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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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

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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

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

Ideally, a definitive evaluation of the efficacy of gabapentin in the management of CPP with no obvious underlying pathology requires a large multicentre randomised controlled trial (RCT). This protocol outlines a pilot study to assess the processes that are vital to the delivery of such a trial.

Objectives

Primary objective

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

Secondary objectives

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

2. To determine whether gabapentin is likely to be cost effective given the current level of uncertainty, and to ascertain what further evidence is needed for the evaluation of gabapentin.

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

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

Data collection

Screening

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

Participant log

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

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

participants to complete a brief anonymous questionnaire once they have submitted their treatment diaries to assess level of adherence to diary keeping.

Focus groups

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

Healthcare resource utilisation measures

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

Adverse events

Participants will collect information about adverse events in their treatment diaries. However, they will be instructed to contact the clinical research team at any time after consenting to join the trial if they have an event that requires hospitalisation, or an event that results in persistent or significant disability or incapacity. Gabapentin is generally well tolerated in the management of other

chronic pain conditions and serious adverse events (SAEs) are not anticipated. Any SAEs that occur after joining the trial will be reported in detail in the participant's medical notes, followed up until resolution of the event, and reported to the ACCORD Research Governance (www.accord.ed.ac.uk) and QA Office based at the University of Edinburgh immediately or within 24 hours.

Termination of study

Participants (and their gynaecologists) will be unblinded at the end of the study period (6 months). There will be no central unblinding facility but the site pharmacies will be provided with the key which links drug pack number to treatment. Thus, it will be possible for unblinding (emergency or otherwise) to be carried out by a pharmacist if requested. All participants will be given the right to be unblinded, discontinue the drug or completely withdraw from the study at any time for any reason. Reasons for unblinding, before the termination of the study, will be collected. Those participants who feel that they have benefited from treatment with gabapentin, during the study period, will be advised to discuss continuation of treatment with their gynaecologist.

Proposed analyses

Determine recruitment and retention rates

Using the information collected from the participant log, we will determine the number of patients recruited from the pool of eligible women and a >50% recruitment will be deemed acceptable. While a retention rate of 100% would be ideal, we will consider a rate of 90% satisfactory. We will provide an estimate of

the proportion and its 95% confidence interval. If retention rates are low, we will use the information collected from the focus group discussions to ascertain why and improve compliance in the future trial. In addition, we will determine the nature and number of unanswered questions in each questionnaire and identify reasons for non-response through the focus groups and participant interviews in order to optimise data collection in the future trial.

Effectiveness and acceptability of proposed methods of recruitment, randomisation, drug treatments and assessment tools

These areas will be explored in the focus group discussions and assessed quantitatively using additional questions included in participant questionnaires administered at 6 months. Due to the conflicting literature about the benefits of methods such as prescription monitoring, pill counting and devices for monitoring the self-administration of medicines, [9] data on blinding and compliance to treatment will be derived from questionnaires at 6 months. We aim to determine if treatment is acceptable in terms of self-reported compliance (from treatment diaries). Although this is a pilot study and the sample size is small, we will assess the effect of any non-compliance on the LICKERT score by performing protocol and intention to treat analyses. This information along with health professionals' and clinical research nurses' views (as assessed by questionnaire) will be used to inform the design of the future RCT. In addition, the difference in VAS scores between participants on gabapentin and placebo at 0 and 6 months will be assessed using analysis of covariance adjusting for baseline VAS score.

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.

The criteria do not take into account pain intensity, do not exclude women with non-reproductive comorbidities (e.g. irritable bowel syndrome, interstitial cystitis) that could explain their symptoms, and allow participants the use of concomitant medications. We are aware that these characteristics may increase variability in patient responsiveness to treatment and carry the risk of failing to demonstrate treatment effect. We will therefore capture this information in our pilot study in the participants' questionnaires and treatment diaries to inform interpretation of our results and the planning of the future RCT.

Like many of the medications used for chronic pain, gabapentin requires titration to achieve an efficacious dose so that the rate and severity of adverse effects are minimised. The duration of this titration period may be as many as 8-10 weeks. The 6-month follow-up in our pilot study allows for a 12-week maintenance phase that has become standard for confirmatory trials. It could be argued that a longer trial would be better to assess the long-term effects of gabapentin. On the other hand, we are aware that extended duration could be problematic because of the number of drop-outs from the placebo arm due to inadequate pain relief. We believe that focus group assessment of the acceptability of the drug treatment and titrating regime in our pilot will therefore be essential in designing the future RCT.

The comparison of an investigational treatment with placebo is considered the gold standard for assessing efficacy and safety when a delay in the onset of treatment does not cause any lasting adverse effects and assuming that subjects fully understand their right to withdraw from the trial at any time for any reason.

[12,13] However, gabapentin is sedating and it can be argued that this increases the likelihood that both subjects and investigators can successfully guess to which group a subject has been allocated. We are therefore going to ask the subjects and investigators at the conclusion of the trial to guess the subjects' treatment group and the primary reason for the guess to determine whether significant 'unblinding' was present within the trial. This will determine whether we need to use an 'active placebo' mimicking the side effects of gabapentin in the future RCT.

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

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

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

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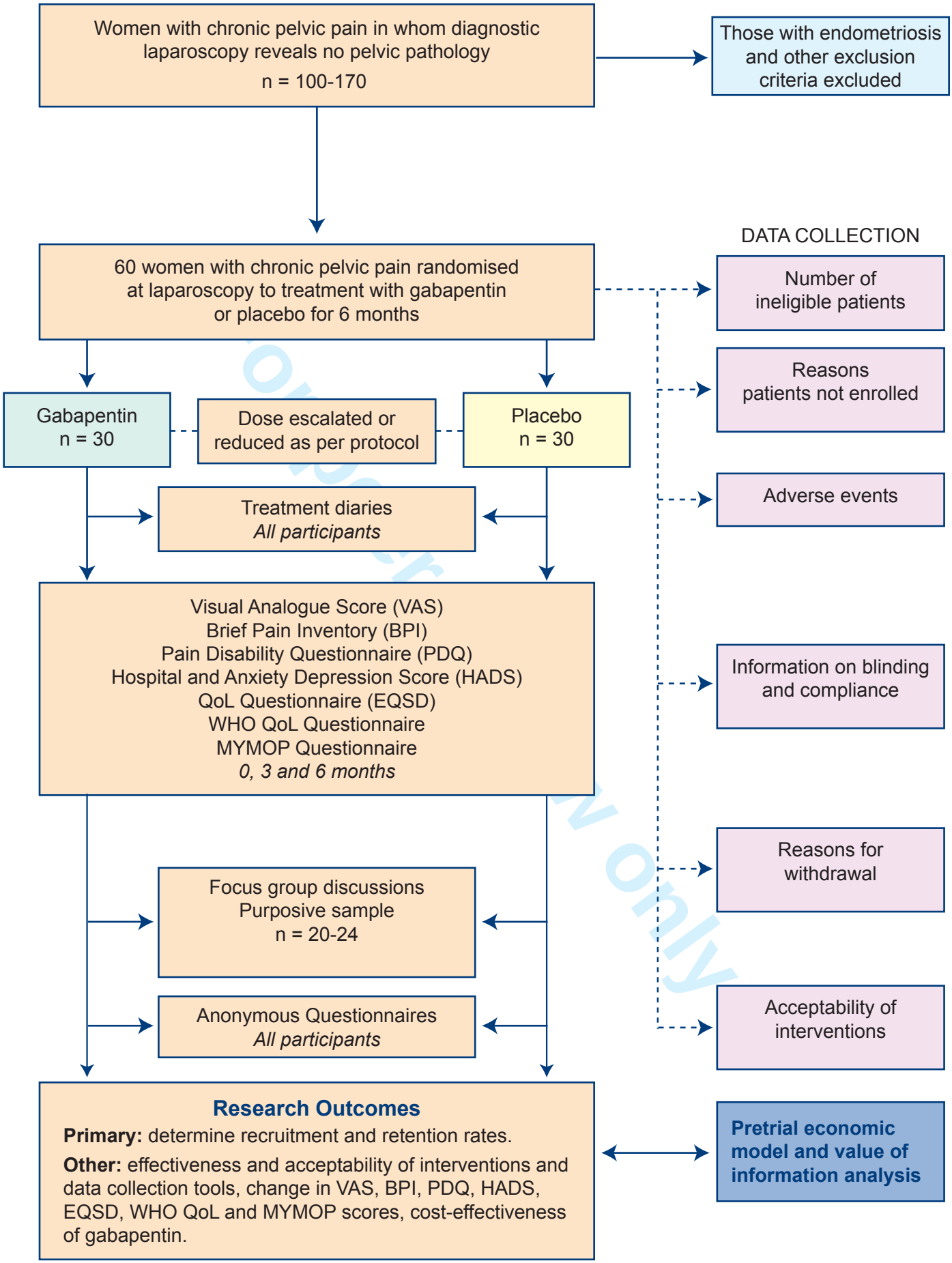
COMPETING INTERESTS

None.

FIGURE LEGEND

Figure 1. Flow of participants through the study.


Women with chronic pelvic pain in whom diagnostic laparoscopy reveals no pelvic pathology
n = 100-170
Those with endometriosis and other exclusion criteria excluded
60 women with chronic pelvic pain randomised at laparoscopy to treatment with gabapentin or placebo for 6 months
Gabapentin
n = 30
Dose escalated or reduced as per protocol
Placebo
n = 30
Treatment diaries
All participants
Visual Analogue Score (VAS)
Brief Pain Inventory (BPI)
Pain Disability Questionnaire (PDQ)
Hospital and Anxiety Depression Score (HADS)
QoL Questionnaire (EQSD)
WHO QoL Questionnaire
MYMOP Questionnaire
0, 3 and 6 months
Focus group discussions
Purposive sample
n = 20-24
Anonymous Questionnaires
All participants
Research Outcomes
Primary: determine recruitment and retention rates.
Other: effectiveness and acceptability of interventions and data collection tools, change in VAS, BPI, PDQ, HADS, EQSD, WHO QoL and MYMOP scores, cost-effectiveness of gabapentin.
DATA COLLECTION
Number of ineligible patients
Reasons patients not enrolled
Adverse events
Information on blinding and compliance
Reasons for withdrawal
Acceptability of interventions
Pretrial economic model and value of information analysis

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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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Ideally, a definitive evaluation of the efficacy of gabapentin in the management of CPP with no obvious underlying pathology requires a large multicentre randomised controlled trial (RCT). This protocol outlines a pilot study to assess the processes that are vital to the delivery of such a trial.

Objectives

Primary objective

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

Secondary objectives

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

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.

Study settings

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

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

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)

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

Intervention and randomisation

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.

Dose regime

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 dose of 2700 mgs. Patients will be advised regarding their dosing regime weekly by a member of the research team who will phone until optimum dose is reached. It will be recommended that the drug should be taken in three equally divided doses daily. Participants will be advised to remain on the maximum tolerated dose for up to 6 months. The same protocol will be used for the placebo. When the participant stops treatment then the dose will be tapered down over 7 - 10 days at the clinician's discretion. Patients will be allowed to use other medication (including analgesics, self-medication and alternative treatments e.g. acupuncture) throughout the study period.

Data collection

Data storage

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

Screening

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

Participant log

The clinical research team will keep an electronic log of women who fulfil the eligibility criteria, women who are invited to participate in the study, women recruited and women who leave the trial early. Reasons for non-recruitment (eg non-eligibility, refusal to participate, administrative error) will also be recorded. We will attempt to collect reasons for non-participation from women who decline to take part after previously providing contact details. During the course

of the study, we will document reasons for withdrawal from the study and loss to follow-up. Participants will be reviewed by the clinical research team at 6 weeks, 3 months and 6 months.

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 participants to complete a brief anonymous questionnaire once they have submitted their treatment diaries to assess level of adherence to diary keeping.

Focus groups

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

Healthcare resource utilisation measures

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

Adverse events

Participants will collect information about adverse events in their treatment diaries. However, they will be instructed to contact the clinical research team at any time after consenting to join the trial if they have an event that requires hospitalisation, or an event that results in persistent or significant disability or incapacity. Gabapentin is generally well tolerated in the management of other chronic pain conditions and serious adverse events (SAEs) are not anticipated. Any SAEs that occur after joining the trial will be reported in detail in the participant's medical notes, followed up until resolution of the event, and reported to the ACCORD Research Governance (www.accord.ed.ac.uk) and QA Office based at the University of Edinburgh immediately or within 24 hours.

Termination of study

Participants (and their gynaecologists) will be unblinded at the end of the study period (6 months). There will be no central unblinding facility but the site pharmacies will be provided with the key which links drug pack number to treatment. Thus, it will be possible for unblinding (emergency or otherwise) to be carried out by a pharmacist if requested. All participants will be given the right to be unblinded, discontinue the drug or completely withdraw from the study at any time for any reason. Reasons for unblinding, before the termination of the study, will be collected. Those participants who feel that they have benefited from treatment with gabapentin, during the study period, will be advised to discuss continuation of treatment with their gynaecologist.

Proposed analyses

Determine recruitment and retention rates

Using the information collected from the participant log, we will determine the number of patients recruited from the pool of eligible women and a >50% recruitment will be deemed acceptable. While a retention rate of 100% would be ideal, we will consider a rate of 90% satisfactory. We will provide an estimate of the proportion and its 95% confidence interval. If retention rates are low, we will use the information collected from the focus group discussions to ascertain why and improve compliance in the future trial. In addition, we will determine the nature and number of unanswered questions in each questionnaire and identify reasons for non-response through the focus groups and participant interviews in order to optimise data collection in the future trial.

Effectiveness and acceptability of proposed methods of recruitment, randomisation, drug treatments and assessment tools

These areas will be explored in the focus group discussions and assessed quantitatively using additional questions included in participant questionnaires administered at 6 months. Due to the conflicting literature about the benefits of methods such as prescription monitoring, pill counting and devices for monitoring the self-administration of medicines, [9] data on blinding and compliance to treatment will be derived from questionnaires at 6 months. We aim to determine if treatment is acceptable in terms of self-reported compliance (from treatment diaries). Although this is a pilot study and the sample size is small, we will assess the effect of any non-compliance on the LICKERT score by

performing protocol and intention to treat analyses. This information along with health professionals' and clinical research nurses' views (as assessed by questionnaire) will be used to inform the design of the future RCT. In addition, the difference in VAS scores between participants on gabapentin and placebo at 0 and 6 months will be assessed using analysis of covariance adjusting for baseline VAS score.

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.

The criteria do not take into account pain intensity, do not exclude women with non-reproductive comorbidities (e.g. irritable bowel syndrome, interstitial cystitis) that could explain their symptoms, and allow participants the use of concomitant medications. We are aware that these characteristics may increase variability in patient responsiveness to treatment and carry the risk of failing to demonstrate treatment effect. We will therefore capture this information in our pilot study in the participants' questionnaires and treatment diaries to inform interpretation of our results and the planning of the future RCT.

Like many of the medications used for chronic pain, gabapentin requires titration to achieve an efficacious dose so that the rate and severity of adverse effects are minimised. The duration of this titration period may be as many as 8-10 weeks. The 6-month follow-up in our pilot study allows for a 12-week maintenance phase that has become standard for confirmatory trials. It could be argued that a longer trial would be better to assess the long-term effects of gabapentin. On the other hand, we are aware that extended duration could be problematic because of the number of drop-outs from the placebo arm due to inadequate pain relief. We believe that focus group assessment of the acceptability of the drug treatment and titrating regime in our pilot will therefore be essential in designing the future RCT.

The comparison of an investigational treatment with placebo is considered the gold standard for assessing efficacy and safety when a delay in the onset of treatment does not cause any lasting adverse effects and assuming that subjects fully understand their right to withdraw from the trial at any time for any reason.

[12,13] However, gabapentin is sedating and it can be argued that this increases the likelihood that both subjects and investigators can successfully guess to which group a subject has been allocated. We are therefore going to ask the subjects and investigators at the conclusion of the trial to guess the subjects' treatment group and the primary reason for the guess to determine whether significant 'unblinding' was present within the trial. This will determine whether we need to use an 'active placebo' mimicking the side effects of gabapentin in the future RCT.

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

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

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

Finally, although the primary outcome in our pilot study is to determine recruitment and retention rates, we will also measure change in visual analogue scale (VAS) over 6 months. This combination of information will allow us to determine the effect size and standard deviation (SD) and plan the sample size for the definitive RCT. Analyses of similar studies using gabapentin for chronic pain with VAS score as primary outcome indicate that the mean absolute difference in the VAS score comparing gabapentin against placebo ranges between 0.8 and 1.8 with an SD of ~2.5 after 1-2 months' treatment. [6] Thus, our definitive RCT is likely to be powered to find a difference of >1.2 on the VAS scale (a clinically important symptom alleviation is defined as a reduction in VAS 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, AD, DF, JW, SJ: contribution of original material, editing and approval of final manuscript; OW, MP, SL, SB: research, contribution of original material, editing and approval of final manuscript.

FUNDING

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COMPETING INTERESTS

AWH, HODC, SJ, JW, SL, OW, MP and SB are all co-investigators on the grant from the Chief Scientist's Office Scotland (CZH/4/688) that has been secured to support this study. AWH is funded by an MRC Clinician Scientist Fellowship (G0802808). HODC holds an MRC Centre Grant (G1002033) and a project grant from Bayer Schering Pharma AG. AWH and HODC hold the University of 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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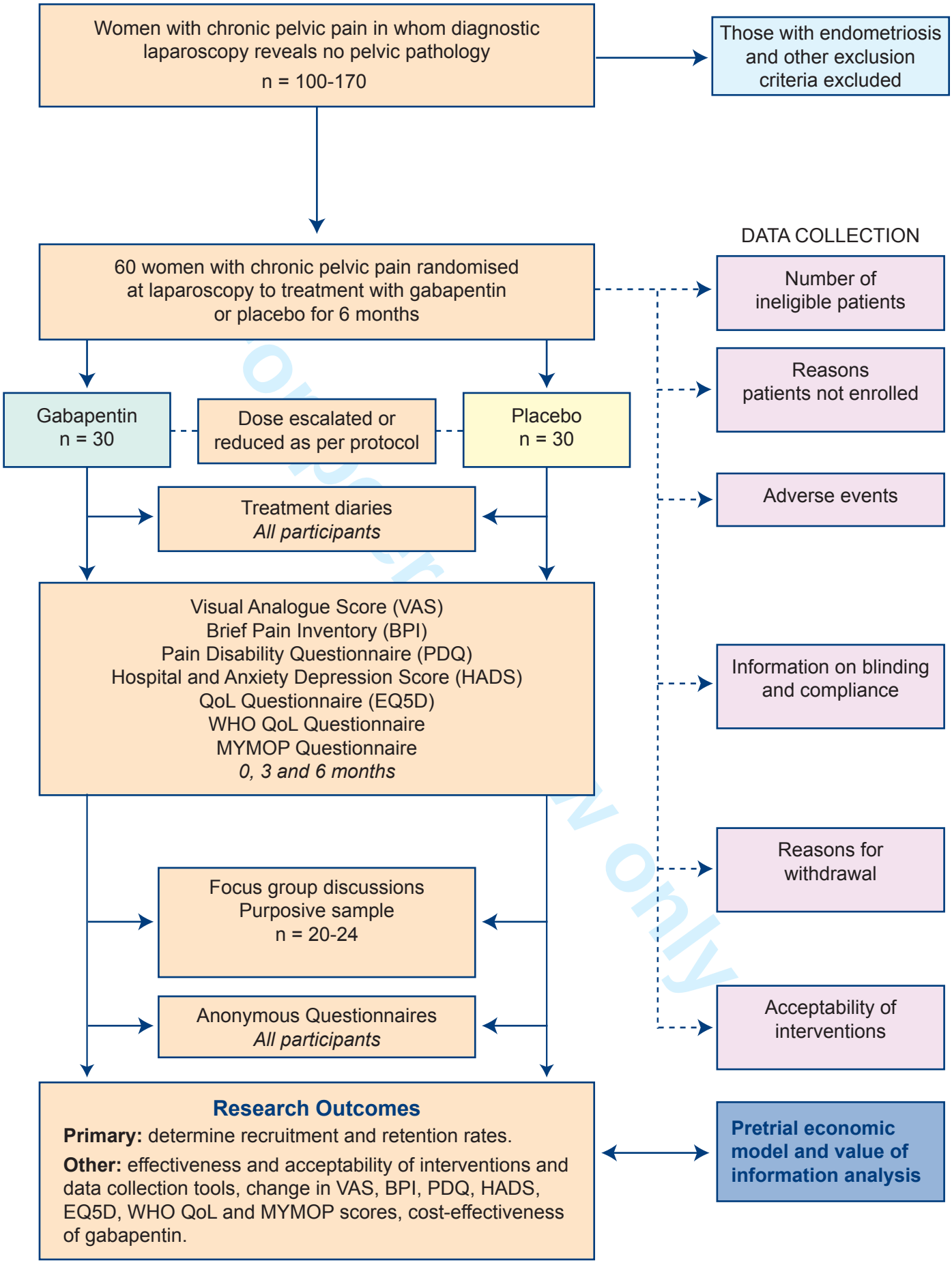
Women with chronic pelvic pain in whom diagnostic laparoscopy reveals no pelvic pathology
n = 100-170
Those with endometriosis and other exclusion criteria excluded
DATA COLLECTION
60 women with chronic pelvic pain randomised at laparoscopy to treatment with gabapentin or placebo for 6 months
Number of ineligible patients
Reasons patients not enrolled
Gabapentin n = 30
Dose escalated or reduced as per protocol
Placebo n = 30
Adverse events
Treatment diaries
All participants
Visual Analogue Score (VAS)
Brief Pain Inventory (BPI)
Pain Disability Questionnaire (PDQ)
Hospital and Anxiety Depression Score (HADS)
QoL Questionnaire (EQ5D)
WHO QoL Questionnaire
MYMOP Questionnaire
0, 3 and 6 months
Information on blinding and compliance
Reasons for withdrawal
Focus group discussions
Purposive sample
n = 20-24
Acceptability of interventions
Anonymous Questionnaires
All participants
Research Outcomes
Primary: determine recruitment and retention rates.
Other: effectiveness and acceptability of interventions and data collection tools, change in VAS, BPI, PDQ, HADS, EQ5D, WHO QoL and MYMOP scores, cost-effectiveness of gabapentin.
Pretrial economic model and value of information analysis

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[1], HOD Critchley[1], A Doust[1], D Fehr[2], J Wilson[3], O Wu[4], S Jack[5], M Porter[6], S Lewis[7], S Bhattacharya[6]

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

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KEY WORDS:
Pelvic pain, gabapentin.

WORD COUNT:
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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

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

Ideally, a definitive evaluation of the efficacy of gabapentin in the management of CPP with no obvious underlying pathology requires a large multicentre randomised controlled trial (RCT). This protocol outlines a pilot study to assess the processes that are vital to the delivery of such a trial.

Objectives

Primary objective

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

Secondary objectives

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

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.

Study settings

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

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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

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) will be employed for the duration of the study to approach eligible women, provide them with patient information sheets and offer them the opportunity to discuss the trial, and obtain informed consent. Consent will only be taken once

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the patient has had ample time to read the patient information sheet and had her questions answered.

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Intervention and randomisation

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.

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~~Intervention~~Dose regime

~~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 dose of 2700 mgs. Patients will be advised regarding their dosing regime weekly by a member of the research team who will phone until optimum dose is reached. It will be recommended that the drug should be taken in three equally divided doses daily. Participants will be advised to remain on the maximum tolerated dose for up to 6 months. The same protocol will be used for the placebo. When the participant stops treatment then the dose will be tapered down over 7 - 10 days at the clinician's discretion. Patients will be allowed to use other medication (including analgesics, self-medication and alternative treatments e.g. acupuncture) throughout the study period.

Data collection

Data storage

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

Screening

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

Participant log

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

decline to take part after previously providing contact details. During the course of the study, we will document reasons for withdrawal from the study and loss to follow-up. Participants will be reviewed by the clinical research team at 6 weeks, 3 months and 6 months.

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 participants to complete a brief anonymous questionnaire once they have submitted their treatment diaries to assess level of adherence to diary keeping.

Focus groups

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

Healthcare resource utilisation measures

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

Adverse events

Participants will collect information about adverse events in their treatment diaries. However, they will be instructed to contact the clinical research team at any time after consenting to join the trial if they have an event that requires hospitalisation, or an event that results in persistent or significant disability or incapacity. Gabapentin is generally well tolerated in the management of other chronic pain conditions and serious adverse events (SAEs) are not anticipated. Any SAEs that occur after joining the trial will be reported in detail in the participant's medical notes, followed up until resolution of the event, and reported to the ACCORD Research Governance (www.accord.ed.ac.uk) and QA Office based at the University of Edinburgh immediately or within 24 hours.

Termination of study

Participants (and their gynaecologists) will be unblinded at the end of the study period (6 months). There will be no central unblinding facility but the site pharmacies will be provided with the key which links drug pack number to treatment. Thus, it will be possible for unblinding (emergency or otherwise) to be carried out by a pharmacist if requested. All participants will be given the right to be unblinded, discontinue the drug or completely withdraw from the study at any time for any reason. Reasons for unblinding, before the termination of the study, will be collected. Those participants who feel that they have benefited from treatment with gabapentin, during the study period, will be advised to discuss continuation of treatment with their gynaecologist.

Proposed analyses

Determine recruitment and retention rates

Using the information collected from the participant log, we will determine the number of patients recruited from the pool of eligible women and a >50% recruitment will be deemed acceptable. While a retention rate of 100% would be ideal, we will consider a rate of 90% satisfactory. We will provide an estimate of the proportion and its 95% confidence interval. If retention rates are low, we will use the information collected from the focus group discussions to ascertain why and improve compliance in the future trial. In addition, we will determine the nature and number of unanswered questions in each questionnaire and identify reasons for non-response through the focus groups and participant interviews in order to optimise data collection in the future trial.

Effectiveness and acceptability of proposed methods of recruitment, randomisation, drug treatments and assessment tools

These areas will be explored in the focus group discussions and assessed quantitatively using additional questions included in participant questionnaires administered at 6 months. Due to the conflicting literature about the benefits of methods such as prescription monitoring, pill counting and devices for monitoring the self-administration of medicines, [9] data on blinding and compliance to treatment will be derived from questionnaires at 6 months. We aim to determine if treatment is acceptable in terms of self-reported compliance (from treatment diaries). Although this is a pilot study and the sample size is small, we will assess the effect of any non-compliance on the LICKERT score by

performing protocol and intention to treat analyses. This information along with health professionals' and clinical research nurses' views (as assessed by questionnaire) will be used to inform the design of the future RCT. In addition, the difference in VAS scores between participants on gabapentin and placebo at 0 and 6 months will be assessed using analysis of covariance adjusting for baseline VAS score.

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.

The criteria do not take into account pain intensity, do not exclude women with non-reproductive comorbidities (e.g. irritable bowel syndrome, interstitial cystitis) that could explain their symptoms, and allow participants the use of concomitant medications. We are aware that these characteristics may increase variability in patient responsiveness to treatment and carry the risk of failing to demonstrate treatment effect. We will therefore capture this information in our pilot study in the participants' questionnaires and treatment diaries to inform interpretation of our results and the planning of the future RCT.

Like many of the medications used for chronic pain, gabapentin requires titration to achieve an efficacious dose so that the rate and severity of adverse effects are minimised. The duration of this titration period may be as many as 8-10 weeks. The 6-month follow-up in our pilot study allows for a 12-week maintenance phase that has become standard for confirmatory trials. It could be argued that a longer trial would be better to assess the long-term effects of gabapentin. On the other hand, we are aware that extended duration could be problematic because of the number of drop-outs from the placebo arm due to inadequate pain relief. We believe that focus group assessment of the acceptability of the drug treatment and titrating regime in our pilot will therefore be essential in designing the future RCT.

The comparison of an investigational treatment with placebo is considered the gold standard for assessing efficacy and safety when a delay in the onset of treatment does not cause any lasting adverse effects and assuming that subjects fully understand their right to withdraw from the trial at any time for any reason.

[12,13] However, gabapentin is sedating and it can be argued that this increases the likelihood that both subjects and investigators can successfully guess to which group a subject has been allocated. We are therefore going to ask the subjects and investigators at the conclusion of the trial to guess the subjects' treatment group and the primary reason for the guess to determine whether significant 'unblinding' was present within the trial. This will determine whether we need to use an 'active placebo' mimicking the side effects of gabapentin in the future RCT.

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

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

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

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

FUNDING

This work is supported by a grant from the Chief Scientist's Office Scotland (CZH/4/688). AWH is funded by an MRC Clinician Scientist Fellowship (G0802808). The funders and study sponsor will have no role in the study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

COMPETING INTERESTS

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

FIGURE LEGEND

Figure 1. Flow of participants through the study.

Scotland A Research Ethics Committee

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NHS SCOTLAND

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Date: 31 January 2012
Your Ref.:
Our Ref.: 12/SS/0005
Enquiries to: Walter Hunter
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Dear Dr Horne

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

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

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

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

Ethical opinion

The Committee noted this was a pilot for a larger study and that it was a new indication for a licensed drug. The Committee recognised the significant problems faced by women affected by chronic pelvic pain and the burden placed on health services. The aim of the study was to treat the condition in a more robust way. The study involved the participants having an MRI scan but the application had made a case for doing this. The study design was straightforward and involved the completion of weekly pain scores and a series of visits to the clinic. If the treatment was effective participants would be allowed to continue the treatment after the conclusion of the study. The participant information sheet was considered to be satisfactory.

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

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.

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:

Document	*Version*	*Date*
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

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	

Also in attendance:

Name	*Position (or reason for attending)*
Mr Walter Hunter	Committee Coordinator

Written comments received from:

Name	*Position*
Dr Richard Quigley	General Practitioner
Dr Rachel Smith	Project Manager

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