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.

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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]. 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.

METHODS

Inclusion criteria for RCTs

We previously applied the appraisal methods for RoB and for model validity of homeopathic treatment (MVHT), as described [1, 3, 4, 5], to papers that reported peer-reviewed, 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].

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: 'Unacceptable MVHT' for any one or more domains.

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.

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**.

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.

Inter-relationship between trial attributes

We planned to use the Chi-squared ($Ç^2$) 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.

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.

RESULTS

MVHT overall

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

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 'high quality', and so remain the top-ranked RCTs of individualised homeopathic treatment. Of the other nine trials that had uncertain RoB, eight had acceptable or uncertain MVHT, and one had unacceptable MVHT; with appropriate downgrading by quality, these trials were designated respectively as 'moderate quality' (N=8) and 'low quality' (N=1). Thus, 11 RCTs were not importantly deficient in quality overall. Of the remaining 21 RCTs, 18 were designated 'low quality' and three as 'very low quality'.

Direction of treatment effect (Table 2)

Only 22 of the 32 trials had data that were extractable for meta-analysis [2]. Fifteen of these 22 had a direction of treatment effect favouring homeopathy; seven favoured placebo.

Inter-relationship between trial attributes

MVHT and risk of bias

There was no evidence to support an association between MVHT and RoB (Fisher's Exact $P = 0.882$) – **Table 3**.

MVHT and direction of treatment effect

There was no evidence to support an association between a trial's MVHT and its direction of treatment effect (Fisher's Exact $P = 0.381$) – **Table 4**.

Risk of bias and direction of treatment effect

There was no evidence to support an association between a trial's RoB and its direction of treatment effect (Fisher's Exact $P = 0.690$) – **Table 5**.

Sensitivity analysis

Table 6 shows the effect of removing data by trials' overall quality designation: i.e. removing 11 'low-quality' RCTs, then eight 'moderate-quality' RCTs. The pooled OR showed a small, statistically significant, effect in favour of homeopathy for each set of N trials, including for the final N=3 RCTs (those designated 'high quality').

DISCUSSION

Our study has successfully brought together RoB and MVHT assessments using an approach based on the *GRADE* system of 'downgrading' lesser-quality trials. Merging together the two quality attributes revealed 11 out of 32 trials with either high or moderate quality overall. Those with 'high quality' are the three RCTs that comprise 'reliable evidence' based on RoB [2] and that also possess acceptable MVHT [3]. The main finding from our prior meta-analysis [2] has therefore not been modified by

accommodating MVHT: there is cautious support for the hypothesis that the effect of the individualised homeopathic intervention is distinguishable from the same approach using placebos.

The trials with 'moderate quality' overall are eight of nine RCTs that comprise uncertain risk of bias [2]. The MVHT-deficient trial with uncertain risk of bias (study number A25) displayed a direction of treatment effect favouring homeopathy.[n] There was no trial that had inadequate MVHT and whose direction of effect favoured placebo, though other MVHT-deficient trials did not contain extractable data for meta-analysis, preventing their quantitative examination.

It is notable that many trials with acceptable MVHT had high RoB. Indeed, high RoB comprised the major proportion of trials in each class of MVHT (Table 3), though no statistically significant inter-relationships were evident. The proportion of trials with a given direction of treatment effect appeared to be little affected by RoB and/or MVHT; the total number of trials is too small, however, to enable definitive conclusions. The absence of such relationships is supported by our sensitivity analysis, which showed a small, significant treatment, effect toward homeopathy irrespective of the quality of trial retained in analysis. To date, therefore, there is no evidence that the MVHT method merely intercepts those trials with evidence against homeopathy, as has been suggested recently [7].

It remains a matter of concern to homeopathy that two-thirds (21 of 32) RCTs of individualised homeopathic treatment have importantly deficient quality overall. Although RCTs in conventional medicine have not benefitted from a two-attribute appraisal of quality such as ours, systematic reviews that solely examined RoB have frequently expressed concern about the insufficient quantity of evidence available to answer a given research question [8]. It is reassuring, at least, that so few of our 32 homeopathy trials have overtly inadequate MVHT [3] and that the majority thus seem to involve 'genuine homeopathy' [9]. It is unknown to what extent model validity might impact on the interpretation of RCT findings in other branches of Complementary/Alternative Medicine (CAM); our MVHT method seems adaptable to addressing that question, as previously proposed [5]. It is also

[n] Additional sensitivity analysis based on the original authors' selection of 'primary outcome measure' has identified potentially a fourth RCT in the category 'Uncertain RoB – reliable evidence': http://www.britishhomeopathic.org/wp-content/uploads/2015/01/BHA-16-Jan-2015.pdf. That RCT (White 2003: study number A39 in tabulated material) would then be upgraded in our current rank order classification – see **Supplementary File 1** – as a second trial that is MVHT-deficient and with uncertain risk of bias, displaying a direction of treatment effect favouring homeopathy: its overall designation would be 'low quality' rather than 'very low quality'.

231 currently unknown if other potential flaws, connected with deficiencies of external validity for example
232 [10], might impinge on overall quality ratings of the trials we examined.
233
234 In classifying each of MVHT and RoB, we considered some domains of assessment to have lesser
235 importance than others. This judgmental approach to the relative importance of domains is consistent
236 with the Cochrane method of attributing overall RoB per trial [6]. It preserves *PRISMA* standards of
237 reporting, and it has successfully identified trials of individualised homeopathy that comprise 'reliable
238 evidence'. Similar dual assessment and analysis will feature in our subsequent systematic review of
239 placebo-controlled RCTs of *non*-individualised homeopathy.
240
241 **CONCLUSIONS**
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243 The quality appraisal of 32 RCTs of individualised homeopathic treatment, merging the assessments of
244 MVHT and RoB, identified three trials of 'high quality', eight of 'moderate quality', 18 of 'low quality'
245 and three of 'very low quality'. Since the three 'high quality' trials are those that were already identified
246 as 'reliable evidence', there is no change in our main conclusion from previous meta-analysis based on
247 the best-quality RCTs: the medicines prescribed in individualised homeopathy may have small, specific,
248 treatment effects.
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250 **ADDITIONAL FILES**
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252 **Supplementary file 1**: Rank order of 32 trials by overall quality designation, and showing direction of
253 treatment effect (from meta-analysis data): if reclassifying White (2003) as 'Uncertain RoB – reliable
254 evidence'.
255
256 **Declaration of competing interests**

257 RTM, JC and SM are employed by, or associated with, a homeopathy charity to clarify and extend an
258 evidence base in homeopathy. The study is intrinsic to the charity work of the British Homeopathic
259 Association (BHA) through its Research Development Adviser, RTM; no other member of the BHA's
260 staff, nor its trustees, contributed to the design, analysis or write-up of the work. Each of the following is
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262 RTM, MVW, JJ, MO, JF, RJM, HR, FD, PF. The University of Glasgow was supported by a grant from
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264 honoraria or royalties from a number of organisations, including universities and pharmaceutical
265 companies.
266

267 **Authors' contributions**

268 RTM devised and led the study in collaboration with all co-authors. SML, LAL, JC, SM, JRTD and IF
269 are co-authors of the original paper on risk-of-bias [2]; MVW, JJ, MO, JF, RJM, HR, FD and PF are co-
270 authors of the original paper on model validity [3]. Each co-author contributed to interpretation of the
271 merged data, and edited and approved the final manuscript.
272

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277

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Table 1: **Method for merging RoB and MVHT into single overall designation of quality**

Attribute of quality				
RoB	**MVHT**	**Descriptive criteria for downgrading**	**Downgrading**	**Overall designation**
Low risk	**Acceptable**	Neither attribute has important flaws	0	High quality
Uncertain risk**	**Acceptable**			
Uncertain risk	**Acceptable**	One attribute is 'uncertain'; the other attribute is 'uncertain' or better	-1	Moderate quality
Uncertain risk	**Uncertain**			
Uncertain risk	**Inadequate**	One attribute has important flaws	-2	Low quality
High risk	**Acceptable**			
High risk	**Uncertain**			
High risk	**Inadequate**	Both attributes have important flaws	-3	Very low quality

**Includes those trials designated ‘reliable evidence’.

No trial in the current study was designated ‘low risk of bias’ – see Results.

Table 2: Rank order of 32 trials by overall quality designation, and showing direction of treatment effect (from meta-analysis data[2])

Ref.	First author	Year	Overall RoB	Overall MVHT	Downgrading	Overall designation	Direction of effect
A5	**Bell**	2004	**Uncertain****	Acceptable	0	High quality	Homeopathy
A19	**Jacobs**	1994	**Uncertain****	Acceptable	0	High quality	*Homeopathy
A20	**Jacobs**	2001	**Uncertain****	Acceptable	0	High quality	Homeopathy
A10	**Chapman**	1999	Uncertain	Acceptable	-1	Moderate quality	Homeopathy
A14	**Frass**	2005	Uncertain	Acceptable	-1	Moderate quality	*Homeopathy
A23	**Jacobs**	2005a	Uncertain	Acceptable	-1	Moderate quality	Placebo
A36	**Thompson**	2005	Uncertain	Acceptable	-1	Moderate quality	Homeopathy
A41	**Yakir**	2001	Uncertain	Acceptable	-1	Moderate quality	Homeopathy
A6	**Bonne**	2003	Uncertain	Uncertain	-1	Moderate quality	Placebo
A11	**de Lange de Klerk**	1994	Uncertain	Uncertain	-1	Moderate quality	Homeopathy
A35	**Straumsheim**	2000	Uncertain	Uncertain	-1	Moderate quality	Placebo
A7	**Brien**	2011	High	Acceptable	-2	Low quality	Placebo
A9	**Cavalcanti**	2003	High	Acceptable	-2	Low quality	Homeopathy
A13	**Fisher**	2006	High	Acceptable	-2	Low quality	Homeopathy
A18	**Jacobs**	1993	High	Acceptable	-2	Low quality	----
A21	**Jacobs**	2000	High	Acceptable	-2	Low quality	----
A22	**Jacobs**	2005b	High	Acceptable	-2	Low quality	*Homeopathy
A24	**Jansen**	1992	High	Acceptable	-2	Low quality	----
A31	**Rastogi** (a)	1999	High	Acceptable	-2	Low quality	Homeopathy
A31	**Rastogi** (b)	1999	High	Acceptable	-2	Low quality	Placebo
A33	**Siebenwirth**	2009	High	Acceptable	-2	Low quality	Placebo
A38	**Weatherley-Jones**	2004	High	Acceptable	-2	Low quality	Homeopathy
A16	**Gaucher**	1994	High	Uncertain	-2	Low quality	----
A26	**Katz**	2005	High	Uncertain	-2	Low quality	----
A30	**Naudé**	2010	High	Uncertain	-2	Low quality	----
A32	**Sajedi**	2008	High	Uncertain	-2	Low quality	Placebo
A37	**Walach**	1997	High	Uncertain	-2	Low quality	----
A40	**Whitmarsh**	1997	High	Uncertain	-2	Low quality	Homeopathy
A25	**Kainz**	1996	Uncertain	Inadequate	-2	Low quality	Homeopathy
A1	**Andrade**	1991	High	Inadequate	-3	Very low quality	----
A34	**Steinsbekk**	2005	High	Inadequate	-3	Very low quality	----
A39	**White**	2003	High	Inadequate	-3	Very low quality	----

** Reliable evidence. * Homeopathy significantly superior to placebo ($P < 0.05$)

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Table 3: **Frequency table of MVHT and RoB**

Number of trials		Risk of bias			Totals
		Uncertain**	Uncertain	High	
MVHT	Acceptable	3	5	11	19
	Uncertain	0	3	6	9
	Inadequate	0	1	3	4
Totals		**3**	**9**	**20**	**32**

** Reliable evidence

Table 4: **Frequency table of MVHT and direction of treatment effect**

Number of trials		Direction of treatment effect		Totals
		Favours homeopathy	Favours placebo	
MVHT	Acceptable	12	4	16
	Uncertain	2	3	5
	Inadequate	1	0	1
Totals		**15**	**7**	**22**

Table 5: **Frequency table of RoB and direction of treatment effect**

Number of trials		Direction of treatment effect		Totals
		Favours homeopathy	Favours placebo	
RoB	Uncertain**	3	0	3
	Uncertain	6	3	9
	High	6	4	10
Totals		**15**	**7**	**22**

** Reliable evidence

Table 6: **Sensitivity analysis by overall quality designation**

Ref.	First author	Year	Overall designation	OR [95%CI]	Pooled OR [95% CI] for N trials	N trials included	*P* for N trials
A5	**Bell**	2004	High quality	1.77 [0.66, 4.72]	1.98 [1.16, 3.38]	3	0.013
A19	**Jacobs**	1994	High quality	2.22 [1.00, 4.94]			
A20	**Jacobs**	2001	High quality	1.84 [0.63, 5.36]			
A10	**Chapman**	1999	Moderate quality	1.98 [0.72, 5.49]	1.64 [1.24, 2.17]	11	< 0.001
A14	**Frass**	2005	Moderate quality	3.13 [1.10, 8.86]			
A23	**Jacobs**	2005a	Moderate quality	0.80 [0.25, 2.57]			
A36	**Thompson**	2005	Moderate quality	1.94 [0.66, 5.64]			
A41	**Yakir**	2001	Moderate quality	5.50 [0.96, 31.62]			
A6	**Bonne**	2003	Moderate quality	0.87 [0.28, 2.73]			
A11	**de Lange de Klerk**	1994	Moderate quality	1.67 [0.96, 2.89]			
A35	**Straumsheim**	2000	Moderate quality	0.80 [0.34, 1.90]			
A7	**Brien**	2011	Low quality	0.86 [0.16, 4.47]	1.53 [1.22, 1.91]	22	< 0.001
A9	**Cavalcanti**	2003	Low quality	3.50 [0.55, 22.30]			
A13	**Fisher**	2006	Low quality	1.33 [0.34, 5.30]			
A22	**Jacobs**	2005b	Low quality	3.84 [1.06, 13.90]			
A31	**Rastogi (a)**	1999	Low quality	1.36 [0.45, 4.10]			
A31	**Rastogi (b)**	1999	Low quality	0.53 [0.17, 1.69]			
A33	**Siebenwirth**	2009	Low quality	0.49 [0.07, 3.65]			
A38	**Weatherley-Jones**	2004	Low quality	1.47 [0.62, 3.47]			
A32	**Sajedi**	2008	Low quality	0.55 [0.09, 3.34]			
A40	**Whitmarsh**	1997	Low quality	1.72 [0.69, 4.34]			
A25	**Kainz**	1996	Low quality	1.41 [0.45, 4.45]			

Additional File 1: Rank order of 32 trials by overall quality, and showing direction of treatment effect (from meta-analysis data): if reclassifying White (2003) as 'Uncertain RoB – reliable evidence' (see also http://www.britishhomeopathic.org/wp-content/uploads/2015/01/BHA-16-Jan-2015.pdf)

Ref.	First author	Year	Overall RoB	Overall MVHT	Downgrading	Overall designation	Direction of effect
A5	**Bell**	2004	**Uncertain****	Acceptable	0	High quality	Homeopathy
A19	**Jacobs**	1994	**Uncertain****	Acceptable	0	High quality	*Homeopathy
A20	**Jacobs**	2001	**Uncertain****	Acceptable	0	High quality	Homeopathy
A10	**Chapman**	1999	Uncertain	Acceptable	-1	Moderate quality	Homeopathy
A14	**Frass**	2005	Uncertain	Acceptable	-1	Moderate quality	*Homeopathy
A23	**Jacobs**	2005a	Uncertain	Acceptable	-1	Moderate quality	Placebo
A36	**Thompson**	2005	Uncertain	Acceptable	-1	Moderate quality	Homeopathy
A41	**Yakir**	2001	Uncertain	Acceptable	-1	Moderate quality	Homeopathy
A6	**Bonne**	2003	Uncertain	Uncertain	-1	Moderate quality	Placebo
A11	**de Lange de Klerk**	1994	Uncertain	Uncertain	-1	Moderate quality	Homeopathy
A35	**Straumsheim**	2000	Uncertain	Uncertain	-1	Moderate quality	Placebo
A7	**Brien**	2011	High	Acceptable	-2	Low quality	Placebo
A9	**Cavalcanti**	2003	High	Acceptable	-2	Low quality	Homeopathy
A13	**Fisher**	2006	High	Acceptable	-2	Low quality	Homeopathy
A18	**Jacobs**	1993	High	Acceptable	-2	Low quality	----
A21	**Jacobs**	2000	High	Acceptable	-2	Low quality	----
A22	**Jacobs**	2005b	High	Acceptable	-2	Low quality	*Homeopathy
A24	**Jansen**	1992	High	Acceptable	-2	Low quality	----
A31	**Rastogi** (a)	1999	High	Acceptable	-2	Low quality	Homeopathy
A31	**Rastogi** (b)	1999	High	Acceptable	-2	Low quality	Placebo
A33	**Siebenwirth**	2009	High	Acceptable	-2	Low quality	Placebo
A38	**Weatherley-Jones**	2004	High	Acceptable	-2	Low quality	Homeopathy
A16	**Gaucher**	1994	High	Uncertain	-2	Low quality	----
A26	**Katz**	2005	High	Uncertain	-2	Low quality	----
A30	**Naudé**	2010	High	Uncertain	-2	Low quality	----
A32	**Sajedi**	2008	High	Uncertain	-2	Low quality	Placebo
A37	**Walach**	1997	High	Uncertain	-2	Low quality	----
A40	**Whitmarsh**	1997	High	Uncertain	-2	Low quality	Homeopathy
A39	**White**	2003	**Uncertain****	Inadequate	-2	Low quality	Homeopathy
A25	**Kainz**	1996	Uncertain	Inadequate	-2	Low quality	Homeopathy
A1	**Andrade**	1991	High	Inadequate	-3	Very low quality	----
A34	**Steinsbekk**	2005	High	Inadequate	-3	Very low quality	----

** Reliable evidence. * Homeopathy significantly superior to placebo ($P < 0.05$)