Homeopathy (2006) 95, 215–222
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doi:10.1016/j.homp.2006.07.006, available online at http://www.sciencedirect.com

ORIGINAL PAPER

Evaluation of specific and non-specific effects in homeopathy: Feasibility study for a randomised trial

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Objective: **To determine the feasibility, in terms of acceptability to patients, physicians and other staff; data return and statistical power of a study to elucidate the relative contributions of specific and non-specific effects in homeopathic treatment of dermatitis.**
Design: **Randomised, controlled 4-arm trial, 2 arms double-blind.**
Setting: **Outpatient clinic, Royal London Homoeopathic Hospital.**
Participants: **Seventy-five adult patients with dermatitis.**
Interventions: **Patients were randomly allocated to: 'fast track' open verum homeopathy, 'fast track' double-blind verum homeopathy, 'fast track' double-blind placebo homeopathy or waiting list control.**
Main outcome measures: **One hundred millimeter visual analogue scale of overall symptom severity; 10 point digital scores of sleep, itching, skin condition; weekly 5-point Likert scale of topical steroid use; Dermatology Life Quality Index at entry and completion.**
Results: **Recruitment was below target, but the study was acceptable to staff and feasible. Blinded patients were more likely to withdraw ($P = 0.021$, χ^2 test). After correction for baseline differences and multiple comparisons, no outcome measure showed statistically significant between group differences. Blindness appeared to have a negative effect, but this was confounded by differential withdrawal.**
Conclusions: **A definitive trial of this design is unlikely to discriminate the relative contributions of the non-specific and specific effects to the outcome of homeopathic treatment of dermatitis, because of patient preference issues.** *Homeopathy* (2006) **95,** 215–222.

Keywords: Specific effects; non-specific effects; dermatitis; randomised controlled trial; placebo control waiting list control

Introduction

The effects of medical treatment are traditionally divided into specific: the direct physiological or pharmacological effects, and non-specific: all other components of the treatment process. It has been argued that, whatever the specific effects of homeopathic medicines, the homeopathic intervention as a whole is of benefit, due to factors including the in-depth consultation and careful attention to the individual case.[1] However, these beliefs have never been systematically tested: it is widely assumed, but not known for certain, that the homeopathic consultation is itself of benefit. Nor is the relative contribution of specific and non-specific factors in homeopathic treatment known.

We report here the evaluation of specific and non-specific effects in homeopathy (ESANSE) trial: a study

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Received 21 April 2006; revised 12 June 2006; accepted 13 July 2006

aimed at determining the feasibility of a randomised-controlled trial to empirically elucidate the relative importance of specific and non-specific treatment effects in routine homeopathic practice.

The research questions for this study were:

1. Is the study design acceptable to patients? In other words, what proportion of patients consent to take part in the trial?
2. Is the study design acceptable to the homeopathic physicians? For example, does it cause undue interference with clinical practice?
3. Is the study design acceptable to non-clinical staff at the RLHH? For example, does the study cause unacceptable difficulties with the appointments system?
4. Does the study produce interpretable data? Are sufficient numbers of evaluable patient records returned?
5. Preliminary indication of the size of the specific and non-specific effects enabling statistical power calculation for definitive study.

This would open the way for a definitive study to answer the questions:

1. Is homeopathic consultation plus placebo more effective than no treatment?
2. Is homeopathic consultation with a true homeopathic medicine more effective than a homeopathic consultation with placebo?
3. Is homeopathic consultation where the patient knows they will be getting verum more effective than a consultation where the patient is randomised to placebo or verum on a blinded basis?

The answers to these questions will not only provide information about the value of homeopathy as practised but provide an important theoretical link between data from placebo-controlled trials and the real world of clinical practice.

Dermatitis was selected as a model since it is a chronic condition with relatively large numbers of patients referred to the Royal London Homoeopathic Hospital, where the study was conducted. The study model could be adapted to other conditions.

Methods and patients

This was a 4-arm randomised-controlled trial, the arms were:
fast track open verum homeopathy;
fast track double-blind verum homeopathy;
fast track double-blind placebo homeopathy;
waiting list control.

This permitted double-blind comparison between verum and placebo homeopathy (specific effect of homeopathic medicines), comparison between fast track open verum homeopathy and waiting list control (effect of the homeopathic 'package of care'); and comparison between blind and unblind groups (effect of blinding). It was of 12 weeks duration. The study design is shown schematically in Figure 1.

The trial was designed to be as naturalistic as possible. It used as a recruitment base incident patient referrals to the Royal London Homoeopathic Hospital (RLHH) with minimum interference with normal practice. The setting, consultation, doctor and verum medication were the same as in routine practice. The divergences from normal practice were: all recruited patients recorded data, 75% attended a 'fast track' clinic, approximately 12 weeks earlier than normal, 50% were treated double blind and 25% received placebo. We did not incorporate a formal assessment of area of skin involved because this would have interfered substantially with normal practice, and was not feasible for the waiting list control group.

We took advantage of the fact the waiting time between receipt of the referral letter and appointment for patients with dermatitis at the RLHH was about 14 weeks. We established a 'fast-track' research clinic with a short waiting time ($\leq$2 weeks). Consenting patients were randomised to:

Fast track, but otherwise normal homeopathic care (open verum homeopathy).
Fast track, double-blind verum homeopathy.
Fast track, double-blind placebo homeopathy.
Normal care, routine appointment in ~12 weeks (waiting list control).

All letters of referral mentioning eczema or dermatitis were screened by one of the study doctors (PF). Patients who appeared to meet the entry criteria were sent information about the trial with an invitation to call a recruitment hotline. When it became clear, at 6 month review, that considerable numbers of eligible patients were not responding, the invitation to participate was modified to make it more welcoming. The hotline was staffed by a research nurse who took potential participants through a prepared script, obtained oral consent and arranged the appointment. Subjects were then sent further information and the written consent form. Baseline data was also taken for age sex and duration of dermatitis. Patients were sent an appointment for a date within 2 weeks of receipt of their signed consent form, those randomised to the waiting list control group were sent a diary, with instructions and asked to start completing it immediately. The recruitment target of 100 patients in 12 months was estimated from diagnostic coding data obtained from the RLHH Patient Administration System.

Inclusion criteria were:
Planned treatment for dermatitis at the RLHH
Age 18–65.
Exclusion criteria:

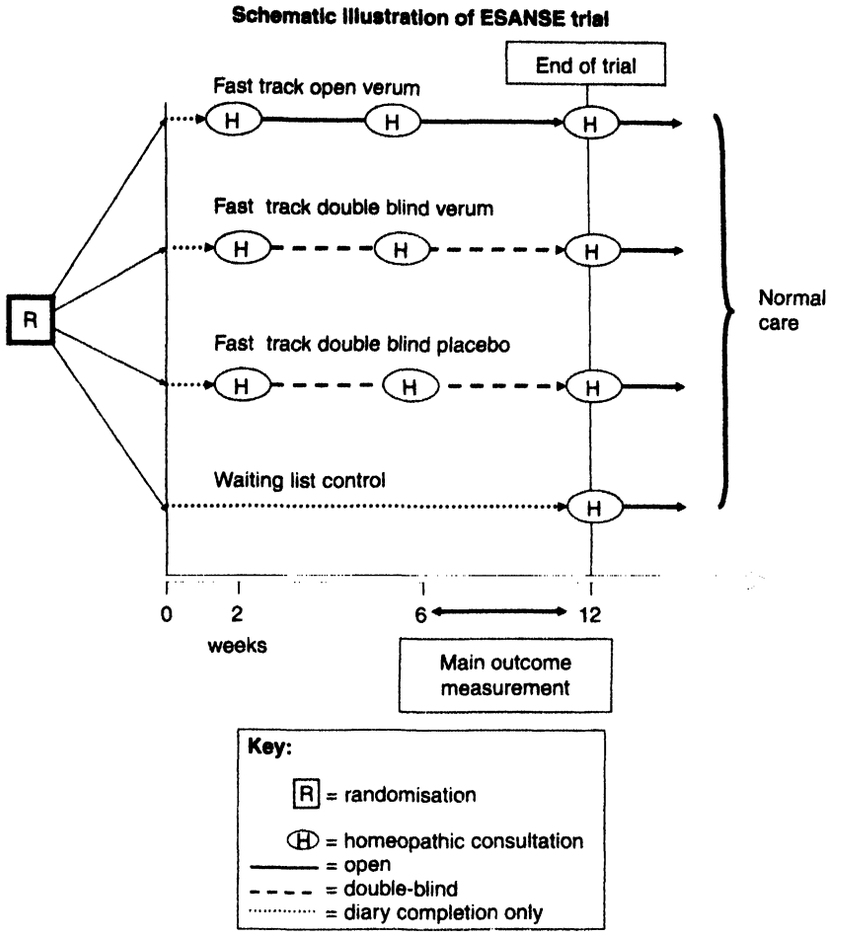

Figure 1 Schematic illustration of trial.

Pregnancy or intended pregnancy.
Malignant disease.
Other serious pathology.
Current use of systemic corticosteroids.
Previous attendance at the RLHH or previous homoeopathic treatment from a qualified practitioner.

On receipt of written consent, subjects were assigned a unique, four figure code number and randomised by a computer algorithm in permuted blocks of 8 and 12 into one of the four groups listed above. Treatment allocation was concealed from clinical staff by holding the randomisation list on a secure database system to which they had no access.

Subjects in the immediate treatment, double-blind verum and placebo groups saw a qualified homeopathic doctor, at the RLHH in a 'fast track' research clinic. Treatment was entirely at the discretion of the treating homeopathic doctor. Subjects in the fast track open verum group received unblinded homeopathic medication immediately. Subjects in the double-blind verum or placebo groups immediately received verum or placebo homeopathy double blind. Patients in the waiting list control group were sent a diary and instructions on its completion, and asked to start keeping the diary immediately. Patients (apart from the waiting list control group) had a follow-up appointment with the same doctor, approximately 6 weeks after starting treatment. At this appointment treatment could be adjusted, following normal practice. Twelve weeks after the start of data collection (ie after the trial) they had a second follow-up appointment at which their treatment allocation was revealed. Further appointments followed normal RLHH practice, at the discretion of the homeopathic doctor.

Subjects in the waiting list control group had their consultation with a homeopathic doctor approximately 12 weeks after the start of data collection. They were treated according to normal practice. All patients were asked not to start new conventional treatment during the study period or to take homeopathic medicines other than those prescribed by the trial doctors.

The diagnostic category 'atopic dermatitis' or 'other dermatitis' was assigned by the homeopathic doctor at the appointment (for waiting list control patients, this meant that diagnostic category was defined only after the trial was complete). Standard diagnostic criteria were used for atopic dermatitis: an itchy skin condition plus 3 or more of the following: history of flexural involvement; history of asthma or hay fever; history of dry skin in the previous year; visible flexural eczema; onset under 2 years of age.[2]

Verum and placebo homeopathic medication was dispensed by the pharmacy of the RLHH according to the randomisation list. Placebo consisted of lactose pills impregnated with 95% pharmaceutical ethanol. They were identical in appearance, odour and taste to verum.

Outcome measures

Subjects completed a symptom score diary daily for 13 weeks. For the three fast track groups (open verum, double-blind verum and double-blind placebo) diary taking started 1 week before treatment. For the waiting list control group, diary taking started on receipt of the diary forms.

The diary consisted of 10 point digital scores of sleep, itching, skin condition and a 100 mm visual analogue scale (VAS) of overall symptom severity. The latter was the main outcome measure. In addition, the outcome diary included a weekly 5-point Likert scale asking how often steroid creams or ointments have been used in the preceding week (more than once a day; more than once a day on most days; once or more a day on several days; once a day on one or for a few days; not at all). The Dermatology Life quality Index (DLQI) was completed at entry and completion of the trial.[3] Failures to attend appointments were recorded.

The study was approved by the UCL/UCLH Ethics Committees on the Ethics of Human Research. The first patient entered the study on 8 March 1999, the last patient completed the study on 28 November 2001.

Statistics

Post-treatment outcomes were entered into a linear regression model with baseline score as a covariate

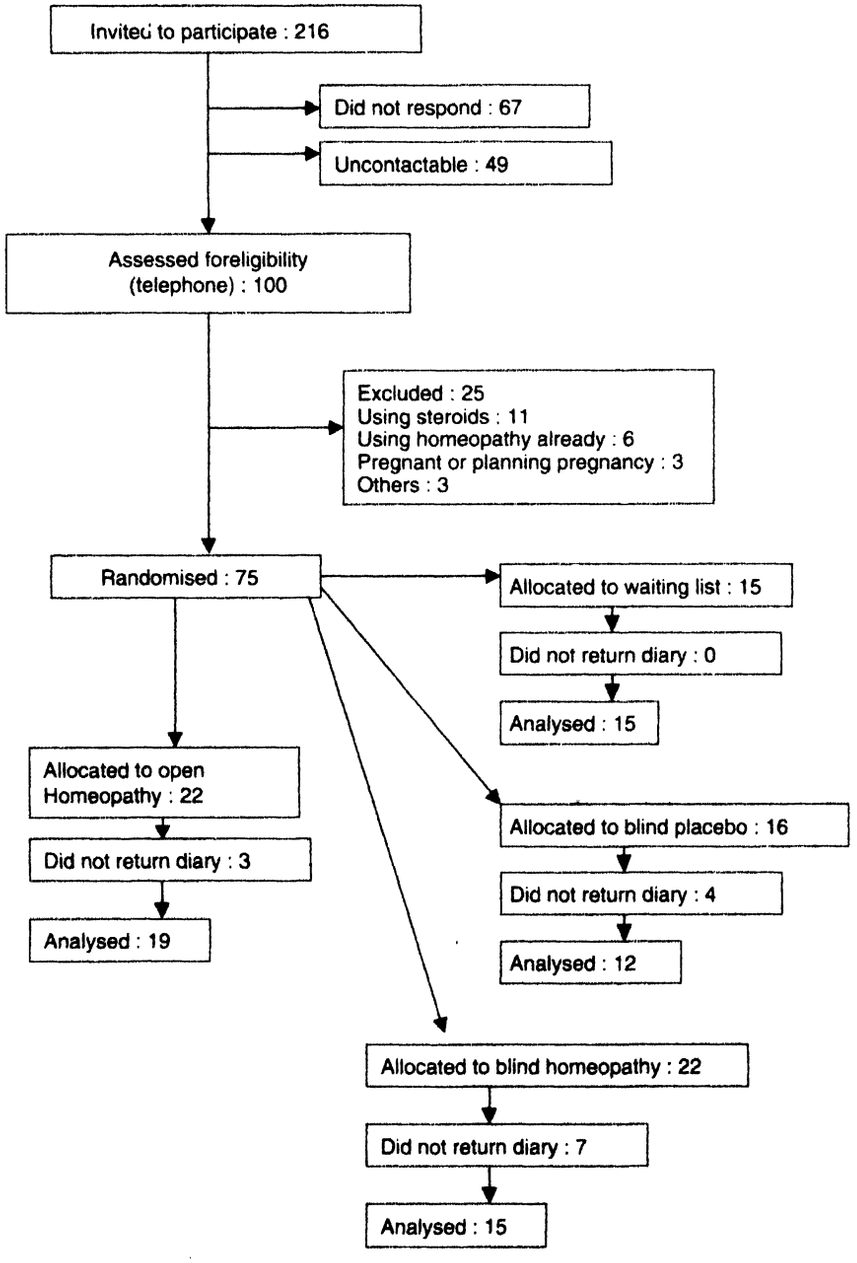

Figure 2 Patient flow through trial.

(ANCOVA).[4] Treatment allocation was entered as dummy variables corresponding to the three presumed aspects of homeopathic effect: seeing a homeopath, receiving a homeopathic medicine, knowing that treatment is being received. Thus the groups were coded as follows: waiting list control (0,0,0); blinded placebo (1,0,0); blinded verum (1,1,0); open homeopathy (1,1,1). Analyses were conducted using Stata 7 (Stata Corp., College Station, TX). Analyses were performed on 'intention to treat' basis and corrected for baseline differences and multiple comparisons.

Results

Recruitment fell well below target because of two factors: the estimate of the number of suitable patients attending the RLHH was overoptimistic, but the larger factor was the number of eligible patients who did not respond to the invitation to participate, or who responded but were then uncontactable by telephone.

Two hundred and sixteen information packs were sent out, 149 patients (69%) returned the form indicating that they were willing to participate. Of these, 49 (23%) were uncontactable by telephone and 25 (12%) patients were ineligible. We terminated the study when 75 patients had been recruited, of whom 61 completed and 14 lost to follow up. Figure 2 shows patient flow through the trial.

Blinded patients were much more likely to withdraw: 11 of 38 (29%) blinded patients dropped out compared to 3 of 38 (8%) unblinded ($P = 0.021$, χ^2 test)). There were no other significant differences between completers and dropouts (Table 1).

There were no statistically significant differences at baseline between completers in the four groups (Table 2), and no notable differences in homeopathic medicines prescribed (Tables 3 and 4).

Analysis of the different aspects of homeopathic effect showed apparent modest positive effects of seeing a homeopath and receiving verum homeopathy in terms of the primary outcome measure (overall VAS). Blindness appeared to have a positive effect on outcome; however, this was confounded by the large differential in withdrawal between the blind and unblind groups. Eleven of 38 (29%) blind patients withdrew, compared to 3/37 (8%) patients in the open groups. After correction for baseline differences, the only outcome which showed a statistically significant between-group difference was use of topical steroids which was greater in the unblinded groups but the *P*-value was 0.043: it would not be unusual to see one marginally significant result under the null hypothesis given the large number of tests conducted. Moreover, comparisons between blinded and unblinded groups are confounded by differential drop-out (see Figure 3 and Table 5).

Discussion

In this study, by far the largest between-group difference, and the only one reaching statistical significance, was the differential dropout rate between the blind and open groups. It appears that many patients in this cohort were averse to the blind knowledge condition. This affected both the recruitment phase and the treatment phase: it seems that

Table 1 Baseline comparison between dropouts and completers

	Drop outs n = 14	*Completers n = 61*
Age (years)	35 (12.3)	31 (10.3)
Disease duration (y)	10.9 (7.49)	11 (10.29)
Female:Male	8:6	47:14
Baseline skin condition	4.4 (1.86)	4.9 (1.73)
Baseline itching	4.5 (1.89)	4.4 (1.98)
Baseline sleep	3.8 (2.47)	2.8 (2.12)
Baseline overall condition	4.8 (2.09)	5.2 (2.19)
DLQI	2.3 (0.48)	2.1 (0.58)
Use of steroid creams	1.9 (1.56)	1.6 (1.43)
Group		
Waiting list control	0 (0%)	15 (100%)
Fast track, double-blind placebo	4 (25%)	12 (75%)
Fast track, double-blind verum	7 (32%)	15 (68%)
Fast track, open verum	3 (14%)	19 (86%)
Total blinded	11 (29%)	27 (71%)*

Data are mean and SD (x) = SD, (%) = percentage.
*$P = 0.021$.

Table 2 Baseline between group comparison for completers

Group	*n*	*Age mean (SD)*	*Duration of dermatitis (y) mean (SD)*	*Female:Male*
Waiting list control	15	29 (6.1)	9.9 (8.5)	8:4
Fast track, double-blind placebo	12	29 (9.7)	13.1 10.6)	13:2
Fast track, double-blind verum	15	37 (13.2)	12 (11.7)	12:3
Fast track, open verum	19	30 (9.4)	13 (10.8)	14:5

Table 3 Medicines prescribed to patients treated in the trial (includes prescriptions at both appointments)

Homeopathic medicines prescribed	*Blind placebo*	*Blind verum*	*Open verum*
Arsenicum album 6c		1	1
Arsenicum iodatum 6c	1		
Calcarea carbonica 6c		1	
Carcinosin 200c		2	
Euphrasia 6c		6	1
Graphites 6c			1
Mercurius soubilis 6c			1
Mixed pollen 30c	4	3	4
Mixed pollen and mixed fungal spores 30c	1	4	2
Natrum carbonicum 6c	1		
Natrum muriaticum 6c		2	2
Petroleum 6c		1	
Phosphorus 6c	4	5	7
Pulsatilla 6c	1	3	1
Sepia 6c	1		1
Silicea 6c	1	1	
Staphysagria 30c		1	
Sulphur 6c	3	4	3
Urtica urens 6c	1		

many of the patients approached were deterred by the 50% risk of receiving blind treatment. Furthermore, knowledge condition and patient compliance with data collection were linked: blinded patients were much less likely to return data, and it is likely that among the blinded patients those who did not improve were most likely to dropout, leaving those who had done relatively well, hence the apparent positive effect of blinding.

The fact that 31% of patients initially approached did not respond to the invitation to participate appears irrational, since we were making a 'no lose' offer: responding patients had a 75% chance of having their appointments brought forward and a 50% chance of receiving active homeopathy earlier than they otherwise would have done. The worst case was that they had an appointment at the normal time. We revised the recruitment letter to emphasise these points, but this had little impact on recruitment. This surprised us and we can only account for it on the basis of an aversion to being blind to treatment allocation.

One can conceive of measures which might reduce data collection compliance bias, for instance the use of incentives to return data or more intensive follow up. But these would reduce the naturalism of the trial, introduce additional biases, and in some cases (such as the use of incentives) raise ethical issues.

Other weaknesses of this trial include the relatively short treatment period for a chronic disease. It is believed by homeopaths that the duration of treatment required is proportionate to the duration of the disease, sometimes expressed as the 'rule of 12' (1 month of treatment is required for every year of the disease). It is also possible that 'aggravations' or 'healing crises' (temporary deteriorations at the beginning of homeopathic treatment, associated with long-term improvement) occurred in the verum groups.

Table 4 Baseline and follow-up values (SD)

Group	*n*	*Skin*		*Itching*		*Sleep*		*DLQI*		*Steroid cream*		*Overall* (cm)	
		Baseline	*Follow up*	*Baseline*	*Follow up*	*Baseline*	*Follow up*	*Baseline*	*Follow up*	*Baseline*	*Follow up*	*Baseline*	*Follow up*
Waiting list control	15	5.51 (1.75)	4.08 (2.35)	4.97 (2.05)	4.02 (2.37)	2.81 (2.16)	2.8 (2.47)	1.82 (0.71)	2.05 (0.56)	1.6 (1.55)	1.07 (1.18)	5.87 (1.69)	4.14 (2.51)
Fast track, double-blind placebo	12	4.32 (1.41)	3.94 (1.71)	3.41 (1.91)	2.77 (1.92)	2.31 (2.22)	2.04 (1.73)	2.28 (0.32)	2.38 (0.3)	1.33 (1.44)	1.13 (1.11)	5.13 (3.73)	3.83 (1.9)
Fast track, double-blind verum	15	4.99 (1.64)	3.85 (1.69)	4.31 (1.97)	3.54 (2.05)	3.06 (2.07)	2.2 (2.02)	2.12 (0.51)	2.37 (0.4)	1.47 (1.3)	0.9 (0.87)	4.92 (1.82)	3.51 (1.99)
Fast track, open verum	19	5.12 (1.57)	4.71 (2.26)	4.77 (1.88)	3.88 (2.32)	3.11 (2.11)	2.84 (2.54)	2.05 (0.63)	2.01 (0.72)	1.94 (1.47)	1.76 (1.23)	5.08 (1.48)	4.28 (2.44)

A recent study in a setting similar to that in which this trial was conducted reported the incidence of aggravations as 24%.[5]

We are aware of only one other randomised, placebo-controlled clinical trial of homeopathy for eczema.[6] This study was different in many respects from ours: it had a much lower inclusion ratio (4.5% of screened patients), and there is little overlap between the homeopathic medicines prescribed in the two studies.

This trial was designed to elucidate the relative importance of specific and non-specific treatment effects in routine homeopathic practice, not any link between these two components of the treatment effect. However, the question of interactions between specific and non-specific effects is of considerable theoretical interest. It is an underlying assumption of placebo-controlled clinical trials is that there is no interaction between specific and non-specific effects: their effects are presumed simply to summate. This assumption has rarely been tested in the context of the treatment of chronic disease. A number of studies have addressed the issue of 'knowledge condition' (such as blindness) of patients and individuals administering active or placebo treatment, mostly analgesics in acute situations. A systematic review concluded: 'specific and non-specific effects are sometimes synergistic, and at other times antagonistic, so the implicit additive model of the randomised clinical trial is too simple'.[7] There have been a number of studies of interactions between knowledge condition and the physiological effects of drugs (particularly caffeinated and decaffeinated coffee), in healthy volunteers. These suggest complex interactions between knowledge condition and specific drug effects.[8-11]

Although our results could be interpreted as showing such an interaction (through an inevitable link between knowledge condition and specific effects, via compliance), it was not designed to investigate this question. Logically, in order to draw any conclusion on interaction between specific and non-specific components of treatment, a fifth arm would be required: an open arm in which patients had homeopathic consultations but did not receive homeopathic treatment and were aware of this. However this seems unrealistic and likely to be associated with poor compliance.

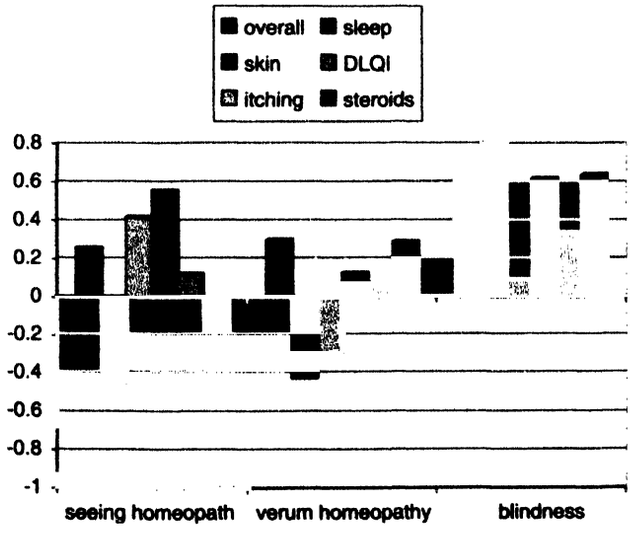

Figure 3 Effects attributable to different aspects of homeopathic effect.

Conclusions

This feasibility study set out to answer the following questions:

1. Is the study design acceptable to patients?.
   A considerable proportion of patients (31%) did not accept the offer to participate. There were more dropouts in the blind than open groups.
2. Is the study design acceptable to the homeopathic physicians?
   The design was generally acceptable to the physicians.
3. Is the study design acceptable to non-clinical staff at the RLHH?
   The design was generally acceptable to the patient services and other non-clinical staff. It was possible to implement it in the outpatients department of the RLHH without undue disruption.
4. Does the study produce interpretable data?
   The study data is difficult to interpret because the number of evaluable records returned was below expectation and there were large variations in the rates of return between groups.
5. Preliminary data to enable a statistical power calculation for a definitive study.
   For the same reason it was not possible to conduct a power calculation for definitive study of the interaction

Table 5 Effects attributable to different aspects of homeopathic effect: mean (95% CIs)

	Seeing homeopath	*Verum medicine*	*Unblinding*
Overall* (100 mm VAS)	−0.26 (12.03 to 1.51), $P = 0.8$	−0.3 (−2.06 to 1.46), $P = 0.7$	0.75 (−0.82 to 2.32), $P = 0.3$
Skin* (10 point)	0.45 (−1.08 to 1.98), $P = 0.6$	−0.43 (−1.92 to 1.07), $P = 0.6$	0.8 (−0.54 to 2.14), $P = 0.2$
Itching* (10 point)	−0.42 (−1.99 to 1.16), $P = 0.6$	0.29 (−1.25 to 1.83), $P = 0.9$	0.09 (−1.27 to 1.45), $P = 0.9$
Sleep* (10 point)	−0.56 (−2.21 to 1.09), $P = 0.5$	−0.13 (−1.79 to 1.53), $P = 0.9$	0.63 (−0.86 to 2.11), $P = 0.4$
DLQI†	0.12 (−0.27 to 0.51), $P = 0.5$	0.07 (−0.31 to 0.45), $P = 0.7$	−0.34 (−0.67 to 0), $P = 0.05$
Topical steroid use*	0.19 (−0.49 to 0.87), $P = 0.6$	−0.29 (−0.97 to 0.39), $P = 0.6$	0.64 (0.02 to 1.26), $P = 0.043$

*negative score indicates improvement.
†positive score indicates improvement.

between specific and non-specific effects. However, this data could inform a double-blind placebo-controlled RCT of homeopathy for dermatitis.

It appears that a trial of this design is unlikely to be able identify the relative contributions to the effects of homeopathic treatment in a 'real-life' setting of the non-specific and specific effects. This appears to be due to patient preference issues, those who were blind were much more likely to drop out. It is likely that blind patients who did not notice an improvement were most likely to drop out, while those who did improve continued to provide data, hence the apparent positive effect of blinding.

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