GaPP^2 : A multi-centre randomised controlled trial of the efficacy and mechanism of action of gabapentin for the management of chronic pelvic pain in women.

You have been invited to take part in our research study because you have chronic (long term) pelvic pain. Before you decide whether you wish to take part, it is important for you to understand why the research is being done and what it will involve. Please take ample time to read the following leaflet carefully and discuss with friends, relatives or your GP. Ask us if there is anything that is not clear or if you would like more information. Please take time to decide whether or not you wish to take part.

What is the purpose of the study?

Chronic pelvic pain (CPP) affects over 1 million women in the UK. The reason why women suffer from CPP is poorly understood. In as many as half of the women with CPP, no cause can be found. The management of CPP is therefore difficult.

In this study we will use a drug called gabapentin. Gabapentin is a commonly used drug for other chronic or long term pain conditions but there is no proof that it helps women with CPP. We carried out a small study comparing gabapentin against placebo (an identical dummy capsule) and this showed that it might help with this pain but we need more evidence, therefore we are asking you to take part in this larger study to try and prove whether it works. We will give half the women in our study gabapentin and half a placebo for sixteen weeks. You will not know whether you are taking gabapentin or placebo until the end of the study. We will ask you to tell us how your pain is at the beginning of the study before you take any capsules and again for the last 4 weeks of taking them. We hope that this will tell us whether gabapentin is helpful for women with CPP.

With your consent, we would also like to take a saliva sample to look at inherited factors that might be linked to how effective gabapentin is for your pain. Saliva contains cells, which contain genes ('DNA'). Genes provide instructions for processes in the body and for traits such as eye colour. Everyone's genes are a little different. Information about these differences among people can help researchers understand how to best use drugs to treat pain.

Do I have to take part?

No - taking part is completely voluntary. If you do decide to take part, you can withdraw from the trial at any time, without providing a reason. This will not affect your care in any way.

What will happen to me if I take part?

You will be asked to sign a consent form by a member of the research team. We will then ask you some questions to make sure that it is safe for you to take part in the trial and this will include questions about your medical history and any medications you are on. Once we know it is safe for you to take part we will ask you over the next four weeks to

text or phone us with your average and worst pain score for each week. This will be three messages, one telling you that other messages about your pain are about to come, and two messages asking about your worst and average pain for that week. At your first appointment the research nurse will talk you through this and how you should reply. Once we have this information, we can see if you can take part in the study.

If you are not eligible to take part, you will not be randomised to any treatment and your care will return to your usual doctor.

If you are eligible to take part, you will be asked to come into the hospital for a visit to fill in some questionnaires. Some of the questions are of a sensitive nature (for example, about your pain and sexual history) but you will complete them in private and they will not contain any information that can identify you. We will carry out a pregnancy test to ensure it is safe for you to take the study medication and if negative you will be given, at random, either gabapentin or placebo capsules. These capsules look exactly the same so nobody will know which treatment you are on. You will also be given a diary and shown how to fill this out. This will need to be completed every day. This is important as it will tell how much of the study drug you have taken and also what other medication you may take to help with your pain. Filling out the diary will take about five minutes at the end of each day. This can either be on paper form or over the internet. We will send you a brief text message or phone you every week to remind you complete this.

It is important that you do not get pregnant while taking this drug so we will ask you to use effective contraception (if necessary) for the time you are in the trial.

For the first few weeks, we will get you will increase the dose of the capsules that you take– instructions will be given to you and you can contact the trial team at any time for help with this. Once you are at the dose that gives you the best pain relief, with no or few acceptable side effects, you will stay on this dose until your next visit at 4 weeks when you will be asked to come in to see the research nurse briefly and to pick up more study medication. You will stay on this dose for the next 12 weeks. You may have to come into the hospital about half way through the study for a short visit with the research nurse to pick up some more medication. For the last 4 weeks we will ask you to text or phone us to tell us your pain scores again each week. At the end of the 12 weeks you will come into the hospital for another visit with the research nurse to hand in your unused drugs and your diary, and to complete some questionnaires again. At this visit you will be told what drug you were taking, e.g. gabapentin or placebo. You will then have the opportunity to continue or start on gabapentin (if on placebo) if you wish. Please see page 4 for full details of what will happen during the study.

If you are willing, we would also like to take a saliva sample at your second visit for genetic studies. This would allow us to find out if we can predict which women will respond to gabapentin treatment based on their genes. We would investigate specific genes that are already known to influence whether people respond to certain types of medication. We would also look for genes not yet known to influence response to medication - and gapapentin in particular - by investigating your entire genome through e.g. DNA sequencing ('reading' the code of your DNA). The results from your genetic analyses are not diagnostic in any way, will not be fed back to you, and will only used for the specified research purposes. All data will be anonymised before analysis. You can still take part in the main study if you don't want to do this. In the unlikely event that we find a gene that strongly predicts how you respond to drug treatment, and we think this

information is of benefit to you for future treatment, we will pass this information on to you and your doctor if you so wish.

Reasonable travel expenses will be reimbursed for all research visits.

What are the possible disadvantages and risks of taking part?

All medications can sometimes cause side effects. If you experience any side effects, or are worried about them, please contact us using the details provided at the end of this leaflet. Alternatively, you can contact your GP.

You will have a 50% chance of getting gabapentin which is a drug commonly used for pain although we don't know if it works for chronic pelvic pain.

Gabapentin is not a new drug and is widely used for the treatment of pain. It is a strong painkiller and can be safely taken by most people but, as with every drug, some people can suffer side effects.

The most common side effects from gabapentin include drowsiness, dizziness, fatigue, fever, increased infections/risk of infections, a change in appetite (may increase or decrease), changes in blood pressure, visual disturbances, changes to your skin (including rash or swelling) pain (including joint/muscle or abdominal), respiratory conditions (including shortness of breath), digestive/urinary disturbance and a change in mood (including feeling anxious or depressed). You may feel drowsy so it is advised not to drive or operate machinery until you know that you feel you are safe to do so. If you do suffer from any side effects reducing the dose or stopping the capsules stop these. It is not known if gabapentin is of any risk to pregnant women, so we will ask you to not get pregnant during the course of the study. We will ask you what contraception you are using, if necessary at each visit.

What are the possible benefits of taking part?

You may or may not get a direct benefit from taking part in this trial. It is hoped that the findings will demonstrate that gabapentin is a safe, acceptable and effective treatment for chronic pelvic pain.

What will happen if I don't want to carry on with the study?

You are free to withdraw from the study at any time without giving a reason. If you decide not to take part in the study or withdraw at any time, the standard of care you receive will not be affected. If you withdraw we may still wish, with your permission, to use any anonymised data already obtained as a result of your participation.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the clinical researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do so through the NHS Complaints Procedure. Details can be found at the end of this leaflet.

Will my taking part in this study be kept confidential?

Yes. All information which is collected about you during the course of the research will be kept strictly confidential. You will be allocated a unique code and your responses to the questions will be held in a coded form in a secure central database which is only accessible to the research team. Your responses will not be identified when the results of the study are published. However, we do ask permission to contact your GP to let them know that you are taking part in the study.

What will happen to the results of the current research study and samples?

The results of this study will be published e.g. in medical journals, reports and textbooks. The anonymised data will be stored for five years at the University of Edinburgh and may be considered for possible use in future ethically approved projects related to pain.

The investigator will be responsible for the samples and will ensure they are kept securely. The samples will be kept until they are all used up, which may take up to several years. This will allow the researchers to study future questions about pain and treatment. The researcher and collaborators may have access to your anonymised samples and data for scientific research into pain and treatment.

Samples can be preserved for many years. However, it may eventually become necessary to dispose of the samples. This will be done in accordance with the law and government guidance in effect at that date.

Who is organising and funding the research?

The research is being organised by Prof Andrew Horne (Consultant Gynaecologist), University of Edinburgh and funded by National Institute for Health Research. This trial is jointly sponsored by the University of Edinburgh and NHS Lothian. It is being run with support from Birmingham Clinical Trials Unit.

Who has reviewed the study?

This study has been given a favourable ethical opinion for conduct in the NHS by the National Research Ethics Committee – Coventry and Warwickshire

Contact details:

You may contact our clinical research team directly by telephoning for further information at any time. Contact details are provided at the end of this leaflet. If you require any further information, or would like to discuss the trial with a doctor who is not involved in any way in this study you can contact Dr Colin Duncan, Consultant Gynaecologist, Royal Infirmary of Edinburgh on 0131 242 1000.

Thank you for reading this information sheet.

>> Contact details for each centre

>> Local NHS Complaints Department details

Step-by-step guide to the study

We will initially ask you to sign a consent form and to answer some questions about your medical history and what medications you take for your pain symptoms.

Weeks 1 - 4
In order to determine if you are eligible to take part in the study, we will monitor your pain scores for 4 weeks. We will text or phone you and ask you your average and worst pain scores for that week.

At the end of this 4 week period you may not be eligible for entry into the study and you will return to normal care with your doctor.

If you are eligible, you will be invited to come into the hospital for a visit with the research nurse.

Week 4
We will ask you to come into the hospital and fill in some questionnaires. We will carry out a pregnancy test, discuss contraception and ask you a few more questions to confirm it is safe for you to come into the study. We will then randomly allocate you to either gabapentin or placebo capsules. You will have a 50/50 chance of receiving either the trial drug or the placebo. This will be unknown to you and to the research team. We will give you instructions on how to take the capsules and how to gradually increase the dose. We will also give you a diary to complete each day with instructions and contact numbers of the research team. We will ask you to fill in your daily diary and let us know if you have any problems. In addition, we will ask you for a sample of your saliva.

Weeks 4 - 8
You will start taking your capsules and increase the dose every three days until you reach the maximum dose or the highest dose you need to relieve your pain with the least side effects. Instructions will be given.

Week 8

We will ask you come into the hospital for a short visit (about 10 minutes) to pick up some more medication and discuss how you have been.

Weeks 8 - 20
We will ask you to stay on the dose of the drug that you feel most comfortable with. We will ask you to fill in your daily diary and let us know if you have any problems.

Week 14

You may need to come into the hospital again to pick up some more medication depending on the dose you are taking.

For the last 4 weeks
We will text or phone you again, as we did at the beginning to ask you to send us your worst and average pain scores for the week. You will continue to take your medication and fill in your daily diary.

Week 20
We will ask you to come into the hospital again to see the research nurse. You will be asked to bring with you any unused capsules and your diary We will then ask you to fill in the same questionnaires you completed at the start of the study. After you have completed the questionnaires you will be told what capsules you were on. If you were taking gabapentin and you felt that it was helping your pain then you will be able to continue on this. If you don't want to carry on taking it, we will ask you to reduce the number of capsules that you were taking which usually takes about 7-10 days before you can stop completely. The research nurse will help you

with this decrease. If you were taking placebo then you will have the opportunity to have gabapentin prescribed if you feel that it might help your pain.