



**GaPP - A pilot randomised controlled trial of the efficacy of action of gabapentin for the management of chronic pelvic pain in women**

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Complete List of Authors:	Horne, Andrew Critchley, Hilary; University of Edinburgh, Obstetrics and Gynaecology Doust, Ann Fehr, Daniel Wilson, John Wu, Olivia Porter, Maureen Lewis, Steff Bhattacharya, Siladitya; Aberdeen University, Obstetrics and Gynaecology
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**STUDY PROTOCOL**

**TITLE:** *GaPP* - A pilot randomised controlled trial of the efficacy of action of gabapentin for the management of chronic pelvic pain in women

**AUTHORS:** AW Horne<sup>1</sup>, HOD Critchley<sup>1</sup>, A Doust<sup>1</sup>, D Fehr<sup>2</sup>, J Wilson<sup>3</sup>, O Wu<sup>4</sup>, S Jack<sup>5</sup>, M Porter<sup>6</sup>, S Lewis<sup>7</sup>, S Bhattacharya<sup>6</sup>

**AFFILIATIONS:** <sup>1</sup>MRC Centre for Reproductive Health, University of Edinburgh, UK; <sup>2</sup>Universitäres Interdisziplinäres Kinderwunschzentrum Düsseldorf, Germany; <sup>3</sup>Department of Anaesthesia, Royal Infirmary of Edinburgh, UK; <sup>4</sup>Health Economics and Health Technology Assessment, Institute of Health and Wellbeing, University of Glasgow, UK; <sup>5</sup>Department of Gynaecology, Aberdeen Royal Infirmary, UK; <sup>6</sup>Division of Applied Health Sciences, University of Aberdeen, UK; <sup>7</sup>Centre for Population Health Sciences, University of Edinburgh, UK

**CORRESPONDING AUTHOR:**

Dr Andrew Horne  
MRC Centre for Reproductive Health  
Queen's Medical Research Institute  
47 Little France Crescent  
Edinburgh EH16 4TJ  
Tel: +44 131 242 6609  
Fax +44 131 242 6441  
Email: [andrew.horne@ed.ac.uk](mailto:andrew.horne@ed.ac.uk)

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## ABSTRACT

**Introduction:** Chronic pelvic pain (CPP) affects >1 million UK women. Annual healthcare costs are estimated at >£150 million. Proven interventions for CPP are limited and treatment is often unsatisfactory. Gabapentin is increasingly prescribed due to reports of effectiveness in other chronic pain conditions, but there are insufficient data supporting value in CPP specifically. The mechanism by which gabapentin exerts its analgesic action is unknown. Given the prevalence and costs of CPP, we believe a large multi-centre placebo-controlled double-blind randomised-controlled trial (RCT) to evaluate the efficacy of gabapentin in management of CPP is required. The focus of this study is a pilot to inform planning of a future RCT.

**Methods and analysis:** We plan to perform a two-arm parallel randomised-controlled pilot trial. We aim to recruit 60 women with CPP in NHS Lothian and NHS Grampian (UK) and randomise them to gabapentin or placebo. Response to treatment will be monitored by questionnaire compared at 0, 3 and 6 months. Our primary objective is to assess recruitment and retention rates. Our secondary objectives are to determine the effectiveness and acceptability to participants of the proposed methods of recruitment, randomisation, drug treatments, and assessment tools; and to perform a pre-trial cost-effectiveness assessment of treatment with gabapentin.

**Ethics and dissemination:** Ethical approval has been obtained from the Scotland A Research Ethics Committee (LREC 12/SS/0005). Data will be presented at international conferences and published in peer-reviewed journals.

**Trial registration number:** ISRCTN70960777.

## INTRODUCTION

Chronic pelvic pain (CPP) affects over 1 million women in the UK. [1,2] It is the reason for 20% of gynaecological consultations and causes a 45% reduction in work productivity. [3] The annual cost for caring for UK women with CPP has been estimated at £154 million. The cause of the painful symptoms experienced by women with CPP is poorly understood. Pain is often associated with specific pathological processes, such as endometriosis, but up to 55% of women with CPP appear to have no obvious underlying pathology. [2] The management of CPP is difficult [4] because in the absence of underlying pathology, no established gynaecological treatments are available.

Gabapentin (a GABA analogue) is being increasingly prescribed in general practice for CPP. It is also recommended by some practitioners as a treatment of choice for CPP in a multi-disciplinary setting, despite no clinical evidence on which to base this recommendation. To our knowledge, only one study has evaluated the use of gabapentin for CPP. This small study (56 patients) compared gabapentin against amitriptyline for treatment of CPP and showed that gabapentin had greater efficacy (80% compared to 70% improvement in pain scores at 12 months). [5] Unfortunately, this study had no placebo arm and the significance of the effect on quality of life provided by gabapentin in the management of CPP was not evaluated. Nevertheless, the efficacy of gabapentin has been documented for other chronic pain conditions: painful diabetic neuropathy, postherpetic neuralgia, mixed neuropathic pain conditions, spinal-cord injury and phantom limb pain. [6] The number needed to treat for

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3 improvement in all trials with evaluable data is 4.3 (95% CI 3.5 to 5.7). In some  
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5 of these trials, gabapentin also improved sleep, mood and other elements of  
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7 quality of life. The mechanism by which gabapentin exerts its analgesic action is  
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9 unknown.  
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14 Ideally, a definitive evaluation of the efficacy of gabapentin in the management of  
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16 CPP with no obvious underlying pathology requires a large multicentre  
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18 randomised controlled trial (RCT). This protocol outlines a pilot study to assess  
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20 the processes that are vital to the delivery of such a trial.  
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## 24 25 26 **Objectives**

### 27 28 29 30 Primary objective

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32 The primary objective is to determine whether it is possible to achieve  
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34 acceptable recruitment and retention rates in two UK centres (NHS Lothian and  
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36 NHS Grampian) within defined inclusion/exclusion criteria.  
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### 40 41 42 Secondary objectives

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44 1. To determine the effectiveness and acceptability to patients of the proposed  
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46 methods of recruitment, randomisation, drug treatments and assessment tools.  
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48 2. To determine whether gabapentin is likely to be cost effective given the  
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50 current level of uncertainty, and to ascertain what further evidence is needed for  
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52 the evaluation of gabapentin.  
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## Endpoints

### Primary endpoints

1. The proportion of eligible patients randomised into the study.
2. The proportion of randomised patients who take all their medication and fully complete questionnaires at final follow up.

### Secondary endpoints

Data on effectiveness and acceptability of proposed methods of recruitment, randomisation, drug treatments and assessment tools will be used to refine the design of the definitive RCT. The potential cost effectiveness of gabapentin in the management of chronic pelvic pain will also be determined.

## METHODS AND ANALYSIS

### Study design

We aim to perform a two-arm parallel randomised-controlled pilot trial. This will be a two-centre study with recruiting in NHS Lothian (Edinburgh) and NHS Grampian (Aberdeen). We will recruit 60 patients over approximately 9 months. After randomisation the participants will receive treatment for 6 months. Participants and the health care team will be unblinded at the end of their treatment.

### Subjects

A total of 60 women aged 18-50 with a history of pelvic pain (cyclical or non-cyclical) and/or dyspareunia with no obvious pelvic pathology detected at laparoscopy will be invited to participate in the trial.

### Sample size

We have used a confidence interval (CI) approach [7] to estimate the sample size to establish feasibility based on a loss to follow-up of <20%. A 95% CI for 20% of 60 patients (12/60) is 11% to 32%. We estimate that we will recruit ~3-4 patients per month from each centre and aim to recruit 60 patients over a 9-month recruitment period. Each centre performs 6-7 laparoscopies per month that fit the inclusion criteria.

### Inclusion criteria

- Women aged between 18-50
- Pelvic pain of > 6 months
- Pain located within the true pelvis or between and below anterior iliac crests, associated functional disability
- No obvious pelvic pathology at laparoscopy (<6 months and >2 weeks ago)
- Using effective contraception

### Exclusion criteria

- Known pelvic pathology e.g. endometriosis, cyst
- Taking gabapentin or pregabalin
- Due to undergo surgery in the next 6 months
- History of significant renal impairment
- Allergic to gabapentin
- Breast feeding
- Pregnancy or planning pregnancy in the next 6 months

### Intervention

Eligible women will be randomised to either gabapentin or placebo using a web-based system. Women will be stratified by centre (NHS Lothian and NHS Grampian). We will use randomised blocks of varying sizes. Participants will start on 300mg gabapentin daily and will increase in 300 mg increments each week until they report a 50% pain reduction, or side effects (eg dizziness, somnolence, mood changes, appetite and poor concentration), up to a maximum



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3 dose of 2700 mgs. Patients will be advised regarding their dosing regime weekly  
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5 by a member of the research team who will phone until optimum dose is  
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7 reached. It will be recommended that the drug should be taken in three equally  
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9 divided doses daily. Participants will be advised to remain on the maximum  
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11 tolerated dose for up to 6 months. The same protocol will be used for the  
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13 placebo. When the participant stops treatment then the dose will be tapered  
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15 down over 7 - 10 days at the clinician's discretion.  
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## 21 **Data collection**

### 22 Screening

23  
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25 A member of the research team will carry out a screening visit to assess  
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27 eligibility. All data will be recorded on a case record form (CRF) and transferred  
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29 to a secure database.  
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### 36 Participant log

37  
38 The clinical research team will keep an electronic log of women who fulfil the  
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40 eligibility criteria, women who are invited to participate in the study, women  
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42 recruited and women who leave the trial early. Reasons for non-recruitment (eg  
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44 non-eligibility, refusal to participate, administrative error) will also be recorded.  
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46 We will attempt to collect reasons for non-participation from women who  
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48 decline to take part after previously providing contact details. During the course  
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50 of the study, we will document reasons for withdrawal from the study and loss to  
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52 follow-up.  
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### Treatment diaries

All medications and healthcare resource use taken after screening and any medication other than the trial treatment taken during the study will be recorded in a treatment diary. This includes prescription and non-prescription treatment such as contraceptives, vitamins, topical preparations, herbal preparations and non-pharmacological therapies.

### Questionnaires

A questionnaire will be given to all participants at randomisation (0 months) and at 3 months. This will include the following validated tools:

1. Visual analogue scale (VAS)
2. Brief Pain Inventory (BPI)
3. Pain Disability Questionnaire (PDQ)
4. Hospital Anxiety and Depression Score (HADS)
5. EQ5D QoL
6. WHO QoL
7. MYMOP patient-generated outcome questionnaire

The questionnaire at 0 months will include questions to capture the baseline demographic and clinical characteristics of the participants.

A further questionnaire will also be given to all participants at 6 months which will include the above and additional questions on whether they believed they were receiving gabapentin or placebo, and also questions on acceptability of the allocated medication/treatment regimes (and compliance) and on the acceptability of the above data collection methods. Lastly, we will ask the

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3 participants to complete a brief anonymous questionnaire once they have  
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5 submitted their treatment diaries to assess level of adherence to diary keeping.  
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### 8 9 10 Focus groups

11 A purposive sample (based on age, social class and severity of symptoms) of 10  
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13 Edinburgh women (including some undergoing fMRI) and 10 Aberdeen women  
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15 will be invited to participate in focus group discussions of the trial experience six  
16  
17 months into the trial. [8] Women who do not wish to participate in a focus group  
18  
19 will be offered individual interviews using the same interview schedule. This will  
20  
21 enable important issues arising in the focus groups to be explored in greater  
22  
23 depth. Up to 20 interviews will be performed. Group/individual interviews will  
24  
25 be audio-recorded, transcribed verbatim and analysed thematically to identify  
26  
27 the issues of importance to participants not covered in the questionnaires, their  
28  
29 feelings about trial participation and experiences with prescribed medication.  
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### 37 Healthcare resource utilisation measures

38 Information will be derived from treatment diaries and from research nurse  
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40 reviews of the participants' hospital and general practitioners' records.  
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### 45 Adverse events

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47 Participants will collect information about adverse events in their treatment  
48  
49 diaries. However, they will be instructed to contact the clinical research team at  
50  
51 any time after consenting to join the trial if they have an event that requires  
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53 hospitalisation, or an event that results in persistent or significant disability or  
54  
55 incapacity. Gabapentin is generally well tolerated in the management of other  
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3 chronic pain conditions and serious adverse events (SAEs) are not anticipated.  
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5 Any SAEs that occur after joining the trial will be reported in detail in the  
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7 participant's medical notes, followed up until resolution of the event, and  
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9 reported to the ACCORD Research Governance ([www.accord.ed.ac.uk](http://www.accord.ed.ac.uk)) and QA  
10  
11 Office based at the University of Edinburgh immediately or within 24 hours.  
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### 14 15 16 17 Termination of study

18  
19 Participants (and their gynaecologists) will be unblinded at the end of the study  
20  
21 period (6 months). There will be no central unblinding facility but the site  
22  
23 pharmacies will be provided with the key which links drug pack number to  
24  
25 treatment. Thus, it will be possible for unblinding (emergency or otherwise) to  
26  
27 be carried out by a pharmacist if requested. All participants will be given the  
28  
29 right to be unblinded, discontinue the drug or completely withdraw from the  
30  
31 study at any time for any reason. Reasons for unblinding, before the termination  
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33 of the study, will be collected. Those participants who feel that they have  
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35 benefited from treatment with gabapentin, during the study period, will be  
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37 advised to discuss continuation of treatment with their gynaecologist.  
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### 44 **Proposed analyses**

#### 45 46 47 48 Determine recruitment and retention rates

49  
50 Using the information collected from the participant log, we will determine the  
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52 number of patients recruited from the pool of eligible women and a >50%  
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54 recruitment will be deemed acceptable. While a retention rate of 100% would be  
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56 ideal, we will consider a rate of 90% satisfactory. We will provide an estimate of  
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3 the proportion and its 95% confidence interval. If retention rates are low, we will  
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5 use the information collected from the focus group discussions to ascertain why  
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7 and improve compliance in the future trial. In addition, we will determine the  
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9 nature and number of unanswered questions in each questionnaire and identify  
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11 reasons for non-response through the focus groups and participant interviews in  
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13 order to optimise data collection in the future trial.  
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19 Effectiveness and acceptability of proposed methods of recruitment,  
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21 randomisation, drug treatments and assessment tools  
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23 These areas will be explored in the focus group discussions and assessed  
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25 quantitatively using additional questions included in participant questionnaires  
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27 administered at 6 months. Due to the conflicting literature about the benefits of  
28  
29 methods such as prescription monitoring, pill counting and devices for  
30  
31 monitoring the self-administration of medicines, [9] data on blinding and  
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33 compliance to treatment will be derived from questionnaires at 6 months. We  
34  
35 aim to determine if treatment is acceptable in terms of self-reported compliance  
36  
37 (from treatment diaries). Although this is a pilot study and the sample size is  
38  
39 small, we will assess the effect of any non-compliance on the LICKERT score by  
40  
41 performing protocol and intention to treat analyses. This information along with  
42  
43 health professionals' and clinical research nurses' views (as assessed by  
44  
45 questionnaire) will be used to inform the design of the future RCT. In addition,  
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47 the difference in VAS scores between participants on gabapentin and placebo at  
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49 0 and 6 months will be assessed using analysis of covariance adjusting for  
50  
51 baseline VAS score.  
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### Pre-trial economic model and value of information analysis

In addition to data relating to the clinical and quality of life parameters, data on healthcare resource use will also be collected. A decision model will be developed, from the perspective of the NHS, to estimate the costs and health outcomes in terms of quality of life and quality adjusted life years associated with gabapentin and placebo based on the data from this pilot study and the literature. A probabilistic decision model will be constructed to simulate the clinical pathways associated with gabapentin and placebo, according to the guidance set out by NICE. [10] The basic model structure will consist of two arms, replicating the clinical consequences of patients receiving gabapentin and placebo. The main data source relating to the key parameters of the model will be provided by the pilot study. The mean costs and quality adjusted life years associated with both arms will be calculated for the modelling period (duration of the trial). Cost utility analysis will be carried out and incremental cost per quality-adjusted life years gained will be calculated. Particular consideration will be given to the potential for cost effectiveness to vary by particular patient characteristics or risk groups where suggested by the literature. Probabilistic sensitivity analysis will be used to characterise uncertainty in parameters of the model, and presented using cost-effectiveness acceptability curves. Standard univariate sensitivity analysis will be carried out to explore areas of structural uncertainty in the analysis. Finally, a value of information analysis on the expected value of perfect information will also be carried out to quantify potential value of further research based on the difference between expected net benefit with perfect information and existing information.

## ETHICS AND DISSEMINATION

Ethical approval has been obtained from the Scotland A Research Ethics Committee (LREC 12/SS/0005). 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 efficacy of gabapentin in the management of CPP requires a multicentre randomised placebo-controlled trial (RCT). Recognising that there may be potential difficulties in mounting a large RCT for a chronic pain condition using a medication with known sedating side effects and that requires a titrated dosing regime, we have designed this pilot study to assess practical feasibility following the IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) recommendations for the design of chronic pain clinical trials. [11] We are aware that our pilot study has a number of positive and negative aspects and these are discussed below.

For our pilot study, we are using the most common design in confirmatory trials of chronic pain treatments: a 'parallel groups' design. [11] We will randomise participants to either gabapentin or placebo, and then evaluate recruitment and retention rates as our primary outcome. We appreciate that this design may be limited by the fact that the severity of the participants' pain may preclude them from remaining on the placebo for the 6-month follow-up period. Therefore, the outcome of the pilot will determine whether we need to consider alternative designs, such as 'crossover', randomised withdrawal' and 'dose response' designs, for the future RCT assessing efficacy of gabapentin for CPP.

The criteria for inclusion and exclusion of study subjects into our pilot study are broad in attempt to reflect the real clinical scenario for prescribing gabapentin.



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3 The criteria do not take into account pain intensity, do not exclude women with  
4 non-reproductive comorbidities (e.g. irritable bowel syndrome, interstitial  
5 cystitis) that could explain their symptoms, and allow participants the use of  
6 concomitant medications. We are aware that these characteristics may increase  
7 variability in patient responsiveness to treatment and carry the risk of failing to  
8 demonstrate treatment effect. We will therefore capture this information in our  
9 pilot study in the participants' questionnaires and treatment diaries to inform  
10 interpretation of our results and the planning of the future RCT.  
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23 Like many of the medications used for chronic pain, gabapentin requires  
24 titration to achieve an efficacious dose so that the rate and severity of adverse  
25 effects are minimised. The duration of this titration period may be as many as 8-  
26 10 weeks. The 6-month follow-up in our pilot study allows for a 12-week  
27 maintenance phase that has become standard for confirmatory trials. It could be  
28 argued that a longer trial would be better to assess the long-term effects of  
29 gabapentin. On the other hand, we are aware that extended duration could be  
30 problematic because of the number of drop-outs from the placebo arm due to  
31 inadequate pain relief. We believe that focus group assessment of the  
32 acceptability of the drug treatment and titrating regime in our pilot will  
33 therefore be essential in designing the future RCT.  
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50 The comparison of an investigational treatment with placebo is considered the  
51 gold standard for assessing efficacy and safety when a delay in the onset of  
52 treatment does not cause any lasting adverse effects and assuming that subjects  
53 fully understand their right to withdraw from the trial at any time for any reason.  
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3 [12,13] However, gabapentin is sedating and it can be argued that this increases  
4 the likelihood that both subjects and investigators can successfully guess to  
5 which group a subject has been allocated. We are therefore going to ask the  
6 subjects and investigators at the conclusion of the trial to guess the subjects'  
7 treatment group and the primary reason for the guess to determine whether  
8 significant 'unblinding' was present within the trial. This will determine whether  
9 we need to use an 'active placebo' mimicking the side effects of gabapentin in the  
10 future RCT.  
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23 Our data collection tools were chosen with advice from a clinical psychologist  
24 with a specialist interest in chronic pain and a general practitioner with a  
25 research interest in medically unexplained symptoms. The selection of these  
26 tools was also again based on the IMMPACT recommendations [11] i.e. the need  
27 to assess the core domains of pain, physical/emotional functioning (including  
28 sleeping difficulties), improvement/satisfaction with treatment, symptoms and  
29 adverse events and participant disposition. We plan to use a wide range of data  
30 collection tools but it is our intention to use fewer in our future RCT depending  
31 on their effectiveness in the pilot study (defined by lack of missing data, ability to  
32 detect effect and independence) and participant feedback on acceptability.  
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48 We also aim to determine whether gabapentin is expected to be cost effective  
49 given the current level of evidence and uncertainty through an iterative  
50 approach to economic evaluation of health technologies. [14,15] Important gaps  
51 and uncertainty surrounding existing data and the expected cost effectiveness  
52 will be explored through synthesis, modelling and value of information analysis  
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3 prior to a definitive RCT. We will determine whether further evidence is needed  
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5 to reduce the uncertainty surrounding cost effectiveness, and if so, identify the  
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7 focus of further research in terms of study design and data collection; this may  
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9 have implications on determining an appropriate sample size (e.g. powered to  
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11 detect difference in clinical effect or cost effectiveness).  
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16 Finally, although the primary outcome in our pilot study is to determine  
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18 recruitment and retention rates, we will also measure change in visual analogue  
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20 scale (VAS) over 6 months. This combination of information will allow us to  
21  
22 determine the effect size and standard deviation (SD) and plan the sample size  
23  
24 for the definitive RCT. Analyses of similar studies using gabapentin for chronic  
25  
26 pain with VAS score as primary outcome indicate that the mean absolute  
27  
28 difference in the VAS score comparing gabapentin against placebo ranges  
29  
30 between 0.8 and 1.8 with an SD of ~2.5 after 1-2 months' treatment. [6] Thus,  
31  
32 our definitive RCT is likely to be powered to find a difference of >1.2 on the VAS  
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34 scale (a clinically important symptom alleviation is defined as a reduction in VAS  
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36 of >1.2 [16] between the gabapentin and placebo arms of the study.  
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## AUTHORS' CONTRIBUTIONS

AWH: research, contribution of original material, editing and approval of final manuscript; HODC: editing and approval of final manuscript; AD: contribution of original material, editing and approval of final manuscript; DF: editing and approval of final manuscript; JW: editing and approval of final manuscript; OW: research, contribution of original material, editing and approval of final manuscript; SJ: editing and approval of final manuscript; MP: research, contribution of original material, editing and approval of final manuscript; SL: research, contribution of original material, editing and approval of final manuscript; SB: research, contribution of original material, editing and approval of final manuscript.

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**COMPETING INTERESTS**

None.

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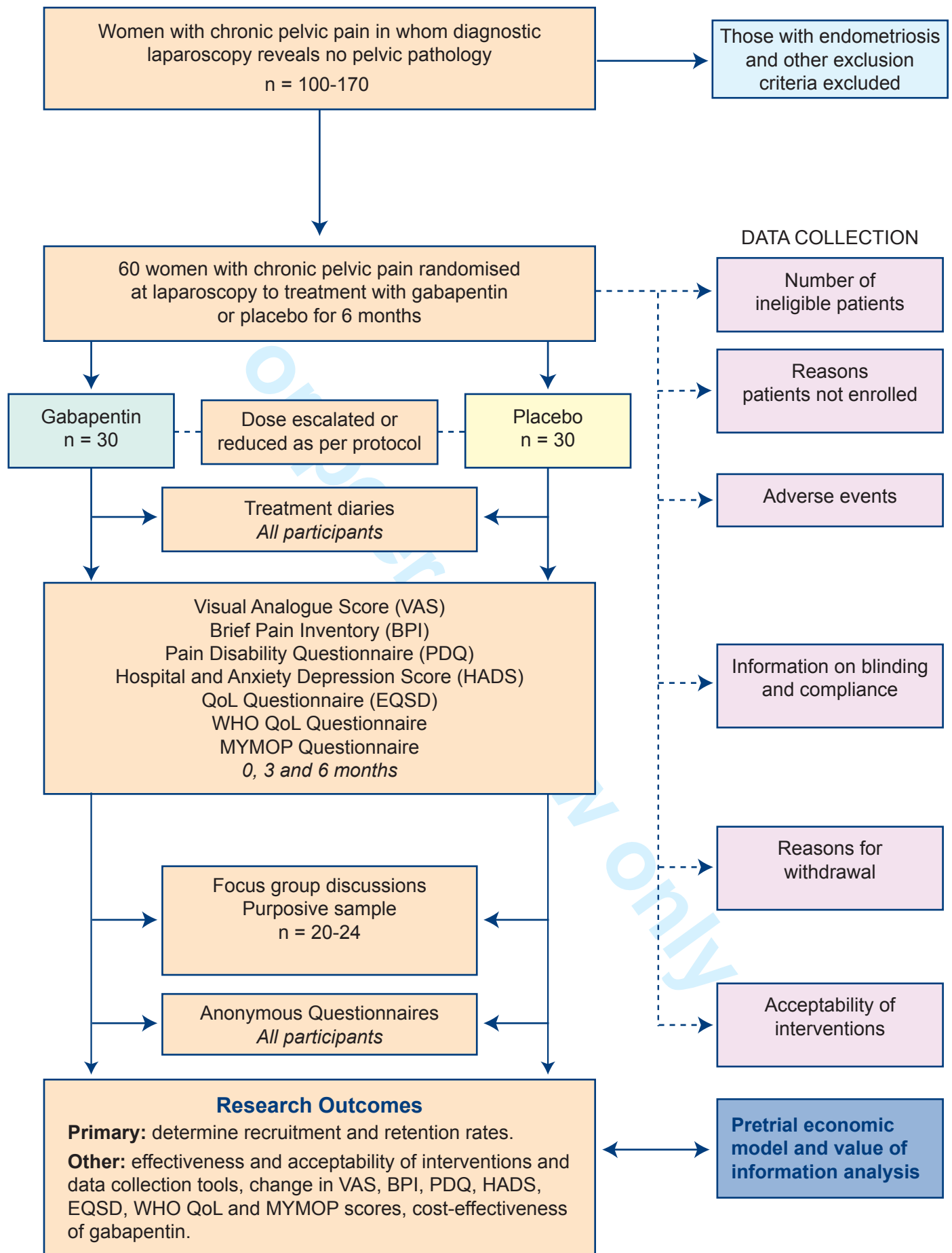


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3 **FIGURE LEGEND**  
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7 **Figure 1.** Flow of participants through the study.  
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**GaPP - A pilot randomised controlled trial of the efficacy of action of gabapentin for the management of chronic pelvic pain in women: study protocol**

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-001297.R1
Article Type:	Protocol
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<b>Primary Subject Heading</b>:	Reproductive medicine, obstetrics and gynaecology
Secondary Subject Heading:	Health economics, Health services research
Keywords:	PAIN MANAGEMENT, REPRODUCTIVE MEDICINE, HEALTH ECONOMICS, STATISTICS & RESEARCH METHODS

SCHOLARONE™  
Manuscripts

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3 **1 STUDY PROTOCOL**  
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6 **3 TITLE:** *GaPP* - A pilot randomised controlled trial of the efficacy of action of  
7 gabapentin for the management of chronic pelvic pain in women: study protocol.  
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10  
11 **6 AUTHORS:** AW Horne<sup>1</sup>, HOD Critchley<sup>1</sup>, A Doust<sup>1</sup>, D Fehr<sup>2</sup>, J Wilson<sup>3</sup>, O Wu<sup>4</sup>, S  
12 Jack<sup>5</sup>, M Porter<sup>6</sup>, S Lewis<sup>7</sup>, S Bhattacharya<sup>6</sup>  
13  
14

15  
16 **9 AFFILIATIONS:** <sup>1</sup>*MRC Centre for Reproductive Health, University of Edinburgh,*  
17 *UK;* <sup>2</sup>*Universitäres Interdisziplinäres Kinderwunschzentrum Düsseldorf, Germany;*  
18 <sup>3</sup>*Department of Anaesthesia, Royal Infirmary of Edinburgh, UK;* <sup>4</sup>*Health Economics*  
19 *and Health Technology Assessment, Institute of Health and Wellbeing, University of*  
20 *Glasgow, UK;* <sup>5</sup>*Department of Gynaecology, Aberdeen Royal Infirmary, UK;* <sup>6</sup>*Division*  
21 *of Applied Health Sciences, University of Aberdeen, UK;* <sup>7</sup>*Centre for Population*  
22 *Health Sciences, University of Edinburgh, UK*  
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29

30 **17 CORRESPONDING AUTHOR:**

31 Dr Andrew Horne  
32  
33 MRC Centre for Reproductive Health  
34  
35 Queen's Medical Research Institute  
36  
37 47 Little France Crescent  
38  
39 Edinburgh EH16 4TJ  
40  
41 Tel: +44 131 242 6609  
42  
43 Fax +44 131 242 6441  
44  
45 Email: [andrew.horne@ed.ac.uk](mailto:andrew.horne@ed.ac.uk)  
46

47 **27 KEY WORDS:**

48 Pelvic pain, gabapentin.  
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52 **30 WORD COUNT:**

53 3,555  
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3 **ABSTRACT**  
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3 **Introduction:** Chronic pelvic pain (CPP) affects >1 million UK women. Annual  
4 healthcare costs are estimated at >£150 million. Proven interventions for CPP  
5 are limited and treatment is often unsatisfactory. Gabapentin is increasingly  
6 prescribed due to reports of effectiveness in other chronic pain conditions, but  
7 there are insufficient data supporting value in CPP specifically. The mechanism  
8 by which gabapentin exerts its analgesic action is unknown. Given the prevalence  
9 and costs of CPP, we believe a large multi-centre placebo-controlled double-blind  
10 randomised-controlled trial (RCT) to evaluate the efficacy of gabapentin in  
11 management of CPP is required. The focus of this study is a pilot to inform  
12 planning of a future RCT.

13 **Methods and analysis:** We plan to perform a two-arm parallel randomised-  
14 controlled pilot trial. We aim to recruit 60 women with CPP in NHS Lothian and  
15 NHS Grampian (UK) and randomise them to gabapentin or placebo. Response to  
16 treatment will be monitored by questionnaire compared at 0, 3 and 6 months.  
17 Our primary objective is to assess recruitment and retention rates. Our  
18 secondary objectives are to determine the effectiveness and acceptability to  
19 participants of the proposed methods of recruitment, randomisation, drug  
20 treatments, and assessment tools; and to perform a pre-trial cost-effectiveness  
21 assessment of treatment with gabapentin.

22 **Ethics and dissemination:** Ethical approval has been obtained from the  
23 Scotland A Research Ethics Committee (LREC 12/SS/0005). Data will be  
24 presented at international conferences and published in peer-reviewed journals.

25 **Trial registration number:** ISRCTN70960777.  
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## 1 INTRODUCTION

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Chronic pelvic pain (CPP) affects over 1 million women in the UK. [1,2] It is the reason for 20% of gynaecological consultations and causes a 45% reduction in work productivity. [3] The annual cost for caring for UK women with CPP has been estimated at £154 million. The cause of the painful symptoms experienced by women with CPP is poorly understood. Pain is often associated with specific pathological processes, such as endometriosis, but up to 55% of women with CPP appear to have no obvious underlying pathology. [2] The management of CPP is difficult [4] because in the absence of underlying pathology, no established gynaecological treatments are available.

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Gabapentin (a GABA analogue) is being increasingly prescribed in general practice for CPP. It is also recommended by some practitioners as a treatment of choice for CPP in a multi-disciplinary setting, despite no clinical evidence on which to base this recommendation. To our knowledge, only one study has evaluated the use of gabapentin for CPP. This small study (56 patients) compared gabapentin against amitriptyline for treatment of CPP and showed that gabapentin had greater efficacy (80% compared to 70% improvement in pain scores at 12 months). [5] Unfortunately, this study had no placebo arm and the significance of the effect on quality of life provided by gabapentin in the management of CPP was not evaluated. Nevertheless, the efficacy of gabapentin has been documented for other chronic pain conditions: painful diabetic neuropathy, postherpetic neuralgia, mixed neuropathic pain conditions, spinal-cord injury and phantom limb pain. [6] The number needed to treat for

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3 1 improvement in all trials with evaluable data is 4.3 (95% CI 3.5 to 5.7). In some  
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5 2 of these trials, gabapentin also improved sleep, mood and other elements of  
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7 3 quality of life. The mechanism by which gabapentin exerts its analgesic action is  
8  
9 4 unknown.

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14 6 Ideally, a definitive evaluation of the efficacy of gabapentin in the management of  
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16 7 CPP with no obvious underlying pathology requires a large multicentre  
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18 8 randomised controlled trial (RCT). This protocol outlines a pilot study to assess  
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20 9 the processes that are vital to the delivery of such a trial.  
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## 25 11 **Objectives**

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### 27 13 Primary objective

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30 14 The primary objective is to determine whether it is possible to achieve  
31  
32 15 acceptable recruitment and retention rates in two UK centres (NHS Lothian and  
33  
34 16 NHS Grampian) within defined inclusion/exclusion criteria.  
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### 40 18 Secondary objectives

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43 19 1. To determine the effectiveness and acceptability to patients of the proposed  
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45 20 methods of recruitment, randomisation, drug treatments and assessment tools.

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48 21 2. To determine whether gabapentin is likely to be cost effective given the  
49  
50 22 current level of uncertainty, and to ascertain what further evidence is needed for  
51  
52 23 the evaluation of gabapentin.  
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3 **1 Endpoints**  
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7 **3 Primary endpoints**  
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10 4 1. The proportion of eligible patients randomised into the study.

11 5 2. The proportion of randomised patients who take all their medication and fully

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13 complete questionnaires at final follow up.  
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18 **8 Secondary endpoints**  
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20 9 Data on effectiveness and acceptability of proposed methods of recruitment,

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22 randomisation, drug treatments and assessment tools will be used to refine the  
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25 10 design of the definitive RCT. The potential cost effectiveness of gabapentin in the  
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28 11 management of chronic pelvic pain will also be determined.  
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## 1    **METHODS AND ANALYSIS**

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### 3    Study design

4    We aim to perform a two-arm parallel randomised-controlled pilot trial. This will  
5    be a two-centre study with recruiting in NHS Lothian (Edinburgh) and NHS  
6    Grampian (Aberdeen). We will recruit 60 patients over approximately 9 months.  
7    After randomisation the participants will receive treatment for 6 months.  
8    Participants and the health care team will be unblinded at the end of their  
9    treatment.

10

### 11    Subjects

12    A total of 60 women aged 18-50 with a history of pelvic pain (cyclical or non-  
13    cyclical) and/or dyspareunia with no obvious pelvic pathology detected at  
14    laparoscopy will be invited to participate in the trial.

15

### 16    Study settings

17    We will recruit patients from gynaecology out patient clinics, gynaecology wards  
18    and day surgery units within NHS Lothian and NHS Grampian.

19

### 20    Sample size

21    We have used a confidence interval (CI) approach [7] to estimate the sample size  
22    to establish feasibility based on a loss to follow-up of <20%. A 95% CI for 20% of  
23    60 patients (12/60) is 11% to 32%. We estimate that we will recruit ~3-4  
24    patients per month from each centre and aim to recruit 60 patients over a 9-

1 month recruitment period. Each centre performs 6-7 laparoscopies per month that fit the inclusion criteria.

#### Inclusion criteria

- Women aged between 18-50
- Pelvic pain of > 6 months
- Pain located within the true pelvis or between and below anterior iliac crests, associated functional disability
- No obvious pelvic pathology at laparoscopy (<6 months and >2 weeks ago)
- Using effective contraception

#### Exclusion criteria

- Known pelvic pathology e.g. endometriosis, cyst
- Taking gabapentin or pregabalin
- Due to undergo surgery in the next 6 months
- History of significant renal impairment
- Allergic to gabapentin
- Breast feeding
- Pregnancy or planning pregnancy in the next 6 months

#### Participant enrolment

All gynaecology consultants within NHS Lothian and NHS Grampian will be sent a letter informing them of the study and requesting permission to approach their patients. Two research nurses (one in NHS Lothian and one in NHS Grampian)

1 will be employed for the duration of the study to approach eligible women,  
2 provide them with patient information sheets and offer them the opportunity to  
3 discuss the trial, and obtain informed consent. Consent will only be taken once  
4 the patient has had ample time to read the patient information sheet and had her  
5 questions answered.

#### 6 7 Intervention and randomisation

8 Eligible women will be randomised to either gabapentin or placebo using a web-  
9 based system. Women will be stratified by centre (NHS Lothian and NHS  
10 Grampian). We will use randomised blocks of varying sizes.

#### 11 12 Dose regime

13 Participants will start on 300mg gabapentin daily and will increase in 300 mg  
14 increments each week until they report a 50% pain reduction, or side effects (eg  
15 dizziness, somnolence, mood changes, appetite and poor concentration), up to a  
16 maximum dose of 2700 mgs. Patients will be advised regarding their dosing  
17 regime weekly by a member of the research team who will phone until optimum  
18 dose is reached. It will be recommended that the drug should be taken in three  
19 equally divided doses daily. Participants will be advised to remain on the  
20 maximum tolerated dose for up to 6 months. The same protocol will be used for  
21 the placebo. When the participant stops treatment then the dose will be tapered  
22 down over 7 - 10 days at the clinician's discretion. Patients will be allowed to use  
23 other medication (including analgesics, self-medication and alternative  
24 treatments e.g. acupuncture) throughout the study period.

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3 **1 Data collection**  
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7 3 Data storage  
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10 4 A log with the patients' name and date of birth will be kept along with their  
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12 5 unique study number in a separate file. All of the data generated from the study  
13  
14 6 will be stored in an anonymised form in a bespoke database which will also be  
15  
16 7 password protected . Only anonymised information will be stored on this and  
17  
18 8 participants will only be identifiable by their study number. All paperwork will  
19  
20 9 be kept in a locked filing cabinet in a locked office. All data will be stored on  
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22 10 university server on a password-protected computer with limited access to the  
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24 11 research team, in accordance with NHS and University of Edinburgh guidelines  
25  
26 12 and in accordance with the Data Protection Act.  
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32 14 Screening  
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35 15 A member of the research team will carry out a screening visit to assess  
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37 16 eligibility. All data will be recorded on a case record form (CRF) and transferred  
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39 17 to a secure database.  
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44 19 Participant log  
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46 20 The clinical research team will keep an electronic log of women who fulfil the  
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48 21 eligibility criteria, women who are invited to participate in the study, women  
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50 22 recruited and women who leave the trial early. Reasons for non-recruitment (eg  
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52 23 non-eligibility, refusal to participate, administrative error) will also be recorded.  
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54 24 We will attempt to collect reasons for non-participation from women who  
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56 25 decline to take part after previously providing contact details. During the course  
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1 of the study, we will document reasons for withdrawal from the study and loss to  
2 follow-up. Participants will be reviewed by the clinical research team at 6 weeks,  
3 3 months and 6 months.

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#### 5 Treatment diaries

6 All medications and healthcare resource use taken after screening and any  
7 medication other than the trial treatment taken during the study will be  
8 recorded in a treatment diary. This includes prescription and non-prescription  
9 treatment such as contraceptives, vitamins, topical preparations, herbal  
10 preparations and non-pharmacological therapies.

11

#### 12 Questionnaires

13 A questionnaire will be given to all participants at randomisation (0 months) and  
14 at 3 months. This will include the following validated tools:

- 15 1. Visual analogue scale (VAS)
- 16 2. Brief Pain Inventory (BPI)
- 17 3. Pain Disability Questionnaire (PDQ)
- 18 4. Hospital Anxiety and Depression Score (HADS)
- 19 5. EQ5D QoL
- 20 6. WHO QoL
- 21 7. MYMOP patient-generated outcome questionnaire

22 The questionnaire at 0 months will include questions to capture the baseline  
23 demographic and clinical characteristics of the participants.

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3 1 A further questionnaire will also be given to all participants at 6 months which  
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5 2 will include the above and additional questions on whether they believed they  
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7 3 were receiving gabapentin or placebo, and also questions on acceptability of the  
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10 4 allocated medication/treatment regimes (and compliance) and on the  
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12 5 acceptability of the above data collection methods. Lastly, we will ask the  
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14 6 participants to complete a brief anonymous questionnaire once they have  
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16 7 submitted their treatment diaries to assess level of adherence to diary keeping.  
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#### 20 21 9 Focus groups

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23 10 A purposive sample (based on age, social class and severity of symptoms) of 10  
24  
25 11 Edinburgh women (including some undergoing fMRI) and 10 Aberdeen women  
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27  
28 12 will be invited to participate in focus group discussions of the trial experience six  
29  
30 13 months into the trial. [8] Women who do not wish to participate in a focus group  
31  
32 14 will be offered individual interviews using the same interview schedule. This will  
33  
34 15 enable important issues arising in the focus groups to be explored in greater  
35  
36 16 depth. Up to 20 interviews will be performed. Group/individual interviews will  
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38 17 be audio-recorded, transcribed verbatim and analysed thematically to identify  
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40 18 the issues of importance to participants not covered in the questionnaires, their  
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42 19 feelings about trial participation and experiences with prescribed medication.  
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#### 47 48 21 Healthcare resource utilisation measures

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50 22 Information will be derived from treatment diaries and from research nurse  
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52 23 reviews of the participants' hospital and general practitioners' records.  
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3 1 Adverse events  
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5 2 Participants will collect information about adverse events in their treatment  
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7 3 diaries. However, they will be instructed to contact the clinical research team at  
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9 4 any time after consenting to join the trial if they have an event that requires  
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11 5 hospitalisation, or an event that results in persistent or significant disability or  
12  
13 6 incapacity. Gabapentin is generally well tolerated in the management of other  
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15 7 chronic pain conditions and serious adverse events (SAEs) are not anticipated.  
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17 8 Any SAEs that occur after joining the trial will be reported in detail in the  
18  
19 9 participant's medical notes, followed up until resolution of the event, and  
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21 10 reported to the ACCORD Research Governance ([www.accord.ed.ac.uk](http://www.accord.ed.ac.uk)) and QA  
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23 11 Office based at the University of Edinburgh immediately or within 24 hours.  
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30 13 Termination of study  
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32 14 Participants (and their gynaecologists) will be unblinded at the end of the study  
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34 15 period (6 months). There will be no central unblinding facility but the site  
35  
36 16 pharmacies will be provided with the key which links drug pack number to  
37  
38 17 treatment. Thus, it will be possible for unblinding (emergency or otherwise) to  
39  
40 18 be carried out by a pharmacist if requested. All participants will be given the  
41  
42 19 right to be unblinded, discontinue the drug or completely withdraw from the  
43  
44 20 study at any time for any reason. Reasons for unblinding, before the termination  
45  
46 21 of the study, will be collected. Those participants who feel that they have  
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48 22 benefited from treatment with gabapentin, during the study period, will be  
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50 23 advised to discuss continuation of treatment with their gynaecologist.  
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3 **1 Proposed analyses**  
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7 **3 Determine recruitment and retention rates**  
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10 4 Using the information collected from the participant log, we will determine the  
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12 5 number of patients recruited from the pool of eligible women and a >50%  
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14 6 recruitment will be deemed acceptable. While a retention rate of 100% would be  
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16 7 ideal, we will consider a rate of 90% satisfactory. We will provide an estimate of  
17  
18 8 the proportion and its 95% confidence interval. If retention rates are low, we will  
19  
20 9 use the information collected from the focus group discussions to ascertain why  
21  
22 10 and improve compliance in the future trial. In addition, we will determine the  
23  
24 11 nature and number of unanswered questions in each questionnaire and identify  
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26 12 reasons for non-response through the focus groups and participant interviews in  
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28 13 order to optimise data collection in the future trial.  
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34 **15 Effectiveness and acceptability of proposed methods of recruitment,**  
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36 **16 randomisation, drug treatments and assessment tools**  
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39 17 These areas will be explored in the focus group discussions and assessed  
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41 18 quantitatively using additional questions included in participant questionnaires  
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43 19 administered at 6 months. Due to the conflicting literature about the benefits of  
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45 20 methods such as prescription monitoring, pill counting and devices for  
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47 21 monitoring the self-administration of medicines, [9] data on blinding and  
48  
49 22 compliance to treatment will be derived from questionnaires at 6 months. We  
50  
51 23 aim to determine if treatment is acceptable in terms of self-reported compliance  
52  
53 24 (from treatment diaries). Although this is a pilot study and the sample size is  
54  
55 25 small, we will assess the effect of any non-compliance on the LICKERT score by  
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1 performing protocol and intention to treat analyses. This information along with  
2 health professionals' and clinical research nurses' views (as assessed by  
3 questionnaire) will be used to inform the design of the future RCT. In addition,  
4 the difference in VAS scores between participants on gabapentin and placebo at  
5 0 and 6 months will be assessed using analysis of covariance adjusting for  
6 baseline VAS score.

7

#### 8 Pre-trial economic model and value of information analysis

9 In addition to data relating to the clinical and quality of life parameters, data on  
10 healthcare resource use will also be collected. A decision model will be  
11 developed, from the perspective of the NHS, to estimate the costs and health  
12 outcomes in terms of quality of life and quality adjusted life years associated  
13 with gabapentin and placebo based on the data from this pilot study and the  
14 literature. A probabilistic decision model will be constructed to simulate the  
15 clinical pathways associated with gabapentin and placebo, according to the  
16 guidance set out by NICE. [10] The basic model structure will consist of two  
17 arms, replicating the clinical consequences of patients receiving gabapentin and  
18 placebo. The main data source relating to the key parameters of the model will  
19 be provided by the pilot study. The mean costs and quality adjusted life years  
20 associated with both arms will be calculated for the modelling period (duration  
21 of the trial). Cost utility analysis will be carried out and incremental cost per  
22 quality-adjusted life years gained will be calculated. Particular consideration will  
23 be given to the potential for cost effectiveness to vary by particular patient  
24 characteristics or risk groups where suggested by the literature. Probabilistic  
25 sensitivity analysis will be used to characterise uncertainty in parameters of the

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3 1 model, and presented using cost-effectiveness acceptability curves. Standard  
4  
5 2 univariate sensitivity analysis will be carried out to explore areas of structural  
6  
7 3 uncertainty in the analysis. Finally, a value of information analysis on the  
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9 4 expected value of perfect information will also be carried out to quantify  
10  
11 5 potential value of further research based on the difference between expected net  
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13 6 benefit with perfect information and existing information.  
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## 19 8 **ETHICS AND DISSEMINATION**

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23 10 Ethical approval has been obtained from the Scotland A Research Ethics  
24  
25 11 Committee (LREC 12/SS/0005). Data will be presented at international  
26  
27 12 conferences and published in peer-reviewed journals. We will make the  
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29 13 information obtained from the study available to the public through national  
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31 14 bodies and charities.  
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3 **1 DISCUSSION**  
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3 We believe that a definitive evaluation of the efficacy of gabapentin in the  
4 management of CPP requires a multicentre randomised placebo-controlled trial  
5 (RCT). Recognising that there may be potential difficulties in mounting a large  
6 RCT for a chronic pain condition using a medication with known sedating side  
7 effects and that requires a titrated dosing regime, we have designed this pilot  
8 study to assess practical feasibility following the IMMPACT (Initiative on  
9 Methods, Measurement, and Pain Assessment in Clinical Trials)  
10 recommendations for the design of chronic pain clinical trials. [11] We are aware  
11 that our pilot study has a number of positive and negative aspects and these are  
12 discussed below.

13  
14 For our pilot study, we are using the most common design in confirmatory trials  
15 of chronic pain treatments: a 'parallel groups' design. [11] We will randomise  
16 participants to either gabapentin or placebo, and then evaluate recruitment and  
17 retention rates as our primary outcome. We appreciate that this design may be  
18 limited by the fact that the severity of the participants' pain may preclude them  
19 from remaining on the placebo for the 6-month follow-up period. Therefore, the  
20 outcome of the pilot will determine whether we need to consider alternative  
21 designs, such as 'crossover', randomised withdrawal' and 'dose response'  
22 designs, for the future RCT assessing efficacy of gabapentin for CPP.

23  
24 The criteria for inclusion and exclusion of study subjects into our pilot study are  
25 broad in attempt to reflect the real clinical scenario for prescribing gabapentin.

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3 1 The criteria do not take into account pain intensity, do not exclude women with  
4  
5 2 non-reproductive comorbidities (e.g. irritable bowel syndrome, interstitial  
6  
7 3 cystitis) that could explain their symptoms, and allow participants the use of  
8  
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10 4 concomitant medications. We are aware that these characteristics may increase  
11  
12 5 variability in patient responsiveness to treatment and carry the risk of failing to  
13  
14 6 demonstrate treatment effect. We will therefore capture this information in our  
15  
16 7 pilot study in the participants' questionnaires and treatment diaries to inform  
17  
18 8 interpretation of our results and the planning of the future RCT.  
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23 10 Like many of the medications used for chronic pain, gabapentin requires titration  
24  
25 11 to achieve an efficacious dose so that the rate and severity of adverse effects are  
26  
27 12 minimised. The duration of this titration period may be as many as 8-10 weeks.  
28  
29 13 The 6-month follow-up in our pilot study allows for a 12-week maintenance  
30  
31 14 phase that has become standard for confirmatory trials. It could be argued that a  
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33 15 longer trial would be better to assess the long-term effects of gabapentin. On the  
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35 16 other hand, we are aware that extended duration could be problematic because  
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37 17 of the number of drop-outs from the placebo arm due to inadequate pain relief.  
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39 18 We believe that focus group assessment of the acceptability of the drug  
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41 19 treatment and titrating regime in our pilot will therefore be essential in  
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43 20 designing the future RCT.  
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50 22 The comparison of an investigational treatment with placebo is considered the  
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52 23 gold standard for assessing efficacy and safety when a delay in the onset of  
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54 24 treatment does not cause any lasting adverse effects and assuming that subjects  
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56 25 fully understand their right to withdraw from the trial at any time for any reason.  
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1 [12,13] However, gabapentin is sedating and it can be argued that this increases  
2 the likelihood that both subjects and investigators can successfully guess to  
3 which group a subject has been allocated. We are therefore going to ask the  
4 subjects and investigators at the conclusion of the trial to guess the subjects'  
5 treatment group and the primary reason for the guess to determine whether  
6 significant 'unblinding' was present within the trial. This will determine whether  
7 we need to use an 'active placebo' mimicking the side effects of gabapentin in the  
8 future RCT.

9  
10 Our data collection tools were chosen with advice from a clinical psychologist  
11 with a specialist interest in chronic pain and a general practitioner with a  
12 research interest in medically unexplained symptoms. The selection of these  
13 tools was also again based on the IMMPACT recommendations [11] i.e. the need  
14 to assess the core domains of pain, physical/emotional functioning (including  
15 sleeping difficulties), improvement/satisfaction with treatment, symptoms and  
16 adverse events and participant disposition. We plan to use a wide range of data  
17 collection tools but it is our intention to use fewer in our future RCT depending  
18 on their effectiveness in the pilot study (defined by lack of missing data, ability to  
19 detect effect and independence) and participant feedback on acceptability.

20  
21 We also aim to determine whether gabapentin is expected to be cost effective  
22 given the current level of evidence and uncertainty through an iterative  
23 approach to economic evaluation of health technologies. [14,15] Important gaps  
24 and uncertainty surrounding existing data and the expected cost effectiveness  
25 will be explored through synthesis, modelling and value of information analysis

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2  
3 1 prior to a definitive RCT. We will determine whether further evidence is needed  
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5 2 to reduce the uncertainty surrounding cost effectiveness, and if so, identify the  
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7 3 focus of further research in terms of study design and data collection; this may  
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10 4 have implications on determining an appropriate sample size (e.g. powered to  
11  
12 5 detect difference in clinical effect or cost effectiveness).  
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17 7 Finally, although the primary outcome in our pilot study is to determine  
18  
19 8 recruitment and retention rates, we will also measure change in visual analogue  
20  
21 9 scale (VAS) over 6 months. This combination of information will allow us to  
22  
23 10 determine the effect size and standard deviation (SD) and plan the sample size  
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25 11 for the definitive RCT. Analyses of similar studies using gabapentin for chronic  
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27 12 pain with VAS score as primary outcome indicate that the mean absolute  
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29 13 difference in the VAS score comparing gabapentin against placebo ranges  
30  
31 14 between 0.8 and 1.8 with an SD of ~2.5 after 1-2 months' treatment. [6] Thus,  
32  
33 15 our definitive RCT is likely to be powered to find a difference of >1.2 on the VAS  
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35 16 scale (a clinically important symptom alleviation is defined as a reduction in VAS  
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37 17 of >1.2 [16] between the gabapentin and placebo arms of the study.  
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3 **AUTHORS' CONTRIBUTIONS**  
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8 3 AWH: research, contribution of original material, editing and approval of final  
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10 4 manuscript; HODC, AD, DF, JW, SJ: contribution of original material, editing and  
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12 5 approval of final manuscript; OW, MP, SL, SB: research, contribution of original  
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14 6 material, editing and approval of final manuscript.  
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3 **FUNDING**  
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6

7 3 This work is supported by a grant from the Chief Scientist's Office Scotland  
8  
9  
10 4 (CZH/4/688). AWH is funded by an MRC Clinician Scientist Fellowship  
11  
12 5 (G0802808). The funders and study sponsor will have no role in the study  
13  
14 6 design; collection, management, analysis, and interpretation of data; writing of  
15  
16 7 the report; and the decision to submit the report for publication.  
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3 **1 COMPETING INTERESTS**  
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7  
8 3 AWH, HODC, SJ, JW, SL, OW, MP and SB are all co-investigators on the grant from  
9  
10 4 the Chief Scientist's Office Scotland (CZH/4/688) that has been secured to  
11  
12 5 support this study. AWH is funded by an MRC Clinician Scientist Fellowship  
13  
14 6 (G0802808). HODC holds an MRC Centre Grant (G1002033) and a project grant  
15  
16 7 from Bayer Schering Pharma AG. AWH and HODC hold the University of  
17  
18 8 Edinburgh Patent "Identification of Ectopic Pregnancies" # 0712801.0.  
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1 **FIGURE LEGEND**

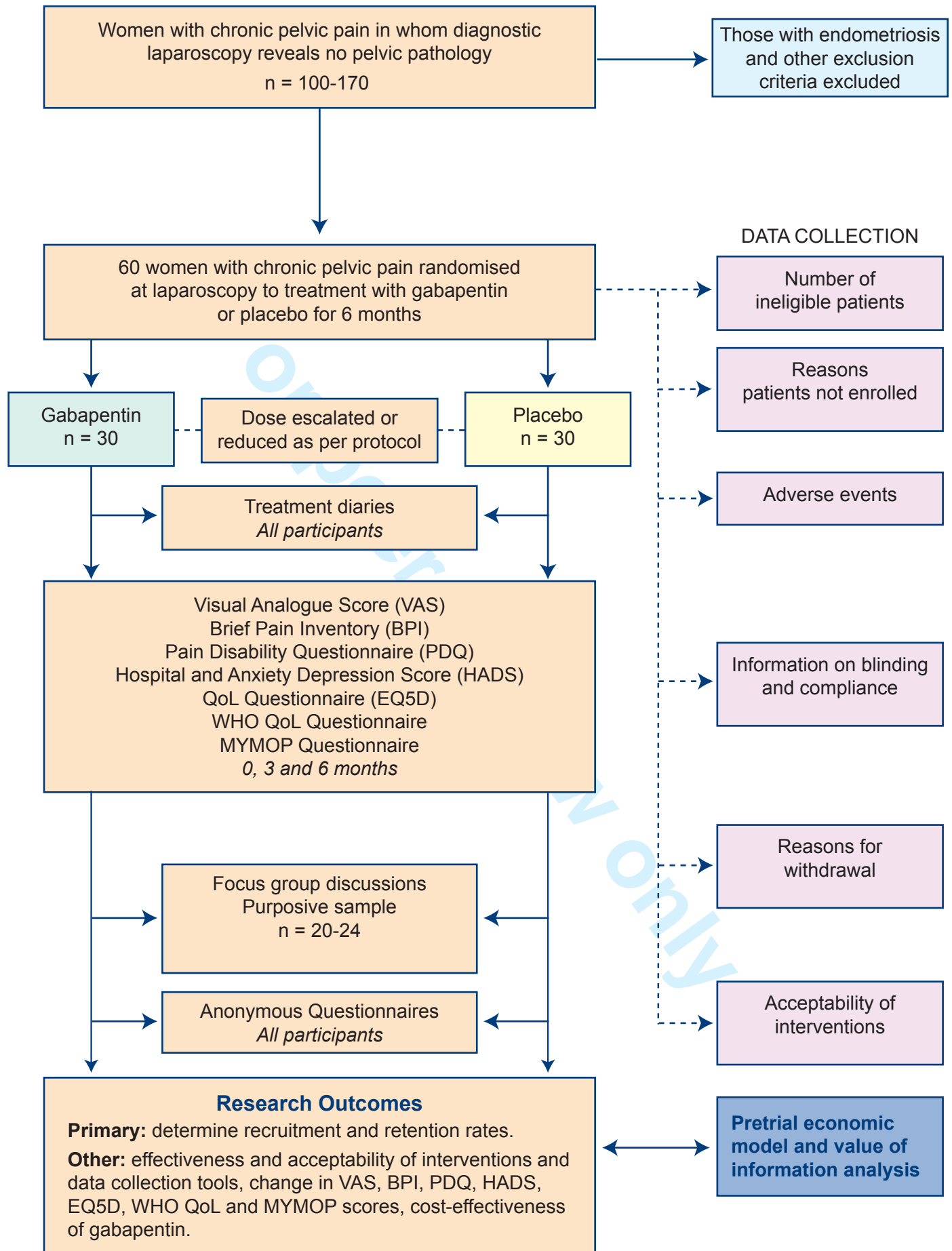
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3 **Figure 1.** Flow of participants through the study.

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**STUDY PROTOCOL**

**TITLE:** *GaPP* - A pilot randomised controlled trial of the efficacy of action of gabapentin for the management of chronic pelvic pain in women: [study protocol](#).

**AUTHORS:** AW Horne<sup>1</sup>, HOD Critchley<sup>1</sup>, A Doust<sup>1</sup>, D Fehr<sup>2</sup>, J Wilson<sup>3</sup>, O Wu<sup>4</sup>, S Jack<sup>5</sup>, M Porter<sup>6</sup>, S Lewis<sup>7</sup>, S Bhattacharya<sup>6</sup>

**AFFILIATIONS:** <sup>1</sup>MRC Centre for Reproductive Health, University of Edinburgh, UK; <sup>2</sup>Universitäres Interdisziplinäres Kinderwunschzentrum Düsseldorf, Germany; <sup>3</sup>Department of Anaesthesia, Royal Infirmary of Edinburgh, UK; <sup>4</sup>Health Economics and Health Technology Assessment, Institute of Health and Wellbeing, University of Glasgow, UK; <sup>5</sup>Department of Gynaecology, Aberdeen Royal Infirmary, UK; <sup>6</sup>Division of Applied Health Sciences, University of Aberdeen, UK; <sup>7</sup>Centre for Population Health Sciences, University of Edinburgh, UK

**CORRESPONDING AUTHOR:**

Dr Andrew Horne  
MRC Centre for Reproductive Health  
Queen's Medical Research Institute  
47 Little France Crescent  
Edinburgh EH16 4TJ  
Tel: +44 131 242 6609  
Fax +44 131 242 6441  
Email: [andrew.horne@ed.ac.uk](mailto:andrew.horne@ed.ac.uk)

**KEY WORDS:**

Pelvic pain, gabapentin.

**WORD COUNT:**

[32773,555](#)

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6 1 **ABSTRACT**  
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10 3 **Introduction:** Chronic pelvic pain (CPP) affects >1 million UK women. Annual  
11 4 healthcare costs are estimated at >£150 million. Proven interventions for CPP  
12 5 are limited and treatment is often unsatisfactory. Gabapentin is increasingly  
13 6 prescribed due to reports of effectiveness in other chronic pain conditions, but  
14 7 there are insufficient data supporting value in CPP specifically. The mechanism  
15 8 by which gabapentin exerts its analgesic action is unknown. Given the prevalence  
16 9 and costs of CPP, we believe a large multi-centre placebo-controlled double-blind  
17 10 randomised-controlled trial (RCT) to evaluate the efficacy of gabapentin in  
18 11 management of CPP is required. The focus of this study is a pilot to inform  
19 12 planning of a future RCT.

20 13 **Methods and analysis:** We plan to perform a two-arm parallel randomised-  
21 14 controlled pilot trial. We aim to recruit 60 women with CPP in NHS Lothian and  
22 15 NHS Grampian (UK) and randomise them to gabapentin or placebo. Response to  
23 16 treatment will be monitored by questionnaire compared at 0, 3 and 6 months.  
24 17 Our primary objective is to assess recruitment and retention rates. Our  
25 18 secondary objectives are to determine the effectiveness and acceptability to  
26 19 participants of the proposed methods of recruitment, randomisation, drug  
27 20 treatments, and assessment tools; and to perform a pre-trial cost-effectiveness  
28 21 assessment of treatment with gabapentin.

29 22 **Ethics and dissemination:** Ethical approval has been obtained from the  
30 23 Scotland A Research Ethics Committee (LREC 12/SS/0005). Data will be  
31 24 presented at international conferences and published in peer-reviewed journals.

32 25 **Trial registration number:** ISRCTN70960777.  
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## 1 INTRODUCTION

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Chronic pelvic pain (CPP) affects over 1 million women in the UK. [1,2] It is the reason for 20% of gynaecological consultations and causes a 45% reduction in work productivity. [3] The annual cost for caring for UK women with CPP has been estimated at £154 million. The cause of the painful symptoms experienced by women with CPP is poorly understood. Pain is often associated with specific pathological processes, such as endometriosis, but up to 55% of women with CPP appear to have no obvious underlying pathology. [2] The management of CPP is difficult [4] because in the absence of underlying pathology, no established gynaecological treatments are available.

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Gabapentin (a GABA analogue) is being increasingly prescribed in general practice for CPP. It is also recommended by some practitioners as a treatment of choice for CPP in a multi-disciplinary setting, despite no clinical evidence on which to base this recommendation. To our knowledge, only one study has evaluated the use of gabapentin for CPP. This small study (56 patients) compared gabapentin against amitriptyline for treatment of CPP and showed that gabapentin had greater efficacy (80% compared to 70% improvement in pain scores at 12 months). [5] Unfortunately, this study had no placebo arm and the significance of the effect on quality of life provided by gabapentin in the management of CPP was not evaluated. Nevertheless, the efficacy of gabapentin has been documented for other chronic pain conditions: painful diabetic neuropathy, postherpetic neuralgia, mixed neuropathic pain conditions, spinal-cord injury and phantom limb pain. [6] The number needed to treat for



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6 1 improvement in all trials with evaluable data is 4.3 (95% CI 3.5 to 5.7). In some  
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8 2 of these trials, gabapentin also improved sleep, mood and other elements of  
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10 3 quality of life. The mechanism by which gabapentin exerts its analgesic action is  
11  
12 4 unknown.

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16 6 Ideally, a definitive evaluation of the efficacy of gabapentin in the management of  
17  
18 7 CPP with no obvious underlying pathology requires a large multicentre  
19  
20 8 randomised controlled trial (RCT). This protocol outlines a pilot study to assess  
21  
22 9 the processes that are vital to the delivery of such a trial.

## 10 11 **Objectives**

### 12 13 Primary objective

14 The primary objective is to determine whether it is possible to achieve  
15 acceptable recruitment and retention rates in two UK centres (NHS Lothian and  
16 NHS Grampian) within defined inclusion/exclusion criteria.

### 17 18 Secondary objectives

- 19 1. To determine the effectiveness and acceptability to patients of the proposed  
20 methods of recruitment, randomisation, drug treatments and assessment tools.  
21 2. To determine whether gabapentin is likely to be cost effective given the  
22 current level of uncertainty, and to ascertain what further evidence is needed for  
23 the evaluation of gabapentin.

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6 **1 Endpoints**  
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10 **3 Primary endpoints**  
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12 4 1. The proportion of eligible patients randomised into the study.  
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14 5 2. The proportion of randomised patients who take all their medication and fully  
15  
16 6 complete questionnaires at final follow up.  
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20 **8 Secondary endpoints**  
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22 9 Data on effectiveness and acceptability of proposed methods of recruitment,  
23  
24 10 randomisation, drug treatments and assessment tools will be used to refine the  
25  
26 11 design of the definitive RCT. The potential cost effectiveness of gabapentin in the  
27  
28 12 management of chronic pelvic pain will also be determined.  
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## 1 METHODS AND ANALYSIS

### 3 Study design

4 We aim to perform a two-arm parallel randomised-controlled pilot trial. This will  
5 be a two-centre study with recruiting in NHS Lothian (Edinburgh) and NHS  
6 Grampian (Aberdeen). We will recruit 60 patients over approximately 9 months.  
7 After randomisation the participants will receive treatment for 6 months.  
8 Participants and the health care team will be unblinded at the end of their  
9 treatment.

### 11 Subjects

12 A total of 60 women aged 18-50 with a history of pelvic pain (cyclical or non-  
13 cyclical) and/or dyspareunia with no obvious pelvic pathology detected at  
14 laparoscopy will be invited to participate in the trial.

### 16 Study settings

17 We will recruit patients from gynaecology out patient clinics, gynaecology wards  
18 and day surgery units within NHS Lothian and NHS Grampian.

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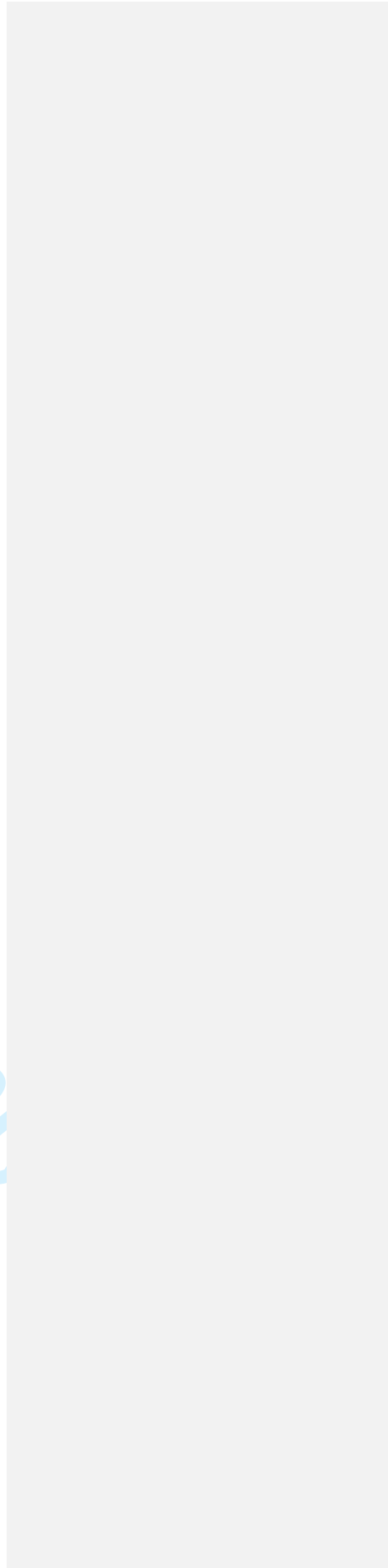
### 20 Sample size

21 We have used a confidence interval (CI) approach [7] to estimate the sample size  
22 to establish feasibility based on a loss to follow-up of <20%. A 95% CI for 20% of  
23 60 patients (12/60) is 11% to 32%. We estimate that we will recruit ~3-4  
24 patients per month from each centre and aim to recruit 60 patients over a 9-

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1 month recruitment period. Each centre performs 6-7 laparoscopies per month  
2 that fit the inclusion criteria.  
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For peer review only



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6 Inclusion criteria  
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- 8 • Women aged between 18-50  
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10 • Pelvic pain of > 6 months  
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12 • Pain located within the true pelvis or between and below anterior iliac  
13 crests, associated functional disability  
14  
15 • No obvious pelvic pathology at laparoscopy (<6 months and >2 weeks  
16 ago)  
17  
18 • Using effective contraception  
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24 Exclusion criteria  
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- 26 • Known pelvic pathology e.g. endometriosis, cyst  
27  
28 • Taking gabapentin or pregabalin  
29  
30 • Due to undergo surgery in the next 6 months  
31  
32 • History of significant renal impairment  
33  
34 • Allergic to gabapentin  
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36 • Breast feeding  
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38 • Pregnancy or planning pregnancy in the next 6 months  
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43 Participant enrolment  
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45 All gynaecology consultants within NHS Lothian and NHS Grampian will be sent a  
46 letter informing them of the study and requesting permission to approach their  
47 patients. Two research nurses (one in NHS Lothian and one in NHS Grampian)  
48 will be employed for the duration of the study to approach eligible women,  
49 provide them with patient information sheets and offer them the opportunity to  
50 discuss the trial, and obtain informed consent. Consent will only be taken once  
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6 1 the patient has had ample time to read the patient information sheet and had her  
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8 2 questions answered.

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14 5 Intervention and randomisation

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16 6 Eligible women will be randomised to either gabapentin or placebo using a web-  
17  
18 7 based system. Women will be stratified by centre (NHS Lothian and NHS  
19  
20 8 Grampian). We will use randomised blocks of varying sizes.

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24 10 Intervention Dose regime

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26 11 ~~Eligible women will be randomised to either gabapentin or placebo using a web-~~  
27  
28 12 ~~based system. Women will be stratified by centre (NHS Lothian and NHS~~  
29  
30 13 ~~Grampian). We will use randomised blocks of varying sizes.~~ Participants will  
31  
32 14 start on 300mg gabapentin daily and will increase in 300 mg increments each  
33  
34 15 week until they report a 50% pain reduction, or side effects (eg dizziness,  
35  
36 16 somnolence, mood changes, appetite and poor concentration), up to a maximum  
37  
38 17 dose of 2700 mgs. Patients will be advised regarding their dosing regime weekly  
39  
40 18 by a member of the research team who will phone until optimum dose is  
41  
42 19 reached. It will be recommended that the drug should be taken in three equally  
43  
44 20 divided doses daily. Participants will be advised to remain on the maximum  
45  
46 21 tolerated dose for up to 6 months. The same protocol will be used for the  
47  
48 22 placebo. When the participant stops treatment then the dose will be tapered  
49  
50 23 down over 7 - 10 days at the clinician's discretion. Patients will be allowed to use  
51  
52 24 other medication (including analgesics, self-medication and alternative  
53  
54 25 treatments e.g. acupuncture) throughout the study period.

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## 2 **Data collection**

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### 4 Data storage

5 A log with the patients' name and date of birth will be kept along with their  
6 unique study number in a separate file. All of the data generated from the study  
7 will be stored in an anonymised form in a bespoke database which will also be  
8 password protected . Only anonymised information will be stored on this and  
9 participants will only be identifiable by their study number. All paperwork will  
10 be kept in a locked filing cabinet in a locked office. All data will be stored on  
11 university server on a password-protected computer with limited access to the  
12 research team, in accordance with NHS and University of Edinburgh guidelines  
13 and in accordance with the Data Protection Act.

14

### 15 Screening

16 A member of the research team will carry out a screening visit to assess  
17 eligibility. All data will be recorded on a case record form (CRF) and transferred  
18 to a secure database.

19

### 20 Participant log

21 The clinical research team will keep an electronic log of women who fulfil the  
22 eligibility criteria, women who are invited to participate in the study, women  
23 recruited and women who leave the trial early. Reasons for non-recruitment (eg  
24 non-eligibility, refusal to participate, administrative error) will also be recorded.  
25 We will attempt to collect reasons for non-participation from women who

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6 1 decline to take part after previously providing contact details. During the course  
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8 2 of the study, we will document reasons for withdrawal from the study and loss to  
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10 3 follow-up. Participants will be reviewed by the clinical research team at 6 weeks,  
11  
12 4 3 months and 6 months.  
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#### 16 Treatment diaries

17 All medications and healthcare resource use taken after screening and any  
18  
19 8 medication other than the trial treatment taken during the study will be  
20  
21 9 recorded in a treatment diary. This includes prescription and non-prescription  
22  
23 10 treatment such as contraceptives, vitamins, topical preparations, herbal  
24  
25 11 preparations and non-pharmacological therapies.  
26  
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#### 30 Questionnaires

31  
32 14 A questionnaire will be given to all participants at randomisation (0 months) and  
33  
34 15 at 3 months. This will include the following validated tools:

- 35  
36 16 1. Visual analogue scale (VAS)
- 37  
38 17 2. Brief Pain Inventory (BPI)
- 39  
40 18 3. Pain Disability Questionnaire (PDQ)
- 41  
42 19 4. Hospital Anxiety and Depression Score (HADS)
- 43  
44 20 5. EQ5D QoL
- 45  
46 21 6. WHO QoL
- 47  
48 22 7. MYMOP patient-generated outcome questionnaire
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50 23 The questionnaire at 0 months will include questions to capture the baseline  
51  
52 24 demographic and clinical characteristics of the participants.  
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1 A further questionnaire will also be given to all participants at 6 months which  
2 will include the above and additional questions on whether they believed they  
3 were receiving gabapentin or placebo, and also questions on acceptability of the  
4 allocated medication/treatment regimes (and compliance) and on the  
5 acceptability of the above data collection methods. Lastly, we will ask the  
6 participants to complete a brief anonymous questionnaire once they have  
7 submitted their treatment diaries to assess level of adherence to diary keeping.

#### 8 9 Focus groups

10 A purposive sample (based on age, social class and severity of symptoms) of 10  
11 Edinburgh women (including some undergoing fMRI) and 10 Aberdeen women  
12 will be invited to participate in focus group discussions of the trial experience six  
13 months into the trial. [8] Women who do not wish to participate in a focus group  
14 will be offered individual interviews using the same interview schedule. This will  
15 enable important issues arising in the focus groups to be explored in greater  
16 depth. Up to 20 interviews will be performed. Group/individual interviews will  
17 be audio-recorded, transcribed verbatim and analysed thematically to identify  
18 the issues of importance to participants not covered in the questionnaires, their  
19 feelings about trial participation and experiences with prescribed medication.

#### 20 21 Healthcare resource utilisation measures

22 Information will be derived from treatment diaries and from research nurse  
23 reviews of the participants' hospital and general practitioners' records.

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6 1 Adverse events  
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8 2 Participants will collect information about adverse events in their treatment  
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10 3 diaries. However, they will be instructed to contact the clinical research team at  
11  
12 4 any time after consenting to join the trial if they have an event that requires  
13  
14 5 hospitalisation, or an event that results in persistent or significant disability or  
15  
16 6 incapacity. Gabapentin is generally well tolerated in the management of other  
17  
18 7 chronic pain conditions and serious adverse events (SAEs) are not anticipated.  
19  
20 8 Any SAEs that occur after joining the trial will be reported in detail in the  
21  
22 9 participant's medical notes, followed up until resolution of the event, and  
23  
24 10 reported to the ACCORD Research Governance ([www.accord.ed.ac.uk](http://www.accord.ed.ac.uk)) and QA  
25  
26 11 Office based at the University of Edinburgh immediately or within 24 hours.  
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32 13 Termination of study  
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34 14 Participants (and their gynaecologists) will be unblinded at the end of the study  
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36 15 period (6 months). There will be no central unblinding facility but the site  
37  
38 16 pharmacies will be provided with the key which links drug pack number to  
39  
40 17 treatment. Thus, it will be possible for unblinding (emergency or otherwise) to  
41  
42 18 be carried out by a pharmacist if requested. All participants will be given the  
43  
44 19 right to be unblinded, discontinue the drug or completely withdraw from the  
45  
46 20 study at any time for any reason. Reasons for unblinding, before the termination  
47  
48 21 of the study, will be collected. Those participants who feel that they have  
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50 22 benefited from treatment with gabapentin, during the study period, will be  
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52 23 advised to discuss continuation of treatment with their gynaecologist.  
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6 **1 Proposed analyses**  
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10 **3 Determine recruitment and retention rates**  
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12 4 Using the information collected from the participant log, we will determine the  
13  
14 5 number of patients recruited from the pool of eligible women and a >50%  
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16 6 recruitment will be deemed acceptable. While a retention rate of 100% would be  
17  
18 7 ideal, we will consider a rate of 90% satisfactory. We will provide an estimate of  
19  
20 8 the proportion and its 95% confidence interval. If retention rates are low, we will  
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22 9 use the information collected from the focus group discussions to ascertain why  
23  
24 10 and improve compliance in the future trial. In addition, we will determine the  
25  
26 11 nature and number of unanswered questions in each questionnaire and identify  
27  
28 12 reasons for non-response through the focus groups and participant interviews in  
29  
30 13 order to optimise data collection in the future trial.  
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34 **15 Effectiveness and acceptability of proposed methods of recruitment,**  
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36 **16 randomisation, drug treatments and assessment tools**  
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38 17 These areas will be explored in the focus group discussions and assessed  
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40 18 quantitatively using additional questions included in participant questionnaires  
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42 19 administered at 6 months. Due to the conflicting literature about the benefits of  
43  
44 20 methods such as prescription monitoring, pill counting and devices for  
45  
46 21 monitoring the self-administration of medicines, [9] data on blinding and  
47  
48 22 compliance to treatment will be derived from questionnaires at 6 months. We  
49  
50 23 aim to determine if treatment is acceptable in terms of self-reported compliance  
51  
52 24 (from treatment diaries). Although this is a pilot study and the sample size is  
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54 25 small, we will assess the effect of any non-compliance on the LICKERT score by  
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1 performing protocol and intention to treat analyses. This information along with  
2 health professionals' and clinical research nurses' views (as assessed by  
3 questionnaire) will be used to inform the design of the future RCT. In addition,  
4 the difference in VAS scores between participants on gabapentin and placebo at  
5 0 and 6 months will be assessed using analysis of covariance adjusting for  
6 baseline VAS score.

#### 8 Pre-trial economic model and value of information analysis

9 In addition to data relating to the clinical and quality of life parameters, data on  
10 healthcare resource use will also be collected. A decision model will be  
11 developed, from the perspective of the NHS, to estimate the costs and health  
12 outcomes in terms of quality of life and quality adjusted life years associated  
13 with gabapentin and placebo based on the data from this pilot study and the  
14 literature. A probabilistic decision model will be constructed to simulate the  
15 clinical pathways associated with gabapentin and placebo, according to the  
16 guidance set out by NICE. [10] The basic model structure will consist of two  
17 arms, replicating the clinical consequences of patients receiving gabapentin and  
18 placebo. The main data source relating to the key parameters of the model will  
19 be provided by the pilot study. The mean costs and quality adjusted life years  
20 associated with both arms will be calculated for the modelling period (duration  
21 of the trial). Cost utility analysis will be carried out and incremental cost per  
22 quality-adjusted life years gained will be calculated. Particular consideration will  
23 be given to the potential for cost effectiveness to vary by particular patient  
24 characteristics or risk groups where suggested by the literature. Probabilistic  
25 sensitivity analysis will be used to characterise uncertainty in parameters of the

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6 1 model, and presented using cost-effectiveness acceptability curves. Standard  
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8 2 univariate sensitivity analysis will be carried out to explore areas of structural  
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10 3 uncertainty in the analysis. Finally, a value of information analysis on the  
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12 4 expected value of perfect information will also be carried out to quantify  
13  
14 5 potential value of further research based on the difference between expected net  
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16 6 benefit with perfect information and existing information.  
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## 8 **ETHICS AND DISSEMINATION**

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10 Ethical approval has been obtained from the Scotland A Research Ethics  
11  
12 Committee (LREC 12/SS/0005). Data will be presented at international  
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14 conferences and published in peer-reviewed journals. We will make the  
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16 information obtained from the study available to the public through national  
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18 bodies and charities.  
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6 **1 DISCUSSION**  
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10 3 We believe that a definitive evaluation of the efficacy of gabapentin in the  
11 4 management of CPP requires a multicentre randomised placebo-controlled trial  
12 5 (RCT). Recognising that there may be potential difficulties in mounting a large  
13 6 RCT for a chronic pain condition using a medication with known sedating side  
14 7 effects and that requires a titrated dosing regime, we have designed this pilot  
15 8 study to assess practical feasibility following the IMMPACT (Initiative on  
16 9 Methods, Measurement, and Pain Assessment in Clinical Trials)  
17 10 recommendations for the design of chronic pain clinical trials. [11] We are aware  
18 11 that our pilot study has a number of positive and negative aspects and these are  
19 12 discussed below.  
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32 14 For our pilot study, we are using the most common design in confirmatory trials  
33 15 of chronic pain treatments: a 'parallel groups' design. [11] We will randomise  
34 16 participants to either gabapentin or placebo, and then evaluate recruitment and  
35 17 retention rates as our primary outcome. We appreciate that this design may be  
36 18 limited by the fact that the severity of the participants' pain may preclude them  
37 19 from remaining on the placebo for the 6-month follow-up period. Therefore, the  
38 20 outcome of the pilot will determine whether we need to consider alternative  
39 21 designs, such as 'crossover', randomised withdrawal' and 'dose response'  
40 22 designs, for the future RCT assessing efficacy of gabapentin for CPP.  
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52 24 The criteria for inclusion and exclusion of study subjects into our pilot study are  
53 25 broad in attempt to reflect the real clinical scenario for prescribing gabapentin.  
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6 1 The criteria do not take into account pain intensity, do not exclude women with  
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8 2 non-reproductive comorbidities (e.g. irritable bowel syndrome, interstitial  
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10 3 cystitis) that could explain their symptoms, and allow participants the use of  
11  
12 4 concomitant medications. We are aware that these characteristics may increase  
13  
14 5 variability in patient responsiveness to treatment and carry the risk of failing to  
15  
16 6 demonstrate treatment effect. We will therefore capture this information in our  
17  
18 7 pilot study in the participants' questionnaires and treatment diaries to inform  
19  
20 8 interpretation of our results and the planning of the future RCT.  
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23  
24 10 Like many of the medications used for chronic pain, gabapentin requires titration  
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26 11 to achieve an efficacious dose so that the rate and severity of adverse effects are  
27  
28 12 minimised. The duration of this titration period may be as many as 8-10 weeks.  
29  
30 13 The 6-month follow-up in our pilot study allows for a 12-week maintenance  
31  
32 14 phase that has become standard for confirmatory trials. It could be argued that a  
33  
34 15 longer trial would be better to assess the long-term effects of gabapentin. On the  
35  
36 16 other hand, we are aware that extended duration could be problematic because  
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38 17 of the number of drop-outs from the placebo arm due to inadequate pain relief.  
39  
40 18 We believe that focus group assessment of the acceptability of the drug  
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42 19 treatment and titrating regime in our pilot will therefore be essential in  
43  
44 20 designing the future RCT.  
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48 22 The comparison of an investigational treatment with placebo is considered the  
49  
50 23 gold standard for assessing efficacy and safety when a delay in the onset of  
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52 24 treatment does not cause any lasting adverse effects and assuming that subjects  
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54 25 fully understand their right to withdraw from the trial at any time for any reason.  
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1 [12,13] However, gabapentin is sedating and it can be argued that this increases  
2 the likelihood that both subjects and investigators can successfully guess to  
3 which group a subject has been allocated. We are therefore going to ask the  
4 subjects and investigators at the conclusion of the trial to guess the subjects'  
5 treatment group and the primary reason for the guess to determine whether  
6 significant 'unblinding' was present within the trial. This will determine whether  
7 we need to use an 'active placebo' mimicking the side effects of gabapentin in the  
8 future RCT.

9  
10 Our data collection tools were chosen with advice from a clinical psychologist  
11 with a specialist interest in chronic pain and a general practitioner with a  
12 research interest in medically unexplained symptoms. The selection of these  
13 tools was also again based on the IMMPACT recommendations [11] i.e. the need  
14 to assess the core domains of pain, physical/emotional functioning (including  
15 sleeping difficulties), improvement/satisfaction with treatment, symptoms and  
16 adverse events and participant disposition. We plan to use a wide range of data  
17 collection tools but it is our intention to use fewer in our future RCT depending  
18 on their effectiveness in the pilot study (defined by lack of missing data, ability to  
19 detect effect and independence) and participant feedback on acceptability.

20  
21 We also aim to determine whether gabapentin is expected to be cost effective  
22 given the current level of evidence and uncertainty through an iterative  
23 approach to economic evaluation of health technologies. [14,15] Important gaps  
24 and uncertainty surrounding existing data and the expected cost effectiveness  
25 will be explored through synthesis, modelling and value of information analysis



1 prior to a definitive RCT. We will determine whether further evidence is needed  
2 to reduce the uncertainty surrounding cost effectiveness, and if so, identify the  
3 focus of further research in terms of study design and data collection; this may  
4 have implications on determining an appropriate sample size (e.g. powered to  
5 detect difference in clinical effect or cost effectiveness).

6  
7 Finally, although the primary outcome in our pilot study is to determine  
8 recruitment and retention rates, we will also measure change in visual analogue  
9 scale (VAS) over 6 months. This combination of information will allow us to  
10 determine the effect size and standard deviation (SD) and plan the sample size  
11 for the definitive RCT. Analyses of similar studies using gabapentin for chronic  
12 pain with VAS score as primary outcome indicate that the mean absolute  
13 difference in the VAS score comparing gabapentin against placebo ranges  
14 between 0.8 and 1.8 with an SD of ~2.5 after 1-2 months' treatment. [6] Thus,  
15 our definitive RCT is likely to be powered to find a difference of >1.2 on the VAS  
16 scale (a clinically important symptom alleviation is defined as a reduction in VAS  
17 of >1.2 [16] between the gabapentin and placebo arms of the study.

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6 **1 AUTHORS' CONTRIBUTIONS**  
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10 3 AWH: research, contribution of original material, editing and approval of final  
11 manuscript; ~~HODC, -: editing and approval of final manuscript; AD, DF, JW, SJ:~~  
12 4 ~~contribution of original material, editing and approval of final manuscript; DF:~~  
13 5 ~~editing and approval of final manuscript; JW: editing and approval of final~~  
14 6 ~~manuscript; OW, MP, SL, SB: research, contribution of original material, editing~~  
15 7 ~~and approval of final manuscript; SJ: editing and approval of final manuscript;~~  
16 8 ~~MP: research, contribution of original material, editing and approval of final~~  
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18 10 ~~of final manuscript; SB: research, contribution of original material, editing and~~  
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6 **FUNDING**  
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8 2

9  
10 3 This work is supported by a grant from the Chief Scientist's Office Scotland

11 4 (CZH/4/688). AWH is funded by an MRC Clinician Scientist Fellowship

12 5 (G0802808). The funders and study sponsor will have no role in the study

13 6 design; collection, management, analysis, and interpretation of data; writing of

14 7 the report; and the decision to submit the report for publication.  
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1 **COMPETING INTERESTS**

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3 None. AWH, HODC, SJ, JW, SL, OW, MP and SB are all co-investigators on the grant  
4 from the Chief Scientist's Office Scotland (CZH/4/688) that has been secured to  
5 support this study. AWH is funded by an MRC Clinician Scientist Fellowship  
6 (G0802808). HODC holds an MRC Centre Grant (G1002033) and a project grant  
7 from Bayer Schering Pharma AG. AWH and HODC hold the University of  
8 Edinburgh Patent "Identification of Ectopic Pregnancies" # 0712801.0.

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6 **1 FIGURE LEGEND**  
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10 3 **Figure 1.** Flow of participants through the study.  
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For peer review only



1 **Scotland A Research Ethics**  
2 **Committee**

Secretariat  
2<sup>nd</sup> Floor Waverley Gate  
2-4 Waterloo Place  
Edinburgh  
EH1 3EG  
Telephone: 0131 465 5680  
Fax: 0131 465 5789  
[www.nres.nhs.uk](http://www.nres.nhs.uk)

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9 Dr Andrew Horne  
10 University of Edinburgh  
11 MRC Centre for Reproductive Health  
12 The Queen's medical Research Institute  
13 47 Little France Crescent  
14 Edinburgh  
15 EH16 4SA

Date: 31 January 2012  
Your Ref.:  
Our Ref.: 12/SS/0005  
Enquiries to: Walter Hunter  
Extension: 35680  
Direct Line: 0131 465 5680  
Email: [walter.hunter@nhslothian.scot.nhs.uk](mailto:walter.hunter@nhslothian.scot.nhs.uk)

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22 Dear Dr Horne

23  
24 **Study title: GaPP: A pilot randomised controlled trial of the efficacy and**  
25 **mechanism of action of gabapentin for the management of**  
26 **chronic pelvic pain in women**  
27

28  
29 **REC reference: 12/SS/0005**

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31 **EudraCT number: 2011-005494-22**  
32

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34  
35 The Scotland A Research Ethics Committee reviewed the above application at the meeting  
36 held on 26 January 2012. Thank you for being available to discuss the study.  
37

38 **Ethical opinion**

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41 The Committee noted this was a pilot for a larger study and that it was a new indication for  
42 a licensed drug. The Committee recognised the significant problems faced by women  
43 affected by chronic pelvic pain and the burden placed on health services. The aim of the  
44 study was to treat the condition in a more robust way. The study involved the participants  
45 having an MRI scan but the application had made a case for doing this. The study design  
46 was straightforward and involved the completion of weekly pain scores and a series of  
47 visits to the clinic. If the treatment was effective participants would be allowed to continue  
48 the treatment after the conclusion of the study. The participant information sheet was  
49 considered to be satisfactory.  
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52  
53 The members of the Committee present gave a favourable ethical opinion of the above  
54 research on the basis described in the application form, protocol and supporting  
55 documentation, subject to the conditions specified below.  
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## Ethical review of research sites

The favourable opinion applies to all NHS sites listed in the application, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see “Conditions of the favourable opinion” below).

### Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission (“R&D approval”) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

Where a NHS organisation’s role in the study is limited to identifying and referring potential participants to research sites (“participant identification centre”), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Clinical trial authorisation must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming clinical trial authorisation or giving grounds for non-acceptance, as soon as this is available.

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## Other conditions specified by the REC

1. The participation information sheet should:
  1. mention how much blood would be taken i.e. teaspoonful etc
  2. provide more information about the dosing increase and the amount
  3. information on the side effects should be in more depth
  4. the placebo should not be referred to 'sugar' pill but to something along the lines 'dummy or inactive' pill
2. Correct the typographical errors in the HAD and EQ5D questionnaires.

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Confirmation should also be provided to host organisations together with relevant documentation

## Approved documents

The documents reviewed and approved at the meeting were:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Covering Letter		13 January 2012
REC application: IRAS Form	3.4	13 January 2012
Protocol	1	12 January 2012
Investigator CV		12 January 2012
Participant Information Sheet		12 January 2012
Participant Information Sheet: MRI	1	12 January 2012
Participant Consent Form: Lothian	1	12 January 2012
Participant Consent Form: Grampian	1	12 January 2012
Participant Consent Form: Focus Group	1	12 January 2012
GP/Consultant Letter: Lothian	1	12 January 2012
GP/Consultant Letter-Grampian	1	12 January 2012
Letter of invitation to participant: Grampian	1	12 January 2012
Letter of invitation-Lothian	1	12 January 2012
Letter of invitation: Focus Group-Lothian	1	12 January 2012



Letter of invitation: Focus Group-Grampian	1	12 January 2012
Treatment Diary	1	12 January 2012
Questionnaire: MYPOP2 Follow-up		
Questionnaire: Neuropathic Pain Questionnaire		
Questionnaire: PDQ		
Questionnaire: HADS		
Questionnaire: EQ-5D-5L		
Questionnaire: MYPOP 2		
Questionnaire: BPI		
Questionnaire: WHOQoL		

### Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

### Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

### After ethical review

#### Reporting requirements

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

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The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

### Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review.

**REC reference number: 12/SS/0005-Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely



**Dr Ian Zealley**

**Committee Chairman**

*cc: Ms Lynn Morrice, University of Edinburgh*

*Dr Karen Maitland, NHS Lothian*



## Scotland A REC

Attendance at Committee meeting on 26 January 2012

### Committee Members:

Name	Profession	Present	Notes
Professor Richard Anderson	Professor of Clinical Reproductive Science	Yes	
Dr Susan Gregory	Social Scientist (retired)	No	
Dr Bridget Harris	Clinical Nurse Researcher	Yes	
Mrs Fiona Mack	Clinical Pharmacist	Yes	
Dr Mary J Macleod	Clinical Pharmacologist/Consultant Physician	Yes	
Mrs Angela Macpherson	Retired	Yes	
Mrs Margaret McDonald	Retired Civil Servant	Yes	
Mrs Katherine McGuigan	Nurse	Yes	
Canon Matt McManus	Parish Priest	Yes	
Dr Craig Melville	Senior Lecturer in Learning Disabilities Psychiatry	Yes	
Mrs Wendy Nganasurian	Retired	Yes	
Dr Richard Quigley	General Practitioner	No	
Dr Colin Selby	Consultant Physician	Yes	
Dr Rachel Smith	Project Manager	No	
Mrs Mary Sweetland	Statistician	Yes	
Mrs Margaret Thomson	Retired	Yes	
Professor Nigel R Webster	Professor of Anaesthesia and Intensive Care	Yes	

Dr Ian Zealley	Consultant	Yes	
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**Also in attendance:**

<i>Name</i>	<i>Position (or reason for attending)</i>
Mr Walter Hunter	Committee Coordinator

**Written comments received from:**

<i>Name</i>	<i>Position</i>
Dr Richard Quigley	General Practitioner
Dr Rachel Smith	Project Manager

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