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Model validity and risk of bias in randomised placebo-controlled trials of individualised homeopathic treatment

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ABSTRACT

Background: To date, our programme of systematic reviews has assessed randomised controlled trials (RCTs) of individualised homeopathy separately for risk of bias (RoB) and for model validity of homeopathic treatment (MVHT).
Objectives: The purpose of the present paper was to bring together our published RoB and MVHT findings and, using an approach based on *GRADE* methods, to merge the quality appraisals of these same RCTs, examining the impact on meta-analysis results.
Design: Systematic review with meta-analysis.
Methods: As previously, 31 papers (reporting a total of 32 RCTs) were eligible for systematic review and were the subject of study.
Main outcome measures: For each trial, the separate ratings for RoB and MVHT were merged to obtain a single overall quality designation ('high', 'moderate, "low", 'very low'), based on the *GRADE* principle of 'downgrading'.
Results: Merging the assessment of MVHT and RoB identified three trials of 'high quality', eight of 'moderate quality', 18 of 'low quality' and three of 'very low quality'. There was no association between a trial's MVHT and its RoB or its direction of treatment effect ($P > 0.05$). The three 'high quality' trials were those already labelled 'reliable evidence' based on RoB, and so no change was found in meta-analysis based on best-quality evidence: a small, statistically significant, effect favouring homeopathy.
Conclusion: Accommodating MVHT in overall quality designation of RCTs has not modified our pre-existing conclusion that the medicines prescribed in individualised homeopathy may have small, specific, treatment effects.

1. Background

Our programme of systematic reviews of randomised controlled trials (RCTs) in homeopathy is focusing its quality assessment both on internal validity (risk of bias, RoB) and on model validity (MV).[1]

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Our earlier work on RoB showed that, of 32 eligible RCTs of individualised homeopathy, none was totally free from potential bias, though three comprised 'reliable evidence'.[2] As regards MV of the same 32 RCTs, 19 were considered acceptable, nine uncertain, and four inadequate.[3] Sensitivity analysis reflecting the 'reliable evidence' produced cautious support for the hypothesis that the effect of the individualised homeopathic intervention is distinguishable from the same approach using placebos.[2]

The purpose of the present paper is to merge together our previously published RoB and MV findings,[2,3] and, using an approach based on the *GRADE* method[4] to establish an overall quality designation for each of the 32 RCTs and to examine its impact on the sensitivity analysis findings. Inter-relationships between RoB, MV and direction of treatment effect are also explored.

2. Methods

2.1. Inclusion criteria for RCTs

We previously applied the appraisal methods for RoB and for model validity of homeopathic treatment (MVHT), as described,[1,3–5] to peer-reviewed papers that reported randomised placebo-controlled trials of individualised homeopathy, published up to the end of 2013. Through formal literature search methods, and after application of defined exclusion criteria, 31 papers (reporting a total of 32 RCTs) were found to be eligible for systematic review.[2]

2.2. Assessment of model validity of homeopathic treatment

For each trial, the domains for MVHT assessment are summarised as follows[3,5]:

Domain I (***Rationale***): Would a significant body of accredited homeopaths support the rationale for the intervention used in the study?

Domain II (***Principles***): Is the specific intervention used consistent with homeopathic principles?

Domain III (***Practitioner***): Does the study have suitably qualified and experienced homeopathic practitioner input?

Domain IV (***Outcome measure***): Does the main outcome measure reflect the main effect expected of the intervention used?

Domain V (***Outcome sensitivity***): Is the main outcome measure capable of detecting change?

Domain VI (***Follow-up***): Is the length of follow-up for the main outcome measure appropriate to detect the intended effect of the intervention?

The *overall MVHT classification per trial* was assigned as follows[3,5]:

Acceptable MVHT: acceptable rationale (domain I) and principles (domain II); acceptable outcome measure (domain IV) and sensitivity (domain V); not 'inadequate MVHT' in either of the other two domains (III, VI).

Uncertain MVHT: 'unclear' for at least one of the four key domains (I, II, IV, V); not 'inadequate MVHT' for either of the other domains (III, VI).

Inadequate MVHT: 'inadequate MVHT' for any one or more domains.

2.3. Assessment of risk of bias

For each trial, the domains for RoB are summarised as follows[6]:

Domain I: sequence generation.

Domain II: allocation concealment used to implement the random sequence.

Domain IIIa: blinding of participants and study personnel.

Domain IIIb: blinding of outcome assessors.

Domain IV: incomplete outcome data.

Domain V: selective outcome reporting.

Domain VI: other sources of bias.

The *overall RoB classification per trial* was assigned as follows[2]:

- Low risk of bias overall: low risk of bias for each of the seven domains above (designated *reliable evidence*).
- Uncertain risk of bias overall: unclear RoB for at least one domain; low RoB for all other domains.
  - A trial was designated *reliable evidence* if the uncertainty in its risk of bias was for *one* of domains IV, V or VI *only* (and free of overt bias for each of domains I, II, IIIA and IIIB).
- High risk of bias overall: high RoB for any one or more domains.

2.4. Merging RoB and MVHT into single overall quality designation

Our separate ratings for RoB[2] and MVHT[3] were merged to obtain a single overall designation, based on the *GRADE* principle of 'downgrading' trials with lesser degrees of quality.[4] For the current study, a trial was downgraded using the specific approach shown in Table 1.

2.5. Direction of treatment effect

For each trial, the 'direction of treatment effect' was described statistically as 'favouring homeopathy' or 'favouring placebo', as per the findings of our previous meta-analysis.[2] These descriptions reflect, respectively, a mean odds ratio (OR) greater than or less than 1.00; statistical significance at $P \leq 0.05$ was attributed if the 95% confidence interval (CI) did not overlap the value OR = 1.00.

2.6. Inter-relationship between trial attributes

We planned to use the Chi-squared (χ^2) test to compare frequencies of observations, and thus the inter-relationships between RoB and MVHT and direction of treatment effect. Fisher's Exact test was preferred when expected frequency was less than 5 in at least one cell of a given frequency table.

2.7. Sensitivity analysis

Sensitivity analysis, using methods corresponding to those in our associated paper,[2] examined the impact on the pooled OR of trials' overall quality designation.

3. Results

3.1. MVHT overall

As previously reported,[3] there were 19 trials with acceptable MVHT, nine with uncertain MVHT, and four with inadequate MVHT (Table 2).

3.2. RoB overall

No trials had low RoB.[2] There were 12 trials with uncertain RoB (three of which were designated 'reliable evidence': study numbers A5, A19 and A20 in Table 2), and 20 with high RoB (Table 2).

3.3. Overall quality designation (Table 2)

Each of the three trials assessed as 'reliable evidence'[2] had acceptable MVHT[3]: these three trials were therefore designated