Recurrence of Endometriosis: A randomised controlled trial of clinical and cost-effectiveness of Gonadotrophin Releasing Hormone Analogues with add-back hormone replacement therapy versus repeat Laparoscopic surgery

PATIENT INFORMATION LEAFLET

INVITATION TO TAKE PART

We would like to invite you to take part in a research study. This study is looking at treatment for recurrent pain following surgery for endometriosis. We are trying to find out if a medication called Gonadotrophin Releasing Hormone Analogues (GnRHa) with add-back hormone replacement therapy (HRT) is an alternative treatment to further laparoscopic (keyhole) surgery for endometriosis. This study is funded by the National Institute of Health Research (the research arm of the NHS).

You are being inviting to take part in the study because you have had recurrence of pain following previous surgery to treat endometriosis.

Before you decide if you would like to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information.

WHAT IS ENDOMETROSIS?

Endometriosis is a common condition which affects one in ten women from puberty to menopause. It occurs when cells similar to those lining the womb grow outside it, generally within the pelvis. These cells behave like the cells lining the womb, causing internal bleeding at the time of periods, scarring and pain and results in poor quality of life and reduced work productivity. Endometriosis depends on the female hormone oestrogen (produced by the ovaries) for growth, and symptoms improve after menopause due to lack of oestrogen.

The condition is diagnosed by laparoscopy (keyhole surgery) to identify areas of endometriosis which can be destroyed or removed to treat pain. Surgery may not provide lasting relief and pain can return in up to half of treated women within five years despite the use of the contraceptive pill or other hormones called progestogens to lower the risk of endometriosis and pain coming back.

WHY ARE WE DOING THIS RESEARCH?

Despite surgery and hormonal contraceptives, about two in three women will need further surgery to treat recurrent pain due to endometriosis. Repeat surgery to remove endometriosis comes with risks and does not guarantee a cure. The most successful surgery is removal of both ovaries to stop the supply of oestrogen (often combined with removal of the womb) but it is not an acceptable option for many women before they have reached menopause.

The alternative medical treatment using GnRHa is less invasive and shrinks the endometriosis by temporarily stopping the ovaries from producing oestrogen. GnRHa is administered as an injection once every month or 3 months or as an implant. This treatment is very effective in reducing pain but is generally only used for 6 months to a year because of side effects such as hot flushes, night sweats and concerns about osteoporosis (thinning of the bones). Recent research has shown that adding small doses of HRT (a treatment used to relieve the symptoms of menopause) in women on GnRHa, reduces the risk of side effects and osteoporosis without causing pain to return. This allows GnRHa to be used for a longer period of time. HRT has been shown to be safe in this group of women.

Doctors and nurses working in the NHS and patient groups representing women who experience recurrence of pain after endometriosis surgery agree that a study is needed to compare long-term GnRHa (with added HRT) to keyhole surgery to destroy or remove endometriosis.

WHAT IS THE PURPOSE OF THE STUDY?

This clinical research study will help healthcare professionals, women and health services decision-makers understand what is the most effective treatment for women who have recurrence of pain after surgery for endometriosis

In the REGAL study, we want to find out whether using GnRHa with added HRT can improve the quality of life for women by controlling pain when compared to repeat laparoscopic surgery to treat endometriosis. We also want to find out which treatment makes best use of NHS resources.

The most reliable way to determine which treatment is best is to conduct what is called a randomised controlled trial, also known as a RCT.

We aim to recruit 400 participants from hospitals across the UK. Each woman who joins the study will be in the study for a maximum of 2 years. The study team may approach you at your usual clinic appointments or may send this information in advance of your appointment.

DO I HAVE TO TAKE PART?

No. It is entirely up to you whether you take part. Please take as much time you need to make this decision. You can read this information leaflet and ask your doctor and/or research nurse as many questions as you like.

If you do decide to take part, you will be asked to sign a form giving your consent to be included in the study. You can decide at any time to withdraw from the study. This decision will not affect the standard of care you receive now or in the future.

WHAT WOULD TAKING PART INVOLVE?

If you decide to take part, you will be randomly assigned (using a computer) to join one of the two study groups, either keyhole surgery to remove or destroy endometriosis or GnRHa with add back HRT for 2-years. You and your healthcare team will not be able to choose which group you join. There is an equal chance you will be placed into either treatment group.

If you are in the study group receiving laparoscopic (keyhole) surgery:

Laparoscopic surgery is regularly used in the NHS to treat recurrence of pain after endometriosis surgery, and you will receive the current standard NHS care. You will be added to a waiting list for the surgery. You should continue using your usual contraception until you receive your operation. If you do not normally use contraception, please use barrier contraception until your operation. You will be asked you to perform a pregnancy test at the hospital to confirm you are not pregnant before your operation.

You will be admitted to hospital for the day or overnight. If you have severe endometriosis, the stay might be longer after surgery. You will be given a general anaesthetic. Small cuts are made on your abdomen so instruments can be inserted to visualise the organs and to destroy or remove areas of endometriosis. Recovery time is normally 2 weeks.

It is recommended that you take hormonal treatment after surgery as recommended by your doctor, to reduce the chance of your endometriosis coming back. This will be a decision made between you and your doctor.

If you are in the study group receiving GnRHa with added HRT:

GnRHa with added HRT is regularly used in the NHS to treat recurrence of pain after endometriosis surgery. You will be given this medication in the way it is usually given in the NHS, but you will be prescribed the medication for 24 months instead of the usual 6-12 months.

There are different types of GnRHa and HRT and each type varies in the way, and how frequently, it is given. Your consultant will discuss with you the advantages and disadvantages of each type of treatment. GnRHa along with HRT will both start on the same day and is usually administered at your GP practice but can also be administered in hospital. Subsequent doses will be taken as prescribed by your GP or hospital consultant.

GnRHa will be given either by injections or implants every month or 3 months into the buttock, thigh muscle or under the skin of the abdomen or arm.

HRT contains oestrogenic and progestogenic properties and can be given either as a tablet, patch or gel applied to the skin. If you already have a hormonal coil (e.g. Mirena), it can be used as the progesterone arm of your HRT and additional oestrogen will be prescribed. To minimise any side effects of the GnRHa, the dose of HRT may be adjusted over time.

You should continue using your usual contraception until you receive the GnRHa. If you do not normally use contraception, please use barrier contraception until you receive the GnRHa. If you receive the GnRHa at your GP practice, a few days before your appointment we will ask you to perform a pregnancy test at home to confirm you are not pregnant. We will send you a pregnancy test to your home address. Even if the pregnancy test is negative, please speak to your doctor or nurse before having GnRHa if you think you may be pregnant – in such cases a repeat pregnancy test would be recommended before having GnRHa.

If the home pregnancy test is positive, please get in touch with your local research team or the REGAL study office (contact details at the back of this leaflet).
If you receive the GnRHa at the hospital, they will ask you to perform a pregnancy test at the hospital to confirm you are not pregnant before they give you the GnRHa.

To prevent pregnancy while you are on GnRHa and HRT, you will be advised to use a barrier contraceptive, such as a condom. You will not require barrier contraceptives if you have a hormonal coil such as Mirena.

Both study groups:

When you join the study, we will ask you to complete a questionnaire about your pain and quality of life, which should take about 20 minutes to complete. Every six months for 2-years, we will ask you to complete additional questionnaires about your pain, quality of life and any treatment you have had for endometriosis (4 additional questionnaires in total, each taking about 20 minutes to complete).

These will be sent by the study office in Aberdeen either by post (and returned to Aberdeen in the pre-paid envelope provided) or by email with a link to complete the questionnaire online. We may send you reminders about completing the questionnaires to make sure that relevant information about you is recorded for the study. If you become pregnant, we will stop treatment with GnRHa and added HRT but continue to collect data for the study.

In some centres women participating in the REGAL study will be offered bone density (DEXA) scans to measure the strength of their bones. Women in these centres will receive a separate information leaflet about this part of the study.

We will also ask a small number of eligible women to take part in telephone interviews to find out how they make decisions about taking part (or not) in the REGAL study and how their symptoms change over time. We will ask you whether you would like to participate in these interviews and give you a further information leaflet to read if you are interested.

After the study ends, we would like to collect more information about your endometriosis and any further gynaecological treatment up until the age of menopause. We will collect relevant data from NHS and government bodies and GP and hospital notes. We will use this data to understand the healthcare burden associated with endometriosis.

In the next 10 years, we may want to carry out further research studies with women who have endometriosis. We would like to ask your permission to contact you about these research studies.

This is optional, and you can take part in the REGAL study without agreeing to be contacted about further research studies. If we invite you to participate in these further research studies, you can choose whether to take part or not.

WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART?

You will receive the same health care from your doctors whether or not you choose to participate in the study. By taking part, you will be directly helping us to find the best treatment for women with recurrence of pain following surgery for endometriosis and helping women who have this condition in the future. The results of the study will also help plan effective services offered to women with endometriosis.

WHAT ARE THE POSSIBLE DISADVANTAGES OF TAKING PART?

We do not think that there are any possible disadvantages in taking part in this study. Whichever treatment you are allocated to, this will be performed by a competent and trained clinician. There are risks associated with all procedures, anaesthetics and medications. Steps are always taken to ensure that these risks are minimised. As part of routine care, you will be well informed of potential risks. You will not be able to participate in other drug studies or surgical studies at the same time.

WHAT ARE THE SIDE EFFECTS OF ANY TREATMENT RECEIVED WHEN TAKING PART?

Laparascopic (keyhole) surgery:

Laparoscopic (keyhole) surgery to remove/destroy endometriosis is performed frequently to treat pain. It will be performed by a trained specialist.

Your surgeon and anaesthetist will discuss risks and benefits with you in detail. You should not experience side effects from anaesthesia for more than a day after your operation. Feeling or being sick after an anaesthetic is quite common and you may feel more sleepy than usual.

Common side effects from the surgery include pain in the lower abdomen, around the wounds and in the shoulder. There may be some swelling or bruising around the wounds and some light bleeding from the vagina. These side effects should settle down in the first few weeks after surgery.

There will be small scars from the incisions (cuts). There is a small risk of wound, bladder or urine infection. Your medical team will give you advice about how to care for your wounds, manage pain after surgery and what symptoms to look out for and how to seek help.

Less common, but more serious risks, include blood clot in the leg or lungs; damage to an organ, such as a hole accidentally being made in the womb, bladder or bowel; and severe bleeding inside the abdomen. Rarely, in an emergency, the surgeon may need to change from keyhole surgery to open surgery. As with all surgery, there is a very small (1 in 12,000 women) risk of death.

GnRHa with added HRT:

When used in combination with added HRT, GnRHa is generally well tolerated by most women. Your clinician will discuss the possible side effects with you. If they cause you concern, please contact your GP or the research nurse.

The GnRHa injection or implant can cause temporary bruising or pain around the site of injection or placement of implant. Some women will experience a temporary worsening of endometriosis symptoms in the first 2 weeks of treatment.

Your periods are likely to stop, usually within the first 2 months of starting treatment, and will return within a few months of finishing treatment. Once treatment has stopped, endometriosis symptoms may return gradually.

Menopausal-type symptoms are common. Most women will experience hot flushes or night sweats or both.

Other side effects may include insomnia (problems sleeping), somnolence (drowsiness), reduced sex drive, headaches, mood changes including depression (which may be severe), vaginal dryness, changes in breast size, acne, muscle pains and dizziness. If you experience dizziness or drowsiness or if your vision is affected (rare side effect), your ability to drive and use machines may be impaired and should be avoided. However, added HRT will reduce these side effects. Your GP will adjust the dose of HRT to best manage these symptoms.

If you become worried about your mood at any point during the study, please contact the local research team. Also, If the study office become concerned about your mood when they receive your questionnaires, they will notify the local research team who may contact you to discuss further.
A more serious side effect of treatment with GnRHa is thinning of the bones.

This can lead to osteoporosis, where bones are fragile and more prone to breaking. Osteoporosis is more likely in women already at risk of developing the condition. Bones recover 1 to 2 years after stopping treatment. Recent studies have shown that added HRT prevents the thinning of the bones. It is therefore very important that you take your HRT regularly.

Side effects of HRT in women under 50 (pre-menopausal women) are less common and usually settle with time. They include breast discomfort, bloating or swelling, headaches or migraines, leg cramps, a feeling of sickness, mood swings, acne, indigestion, tummy pain, back pain and vaginal bleeding. Less common, but more serious side effects include a small increased risk of blood clot in the legs or lungs and stroke.

Women in their 50s or older have a small increased risk of developing breast cancer, heart disease, endometrial cancer and ovarian cancer. This is not applicable to women prior to menopause.

If using an HRT patch, some women find that this can cause irritation of their skin.

There is a very small risk of getting pregnant when on GnRHa, even when your periods have stopped. We therefore recommend you use a barrier contraception throughout the duration of treatment, unless you have a Levonorgestrel IUS (for example, Mirena coil). There is limited evidence about the safety of GnRHa when taken during pregnancy. If you become pregnant, advise your GP and study team and treatment will be discontinued.

WHAT HAPPENS WHEN THE RESEARCH STUDY STOPS?

You will continue your care and treatment in line with NHS standard care.

If the study is stopped earlier than expected for any reason, we will tell you and your continuing care will be arranged.

WHAT IF THERE IS A PROBLEM?

We do not expect any harm to come to you by taking part in this study. All procedures and techniques are already being used in the NHS to treat women with recurrence of pain following surgery for endometriosis. Your participation is only to help us evaluate these procedures and should not involve any additional risk to you.
However, if you believe that you are harmed by taking part in this study, you have the right to pursue a complaint and seek compensation through the research sponsors of this study, the University of Aberdeen and NHS Grampian.

As a patient of the NHS, if you are harmed due to someone's negligence, then you may have grounds for a legal action, but you may have to pay for your legal costs. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during this study, the normal NHS complaints mechanisms would be available to you.

If you have a concern about any aspect of the study, you can ask to speak with the research team who will do their best to answer your questions (contact details of your local study nurse and the Study Office can be found at the end of this information sheet).

You may contact the chair of the Trial Steering Committee, who is independent from the study, through the study office. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from your hospital.

WILL MY TAKING PART IN THE STUDY BE KEPT CONFIDENTIAL?

Yes. We will follow ethical and legal practice and all information which is collected about you for the purpose of this research study will be handled in strict confidence and securely stored by the University of Aberdeen.

We will use information from you, your medical records and your GP for this research project. This information will include your name, contact details, date of birth and NHS number. People will use this information to do the research or to check your records to make sure that the research is being done properly.

With your permission, we will write to your GP to tell them that you are taking part in the REGAL study.

After the study ends, we would like to collect relevant readmission hospital data (e.g repeat surgery and pregnancy) from the NHS central registers: in England this is NHS Digital, in Scotland this is the Information Services Division (ISD), and in Wales this is the NHS Wales Informatics Service (NWIS). The reason for this is to make sure that we have the correct information about all the women taking part in this study and ensure that the results are as accurate as possible. In order to do this, we would need to securely send the NHS central registers some information about you (e.g. date of birth, hospital number, name, and address).

They will then match this information to their records and using your study number to securely send any hospital readmission data back to the REGAL Study Office.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

Other researchers in this and/or other organisations (e.g. Universities, NHS or companies involved in health and care research in this country or abroad) may wish to access anonymous data from this study for future research. They must follow our rules about keeping your information safe.

WHAT IF RELEVANT NEW INFORMATION BECOMES AVAILABLE?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied.

If this happens, the REGAL Study Office staff will contact you to let you know about the choices available to you. However, we are not aware that any new, relevant information is likely to become available before the end of this study.

WHAT WILL HAPPEN IF I DON'T WANT TO CARRY ON WITH THE STUDY?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

If you choose to stop taking part in the study, we would like to continue collecting information about your health from central NHS records, your hospital and your GP. If you do not want this to happen, tell us and we will stop.

We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?

You can find out more about how we use your information:

- at www.hra.nhs.uk/information-about-patients/
- by asking one of the research team
- by sending an email to nhsg.infogovernance@nhs.scot, or
- by ringing us on 0345 456 6000.

WHAT WILL HAPPEN TO THE RESULTS OF THE STUDY?

The results of the study will be used to make recommendations on treatments for women with recurrence of pain following surgery for endometriosis. We shall publish the results of this study in scientific journals and present the information at appropriate meetings including patient groups.

You will not be identified in any publication of results of the study. We will let you know the results of the study when it is finished unless you tell us that you do not wish to know.

HOW LONG WILL MY INFORMATION BE KEPT?

All information which is collected about you during the research, including identifiable data, will be held securely for 25 years in accordance with Sponsor requirements and data legislation.

WHO IS ORGANISING AND FUNDING THE STUDY?

This study is sponsored by the University of Aberdeen and NHS Grampian who have overall responsibility for the management of the study. The study is funded by the National Institute of Health Research, (the research arm of the NHS).

The research is being carried out by a group of experienced doctors and researchers from the Centre for Healthcare Randomised Trials (CHaRT), a UKCRC registered Clinical Trials Unit at the University of Aberdeen.

WHO HAS REVIEWED THE STUDY?

The East of Scotland Research Ethics Service REC 2, which has responsibility for scrutinising all proposals for medical research on humans, has examined the proposal and has raised no objections from the point of view of research ethics. In addition, the study has also been reviewed and approved by the Medicines and Healthcare Products Regulatory Agency. The Research and Development Department of your local hospital has also reviewed and approved the study.

It is a requirement that your records in this research, together with any relevant medical records, be made available for scrutiny by monitors from the University of Aberdeen and NHS Grampian (who are sponsoring the study) and from your local hospital, whose role is to check that research is properly conducted and the interests of those taking part are adequately protected.

Thank you for reading this

Thank you for taking the time to read this information leaflet. We hope that it has been helpful in enabling you to decide if you would like to participate in the REGAL study. Please ask us if you have questions or would like more information about the study.

FURTHER INFORMATION AND CONTACT DETAILS
If you have any questions or would like any more information, please contact:

REGAL Study Office
Centre for Healthcare Randomised Trials (CHaRT),
Health Services Research Unit
University of Aberdeen
Health Sciences Building
Foresterhill
Aberdeen AB25 2ZD
Tel: 01224 438196
Fax: 01224 438165
Email: regal@abdn.ac.uk
Web: https://w3.abdn.ac.uk/hsru/REGAL

Local centre contact details