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Original article

Polycystic Ovary syndrome: A Randomised feasibility and pilot study using Chinese Herbal medicine to explore Impact on Dysfunction (ORCHID)—Study protocol

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Abstract

Introduction: We aim to evaluate the feasibility of, and pilot procedures for, a randomised study in the UK administering Chinese herbal medicine (CHM) to women with polycystic ovary syndrome (PCOS) related oligo- and/or amenorrhoea. Our primary aim of this feasibility study is to evaluate how appropriate oligo- and amenorrhoea is as the primary outcome of the main study.
Methods: A prospective, multi-centre, randomised, patient- and practitioner-blind, feasibility and pilot study will be conducted. 40 women with PCOS-related oligo- and/or amenorrhoea will be randomised to one of two parallel arms comparing standardised CHM treatment against individualised CHM treatment as usual for 6 months. Participants will be prescribed 8 g of CHM granulated extracts twice daily, totalling 16 g per day. Feasibility will be determined by collecting data on menstrual regularity, body mass index, waist hip ratio, weight, Polycystic Ovary Syndrome Questionnaire, Measure Yourself Medical Outcome Profile, Dermatology Life Quality Index, Morisky Medication Adherence Scale, modified Ferriman–Gallwey scale, liver and kidney function, practitioner-blinding questionnaire and participant feedback forms. Process data will also inform feasibility such as recruitment rate, completion rate and reasons for dropout. Statistical analysis will be piloted in this study. We will present descriptive statistics for primary and secondary variables and use analysis of variance and Chi-squared tests where appropriate.
Results and conclusion: This study received ethical approval in December 2012. 40 participants were recruited between January 2013 and August 2013 and the study is expected to complete in March 2014.

Keywords: Chinese herbal medicine; Polycystic ovary syndrome; Feasibility study; Pilot; Menstrual disorders; Randomised controlled trial

Introduction

Polycystic ovary syndrome (PCOS) affects an estimated 6–18% of women of reproductive age and is a heterogeneous condition characterised by endocrine and metabolic disturbances [1–3]. Oligomenorrhoea and amenorrhoea are cardinal symptoms of PCOS and primary care management typically involves oral contraceptives and insulin-sensitising agents. However, there is evidence of dissatisfaction with such treatments which has been associated with intolerable side-effects, poor adherence rates and a potential increase in cardiovascular and metabolic risk [4–8]. This highlights a number of issues and barriers with current management and thus warrants exploration of other potentially more effective treatments that could be offered in primary care.

There is anecdotal evidence and emerging evidence from randomised controlled trials (RCTs) suggesting Chinese herbal medicine (CHM) could play an important role in the treatment of oligo- and amenorrhoea [9]. However, such studies are conducted in China, limiting the generalisability of findings to Western populations and which necessitates further exploration with a fully powered RCT in a UK setting. Prior to such a study

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and given the novel nature of offering CHM in primary care, it is important to first conduct a feasibility and pilot study to plan resources and reduce uncertainties [10–14]. The aims of this study are to determine the feasibility of conducting a randomised study in the UK administering CHM to women with PCOS-related oligo- and/or amenorrhoea, and to pilot and evaluate the study procedures.

Our primary feasibility question is:

1. Is oligomenorrhoea and amenorrhoea appropriate as the primary outcome measure for the main study?

Our secondary feasibility questions are:

2. Are other measures more appropriate for investigation as the primary outcome measure for the main study?
3. What is the safety profile of CHM?
4. How should the CHM intervention in the main study be delivered?
5. Can a double-blind, randomised trial with CHM for PCOS be conducted?

Methods

Design

A prospective, multi-centre, randomised, patient- and practitioner-blind, feasibility and pilot study will be conducted. This is a pragmatic study with two parallel arms comparing standardised CHM treatment against individualised CHM treatment as usual for PCOS-related oligo- or/and amenorrhoea. Although both standardised and individualised CHM are routinely available in the UK, individualised CHM is typically regarded as 'gold standard' practice, a view that is supported in the clinical literature [15] as well as an earlier Delphi study conducted by this research team (unpublished results). However, we are interested in exploring differences that may exist between the two interventions and preliminary scientific data gathered from this present study will inform the CHM intervention for the main study.

This study received ethical approval in December 2012 from the Register of Chinese Herbal Medicine (RCHM) and University of Southampton ethics committees (Approvals ID 3977) and is registered with Current Controlled Trials. It is conducted in accordance with the Declaration of Helsinki (1964) and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) (1996).

Eligibility criteria

Participants will be included if they: (1) are females aged 18–44, (2) present with oligo- and/or amenorrhoea with oligomenorrhoea defined as intervals between periods of >35 days and <200 days and amenorrhoea as intervals between periods of ≥200 days, (3) have received a diagnosis of PCOS consistent with the Rotterdam criteria [16].

Participants will be excluded if they: (1) present with other causes of hyperandrogenism or menstrual irregularities, (2) are currently pregnant, suspected to be pregnant, or actively trying to conceive, (3) are breastfeeding within 6 months of joining the study, (4) are receiving prohibited treatments such as hormonal contraceptives, (5) have a history of liver or kidney pathologies such as cirrhosis, glomerulonephritis, pyelonephritis, (6) have a history of psychotic illness or have been diagnosed with an eating disorder, (7) have currently active major depression, (8) are currently at risk of harmful and hazardous drinking, (9) have allergies to any of the following common herbal ingredients that are contained within the standardised CHM treatment: nuts, citrus fruit peel, goji berry, licorice or cinnamon, (10) do not have the spoken or written language skills necessary to take part, (11) are unable to attend the proposed study visits, (12) present with abnormal liver and/or kidney function at screening.

Recruitment and setting

Recruitment will take place in the community inviting self-referrals and using a study website, posters and flyers, online forums, social media and press releases and which have been used in similar studies [17–20]. Recruitment methods and literature were ethically approved prior to study commencement.

Eligibility will be initially assessed via a self-completed screening questionnaire or telephone interview with a member of the study team. Final eligibility criteria will be checked at the screening visit by the study practitioner who will explain in full the study procedures before asking for written informed consent.

Study visits will take place in UK-based CHM clinics and conducted by CHM practitioners who will be required to have a minimum 5 years in practice, be registered with a professional CHM organisation, be fully insured, have access to liver and kidney function testing and agree to carry out the study procedures as stated in the protocol. A list of active study sites can be obtained from the lead author.

This feasibility study requires a sample size of 40, based on requiring data from 15 participants per arm to calculate an estimate of the treatment effect and associated variability of the treatment effect to inform the power calculation for a main study [14]. Accounting for a 25% dropout rate based on similar studies [21,22], 20 participants will be required from each group, totalling 40 participants. A feasibility search conducted at a Wiltshire general practice surgery suggested a 10% eligibility rate and 400 enquiries will therefore be required to meet our recruitment target.

Study visits and assessments

Participants will undergo 8 study assessments in total at weeks 0, 2, 4, 8, 12, 16, 20 and 24. Of these assessments, the participant will be asked to physically attend visits at weeks 0, 4, 8, 12 and 24 whilst other assessments may be conducted by telephone or email at the practitioner's discretion. A participant flow diagram can be seen in Fig. 1.

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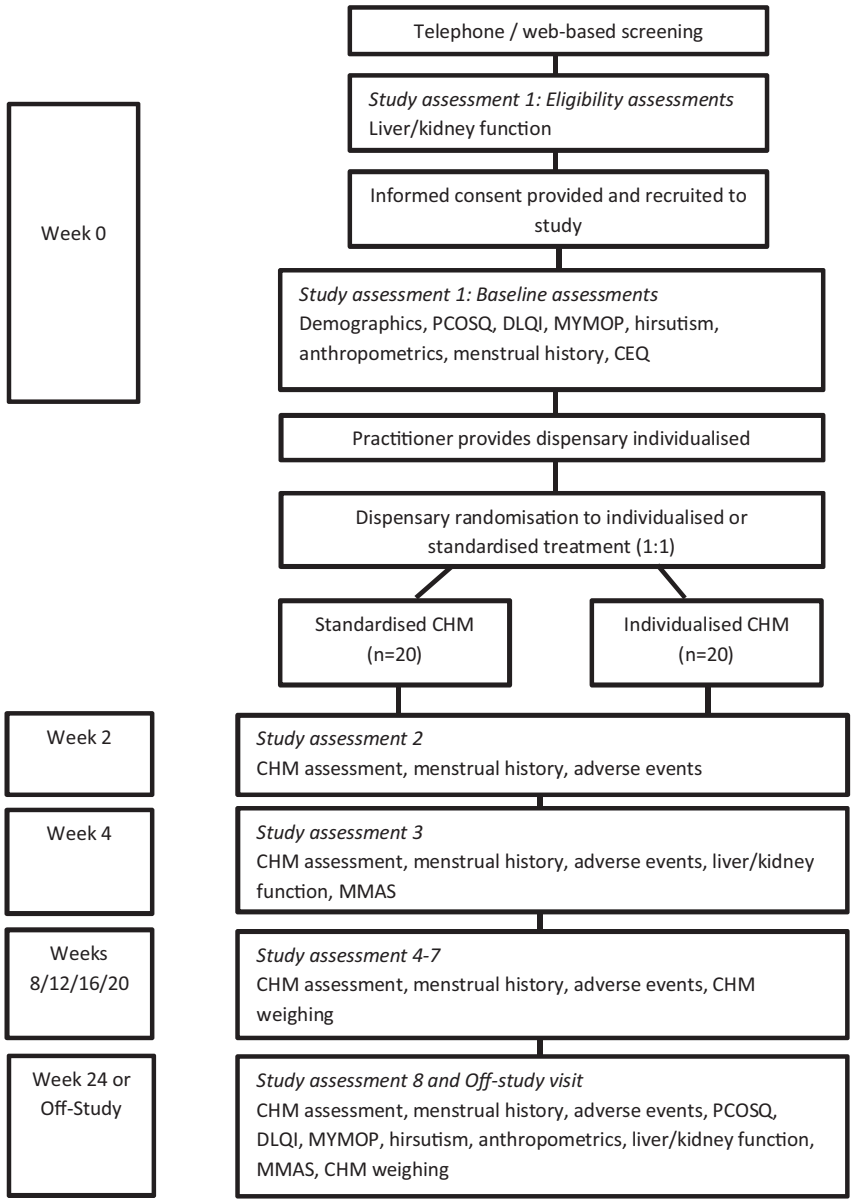

Fig. 1. Participant flow diagram.
Abbreviations: CHM = Chinese herbal medicine; PCOSQ = Polycystic Ovary Syndrome Questionnaire; DLQI = Dermatology Life Quality Index; MYMOP = Measure Yourself Medical Outcome Profile; CEQ = Credibility/Expectancy Questionnaire; MMAS = Morisky Medication Adherence Scale.

Randomisation, allocation concealment and blinding

Prior to the study, an independent statistician (PP) will use computer-generated random numbers with allocation ratio 1:1 to provide an irregular block allocation sequence. Allocation codes describing group allocation will be transferred to sealed opaque envelopes and sent to the dispensary prior to recruitment. Prior to and during the study, practitioners and members of the study team will have no knowledge of the randomisation sequence generated or of treatment allocation.

Participants and practitioners will be blinded throughout this study. Participants will be informed they will be randomised to one of two active CHM treatments but will remain blind to the difference between treatments during the study. At the final visit, this information will be revealed to the participants although their allocation will not be disclosed until the study is complete.

Practitioners will be informed of the difference between the two interventions but will remain blind to allocation to minimise performance bias. As practitioners will also be conducting assessments during the study, practitioner-blinding will be required to minimise measurement bias. Following each assessment, the practitioner will write an individualised prescription and send this to the dispensary. Upon receipt of an individualised prescription for a new participant, a member of the dispensary team will open the next randomisation envelope containing the allocation codes, note the participant's allocation and dispense the corresponding prescription. Where

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Table 1
Contents of standardised Chinese herbal medicine prescription.

Chinese Pinyin name	Common name	Family name	Part used	Botanical name	Dried herbal daily dosage (g)	Percentage (%)
Bai Shao (Chao)	Peony (dry fried)	Paeoniaceae	Root	*Paeonia lactiflora* Pall.	15	10.64
Chai Hu	Bupleurum	Umbelliferae	Root	*Bupleurum chinense* DC.	9	6.38
Chen Pi	Tangerine peel	Rutaceae	Peel	*Citrus reticulatata* Blanco	9	6.38
Chuan Xiong	Szechwan lovage rhizome	Umbelliferae	Rhizome	*Ligusticum chuanxiong* Hort.	9	6.38
Dang Gui Wei	Angelica extremitas	Umbelliferae	Root tail	*Angelica sinensis* (Oliv.) Diels	9	6.38
Gan Cao (Mi Zhi)	Liquorice root (honey-fried)	Fabaceae	Root	*Glycyrrhiza uralensis* Fisch.	6	4.26
Gou Qi Zi	Goji berry	Solanaceae	Fruit	*Lycium barbarum* L.	9	6.38
Gui Zhi	Cinnamon twig	Lauraceae	Twig	*Cinnamomum cassia* Presl.	9	6.38
Hong Hua	Safflower	Asteraceae	Flower	*Carthamus tinctorius* L.	9	6.38
Tao Ren	Peach kernel	Rosaceae	Seed	*Prunus persica* (L.) Batsch.	9	6.38
Tu Si Zi	Chinese dodder seed	Convolvulaceae	Seed	*Cuscuta chinensis* Lam.	12	8.52[a]
Xiang Fu (Cu Zhi)	Purple nutsedge (vinegar-fried)	Cyperaceae	Rhizome	*Cyperus rotundus* L.	12	8.52[a]
Yi Mu Cao	Motherwort	Lamiaceae	Top	*Leonurus japonicus* Houtt.	15	10.64
Zhi Ke	Bitter orange	Rutaceae	Mature fruit	*Citrus aurantium* L.	9	6.38
		Total prescription weight			141	

[a] Rounded up for column total to equal 100%.

a participant is allocated to standardised CHM, all future individualised prescriptions provided by the practitioner for that participant will be ignored by the dispensary.

Unblinding is permissible when a compelling medical need arises such as a serious adverse event. Unblinding will be conducted by a member of the research team not involved in data collection or analysis.

Interventions

All information presented fulfils the requirements of the elaborated CONSORT statement for reporting RCTs of herbal interventions [23].

Usual CHM practice combines a number of single herbs to produce a CHM prescription that is individualised to the patient. In this pragmatic comparative study, standardised treatment will be compared against individualised treatment as usual. Although a placebo-controlled study in primary care was initially planned, the time required by the herbal manufacturer to collect the required information for clinical trials approval was inconsistent with project deadline commitments and which necessitated a revision of the initial study design to our present protocol. The reason for our present choice of interventions is that we are interested in exploring potential differences between these two groups in clinical and safety effects and, should this study progress to a main study, to inform the design of a CHM intervention in primary care.

Standardised treatment consists of a pre-defined prescription of 14 single CHM granulated extracts, the contents of which can be seen in Table 1. This prescription is based on frequently occurring Chinese medicine presentations and treatment strategies extrapolated from a Delphi study, and on herbs used in RCTs for PCOS-related menstrual irregularities from a systematic review conducted by this study team (unpublished results). This prescription is not licensed for purchase over the counter and is available in the UK through registered CHM practitioners following a one-to-one consultation.

Individualised treatment will follow usual practice whereby the study practitioner will write an individualised prescription following an assessment with a participant, containing details of the base formulae if relevant, and details of the single herbs and dosages.

Both CHM treatments will be offered as granulated extracts for 6 months (24 weeks). Following good practice guidelines developed from our Delphi study, granulated extracts have been regarded by our panel of UK CHM practitioners as suitably effective in the treatment of PCOS, and 6 months deemed an appropriate length of treatment to observe improvements in oligo- and amenorrhoea (unpublished results).

Following each assessment, participants will receive a bottled container containing sufficient CHM until the next scheduled assessment. Participants will be instructed to use a measuring spoon provided to mix five level spoons (8 g) of granules with hot water and to take morning and evening after meals, totalling 16 g per day.

CHM dispensary and manufacturer

Phoenix Medical Direct Limited will dispense all CHM granulated extracts which are manufactured in China by Jiangyin Tianjiang Pharmaceutical Company Limited, a certified Good Manufacturing Practice (GMP) company. The solvent used for extraction is purified water to generate an 8:1 source to product extraction ratio. Authentication of raw materials and of the finished product is conducted using macroscopic and microscopic examination, and chemical methods such as thin layer chromatography for product identity and high-pressure liquid chromatography for potency which are checked for conformity to specifications in the Chinese Pharmacopoeia. Heavy metal testing and microbiological testing is conducted to confirm absence of microorganisms and pesticide residue. For each batch of single CHM granulated extract used, certificates of analysis and voucher specimens will be retained.

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Dispensing procedures and quality assurance measures follow the standards set by the RCHM and are compliant with and the European Directive on Traditional Herbal Medicinal Products (THMPD) 2004/24/EC. No animal or mineral products will be dispensed and only plant materials will be used.

Concomitant care

Permitted medications and interventions prior to, and at any point during, the study include analgesics, antidepressants, vitamin and mineral supplements, weight loss interventions and selected natural supplements such as evening primrose oil, milk thistle and mint.

Medications and interventions that are permitted only after 6 months' use include insulin-sensitising agents, anti-androgens and acupuncture. 6 months is deemed a sufficient period of time to have lapsed in order for clinical improvements from such treatments to have stabilised prior to administering CHM.

Medications and interventions that are not permitted at any time during the study due to potential interactions with study medication or potential effects on the study outcome measures include: hormonal contraceptives, anticoagulants such as heparin and warfarin, anti-hypertensives, diuretics, cardiac glycosides, ciprofloxacin, corticosteroids, lithium, ovulation-inducing agents, laparoscopic ovarian cauterization and fertility procedures. CHM and other herbal supplements that have a potential action on symptoms of PCOS or could interact with the study medication will also not be permitted and include St. Johns wort, black cohosh, vitex agnus castus and saw palmetto.

Practitioners will be permitted to provide participants with additional advice such as lifestyle, stress-management or general wellbeing according to Chinese medicine theory. It is acknowledged that offering such advice could be a potential confounder but since it will be offered to both treatment groups as part of pragmatic practice, we consider this to be an acceptable co-intervention. Practitioners will be asked not to offer advice outside of routine CHM practice.

Study restrictions

There is no available safety data regarding CHM use during pregnancy and participants will be strongly advised against trying to conceive whilst participating in this study. Participants will be asked not to change their diet or activity level during the study other than what their practitioner has recommended. To maintain participant-blinding, practitioners will be asked not to disclose information to participants regarding individualising prescriptions during the study.

Modifications, discontinuation and post-trial care

Modification to the standard 16 g daily dosage is permitted in response to adverse effects or at the participant's request and a daily dose range of 5–25 g is considered adherent to the protocol. Temporary discontinuation of CHM treatment is permitted for reasons such as experiencing side-effects or whilst on holidays and should be for a maximum period of 7 days each time to be considered adherent to the protocol. Changes in study practitioner and to the prescription between scheduled assessments are not permitted owing to resource constraints.

Should a compelling medical need arise for any participant, subsequent medical treatment will take precedent. Since this study has been approved by our sponsor and study interventions are routinely available and provided by fully qualified practitioners, study participants are insured both in terms of treatments provided as well as for research-related activities.

Participants will be withdrawn from the study either at their own request for personal reasons, or for other reasons without their consent, including situations in which continuing the study could be harmful to the participant's health, becoming pregnant or requiring treatment that is prohibited during the study. Participants will be invited to attend an end of study visit to collect final outcome data. Where appropriate, participants may be withdrawn from the interventional aspect but invited for monitoring of safety and other outcomes for the remainder of the study. Participants withdrawn from this study will not be replaced.

Upon study completion, participants will be offered a final telephone consultation with their practitioner within 4 weeks of their final visit.

Data management

Standardised online questionnaires will be used where possible to maximise completeness of data collection, and standardised electronic or paper-based forms where this is not possible. All source data will be transferred to standardised case report forms (CRFs) which will be anonymised.

Access to, and handling of, data will be restricted to delegated study staff who must comply with the requirements of the Data Protection Act 1998. Disclosure of confidential information can only be made during routine procedures such as monitoring and auditing by the study sponsor or in emergency situations such as when a compelling medical need arises.

Outcome measures

The clinical outcome of primary interest is regularity of menses measured as the number of days between menses. As there will be no run-in period, participants will be asked to recall data for a minimum of 3 menstrual cycles preceding the baseline visit. These will be used to calculate a baseline mean cycle length and standard deviation which will be compared with menstrual data obtained during the 6-month study period. An improvement is determined as a reduction from baseline in standard deviation to reflect stability in the variability of cycle length, and a reduction from baseline in the mean number of days between menses towards a 21–35 days interval which is clinically accepted as a regular cycle length. On-study menstrual data will be analysed from the first menses since randomisation onto the study. Self-reported confidence in the accuracy of baseline menstrual data using a 4-point Likert scale will be recorded.

Secondary outcomes of interest will be measured at baseline and at end of study. These include anthropometric measurements such as body mass index [24]; weight (kg) where a clinically

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significant loss in weight for overweight and obese patients is determined as a loss of ≥5% of initial weight [25]; waist circumference (WC) where risk of metabolic complications is increased with a WC >80 cm and substantially increased with a WC >88 cm [26]; and waist hip ratio (WHR) where WHR ≥0.85 is considered to substantially increase risk of metabolic complications [26]. Clinically validated instruments will be used for anthropometric measurements such as a constant-tension stretch-resistant measuring tapes and weighing scales that are minimum class III. Quality of life questionnaires administered include Polycystic Ovary Syndrome Questionnaire (PCOSQ), where a minimally important difference in the score of 0.5 on the 1–7 scale represents the smallest change in score that is important to women [27]; Measure Yourself Medical Outcome Profile (MYMOP), where the minimal important difference for change in score is 1.0 [28,29]; and Dermatology Life Quality Index (DLQI) where the minimal important difference for general skin conditions is a change in DLQI score of ≥3.2 points [30,31]. Hirsutism will be assessed by the practitioner using the validated modified Ferriman–Gallwey Questionnaire (mFG), that scores 9 body areas between 1 and 4 and where an mFG score of >6 is indicative of hirsutism [32].

Safety will be assessed by monitoring liver and kidney function at week 4 and end of study using serum blood tests or the validated point-of-care device Reflotron Desktop Analyzer [21,33]. We will also examine frequency and type of adverse events (AEs) and serious adverse events (SAEs) which will be captured at each study assessment from time of consent until the last study assessment. Monitoring will be conducted by asking non-leading questions such as 'How are you feeling?' or 'Since you were last asked, have you felt unwell or different from usual?' Such events will be recorded in clinical notes and using a standardised adverse event form. Relevant documentation such as laboratory reports relating to the event will be collected and will include an assessment of type of event, onset date, severity and causality, expectedness, date of resolution as well as treatment required and outcome. AEs will be evaluated as routine study data and will not need to be reported to the study sponsor. SAEs should be reported immediately by telephone or by email to the study sponsor within 24 hours of learning of the event and an SAE form completed providing all available details of the event. After recording an AE, or recording and reporting an SAE, the study team will make all attempts to follow up each participant until resolution.

Practitioner-blinding will be assessed at weeks 4, 12 and at end of study by administering a 3-item standardised questionnaire that asks practitioners: '(1). Given the information that you have received about the participant to date, which treatment group do you feel this participant was assigned to? (Response: Standardised/Individualised), (2). How certain are you of your answer? (Response: Not at all sure, just guessed/Fairly sure/Entirely sure), (3). Why do you think this participant was assigned to this treatment group? Please provide as much information as you would like (Response: Free text)' [34].

Adherence will be monitored using the Morisky Medication Adherence Scale (MMAS-8) administered at week 4 and at end of study, where a score of >2 is indicative of low adherence, 1–2 medium adherence and 0 high adherence [35]. Adherence will also be measured by calculating total CHM usage by weighing prescription containers during the study.

Baseline comparisons will be checked for characteristics such as age, history of conventional medication and complementary and alternative medicine use, time since diagnosis, education level and smoking status. Baseline comparisons will also be made for treatment expectations using the Credibility/Expectancy Questionnaire [36] (CEQ) administered once via online questionnaire after the baseline visit but prior to CHM administration.

Clinical treatment data will be collected including CHM diagnoses, individualised prescription details and concomitant advice. Practitioners will be asked to provide an assessment at baseline on expected effectiveness of the standardised prescription for each participant based on a 7-point Likert score. This data will inform the CHM intervention for the main study by, for example, assessing frequency and rank order of individual CHM prescribed, frequency and rank order of diagnoses of study participants and doses prescribed. Comparison of treatment effects and of safety between individualised and standardised CHM will also provide further information regarding the choice of CHM intervention for the main study. Other process data such as recruitment rate, dropout rate, reasons for dropout, resource usage will be collected. Evaluation of study participation will be collected via feedback questionnaires administered to participants, practitioners and dispensary at study close.

Analysis

Descriptive statistics will be calculated for primary and secondary variables. Principles of intention-to-treat will be adopted by analysing available data from all randomised participants, regardless of completion and compliance rates. Owing to the feasibility nature of this study, formal data imputation will not be conducted.

Statistical analysis will be piloted in this feasibility study to check suitability of statistical methods for the main study based on the proposed outcomes. The analysis will test for within-patient and between-group differences in measurements taken at baseline and at end of study. Continuous variable comparisons will be assessed at end of study adjusted for baseline assessments for the two groups using analysis of variance, or an analysis of covariance to include the effects of body mass index, waist hip ratio, severity of menstrual disorder, demographic variables, CEQ score and adherence. Categorical data will be analysed using Chi-squared tests. Where assumptions of normality are not met nonparametric methods will be used.

As no formal power calculations have been carried out, results from the statistical analysis should be considered preliminary and must be interpreted cautiously [11].

Textual data that is collected from sources such as clinical notes and evaluation questionnaires will be analysed using content analysis.

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Dissemination and discussion

The recruitment period lasted from January 2013 until August 2013. The final study visit is expected in March 2014.

Disseminated findings shall contain no participant-identifiable data. On completion of the study and regardless of the findings, a clinical study report will be prepared for presentation at scientific meetings and for publication in a peer-reviewed and topically relevant journal. Publications will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement.

At the end of this study, we will examine the feasibility of conducting such a study in the UK, discuss piloting the procedures, and provide comment as to whether or not progression to a main study is recommended.

Conflict of interest

None.

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References

[1] Asuncion M, Calvo RM, San Millan JL, Sancho J, Avila S, Escobar-Morreale HF. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. J Clin Endocrinol Metab 2000;85(7):2434–8.

[2] March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Hum Reprod 2010;25(2):544–51.

[3] Ehrmann DA. Polycystic ovary syndrome. N Engl J Med 2005;352(12):1223–36.

[4] Sills ES, Perloe M, Tucker MJ, Kaplan CR, Genton MG, Schattman GL. Diagnostic and treatment characteristics of polycystic ovary syndrome: descriptive measurements of patient perception and awareness from 657 confidential self-reports. BMC Womens Health 2001;1(1):3.

[5] Fleming R, Hopkinson ZE, Wallace AM, Greer IA, Sattar N. Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial. J Clin Endocrinol Metab 2002;87(2):569–74.

[6] Donnan PT, MacDonald TM, Morris AD. Adherence to prescribed oral hypoglycaemic medication in a population of patients with Type 2 diabetes: a retrospective cohort study. Diabet Med 2002;19(4):279–84.

[7] Grant RW, Devita NG, Singer DE, Meigs JB. Polypharmacy and medication adherence in patients with type 2 diabetes. Diabetes Care 2003;26(5):1408–12.

[8] Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. N Engl J Med 2007;356(6):551–66.

[9] Raja-Khan N, Stener-Victorin E, Wu X, Legro RS. The physiological basis of complementary and alternative medicines for polycystic ovary syndrome. Am J Physiol Endocrinol Metab 2011;301(1):E1–10.

[10] MRC. A framework for development and evaluation of RCTs for complex interventions to improve health. Medical Research Council; 2000.

[11] Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. J Eval Clin Pract 2004;10(2):307–12.

[12] Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ 2008;337:a1655.

[13] Arain M, Campbell MJ, Cooper CL, Lancaster GA. What is a pilot or feasibility study? A review of current practice and editorial policy. BMC Med Res Methodol 2010;10:67.

[14] Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. BMC Med Res Methodol 2010;10:1.

[15] Maciocia M. The foundations of Chinese medicine: a comprehensive text for acupuncturists and herbalists. Edinburgh: Elsevier Churchill Livingstone; 1997.

[16] Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Fertil Steril 2004;81(1):19–25.

[17] Ward E, Bower P, Collier D, Delaney B, Graffy J, Kinmonth A-L, et al. Primary care research recruitment: a practical guide. National Institute for Health Research; 2010.

[18] Jedel E, Labrie F, Oden A, Holm G, Nilsson L, Janson PO, et al. Impact of electro-acupuncture and physical exercise on hyperandrogenism and oligo/amenorrhea in women with polycystic ovary syndrome: a randomized controlled trial. Am J Physiol Endocrinol Metab 2011;300(1):E37–45.

[19] Bell-Syer SE, Thorpe LN, Thomas K, Macpherson H. GP participation and recruitment of patients to RCTs: lessons from trials of acupuncture and exercise for low back pain in primary care. Evid Based Complement Alternat Med 2011;2011:687349.

[20] Johansson J, Redman L, Veldhuis PP, Sazonova A, Labrie F, Holm G, et al. Acupuncture for ovulation induction in polycystic ovary syndrome: a randomized controlled trial. Am J Physiol Endocrinol Metab 2013;304(9):E934–43.

[21] Flower A, Lewith GT, Little P. A feasibility study exploring the role of Chinese herbal medicine in the treatment of endometriosis. J Altern Complement Med 2011;17(8):691–9.

[22] Yasmin E, Glanville J, Barth J, Balen AH. Effect of dose escalation of metformin on clinical features, insulin sensitivity and androgen profile in polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol 2011;156(1):67–71.

[23] Gagnier J, Boon H, Rochon P, Barnes J, Moher D, Bombardier C. Improving the quality of reporting of randomized controlled trials evaluating herbal interventions: implementing the CONSORT statement [corrected]. Explore (NY) 2006;2(2):143–9.

[24] NICE. Obesity: guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children. London, UK: National Institute for Health and Clinical Excellence; 2006.

[25] Moran LJ, Lombard CB, Lim S, Noakes M, Teede HJ. Polycystic ovary syndrome and weight management. Womens Health (Lond Engl) 2010;6(2):271–83.

[26] WHO. Waist circumference and waist–hip ratio: report of a WHO expert consultation; 2008.

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[27] Cronin L, Guyatt G, Griffith L, Wong E, Azziz R, Futterweit W, et al. Development of a health-related quality-of-life questionnaire (PCOSQ) for women with polycystic ovary syndrome (PCOS). J Clin Endocrinol Metab 1998;83(6):1976–87.
[28] Paterson C. Measuring outcomes in primary care: a patient generated measure, MYMOP, compared with the SF-36 health survey. BMJ 1996;312(7037):1016–20.
[29] Guyatt GH, Juniper EF, Walter SD, Griffith LE, Goldstein RS. Interpreting treatment effects in randomised trials. BMJ 1998;316(7132):690–3.
[30] Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)-a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19(3):210–6.
[31] Basra MK, Fenech R, Gatt RM, Salek MS, Finlay AY. The dermatology Life Quality Index 1994–2007: a comprehensive review of validation data and clinical results. Br J Dermatol 2008;159(5):997–1035.
[32] Yildiz BO, Bolour S, Woods K, Moore A, Azziz R. Visually scoring hirsutism. Hum Reprod Update 2010;16(1):51–64.
[33] Thue G, Sandberg S. Performance of the Reflotron and the Seralyzer in primary health care. Scand J Clin Lab Invest 1993;53(3):253–61.
[34] Kolahi J, Bang H, Park J. Towards a proposal for assessment of blinding success in clinical trials: up-to-date review. Community Dent Oral Epidemiol 2009;37(6):477–84.
[35] Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care 1986;24(1):67–74.
[36] Devilly GJ, Borkovec TD. Psychometric properties of the credibility/expectancy questionnaire. J Behav Ther Exp Psychiatry 2000;31(2):73–86.

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