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# Homeopathic trial design in influenza treatment

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**This review presents a critical evaluation of methodological quality in controlled trials on homeopathic treatment of influenza. First, a short summary on the prevalence, quality, and most commonly cited shortcomings of homeopathic controlled trials in general is presented to support the more specific points within influenza trials alone. To this end, three areas of the homeopathic literature are examined; large meta-analyses looking at study quality and results across research areas, reviews on research within specific diagnostic categories, and the available reviews and primary studies on influenza treatment trials. The specific methodological designs of homeopathic influenza treatment trials are then compared, on a point by point basis, to pharmaceutical trials on influenza antiviral drugs. The goal of the evaluation is to highlight frequently cited problems in homeopathic trial design, suggest possible improvement for future studies, and make specific recommendations for homeopathic influenza trials based on a comparison to standard antiviral trials.** *Homeopathy* (2010) **99**, 69–75.

**Keywords:** Influenza; Homeopathic controlled trials; Randomized controlled trials; Homeopathy; Study quality; Design methodology

## Introduction

This review builds on a previous review, by the authors, of randomized controlled trial (RCT) design in influenza studies.[1] In that paper, a literature search was completed for high-quality RCTs examining conventional antiviral treatment of influenza, and a subset of 11 modern studies were examined in detail. From these, important study design elements, including inclusion/exclusion measures, primary and secondary endpoint selection, and data analysis, were extracted and summarized in order to show both the consistency and flexibility within conventional controlled trials of influenza therapy.

The purpose of that review was to present aspects of conventional influenza RCTs that represent a high-quality, validated, and accepted approach to measuring the success of influenza treatments, and suggest that these design elements be mirrored in future trials of complementary and alternative medicine (CAM), including homeopathy, for influenza. The main results of the previous review, including design standards in study demographics, inclusion criteria, exclusion criteria, primary and secondary outcome measures, and lab testing, are summarized in Tables 2 and 3 in the present review.

The present review, after briefly summarizing common criticisms of general RCT design in homeopathy, focuses specifically on controlled homeopathic treatment trial design in influenza and compares the design of existing studies to standards from conventional antiviral trials. Influenza treatment is targeted specifically for three reasons: first, there are a number of available controlled trials in the homeopathic treatment of influenza, and although the body of evidence is small there are few more studied specific areas of disease. Second, there exists a consistent and well-accepted design standard within trials of conventional antiviral treatment of influenza, providing a good basis for offering improvements in homeopathic study design. Finally, the evidence from placebo-controlled homeopathic treatment of influenza available thus far points to a statistically significant, but small-sized positive effect compared to placebo,[2] suggesting the need for further, well-designed studies.

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### Scope of the review

The latest systematic review on homeopathic controlled trials by Shang *et al.*[3] included 110 RCTs of homeopathy, of which 21 (19%) pertained roughly to upper respiratory

tract infections (URTIs). This represents the greatest proportion of studies in a specific area of disease.

Similarly, a 2003 review by Mathie[4] identified URTIs as the most represented disease area of homeopathic study, although no specific diagnosis within the general area (such as influenza, otitis media, common cold, etc.) had more than two or three RCTs.

Our search of PubMed through March 2008, for all English-language RCT and clinical trial articles and with the text word 'homeopath*' revealed 198 results. After manually reviewing these, 9 were found to be RCTs targeting URTI treatment in general, of which 2 were on influenza, 4 on general URTIs, 1 on sinusitis, and 2 on acute otitis media.[5 13] Although there are more English-language studies on general URTI, influenza was targeted because of the greater consistency, more well-defined disease scope, and increased justification for further study based on repeated, positive findings. URTI study design is deserving of further attention, but has been reviewed in part by other authors.[3,4,14,15] Another aspect of homeopathic trials outside the scope of this review is discussion of RCT findings in efficacy (see meta-analyses by Kleijnen *et al.*,[16] Linde *et al.*,[17] and Shang *et al.*[3]), and how trial design and methodological quality relates to that issue (see review by Ludtke and Rutten[18]).

### Commonly cited design issues in homeopathic controlled trials

Before focusing exclusively on influenza, it is valuable to summarize the general study design issues cited by reviewers of homeopathic trial literature, if only to highlight that the same issues are coming up regardless of the diagnostic area examined.

The most recent systematic review of placebo-controlled trials of homeopathy identified 110 reports that met the reviewers' quality criteria, eliminating 60 trials where there was insufficient information, ineligible study design, repetition of publication, or no match in conventional medical trials on the condition addressed.[3]

One of the most frequently cited problems is poor, insufficient, or incomprehensible reporting of study design methodology. Multiple reviews note areas where over 80% of trial reports failed to clearly or sufficiently describe either the randomization process chosen, the funding sources, or the selection process for participant samples.[16,19] Potential bias in the studies was also a concern noted in many of the meta-analyses, due in large part to the poor reporting of methods. These biases will continue to be assumed unless more transparent reporting of design and results of studies is made a primary goal.

The most frequently cited problem within the study design itself is very clearly the lack of well-defined, appropriate, and objective outcome measures.[3,4,16,17,19–23] Among the reviews, the range of studies reported to have either poorly described, insensible, crude, descriptive only, poorly chosen, subjective or otherwise unsuitable outcome measures was anywhere from 27% to 50%. As noted in Merrell and Shalts,[21] the majority of the studies reviewed having a positive findings utilized outcome measures that were subjective and difficult to quantify. A related problem was poor definition of the clinical condition being studied, affecting appropriate inclusion of patients into the study and analysis of results.[17] Objective, well-defined, and acceptable measures for clinical definition, inclusion, analysis, and outcome measures is an important area needing improvement in homeopathy RCTs.

Other noted issues mentioned often among reviews are the small sample sizes used in homeopathic trials and inadequate concealment of allocation found in over half of reviewed trials.[3,16] Overall, the methodological and reporting problems in homeopathic controlled trials are well recognized, agreed upon, and for the most part easily addressable in future studies.

## Methods

In order to identify reviews and meta-analyses on homeopathic controlled trials, a literature search was completed on PubMed, limited to English-language reviews and meta-analyses, for all dates through January, 2009, using the search term 'homeopath*' in all text fields. The search returned 404 results which were manually searched to identify reviews targeting design quality and results of homeopathic controlled trials in general.[3,4,16,27] Reviews that targeted controlled trials within disease-specific areas, and reviews that were not specifically targeting *controlled* trials, were not included. This summary review is not intended to be a systematic review of the literature, but rather to identify methodological design issues commonly cited in reviews on homeopathic trial quality and methods.

## Results

### Quality and design of controlled trials in homeopathic influenza treatment

One clinical area of study that has been frequently assessed in review articles covering homeopathy is the prevention and treatment of influenza.[2,4,14,17,28] Influenza is a particularly relevant topic of discussion in the current research on CAM, as can be seen in recent reviews.[14] As concluded by Vickers and Smith[2] the current evidence points to a positive effect of the remedy *Oscillococcinum* in influenza treatment, though the results only point to a 0.28 day reduction in length of illness, a number which, if accurate, will require much larger studies to confirm. However, there are methodological issues even with the positive studies that, if improved upon, might clarify the data regarding homeopathy and influenza.

The updated meta-analysis by Vickers and Smith[2] reviews four RCTs[11,29–31] examining efficacy of the homeopathic remedy *Oscillococcinum* in treating influenza. The other reviews that cover influenza treatment either refer to this study, or analyze some subset of the same four RCTs included. A search of PubMed and the Cochrane Central Register of Controlled Trials through February 2009 reveals no further published trials on homeopathic influenza controlled trials in English (search: homeopath* AND

influenza). The reviews are in agreement as to the quality of the studies, and the possible issues and biases inherent to them. In general, the two studies by Casanova[30] and Casanova and Gerard[31] are similar and can be looked at as a group, as can the studies by Ferley *et al.*[11] and Papp *et al.*,[29] in which the second is specifically designed to mirror and reconfirm the first. For the various criteria examined by Vickers and Smith,[2] which were graded A, B, or C indicating a low, medium, and high risk of bias, the two studies by Casanova and Gerard received all B ratings, while the studies by Ferley *et al.* and Papp *et al.* received all A ratings. Table 1 presents the individual categories and scores for the rating of quality assessment of these four RCTs as presented in three reviews.[2,14,17] The following sections present more specific comments on both the positive and negative attributes of these RCTs.

### Casanova[30] and Casanova and Gerard[31]

The two trials by Casanova and Gerard generally received more criticism and have more omissions of important information as compared to the studies by Ferley *et al.* and Papp *et al.* The 1992 study by Casanova and Gerard is unpublished, and the other Casanova and Gerard study was only reported in a general medical periodical rather than a peer-reviewed scientific journal. As a result, there is scanty information available on both. One criticism made in both Guo *et al.*[14] and Vickers and Smith[2] is that, though the two trials had basically the same design, it appears that the 1992 trial eliminated 2 of the 5 symptoms that had been examined as outcome measures in the 1984 study,[31] raising questions of selective reporting biasing more positive outcome measures.

The 1984 study reported data for patient assessment of temperature, chills, aches, rhinitis, night cough, and daytime cough; the 1992 study only reported temperature, chills, and aches. Furthermore, the length of the follow up varied between the two studies, with the first reporting data for day 8 and the second for day 4, which may have been a more favorable comparison. Also, there are no details about which participants were excluded, or on numbers of or reasons for withdrawals in either of the trials.

Vickers and Smith[2] conclude that outcome measures based on individual symptoms are more likely to be biased, and that a more appropriate outcome measure to ensure unbiased study results would be based on the presence or absence of clinically identifiable influenza, or possibly the use of concomitant medications.

### Ferley *et al.*[11] and Papp *et al.*[29]

Unlike the two Casanova and Gerard studies, these RCTs did report outcomes that depended on the presence or absence of clinically determined influenza-like syndrome, although neither of these studies identified the true influenza population through laboratory testing. The pre-specified main outcome measure that both studies used was comparing the number of participants with 'recovery after 48 h' (no fever, no key influenza symptoms) in homeopathic treatment *versus* placebo. These studies also reported patient

**Table 1** Quality assessment scores in homeopathic influenza RCTs

| | *Specific criteria* | *Casanova*[30] | *Casanova and Gerard*[31] | *Ferley* et al.[11] | *Papp* et al.[29] |
|---|---|---|---|---|---|
| Jadad score (Guo *et al.*[14], Linde *et al.*[17])* | | 2 | 2 | 3 | 5 |
| Internal-validity score (Linde *et al.*[17])† | | Not rated | 57 | 79 | Not rated |
| 8 Criteria‡ (Guo *et al.*[14]) | Randomization performed using adequate method? | D | D | D | Y |
| | Treatment allocation concealed? | D | D | Y | Y |
| | Groups similar at baseline regarding important prognostic indicators? | Y | Y | Y | Y |
| | Patient blinded? | Y | D | Y | Y |
| | Care provider blinded? | Y | D | Y | Y |
| | Withdrawal/dropout rate unlikely to cause bias? | D | D | D | Y |
| | Outcome assessor blinded? | D | D | Y | Y |
| | Pre-defined primary outcome measure and result reported? | N | N | Y | Y |
| 5 Criteria§ (Vickers and Smith[2]) | Treatment allocation rating | B | B | A | A |
| | Performance bias rating | B | B | A | A |
| | Observer blinding rating | B | B | A | A |
| | Exclusions/withdrawals rating | B | B | A | A |
| | Allocation concealment rating | B | B | A | A |

* A score based on methodological quality criteria developed by Jadad *et al.*[32]. Scores is out of 5.
† An internal-validity score developed by the authors based on 7 quality criteria. Score is out of 100.
‡ Y = Yes, N = No, D = Do not know.
§ A = Low risk of bias, B = Possible bias or partially met, C = High risk of bias.

assessment of treatment success, and the use of concomitant medications. Participants were required to meet a pre-defined standard for influenza-like syndrome based on temperature and the presence of certain key symptoms, and there were clear exclusion criteria outlined, including presenting after 24 h since influenza onset, immune deficiency, influenza vaccination, and certain medication uses. These studies were generally rated as being well reported, with sufficient data presented, as compared to the two Casanova and Gerard studies which were poorly reported.[2]

In general, these four influenza treatment trials as a group are rated as moderate in methodological bias, but meeting basic criteria of good studies such as being multi-centered and using blinded medication.[2] Vickers and Smith[2] also conclude that there was insufficient data to determine the effect of *Oscillococcinum* on concomitant medication use, or on vulnerable sub-groups such as the elderly. They conclude that confirmatory trials of *Oscillococcinum* as treatment are warranted, but will require a very large sample size.

Based on the quarter day difference found between control and treatment in the better studies by Papp *et al.*[29] and Ferley *et al.*,[11] and with the power set at 90%, the required sample size quoted is 2000 participants. A similar or larger sample size would be needed to confirm other outcomes as well, such as days to return to work.[2] Other than conducting larger studies, they also suggest planning further sub-group analyses to look at specific populations within the study.

## Comparison of homeopathic influenza trials to conventional antiviral trials

An item by item comparison of relatively standardized design elements most commonly seen in conventional influenza antiviral studies *versus* the study design of the four homeopathy RCTs reviewed in this section is presented in Tables 2 and 3. Comparison is made to the design aspects of conventional antiviral trials that are most consistent in terms of quality and acceptability as cited by reviewers. However, design elements that are poorly rated in a majority

**Table 2** Homeopathic *versus* conventional RCT design in influenza (Casanova[30], Casanova and Gerard[31])

| | *Design criteria* | *Casanova*[30] | *Casanova and Gerard*[31] | *Conventional antiviral standards** |
|---|---|---|---|---|
| Demo-graphics | Study size | 100 | 300 | 350–650 |
| | Study length | NR† | NR | 21 OR 28 |
| | Study design | RCT | RCT | RCT |
| Inclusion criteria | Age (years) | NR | NR | 12+ OR 16–65 |
| | Flu onset (h) | <48 | NR | 36 OR 48 |
| | Fever (°C) | NR | NR | >37.8 OR Feverishness |
| | Subjective symptoms | Influenza-like syndrome | NR | 2 or more of headache, myalgia, cough, sore throat OR 1 respiratory symptom (cough, sore throat, nasal symptom) and 1 constitutional symptom (headache, malaise, myalgia, sweats/chills, fatigue) |
| Exclusion criteria | Chronic illness | NR | NR | Immunocompromised OR unstable chronic disease |
| | Drug use | NR | NR | Antiviral drug use (recent/current) OR immunosuppressant medications OR drug/alcohol abuse history |
| | Pregnancy | NR | NR | Pregnant or risk of pregnancy |
| | Vaccination | NR | NR | Vaccinated this year |
| | Bacterial infection | NR | NR | Suspected concurrent bacterial infection |
| Primary outcome measures | Time to alleviation of influenza | NR | NR | Temperature < 37.8 °C, score of 0 on feverishness, score of 0–1 on other influenza inclusion symptoms maintained for 24 h |
| Secondary outcome measures | Individual symptom scores | Chills, aches, rhinitis, night cough, day cough, fever (day 8 only) | Temp (daily), chills, aches (day 4 only) | Temp, headache, myalgia, cough, sore throat, nasal symptoms, fatigue, feverishness, loss of appetite (all recorded daily) |
| | Quality of life scores | Patient global assessment of health | NR | Sleep disturbance OR time to return to normal activities OR overall symptom severity rating |
| | Viral load | NR | NR | Viral shedding/viral load |
| | Relief medication use | NR | NR | Use of relief medications for influenza symptoms |
| | Complications | NR | NR | Secondary complications of influenza OR use of antibiotics |
| | Adverse events | NR | NR | Effects of study drug (safety measures) |
| Lab testing | Lab confirmation of influenza status | No | No | Yes |

* Standard design criteria from conventional influenza antiviral treatment trials, as reported by Kirkby *et al.*[1]
† NR = Not reported in the literature.

**Table 3** Homeopathic *versus* conventional RCT design in influenza (Ferley *et al.*[11], Papp *et al.*[29])

| | *Design criteria* | *Ferley* et al.[11] | *Papp* et al.[29] | *Conventional antiviral standards** |
|---|---|---|---|---|
| Demo-graphics | Study size | 487 | 372 | 350–650 |
| | Study length | 7 | 7–10 | 21 OR 28 |
| | Study design | RCT | RCT | RCT |
| Inclusion criteria | Age (years) | >12 | 12–60 | 12+ OR 16–65 |
| | Flu onset (h) | <24 | <24 | 36 OR 48 |
| | Fever (°C) | >38 (rectal) | >38 (rectal) | >37.8 °C OR Feverishness |
| | Subjective symptoms | At least two of: headache, stiffness, lumbar and joint pain, shivers | Muscle pain or headache, plus one of: shivering, cough, spinal pain, nasal irritation, malaise, thoracic pain, joint pain | 2 or more of headache, myalgia, cough, sore throat OR 1 respiratory symptom (cough, sore throat, nasal symptom) and 1 constitutional symptom (headache, malaise, myalgia, sweats/chills, fatigue) |
| Exclusion criteria | Chronic illness | Immune deficiency, depression | Immune deficiency | Immunocompromised OR unstable chronic disease |
| | Drug use | Immunomodulating medication use | Immunomodulating treatment OR use of antibiotics, analgesics, or anti-influenza agents in first 48 h post-randomization | Antiviral drug use (recent/current) OR immunomodulating medications OR drug/alcohol abuse history |
| | Pregnancy | NR† | NR | Pregnant or risk of pregnancy |
| | Vaccination | Immunization against influenza | Immunization against influenza | Vaccinated this year |
| | Bacterial infection | Local infection | NR | Suspected concurrent bacterial infection |
| Primary outcome measures | Time to alleviation of influenza | *Illness status at 48 h* post-treatment (temp < 37.5, absence of five flu inclusion symptoms) | *Illness status at 48 h* post-treatment (rectal temp < 37.5 and no headache or muscle pain) | Temperature < 37.8 °C, score of 0 on feverishness, score of 0–1 on other influenza inclusion symptoms *maintained for 24 h* |
| Secondary outcome measures | Individual symptom scores | Temp, flu inclusion symptoms (morning and night), also recorded cough, coryza, fatigue, side effects | Temp, presence of aches, headache, shivers, back or side pain, joint pain, spinal pain, cough, rhinitis, sore throat (2*x*/day) | Headache, myalgia, cough, sore throat, nasal symptoms, fatigue, feverishness, loss of appetite |
| | Quality of life scores | Patient assessment of success, time until return to work | Patient assessment of success, time until return to work | Sleep disturbance OR time to return to normal activities OR overall symptom severity |
| | Viral load | NR | NR | Viral shedding/viral load |
| | Relief medication use | Y | Y | Use of relief medications for influenza symptoms |
| | Complications | NR | NR | Secondary complications OR use of antibiotics |
| | Adverse events | NR | Y | Effects of study drug (safety measures) |
| Lab testing | Lab confirmed influenza status | No | No | Yes |

* Standard design criteria from conventional influenza antiviral treatment trials, as reported by Kirkby *et al.*[1]
† NR = Not reported in the literature.

of cases, such as allocation concealment or reporting, are not looked at in this study.[1]

As can be seen, the two studies by Casanova and Gerard either provide no information on, or do not meet many of the design criteria found in most antiviral studies. The two RCTs by Ferley *et al.* and Papp *et al.*, in contrast, do mirror many of the design criteria, albeit with some important differences. General inclusion criteria are similar to conventional studies, as both are looking for clinical confirmation of influenza through fever plus some specific respiratory and body symptoms. However, the specific symptoms are variable among Papp *et al.* and Ferley

*et al.*, and both of these differ from the more standard set of inclusion symptoms in conventional trials. Most of the exclusion criteria are the same, yet there is one central distinction. In Papp *et al.*, patients are excluded from the study if, within 48 h of beginning the study medication, they receive any anti-influenza treatment, including antiviral, vaccination, analgesics, antibiotics, or immune stimulatory or suppressive therapies. It is unstated in the original literature report why this exclusion is made, though it is possible that it is due to concern with anti-influenza drugs disrupting the action of the homeopathic study medication. A more beneficial way to handle this situation may be to include those patients, recording any drug use, and later analyze them as a sub-population if need be.

Both the Ferley *et al.* and Papp *et al.* studies, like the majority of antiviral studies, use as a primary outcome measure the alleviation of influenza-like illness. These two RCTs however define the primary comparison as absence of influenza at 48 h, rather than just looking at time to alleviation of influenza *versus* placebo. Also, in Papp *et al.*, not all the inclusion symptoms had to be eliminated for the patient to count as recovered, only fever, headache, and muscle pain. In Ferley *et al.*, all five of the inclusion criteria for influenza-like illness, as well as the fever, must be gone to count as recovery. In most conventional studies, the requirement to meet the 'recovered' status is the loss of fever, and a rating of mild or none on the influenza inclusion symptoms, and this must be maintained for 24 h. These are significant differences in outcomes.

In terms of secondary measurements of outcome, the homeopathy RCTs and the conventional antiviral studies cover some range of individual symptoms, patient assessments of health and normal activity, adverse affects, concomitant drug use, and other measures.

Perhaps the largest difference between conventional antiviral studies and the homeopathy RCTs on influenza treatment that have been published to date concerns laboratory confirmation of influenza infection. Laboratory testing and confirmation of influenza virus and subtype is a standard component of influenza antiviral studies,[1] and allows for the retrospective analysis of the specific sub-group of the study population who actually has influenza infection *versus* other upper respiratory tract infections that may present like influenza. A review of antiviral studies[1] shows demographics of the proportion of influenza study populations that have laboratory confirmed influenza ranging from 57% to 78%. This indicates that in some studies, over 40% of patients may be presenting with an influenza-like illness not caused by influenza virus; thus the study is not specifically giving feedback just on the treatment of influenza. None of the homeopathic influenza treatment studies have looked at this subset, thus conclusions drawn from these studies are only applicable to influenza-like illness which comprises a number of different specific conditions.

The general criticism of homeopathy studies in influenza appears to be mostly aimed at the possible introduction of biases into the study, either through poorly chosen outcome measures, selective reporting of symptoms, simple omission of important methodological standards, or other biases in study reporting. However, what is also clear from comparison to conventional trials is that many of the specific design elements, even if generally similar, lack consistency between homeopathy trials and standard antiviral trials. As Mathie[4] suggests, the study of acute conditions with homeopathy does lend itself to placebo-controlled randomized trials, and the initial body of evidence from homeopathy studies such as those reviewed in Vickers and Smith[2] evidences statistically significant positive effects. However, based on the small effect sizes observed and the need for reconfirmation through much larger trials, it may be useful to explore whether it is not changes in basic methodological design and study quality, rather than larger study groups, that will yield the most significant and telling results. In addition, these specific suggestions pertain most specifically to further trials of *Oscillococcinum*, but trials with different remedies using different inclusion and exclusion criteria, outcome measures, and other design elements would have different requirements not predictable from these trial results.

As suggested by Walach *et al.*,[20] pre-trial pilot studies are an important way of gaining valuable predictions of necessary study size and length, and should be considered in future trials in order to optimize methodological design. In regards to specific, acceptable design criteria for elements like inclusion criteria, clinical definition, and outcome measures, attempting to mirror the current standards in conventional antiviral trials is one possible approach.

## Discussion and conclusion

Within the specific group of homeopathic influenza treatment trials, four trials of moderate to good quality exist. The two higher quality studies, while having similar basic design to conventional antiviral trials as RCTs, nevertheless differ in some important areas. Definitions for inclusion criteria, exclusion criteria, and outcome measures vary significantly between the homeopathic and conventional trials. Instead of following the length of illness as in conventional trials, the homeopathic trials look specifically at those who have recovered by a particular time. In addition, because the homeopathic trials fail to verify influenza through lab testing, the analysis can only pertain to influenza-like illness whereas conventional trials can do a sub-group analysis of actual flu sufferers, and thus be able to report more specific efficacy of the drug against influenza in particular.

Overall, the flu studies suggest a positive effect of relatively small size for one specific homeopathic remedy in a group of both flu sufferers and those with influenza-like illnesses, both necessitating much larger trials for confirmation and raising the question of what exactly is being tested. These same concerns and questions are not raised with conventional antiviral trials precisely because of the higher quality and general acceptability of their study design. Thus, there is considerable justification for mirroring conventional RCT design elements in future homeopathic treatment trials in influenza.

Although this paper focuses on methodological concerns in RCTs, which is where the burden of proof will continue

to lie for homeopathy clinical research, it is important to note the ongoing discussion on what basic types of research are most applicable to homeopathy. Important areas of consideration not discussed in this paper are observational studies and other alternatives to the RCT, which are also deserving of further attention. Simultaneously to exploration of these questions, however, RCTs in homeopathy will continue, and there is good reason to improve their quality. As presented in this paper, one possible way to proceed is by mirroring conventional study design parameters.

## Conflict of interest

There were no conflicts of interest.

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