Meta-analysis of randomised controlled trials (RCTs) of individualised homeopathy: sensitivity of results to using original authors' 'primary outcome measure'

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Our paper, published in the journal *Systematic Reviews* on 6 December 2014, reached the cautious conclusion from meta-analysis that individually prescribed homeopathic medicines may have small specific treatment effects (Mathie et al. 2014). From the most reliable evidence, and based solely on the most clinically important and objective outcome measure per RCT, the pooled odds ratio (OR) for homeopathy compared with placebo was 1.98 (95% confidence interval [CI], 1.16 to 3.38). Therefore, for those 'main outcome measures', the participants randomised to homeopathy were approximately twice as likely to have a favourable outcome as those randomised to placebo.

Our review's selection of the single outcome measure to represent each trial was based on the World Health Organization (WHO) hierarchical criteria for classifying human health and functioning (WHO, 2002 [with URL]):

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

Testing the hypothesis underlying our review depended on our identifying the most clinically important measure per trial. To ensure that this occurred, we favoured our own selection of 'main outcome measure', if necessary, over that of the original RCT's authors, even if that approach entailed rejection of those authors' own designated 'primary outcome measure' (Mathie et al. 2013). For the purposes of meta-analysis based on optimum clinical importance, the review's methods explicitly disallowed our use of a different outcome measure if our selected one failed to yield extractable data.

The policy always to err on the side of stringency was aimed at enhancing the robustness of any positive conclusions we might reach. Nevertheless, it is known that the review of Complementary & Alternative Medicine (CAM) research is prone to conflicting conclusions depending on the precise data extraction and other methods employed (Linde 2009). The most recent systematic reviews and meta-analyses of homeopathy used the original RCT authors' designated 'primary outcome measure' as the one preferred for meta-analysis (Linde et al. 1997; Shang et al. 2005).

Purpose of this study:

Aware that using differing (less clinically important) outcome measures might potentially have yielded a different statistical result and hence conclusion from our meta-analysis, here we test the sensitivity of our data extraction method to allowing instead the use of the original authors' own 'primary outcome measure' for each RCT from which we found it impossible to extract data for a different measure that we had independently selected to represent that trial.

Methods:

For each trial in which a 'primary outcome measure' was identified and reported by the original trial authors, we examined the extent to which our own ascribed 'main outcome measure' was the same or a different one. For an RCT in the latter category, we re-rated its Cochrane domain V from our original 'No' ('high risk of bias', due to inability to extract any data for the analysis) to 'U' ('unclear risk of bias', due to

inability to extract other key data [our designated 'main outcome measure'] for the analysis).

Results:

Only 11 papers defined a 'primary outcome measure' (**Table 1**). For 9 of the 11 RCTs, our selection of 'main outcome measure' was the same as the 'primary outcome measure'; the 2 trials for which it differed were Siebenwirth et al. 2009 and White et al. 2003.

Table 1: Eleven papers that defined a 'primary outcome measure'

A19	**Jacobs**	1994
A21	**Jacobs**	2000
A41	**Yakir**	2001
A06	**Bonne**	2003
A39	**White**	2003
A05	**Bell**	2004
A38	**Weatherley-Jones**	2004
A23	**Jacobs**	2005a
A22	**Jacobs**	2005b
A13	**Fisher**	2006
A33	**Siebenwirth**	2009

See Additional File 4 of our original paper for details of records of RCTs (*Systematic Reviews* 2014; **3**: 142. doi: 10.1186/2046-4053-3-142)

For Siebenwirth, the difference was merely that the original authors had selected *change* in the same outcome measure as we had ascribed; in any event, that trial was already ascribed 'high risk of bias' for reasons other than domain V (Mathie et al. 2014), and so it was not re-examined further here. For White, the original authors had selected a 'primary outcome measure' that reflected the participants' quality of life, and was thus of lower ranking in the WHO classification than our selection of 'main outcome measure' (symptom severity).

Scrutinising Table 2 of the White paper, to interpret the 'pooled standardised score', it was apparent that the authors had not presented the mean or the standard deviation (SD) of their outcome measure at the trial's end-point. Nevertheless, using the same Cochrane methods as we applied when necessary for other trials in our meta-analysis paper (Mathie et al. 2014), we were able to approximate the required SDs by assuming that the SD per group at the trial end-point was the same as the corresponding SD at baseline. The mean for each group at end-point was obtained arithmetically from the tabulated data in the White paper.

Using the same mathematical methods and assumptions as per our original review, we were then able to calculate the standardised mean difference (SMD) and thus the OR for the White trial: SMD = –0.05 (95% CI, –0.50 to 0.41); OR = 1.08 (95% CI, 0.47 to 2.48).

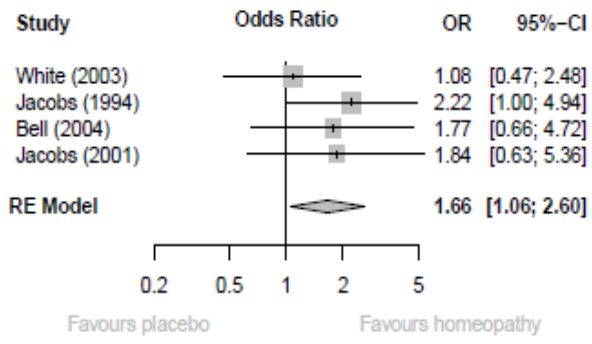
Given that an alternative data extraction was possible, for the present purpose the domain V rating for the White trial could be amended from 'N' to 'U', and so the trial became 'B1'-rated (Mathie et al. 2014). The trial also became a fourth in the category 'reliable evidence' (**Table 2**).

Table 2: Four RCTs regarded as 'reliable evidence' for the present analysis

A19	**Jacobs**	1994
A20	**Jacobs**	2001
A39	**White**	2003
A05	**Bell**	2004

The resulting *N*=4 sensitivity analysis based on 'reliable evidence' is shown in **Figure 1**: pooled OR = 1.66 (95% CI, 1.06 to 2.60); *P* = 0.028.[1]

Figure 1: Meta-analysis of the four RCTs in Table 2



[1] The pooled OR for our original, corresponding, *N*=3 sensitivity analysis for 'reliable evidence' was 1.98 (95% CI, 1.16 to 3.38); *P* = 0.013 (Mathie et al. 2014).

Conclusions:

The results of this sensitivity analysis of RCTs with 'reliable evidence' show that our original data extraction method (Mathie et al. 2014) is robust to allowing instead the original authors' 'primary outcome' if the data for our own selected 'main outcome measure' are not extractable.

This conclusion is reassuring in relation to the previous cautionary comments about systematic reviews in CAM research (Linde 2009). It also highlights that clinical trialists in homeopathy might wish to reflect whether their selected 'primary outcome' is the optimum in terms of clinical importance; certainly they should report key data with tabulated clarity to enable unambiguous and precise data extraction in subsequent systematic review and meta-analysis.

We remain clear that our use of the WHO classification approach is fit for purpose in informing the selection of 'main outcome measure' per RCT in homeopathy for meta-analysis that is based on optimum clinical importance.

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