (pragmatic trials) are / is superior to placebo/standard therapy regarding primary outcome measure in patients with disease x. ***See "Guidance for homeopathy RCT" digit 2.***
Trial design	8	Description of trial design, including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g. superiority, equivalence, non-inferiority, explanatory)	***Different homeopathic methods (see item 6) require different study designs depending on research question, see "Guidance for homeopathy RCT" digit 3.***
Methods			
Participants, interventions and outcomes			
Study setting	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Statement whether the trial is monocentric or multicentric and description of study site(s) as office-based practice(s), community or university hospitals or outpatient clinics or outpatients or experimental units in veterinary medicines. 'Legal aspects', especially when planning an international trial have to be considered: ***different legal statuses of homeopathy, homeopathic professionals, and HMPs between countries have to be considered before starting a study on homeopathy [18].*** Description of the qualification of the investigators, including proof of Good Clinical Practice (GCP) training. The list of study sites is kept apart from the protocol in order to have the possibility to include more centres without an amendment procedure [79].
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria	Detailed explanation of the selection criteria of the study participants including considerations for patients with special

		for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists)	vulnerability (consult law department of local facilities if needed). ***For patients, homeopathic qualification of study centres and prescription strategies see "Guidance for homeopathy RCT" digit 4b, 4c i.***
Interventions	11	11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Description of all interventions (e.g. study medication, placebo and permitted co-interventions) in detail: -Manufacturer -Active and excipient substances -Dosage and type of administration -Description of storage, handling and dispense -Description of permitted and surveillance of unpermitted co-interventions Submission of an 'Investigators Brochure' (study medication) and the 'Investigational Medicinal Product Dossier (IMPD)' (placebo or other comparator) is commonly required by regulatory authorities for clinical trials with pharmaceutics (provided usually by the study pharmacy). Cross-reference to labelling and blinding techniques are recommended. ***Detailed description of symptom- and HMP-selection for individualized treatment, to allow replication. See "Guidance for homeopathy RCT" digit 4c ii, 4c ix.*** ***Specific homeopathic description and suitable handling and storage of HMPs and the corresponding placebos, see "Guidance for homeopathy RCT" digit 4c iv.***
		11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)	Statement possibly with cross-reference to other safety parameters and variables, which are described later in the protocol (e.g. harms, procedure in case of emergency, overdose or pregnancy, discontinuation parameters, data-safety, monitoring and standard operating procedures (SOPs)).
		11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)	Description of the drug accountability (keyword: drug accountability log) and compliance-checks (e.g. at visits). Statement of expense compensation, allowance or rewards, if part of the adherence-strategy.
		11d Relevant concomitant care and interventions that are permitted or prohibited during the trial	Description of permitted co-interventions (see 11a) and the possibility of non-permitted co-interventions. Description of monitoring of non-permitted co-interventions (see 11c). ***Treatment flexibility including treatment of acute diseases, see "Guidance for homeopathy RCT" 4c v, 4c vi, 4c vii, 4d i.*** ***Consider unconventional strategies to enhance compliance, e.g. travel vouchers or "finisher party" for children.*** ***For quality control of HMPs, see "Guidance for homeopathy RCT" digit 4c iii, 4c iv, 4c viii.***
Outcomes	12	Primary, secondary, and other outcomes, including the	Description of type and time point of outcome measures proven to be valid, reliable and

		specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each	clearly described. Whether clinical outcome measures **(*e.g., symptom change*)** are preferably primary outcome measures and imaging, laboratory results or others **(*e.g. reduction of concomitant treatment*)** are preferably secondary outcome measures, depends on the research question. External validity depends on clinically important results, in secondary line on laboratory data. Statement of clinical relevance of the outcome measures (e.g., at best, biomarkers, validated tools, and patient related outcome measures (PROMs) are used simultaneously; ***see "Guidance for homeopathy RCT" digit 4d ii, 4d iii, 4d iv.*** **For the *individualized homeopathic method, treatment flexibility is desired, see "Guidance for homeopathy RCT" digit 4c v, 4c vi, 4d i.***
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (Figure).	Description of design and conduct of the studies (see Table 2 and Figure 1); ***see "Guidance for homeopathy RCT" digit 4e. To address the dilemma between fluctuations in individual course of disease and fixed follow-up intervals, see "Guidance for homeopathy RCT" digit 4c vi. See Figure 1 and Table 2.***
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Calculated sample size depends on the estimated effect, the chosen confidence interval and the desired power of the study. Commonly, α=0.05 and power of 80% are regarded as sufficient. Sample size considerations should include sample size determination at each level of organizational structure and the assumptions used to account for any non-independence among groups or individuals within a group [43]. ***In case of missing previous data, see "Guidance for homeopathy RCT" digit 4f.***
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Advertisements are part of the submission to the ethics committee and regulatory authorities. ***Homeopathy considerations, see "Guidance for homeopathy RCT" digit 4g.***
Assignment of interventions			

Allocation sequence generation	16	16a Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions.	Description of responsibilities. Cross-reference to list of responsibilities is recommended. ***For recommended randomization strategies and case-taking, see "Guidance for homeopathy RCT" digit 5a, 5b.***
Allocation concealment mechanism		16b Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes, double-blind computerized sequence), describing any steps to conceal the sequence until interventions are assigned	If possible, it is recommended that randomization is carried out by a biometrician different from the outcome assessor and data manager (see 16a).
Implementation		16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding	17	17a Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how	Description of blinded persons, labelling and cross-reference to allocation concealment mechanisms.
		17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Description of "unblinding"-mechanisms (e.g. emergency envelopes). Cross-reference to safety-parameters and variables (see 11b). ***A clear distinction of 'reactions towards HMPs', adverse events and serious adverse events is recommended, see item 11b and "Guidance for homeopathy RCT" digit 5d.***
Data collection, management, and analysis			
Data collection methods	18	18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol.	Data collection and management is commonly carried out according to International Classification of Helsinki Good Clinical Practice (ICH-GCP) Guidelines [80] and supplemented by a quality management manual (from the sponsor). Detailed description of outcome assessments, documentation tools, case report forms and their storage. Generally, software with audit tracks is recommended.
		18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who	Cross-reference to documentation forms for safety parameters and data-analysis (see items 20-22).

		discontinue or deviate from intervention protocols	
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol.	Cross-reference to a data management plan (DMP) for the description of data acquisition and coding, data flow, database management, etc, a data validation plan (DVP) for the description of plausibility checks and a system validation plan (SVP) is recommended. Description of archiving and storage after the trial is finished according to ICH-GCP guidelines [80].
Statistical methods	20	20a Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol. 20b Methods for any additional analyses (e.g., subgroup and adjusted analyses) 20c Definition of analysis population relating to protocol nonadherence (e.g., as-randomized analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	This section contains details about: -Sample size calculation -Demographics and baseline characteristics -Analysis sets (Intention-to-treat (ITT) and Per-protocol (PP)) -Management of missing data -Primary and secondary hypotheses and methods of analysis -Sensitivity analyses -Safety analyses -Possibly planned interim analyses (or cross-referenced to item 21b) -Randomization Statement of the rationale for the choice of each particular analysis-method. For details see Cochrane handbook [81].
Monitoring			
Data monitoring	21	21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed. 21b Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	External monitoring is recommended. CTU commonly provide trained monitors or guidance.
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Reference local regulatory guidelines. The European Medical Agency (EMA) provides a glossary with updated versions of the current definition and detailed information on safety responsibilities, handling and reporting of (serious) adverse events. Do also consult updated versions of the ICH-GCP-guidelines [80]. ***See "Guidance for homeopathy RCT" digit 5d, for reporting reactions towards HMPs.***

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Statement as to whether inspections take place. Commonly, competent state or local authorities or the sponsor are conducting audits as an important part of quality assurance.
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee (REC) / institutional review board (IRB) approval	Consultation of the regional REC/IRB (statement of name and address). For submission to the REC/IRB the following documents are required as appendices: -Contracts with the investigators including declarations of confidentiality and conflict of interest. -The 'investigators brochure' and the IMPD provided by the pharmacy. -Content of flyers and posters for recruitment. -Signatures of all investigators.
Protocol and amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, RECs/IRBs, trial participants, trial registries, journals, regulators)	Amendments to the protocol are tracked and dated. They need re-approval of the REC/IRBs and are then disseminated to the relevant parties of the trial. Commonly, it is distinguished between substantial and non-substantial amendments by the primary investigators, following the European Commission Guidance document CT-1 [82].
Consent or assent	26	26a Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see item 32) 26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Description of the process for obtaining informed consent. Commonly, the investigators or their delegates (employees of the study centres) explain purpose, advantages and risks of the trial to the participants respectively animal owners, who receive additional written information and enough time for their considerations. Afterwards, written informed consent must be signed with date and time by both, investigator and participant respectively animal owner, before any trial-specific procedures can start. The 'informed consent' form must be approved by regional legislative and data-safety authorities.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Consultation of Clinical Trial Unit (CTU) for contacts with data safety departments and search for advice at the latter.
Declaration of interest	28	Financial and other competing interests for principal investigators (PI) for the overall trial and each study site	Declaration of both, medical and financial private interests (e.g., list of pharma bonds) for all participants of the trial (e.g. sponsor, PI, trial coordinator, biometrician and investigators at the trial centres).
Access to data	29	Statement of who will have access to the final trial data set, and disclosure of contractual agreements that limit such access for investigators	It is recommended, that all authors of publication manuscript have access to the final data set. Use of platforms like https://datadryad.org/stash is recommended.
Ancillary post-trial care	30	Provisions, if any, for ancillary and post-trial care,	Statement concerning the possibility for treatment after the trial or after

		and for compensation to those who suffer harm from trial Participation	discontinuation from the trial (cross-reference to items 11b and 22.) Statement of insurance (name and number). An appropriate insurance policy covers at least € 5.000.000 to compensate harm from trial participation.
Dissemination policy	31	31a Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data-sharing arrangements), including any publication restrictions 31b Authorship eligibility guidelines and any intended use of professional writers 31c Plans, if any, for granting public access to the full protocol, participant-level data set, and statistical code	Commonly, results should be published in peer-reviewed journals, preferably English language journals. If applicable, include statement of number of publications and intended journals for publications. Statement of additional interfaces for the dissemination (e.g. conferences, reports, data bases) may also be included. Consultation of the information provided by the EQUATOR-network for additional information [83] and CONSORT Extension for Nonpharmacologic Trial Abstracts [84]. ***See "Guidance for homeopathy RCT" digit 6.*** It is recommended, to adhere to the guidelines for authorship eligibility by the Ottawa hospital research institute (OHRI) [85]. Statement of intended native speaker editing. Statement as to where the protocol is accessible and when it was published. State where confidential data is stored and if and where the pseudonymised full data set is available (cross reference to item 27).
Appendices			
Informed consent material	32	Model consent form and other related documentation given to participants and authorized surrogates	It is recommended, to attach a template of the material used for recruitment as well.
Biological specimen	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

Table 1: Adapted SPIRIT-checklist to address homeopathy RCT requirements

[1] It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation and Elaboration [41] for important clarification on the items.

The SPIRIT checklist [41] is copyrighted by the SPIRIT Group and is reproduced with permission.

[2] 5c: if any role, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities

[3] 5d: of coordinating centre, steering committee, end point adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable

As the complex and abundant possibilities of homeopathic methods and RCT-designs cannot be summarised in a single overall guidance or action plan, it was decided to focus on general remarks and guidelines in the checklist (Table 1) with reference to a “Guidance for RCTs in homeopathy”. For each item of the checklist, relevant to specific homeopathic considerations, the latter are summarised in Supplement 1.

Figure 1 shows a *fictitious* sketch of a three-arm RCT design for any acute or chronic indication comparing two homeopathic approaches and placebo.

Figure 1: Fictitious trial design template

Table 2 displays an example of proposed procedures for a study design with an acute situation of e.g. 6 weeks or months study length, and – in a mixed-methods approach – an additional or optional qualitative research phase afterwards.

Table 2: Study procedures

4. Discussion

Homeopathic principles require special considerations in the planning, conduct and reporting of clinical trials with homeopathic interventions. We reviewed, discussed, and summarised recommendations for future homeopathy RCTs in this article. The results, though extensive, are not a fixed guideline, but an approximation to better research standards. Thus, the present recommendations are a pioneering attempt to provide systematic methodological guidance for future research with homeopathic RCTs, especially when evaluating the individualized homeopathic approach. Obviously, each clinical condition and homeopathic research question has its own particular considerations in addition to these general recommendations and not all recommendations are applicable to all RCTs.

Although an RCT with placebo control is seen as the "gold standard" technique in clinical research generating evidence of the efficacy of a medical intervention this design may not be

the most appropriate method for complex medical interventions like homeopathy [14, 38]. Our review of literature showed that the conduct of such trials is still perfectly feasible, especially in acute clinical conditions or conditions with little therapeutic benefit from conventional medicine [55, 66-69]. In the expert discussions it was, however, emphasized to focus on the investigation of homeopathic treatment in daily practice, for example with the *TwiCs* design [5, 13, 23] and/ or reproducible HMP selection strategies, such as *semi-individualized strategies* [17, 18], because these designs reflect the homeopathic method better and the results are therefore of higher clinical relevance. For further discussion of the pros and cons of TwiCs/cmRCTs, the literature about these trial designs is recommended [92-94]. Add-on designs with placebo-control [74] or studies with standard treatment (best care) as a comparator to the individualized homeopathic intervention as a whole may be further options to optimize generalisability. In this respect, we recommend to consider replicating the successfully conducted homeopathy RCTs listed above [55, 66-70], as independently conducted trials with the same research question increase the evidence of effectiveness [26].

Additional issues that were discussed are quality assurance and cost effectiveness. Firstly, model validity: if the simile principle is followed, individualized homeopathic therapy is based on individual symptoms and not on indications. It appears therefore logical that this therapeutic method, if shown to be effective in one indication, is effective in other indications as well. Still, in order to have comparable interventions in different clinical studies, the homeopathy used in the studies needs to comply with “homeopathic best care” and should be thoroughly reported in order to be replicable. And secondly, it was the unanimous opinion that for quality assurance of RCTs adequate resources, namely a trained research team, preferably an academic research environment and an independent financial back-up are required. Four out of the five homeopathy trials which have been assessed as best quality by Mathie et al. have been conducted in collaboration with universities [31-34]. A quick check by

one of the authors (KvA) reveals that this is in contrast with a large majority trials with homeopathy: in four reviews (135 trials) only 20 % of non-individualized and 28% of individualized homeopathy trials have been university-based or conducted in collaboration with universities [31-34]. Hence, if the cooperation with academic institutions can be strengthened, homeopathy trials may be of better quality overall.

With regard to cost-effectiveness, RCTs in veterinary homeopathy seem to be more cost-efficient. Here, large numbers of farm animals can be treated under standardised conditions. In epidemiological diseases a whole herd of farm animals can be treated as one individual and, thus, with the same HMP. This offers the possibility to exclude any placebo effect especially because in farm animals the HMPs are, in most cases, administered without direct contact with the animal.

To summarise, the question how to perform high quality homeopathy RCTs remains complex. Their successful conduction roughly depends on four factors: thorough planning, congruency with the homeopathic principles as well as general medical research standards, trained research staff and sufficient financial resources. In order to implement the formulised recommendations each of these aspects needs to be given.

5. Conclusion

The compilated recommendations may serve to better plan, design, conduct and report RCTs in homeopathy in addition to the SPIRIT-checklist. Whereby, the specific challenges of the *individualized* homeopathic approach need special attention, including possibilities to reproduce the individualized HMP selection, and to reflect daily homeopathic practice. Replication of RCTs increases the credibility and recognition of the results by the academic community and enables to conduct systematic reviews and/or meta-analysis of particular

interventions. Hereby, the various innovative and previously tested designs that were presented in this paper, each one suitable for a different type of research question, are to be considered

Highlights

- The present recommendations provide systematic methodological guidance for future research with homeopathic RCTs, especially when evaluating the individualized homeopathic approach.
- The recommendations include: the reflection on the importance of a precise research question, the choice of research design based on prior evidence and feasibility as well as a homeopathy-specific point by point guidance.
- It is emphasized to evaluate the effectiveness of homeopathic treatment in daily practice, e.g. with the *TwiCs* design [5, 13, 23] and/ or reproducible HMP selection strategies, such as *semi-individualized strategies* [18].
- For future research: consider replicating successfully conducted homeopathy RCTs [55, 66-70] including reproducible HMP selection strategies.
- For quality assurance: usage of a university-based research infrastructure might be essential for high quality homeopathy RCTs.

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Credit authorship contribution statement

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.

Conflict of interest

The authors are homeopathic practitioners and researchers. Conflicts of interest: None.

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Ethical consideration

The research project did not concern a human research project and ethical approval was therefore not needed.

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Figure captions

Table 1: Adapted SPIRIT-Checklist to address homeopathy RCT requirements

Supplement 1: Specific guidance "*Considerations for homeopathy"*

Figure 1: Fictitious trial design template

Table 2: Study procedures

Footnotes

[1] It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation and Elaboration [41] for important clarification on the items.

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[2] 5c: if any role, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities

[3] 5d: of coordinating centre, steering committee, end point adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable

[4] For trials with individualized homeopathic strategy with placebo or another medication for the control group, homeopathic consultation takes place after the baseline-assessment and before randomization.

[5] Assessments of treatment effects, commonly with validated questionnaires.

[6] May serve as additional outcome measure and may be used for compliance-assessment.

[7] A subsequent qualitative study with patient or investigator-interviews may provide additional results for unresolved questions in the field of homeopathy.

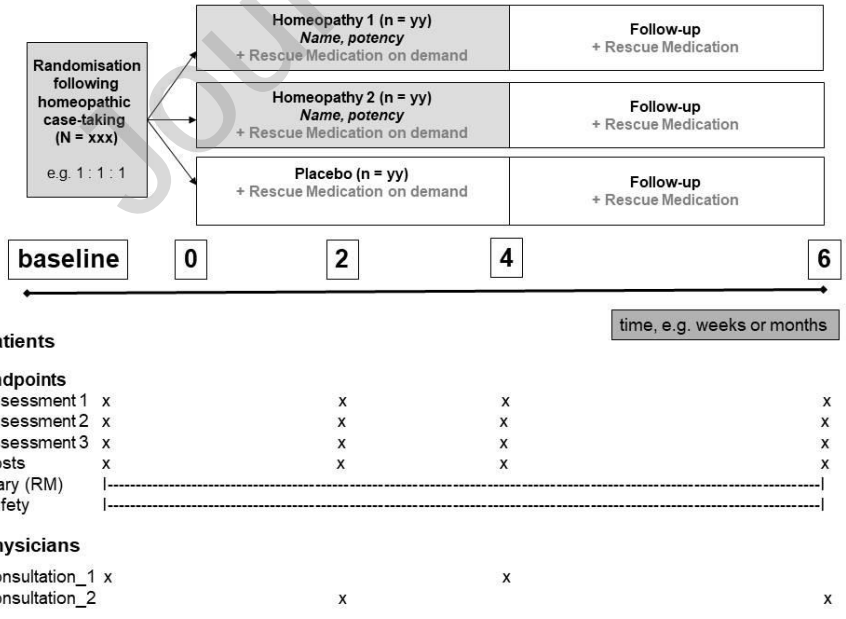

Figure 1: Fictitious trial design template. (RM = rescue medication)

Table 2: Study procedures:

Time, e.g. weeks or months	**<0**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**>6**
Pre-Screening	x								
Baseline-assessment		x							
Homeopathic consultation[4]		x		x		x		x	
Endpoints[5]									
Assessment 1		x		x		x		x	
Assessment 2		x		x		x		x	
Assessment 3		x		x		x		x	
Costs		x		x		x		x	
Questions on expectations[6]		x							
Questions about treatment effect[6]				x		x			
Questions about intervention[6]				x			x		
Patient diary[6]		x	x	x	x	x	x	x	
Safety/ Adverse Events		x	x	x	x	x	x	x	
Qualitative sub-study[7]									x

[4] For trials with individualised homeopathic strategy with placebo or another medication for the control group, homeopathic consultation takes place after the baseline-assessment and before randomisation. **[5]** Assessments of treatment effects, commonly with validated questionnaires; **[6]** may serve as additional endpoint and may be used for compliance-assessment. **[7]** A subsequent qualitative study with patient or investigator-interviews may provide additional results for unresolved questions in the field of homeopathy.

Declaration of Competing Interest

none