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# The impact of meridian balanced method electro-acupuncture on women with chronic pelvic pain: a three-arm randomised controlled pilot study.

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| | |

**STUDY PROTOCOL**

TITLE: The impact of meridian balanced method electro-acupuncture on women with chronic pelvic pain: a three-arm randomised controlled pilot study

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**KEY WORDS:** Chronic pelvic pain, electro-acupuncture, meridian balanced method, context effects.

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## ABSTRACT

**Introduction:** Chronic pelvic pain (CPP) affects 3-4% of women worldwide. Proven treatments for CPP are limited and unsatisfactory. The meridian balance method (BM) electro-acupuncture (EA) treatment (BMEA + Traditional Chinese Medicine Health Consult (TCM HC) may be effective for CPP. Previous EA studies have demonstrated an analgesic effect. Large-scale studies on acupuncture for other chronic pain conditions suggest that patient-healthcare provider interaction might play a role in pain reduction. We propose a pilot study to explore the effectiveness of the meridian BMEA treatment in managing women with CPP to inform a future large randomised controlled trial.

**Methods and analysis:** A three-armed randomised controlled pilot study is proposed with an aim to recruit 30 women with CPP in NHS Lothian. Randomisation will be to BMEA treatment, TCM HC or standard care (SC). Validated pain, physical and emotional functioning questionnaires will be administered to all participants at weeks 0, 4 (end of study) 8 and 12. Focus group discussions will be conducted when week twelve questionnaire are completed. The primary objective is to determine recruitment and retention rates. The secondary objectives are to assess the effectiveness and acceptability of the proposed methods of recruitment, randomisation, interventions and assessment tools.

**Ethics and dissemination:** Ethical approval has been obtained from the Scotland Research Ethics Committee (REC 14/SS/1022). Data will be published in peer-reviewed journals and presented at international conferences.

**Trial registration number:** NCT02295111

## INTRODUCTION

Over 1 million women in the UK suffer from chronic pelvic pain (CPP). Annual healthcare expenditures are estimated at over £150 million.(1, 2) CPP impacts negatively on quality of life and work productivity.(3) CPP is associated with conditions such as endometriosis, painful bladder syndrome and irritable bowel syndrome. Up to 40% of women with CPP referred for diagnostic laparoscopy, have no apparent underlying cause identified for their painful symptoms.(4) The management of CPP is complex and treatment is often unsatisfactory.(5)

For this study we have chosen the meridian BM acupuncture because it is specifically indicated in painful conditions.(6) We believe that it maybe a helpful adjunct in managing CPP. The meridian BM acupuncture provides a systematic and interactive way to formulate a treatment strategy for pain management. The patient is instructed to point with one finger at the most painful area to identify the "sick" meridian. Once the "sick" meridian has been identified, a point on a healthy meridian will be used to balance the sick meridian. The acupuncturist presses on the chosen point and when the patient reports a reduction in pain level, the needle is inserted.

To maximise the specific effects of acupuncture needling, the needles may be stimulated manually (MA) or with micro electric current (EA). EA is the method of choice because of several reasons. Evidence from animals and human studies showed that both MA and EA produce analgesic effect. EA appears to be more effective than MA in some painful conditions. To obtain an analgesic effect in EA, the optimum time for the needle stimulation is 20 to 30 minutes and the frequencies set at 2Hz and 100Hz. (7, 8) Based on these parameters, it is impractical to be manually manipulating the acupuncture needles for 20-30

minutes and also be consistent. With EA one can precisely set both parameters at every treatment. EA may be measured objectively, is easier to control and standardize than MA. We will use the AS SUPER 4 Digital stimulator with four outputs, with an alternating low (2Hz) and high frequency (100 Hz) facility that is informed by the work of Han and his group.(9)

There is mounting evidence that acupuncture treatments for chronic pain, such as low back pain,(10, 11) headache,(12, 13) shoulder and neck pain,(14) are effective. Because acupuncture treatment is a complex intervention, the patient-healthcare provider interactions (15) and expectation (16) might play a role in its analgesic effect. Indeed, a study of pain management in patients with irritable bowel syndrome demonstrated the effect of the former. Patients were randomised on to waiting list (no placebo or interaction with healthcare provider), therapeutic ritual (placebo sham acupuncture with limited interaction) and a supportive relationship (placebo sham acupuncture with enhanced relationship). The supportive relationship produced the most adequate relief of symptoms and enhanced quality of life.(17)

The proposed pilot study will compare the specific effects of the meridian balanced method (BM) electro-acupuncture needling + the context effects of a TCM HC (BMEA treatment), with context effects of a TCM HC (patient-healthcare provider interaction) and standard care. This study will enable us to tease out the different components of acupuncture treatment that contribute to its analgesic effect and to collect important information to inform a future definitive RCT.

## Objectives

Primary objective

The primary objective is to determine recruitment and retention rates in NHS Lothian within defined inclusion/exclusion criteria.

Secondary objectives

To determine the effectiveness and acceptability to participants of the proposed methods of recruitment, randomisation, interventions and assessment tools.

## Endpoints

Primary endpoints

1. The proportion of eligible patients randomised into the study
2. The proportion of randomised patients who complete all treatment interventions and questionnaires at the final follow-up.

Secondary endpoints

Data on the effectiveness and acceptability of proposed methods of recruitment, randomisation, interventions and assessment tools.

## METHODS AND ANALYSIS

Study design

This is a single centre, open, three-armed parallel randomised controlled pilot study comparing a meridian BM electro-acupuncture + TCM HC (Group 1), with TCM HC (Group 2) and SC (Group 3), (Figure 1), using a mixed methods approach.(18) This includes quantitative method using validated questionnaires and qualitative method using focus groups post-study completion, as well as field notes and a reflective diary.

Subjects

30 women (aged greater than or equal to 18 years) with a history of CPP will be invited to participate.

Sample size

We believe that a sample size of 30 patients is appropriate for a pilot study and will allow estimation of percentage rates of recruitment and retention to within a standard error of at most 10%.

Inclusion criteria

- Chronic pelvic pain longer than 6 months duration
- Average numerical pain score of at least 4 out of 10 in the previous week
- Able and willing to comply with intervention
- Women aged 18 and above

Exclusion criteria

- Pregnancy
- Malignancy
- Severe bleeding disorders (e.g. Type 2, 3 Von Willebrand disease)
- Regular anticoagulant administration
- Severe needle phobia
- A history of seizures
- A pace-maker in situ
- Moderate to severe psychiatric illness (currently under the care of a Psychiatrist)
- Received electro-acupuncture and meridian BM within the last 6 months

Randomisation procedure

We will use an envelope randomisation system created by our statistician. There will be no stratification

Intervention

Eligible women will be randomised into meridian BMEA + TCM HC (Group 1), TCM HC (Group 2), and SC (Group 3). Participants in Group 1 will receive 8 treatments: twice a week x 4 weeks. Participants in Group 2 will receive 8 TCM HC: twice a week x 4 weeks. Participants in Group 3 will receive optimal standard care. (Table 1) The PI (OTC) who has been treating patients with acupuncture since 2002 will carry out all interventions. With permission from the participants, all interventions in Groups 1 and 2 will be audiotaped to ensure standardisation of procedures and techniques.

**Table 1: Study Intervention and Treatment Schedule**

| | | **Group 1** | **Group 2** | **Group 3** |
|---|---|---|---|---|
| | Baseline WK 0 | BMEA +TCM HC | TCM HC alone | Standard Care |
| | Week 1 | 2 Sessions | 2 Sessions | SC |
| | Week 2 | 2 Sessions | 2 Sessions | SC |
| | Week 3 | 2 Sessions | 2 Sessions | SC |
| | Week 4 | 2 Sessions | 2 Sessions | SC |
| **Total** | 4 Weeks | 8 sessions | 8 sessions | SC |

## Data collection

Screening

Eligible women will be consented and screened by a member of the research team. They will be randomised when they have passed screening. All data will be recorded on a case record form (CRF) and transferred to a secure database.

Assessment tools

Before randomisation, a questionnaire (Baseline week 0) will be given to all participants. This will include the following validated tools:

1. VAS scale
2. Brief Pain Inventory (BPI)
3. Hospital Anxiety and Depression Scale (HADS)
4. Quality Of Life: SF 12
5. Sexual Activity Questionnaire (SAQ)
6. Pain Catastrophising questionnaire (PCQ)
7. Work productivity & activity impairment questionnaire (WPAIQ)

The questionnaire at baseline (week 0) will include participants' demographic and relevant clinical information. The same questionnaire will be posted at weeks 4, 8 and 12 to all participants with an addressed envelope enclosed.

Focus groups

Three focus group discussions will be conducted after questionnaires in week twelve are completed. In order not to bias the group discussions, the PI (OTC) who provides the interventions will not be conducting the focus groups. A separate member of the research team will conduct the three focus group discussions lasting 90 minutes each. A content guide will be used in each group to focus the discussions,(19) which will provide additional data relevant to the study. The topic guide will focus on questions that will explore the participants'

perceived benefits or otherwise of the BMEA treatment (Group 1), TCM Health Consultation (Group2) and NHS standard care (Group 3). The focus groups will provide in-depth exploration of how and if the perceived benefits affect the quality of their lives such as sleep quality, energy levels and sexual activities. The discussions will be audiotaped, transcribed and thematically analysed.

Field notes and a reflexive diary

The PI will keep field notes and a reflexive diary during the course of the study. After each intervention the PI will write notes related to her own observation of salient events, discussions, remarks or behaviours that provide more information about the participant and her experience of pain as well as the possible impact or otherwise of the intervention. For example, the PI might notice changes in facial colour or expression when a participant described how the chronic pelvic pain impacted her life; or a participant who started a treatment intervention apparently agitated but looking calmer at the close of the session. Such data can add scope and depth as well as illuminate the different aspects of the interventions and the patient-healthcare provider interactions that might not be captured otherwise. In her reflexive diary the PI will make note of her thoughts, feelings, and insights of such observations. This reflexive practice involves the PI to be introspective, conscious of her role, reactions and assumptions she brings to the intervention and the research process.(20)

Adverse events

When administered by an appropriately trained and qualified acupuncturist, electro-acupuncture is safe and serious adverse events (SAEs) are not anticipated. However, any SAEs that occur during the study will be reported in

the participant's medical record and followed up until resolution of the event. We will also report it to the ACCORD Research Governance (www.accord.ed.ac.uk) and QA Office based at the University of Edinburgh within 24 hours. After randomisation, participants in Groups 1 and 2 will be instructed to contact a member of the clinical research team if they have an event that necessitates hospitalisation, or results in significant disability or incapacity. In addition they will be asked about the occurrence of adverse effects at every of the 8 visits during the study. Open-ended and non-leading verbal questioning of the participant will be used to enquire about adverse events, or if they have been admitted to hospital. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded.

End of study

The end of study is defined as the last participant's last visit.

**Proposed analyses**

Determine recruitment and retention rates

The recruitment rate will be calculated from the number of eligible patients in the participant log. An acceptable recruitment rate is about 50%. We aim to retain 90% of those recruited to the study. If retention rates are low, we will explore the reasons why at the post study focus group discussions. Information obtained in the discussions will be used to improve compliance in future study.

Effectiveness and acceptability of proposed methods of recruitment, randomisation, BMEA treatments, TCM HC and assessment tools

Effectiveness will be measured by reductions in pain and associated symptoms covered in the questionnaires. Additional information on effectiveness, not

covered in the questionnaires, will be captured in the focus groups. The appropriateness of assessment tools used can be assessed through examination of data completion and patterns of missing data. The focus groups will be complementary to understanding if the tools chosen are appropriate and will also provide information on acceptability of recruitment, randomisation and the treatments themselves.

## ETHICS AND DISSEMINATION

Ethical approval has been obtained from the Scotland Research Ethics Committee (REC 14/SS/1022). Data will be presented at international conferences and published in peer-reviewed journals. We will make the information obtained from the study available to the public through national bodies and charities.

## DISCUSSION

We believe that a definitive evaluation of the effectiveness of the meridian BM electro-acupuncture treatment in the management of CPP requires a multicentre randomised controlled trial (RCT). We anticipate potential difficulties in a large RCT in acupuncture for chronic pain and therefore we've designed this pilot study to evaluate its feasibility.

Both MA (21) and EA (22, 23) are safe when performed by appropriately trained acupuncturists. However because of some theoretical safety concerns, we have erred on the side of caution to exclude for example, patients who have a history of seizures or implanted pace maker.

The meridian BM acupuncture, deeply rooted in classical Chinese medicine (CCM) is used clinically in pain management. According to CCM theory, pain results from blocked meridians leading to an imbalance in the system. On the surface of the body is a network of 12 meridians (6 yin and 6 yang) that connect acupuncture points together.(24) Theoretically, these meridians act as a conduit between the surface of the body and the internal organs. The meridian BM method acupuncture treats pain by balancing these meridians, for example using a "healthy" yin meridian to balance a "blocked" yang meridians. (25) However there are considerable skepticisms and controversies surrounding these theories and the existence as physical entities of acupuncture points and the meridian system. Despite efforts to understand these systems, there is no agreement as to what they constitute.(26, 27) Indeed, the PI (OTC) argues that it is more useful to view these systems as conceptual framework that guides the clinical practice of acupuncture rather than arguing if they exist. Tangentially related to this view is work undertaken by Langevin whereby it is hypothesized that acupuncture points and meridians has correspondence to the connective tissue (28) and not directly as drawn out in Chinese medicine text.

A survey of the literature indicates that this is the first study to investigate the effectiveness of the meridian BM electro-acupuncture treatment for chronic pelvic pain in women using a mixed methods approach. This mixed methods approach utilises validated questionnaire and focus group discussions, field notes and a reflexive diary. Undertaking a mixed methods approach is one of the strengths of the study because we are examining the feasibility of studying a complex intervention, which involves a number of phenomena which include: TCM health consult, electro-acupuncture, context effects and patient expectations. Alongside an understanding of participants' perceived benefits or

otherwise of the interventions, this methodology will also help us to understand the role of the researcher in the study intervention. The focus group discussions will capture participants' subjective experience of the study intervention.

It is generally considered that the gold standard in effectiveness RCTs is the use of a placebo control for the study intervention. However, our pilot study does not employ a placebo (sham acupuncture treatment) for several reasons. A considerable body of evidence from large-scale effectiveness studies have demonstrated that sham acupuncture treatments as controls are problematic. For some chronic pain conditions, the observed effects of acupuncture treatments are larger in usual care controls when compared with sham controls. This might suggest that sham acupuncture treatments have physiological effects, and thus not inert. Past sham controlled studies have employed techniques such as shallow needling, and needling with a retractable needle or toothpick.(10, 29) Such techniques create a sensation not dissimilar to light touch which has some data to show that it has physiological effects.(30) It is also conceivable and probable that shallow needling and needling with a retractable needle elicit similar physiological effects as deep needling. These sham acupuncture techniques are therefore inappropriate. We feel that until better sham techniques are available, it is prudent to design a study that does not employ a placebo control.

Context effects such as expectancy (31) treatment rituals (32) or patient-provider interactions (15, 17) have been shown to have an impact on the experience of pain. These might have confounded past studies and might explain the small effect sizes when sham acupuncture treatments were compared to true acupuncture treatments. Attempting to separate the context effects of

acupuncture treatment from the specific effects of acupuncture needling presents a major challenge in this area of research. In response, we have designed a three arm RCT to address these challenges. The first arm includes acupuncture needling, electro-stimulation (specific effects of needling) and the patient-healthcare provider interactions (context effects) via a traditional Chinese medicine consult (TCM HC). Each consult will evolve based on participants' health status but will include typically tongue diagnosis, breath-work and advice on self-care. Arm 2 (participants receive only TCM HC) controls for the patient-healthcare provider interactions (context effect). Participants in arm 3 (standard care) will receive the standard NHS care for CPP. Having these 2 control groups is likely to yield the true effect size of the specific effect of electro-acupuncture needling and the non-specific (context effect) of the patient-healthcare provider interactions. We acknowledge that this pilot study is investigating only one aspect of the several context effects of acupuncture treatment. However, we believe that understanding the clinical outcome of the patient-healthcare provider relationship will create a critical mass of literature to influence the education of future generations of healthcare professionals. The UK SIGN 136 guideline for the management of chronic pain acknowledged that while preliminary data showed that the nature of such a relationship could influence clinical outcome, there is not enough high quality studies to recommend widespread training.(33) (Management of chronic pain. Edinburgh: SIGN; December 2013]. Available from URL: http://www.sign.ac.uk. Accessed March 2015)

In conclusion, our pilot study protocol will enable us to determine the retention and recruitment rate as well as the patients' experience of the study intervention. It will help us gain better insight into the impact of meridian BM electro-acupuncture needling and the patient-practitioner relationship on

chronic pelvic pain in women.

## AUTHORS' CONTRIBUTIONS

OTC: research, contribution of original material, editing and approval of final manuscript; HODC, AH, MF: research, contribution of original material, editing and approval of final manuscript; RE, EH: editing and approval of final manuscript.

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## COMPETING INTERESTS

None.

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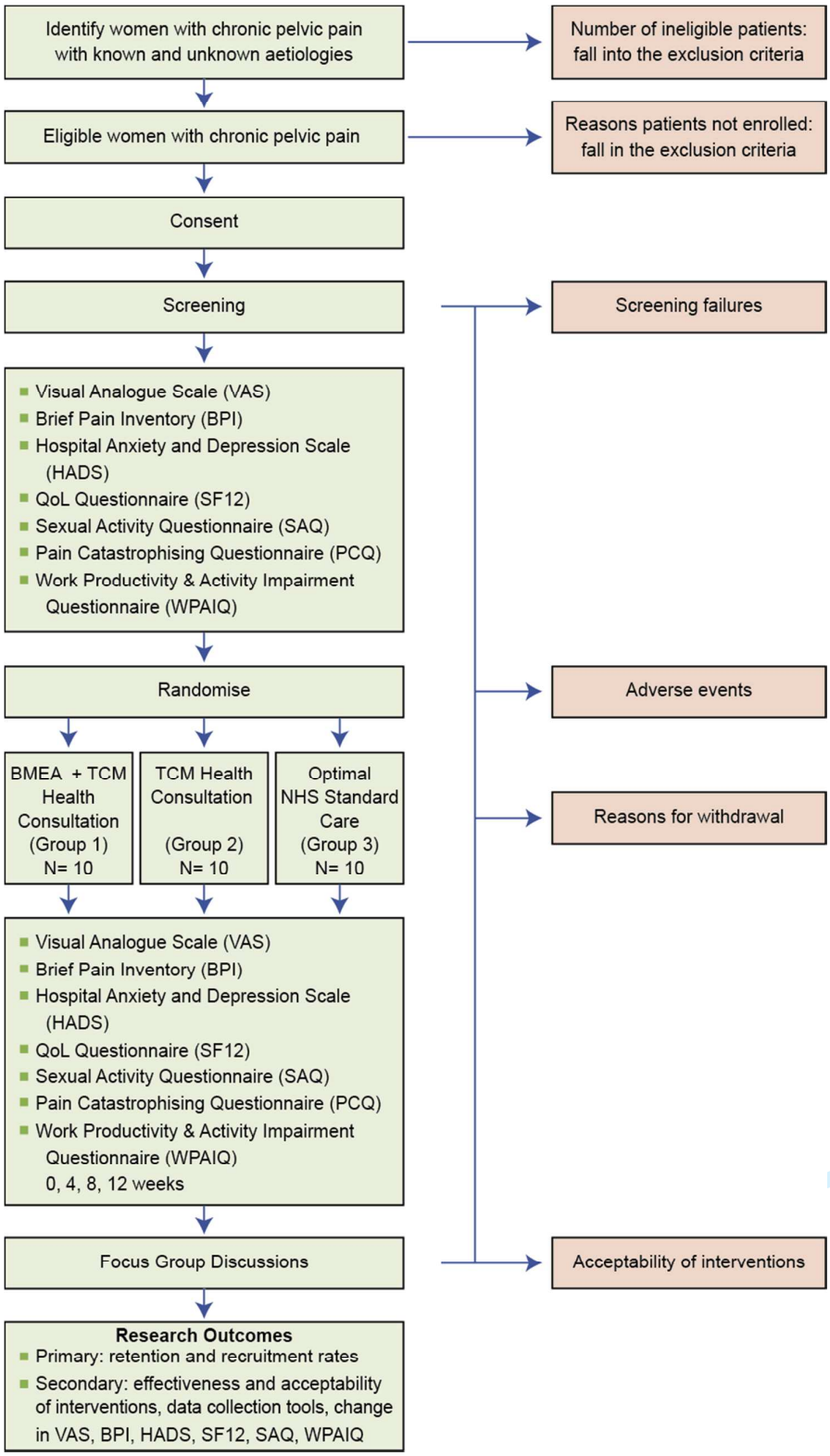
## Figure Legend

**Figure 1.** Flow of participants through the study

**Figure 1**



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# The BMEA Study: The impact of meridian balanced method electro-acupuncture on women with chronic pelvic pain: a three-arm randomised controlled pilot study using a mixed methods approach.

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**STUDY PROTOCOL**

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**KEY WORDS:** Chronic pelvic pain, electro-acupuncture, meridian balanced method, context effects.

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## ABSTRACT

**Introduction:** Chronic pelvic pain (CPP) affects 3-4% of women worldwide. Proven treatments for CPP are limited and unsatisfactory. The meridian balance method (BM) electro-acupuncture (EA) treatment (BMEA + Traditional Chinese Medicine Health Consult (TCM HC) may be effective for CPP. Previous EA studies have demonstrated an analgesic effect. Large-scale studies on acupuncture for other chronic pain conditions suggest that patient-healthcare provider interaction might play a role in pain reduction. We propose a pilot study to explore the effectiveness of the meridian BMEA treatment in managing women with CPP to inform a future large randomised controlled trial.

**Methods and analysis:** A three-armed randomised controlled pilot study is proposed with an aim to recruit 30 women with CPP in NHS Lothian. Randomisation will be to BMEA treatment, TCM HC or standard care (SC). Validated pain, physical and emotional functioning questionnaires will be administered to all participants at weeks 0, 4, 8 and 12. Focus group discussions will be conducted when week twelve questionnaires are completed. The primary objective is to determine, recruitment and retention rates. The secondary objectives are to assess the effectiveness and acceptability of the proposed methods of recruitment, randomisation, interventions and assessment tools.

**Ethics and dissemination:** Ethical approval has been obtained from the Scotland Research Ethics Committee (REC 14/SS/1022). Data will be published in peer-reviewed journals and presented at international conferences.

**Trial registration number:** NCT02295111

**Registry Name**: ClinicalTrials.gov

**Strengths and limitations of this study**

- We anticipate that there maybe potential difficulties in conducting a large RCT for chronic pelvic pain using acupuncture
- The study is designed to assess the practical feasibility
- This is the first pilot study to employ the meridian balanced method acupuncture style for chronic pelvic pain
- We will conduct focus groups to assess the acceptability of the interventions and the schedule
- We recognise that the context in which the intervention is given might play a role in pain reduction, thus the study is designed to separate the specific effects of acupuncture needling from the context effects of acupuncture treatment.
- We acknowledge that failure to use sham acupuncture as a control could be seen as a weakness in our study, however, well-designed large-scale RCTs of acupuncture have shown that sham acupuncture could lead to an underestimation of treatment effectiveness.

## INTRODUCTION

Over 1 million women in the UK suffer from chronic pelvic pain (CPP). Annual healthcare expenditures are estimated at over £150 million.(1, 2) CPP impacts

negatively on quality of life and work productivity.(3) CPP is associated with conditions such as endometriosis, painful bladder syndrome and irritable bowel syndrome. Up to 40% of women with CPP referred for diagnostic laparoscopy, have no apparent underlying cause identified for their painful symptoms.(4) The management of CPP is complex and treatment is often unsatisfactory.(5) We believe that acupuncture may be a helpful adjunct in the management of CPP. Our hypothesis is that the meridian BMEA treatment alleviates pain, and improves physical and emotional functioning, in women with CPP.

## Meridian Balance Method (BM) Acupuncture

For this study we have chosen the meridian Balance Method (BM) acupuncture (6) which is a novel approach for the management of painful conditions. With this style of acupuncture, pain relief is expected once the needle is inserted in the appropriately chosen acupuncture points.

The meridian BM acupuncture offers an interactive and systematic strategy to formulate a treatment plan through the diagnosis of the sick meridian and selection of a healthy meridian and acupuncture points. Meridian balancing has been well described in the Huang Di Nei Jing, a seminal classical Chinese medicine (CCM) text (7) as well as in modern text. (6, 8, 9) Modern Traditional Chinese Medicine (TCM) emerges out of the standardization of CCM, and is one of the most popular approaches used by professional acupuncturists in the United Kingdom. In comparison, the meridian BM acupuncture is relatively unknown and rarely included in the curriculum of Chinese medicine schools. The meridian BM acupuncture has several key features: the 5 systems of meridian balancing (Table 1), Mirror and Image methods. (6)

The Five Systems of Meridian Balance Method

The meridian BM acupuncture utilizes the five systems shown in Table 1. Each sick meridian (painful area) can be balanced (treated) by any one of the five systems. For example the "Sick Meridian", Lung meridian (Lung Hand Taiyin) can be balanced by systems 1, 2, 3, 4 or 5.

Table 1: Five Systems of Meridian Balance Method

| | System1 | System 2 | System 3 | System 4 | System 5 |
|---|---|---|---|---|---|

| Sick Meridian | Name Sharing | Branching Bie Jing | Interior/ Exterior Biao Li | Clock Opposite | Clock Neighbour |
|---|---|---|---|---|---|
| LU/Hand Taiyin | SP | UB | LI | UB | LR |
| LI/Hand Yangming | ST | LR | LU | KI | ST |
| ST/Foot Yangming | LI | PC | SP | PC | LI |
| SP/Foot Taiyin | LU | SI | ST | TH | HT |
| HT/Hand Shaoyin | KI | GB | SI | GB | SP |
| SI/Hand Taiyang | UB | SP | HT | LR | UB |
| UB/Foot Taiyang | SI | LU | KI | LU | SI |
| KI/Foot Shaoyin | HT | TH | UB | LI | PC |
| PC/Hand Jueyin | LR | ST | TH | ST | KI |
| TH/Hand Shaoyang | GB | KI | PC | SP | GB |
| GB/Foot Shaoyang | TH | HT | LR | HT | TH |
| LR/Foot Jueyin | PC | LI | GB | SI | LU |

Meridian Names:
LU= Lung, LI=Large Intestine, ST= Stomach, SP= Spleen, HT= Heart, SI= Small Intestine, UB= Urinary Bladder, KI= Kidney, PC= Pericardium, TH= Triple Heater, GB= Gallbladder, LR= Liver.

## Image And Mirror Methods

Once the healthy meridian for treating the sick meridian is identified, the Image or Mirror Method is employed to locate more precisely the areas of the body to be treated. The acupuncturist palpates the meridian of the identified area for the best acupuncture point(s) that will relieve the pain. Thus point selections are individualised.

The Image method maps the relationship between the limb and the whole body (Table 2). For example, the hand images the genitals, coccyx and sacrum and the forearm images the lower abdomen and lower back. (6)

Table 2: Image Method (Upper Limb to Head and Trunk)

| Needled Area | Sick Area (Image) |
|---|---|
| Finger | Testicles & anus |
| Hand | Genitals, coccyx, sacrum |
| Wrist | Bladder area, lumbo-sacral area |
| Forearm | Lower abdomen, lower back |

| | |
|---|---|
| Elbow | Umbilicus level, lumbar 2, waist |
| Upper arm | Upper abdomen, rib cage, chest, mid-upper back |
| Shoulder | Neck, jaw, base of skull |
| Top of shoulder | Top of head |

The Mirror method "maps" one limb onto another or one part of the body to another part of the body. (Table 3) For examples, the finger mirrors the toe and the front mirrors the back of the body and vice versa. (10)

The Image and Mirror knowledge has also been described in Su Wen, another seminal classical Chinese medicine text that detailed the relationship between back and front, up and down and left and right. (11) This kind of mapping is known in the present day as somatotopy where a specific point of the body can be projected to a specific point in the primary somatosensory cortex of the brain. (12)

Table 3: Mirror Method And Reverse Mirror Method

| Mirror Method | Reverse Mirror Method |
|---|---|
| Finger ↔ Toe | Finger ↔ Top of Hip |
| Hand ↔ Foot | Hand ↔Hip |
| Wrist ↔ Ankle | Wrist ↔Hip Joint |
| Forearm ↔ Lower Leg | Forearm ↔ Thigh |
| Elbow ↔ Knee | Elbow ↔ Knee |
| Upper Arm ↔ Thigh | Upper Arm ↔ Lower Leg |
| Shoulder ↔ Hip | Shoulder ↔ Ankle |
| Back ↔ Front (Du ↔ Ren) | Front ↔ Back ( Ren ↔ Du) |

Electro-Stimulation

To maximise the specific effects of acupuncture needling, the needles may be stimulated manually (MA) or with micro electric current (EA). Although there have been no studies to show that EA enhances the analgesic effect of the meridian BM acupuncture, it is, however, the method of choice for several reasons. Evidence from animal and human studies showed that both MA and EA

produce analgesic effect. (13) EA appears to be more effective than MA in some painful conditions. To obtain an analgesic effect in EA, the optimum time for the needle stimulation is 20 to 30 minutes with the frequencies set at 2Hz and 100Hz. (13, 14) Based on these parameters, it is impractical to be manipulating the acupuncture needles manually for 20-30 minutes and also be consistent. With EA one can set both parameters precisely at every treatment. EA may be measured objectively and is easier to control and standardize than MA.

**The Context And Context Effects**

There is mounting evidence that acupuncture treatments for chronic pain, such as low back pain,(15, 16) headache,(17, 18) shoulder and neck pain,(19) are effective. However, a recent individual patient data meta-analysis on the use of acupuncture for chronic pain conditions found a small, statistically significant effect size when compared to sham acupuncture. The effect size was larger and statistically significant when compared to usual care controls. (20) This would suggest that as well as the specific needling effects, other factors within the context of the acupuncture treatment play a role in reducing pain, such as the characteristics of the healthcare providers and patients e.g. their beliefs and expectations; the provider-patient interactions as well as how the treatment is administered. (21) The effects that result from the complex interactions of such characteristics are known as the context effect. (22, 23) This effect was demonstrated in a study of pain management in patients with irritable bowel syndrome, showing that an enhanced provider-patient relationship could help alleviate pain. Patients were randomised on to a waiting list (no placebo or interaction with healthcare provider), therapeutic ritual (placebo sham acupuncture with limited interaction) or a supportive relationship (placebo

sham acupuncture with enhanced relationship). The supportive relationship produced the most adequate relief of symptoms and enhanced quality of life.(24)

The proposed pilot study will compare the specific effects of the meridian balanced method (BM) electro-acupuncture needling + the context effects of a TCM HC (BMEA treatment), with context effects of a TCM HC (patient-healthcare provider interaction) and standard care. This study will enable us to tease out the different components of acupuncture treatment that contribute to its analgesic effect and to collect important information to inform a future definitive RCT.

## Objectives

Primary objective

The primary objective is to determine recruitment and retention rates in NHS Lothian within defined inclusion/exclusion criteria.

Secondary objectives

To determine the effectiveness and acceptability to participants of the proposed methods of recruitment, randomisation, interventions and assessment tools.

## Endpoints

Primary endpoints

1. The proportion of eligible patients randomised into the study
2. The proportion of randomised patients who complete all treatment interventions and questionnaires at the final follow-up.

Secondary endpoints

Data on the effectiveness and acceptability of proposed methods of recruitment, randomisation, interventions and assessment tools.

## METHODS AND ANALYSIS

### Study design

This is a single centre, open, three-armed parallel randomised controlled pilot study comparing a meridian BM electro-acupuncture + TCM HC (Group 1), with TCM HC (Group 2) and SC (Group 3), (Figure 1), using a mixed methods approach.(25) It includes quantitative method using validated questionnaires and qualitative method using focus groups post-week 12 questionnaire completion, as well as field notes and a reflexive diary.

### Delivery of intervention in Groups 1 and 2

The following descriptions of our study interventions adhered to guidelines in the "Revised Standards for Reporting Interventions in Clinical Trial of Acupuncture (STRICTA): Extending the CONSORT Statement". (26)

The PI (OTC) will deliver all eight BMEA + TCM HC interventions for Group 1 and TCM HC for Group 2 within the same setting in NHS Lothian. The first intervention for both Groups will last approximately 60 minutes. Subsequent 7 interventions for both groups will last no longer than 40 minutes. All participants will receive twice weekly interventions for 4 weeks. Participants in Group 2 will not receive the meridian BM electro-acupuncture. With permission from the participants, all interventions in Groups 1 and 2 will be audiotaped to ensure standardisation of procedures and techniques.

All participants in Groups 1, 2 and 3 will complete the questionnaires at weeks 0, 4, 8 and 12, and will be invited to the Focus Group discussions.

Similarly, Group 1 participants will complete the questionnaries at weeks 0, 4, 8 and 12, and will be invited to the Focus Group discussions.

TCM HC (Groups 1 and 2)

*Individualised Traditional Chinese Medicine Health Consultation (TCM HC)*

For Groups 1 and 2 will share the same approach to the TCM HC. The initial TCM HC will be based on Chinese medicine theory that typically includes history taking: inquiring, listening and inspection of the tongue. Each participant will receive individualised advice based on the specific needs and presenting symptoms. Dietary advice based on Chinese Medicine nutrition and other appropriate self-care skills, such as breathing techniques and physical activities maybe be recommended and modified to accommodate the participant's changing pattern of pain, sleep, level of anxiety, or other health needs. Breathing techniques involve getting the participant to focus her attention on each breath in and out. No herbal medicine therapy will be prescribed.

*Individualised and systematic acupuncture point selections*

Step 1: Diagnose the affected/sick meridian(s).

This first fundamental and very important step requires the acupuncturist to instruct the patient to indicate where the pain is located so that the affected meridian(s) can be diagnosed accurately.

Step 2: Identify the balancing meridian(s) based on the 5 systems:

Once the affected meridian(s) is/are identified, one of the following meridians can be chosen to balance the affected meridian(s):

- System 1: Foot Taiyin (Name Sharing meridian)

- System 2: Foot Taiyang (Branching meridian)
- System 3: Hand Yangming (Interior/Exterior)
- System 4: Foot Taiyang (Clock Opposite)
- System 5: Foot Jueyin (Clock Neighbour)

Step 3: Acupuncture point(s) selection for treatment

Once the balancing meridian has been selected, step 3 involves locating the therapeutic points along the balancing meridian by using the Mirror or the Image Method. The acupuncturist will palpate for the most tender and tight point(s) (ashii points) along the balancing meridian. The ashii point(s) is/are the therapeutic point(s) if upon pressing the point(s), the patient reports that the pain has been reduced. Thus point selections are based on the steps outlined and not on TCM pattern diagnosis.

Step 4: Connecting the battery operated AS SUPER 4 digital stimulator to the acupuncture needles

The negatively charged, black lead (to stimulate) will be connected to the acupuncture needle inserted in the point that gave the most pain relief, while the positively charged lead (red) will be connected to another needle inserted in the same area. We will use the "AS SUPER 4" Electro-stimulator (Manufacturer: Schwa-medico, Germany) with four outputs. The electro-stimulator emits a square wave of low frequency (2 Hz) for 3-second alternating with high frequency (100 Hz). Program 2 will be selected and the duration of treatment will be no shorter than 20 minutes and no longer than 30 minutes. These parameters are based on the work of Han and his group.(27) The intensity of the electrical stimulation will be adjusted based on the participant's feedback, to produce a strong sensation without pain or discomfort.

*Depth of needle insertion*

The depth of the needle insertion will be adapted to the thickness of the muscles and subcutaneous fatty tissue. For example, for the gluteal muscle, typically a 0.30 mm x 75 mm (3 inches) long the needle will be inserted to a depth of between 1.0 to 2 inches. For the forearm, typically a 0.18mm x 30mm (1.20 inches) will be inserted to a depth of about 0.25 to 0.75 inch. The number of needles inserted will be individualised. We will use Dong Bang (Korea) and Aculine needles (China).

GROUP 3 – Standard Care (SC)

Participants will follow their standard care as given by their clinician. Standard care is defined here as care and treatment that patients would normally receive at The Pelvic Pain Service, NHS Lothian: oral analgesics, neuromodulators such as anti-convulsants and anti-depressants, hormonal approaches, counselling/behavioural therapy or surgical interventions when indicated. The Pelvic Pain Service consists of Consultant Gynaecologist, Anaesthetist specialising in pain, a Psychologist and a Specialist Nurse. The participants will not receive the meridian BM electro-acupuncture treatment or the TCM HC

**Subjects**

Thirty (30) women (aged greater than or equal to 18 years) with a history of CPP will be recruited.

**Sample size**

We believe that a sample size of 30 patients is appropriate for a pilot study and will allow estimation of percentage rates of recruitment and retention to within a standard error of at most 10%.

**Inclusion criteria**

- Chronic pelvic pain longer than 6 months duration
- Average numerical pain score of at least 4 out of 10 in the previous week
- Able and willing to comply with intervention
- Women aged 18 and above

**Exclusion criteria**

- Pregnancy
- Malignancy
- Severe bleeding disorders (e.g. Type 2, 3 Von Willebrand disease)
- Regular anticoagulant administration
- Severe needle phobia
- A history of seizures
- A pace-maker in situ
- Moderate to severe psychiatric illness (currently under the care of a Psychiatrist)
- Treatment with electro-acupuncture and meridian BM within the last 6 months

**Randomisation procedure**

We will use an envelope randomisation system created by our statistician. There will be 30 sealed envelopes: 10 meridian BMEA + TCM HC (Group 1), 10 TCM HC (Group 2) and 10 SC (Group 3). The envelopes are randomly assigned a number from 1-30. At the start of the study, the first participant who passes the screening will receive envelope number 1; and the second will receive the envelope number 2 and so on. The envelope will be opened in front of the participant by a member of the research team who screens the participant. If randomised into

either Groups 1 or 2, the participant will receive the appropriate treatment on the same day. If randomised into Group 3, the participant will be instructed to continue the NHS standard care. There will be no stratification.

**Intervention**

Eligible women will be randomised into meridian BMEA + TCM HC (Group 1), TCM HC (Group 2), or SC (Group 3). Participants in Group 1 will receive 8 interventions: twice a week x 4 weeks. Participants in Group 2 will receive 8 TCM HC: twice a week x 4 weeks. Participants in Group 3 will receive optimal standard care. (Table 4) With permission from the participants, all interventions in Groups 1 and 2 will be audiotaped to ensure standardisation of procedures and techniques.

**Table 4: Study Intervention Schedule**

| | | Group 1 | Group 2 | Group 3 |
|---|---|---|---|---|
| | Baseline WK 0 | BMEA +TCM HC | TCM HC alone | Standard Care |
| | Week 1 | Twice Weekly | Twice Weekly | SC |
| | Week 2 | Twice Weekly | Twice Weekly | SC |
| | Week 3 | Twice Weekly | Twice Weekly | SC |
| | Week 4 | Twice Weekly | Twice Weekly | SC |
| **Total** | 4 Weeks | 8 Interventions | 8 Interventions | SC |

**Acupuncturist Information**

The PI (OTC) completed 2196 hours of acupuncture training and obtained a Masters of Science Degree in Acupuncture at an accredited school in New York City, USA. She is trained in four styles of acupuncture: traditional Chinese medicine, Kiiko Matsumoto Japanese style, Five Element and the meridian

balanced method. She studied electro-acupuncture as part of her acupuncture training and at the British Medical Acupuncture Society (BMAS). She has over 10 years of experience using Five Element acupuncture to address psycho-emotional issues and the meridian balanced method acupuncture for pain management in hospital settings such as the New York University Cancer Institute and Royal Infirmary of Edinburgh, UK. She is a Professional Registered Nurse, a National Board Certified Acupuncturist and Chinese medicine herbalist in New York State, USA. She is also Professional Registered Nurse in the United Kingdom.

**Data collection**

**Screening**

Eligible women will be consented and screened by a member of the research team. They will be randomised when they have passed screening. All data will be recorded on a case record form (CRF) and transferred to a secure database.

**Assessment tools**

Before randomisation, a questionnaire (Baseline week 0) will be given to all participants. This will include the following validated tools:

1. Visual Analog Scale (VAS scale)
2. Brief Pain Inventory (BPI)
3. Hospital Anxiety and Depression Scale (HADS)
4. Quality Of Life: SF 12
5. Sexual Activity Questionnaire (SAQ)
6. Pain Catastrophising Questionnaire (PCQ)
7. Work Productivity & Activity Impairment Questionnaire (WPAIQ)

The set of questionnaires at baseline (week 0) will include participants' demographic and relevant clinical information. The same questionnaire will be

posted to all participants at weeks 4, 8 and 12 with an addressed envelope enclosed.

**Focus groups**

Three focus group discussions will be conducted after questionnaires in week twelve are completed. All participants from the Groups 1, 2 and 3 will be sent a letter of invitation to the focus group discussions. To ensure a high turnout, a week before the designated date of the respective focus group discussions, a member of the research team will contact each participant to encourage them to attend. In order not to bias the group discussions, the PI (OTC) who provides the interventions will not be conducting the focus groups. A separate member of the research team will conduct the three focus group discussions lasting approximately 60 minutes each. A content guide will be used in each group to focus the discussions,(28) which will provide additional data relevant to the study. The topic guide will focus on questions that will explore the participants' perceived benefits or otherwise of the BMEA treatment (Group 1), TCM Health Consultation (Group2) and NHS standard care (Group 3). The focus groups will provide in-depth exploration of how and if the perceived benefits affect the quality of their lives, such as sleep quality, energy levels and sexual activities. The discussions will be audiotaped, transcribed and thematically analysed.

**Field notes and a reflexive diary**

The PI will keep field notes and a reflexive diary during the course of the study. After each intervention the PI will write notes related to her own observation of salient events, discussions, remarks or behaviours that provide more information about the participant and her experience of pain, as well as the possible impact or otherwise of the intervention. For example, the PI might

notice changes in facial colour or expression when a participant describes how the chronic pelvic pain impacted her life; or a participant who started a treatment intervention apparently agitated but who is looking calmer at the close of the session. Such data can add scope and depth as well as illuminate the different aspects of the interventions and the patient-healthcare provider interactions that might not be captured otherwise. In her reflexive diary the PI will make a note of her thoughts, feelings, and insights of such observations. This reflexive practice involves the PI to be introspective, conscious of her role, reactions and assumptions she brings to the intervention and the research process.(29)

**Adverse events**

When administered by an appropriately trained and qualified acupuncturist, electro-acupuncture is safe and serious adverse events (SAEs) are not anticipated. However, any SAEs that occur during the study will be reported in the participant's medical record and followed up until resolution of the event. We will also report it to the ACCORD Research Governance (www.accord.ed.ac.uk) and Quality Assurance Office based at the University of Edinburgh within 24 hours. After randomisation, participants in Groups 1 and 2 will be instructed to contact a member of the clinical research team if they have an event that necessitates hospitalisation, or results in significant disability or incapacity. In addition, they will be asked about the occurrence of adverse effects at every of the 8 visits during the study. Open-ended and non-leading verbal questioning of the participant will be used to enquire about adverse events, or if they have been admitted to hospital. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded.

## End of study

The end of study is defined as the last participant's last visit.

## Proposed analyses

*Determine recruitment and retention rates*

The recruitment rate will be calculated from the number of eligible patients in the participant log. An acceptable recruitment rate is about 50%. We aim to retain 90% of those recruited to the study. If retention rates are low, we will explore the reasons why at the post study focus group discussions. Information obtained in the discussions will be used to improve compliance in any future study.

Confidence intervals will be calculated for the estimates of rates of recruitment, retention and unanswered questions. The study is not powered to allow comparisons between the randomised groups, and outcomes in each group will just be summarised rather than being compared by formal statistical tests.

Data from the focus groups will be analysed thematically. Thematic analysis aims to highlight and record patterns or themes within a set of data. Such themes capture a certain phenomenon and could be related to the specific research questions or shed light on a specific salient event. Thematic analysis is commonly used in analysis in qualitative research.

*Effectiveness and acceptability of proposed methods of recruitment, randomisation, BMEA treatments, TCM HC and assessment tools*

Effectiveness will be measured by reductions in pain and associated symptoms such as sleep disturbances, anxiety or depression, that are covered in the

questionnaires. Additional information on effectiveness, not covered in the questionnaires, will be captured in the focus groups. The appropriateness of assessment tools used can be assessed through examination of data completion and patterns of missing data. The focus groups will be complementary to understanding if the tools chosen are appropriate and will also provide information on acceptability of recruitment, randomisation and the treatments themselves.

## ETHICS AND DISSEMINATION

Ethical approval has been obtained from the Scotland Research Ethics Committee (REC 14/SS/1022). Data will be presented at international conferences and published in peer-reviewed journals. We will make the information obtained from the study available to the public through national bodies and charities. Participants will be informed of the result of the trial via the Pelvic Pain Clinic, NHS Lothian.

## DISCUSSION

We believe that a definitive evaluation of the effectiveness of the meridian BM electro-acupuncture treatment in the management of CPP requires a multicentre randomised controlled trial (RCT). We anticipate potential difficulties in a large RCT in acupuncture for chronic pain and therefore we have designed this pilot study to evaluate its feasibility.

Both MA (30) and EA (31, 32) are safe when performed by appropriately trained acupuncturists. However, because of some theoretical safety concerns, we have

erred on the side of caution to exclude for example, patients who have a history of seizures or have an implanted pace maker.

According to Chinese medicine theory, pain results from blocked meridians leading to an imbalance in the system. On the surface of the body is a network of 12 meridians (6 yin and 6 yang) that connect acupuncture points together.(33) Theoretically, these meridians act as a conduit between the surface of the body and the internal organs. The meridian BM method acupuncture treats pain by balancing these meridians, for example using a "healthy" yin meridian to balance a "blocked" yang meridians. (9) However there are considerable skepticisms and controversies surrounding these theories and the existence as physical entities of acupuncture points and the meridian system. Despite efforts to understand these systems, there are continued disagreements as to what they constitute.(13, 34) Indeed, the PI (OTC) argues that it is more useful to view these systems as a conceptual framework that guides the clinical practice of acupuncture, rather than to argue if they exist. Tangentially related to this view is work undertaken by Langevin whereby it is hypothesized that acupuncture points and meridians have correspondence to the connective tissue (35) and not as illustrated in Chinese medicine text.

A survey of the literature indicates that this is the first study to investigate the effectiveness of the meridian BM electro-acupuncture treatment for chronic pelvic pain in women using a mixed methods approach. The mixed methods approach utilises validated questionnaires and focus group discussions, field notes and a reflexive diary. Undertaking a mixed methods approach is one of the strengths of the study because we are examining the feasibility of studying a complex intervention, which involves a number of phenomena, which include:

TCM health consult, electro-acupuncture and the context effect. Alongside an understanding of participants' perceived benefits or otherwise of the interventions, this methodology will also help us to understand the role of the researcher in the study intervention. The focus group discussions will capture participants' subjective experiences of the study intervention.

It is generally considered that the gold standard in effectiveness of RCTs is the use of a placebo control for the study intervention. However, our pilot study does not employ a placebo (sham acupuncture treatment) for several reasons. A considerable body of evidence from large-scale effectiveness studies has demonstrated that sham acupuncture treatments as controls are problematic. For some chronic pain conditions, the observed effects of acupuncture treatments are larger in usual care controls when compared with sham controls. This might suggest that sham acupuncture treatments have physiological effects, and arethus not inert. Past sham controlled studies have employed techniques such as shallow needling, and needling with a retractable needle or toothpick.(15, 36) Such techniques create a sensation not dissimilar to light touch which has some data to show that it has physiological effects.(37) It is also conceivable and probable that shallow needling and needling with a retractable needle elicit similar physiological effects as deep needling. These sham acupuncture techniques are therefore inappropriate. We feel that until better sham techniques are available, it is prudent to design a study that does not employ a placebo control.

Context effects such as expectancy (38) treatment rituals (39) or patient-provider interactions (24, 40) have been shown to have an impact on the experience of pain. These may have confounded past studies and might explain

the small effect sizes when sham acupuncture treatments were compared to true acupuncture treatments. Attempting to separate the context effects of acupuncture treatment from the specific effects of acupuncture needling presents a major challenge in this area of research. In response, we have designed a three arm RCT to address these challenges. The first arm includes acupuncture needling, electro-stimulation (specific effects of needling) and the patient-healthcare provider interactions (context effects) via a traditional Chinese medicine consult (TCM HC). Group 2, (participants receive only TCM HC) controls for the patient-healthcare provider interactions (context effect). Participants in Group 3 (standard care) will receive the standard NHS care for CPP. Having these 2 control groups is likely to yield the true effect size of the specific effect of electro-acupuncture needling and the non-specific (context effect) of the patient-healthcare provider interactions. We acknowledge that this pilot study is investigating only one aspect of the several context effects of acupuncture treatment. However, we believe that understanding the clinical outcome of the patient-healthcare provider relationship will create a critical mass of literature to influence the education of future generations of healthcare professionals. The UK SIGN 136 guideline for the management of chronic pain acknowledged that while preliminary data showed that the nature of such a relationship could influence clinical outcome, there are not enough high quality studies to recommend widespread training.(41) (Management of chronic pain. Edinburgh: SIGN; December 2013]. Available from URL: http://www.sign.ac.uk. Accessed March 2015)

In assessing the outcome of the interventions, we have chosen validated assessment tools rather than using TCM outcome measures. This is because there are no standardised or validated TCM outcome measures. Arguably, better

known validated questionnaires might be more meaningful within a biomedical setting than TCM outcome measures.

In conclusion, our pilot study protocol will enable us to determine the retention and recruitment rate as well as the patients' experience of the study intervention. It will help us gain better insight into the impact of meridian BM electro-acupuncture needling and the patient-practitioner relationship on chronic pelvic pain in women.

## AUTHORS' CONTRIBUTIONS

OTC: research, contribution of original material, editing and approval of final manuscript; HODC, AH, MF: research, contribution of original material, editing and approval of final manuscript; RE, EH: editing and approval of final manuscript

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## COMPETING INTERESTS

No, there are no competing interests.

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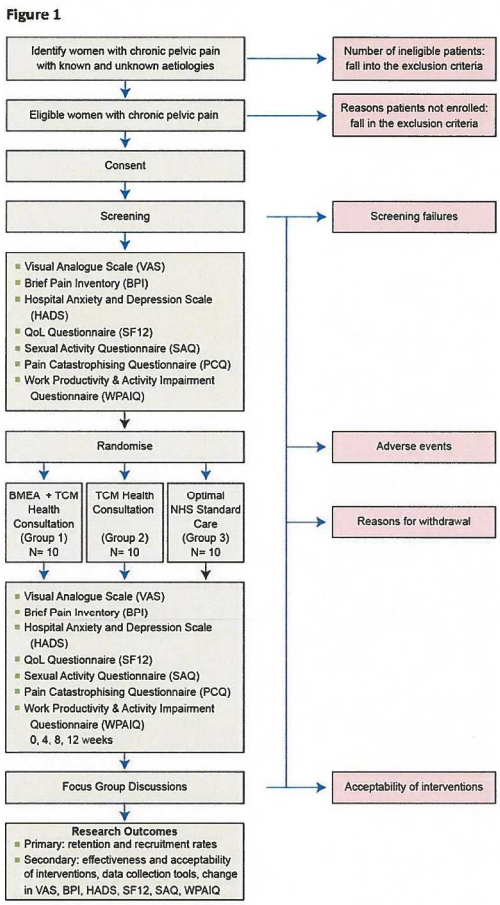


Figure 1. Flow of participants through the study
297x419mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 3 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | N/A |
| Protocol version | 3 | Date and version identifier | All |
| Funding | 4 | Sources and types of financial, material, and other support | 23 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1 and 23 |
| | 5b | Name and contact information for the trial sponsor | 17/18 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | N/A |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | N/A |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 3-8 |
| | 6b | Explanation for choice of comparators | 9 |
| Objectives | 7 | Specific objectives or hypotheses | 8 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 9 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 9 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 13 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 9-12 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | N/A |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | N/A |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | N/A |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 8-9 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 16 |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | _____13_____ |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | _____N/A_____ |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | _____N/A_____ |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | _____14_____ |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | _____14_____ |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | _____N/A_____ |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | _____N/A____ |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | _____15-16____ |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | ____16____ |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | ____15_____ |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | _____18_____ |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | _____18-19___ |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | ____N/A_____ |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | ___19_____ |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | _____N/A___ |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | _____19____ |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | _____N/A____ |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | ____3_____ |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | ____N/A_____ |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 15 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | N/A |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 15 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 24 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 17 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | 17 |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 3 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | 23 |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | N/A |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | App 1, 2 |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | N/A |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.