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A pilot 'cohort multiple randomised controlled trial' of treatment by a homeopath for women with menopausal hot flushes

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ABSTRACT

Introduction: In order to address the limitations of the standard pragmatic RCT design, the innovative 'cohort multiple RCT' design was developed. The design was first piloted by addressing a clinical question " What is the clinical and cost effectiveness of treatment by a homeopath for women with menopausal hot flushes?".

Methods: A cohort with the condition of interest (hot flushes) was recruited through an observational study of women's midlife health and consented to provide observational data and have their data used comparatively. The 'Hot Flush' Cohort were then screened in order to identify patients eligible for a trial of the offer of treatment by a homeopath (Eligible Trial Group). A proportion of the Eligible Trial Group was then randomly selected to the Offer Group and offered treatment.

A "patient centred" approach to information and consent was adopted. Patients were not (i) told about treatments that they would not be offered, and trial intervention information was only given to the Offer Group after random selection. Patients were not (ii) given prior information that their treatment would be decided by chance.

Results: The 'cohort multiple RCT' design was acceptable to the NHS Research Ethics Committee. The majority of patients completed multiple questionnaires. Acceptance of the offer was high (17/24).

Discussion: This pilot identified the feasibility of an innovative design in practice. Further research is required to test the concept of undertaking multiple trials within a cohort of patients and to assess the acceptability of the "patient centred" approach to information and consent.

1. Introduction

Existing pragmatic randomised controlled trial (RCT) designs have shortcomings in a number of areas including: recruitment; ethics, patient preferences; and treatment comparisons [1]. Firstly, the majority of randomised controlled trials have difficulty recruiting sufficient numbers of patients [2], and trial populations are often unrepresentative of the population "with need". Secondly, in routine real world healthcare, patients are rarely told of treatments that their clinicians cannot provide, or that their treatment will be decided by chance, yet this is regarded as ethical requirement for clinical trials. Thirdly, for pragmatic trials with a usual care comparator, where usual care is available outside the trial, the only incentive to participate is to receive the new intervention. Patients allocated to treatment as usual may be disappointed, and then may withdraw from the trial (attrition bias) or report disappointment (disappointment bias) when reporting outcomes. Fourthly, the current style of addressing a clinical research problem with many potential treatments is for each potential treatment to be trialled, one at a time, in different trial populations by different research teams, an approach which is inefficient both financially and scientifically.

In order to address these shortcomings an innovative design was developed [1]. The design was first piloted by addressing a current clinical question for the UK's publicly

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funded healthcare system, the National Health Service, which currently provides homeopathic treatment for women with menopausal hot flushes [3–5] as an alternative to the standard treatment of hormone replacement therapy (HRT) for the substantial numbers of women who suffer severe and frequent menopausal hot flushes but cannot take HRT (Fig. 1).

Homeopathic treatment can be understood as a complex intervention [6] which includes consultations with a homeopath and the prescription of inexpensive homeopathic medicines (the bulk of the cost being consultations with homeopaths [7]). Observational evidence reports that treatment by homeopaths (consultations plus homeopathic medicines) is both acceptable and effective for menopausal hot flushes [3,4], yet RCTs testing the efficacy of homeopathic medicines alone compared to placebos show no significant difference between groups [8,9]. To date, the effectiveness of the whole package of care by homeopaths (consultations plus homeopathic medicines) has not been tested using an RCT design. In order to inform NHS decision making about the clinical and cost effectiveness of this complex intervention, there is a need for information from pragmatic RCTs [10], which test the effectiveness of treatment by homeopaths, for this condition in an NHS setting.

This article reports the results of the pilot trial using a 'cohort multiple RCT' (cmRCT) design [1] to assess the clinical and cost effectiveness of treatment by a homeopath for women with menopausal hot flushes who cannot take HRT.

The **objectives** of this pilot trial were to assess the:

- Acceptability of the cmRCT design to an NHS Research Ethics Committee
- Willingness of patients to fill in questionnaires, consent to further questionnaires and have their data used comparatively
- Willingness of participants to accept the intervention
- Rate of compliance with the intervention
- Suitability of the outcome measures chosen
- Variability of the outcome variable (as measured by its standard deviation)
- Changes in the health condition in the intervention and the control group

2. Materials and methods

2.1. Design

The study was a partial pilot of the 'cohort multiple RCT' (cmRCT) design [1]. Key features of this design are: (I) recruitment of a large observational cohort of patients with the condition of interest and (II) regular outcome measurement for the whole cohort, (III) Capacity for multiple RCTs over time.

For each RCT, (IV) eligible patients are identified in the whole cohort, (V) from which some are randomly selected to be offered the intervention. The outcomes of those randomly selected patients are compared to those of eligible patients not

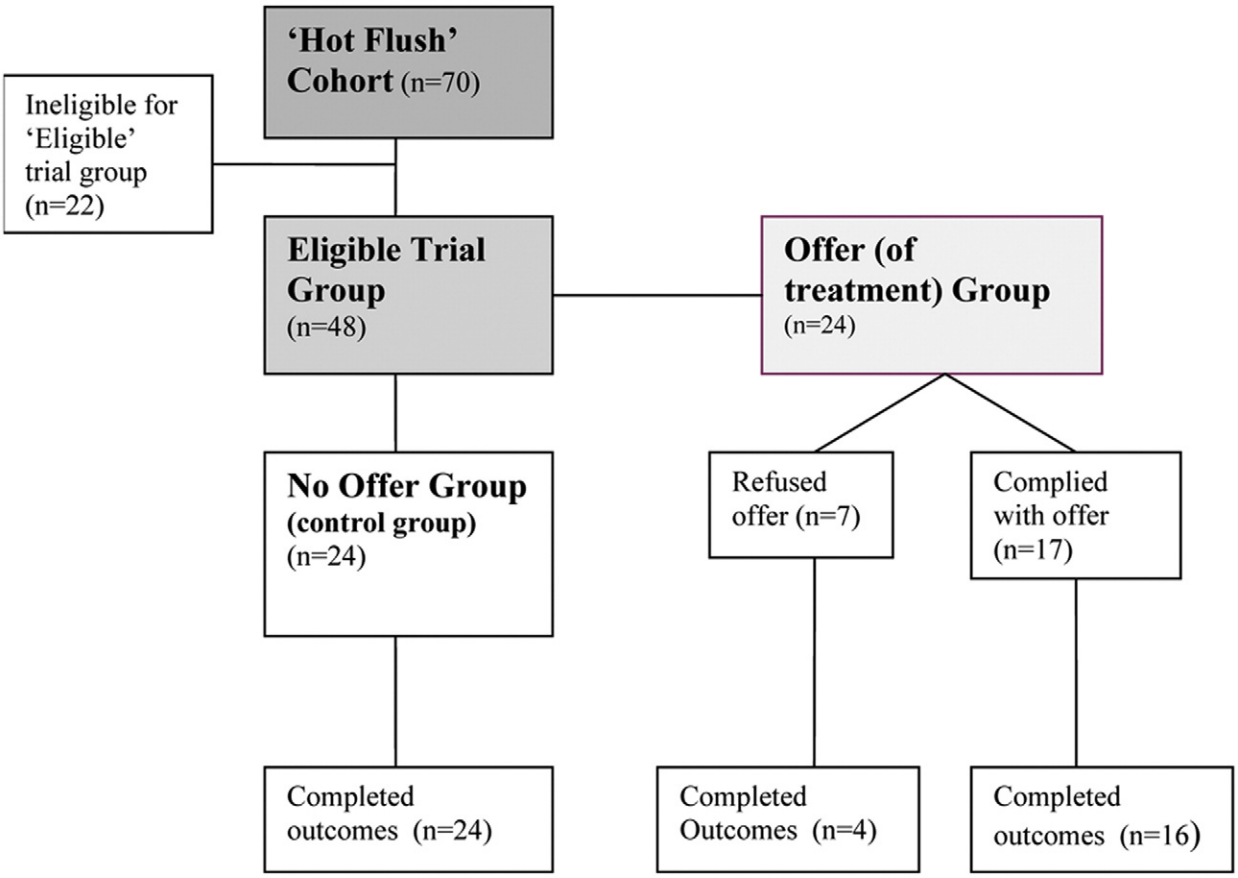

Fig. 1. Flow of participants in pilot 'cmRCT'.

randomly selected to be offered the intervention (VI). Patient information and consent replicate that of real world routine healthcare i.e. patients are not told about treatment that they might not receive (VII).

The recruitment and regular follow-up of a large cohort of patients (features I and II) are characteristics of longitudinal observational studies (and the Comprehensive cohort study design [11] and described in ref. [12]). In the cmRCT design, however, all patients in the cohort consent at the outset to provide data to be used to look at the benefit of treatments for the condition of interest. Feature III, the capacity for multiple randomised controlled trials over time using patients from the same cohort, is unique to the cmRCT design.

Features V, random selection and VI, the comparison of their outcomes with the outcomes in eligible patients not randomly selected, address the issue of prior consent to randomisation. Randomisation is generally conceived as "random allocation of all" and as something that is "done" to all patients and thus requires their prior consent. In the cmRCT design randomisation is conceived of as random selection of some eligible cohort patients, thus nothing is "done" to all patients and prior consent of all patients is not required.

Feature VII states that a "patient centred" approach should be taken to the provision of information and obtaining of consent'. Thus information about the proposed intervention was only given to the Offer Group after random selection to the Offer Group. No information about trial treatments is given to patients prior to randomisation and post randomisation information is given only to those allocated to a treatment—a feature of the single randomised consent (Zelen) design [13–15].

2.2. Sample and settings

2.2.1. Hot Flush Cohort

A cohort of women with the condition of interest (menopausal hot flushes) was recruited through an observational study of women's midlife health conducted in 6 NHS general practices in a large city in the north of England. 1200 women aged 45–64 were identified and selected to the Hot Flush Cohort through a series of postal questionnaires (I–III) sent out between October 2005 and February 2007. Responders to Questionnaire I were screened and those who reported experiencing 14 or more hot flushes a week and were willing to receive a further questionnaire were sent Questionnaire II. The purpose of Questionnaire II was to identify patients who were still experiencing 14+ hot flushes, obtain baseline data for the trial, and gain the information needed to screen patients for their eligibility for the 'Eligible' Trial Group.

For the majority of women, menopausal hot flushes are short term. As it took 11 months to obtain the necessary institutional approvals for the trial, a further questionnaire had to be sent out to responders to Questionnaire II who reported hot flushes. Responders to Questionnaire III who still reported hot flushes then became members of the Hot Flush Cohort.

2.2.2. Eligible Trial Group

The responses of the Hot Flush Cohort were then screened in order to identify patients who were eligible for the trial of the offer of treatment by a homeopath (Eligible Trial Group). In line with the pragmatic purpose of the study, inclusion criteria were as broad as possible. Women were included if they were aged 45–65, reported 14+ menopausal hot flushes/night sweats per week, consented to fill in further questionnaires and for their anonymised data to be used for looking at the benefit of treatments of hot flushes. Patients were excluded if they were taking HRT and not intending to stop, using immuno-suppressants or chemotherapy, homeopathy or acupuncture.

2.2.3. Offer Group

A proportion of the Eligible Trial Group were then selected at random to the Offer Group. Questionnaires from the Eligible Trial Group were assigned a study number by an independent administrator at the University of Sheffield who was blind to patient data. Half of the Eligible Trial Group were then randomly selected to the Offer Group by an independent statistician.

2.3. Randomisation

A random numbers sheet was generated by the statistician on a one to one basis using a block randomisation procedure, with blocks of 8. The random numbers were put into sealed numbered envelopes. Each questionnaire was screened for eligibility by applying the inclusion and exclusion criteria. Eligible questionnaires were assigned a study number by an independent administrator blind to any patient data and blind to whether group A or B was the offer of treatment arm. The numbered envelope corresponding to each woman's study number was then opened to reveal the group to which they had been assigned.

Random selection to the Offer Group took place before information about the proposed intervention was given to those patients randomly selected to the Offer Group and before patient consent to treatment had been requested.

2.3.1. Information

A key feature of the cmRCT design is that information is given to patients in a similar manner to routine healthcare, i.e. a 'non-disclosure-to-non-offerees-policy' was adopted. Thus, Hot Flush Cohort patients were not told that an intervention was going to be trialled. Eligible Trial Group patients were (i) not told about treatments that they would not then be offered and (ii) were not given prior information that their treatment would be decided by chance. However, post randomisation, Offer Group patients were told that they had been selected at random to the Offer Group and were given information about the trial treatment they were being offered.

2.3.2. Consent

Hot Flush Cohort patients were those who had given consent (i) to provide observational data (e.g. 'to fill in further questionnaires'). Eligible Trial Group patients also had given consent (ii) for their data to be used comparatively (i.e. 'for your anonymised data to be used for looking at the benefit of treatments for hot flushes'). Eligible Trial Group patients who were then subsequently randomly selected to the intervention group were asked for consent (iii) to treatment.

The outcomes of all patients who provide both consents (i) and (ii) could then be used to evaluate the outcomes of this trial and also the outcomes of any other trials embedded in the Hot Flush Cohort (for which the patient is eligible).

2.4. Intervention

The intervention was the offer of treatment from one of two study homeopaths. One homeopath was medically qualified (MB BS MFHom) and one was a professional homeopath (RSHom); both practiced individualised homeopathy. Treatment consisted of a maximum of five consultations and the use of homeopathic medicines, delivered at the Sheffield NHS Menopause clinic. Homeopaths were advised to treat patients according to their usual practice. No special restrictions were placed on the homeopaths by the study protocol, no adherence improving strategies were employed, no changes were required to patients existing medication. Homeopathic medicines from two pharmacies were used (Helios Pharmacy, UK and Bhandari Homeopathic Pharmacy, New Dehli, India).

2.5. Data collection methods

Trial baseline and 36 week post randomisation outcomes were measured in postal questionnaires III and IV sent to the Hot Flush Cohort.

2.6. Outcome measures

The primary outcome measure of clinical effectiveness was the Hot Flush Frequency and Severity Scale [16]. Secondary outcome measures included the Greene Climacteric Scale [17], which asks patients to score 'how bothered' they are by each of 21 menopausal symptoms, the primary symptom and wellbeing scores of Measure Your Medical Outcome Profile (MYMOP), a patient generated outcome measure. To facilitate the assessment of cost effectiveness the following outcome measures were chosen: EQ-5D [18] to measure generic quality of life, Medication Change Questionnaire, visits to hospital, visits to GP surgery, visits to other health professionals and days off work.

2.7. Data analysis

Descriptive statistics and a CONSORT type flow diagram [19] were used to describe the selection of patients to the Hot Flush Cohort, the Eligible Trial Group and the Offer Group; consent rates and outcome completion rates. It is argued [20] that the analysis of pilot studies should be descriptive and that hypothesis testing is not valid if no formal power calculation has been carried out because with small numbers there is likely to be imbalance in pre-randomisation covariates. Exploratory analyses were conducted here because the number of patients in this trial was similar to other hot flush intervention trials [21,22]. The methods and results of this pilot cmRCT were evaluated using an intention to treat analysis of all those with complete and analysable data, i.e. the outcomes of those in the Offer Group were compared with the outcomes of those in the No Offer Group.

3. Results

3.1. Acceptability of the design to an NHS Research Ethics Committee

The study protocol was submitted for ethical approval to the local NHS Research Ethics Committee (South Sheffield) who approved the protocol without delay (ref 06/Q2305/181). This ethics committee had no concerns about either (i) Information about the trial intervention was only given to the Offer Group after random selection to the Offer Group or (ii) Patients are not told of treatments that they cannot then obtain, or told that their treatment will be decided by chance (randomisation). The ethics committee were satisfied that the necessary consents were being obtained i.e. (a) consent to be contacted again, (b) consent for their anonymised data to be used for looking at the benefit of treatments for hot flushes and (c) consent to treatment from those in the Offer Group who accepted the offer. However, perhaps we were fortunate that this ethics committee included a clinician who had experience of the randomised consent (Zelen) design approach [11] to pragmatic trial design.

3.2. Willingness of patients to complete questionnaires, to consent to further questionnaires and to consent to have their data used comparatively

856/1,200 (71.3%) women returned postal Questionnaire I (sent October, 2005), of whom 61% reported having experienced side effects from HRT, and 39.3% reported stopping HRT due to side effects or concerns about the risks or long term side effects of HRT. Those responders who reported 14+ hot flushes a week (132/856) were then sent Questionnaire II (May, 2006). Questionnaire II responders who reported hot flushes (82/132) were then sent Questionnaire III in February 2007 (which included the trial baseline outcome measures) of whom 70/82 responded. These 70 women became the Hot Flush Cohort for this pilot study. In this partial pilot, no measures were taken from those without 14+ hot flushes a week.

48/70 women were eligible for the trial intervention (Eligible Trial Group). Reasons for exclusion were: less than 14 hot flushes per week (12/22), taking HRT and not wanting to stop (5/22), immunosuppressant drugs (2/22), incomplete questionnaires (2/22), and already having homeopathic treatment (1/22). 36 week questionnaires were sent out in December 2007. The majority of the Eligible Trial Group were willing to fill in 36 week questionnaires (45/48, 93.8%) and to have their data used comparatively (43/44, 97.7%) at 36 weeks.

3.3. Willingness of participants to accept the intervention

At baseline, half (24/48) of the Eligible Trial Group were randomly selected to the Offer Group, of whom 17/24 accepted the intervention and had one or more consultations with a homeopath.

3.4. Rate of compliance with the intervention

17 women received a total of 57 appointments; accepters attended a mean of 3.29 appointments out of a maximum of five (1 appointment (3 women), 2 appointments (1), 3 appointments ((4), 4 appointments (5), 5 appointments (4).

3.5. Suitability of the outcome measures chosen

The majority of the Eligible Trial Group (42/44) completed the primary outcome measure and the EQ-5D and economic resource data.

Table 1
Baseline characteristics: all participants.

Characteristics	Eligible Trial Group	Offer Group ($n=24$)	No Offer Group ($n=24$)
Age, years (as of Nov 2005)	54.7 (4.29)	54.12 (4.4)	55.42 (4.23)
Menopausal status			
Regular menses	1 [2.1%]	0 [0%]	1 [4.2%]
Irregular menses	5 [10.4%]	4 [16.7%]	1 [4.2%]
No menses in last 12 months	32 [66.7%]	16 [66.7%]	16 [66.7%]
Hysterectomy	10 [20.8]	4 [16.7%]	6 [25.0%]
IMD Band			
Low deprivation	17 [35.4%]	10	7
Medium deprivation	15 [31.3%]	6	9
High deprivation	16 [33.3]	8	8
Hot flush frequency severity score	12.44 (12.10)	16.58 (15.18)	8.30 (5.74)
GCS total score (0–63)	22.38 (10.29)	22.21 (11.14)	22.54 (9.61)
MYMOP	4.09 (0.97)	4.32 (1.13)	3.87 (0.76)
Primary symptom score (0–6)		$N=22$	$N=23$
MYMOP	3.22 (1.50)	3.05 (1.59)	3.37 (1.44)
Wellbeing score (0-6)		N = 23	N = 24
EQ-5D (0-1)	0.73 (0.20)	0.75 (0.22)	0.72 (0.19)
Number of prescribed medications	2.65 (2.35)	2.92 (2.64)	2.64 (2.04)
Number of self prescribed medications	1.29 (1.83)	1.46 (2.09)	1.13 (1.57)
Medication total (MCQ)	3.94 (3.15)	4.38 (3.32)	3.50 (2.96)
HRT ever used (yes)	24 [50%]	11 [45.8%]	13 [54.2%]
HRT side effect any (yes)	12 [25%]	5 [20.8%]	7 ([9.2%]

Data presented as Mean (SD) or n [%].

3.6. Variability of the outcome variable

The standard deviation of the Hot Flush Frequency and Severity variable was different for the intervention and control group at both baseline (Table 1) and 36 weeks adjusted for baseline (Table 2).

3.7. Changes in the health condition in control group

Participants in the control group (No Offer Group) at 36-weeks did not report any significant changes in their health with regards to the clinical outcome measures (Table 1).

3.8. Changes in the health condition in the Offer Group

The standard deviation of the Hot Flush Frequency and Severity score at baseline for the Offer Group was three times that of the No Offer Group. Apart from this, the baseline characteristics of the Offer and the No Offer Groups were well matched.

There were 44 women with both baseline and 36-week outcome data. Thus the number available for an intention to treat analysis was 44/48. Table 2 reports the 36-week outcome data adjusted for baseline value for the Offer and No Offer Groups. Lower scores indicate better health for all outcome measures (HFFS, GCS, MYMOP) apart from EQ-5D where a higher score indicates better health. Not all participants filled

Table 2
Eligible Trial Group: 36-week outcome data adjusted for baseline value.

Characteristics	Offer Group Mean change[a] & SD (Numbers of participants)	No Offer Group Mean change[a] & SD (Numbers of participants)	Difference in mean change 95% Confidence Interval
Hot flush frequency severity score	−6.89 (13.7) ($n=20$)	−1.16 (3.90) ($n=23$)	−5.73 (−12.31, 0.85)
GCS total score (0-63)	−1.95 (7.16) ($n=20$)	1.83 (6.19) ($n=23$)	−3.78 (−7.84, 0.28)
MYMOP Primary symptom score (0-6)	−0.50 (1.25) ($n=18$)	0.09 (0.90) ($n=23$)	−0.59 (−1.26, 0.92)
MYMOP Wellbeing score (0-6)	0.05 (1.51) ($n=19$)	−0.22 (1.48) ($n=23$)	0.27 (−0.66, 1.20)
EQ-5D (0-1)	0.07 (0.13) ($n=20$)	−0.03 (0.18) ($n=22$)	0.10 (−0.00, 0.19)
All medication	−0.80 (2.24) ($n=20$)	0.61 (2.33) ($n=23$)	−1.41 (−2.82, 0.00)
Prescribed medication	1.10 (4.49) ($n=20$)	1.50 (2.27) ($n=23$)	−0.40 (−2.51, 1.71)
Self prescribed medications	−0.45 (1.15) ($n=20$)	0.38 (1.41) ($n=23$)	−0.83 (−1.62, −0.03)

[a] Mean of the difference between the 36-week score and the baseline score.

in all outcome measures (numbers providing each outcome are stated in Table 2).

The pilot data for seven of the eight outcome measures (HFFS, Greene Climacteric Scale score, MYMOP Primary symptom score, EQ-5D, All medication, prescribed medication and self prescribed medication) at 36 weeks adjusted for baseline value favoured the Offer Group. Only the MYMOP Wellbeing score outcome measure favoured the No Offer Group.

3.9. Intervention (advice and medicines)

Homeopaths reported using a total of 18 different homeopathic medicines (the two most commonly prescribed homeopathic medicines were Sepia Officianalis (cuttlefish ink) and Lachesis Mutata (bushmaster snake venom). Some prescriptions were a one-off single dose whereas other prescriptions were to be taken twice daily every day. The most frequently given advice was to increase water intake (4 patients) and reduce/stop coffee (2 patients).

4. Discussion

This pilot identified the feasibility of using the innovative cohort multiple RCT design in practice. The NHS Research Ethics Committee accepted both the pragmatic comparative approach and the cmRCT design, with no objections raised regarding the absence of prior consent to randomisation and the lack of information about the intervention to the control group (No Offer Group).

The majority of women were willing to fill in questionnaires, to consent for further questionnaires, and to have their data used to look at the benefit of healthcare treatments. Completion of the outcome measures was high in this particular patient group. The offer of treatment by a homeopath was accepted by the majority of women, with accepters attending on average three consultations. A measure of variability of the primary outcome was obtained and it differed between Offer and the No Offer control group. We checked the random selection process and found it to be secure. We concluded that having recorded 12 baseline characteristics it is possible to find one or two characteristics showing a significant difference purely due to chance. This baseline imbalance compromised any comparison of clinical outcomes between the Offer and the No Offer groups, although the majority of the pilot data for all measures were in the direction of favouring the Offer Group (Offer of treatment by a homeopath).

Over a quarter (29.2%) of the Offer Group did not accept the offer and thus can be regarded as 'non-accepters'. Unlike standard RCT designs, the multi-stage recruitment process used in the cmRCT design is less likely to screen out non accepters prior to random selection. Therefore in this design the Intention To Treat analysis (which makes no special allowance for non-compliance) runs the risk of a Type II error—concluding that there is no difference when there actually is. Thus, in order to estimate the effect of the treatment on those who complied with the offer of treatment, a CACE analysis can be used [23]. CACE analysis rests on the premise that within the limits of chance the proportion of accepters in the control group and the treatment group will be the same. CACE analysis then measures the average causal effect for the subpopulation of accepters and preserves the benefits of randomisation.

4.1. "Patient centred" approach to information and consent

A key feature of the cmRCT design is the adoption of what we have termed a "patient centred" approach to informed consent, i.e. patients are not told about treatments that they may not then receive nor are they told that their treatment will be decided by chance (randomisation). The adoption of this 'non-disclosure-to-non-offerees-policy' has a number of scientific/practical advantages and ethical implications.

4.2. Scientific/practical advantages

Firstly, the adoption of the "patient centred" approach to information and consent allows the trial to replicate more closely the behaviours and experiences in real world healthcare, (rather than conform to the needs of standard trial design), thus increasing the external validity/ generalisability of trial results.

Secondly, if patients are told about treatments prior to randomisation, then those patients allocated to treatment as usual may be disappointed with their allocation, and then may withdraw from the trial (attrition bias) and/or report disappointment (disappointment bias) when reporting their outcomes. These are biases which the 'non-disclosure-to-non-offerees-policy' of the "patient centred" approach to information and consent avoids.

Thirdly, we conjecture that the "patient centred" approach may address one of the main barriers to trial recruitment for patients (and clinicians) i.e. 'concerns about information and consent' [24], thereby increasing the number of patients recruited to trials.

4.3. Ethical implications

In routine real world healthcare, patients decide to 'try'/trial treatments everyday, yet clinicians rarely inform their patients about treatments that they cannot then provide access to, nor do they inform their patients that their treatment will be decided by chance, yet both types of information are regarded as ethical requirements for clinical trials. Since the majority of patients enter clinical trials not out of a sense of altruism but for their own direct benefit as patients [25], (including obtaining access to treatments that they might not get otherwise), the provision of information about treatments which patients may then not be allocated to can create false expectation and subsequent disappointment, but is avoided by the 'non-disclosure-to-non-offerees-policy' of the "patient centred" approach of the cmRCT design.

This is the first RCT to assess the effectiveness of offering treatment by a homeopath to women with menopausal hot flushes.

This was a partial pilot of the cmRCT design, in that only one RCT was embedded within the cohort trials facility, whereas a full test of the cmRCT design will involve the conduct and analysis of multiple RCTs within the cohort. Instead of focussing on a short term self limiting condition such as menopausal hot flushes, the cmRCT design is better suited for long term chronic conditions. Currently, a number of studies are using the cmRCT design to conduct research into a variety of long term conditions and populations in the UK [26,27], Canada [28] and Iran [29]. These studies vary in the extent to which they implement

the 'non-disclosure- to-non- offerees-policy' of the "patient centred" approach to information and consent.

5. Conclusion

This post hoc evaluation found that the cmRCT design was acceptable to the NHS Research Ethics Committee. However, the concept of multiple trials within a single cohort of patients—a key feature of the cmRCT design—is yet to be fully tested. Further research is also required to assess the acceptability of the 'non-disclosure- to-non- offerees-policy' of the "patient centred" approach to information and consent.

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Contributors

CR had the original idea for the article. This article arose from CR's doctoral research, which was supervised by Professor Jon Nicholl and Professor Alicia O'Cathain at the School for Health and Related Research at the University of Sheffield. CR wrote the article and prepared the initial and all subsequent drafts. JN, AO reviewed and commented on all drafts. We thank the reviewers for their contributions to this article. CR is guarantor for the article.

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