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 (REGAL trial)

PROTOCOL

A UK Collaborative Trial funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (project number NIHR127280)

This Protocol has regard for the HRA guidance and order of content.

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Signature

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

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VERSION HISTORY

Amendment no.	Protocol version no.	Description of changes (*incl. author(s) of changes*)	Date of document
	Version 1	New Document	
	Version 2	Accommodate changes requested by MHRA	27/01/2021
	Version 3	Accommodate changes requested by REC (If MHRA approve Version 2 and REC approve Version 3, an amendment will be submitted to bring all changes into Version 4)	01/02/2021
	Version 4	Accommodate additional changes requested by REC (If MHRA approve Version 2 and REC approve Version 3 and 4, an amendment will be submitted to bring all changes into Version 5)	01/03/2021
	Version 5	Incorporation of changes requested by MHRA into REC approved version. Revision of timelines	01/07/2021

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Trial Summary

Trial Title	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
Internal ref. no (or short title)	REGAL Trial
Clinical phase	Phase IV
Rationale	The conventional surgical treatment pathway for women with endometriosis-related pain is associated with a major problem due to a high risk of recurrence which, in the absence of an effective long-term medical solution, leads to a significant risk of repeat surgery with its attendant risks and costs. An effective non-surgical treatment for endometriosis-related pain has been identified as one of the top 10 research priorities by the James Lind Alliance Priority Setting partnership. An overview of Cochrane reviews has recommended the need for trials of head-to-head comparisons of medical versus surgical treatments for women with pain caused by endometriosis. NICE has also recognised the need to reduce the risk of multiple operations for recurrence.
Trial design	A randomised controlled trial comparing the clinical and cost-effectiveness of long-term Gonadotrophin Releasing Hormone Analogues (GnRHa) with add-back hormone replacement therapy (HRT) compared to laparoscopic surgery (excision or ablation of endometriosis/endometrioma) in women with recurrent pain following surgical treatment of endometriosis. Qualitative research will be embedded in an internal pilot to optimise opportunities for seeking informed consent and explore patient symptoms
Eligibility criteria	***Inclusion criteria:*** • Women aged 21–49 years with recurrent pain following conservative laparoscopic surgery for endometriosis (excision or ablation) who wish to avoid removal of ovaries and hysterectomy, irrespective of site and stage of endometriosis, number of previous surgeries or use of post-operative hormonal treatment • Women who are considered suitable for both treatment arms • Able and willing to give informed consent to participate and to participate in study procedures, including DEXA scans. (There are provisions within the protocol for recording consent from patients who are not able to read or write but who have capacity and can speak English sufficiently to understand the information being provided orally) • Willing to undergo pregnancy test prior to intervention ***Exclusion criteria:*** • Previous diagnostic laparoscopy only (no treatment to endometriosis) • Planning to conceive in the next 2 years • Current pregnancy or breast feeding • Previous bilateral oophorectomy • Current or recent (within the last 3 months) users of GnRHa • Contraindicated concomitant medications with GnRHa. These are women currently using hormonal contraceptives who are

	unwilling to stop their use during the follow-up period (for example, progesterone only pill, combined oral contraceptive pill, depo injection or contraceptive implant); medicinal products that raise prolactin levels (for example domperidone, metoclopramide, haloperidol, risperidone and sulpride); and medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (for example quinidine, disopyramide) or class III (for example amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics • Hypersensitivity to GnRH (gonadotropin releasing hormone, its analogues or to any if the excipients • Women at high risk of serious adverse effects with GnRHa such as a confirmed diagnosis of osteoporosis • Women with risk factors for osteoporosis such as chronic alcohol abuse, current heavy smokers over 20 cigarettes per day, long-term therapy with drugs that reduce bone mineral density currently or in the last 3 months, such as anticonvulsants or oral corticosteroids (2.5mg per day), family history of osteoporosis, and malnutrition, e.g. anorexia nervosa • Diagnosis of severe depression in the last 10 years. For the purposes of REGAL, severe depression includes but is not limited to suicidal thoughts, requirement for hospitalisation and symptoms that makes it almost impossible to get through daily life • Contraindications for add-back HRT use: these are women with a personal history of breast cancer, known carries of BRCA 1 and 2, personal history of venous thrombo-embolism or women with known inherited thrombophilia (e.g.: Factor V Leiden, Protein C or S or Antithrombin deficiency, Prothrombin gene mutation))
Interventions	1) GnRHa with add-back HRT for 2 years. The GnRHa is the Investigational Medicinal Product in the REGAL trial. We are considering the add back HRT to be a Non-Investigational Medicinal Product (NIMP) because it is used for preventive reasons within the study (i.e. to reduce the hypoestrogenic side effects of GnRHa and offers protection against osteoporosis). 2) Laparoscopic ablation or excision of endometriosis (includes peritoneal endometriosis lesions, endometrioma and rectovaginal disease).
Randomisation and blinding	Eligible and consenting participants will be randomised to one of two groups using the proven 24 hour web-based application, hosted by the Centre for Healthcare Randomised Trials (CHaRT) in Aberdeen. The randomisation algorithm will use recruitment site and age as minimisation covariates to allocate to treatment intervention and control groups in a ratio of 1:1. A random element will be incorporated into the randomisation algorithm
Planned sample size	320 women at two years to detect an 8-point difference on the EHP-30 pain domain for 90% power (two-sided alpha 0.05), assuming a standard deviation of 22 points. We have assumed attrition of 20% for the primary outcome (although we will strive to keep this to a minimum) which requires us to randomise 400 women in total.
Duration of study	54 months

	Objectives	Outcome measures
Primary	The primary objective is to compare GnRHa with add-back HRT to laparoscopic ablation or excision of endometriosis in terms of participants' pain measured by the pain domain of the Endometriosis Health Profile-30 (EHP-30) at 24 months post-randomisation. The primary economic objective is to assess the cost-effectiveness of GnRHa with add-back HRT versus laparoscopic ablation of endometriosis in terms of incremental cost per QALY gained at 24 months post-randomisation (costs based on health service resource use; QALYs based on EQ-5D responses).	The primary outcome is the pain domain of the condition-specific Endometriosis Health Profile-30 (EHP-30) at 24 months. The primary economic outcome is incremental cost per QALY gained from a health service perspective.
Secondary	To compare GnRHa with add-back HRT to laparoscopic ablation or excision of endometriosis in terms of: • Participants' functional health and well-being (EHP-30 at 6, 12, 18 and 24 months) • Adverse events, • Bone mineral density at baseline, 12 and 24 months for GnRHa group and baseline and 24 months for the laparoscopic surgery group • Further pharmacological treatment or surgery or other treatments for endometriosis associated pain. • Indirect costs based on time lost from productive activities over the follow-up period • Patient satisfaction • Modelled long-term cost effectiveness	***Clinical:*** • Bone mineral density (BMD) (using Dual Energy X-ray absorptiometry (DEXA) scan) will be measured for all women in the GnRHa group and a subgroup of 90 women in the laparoscopic surgery group). For GnRHa group BMD will be measured at baseline, 12 and 24 months post-randomisation, for the laparoscopic surgery group at baseline and 24 months post-randomisation; • Surgical and anaesthetic complications and adverse events; ***Patient reported*:** • Adverse events that are a result of treatment for endometriosis • Endometriosis treatment received • Discontinuation of GnRHa or endometriosis treatment • Generic (EQ-5D) and condition-specific (EHP-30) Quality of Life, measured at

		baseline, 6, 12, 18 and 24 months post-randomisation. • Pain domain of EHP 30 at 6, 12, and 18 months • Patient satisfaction • Further pharmacological treatment (change of hormonal treatment, increased use of analgesics, start of neuromodulators such as pregabalin, gabapentin, amitryptiline) or surgery for endometriosis or other treatments (eg acupuncture, CBT) for endometriosis associated pain. • Pregnancy
Statistical methods	The primary outcome will be analysed using a mixed effects linear model that includes a random effect for centre and participant, with fixed effects for treatment, time, and minimisation covariates, and baseline outcome score, and intention-to-treat approach. Treatment effects will be estimated at each time-point by time-by-treatment interaction. Secondary outcomes will be analysed in a similar way with generalised linear models appropriate for the distribution of the outcome. We will use causal models for longitudinal data with time-dependant cross-over to generate efficacy estimates. We will also explore time to repeat surgery using joint models for time-to-event and longitudinal data. Subgroup analysis to assess potential treatment moderating effects of age, stage of endometriosis, and number of previous operations (1 v >1), by modelling treatment-by-subgroup interactions. We will assess sensitivities of all treatment effect estimates to missing outcome data using imputation and pattern mixture models where appropriate. Treatment effect estimates will be presented with 95% confidence intervals. For a small proportion of women who become pregnant we plan a sensitivity analysis in which we will censor the primary outcome measured at time points after pregnancy has occurred. The analysis of trial based cost-effectiveness data will follow the same principals as the statistical analysis of the primary and secondary clinical effectiveness outcomes. The long-term cost-effectiveness analysis will rely on decision modelling techniques, with inputs informed by analysis of the trial data.	

Lay Summary

Endometriosis is a common, painful condition which affects one in ten women of childbearing age. 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. 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 (key hole surgery) which identifies areas of endometriosis within the pelvis which can then be destroyed or removed to treat pain. However, surgery rarely provides lasting relief and pain can return in up to half of treated women within five years. To reduce the chance of regrowth of endometriosis and recurrence of pain, women who are not trying to get pregnant are offered the combined oral contraceptive pill (COCP) or other contraceptives containing hormones called progestogens. Despite this, about one in three women will require more operations to treat endometriosis that has come back. Repeat surgery is invasive, expensive and risky, without guaranteeing a cure. Removing the ovaries (often along with the womb) provides the best chance of pain relief and least chance of more operations but is not an option for many premenopausal women with endometriosis.

Taking away the ovaries switches off the supply of oestrogen necessary for endometriosis tissue growth. A less invasive way of shrinking endometriosis is to use a drug called Gonadotrophin Releasing hormone analogue (GnRHa) which temporarily stops the ovaries from producing oestrogen. While very effective in terms of reducing pain, this treatment has only been used for up to a year because of side effects such as hot flushes, and night sweats caused by the lack of oestrogen, and concerns about osteoporosis (thinning of the bones). Recent research has shown that adding small doses of hormone replacement therapy (HRT) in women on GnRHa reduces the risk of side effects and osteoporosis whilst controlling the pain.

An effective long-term non-surgical treatment for endometriosis has been identified as a research priority by patients and clinicians, but to date there have been no attempts to compare long-term use (more than 1 year) of GnRHa with HRT to further key hole surgery to treat endometriosis. We therefore propose a trial comparing long-term GnRHa with added HRT with key hole surgery to treat endometriosis in women who experience recurrence of pain after surgery but wish to preserve their fertility. We have assembled a team of experts including surgeons, trialists, statisticians, health economists and patient representatives to plan the research. Involvement of patients and the public, a key element of our proposal, has been achieved in partnership with the University of Aberdeen Public Interest Research Group, Endometriosis UK and an online survey of women with endometriosis. We have also developed a clear plan to share the results of this trial with GPs, hospital doctors, professional societies, patient support groups, NHS policy makers and patients. Our findings will be made available to stakeholders through national presentations, publication in medical journals and the website of British Society of Gynaecology Endoscopy and the national charity, Endometriosis UK.

Glossary of Abbreviations	
AE	*Adverse Event*
AR	*Adverse Reaction*
AUC	*Area under the curve*
BID or bd	Twice a day
BMD	Bone Mineral Density
BNF	British National Formulary
BSGE	British Society of Gynaecology Endoscopy
CEAC	Cost-effectiveness Acceptability Curve
CHaRT	Centre for Healthcare Randomised Trials
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
COPC	Combined oral contraceptive pill
CRF	Case Report Form
CTA	Clinical Trial Application
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trial Unit
DCE	Discrete Choice Experiment
DEXA	Dual Energy X-ray absorptiometry
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EHP-30	Endometriosis Health Profile-30
EMEA	European Medicines Agency
EQ-5D	EuroQol Group's 5 dimension health status questionnaire
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EudraVIGILANCE	European database for Pharmacovigilance
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GnRHa	Gonadotrophin Releasing Hormone Analogues
GP	General Practitioner
HRQoL	Health Related Quality of Life
HRT	Hormone Replacement Therapy
HSRU	Health Services Research Unit
HTA	Health Technology Assessment
IB	Investigator Brochure
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISD	Information Statistics Division
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
IVR	Interactive Voice Response (randomisation)
LARC	Long Acting Reversible Contraceptives
LNG-IUS	Levonorgesterol Intrauterine system
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
NCT	National Clinical Trial
NHS	National Health Service
NHSG	National Health Service Grampian
NICE	National Institute for Health and Care Excellence
NIHR	National Institute Health Research
NIMP	Non-Investigational Medicinal Product
NRES	National Research Ethics Service

OD	Once a day
PI	Principal Investigator
PIC	Participant Identification Centre
PIL	Patient Information Leaflet
PMG	Project Management Group
PPI	Patient and Public Involvement
PQ	Participant Questionnaire
QA	Quality Assurance
QALY	Quality Adjusted Life Year
QID	Four times a day
QP	Qualified Person
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UK	United Kingdom
UKCRC	United Kingdom Clinical Research Collaboration
UoA	University of Aberdeen

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Project Management Group (PMG)

This group comprises the grant holders along with representatives from the Trial Office central trial team (trial manager, data co-ordinator, senior trial manager, senior IT manager, statistician, health economist).

Trial Steering Committee (TSC) Members

The membership of this committee comprises independent members along with the Chief Investigator (CI) or a nominated delegate. The other REGAL grant-holders and key members of the central office (e.g. the trial manager) may attend TSC meetings.

Data Monitoring Committee (DMC) Members

This committee comprises independent members and the trial statistician contributes as appropriate. The CI and / or a delegate may contribute to the open session of the meetings as appropriate.

Role of the Trial Sponsor and Funder

The Sponsor (co-sponsor) has responsibility for the initiation and management of the trial as defined by the UK Policy Framework for Health and Social Care Research v3.3 07/11/17. This is further defined within a co-sponsorship agreement outlining the roles and responsibilities of the parties involved in the research. Specific responsibilities delegated to another party are formally agreed and documented by the Sponsor.

The funder has oversight of the study through regular reports from the trial office. The funder appoints the independent members of the Data Monitoring and Trial Steering Committees and receives minutes from these. The funder is made aware of all outputs from the study but does not have a role in the decision to publish results from the study. In any publications, the funder is acknowledged, and appropriate disclaimer used to indicate that the views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

1. Introduction

1.1 Background

Endometriosis is a chronic, oestrogen-dependent condition that affects 1 in 10 women of reproductive age.[1,2] It is characterised by the presence of endometrium-like tissue outside the uterus, which grows under the influence of oestrogen, causing painful periods and pelvic pain. These symptoms significantly impair quality of life, require multiple contacts with healthcare providers and reduce work productivity.[3,4] While genetic, inflammatory and environmental factors are implicated in the pathogenesis of endometriosis, oestrogen is the key driver for the proliferation of endometrial cells outside the uterus, creating a pro-inflammatory environment within the pelvis. The disease is therefore rare before puberty and tends to regress spontaneously after menopause.

Definitive diagnosis and treatment involves laparoscopic (keyhole) surgery[5] but women with suspected endometriosis can be treated initially with analgesics and either the combined oral contraceptive pill (COCP) or progestogens (oral or Long Acting Reversible Contraceptives (LARCs) such as the Levo-norgesterol Intrauterine system (LNG-IUS) and Depo Provera) These drugs suppress growth of endometriosis tissue indirectly by reducing circulating levels of oestrogen or directly through the action of progestogens which induce atrophy of endometriosis tissue. Women who either do not respond to empirical hormonal treatment or have unacceptable side-effects or are trying to conceive, are referred to secondary care for laparoscopy. Current guidance from NICE recommends a 'see and treat' approach that involves surgical destruction (ablation) or removal (excision) of minimal, mild, and up to moderate endometriosis visualised at the time of initial diagnostic surgery.[6] Women with more advanced stages of endometriosis involving other organs such as bowel and bladder usually require a planned second stage surgical procedure in tertiary care. Surgical treatment tends to provide temporary pain relief lasting 6–12 months, as continued exposure to circulating oestrogen stimulates regrowth of endometriosis tissue. To prolong the benefits of surgery and prevent pain recurrence, postoperative hormonal treatment (COCP, LARCs or progestogen tablets) is recommended in women who are not planning to conceive.

Despite this approach, pain recurs in 40–50% of women after surgery, and up to 30% have a repeat operation within 5 years.[6,7] Analysis of Scottish data over a 30-year period has shown that two out of three women with a new surgical diagnosis of endometriosis face repeat gynaecological surgery (median time 1.8 years), and 45% undergo three or more operations.[8] Medical and surgical options to treat recurrence are limited. Pain management often requires repeated courses of medical treatment or multiple operations. More radical surgery in the form of removal of the ovaries (oophorectomy), which is conventionally combined with hysterectomy, is considered as a last resort. Observational studies have shown that this approach is associated with the lowest chance of pain recurrence[9,10] but carries major surgical risks, causes permanent loss of fertility, and leads to problems due to early menopause. It is therefore unacceptable to many women with endometriosis.

The most promising alternative to oophorectomy is the use of a group of drugs known as Gonadotrophin Releasing Hormone analogues (GnRHa). GnRHa mimic oophorectomy by suppressing ovarian production of oestrogen thus shrinking endometriotic implants and reducing pain. Although highly effective, GnRHa, which cause circulating oestrogen levels to fall to post-menopausal levels, have only been used for short periods (6–12 months) because of side effects such as hot flushes and concerns about osteoporosis. According to the 'oestrogen threshold hypothesis', complete suppression of oestrogen may not be needed to control endometriosis-associated pain; instead, the oestrogen level may be adjusted such that pain is controlled without significant side effects.[11] Addition of low dose HRT to GnRHa[12] can potentially provide an effective longer term non-surgical option for recurrent endometriosis which offers a reversible medical alternative to removal of the ovaries without the associated surgical and anaesthetic risks.

GnRHa treatment has no adverse effect on fertility, though women cannot get pregnant while using the medication. In a Cochrane review, the use of GnRHa for 3 months prior to IVF in women with endometriosis improves pregnancy rates.[13] The use of gonadotropin-releasing hormone (GnRH)

analogues, both agonists and antagonists, have a protective effect on the ovaries. The primary mechanism of action of GnRHa is to suppress the gonadotropin levels to simulate pre-pubertal hormonal milieu and subsequently prevent primordial follicles from maturation. Hence, they are recommended in young women undergoing chemotherapy to protect ovarian function and fertility.[14,15]

1.2 Rationale for the trial

The conventional surgical treatment pathway for women with endometriosis-related pain is associated with a major problem due to a high risk of recurrence which, in the absence of an effective long-term medical solution, leads to a significant risk of repeat surgery with its attendant risks and costs. This trial is timely as an effective non-surgical treatment for endometriosis-related pain has been identified as one of the top 10 research priorities by the James Lind Alliance Priority Setting partnership.[16] An overview of Cochrane reviews has recommended the need for trials of head-to-head comparisons of medical versus surgical treatments for women with pain caused by endometriosis.[17] NICE has also recognised the need to reduce the risk of multiple operations for recurrence.[6] We therefore propose a randomised trial to evaluate the clinical and cost-effectiveness of longer-term use of GnRHa with add-back HRT as an alternative treatment to further laparoscopic surgery (to excise or ablate endometriosis) in women who present with recurrence of pain following previous surgery for endometriosis but wish to retain their fertility.

1.3 Assessment and management of risk (GnRHa)

GnRHa are widely used for management of endometriosis associated pain. Continuous use of GnRHa leads to down-regulation of GnRH-receptor synthesis in the pituitary resulting in suppression of pituitary-gonadal axis and subsequent suppression of oestrogen and progesterone secretion by the ovary. An initial flare response is noted for the first 7 days followed by suppression of ovarian hormonal production and amenorrhoea. Lack of oestrogen leads to atrophy of endometriotic lesions resulting in improvement of pain. GnRHa can be administered by various routes though commonly given as intramuscular injections and subcutaneous implants. The main side effects include hypoestrogenic effects such as hot flushes, night sweats and other menopausal symptoms. Prolonged use can lead to reduction in bone mineral density. While effective in treating endometriosis pain, GnRHa are only licensed for 6 months use in endometriosis due to concerns regarding osteoporosis. Addition of concomitant HRT reduces hypoestrogenic side effects and protects against osteoporosis.[12] In this trial GnRHa with add back HRT will be used for two years.

There are seven GnRHa preparations that we are considering as appropriate for treatment initiation within the study (described in section 5.1). Five of these are licensed for use in endometriosis for 6 months; one is licensed for endometriosis and the license indicates that the maximum duration of treatment without add back HRT is 6 months; and the seventh is not licensed for use in endometriosis. All are used in clinical practice for the treatment of endometriosis for periods up to (and longer than) 6 months. In the trial, as HRT is commenced concomitantly with GnRHa right from the beginning, we are mitigating the risk of osteoporosis which would be lower than the current license of using GnRHa for 6 months without HRT.

Women at high risk of serious adverse effects with GnRHa such as a confirmed diagnosis of osteoporosis will be excluded from the study.

DEXA scans to monitor bone mineral density will be undertaken in all women in the GnRHa arm and a sub-group of 90 women in the surgery arm. In the GnRHa arm, these will be done at baseline, 12 months and 24 months and in the surgery arm at baseline and 24 months only.

2. Trial Aims and Objectives

The primary aim of the trial is to evaluate the clinical and cost-effectiveness of long-term use of GnRHa with add-back HRT as an alternative treatment to further laparoscopic surgery (excision or ablation of endometriosis) in women who present with recurrence of pain following previous surgery for

endometriosis but wish to retain their fertility. For the purposes of this trial, the term 'women' includes all persons assigned female sex at birth.

2.1 Primary objectives:

- To compare GnRHa with add-back HRT to laparoscopic ablation or excision of endometriosis in terms of participants' pain measured by the pain domain of the Endometriosis Health Profile-30 (EHP-30)[18-22] at 24 months post-randomisation;
- To assess the cost-effectiveness of GnRHa with add-back HRT versus laparoscopic ablation or excision of endometriosis in terms of incremental cost per QALY gained at 24 months post-randomisation (costs based on health service resource use; QALYs based on EQ-5D responses).

2.2 Secondary objectives:

To compare GnRHa with add-back HRT to laparoscopic ablation or excision of endometriosis in terms of:

- Participants' functional health and well-being (EHP-30 at 6, 12, 18 and 24 months)
- Adverse events,
- Bone mineral density at baseline, 12 and 24 months for GnRHa group and baseline and 24 months for the laparoscopic surgery group
- Further pharmacological treatment or surgery or other treatments for endometriosis associated pain.
- Indirect costs based on time lost from productive activities over the follow-up period
- Patient satisfaction
- Modelled long-term cost effectiveness

The outcomes for the primary and secondary objectives are fully described in section 6 of this protocol.

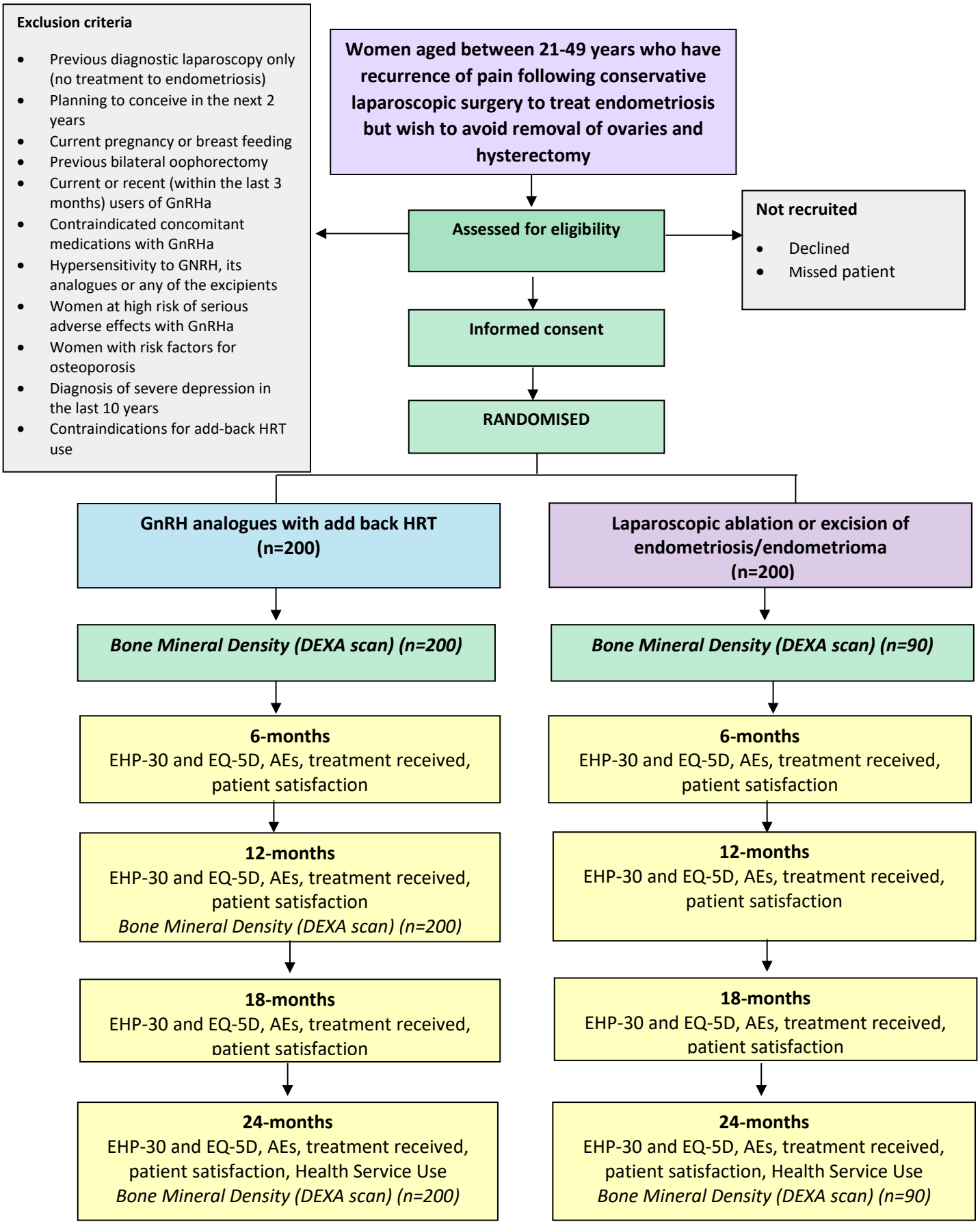
2.3 Qualitative sub-study

There is an embedded qualitative sub-study in REGAL (see appendix 2). The aim of the qualitative sub-study is to identify challenges relating to design and conduct of the trial, particularly around recruitment, and to provide timely feedback and improve successful recruitment and delivery of the REGAL trial.

3. Trial Design

This is a randomised controlled trial comparing the clinical and cost-effectiveness of long-term GnRHa with add-back HRT compared to laparoscopic surgery (excision or ablation of endometriosis/endometrioma) in women with recurrent pain following surgical treatment of endometriosis. The trial structure is shown in Figure 1 (Flow Diagram). Qualitative research will be embedded in an internal pilot to optimise opportunities for seeking informed consent and explore patient symptoms.

Figure 1 Flow diagram



3.1 Interventions to be evaluated

*i) **Laparoscopic ablation or excision of endometriosis/endometrioma***

Laparoscopic ablation or excision of endometriosis/endometrioma is currently the standard surgical procedure for the management of symptomatic endometriosis. At the time of laparoscopy (key hole surgery) endometriosis lesions or endometrioma are ablated or excised to provide relief from pain. Ablation or excision is done for all stages of endometriosis though excision is more common for deep disease. Surgery for moderate to severe endometriosis (stage 3 and 4) is more complex and usually performed in tertiary endometriosis centres.

Ablation or excisional procedures are done under a general anaesthetic. It usually involves three to four small incisions in the abdomen, which allow the surgeon to evaluate and destroy or remove all endometriotic lesions. The operation takes between 45 and 120 minutes depending on the extent and location of lesions and severity of endometriosis. Most patients have the procedure as day case though some may be admitted for one or more nights.

*ii) **Gonadotrophin Releasing Hormone analogues (GnRHa) with add back Hormone Replacement Therapy (HRT)***

GnRHa are widely used for management of endometriosis associated pain. Continuous use of GnRHa leads to down-regulation of GnRH-receptor synthesis in the pituitary resulting in suppression of pituitary-gonadal axis and subsequent suppression of oestrogen and progesterone secretion by the ovary. An initial flare response is noted for the first 7 days followed by suppression of ovarian hormonal production and amenorrhoea. Lack of oestrogen leads to atrophy of endometriotic lesions resulting in improvement of pain. GnRHa can be administered by various routes though commonly given as intramuscular injections and subcutaneous implants. The main side effects include hypoestrogenic effects such as hot flushes, night sweats and other menopausal symptoms. Prolonged use can lead to reduction in bone mineral density. While effective in treating endometriosis pain, GnRHa are only licensed for 6 months use in endometriosis due to concerns regarding osteoporosis. Addition of concomitant HRT reduces hypoestrogenic side effects and protects against osteoporosis. In this trial GnRHa with add back HRT will be used for two years.

The GnRHa is the Investigational Medicinal Product, and its use within the study is described in section 5.1 of this protocol. We are considering the add back HRT to be a Non-Investigational Medicinal Product (NIMP) because it is used for preventive reasons within the study (ie will reduce the hypoestrogenic side effects of GnRHa and offers protection against osteoporosis).

Further details about the intervention are provided in section 5.1.

4. Trial Recruitment

4.1 Trial population

We will recruit 400 women aged between 21–49 years with recurrence of pain following previous conservative surgical treatment (excision or ablation) of endometriosis who wish to avoid removal of ovaries and hysterectomy.

4.2 Setting

This trial will take place in British Society of Gynaecology Endoscopy (BSGE) accredited UK Endometriosis centres. Eligible women referred with recurrence of pain after previous surgical treatment of endometriosis will be approached by the research team for participation.

4.3 Inclusion and exclusion criteria

Inclusion criteria:

- Women aged 21–49 years with recurrent pain following conservative laparoscopic surgery for endometriosis (excision or ablation) who wish to avoid removal of ovaries and hysterectomy, irrespective of site and stage of endometriosis, number of previous surgeries or use of post-operative hormonal treatment
- Women who are considered suitable for both treatment arms
- Able and willing to give informed consent to participate and to participate in study procedures, including DEXA scans. (T*here are provisions within the protocol for recording consent from patients who are not able to read or write (but who have capacity and who can speak English sufficiently to understand the information being provided orally); see section 4.7*)
- Willing to undergo pregnancy test prior to intervention

Exclusion criteria:

- Previous diagnostic laparoscopy only (no treatment to endometriosis)
- Planning to conceive in the next 2 years
- Current pregnancy or breast feeding
- Previous bilateral oophorectomy
- Current or recent (within the last 3 months) users of GnRHa
- Contraindicated concomitant medications with GnRHa. These are women currently using hormonal contraceptives who are unwilling to stop their use during the follow-up period (for example, progesterone only pill, combined oral contraceptive pill, depo injection or contraceptive implant); medicinal products that raise prolactin levels (for example domperidone, metoclopramide, haloperidol, risperidone and sulpride); and medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (for example quinidine, disopyramide) or class III (for example amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics
- Hypersensitivity to GnRH (gonadotropin releasing hormone), its analogues or to any of the excipients
- Women at high risk of serious adverse effects with GnRHa such as a confirmed diagnosis of osteoporosis
- Women with risk factors for osteoporosis such as chronic alcohol abuse, current heavy smokers over 20 cigarettes per day, long-term therapy with drugs that reduce bone mineral density currently or in the last 3 months, such as anticonvulsants or oral corticosteroids (2.5mg per day), family history of osteoporosis, and malnutrition, e.g. anorexia nervosa
- Diagnosis of severe depression in the last 10 years For the purposes of REGAL, severe depression includes but is not limited to suicidal thoughts, requirement for hospitalisation and symptoms that makes it almost impossible to get through daily life.[23]
- Contraindications for add-back HRT use: these are women with a personal history of breast cancer, known carries of BRCA 1 and 2, personal history of venous thrombo-embolism or women with known inherited thrombophilia (e.g.: Factor V Leiden, Protein C or S or Antithrombin deficiency, Prothrombin gene mutation)

4.4 Co-enrolment

Participants will be permitted to take part in non-interventional studies (e.g. questionnaire studies). Those enrolled in the active intervention phase of another gynaecological or other interventional trial will be excluded but they would be eligible for inclusion if they were now in the long term follow up phase of such trials. Patients who were in PRE-EMPT or other relevant endometriosis trials, who have completed the active intervention phase and have recurrence of pain will be eligible for inclusion.

4.5 Identifying and approaching participants

Women will be recruited from endometriosis clinics and general gynaecology clinics of hospitals which are BSGE accredited endometriosis centres. This approach has a number of advantages including:

- Dedicated weekly endometriosis clinics run by specialists who are likely to be able to access a large pool of eligible participants (>5 per centre per month);
- Will capture women with all stages of endometriosis;
- A higher caseload of women with recurrent symptoms – the target population for REGAL;
- Ability to offer optimal surgery performed by specialists thus ensuring standardisation of the comparator arm;
- Presence of endometriosis nurse(s) in each centre, who along with research nurse(s) can monitor compliance with HRT for the GnRHa arm, promote recruitment and provide patient support.

Eligible women who are referred with recurrence of pain after previous laparoscopic surgery will be identified by the REGAL research nurse(s) in each centre as a potential participant, prior to their outpatient appointment. Local procedures at the participating hospitals are different and the timing and mode of approach to women and the consent process may vary to accommodate both the specific circumstances at each site and the needs of the women.

Each eligible woman will be given or sent (generally prior to the outpatient clinic appointment or at the clinic) a Patient Information Leaflet (PIL) describing the study and will have the opportunity to read this before making a decision whether or not to take part. The gynaecologist who will be providing her clinical care will discuss treatment options and establish eligibility, and women will have the opportunity to discuss the study with the gynaecologist – these consultations may occur face-to-face or virtually using NHS platforms accepted locally and will be recorded as part of the qualitative sub-study (see appendix 2). Women can also discuss all aspects of the proposed research with other members of the local clinical team, the Research Nurse, family and friends and, if appropriate, with their GP before deciding whether or not to take part in the study. Women may decide to participate during an initial consultation with their gynaecologist or alternatively at home.

If the woman decides to participate at home, they will be sent or given (if initial consultation is face-to-face) the consent form and baseline questionnaire for completion. If the woman agrees to be contacted at home, she may receive a telephone call from the site Research Nurse to discuss any queries. Women who decide to participate at home will send their completed documents (consent form and baseline questionnaire) through the post to the local team at their treating hospital. Details of the consent discussion, including discussion date, will be recorded on the Trial inclusion CRF.

The PIL and consent form will also refer to the possibility of long-term follow up to determine repeat surgery and pregnancy.

All women who are randomised into the study will be assigned a unique Study Number.

Eligibility will be confirmed by the PI, or by a medically qualified delegate at each recruitment site.

A paper screening log will be kept at site, with limited (non-identifiable) information uploaded onto the study website.

4.6 Non-recruited participants

The following anonymised information will be monitored and collected for all potentially eligible participants

- Year of birth
- Date of consultation when approached about the study
- Reason for not participating if willing to give a reason

4.7 Informed consent

Informed consent to participate in the trial will be sought and obtained according to Good Clinical Practice (GCP) guidelines. As part of the informed consent process, potential participants will be made aware of all aspects of the study, including the potential risks and their responsibilities. Women will be counselled about additional risks depending on the stage and site of endometriosis in line with standard practice. There is no minimum time that potential participants should be given to decide whether to participate in the trial. Potential participants will be given enough time, and as long as they want, to accept or decline involvement and will be given opportunity to ask questions and to have these answered before giving consent.

It will be explained that entry into the trial is entirely voluntary and that treatment and care will not be affected by their decision and they can withdraw at any time. In the event of their withdrawal it will be explained that their data collected to date cannot be erased and will be used in the final analyses.

Participants who cannot give informed consent (e.g. due to their mental state) will not be eligible for participation. Following informed consent, if a participant loses capacity, the consent given when capable remains legally valid. In such circumstances, a decision needs to be made, in conjunction with the participant and any family or carers, in relation to ongoing participation in the study.

Patients who are not able to read or write (but who have capacity and who can speak English sufficiently to understand the information being provided orally) can agree to take part in the study. In such cases, the study team will provide them with written literature about the study and read and discuss this information with the potential participant. There should also be a discussion about the support networks that the patient has to facilitate their participation in the study (for example help to complete questionnaires). If the potential participant is fully informed and wishes to take part in the study, they will be asked to sign or make their mark on the consent form. Their agreement to take part in the study should be witnessed by someone independent from the research team.

Procedures to seek and gain informed consent from eligible potential participants are agreed and confirmed by Research Ethics Committees with responsibility for reviewing applications for research. The application for approval is made via the NHS National Research Ethics Service.

Where informed consent is received in person, this should be received by an appropriately trained individual who is listed on the delegation log. Consent forms that are returned by post are checked, signed and dated with the date of receipt by someone who is listed on the delegation log with appropriate delegated responsibilities.

A copy of the consent form should be forwarded to the trial office for retention in the Trial Master File (TMF).

4.8 Randomisation and allocation

Eligible and consenting participants will be randomised to one of two groups using the proven 24 hour web-based application, hosted by the Centre for Healthcare Randomised Trials (CHaRT) in Aberdeen. The randomisation algorithm will use recruitment site, and age (21-30 years, 31-40 years, 41-49 years) as minimisation covariates to allocate to treatment intervention and control groups in a ratio of 1:1. A random element will be incorporated into the randomisation algorithm. A person with delegated authority will access the web-based system. At randomisation, an email will be sent to the site research team, including the PI, and the trial office, informing them of the allocation.

4.9 Administration arrangements post recruitment

Following trial entry, the trial office will:

- Notify the GP in writing that a participant has joined the trial.
- Write to the woman confirming her randomisation and what will happen next in the study

The site research team should:

- For those randomised to surgery, add them to the waiting list for surgery.
- For those randomised to surgery and who consent to the DEXA sub-study, arrange baseline DEXA scan and follow-up scan at 24 months.
- For those randomised to GnRHa, arrange prescription and initiation of treatment (either via GP or secondary care).
- For those randomised to GnRHa, arrange baseline DEXA scan and follow-up scans at 12 and 24 months.
- File a copy of the consent form in the hospital notes along with information about the trial.
- Enter trial data regarding the participant into the bespoke trial website.
- Maintain trial documentation at site.
- Return a copy of the signed consent form to the Trial Office in Aberdeen.

5. Trial interventions

Both laparoscopic surgery for excision or ablation of endometriosis/endometrioma and GnRHa with add back HRT are widely used for the treatment of endometriosis associated pain, though GnRHa is only licensed for 6 months use for endometriosis treatment.

5.1 Gonadotrophin Releasing Hormone analogues with add back Hormone Replacement Therapy

The GnRHa is the Investigational Medicinal Product for the REGAL trial. We are considering the add back HRT to be a Non-Investigational Medicinal Product (NIMP) because it is used for preventive reasons within the study (i.e. to reduce the hypoestrogenic side effects of GnRHa and offers protection against osteoporosis). Women will be recommended to comply with the HRT whilst taking the GnRHa.

Gonadotrophin Releasing Hormone agonists (GnRHa) contains a family of drugs (e.g. goserelin, triptorelin and leuprorelin acetate) with the same mode of action. GnRHa can be administered through various routes including intramuscular (IM) injections monthly or every 12 weeks, subcutaneously (SC) every 12 weeks or nasal/buccal spray daily.

For the purpose of the trial 3 monthly preparations are preferred to promote compliance, but monthly preparations are acceptable.

GnRHa preparations which can be used at treatment initiation are included in table 1 below. If new preparations of GnRHa become available during the course of the study, consideration will be given as to whether these are acceptable for use at treatment initiation – and an amendment to protocol will be submitted to add the new preparation to table 1. During follow-up, alternative intramuscular and sub-cutaneous GnRHa preparations (not listed in table 1) every 4 or 12 weeks will be acceptable depending on availability at various sites following a discussion between the PI (or delegate) at the site and the CI. For the purposes of the trial, daily spray is not acceptable as the initial form of GnRHa prescribed, but women who change to a daily preparation will continue to be followed up within the study. Women may switch between various forms of GnRHa, depending on their preference and tolerance of various preparations. However, treatment with GnRHa should continue for 24 month post-randomisation unless:

- A serious adverse reaction to GnRHa occurs and in the opinion of the investigator or clinician that it is medically necessary to stop the GnRHa.
- A participant wishes to become pregnant.
- The participant declines to start or declines to continue taking the trial drug for any reason.

Regardless of the compliance to GnRHa women will be continued to be followed up within the study.

GnRHa will not be specifically manufactured or labelled for use within the REGAL trial. The trial will use routine stocks prescribed by the clinical team or their GP and dispensed by hospital or local pharmacy.

Table 1: GnRHa preparations which can be used at treatment initiation

Drug name	Preparation	Dose	Route	Frequency	SmPC	Current license	Off license use within the study
Triptorelin	Decapeptyl® SR	11.25 mg	Intramuscular injection	Every 3 months	https://www.medicines.org.uk/emc/product/780	Licensed for use in endometriosis for 6 months	For a period of longer than 6 months
Triptorelin	Decapeptyl SR	3 mg	Intramuscular injection	Every 28 days	https://www.medicines.org.uk/emc/product/963	Licensed for use in endometriosis for 6 months	For a period of longer than 6 months
Triptorelin	Gonapeptyl Depot	3.75 mg	Intramuscular injection	Every 28 days	https://www.medicines.org.uk/emc/product/2229/smpc	Licensed for use in endometriosis. Maximum duration of treatment without add back treatment 6 months	For a period of longer than 6 months
Leuprorelin acetate	Prostap 3 DCS®	11.25 mg	Intramuscular injection	Every 3 months	https://www.medicines.org.uk/emc/product/4651/smpc	Licensed for use in endometriosis for 6 months	For a period of longer than 6 months
Leuprorelin acetate	Prostap 3 DCS®	3.75 mg	Intramuscular injection	Every 28 days	https://www.medicines.org.uk/emc/product/4650	Licensed for use in endometriosis for 6 months	For a period of longer than 6 months
Goserelin	Zoladex LA®	10.8 mg	Subcutaneous implant in anterior abdominal wall	Every 12 weeks	https://www.medicines.org.uk/emc/product/1567/smpc	Not licensed for use in endometriosis	For use in endometriosis
Goserelin	Zoladex LA®	3.6 mg	Subcutaneous implant in anterior abdominal wall	Every 28 days	https://www.medicines.org.uk/emc/product/1543	Licensed for use in endometriosis for 6 months	For a period of longer than 6 months

5.1.1 Non-Investigational Medicinal Product (add back HRT)

Hormone replacement therapy (HRT) is licensed to treat oestrogen deficiency in peri- and/or post-menopausal women. GnRHa induces menopause in women so HRT is being used within its license. HRT is used currently in standard care in women prescribed GnRHa.

Concomitant add back HRT will be in the form of either continuous combined HRT containing oestrogen and progesterone OR a synthetic steroid Tibolone which has oestrogenic, progestogenic and anti-oestrogenic selective activity on different target tissues. Continuous combined HRT containing oestrogen and progesterone may be given orally or transdermally and it is recommended that they are started at the time of starting the GnRHa. The dose of oestrogen may be titrated to obtain adequate relief from vasomotor side effects of GnRHa injections/implants.

For women having Levonorgesterel Intra Uterine System (LNG IUS) which includes progesterone (e.g. Mirena), oestrogen will be given orally or transdermally and it is recommended that the oestrogen is started at the time of starting the GnRHa. The dose of oestrogen may be titrated to obtain adequate relief from vasomotor side effects of GnRHa injections/implants.

Tibolone is recommended to be prescribed orally as 2.5mg daily. Additional oestrogen (orally or transdermally) can be added to obtain adequate relief from vasomotor side effects of GnRHa injections/implants.

Women may switch between various forms of HRT depending on their preference and tolerance of various preparations. Participants will be recommended to comply with HRT whilst taking GnRHa. Should they decide to continue taking GnRHa but discontinue HRT (for reasons such as intolerance) they will be counselled about the risk of osteoporosis and fractures. After appropriate counselling, participants may choose to remain on GnRHa for the management of pain without taking HRT (or restart HRT or to also discontinue the GnRHa).

HRT will not be specifically manufactured or labelled for use within the REGAL trial. The trial will use routine stocks prescribed by the clinical team or their GP and dispensed by hospital or local pharmacy.

5.1.2 Prescription of REGAL trial drug treatment

The administration of GnRHa and addback HRT will depend on the local policy and can be administered exclusively in secondary care, initiated in secondary care and continued in primary care or administered exclusively in primary care. The intention would be to initiate the allocated treatment as soon as possible to minimise non-compliance and for the convenience of the participant. For women randomised to GnRHa, where this will be administered in primary care, a letter will be sent to the GP specifying the name, dose and duration of GnRHa and add back HRT that is being recommended (based on the preference of the participants and their secondary care clinicians) asking the GP to prescribe and initiate treatment. However, in such cases, all responsibility for monitoring and follow-up will remain with the local PI and research team. Women will be advised to contact the research team directly if they have any issues, concerns or problems related to the GnRHa and HRT. In addition, at each questionnaire follow-up women will be asked to report any side effects of treatment. A pregnancy test will be conducted prior to intervention (see section 5.1.5 for further information).

If the GP does not prescribe/ initiate the GnRHa and add back HRT that is recommended, the treatment can be provided in secondary care if acceptable to the participant. A decision not to prescribe/initiate GnRHa will NOT be considered a breach of protocol within this pragmatic study and the women will be followed up within the study. At each 6-month questionnaire, we will ask women to report the type and frequency of GnRHa, and whether they are taking HRT.

5.1.3 Participants' Compliance

Maximising compliance of women to their allocated treatment
We will try to avoid women not commencing the allocated treatment firstly by careful counselling with respect to childbearing intentions. As described in section 5.1.1, women randomised to GnRHa where this will be administered in primary care, a letter will be sent to the GP asking them to prescribe and initiate treatment. It is expected that women will receive the medication within 4-6 weeks of randomisation depending where they are in their menstrual cycle (GnRHa should be started during the first 5 days of the menstrual cycle). When required, the research nurse will follow up participants in the GnRHa arm by telephone, email or text message to record the date of first administration of GnRHa and HRT. For those who have not received treatment by 6 weeks, a reminder will be sent to the GP or PI as appropriate. To maintain compliance women will be counselled in detail about an initial 'flare response' with GnRHa where symptoms may worsen for the first -10 days before the pain is controlled. Compliance with HRT will be emphasised to minimise vasomotor side effects and protect bone mineral density.

Monitoring compliance
Follow-up questionnaires every 6 months will ask for self-reported compliance to the allocated treatment, including the type and frequency of any GnRHa, and any other treatments received for endometriosis.

5.1.4 Special warnings and precautions for use of GnRHa
There is the potential for other medicinal products to affect GnRHa and conversely the potential for GnRHa to affect other medicinal products. For further details regarding guidance on prohibited and permitted medications and potential interactions with other medications please see section 5.1.6.

The use of GnRHa is likely to cause reduction in bone mineral density (BMD) averaging 1% per month. Every 10% reduction in bone mineral density is linked with about a two to three times increased fracture risk. No specific data are available for patients with established osteoporosis or with risk factors for osteoporosis (e.g. chronic alcohol abuse, smokers, long-term therapy with drugs that reduce bone mineral density, e.g. anticonvulsants or corticosteroids, family history of osteoporosis, malnutrition, e.g. anorexia nervosa). Available data suggests that concomitant addback HRT protects against the loss of bone mineral density. Within the REGAL trial all women randomised to GnRHa will be prescribed HRT to provide this protection. Consideration should be given to additional measures in order to counteract loss of bone mineral density (eg good calcium intake, regular exercise).

In the majority of women, currently available data suggest that recovery of bone loss occurs after cessation of GnRHa therapy.

Women will receive information in the PIL about GnRHa and bone mineral density. This will also form part of the informed consent discussion.

Used at the recommended dose, GnRHa causes constant hypogonadotropic amenorrhoea. Since menses should stop during GnRHa treatment, the patient should be instructed to notify the site research team if regular menstruation persists.

After withdrawal of treatment, ovarian function resumes, and ovulation occurs. A non-hormonal method of contraception should be used throughout treatment including for 3 months after the duration of the last injection (except for those with Levonorgesterel IUS in situ) (see section 5.1.5 for more detail).

Rarely, treatment with GnRHa may reveal the presence of a previously unknown gonadotroph cell pituitary adenoma. These patients may present with a pituitary apoplexy characterised by sudden

headache, vomiting, visual impairment and ophthalmoplegia. In this situation GnRHa should be stopped and where necessary further investigations such as MRI to exclude pituitary adenoma should be considered.

There is an increased risk of incident depression (which may be severe) in patients undergoing treatment with GnRHa. Patients should be informed accordingly and treated as appropriate if symptoms occur. We will screen two questions in returned follow-up questionnaires (anxiety/ depression dimension of EQ-5D and bothersome side effects of treatment) and if either indicate that the women may be depressed, an alert will be sent to the local trial team to follow-up and action as appropriate. Those with a diagnosis of severe depression in the last 10 years will be excluded from the trial.

5.1.5 Overdose

No case of overdose of GnRHa has been reported. Animal data do not predict any effects other than those on sex hormone concentration and consequent effect on the reproductive tract. If overdose occurs, symptomatic management is indicated.

5.1.6 Pregnancy, lactation and contraception

Animal studies have not revealed any teratogenic effects. However, GnRHa should not be used during pregnancy since concurrent use of GnRHa is associated with a theoretical risk of abortion or foetal abnormality. During post-marketing surveillance and in a limited number of pregnant women who were exposed inadvertently to GnRHa, there were no reports of malformation or foetotoxicity attributable to the product. However, the number of patients is too small to draw conclusions regarding the risk of foetal malformations or foetotoxicity.

Women who are currently pregnant or planning to conceive within the two years following recruitment are not eligible for the study. All participants will be asked to use their usual contraception or barrier contraception until their GnRHa is initiated. For women receiving GnRHa in primary care, a pregnancy test will be issued from the trial office and the woman asked to perform the test within seven days prior to initiation of the GnRHa (at recruitment to the study, agreement to do this will be part of the consent process). The GP/practice nurse will be asked by letter (issued after randomisation) to confirm a negative pregnancy test with the participant prior to administration of the GnRHa. . If they have any concerns about the possibility of being pregnant at the time the GnRHa is initiated, they will be asked to raise it with the doctor or nurse initiating treatment and the pregnancy test would be repeated in primary care. For women receiving GnRHa in secondary care, a pregnancy test will be performed as part of routine care prior to administration of the GnRHa.

If a patient becomes pregnant while receiving GnRHa, therapy should be discontinued. GnRHa is not recommended for use during lactation.

The GnRHa should cause constant hypogonadotropic amenorrhoea and therefore act as a hormonal contraception. Women in the GnRHa arm will be provided with contraceptive advice as detailed below.

Women who have LNG-IUS

LNG-IUS can be used as the progesterone arm of HRT, and will offer contraceptive properties. Therefore, additional barrier contraception is not required.

Women who do not have LNG-IUS

Women must use a barrier contraception for the duration of GnRHa use and for three months post GnRHa treatment. These women will be advised to avoid hormonal contraception for the duration of GnRHa use.

5.1.7 Interaction with other medicinal products and other forms of interaction

Prohibited concomitant therapies includes hormonal contraceptive drugs (for example progesterone only pill, combined oral contraceptive pill, depo injection or contraceptive implant), medicinal products that raise prolactin levels (for example domperidone, metoclopramide, haloperidol, risperidone and sulpride) and medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (for example quinidine, disopyramide) or class III (for example amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics.

5.1.8 GnRHa treatment discontinuation criteria

GnRHa therapy should be discontinued following a diagnosis of severe depression, when bone mineral density falls within the osteopenic range (T score <-1.5) or a clinically significant decrease is observed (greater than 6% loss as expected with licensed regime for GnRHa; see Appendix 1 for further details), other intolerable adverse events experienced by the participant, pregnancy and at the participants request.

5.1.9 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines during GnRHa treatment have been performed. However, the ability to drive and use machines may be impaired should the patient experience dizziness, somnolence and visual disturbances (being possible undesirable effects of GnRHa treatment), or resulting from the underlying disease.

5.1.10 Summary of Product Characteristics (SmPCs)

All GnRHa preparations have similar properties. GnRHa are synthetic form of hypothalamic gonadotrophin-releasing hormone. They stimulate the synthesis and release of follicle-stimulating hormone and, in particular, luteinising hormone in the anterior lobe of the pituitary. Continuous use leads to down-regulation of GnRH-receptor synthesis in the pituitary and results in a paradoxical reduction in the oestrogen and progesterone secretion by the ovary.

The acceptable forms of GnRHa to be offered at treatment initiation are listed in table 1, section 5.1. For the assessment of expectedness of serious adverse reactions (SARs; see section 8 for definition), the relevant SmPC for that form of GnRHa will be used. The version of the SmPC to be used for assessment will be clearly documented within the site file and available on the study website. Any updates to the SmPCs for forms of GnRHa used in the study will be reviewed at the time of DSUR preparation and any updates to the SmPC version used will be submitted for review as a substantial amendment.

5.1.11 Drug accountability

Routine stocks of GnRHa and HRT will be used. These will be prescribed by the clinical team or their GP and dispensed by hospital or local pharmacy. As the allocated interventions will be taken from normal, non-trial stock the standard NHS labelling for dispensed medicines will apply and study-specific drug accountability records will not be required. If any stock dispensed to women as part of the trial intervention becomes the subject of a medicine recall or drug alert, this will be handled through routine NHS procedures. Product liability will rest with the holders of the manufacturing authorisations.

5.2 Laparoscopic excision/ablation of endometriosis/endometrioma

Laparoscopic ablation or excision of endometriosis/endometrioma is a well-established procedure in current NHS practice (see section 3.1 for more details). Women randomised to surgery will be added to the waiting list for surgery soon after randomisation. The research nurse will monitor the surgical lists to identify when surgery has been booked. The participant will be asked to use their usual contraception or barrier contraception until their operation and a pregnancy test will be performed as part of routine care prior to the procedure.

Within the study, ablation or excision or a combination of ablation and excision can be used. Excised material will be sent for pathological examination. Women will be recommended to take hormonal contraception of their choice postoperatively to minimise recurrence of endometriosis. This will be recorded in each follow up questionnaire. Women who decline to use hormonal contraception will continue to be followed up within the study.

Any incidental findings that are identified during surgery will be handled as per normal NHS standard of care procedures

5.3 Additional treatment

Women in the GnRHa arm may never initiate or discontinue GnRHa treatment. These women will remain within the trial for follow-up, but can have other treatment (including surgery) for their endometriosis. Women in the surgery arm may not have surgery. Again, these women will remain within the trial for follow-up, but can have other treatment (including GnRHa) for their endometriosis.

6. Outcome Measures

6.1 Primary outcome measure

Primary patient outcome: The primary outcome is the pain domain of the condition-specific Endometriosis Health Profile-30 (EHP-30)[18-22] at 24 months.

***Primary economic outcome*:** Incremental cost per QALY gained from a health service perspective.

6.2 Secondary outcome measures

Clinical:

- Bone mineral density (BMD) (using Dual Energy X-ray absorptiometry (DEXA) scan) will be measured for all women in the GnRHa group and a subgroup of 90 women in the laparoscopic surgery group. For GnRHa group BMD will be measured at baseline, 12 and 24 months post-randomisation, for the laparoscopic surgery group at baseline and 24 months post-randomisation;
- Surgical and anaesthetic complications and adverse events collected from participants medical notes;

***Patient reported (self-completed questionnaires at 6, 12, 18 and 24 months post-randomisation unless stated otherwise)*:**

- Adverse events that are a result of treatment for endometriosis
- Endometriosis treatment received
- Discontinuation of GnRHa or endometriosis treatment
- Generic (EQ-5D) and condition-specific (EHP-30) Quality of Life, measured at baseline, 6, 12, 18 and 24 months post-randomisation.
- Pain domain of EHP 30 at 6, 12, and 18 months post-randomisation
- Patient satisfaction measured on a six-point scale from 'totally satisfied' to 'totally dissatisfied'
- Further pharmacological treatment (change of hormonal treatment, increased use of analgesics, start of neuromodulators such as pregabalin, gabapentin, amitryptiline) or surgery for endometriosis or other treatments (eg acupuncture, CBT) for endometriosis associated pain.
- Pregnancy

***Economic*:**

- Indirect costs based on time lost from productive activity measured over the follow-up period (assessed via patient questionnaires);
- Long-term cost-effectiveness, up to time of menopause, based on decision modelling;

6.3 Long term outcomes (beyond 2 year horizon)

Data on long-term outcomes (beyond 2 years) including repeat surgery and pregnancy will be obtained by linking with Hospital Episode Statistics (HES) for England, Welsh data for Wales and Information Services Division (ISD) data for Scotland. We will seek consent for such linkage at the outset, but any such linkage will require separate funding.

7. Data Collection and Processing

7.1 Measuring outcomes

Clinical and patient reported outcomes will be assessed at baseline, 6, 12, 18 and 24 months post-randomisation using questionnaires. The components of follow-up are shown in the Table 2 below.

Table 2 Measurement of outcomes: components and timing

	Baseline	**Surgery**	**6 mths**	**12 mths**	**18 mths**	**24 mths**	**3 months after last study dose of GnRHa**
Baseline CRF[1]	x						
Surgical details CRF[2]		x					
EHP-30[3]	x		x	x	x	x	
EQ-5D[3]	x		x	x	x	x	
Time lost from productive activity[4]			x	x	x	x	
Health care utilisation[4]			X	X	X	X	
BMD in GnRHa group (200 patients)[5]	x			x		x	
BMD in Laparoscopy group (90 patients)[5]	x					x	
AEs		x[2]	X[3]	X[3]	X[3]	X[3]	X[6]
Case-note review for further treatment						X	

[1] completed by site research team at baseline
[2] completed by site research team after surgery (for those randomised to surgery and having surgery and those randomised to GnRHa and having surgery)
[3] completed by participant at recruitment, and at 6, 12, 18 and 24 months post randomisation
[4] completed by participant at 6, 12, 18 and 24 months post randomisation
[5] completed by site research team after DEXA scan
[6] completed by site research team by telephone

7.2 Baseline

Participants will complete the baseline questionnaire (including EHP-30 and EQ-5D) prior to randomisation.

The site research team will complete the baseline CRF including information on parity; age, ethnicity, stage of endometriosis (highest stage ever recorded from medical notes if available or self-reported), time since previous surgery, total number of previous operations for endometriosis, current and previous treatments used for endometriosis associated pain.

Bone mineral density (BMD) (using Dual Energy X-ray absorptiometry (DEXA) scan) will be measured for all women in the GnRHa group and a subgroup of 90 women in the laparoscopic surgery group.

7.3 Surgery

The site research team will complete a surgical CRF for any patients undergoing surgery. This will include those randomised to surgery who have surgery, and those randomised to GnRHa who go on to have surgery.

7.4 Follow-up

Patient reported outcomes will be collected at, 6, 12, 18 and 24 months post-randomisation using questionnaires completed by women at home. The questionnaires will include EHP-30, EQ-5D, symptoms, and questions about current and recent treatment (including analgesic use), satisfaction with treatment, adverse events, and any pregnancy.

While the chances of pregnancy are very low (based on our eligibility criteria), we will collect and analyse data on women who become pregnant during the follow up period.

At baseline, participants will be asked for their contact preferences for questionnaires. Those selecting email as their preference will have a link to the questionnaire emailed to them. Those selecting post as their preference will have the questionnaire posted to them. Those selecting text messaging as their preference will have a link to the questionnaire texted to them. First reminders will be emailed, posted or texted to participants (according to their stated preference). A second reminder (by telephone) will be attempted but if there is no response by telephone, a final postal reminder will be sent.

Questionnaires will be administered to all women who were randomised in the study, regardless of their compliance to the randomised treatment unless they have opted out of questionnaire follow-up. This means that patients who have not received their allocated treatment, have received the non-randomised treatment (cross-over) or have discontinued the GnRHa treatment will continue to be followed up in the study.

If questionnaires are returned as non-deliverable, attempts will be made by site staff or staff at the Trial Office to trace the participant.

7.5 Capture of data from medical records

At 24 months, data on further treatment will be captured from medical records.

7.6 Change of Status/Withdrawal procedures

Participants remain in the trial unless they choose to withdraw consent. All changes in status with the exception of complete withdrawal of consent means the participant is still followed up for all trial outcomes wherever possible. All data collected up to the point of complete withdrawal is retained and used in the analysis.

Participants who do not receive their allocated treatment, receive the non-randomised treatment (cross-over) or discontinue their GnRHa treatment are not considered withdrawals and will be followed up for all trial outcomes unless they request otherwise. One of the outcomes is treatment received. This is a pragmatic study and will monitor accruing data on treatment initiated and continued during the study which will inform the proportion of participants continuing in the two randomised treatment pathways.

Participants who request that no further questionaires are issued (i.e. completing questionnaires) will be followed up for other trial outcomes unless they are complete withdrawals.

Participants for whom any outcome data are available are included in an intention to treat analysis (analysed as randomised regardless of intervention received).

7.7 Data processing

Research nurses will enter locally collected data in the centres into the study website. Staff in the Trial office will work closely with site Research Nurses to ensure the data are as complete and accurate as possible. Postal questionnaires will be entered into the study website by trial office staff.

7.8 Long term follow-up

We plan to seek funding to follow-up participants in the long-term using data from NHS and other government central registries, and GP and hospital notes. We will seek informed consent for this at the outset of the trial.

8. Safety

The REGAL trial involves two different procedures for treating endometriosis, surgical management and medical management. Surgical management (laparoscopic ablation or excision of endometriosis/endometrioma) is well established in current NHS clinical practice. Medical management includes GnRHa with add back HRT. This is also well established in current NHS clinical practice, but GnRHa is currently licensed for up to 6 months (in the REGAL study it will be used for up to 2 years).

Adverse events in REGAL may occur during or after any type of surgery for endometriosis or may be related to the use of GnRHa (the IMP) and/or the add back HRT (the NIMP) or may be related to other treatment for endometriosis.

At each follow-up questionnaire, we will ask women about adverse events and these will be reported as a secondary outcome. Women may not be able to distinguish between adverse events that occur as a result of the GnRHa from those that occur as a result of the add-back HRT or from other treatment and therefore we ask about side effects as a result of treatment for endometriosis. Each initial AE will be considered for seriousness and may be reclassified as a serious adverse event or serious adverse reaction based on prevailing circumstances. Those meeting the criteria for serious will be reported as serious adverse events through the safety reporting process within the study.

8.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical event affecting a clinical trial participant.
Adverse Reaction (AR)[1]	Where it is suspected that an AE has been caused by a reaction to a trial drug [in this study the GnRHa].
Serious Adverse Event (SAE); Serious Adverse Reaction (SAR)[2]	Where an AE or AR • results in death; • is life threatening (i.e. the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe); • requires hospitalisation or prolongation of existing hospitalisation; • results in persistent or significant disability or incapacity; • is a congenital anomaly or birth defect, • is otherwise considered medically significant by the investigator
Suspected Unexpected Serious Adverse Reaction (SUSAR)	An adverse event that is SERIOUS, RELATED (i.e. possibly, probably, or definitely related) to the trial drug [in this study to the GnRHa] and UNEXPECTED (not listed in the reference safety information [in this study, the SmPC for the relevant GnRHa]). In the following circumstances, a reaction between the IMP (GnRHa) and the NIMP (add back HRT) would require reporting: • A serious, unexpected adverse reaction suspected to be due to an interaction between the NIMP and the IMP • A SUSAR that may have been caused by the NIMP or the IMP and it cannot be determined which caused the reaction

Term	Definition
	Events that are serious and related to NIMP only are not considered SUSARs. **Notes:** A SUSAR can only occur in a patient randomised to GnRHa if the event is related to a GnRHa listed in table 1, it occurs within 3 months of the last dose of study GnRHa and is not expected. Patients who are not randomised to GnRHa as part of the study but receive this treatment as part of standard of care, including patients who are randomised to surgery but who are prescribed GnRHa, cannot have a SUSAR. If they have a serious adverse event that is related to the GnRHa that is not expected this should be reported using the standard yellow card scheme. This holds true if they are prescribed a GnRHa preparation within the license for the preparation, or outwith the license. Similarly, if patients have an unexpected serious adverse reaction to other medication that they may be taking during the trial follow-up, this should be reported using the standard yellow card scheme.

[1] ARs are a subset of AEs. In subsequent text, the term AE is used to encompass both AEs and ARs.
[2] SARs are a subset of SAEs. In subsequent text, the term SAE is used to encompass both SAEs and SARs.

Adverse events are not:

- *continuous and persistent disease or symptom, present before the trial, which fails to progress;*
- *signs or symptoms of the disease being studied; or*
- *treatment failure (persistent pain).*

Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered as a SAE within REGAL. Complications occurring during such hospitalisation will also not be considered, recorded or reported as a SAE – unless there is a possibility that the complication arose because of the study interventions (i.e. a possible adverse reaction).

Planned overnight admission following endometriosis surgery (for example because of social circumstances) is not considered a SAE. Hospital visits (planned or unplanned) associated with further interventions due to endometriosis (eg further surgery) will be recorded as an outcome measure, but will not be reported as serious adverse events. Complications occurring during the procedure or subsequent hospitalisation will be considered, recorded and reported as a SAE.

Any SAEs related to the participants' endometriosis treatment that are not further interventions (eg if a participant is admitted to hospital for treatment of infection) will be recorded and reported as a SAE

Admissions for non-elective procedures or emergency procedures for any condition will be considered, recorded and reported as a SAE.

All deaths for any cause (related or otherwise during the follow up period of 2 years) will be recorded on the serious adverse event form.

8.2 Trial specific expected adverse events

Within the REGAL study, AEs will be reported as a secondary outcome. Those AEs that meet the criteria for serious will be assessed as to whether or not they are expected. In this trial, the events listed in the sections below are potentially expected.

8.2.1 Adverse events related to GnRHa

For the assessment of expectedness of AEs, the relevant SmPC will be used. The version of the SmPC for GnRHa to be used for assessment will be clearly documented within the site file and available on the study website. Any updates to the GnRHa SmPC will be reviewed at the time of DSUR preparation and any updates to the SmPC version used will be submitted for review as a substantial amendment.

8.2.2 Adverse events during or after laparoscopic excision or ablation of endometriosis/ endometrioma and after other surgical treatment of endometriosis

In this trial the following events are potentially expected after laparoscopic excision or ablation of endometriosis/endometrioma and after other surgical treatment of endometriosis:

Intraoperative and immediate postoperative complications

- Bleeding intraoperative or postoperative >500ml
- Blood transfusion
- Injury to abdominal viscera, including bowel, bladder, ureters and blood vessels
- Laparotomy
- Emergency hysterectomy
- Anaesthetic complications (including hypersensitivity to the general anaesthesia and /or any of the medications or material used)
- Uterine perforation during uterine manipulation
- Admission to HDU/ITU
- Infection (wound infection, urinary tract, endometritis, pelvic sepsis, abscess, septicaemia)
- Thrombosis (Deep vein thrombosis/ Pulmonary embolism)
- Urinary retention
- Pain requiring additional analgesia
- Blood stained vaginal discharge
- Bruising/Haematoma
- Return to theatre

Late post-operative complications

- Incisional / port site hernia
- Chronic wound pain
- Infection (sepsis, septicaemia, abscess)
- Colostomy
- Ureteric stenting or reimplantation
- Fistula (e.g. vesicovaginal, ureterovaginal, rectovaginal)
- Adhesions
- Voiding dysfunction

Intraoperative, immediate or late post-operative complications can result in death, and therefore death is listed as an expected adverse event.

8.3 Procedures for detecting, recording, evaluating & reporting AEs, SAEs, ARs, SARs

8.3.1 Detecting AEs

Adverse events related to the treatment of endometriosis will be captured in the follow up questionnaire at 6, 12, 18 and 24 months from the time a participant consents to join the study until the

end of the 24-month follow-up period. However, for women randomised to GnRHa and still taking GnRHa at the 24 month follow-up, a telephone call will be made (by the research nurse at site or the trial office) 3 months after the last dose of study GnRHa was taken to check for any AEs related to the treatment of their endometriosis and these will be recorded on a separate CRF.

AEs that occur during or immediately after surgery for endometriosis will be captured on the surgical CRF. At 24 months, a case note review will identify any other hospitalisations for endometriosis treatment, complications of treatment etc.

8.3.2 Evaluating AEs

When an AE occurs or is reported in a questionnaire, it is the responsibility of the Site Principal Investigator (or delegate) to review appropriate documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the adverse event.

Assessment of Seriousness

The Investigator should make an assessment of seriousness as defined in Section 8.1.

Assessment of Causality

Causality will be assessed for events that meet the criteria for serious. The Site Principal Investigator (or delegate) must make an assessment of whether the SAE is likely to be related to treatment according to the following definitions:

- **Unrelated**: where an event is not considered to be related to the study intervention (GnRHa or any surgical treatment for endometriosis)
- **Possibly**: although a relationship to the trial intervention cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.
- **Probably**: the temporal relationship and absence of a more likely explanation suggest the event could be related to the trial intervention.
- **Definitely**: The known effects of the trial intervention or its therapeutic class, or based on challenge testing, suggest that trial drug/surgery is the most likely cause.

When considering causality, the following REGAL-specific guidance will apply.

Regardless of which arm the woman has been randomised to:

- For women who have taken GnRHa within the last three months, the assessment of causality relates to whether the event may be related to the IMP. SAEs judged as being related (e.g. possibly, probably, definitely) to either the trial drug (GnRHa) or to an interaction between the trial drug and another drug will be considered to be a SAR. If the SAE is judged as being related to the HRT, this is not considered a SAR.
- If the woman has had surgery for endometriosis since joining the trial, the assessment of causality will include consideration of whether the event may be related to the surgery. Events judged as being related (possibly, probably or definitely) to surgery will be considered as a SAE related to treatment.
- If women have not had surgery and have not taken GnRHa within the last three months, any SAEs should be classed as unrelated.

Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered.

Assessment of Severity

Severity will be assessed for events that meet the criteria for serious. The following definitions are used: :

- **Mild**: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.
- **Moderate**: an event that is sufficiently discomforting to interfere with normal everyday activities.
- **Severe**: an event that prevents normal everyday activities.

Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

Assessment of Expectedness
Expectedness will be assessed for events that meet the criteria for serious.

Regardless of which arm the woman has been randomised to:

- For women who have taken GnRHa within the last three months, where the SAE is a SAR (i.e. has been judged as being related (e.g. possibly, probably, definitely) to either the trial drug (GnRHa) or to an interaction between the trial drug and another drug), the evaluation of expectedness should be made based on knowledge of the reaction and the relevant product information documented in the relevant SmPC.
- For women who have taken GnRHa within the last three months, where the SAE is NOT a SAR (i.e. it has been judged as being not related to either the trial drug (GnRHa) or to an interaction between the trial drug and another drug), an evaluation of expectedness is not required (however the Investigator may wish to comment in the narrative as to whether the event was expected on the basis of the participant's medical history.
- If the woman has had surgery for endometriosis since joining the trial, where the SAE is related to the surgery, the evaluation of expectedness should be made based on the expected adverse events listed in section 8.2.3.

8.3.3 Recording AEs and SAEs

Adverse events will be recorded in the case report forms (CRFs) or questionnaires. The Investigator (or delegate) should record all relevant SAEs on a SAE form (see section 8.1 for SAEs for guidance on whether an event should be captured as a SAE or not).

Information to be recorded on the SAE form includes treatment received, type of event, onset date, Investigator assessment of severity, causality and expectedness, date of resolution as well as treatment required, investigations needed and outcome.

8.3.4 Reporting SAEs

Reporting responsibilities of sites
Once the Investigator becomes aware that a SAE has occurred in a study participant, they must report the information to the Trial Office within 24 hours of becoming aware of the event, the Trial Office will report to the Sponsor within 24 hours of becoming aware of the event as per the current Sponsor SOP (SOP-QA-22).

The SAE form must be completed as thoroughly as possible with all available details of the event and signed by the Investigator or delegate. If all the required information is not available at the time of reporting, the Investigator must ensure that any missing information is provided as soon as this becomes available. It should be indicated on the report that this information is follow-up information of a previously reported event.

To report a SAE to the trial office, site staff complete a hard copy of the SAE form and either email it to the trial office or upload the SAE onto the study website. If the SAE form is uploaded onto the study website, the trial manager will be automatically notified.

Reporting responsibilities of the Trial Office
The Trial Office will notify the Sponsor within 24 hours of receiving the signed SAE notification.

The sponsor will provide an assessment of the SAE. A Sponsor cannot downgrade an assessment from the PI or CI. Any disparity will be resolved by further discussion between these parties and documented in the TMF.

8.3.5 Regulatory reporting requirements
Fatal or life threatening SUSARs will be reported to MHRA no later than **7 calendar days** and all other SUSARs will be reported no later than **15 calendar days** after they are first aware of the reaction. The Chief Investigator is responsible for reporting SUSARs to the MHRA and the main REC.

An annual Development Safety Update Report (DSUR) will be submitted to the MHRA and the main REC listing all SARs and SUSARs. The Chief Investigator is responsible for submitting annual DSURs to the MHRA and the main REC on the anniversary of the Clinical Trial Authorisation approval.

8.3.6 Follow up procedures
After initially recording and reporting a SAE, the Investigator is required to follow each participant as indicated by clinical practice. Follow up information on a SAE should be reported to the trial office as described above in the section on "Reporting responsibilities of sites". The trial office will notify the Sponsor about any follow-up information.

8.4 Pregnancy
Pregnancy is not considered an AE or SAE, however we will collect pregnancy information for trial subjects. Participants who become pregnant should have no further treatment with GnRHa and should cease HRT immediately, until the pregnancy has been completed. Those who become pregnant whilst being treated with GnRHa will have a Pregnancy Notification Form completed by the Investigator, which will be submitted to the Sponsor within 24 hours of being made aware of the pregnancy. Any such pregnancy that occurs in a participant during a trial should be followed to outcome. In some circumstances, it may be necessary to monitor the development of the new born for an appropriate period post-delivery. Should the trial subject not wish for the pregnancy to followed to outcome or beyond, this should be noted in the CRF and medical notes as appropriate.

9. DEXA Scans
See Appendix 1 for details.

10. Embedded qualitative work
See Appendix 2 for details

11. Sample size and proposed recruitment rate

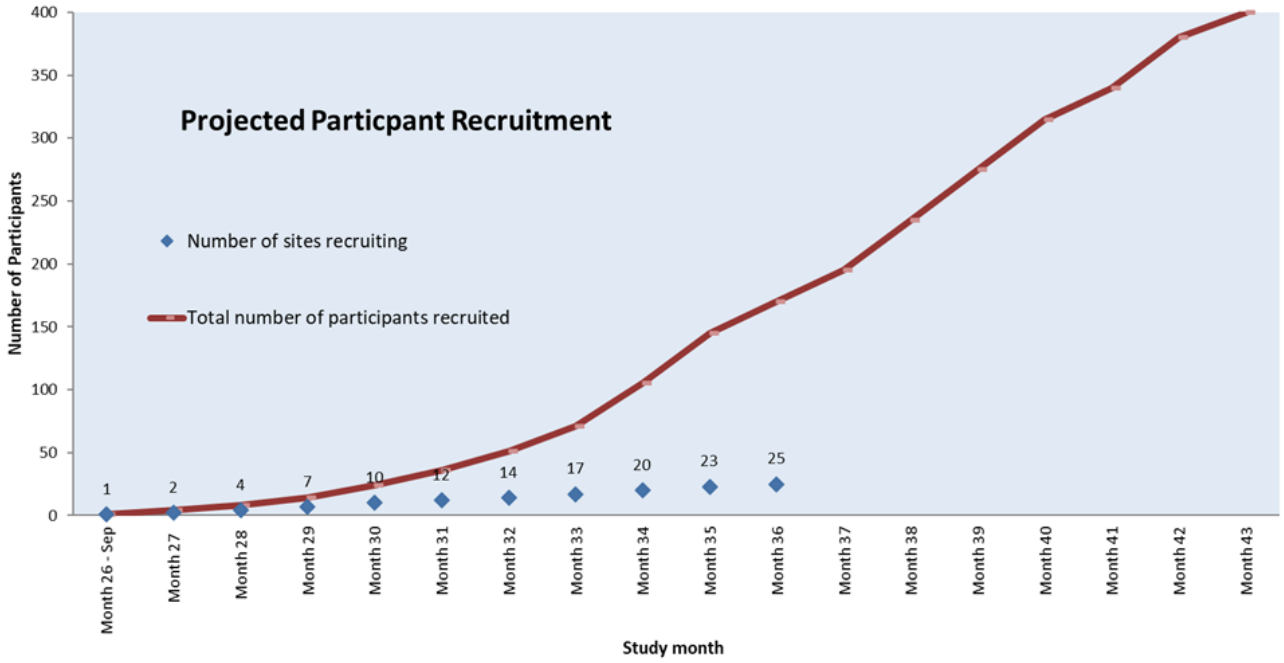
11.1 Sample size
We need primary outcome data on 320 women at two years to detect an 8-point difference on the EHP-30 pain domain for 90% power (two-sided alpha 0.05), assuming a standard deviation (SD) of 22 points. We have assumed attrition of 20% for the primary outcome (although we will strive to keep this to a minimum) which requires us to randomise 400 women in total.

Attrition rates will be monitored to detect differential drop-out, which can bias clinical trial results and reduce the power of the trial to detect important differences.

11.2 Recruitment rates

There are 50 specialist endometriosis centres in the UK. The recruitment projection is based on at least 25 of these centres each contributing an estimated 2 participants per month over 18 months. This allows for staggered centre set-up and fewer recruits in peak holiday months. We aim to recruit the first 36 patients by Month 12, 195 patients by Month 18 and the remaining 205 by Month 24, making a total of 400 participants. The projected recruitment is modelled below in Figure 2.

Figure 2 Recruitment Projections



11.2.1 Internal pilot study

An internal pilot stage has been included in the proposal. A 9-month pilot stage was anticipated to commence in February 2020 (study month 7) and run to end October 2020 (study month 15*)*. However, due to the COVID-19 pandemic, the pilot study will not commence until September 2021 (study month 26) and will run until the end of May 2022 (study month 34).. During this phase 20 sites will be opened and in accordance with recruitment projections we expect to randomise 105 subjects by the end of the May 2022. The area of uncertainty we are addressing in the internal pilot is the willingness of patients to participate.

11.2.2 Stop/go criteria

The proposed stop/go criteria are after 9 months of recruitment, if we recruit:

- At least 95 participants (80% or more): we will continue without modification;
- 59– 95 participants (50– 80%): we will need to modify recruitment approach and continue to monitor recruitment carefully to ensure recovery manoeuvres worked.
- Less than 59 (<50%): we will enter discussions with the funder to determine whether the RCT is feasible with the possibility that the trial may need to be terminated. Full details of the stop-go criteria for the progression to the main trial will be developed in a detailed progression plan in the Statistical Analysis Plan, in consultation with the HTA Board.

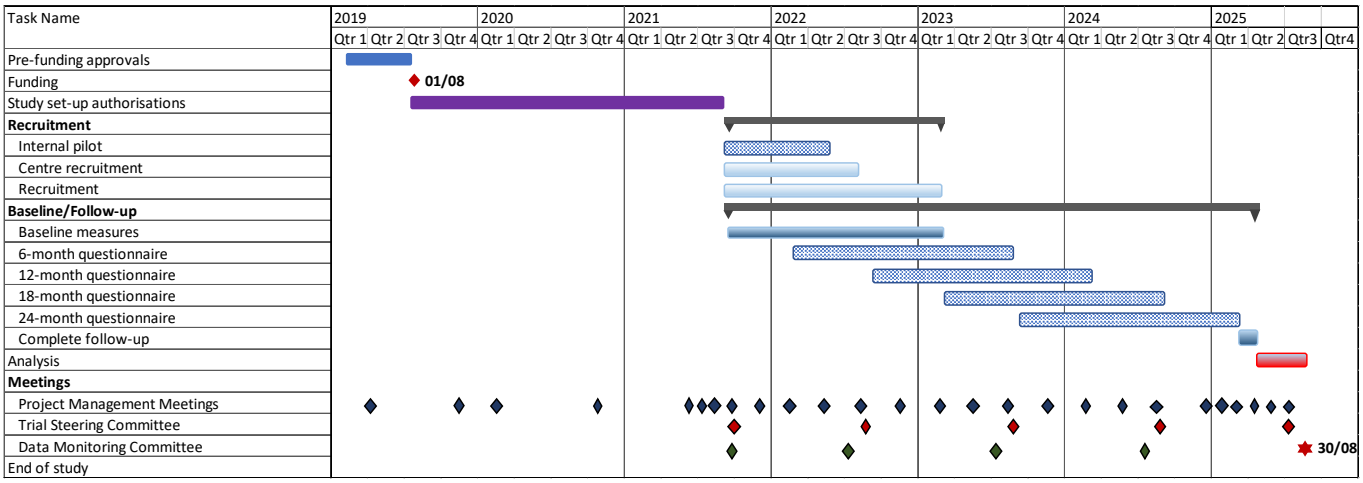
11.2.3 Project timetable and milestones

The projected timetable start date for the study was 1 August 2019: the study duration 54 months. Milestones: Prefunding: MREC and HRA approvals; Month 1–6: set-up, authorisations; Months 7–24: patient recruitment; Months 31–50: patient follow-up to 2 years; Months 51–54: data analysis, interpretation of results, report writing and dissemination. The trial will continue to 31 January 2024.

However, due to the COVID-19 pandemic, the study timelines were modified as follows: Month 1–25: set-up, authorisations; Months 26–43: patient recruitment; Months 50–69: patient follow-up to 2 years;

Months 70–73: data analysis, interpretation of results, report writing and dissemination. A Gantt chart detailing the revised timelines is shown below (Figure 3). A contract variation to extend the study end date will be submitted once recruitment has been established following further discussion with the funder.

Figure 3: Gantt Chart



12. Statistical analysis

The primary outcome will be analysed using a mixed effects linear model that includes a random effect for centre and participant, with fixed effects for treatment, time, and minimisation covariates, and baseline outcome score, and intention-to-treat approach (analysed as randomised regardless of intervention received). Treatment effects will be estimated at each time-point by time-by-treatment interaction. Secondary outcomes will be analysed in a similar way with generalised linear models appropriate for the distribution of the outcome. We will use causal models for longitudinal data with time-dependant cross-over to generate efficacy estimates. We will also explore time to repeat surgery using joint models for time-to-event and longitudinal data. Subgroup analysis to assess potential treatment moderating effects of age, stage of endometriosis, and number of previous operations (1 v >1), by modelling treatment-by-subgroup interactions. We will assess sensitivities of all treatment effect estimates to missing outcome data using imputation and pattern mixture models where appropriate. Treatment effect estimates will be presented with 95% confidence intervals. For a small proportion of women who become pregnant we plan a sensitivity analysis in which we will censor the primary outcome measured at time points after pregnancy has occurred.

Full details of the statistical analyses will be documented in the Statistical Analysis Plan.

13. Economic evaluation

The primary economic analysis will be based on costs and QALYs (derived from EQ-5D responses) accrued by 24 months post-randomisation.

The economic evaluation will include a trial-based analysis using patient level data on costs and QALYs, and a model-based analysis to inform longer-term cost-effectiveness. Data on the resources required to deliver the interventions will be collected using trial case report forms. Further use of health services will be collected using patient questionnaires. The patient questionnaires will also be used to capture productivity effects for the calculation of indirect costs. Health service resource use will be costed using national sources of unit cost data (PSSRU https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2018/; BNF https://bnf.nice.org.uk/). QALYs will be calculated based on responses to the EQ-5D at baseline, 6, 12, 18 and 24 months post-randomisation, using an area under the curve approach. The mean difference in costs and QALYs between the intervention groups will be estimated using general linear models or bivariate (seemingly unrelated) regression, and the incremental cost per QALY gained for GnRHa versus surgery will be assessed at 24 months. Uncertainty surrounding the incremental cost-

effectiveness ratio will be presented graphically on the cost-effectiveness plane and summarised using cost-effectiveness acceptability curves.

Since treatment beyond 24 months may be an important driver of cost-effectiveness, we will develop a Markov type decision model to extrapolate the trial cost-effectiveness data. It is envisaged that the structure of this model will be based on the relevant pathway components of the model recently developed to support the NICE clinical guideline for endometriosis.[6] The model input parameters will be derived, as far as possible, from the trial dataset. Parametric survival analysis will be used to extrapolate ongoing probabilities of further surgery beyond the trial follow-up period. If necessary, the trial data will be supplemented with relevant external data such as the recurrence of symptoms and the need for further surgery.[8] It is anticipated that the model will be analysed up to the age of menopause, but a lifetime perspective will be considered if evidence suggests there is potential for significant differences in long-term sequelae such as osteoporosis. All women in the trial will also be asked to consent to long-term follow-up to determine the need for further gynaecological surgery using routine HES data (England and Wales) or ISD data (Scotland). This will enable the model to be updated based on observed data at a later date (funding to be sought separately).

Whilst the economic evaluation will identify differences in costs and QALYs between the two alternatives, QALYs may fail to capture women's preferences for specific aspects of the treatments being compared, such as the degree of invasiveness, chance of requiring further surgery, and adverse event profiles. Members of the study team (GS, LS) are currently involved in the development of a preference elicitation survey which will be conducted in a related sample of women with recurrent endometriosis. This separately funded but related study will utilise discrete choice methods to quantify the values that women place on aspects of different treatments for recurrent endometriosis.[24] Analysis of the discrete choice data should help provide an understanding of how women's preferences are likely to translate into uptake of alternative treatment options in the future. It is anticipated that these data will be useful to help interpret the results of the trial and economic evaluation from the patient perspective.

14. Organisation: trial management and oversight arrangements

14.1 Trial office in Aberdeen

The Trial Office is in the Centre for Healthcare Randomised Trials (CHaRT) based within the Health Services Research Unit, University of Aberdeen and provides day to day support for the clinical centres. The Trial Manager in CHaRT at Aberdeen will take responsibility for the day to day transaction of trial activities, for example approvals, site set-up and training, oversight of recruitment and follow-up rates etc. The data co-ordinator will provide clerical support to the trial, including organising all aspects of the follow-up questionnaires (mailing, tracking, and entering returned data using the trial web data entry portal).

The Trial Office Team will meet formally at least monthly during the course of the trial to ensure smooth running and trouble-shooting.

14.2 Local organisation in sites

The PI and research nurse(s) in each site are responsible for all aspects of local organisation including identifying potential recruits, consenting, completing and maintaining appropriate documentation. The site agreement documents the full list of responsibilities for sites. Appropriate members of the local site team are knowledgeable about the Protocol and will have appropriate Good Clinical Practice (GCP) training if applicable. A trial-specific delegation log is prepared for each site, detailing the responsibilities of each member of staff working on the trial. The local site team is also responsible for notifying SAEs to the Trial Office (see section 8).

14.3 Project Management Group (PMG)

The trial is supervised by its Project management Group (PMG). This consists of the grant holders and representatives from the Trial Office. Observers may be invited to attend at the discretion of the PMG. We will meet/teleconference every 3-6 months on average.

The research team has the expertise to cover the clinical, methodological and surgical aspects of the research.

14.4 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC), with independent members, oversees the conduct and progress of the trial. The TSC Charter documents the terms of reference of the TSC, the template for reporting and the names and contact details of members of the TSC. This Charter is filed in the Trial Master File (TMF).

14.5 Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) oversees the safety of subjects in the trial. The DMC Charter documents the terms of reference of the DMC and the names and contact details and is filed in the TMF.

14.6 Patient and Public Involvement (PPI)

In a PPI activity undertaken in collaboration with Endometriosis UK, more than 1700 women responded. This survey highlighted the magnitude of problem of recurrence of endometriosis (>90% of treated women were affected by recurrence) and emphasised that research into effective interventions for the treatment of recurrent pain as 'very important'. One in two women expressed willingness to participate in this research while one in three were undecided. Our design and choice of intervention for the trial was informed by our patient survey of >1700 women with endometriosis.

Emma Cox, who facilitated the survey through Endometriosis UK, is a co-applicant. Emma has been involved in the development of this application and will advise the group and lead in the preparation of all patient-facing materials. Emma is CEO of Endometriosis UK, a leading charity supporting patients with endometriosis. We anticipate dissemination of the trial through Endometriosis UK at onset, during recruitment and on completion. Carol Pearson, a patient leader and Emma have affirmed the importance of the research question, provided comments on the proposal, and have examined our plain English language summary.

Our PPI group (up to 6 members) will be generated by identifying interested women via Endometriosis UK and local patients and inviting them to learn more about the trial and the expectations of a PPI contributor. Throughout the course of the study our PPI Panel will contribute to trial delivery, patient engagement and dissemination of results. The PPI group will function both proactively and reactively through involvement in activities as and when required for troubleshooting. The proactive activities will likely include: co-production of patient information leaflets and other key patient facing documents/materials, guidance on acceptability of methods to encourage continued commitment from trial participants, co-production of trial results for dissemination to trial participants, and development and delivery of trial results to the wider endometriosis population (through activities such as patient conferences and events hosted by Endometriosis UK).

Once established it is anticipated the group will hold scheduled meetings that coincide with key project meetings (e.g. TSC meetings) in order to enable the group's recommendations to make a change through the TSC. The trial team and Emma Cox will liaise with the PPI group and facilitate communication between the two (TSC and PPI).

15. Research governance, data protection and sponsorship

15.1 Research Governance

CHaRT is a fully registered Clinical Trials Unit with particular expertise in running multicentre RCTs. The trial will be run under the auspices of CHaRT based at HSRU, University of Aberdeen. This aids compliance with Research Governance and the principles of GCP, and provides centralised trial administration, database support and economic and statistical analyses. CHaRT SOPs are followed.

The CI will ensure that adequate systems are in place for monitoring the quality of the trial and expedited and routine reports, to a level appropriate to the risk assessment of the trial.

15.2 Data protection

Data collected during the course of the research is kept strictly confidential and accessed only by members of the trial team. Data may be looked at by individuals from the Sponsor organisation or NHS sites where it is relevant to the participant taking part in this trial.

The CI and study staff involved with this project will comply with the requirements of the General Data Protection Regulations (GDPR) and the Data Protection Act 2018. The HRA recommended wording to fulfil transparency requirements under the GDPR for health and care research has been included in the PIL.

The CI and study staff based in Scotland will also adhere to the current version of the NHS Scotland Code of Practice on Protecting Patient Confidentiality. Access to collated participant data will be restricted to the CI and appropriate study staff.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

The CHaRT senior IT development manager (in collaboration with the CI) manages access rights to the data set. Participants are allocated an individual trial number which is used to identify questionnaires and case report forms.

We anticipate that anonymised trial data may be shared with other researchers to enable international prospective meta-analyses.

15.3 Sponsorship

The University of Aberdeen and NHS Grampian are the co-sponsors for the trial.

16. Ethics and regulatory approvals

The East of Scotland Research Ethics Committee has reviewed this trial. The trial will be conducted according to the principles of good clinical practice provided by Research Governance Guidelines. Annual progress reports, end of Trial declaration, and a final report are submitted to the Sponsor and the East of Scotland REC within the timelines defined in the regulations.

16.1 Protocol compliance and amendment

The Investigators will conduct the trial in compliance with the Protocol given favourable opinion by the Ethics Committee and regulatory authority. Any amendment to the Protocol or other approved documents will be reviewed by Sponsor (and funder where appropriate) before application to REC, regulatory authority and R&D, unless in the case of urgent safety measures when the Sponsor is notified as soon as possible. Sponsor will advise if an amendment is substantial / non-substantial and which review bodies need to receive it. Any deviations from the Protocol will be fully documented.

17. Quality assurance

The trial is monitored to ensure that it is being conducted as per protocol, adhering to Research Governance, the principles of GCP, and all other appropriate regulations. The approach to, and extent of, monitoring is specified in the trial monitoring plan and is appropriate to the risk assessment of the trial. Investigators and their host institutions are required to permit trial related monitoring and audits to take place by the Sponsor and/ or regulatory representatives, providing direct access to source data and documents as requested.

17.1 Risk assessment

An independent risk assessment has been carried out by the sponsor.

Details of the steps taken to minimise risk to participants and research staff during the COVID-pandemic are detailed in Appendix 5.

17. Finance and insurance

The trial is funded by a grant awarded by the NIHR Health Technology Assessment programme. The necessary trial insurance is provided by the University of Aberdeen.

18. End of trial

The end of follow-up for each participant is defined as the final data capture on that individual. The end of the trial is defined as the end of funding.

The end of the trial will be reported to the Sponsor, REC and Regulatory Authority within 90 days, or 15 days if the trial is terminated prematurely. If terminated prematurely, the Investigators will inform participants and ensure that the appropriate follow up is arranged for all involved, if appropriate.

A summary report of the trial will be provided to the Sponsor, REC and Regulatory Authority within one year of the end of the trial. An end of trial report should also be issued to the funders at the end of funding.

18.1 Continuation of drug following the end of the study

Following completion of the study, participants will continue to have all options of treatment open which includes hormonal treatment, GNRHa with add-back HRT or surgery. Continuation of GnRHa and add back HRT following the end of study is at the discretion of clinician responsible for the patient's care.

19. Data handling, record keeping and archiving

Clinical data will be entered into the database by the designated team members working in each hospital site, together with data from questionnaires completed at clinic. Questionnaires returned by post to the trial office will be entered there. Staff in the trial office will work closely with site research team members to ensure that the data are as complete and accurate as possible. Extensive range and consistency checks will further enhance the quality of the data.

Responsibilities for archiving are documented in the co-sponsorship / site agreement. All essential data and documents (electronic and hard copy) are retained for a period of at least 25 years after close of trial according to the funder requirements and relevant Sponsor and CHaRT archiving SOPs. Electronic data will be archived by UoA.

20. Authorship and publication

Please refer to the Appendix 3 (authorship policy) for full details on authorship.

To safeguard the integrity of the main trial, reports of explanatory or satellite studies will not be submitted for publication without prior arrangement from the PMG.

Once the main trial findings have been published, a lay summary of the findings will be sent to participants through the newsletter and will also be available of the trial website. Trial findings will also be disseminated to professionals involved in the trial, including GPs of participants, PIs at sites, site staff etc.

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Appendix 1: DEXA Scans

The REGAL trial aims to evaluate the effect of long-term use of Gonadotrophin Releasing Hormone Analogues (GnRHa) with add-back hormone replacement therapy (HRT) as an alternative treatment to further laparoscopic surgery for excision or ablation of endometriosis in women who present with recurrence of pain following previous surgery for endometriosis. GnRHa improve endometriosis associated pain by inducing amenorrhoea secondary to suppression of oestrogen secretion by the ovaries. The main side effects include hypoestrogenic effects such as hot flushes, night sweats and other menopausal symptoms. Prolonged use can lead to reduction in bone mineral density. GnRHa are only licensed for 6 months use in endometriosis due to concerns regarding osteoporosis. Addition of concomitant HRT reduces hypoestrogenic side effects and protects against osteoporosis. In a Cochrane review of 910 premenopausal women with endometriosis treated with GnRHa, add-back HRT prevented osteoporosis during, and for up 12-months after treatment.[1] There are reports of the use of a GnRHa with add-back HRT for up to 10 years with adequate pain relief and bone sparing in women with endometriosis. In the REGAL trial GnRHa with add back HRT will be used for two years. Bone mineral density in all participants in the GnRHa arm and a subgroup of 90 participants in laparoscopic arm will be monitored using DEXA scans at baseline and 24 months. Participants in the GnRHa group will receive an additional DEXA scan at 12 months. The DEXA scans should be organised at a time convenient for the study participant.

For women randomised to the surgical arm, DEXA scans will be carried out soon after baseline and around 24 months. Ideally the DEXA scan should be done before the surgery. However, it is acceptable to carry out the DEXA scan within three months of the surgery. If the DEXA has not been carried out within three months of surgery, the women should be excluded from the DEXA sub-study.

For women randomised to the GnRHa arm, DEXA scans will be carried out soon after baseline and at around 12 and 24 months. Ideally the DEXA scan will be done before starting the GnRHa. However, it is acceptable to carry out the DEXA scan within the first three months after starting the drug.

Bone density should be measured at lumbar spine, proximal femur and both hips for all patients. The DEXA should be carried out according to the recruiting centre's local protocols, including quality assurance protocols and prevailing COVID-19 specific measures. Any incidental findings identified during the DEXA scans will be handled as per normal NHS standard of care procedures.

The DEXA scans will be reviewed by the local PI/treating clinician to monitor bone mineral density in the GnRHa group. Women who have a T score of <-1.5 (osteopenia) or greater than 6% loss in bone mineral density (expected loss with licensed regime for GnRHa) at the 12-month DEXA scan (performed on women in the GnRHa arm only) will have further assessment using the FRAX® tool[2]. The FRAX® algorithms give the 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture; Table 1). The recommendations from NOGG 2017[3] and NICE guidance on osteoporosis (2017)[4] will be used to guide further treatment of women who have a T score of <-1.5 (osteopenia) or greater than 6% loss in bone mineral density. In the REGAL trial, for women aged 40 and below the reference range at 40 years will be used.

Women who have a high probability of osteoporotic fracture based on threshold for intervention (ie a 10-year probability of major osteoporotic fracture of 5.9 or above; Table 1); a careful assessment and discussion with the patients would be undertaken to determine whether GnRHa should be discontinued or alternative treatment for osteoporosis such as bisphosphonates should be considered. Most importantly, compliance with HRT should be checked, which is a well-established treatment for osteoporosis.

	10-year probability of a major osteoporotic fracture (%)		
Age (years)	**Lower assessment threshold**	**Upper assessment threshold**	**Intervention threshold**
40	2.6	7.1	5.9
45	2.7	7.2	6.0
50	3.4	8.6	7.2
55	4.5	11	9.4
60	5.9	14	12
65	8.4	19	16
≥70	11	24	20
Reproduced with permission from McCloskey et al. (2015) FRAX-based assessment and intervention thresholds – an exploration of thresholds in women aged 50 years and older in the UK. Osteoporosis International 26 (8), 2091–9			

Table 1. Lower and upper assessment thresholds and intervention thresholds for major osteoporotic fracture probability based on fracture probabilities derived from FRAX (BMI set to 25 kg/m^2) (BMI set to 25 kg/m^2)

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Appendix 2: Qualitative study

Background

REGAL will compare two different treatments, medical versus surgical management for the treatment of recurrent pain following surgery for endometriosis. It is well documented that surgical trials face a number of challenges, particularly around informed consent and recruitment, from both the patient and clinician perspective.[1-3]

The embedded qualitative evaluation will initially concentrate on sites established during the internal pilot. This will allow any challenges relating to the design or conduct of the trial to be identified early so they can be addressed and modified before progression to the full trial. This may include changes to the way trial information is presented, recruitment consultations are framed or requirements for staff training. Demonstrating successful buy-in and implementation of the evaluation across the pilot sites will also lead to more effective delivery across the remainder of the sites during the main trial. Much of this work will be modelled on the Quintet Recruitment Intervention.[2]

The REGAL-Qual work will involve four key stages:
1. Audio-recording of recruitment consultation (face-to-face) with potential trial participants;
2. In-depth semi-structured telephone interviews with patients who consent to the trial;
3. In-depth semi-structured telephone interviews with patients who refuse consent to the trial;
4. In-depth semi-structured telephone interviews with clinical site staff involved in the recruitment process.

Methods

1. Participant invitation and informed consent

1A. Audio-recording of recruitment consultations

The aim of audio-recording the recruitment consultation is to explore trial decision-making by potential trial participants and clinical site staff (consultant or research nurse) involved in the trial. This will enable the trial team to systematically assess the content and presentation of study information by recruiters, the interactions between participants and recruiters, and provide evidence on which to develop appropriate recruitment strategies. This will also provide evidence about how potential participants can be better supported and informed when making a decision about participation in the REGAL trial. The audio-recordings will contribute to determining models of 'good practice' for consent discussions which can be used for site training.

The audio-recording of recruitment consultations is proposed at all sites but will initially focus on pilot sites. As part of the initial approach for the REGAL trial, potential participants will receive a patient information leaflet (PIL) explaining the trial in detail as per section 4.5 of the protocol. To facilitate the audio recording study, a separate PIL will be given to participants at the same time, but before any discussion of the trial is initiated, explaining the purpose and the specific request to audio-record their recruitment consultations. Patients will not be obliged to participate in the audio-recording study and the decision will not affect their invitation to take part in REGAL. Similarly, patients may agree to take part in the audio-recording study but then decline to take part in the main REGAL trial.

Recruitment consultations will be routinely recorded using a digital recorder and after an initial greeting and introduction to the consultation, verbal consent for recording will be sought from participants. If a participant says yes to the audio recording, the recording will continue and there will be a record of consent (having a record of consent is the reason the recording will start before asking for consent). If a participant says no, the audio recording will be stopped, and the file will be deleted. Participants will be able to withdraw their consent at any time. Verbal consent obtained in this manner has been approved for other similar randomised controlled trials with embedded qualitative monitoring of recruitment consultations (e.g. IRAS project ID 226009 and IRAS project ID 201303). The audio recordings of recruitment consultations will be uploaded to a secure area of the study website. If for any reason the upload function is unavailable, a secure file transfer system, such as the University of Aberdeen ZendTo

service, will be used. Clinicians involved in the audio-recording study will provide their written consent at the start of study at their site which will cover their involvement throughout the evaluation, again a process approved in similar studies. Audio recording equipment will be provided to sites for this purpose.

1B. Interviews with potential trial participants
In-depth, semi-structured interviews will be conducted to understand perspectives of participation and equipoise with a range of individuals:
1. Participants who consent to trial participation (n=14, 7 from each arm);
2. Participants eligible for the RCT but who decline trial participation (n=15)

Interview topic guides will be developed for each group, covering aspects of trial rationale, design and conduct with a specific focus on the trial recruitment pathway (specifically exploring barriers and facilitators within local contexts) and considerations of consent for potential participants. In addition to trial-specific processes, an exploration of how patients' symptoms change over time and how this impacts on their quality of life will be conducted only with patients who consent to the REGAL trial.

Potential participants of the interview study (which includes those that have consented to the main REGAL trial and those that have refused consent) will be provided with a separate PIL in the clinic. The PIL will contain a detachable reply-slip to complete and return to the researcher (in a reply paid envelope) if they would like to discuss participating in the Interview study. Those participants who do not return an interest slip will not be contacted further.

Following receipt of the completed slip, the researcher will telephone the interested participant and ensure they are clear about what the study entails and arrange a suitable time for the interview. Interviews will be planned to be as close as possible to the initial decision to participate, or not, in REGAL. To enable all willing participants to be involved in the interview study, and maximize sample variability, telephone interviews will be utilised and verbal consent sought. As with all research studies, participants will be able to withdraw consent at any time.

For the participants who consent to participate in the REGAL trial and consent to the interview study, A second interview will be scheduled for an appropriate time in the future once the patient has received treatment. This timepoint will, as much as possible, be matched between the arms to allow for a comparison in perceptions of symptoms over time for each of the treatment arms.

1C. Interviews with site staff
Clinical and recruitment staff (consultants, research nurses) involved in trial recruitment at each pilot site (4 staff from 4 sites) will be invited to participate in in-depth, semi-structured telephone interviews to explore their understanding of the trial (specifically with regard to eligibility criteria, beliefs about equipoise, and process). Site staff will be emailed an invitation letter outlining the study and inviting them to contact the research team (by email or telephone) if interested in participating in the interview study. Once contact is made with the researcher, potential participants will have the opportunity to ask any further questions before making a decision to participate. To enable all willing participants to be involved in the interview study, and maximize sample variability, telephone interviews will be utilised and verbal consent sought. As with all research studies, participants will be able to withdraw consent at any time.

2. <u>Data collection</u>

2A. Audio-recording of recruitment consultation
All recruitment consultations at sites will be audio-recorded for the duration of the trial for those participants who consent to the audio-recording. Only conversations related to the REGAL trial (where recruiters explain the design and details of the REGAL RCT, and patients decide whether or not to take part) will be transcribed for the purpose of analysis and discussion i.e. targeted transcription by a third party professional transcription service. In addition, a novel mixed-methods approach combining

appointment/consultation timings (time spent explaining aspects of the RCT) and qualitative interpretation of the conversation- 'quanti-qualitative appointment timing' (Q-QAT) may be used for the purpose of analysis as appropriate. This will provide useful information regarding the order of presentation (balanced/unbalanced presentation of the RCT information to potential participants which may inspire or hinder recruitment) and degree of balance between the RCT interventions, the time the RCT is first mentioned and how long is devoted to it.

2B. Interviews with trial participants and site staff
Approximately 15 interviews will be conducted for each group by sampling informed by Francis et al.[4] To provide 15 participants for the patient group who have refused consent to the REGAL trial, it is anticipated that a total of 60 interview study PILs will require to be distributed (anticipate participation rate of ~20%). All staff at each pilot site will be sent an email regarding invitation to participate in this interview study. If the number interested exceeds the sample required, participants will be sampled purposively to ensure a wide variety of experiences is included in the sample. All interviews will last approximately 30-60 minutes and will be audio-recorded and transcribed verbatim using a third party professional transcription service.

3. <u>Data Analysis</u>

3A. Audio-recording of recruitment consultation
Once 10 recordings (which will include conversations with consenters and non-consenters) have been collected for a site the analysis will be conducted. Analysis will focus on modifiable aspects of recruitment consultations e.g. eligibility of participants, exploration of preferences, discussion of uncertainty and balancing of options. Audio-recordings will also be analysed for discussions relating to trial follow-up procedures (i.e. completion of patient questionnaires) and the importance placed on commitment to the trial across the entire timeline. Feedback will be provided to the site on how to improve aspects of the informed consent process based on targeted analysis described above. Whilst we will continue to collect audio-recordings of consultations for sites, the analysis of these will be triggered based on key diagnostics identified using the SEAR framework. This targeted approach for analysis and feedback will continue as new sites come on board and provides a timely and proportionate approach to analysis.

The transcripts of the consultations will be analysed using content and thematic analysis to elucidate reasons for imbalances in presentation, style and content of information provided by the recruiter, participation and engagement of patient, and indications of the presence and origin of 'hidden challenges'.

3B. Interviews with trial participants and site staff
Analysis will begin promptly through preliminary analysis of interview transcripts occurring whilst data collection continues. It is important to ensure an adequate number (previously defined as 12-15 per group) is collected before full analysis is conducted and feedback based on the results provided to sites. However, analysis for interviews in this context (i.e. to inform ongoing delivery of the trial) is conducted pragmatically with a focus on key aspects of trial process that are amenable to change so as to determine problem areas or identify aspects of good practice. A Framework Approach to analysis will be applied. We will familiarise ourselves with each data set (i.e. interviews with trial consenters, with trial decliners, and with site staff) and following initial familiarisation with transcripts we will develop a thematic coding framework based on discussions about both a priori questions and issues identified as emerging from the data. Initial codes (text labels) from this framework will then be systematically applied to the transcript data. Data management and initial analytic coding will be facilitated by the use of NVivo. The primary focus during the analysis will be on the a priori study aims. Particular attention will be paid to the types of judgement, beliefs and attitudes (including concerns) that people expressed in relation to recruitment, including views about the barriers and facilitators affecting trial recruitment.

4. Participant flow

Alongside the primary qualitative data, an in depth analysis of participant flow at each recruiting site will be conducted.

A log of patients, using the SEAR framework[3] will be assessed alongside discussions with staff to identify areas of complexity and protocol compliance. An in-depth analysis of participant flow using the **SEAR** framework at each recruiting site will be conducted. For example, screening logs (containing information on number of participants **S**creened, **E**ligible, **A**pproached, and **R**andomised) will be assessed alongside discussions with staff to identify areas of complexity and protocol compliance. Analysis will take the form of constant comparison alongside case study methods both within and across sites and individuals to determine problem areas or identify aspects of good practice. Comparison across sites will identify any variation and areas of good practice that can be shared. The SEAR data will also help to inform critical aspects for enquiry in the interviews and analysis of the recruitment consultations and provide a focus for site feedback.

Study Management

REGAL-QUAL will be led by experienced qualitative researchers with input and guidance from the Trial Project Management Team. The Research Fellow will conduct the interviews and lead data analysis. Specifically, they will be responsible for organising transcription, ensuring secure transfer of digital audio files to the transcriber and subsequent anonymisation of transcripts. File transfer will be conducted according to the current guidelines laid out in the University of Aberdeen's operating procedures. The qualitative researchers will also be responsible for organising appropriate storage of the digital files and transcripts, which will be stored on password protected University computers that are backed up on a secure SQL server. In addition, the audio recording of the consultation will be managed (including managing recording device and upload recordings to REGAL-Qual study folder) by a research nurse. The audio recordings and anonymised transcripts will be held securely for 25 years in accordance with Sponsor requirements and data legislation.

Impact of embedded qualitative research

Results from all qualitative work will be fed back (as anonymised summaries) to the Project Management Group (PMG) during and at the end of the internal pilot. Potential solutions in the form of action plans will be developed by the qualitative team and PMG in tandem, implemented and evaluated (through improvements in recruitment and retention) on a rolling case basis. The nature of the data collected allows for both aggregate and individual level feedback, which may be more effective than generalised trial feedback. Moreover, the iterative nature of the feedback allows for constant improvements in practice to be made, leading to overall improvements in efficiency.

Timeline

Following ethical approval, the audio recording of recruitment consultations will begin as soon as the process for inviting potential participants (both trial participants and site staff) commences. It is anticipated that this could start in early 2020 in pilot sites on a roll out basis.

Ethical considerations

The study will be conducted according to the principles of good clinical practice provided by Research Governance Guidelines. Some aspects of this qualitative evaluation, as proposed initially, have raised ethical concerns such as the processes of contacting participants who have refused to take part in REGAL to invite them to participate in an interview. Efforts have been made to ensure participants invited to interview feel able to make an informed, voluntary, decision about their participation.

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Appendix 3: Authorship Policy

AUTHORSHIP POLICY FOR THE REGAL STUDY

1. DEFINING AUTHORSHIP

Authorship of published or presented papers is based on the following criteria.[1]

i. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
ii. Drafting the work or revising it critically for important intellectual content; AND
iii. Final approval of the version to be published; AND
iv. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

2. PRINCIPLES OF AUTHORSHIP

The following principles of authorship have been derived from editorial publications from leading journals[2,3] and are in accordance with the rules of the International Committee of Medical Journal Editors (ICMJE).[1]

All contributors must fulfil the criteria detailed in section 1: DEFINING AUTHORSHIP in order to qualify for authorship.

Contributors who meet fewer than all four of the criteria for authorship listed above should not be listed as authors, but they should be acknowledged. For example, participation solely in the acquisition of funding, collection of data or technical editing, language editing or proofreading the article is insufficient by itself to justify authorship[1]. Those persons may be acknowledged and their contribution described. See section 3: ACKNOWLEDGEMENTS.

a. Preferred CHaRT authorship

Where possible, all CHaRT studies should publish using all the named contributors who qualify for authorship in the byline i.e. Jane Doe, John Doe, John Smith and Ann Other.

However, there may be situations where this is not possible, for example if the journal limits the number of authors. In such circumstance, group authorship may be appropriate using bylines similar to “The REGAL trial group” or “Jane Doe, John Doe, John Smith, Ann Other and the REGAL trial group”. The article should carry a footnote of the names of the people (and their institutions) represented by the corporate title. For some journals the journal will provide instructions on how to ensure the names of the collaborators appear on PubMed or equivalent.

Group authorship may also be appropriate for publications where one or more authors take responsibility for a group, in which case the other group members are not authors but may be listed in the acknowledgement (the byline would read 'Jane Doe *for* the Trial Group')[2]. Again, the article should carry a footnote of the names of the people (and their institutions) represented by the corporate title.

b. Determining authorship

These authorship criteria are intended to reserve the status of authorship for those who deserve credit and can take responsibility for the work. The criteria are not intended for use as a means to disqualify colleagues from authorship who otherwise meet authorship criteria by denying them the opportunity to meet criterion numbers (ii) or (iii). Therefore, all individuals who meet the first criterion should have the opportunity to participate in the review, drafting, and final approval of the manuscript[1].

Tentative decisions on authorship should be made as early as possible[3]. These should be justified to, and agreed by, the Project Management Group. Any difficulties or disagreements will be resolved by the Trial Steering Committee (TSC).

c. Ordering of authors

The following rules may help with the ordering of authors, particularly for publications with individual authorship:

i. The person who has taken the lead in writing may be the first author.
ii. The senior author may wish to be the last named author.
iii. Those who have made a major contribution to analysis or writing (i.e. have done more than commenting in detail on successive drafts) may follow the first author immediately; where there is a clear difference in the size of these contributions, this should be reflected in the order of these authors.
iv. All others who fulfil the four authorship criteria described in Section 1: DEFINING AUTHORSHIP may complete the list in alphabetical order of their surnames.

3. ACKNOWLEDGEMENTS

All those who make a contribution to a publication, but who do not fulfil the criteria for authorship, such as interviewers, data processors, staff at the recruiting sites, secretaries and funding bodies, should be acknowledged by name, usually in an 'Acknowledgements' section specifying their contributions. Because acknowledgment may imply endorsement by acknowledged individuals of a study's data and conclusions, authors are advised to obtain written permission to be acknowledged from all acknowledged individuals[1].

4. DISCLAIMERS

All papers arising from CHaRT must include the full title of the Health Services Research Unit (HSRU) and the appropriate disclaimer specified by the Chief Scientist Office (CSO). For the current disclaimer please see Q-Pulse.

Authors should also ensure they include the study funder's disclaimer: refer to the funders website for details. Be aware that other disclaimers may also be required.

5. QUALITY ASSURANCE

Ensuring quality assurance is essential to the good name of the trial group. All reports of work arising from the REGAL trial, including conference abstracts, should be peer reviewed by the Project Management Group. The Project Management Group will be responsible for decisions about submission following internal peer review. Submission may be delayed or vetoed if there are serious concerns about the scientific quality of the report. If individual members of the group are dissatisfied by decisions, the matter may be referred to the TSC.

It is hoped that the adoption and dissemination of this policy will prevent disputes that cannot be resolved by informal discussion. However, any member of the study team with a concern about authorship should discuss it with the relevant Chief Investigator, TSC, Line Manager or Programme Director as appropriate.

REFERENCES

1. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Developed by members of the ICMJE, the document is revised regularly and the current version (updated Dec 2018) is available at (www.icmje.org/#authors)
2. Huth EJ (1986). Guidelines on authorship of medical papers. *Annals of Internal Medicine*, **104**, 269-274.
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Appendix 4 – Risk

Risks associated with trial interventions

☐ A ≡ Comparable to the risk of standard medical care

☑ B ≡ Somewhat higher than the risk of standard medical care

☐ C ≡ Markedly higher than the risk of standard medical care

There are seven GnRHa preparations that can be used within the study at treatment initiation (see table 1). Six of the these are licensed for use in endometriosis; five of which are licensed for a maximum of 6 months use, but are used in routine clinical practice for longer than 6 months. For the sixth preparation (Triptorelin – Gonapeptyl Depot 3.75mg) the SmPC notes that "therapy without add back treatment should not exceed a duration of 6 months". As in the trial HRT is commenced concomitantly with GnRHa right from the beginning, we are mitigating the risk of osteoporosis which would be lower than the current license of using GnRHa for 6 months without HRT. Again, this preparation is used in routine clinical practice for longer than 6 months. One GnRHa preparation described in table 1 is not licensed for use in endometriosis, but is used regularly in clinical practice for this condition for periods of up to 6 months, and longer than 6 months.

The main concern is that the prolonged use of GnRHa preparations is associated with decrease in bone mineral density. Within the REGAL trial, the risk of this is minimised by recommending the use of add back HRT with the GnRHa to counteract any effect of GnRHa on bone mineral density.

Women at high risk of serious adverse effects with GnRHa such as a confirmed diagnosis of osteoporosis will not be enrolled into the REGAL trial.

What are the key risks related to therapeutic interventions you plan to monitor in this trial?		**How will these risks be minimised?**		
IMP/Intervention	Body system/Hazard	Activity	Frequency	Comments
GnRHa (any)	Bone mineral density	1. Addition of HRT to the GnRHa regime	Daily	Will be recommended as part of the GnRHa treatment

Outline any other processes that have been put in place to mitigate risks to participant safety (e.g. DMC, independent data review, etc.)

DEXA scans to monitor bone mineral density will be undertaken in all women in the GnRHa arm and a sub-group of 90 women in the surgery arm. In the GnRHa arm, these will be done at baseline, 12 months and 24 months and in the surgery arm at baseline and 24 months only. The DEXA scans will be reviewed by the local PI/treating clinician as described in Appendix 1.

Adverse reactions will be captured in the eCRF. In addition all SAEs and SARs will be captured. An independent DMC will review accumulating safety data.

Outline any processes (e.g. IMP labelling +/- accountability +/- trial specific temperature monitoring) that have been simplified based on the risk adapted approach.

Routine stocks of GnRHa preparations will be used. There will be no requirement for trial labelling or temperature monitoring. If any stock dispensed to women as part of the trial intervention becomes the subject of a medicine recall or drug alert, this will be handled through routine NHS procedures.

Appendix 5: Benefits and risks of conducting REGAL during COVID pandemic

Benefits of conducting the study during COVID pandemic
While long-term GnRHa with add-back HRT are commonly prescribed to women with endometriosis refractory to other treatments, the use of this regime has increased significantly during the COVID pandemic. As theatre capacity has substantially reduced during the pandemic, more women are being prescribed longer term GnRHa and HRT in the community to manage symptoms. Ongoing pressure on elective surgery in the NHS are likely to continue, therefore REGAL trial is timely to provide the much-needed evidence regarding effectiveness and safety of long term GnRHa with add back HRT for management of pain due to endometriosis.

The following arrangements have been instigated to minimise risk to participants and research staff during the COVID-19 pandemic:

Site set-up and training
During the pandemic, all site initiation visits/training will be conducted remotely by telephone/videoconference/pre-recorded video training. Sites will be opened in a phased manner in accordance with capacity/site readiness which will be considered by sites on an individual basis.

Consent process
Postal consent has been embedded within the protocol to ensure face-to-face contact is limited to clinical need and to avoid any unnecessary face-to-face consent visits during the pandemic. Details of the postal consent process are described in section 4.5.

Delivery of trial interventions
Trial interventions, including DEXA scans, will be delivered in primary and secondary care locations which will have COVID-specific mitigation measures in place (for example, PPE, social distancing, and hand hygiene).

Questionnaire follow-up
Questionnaires are completed remotely by participants, either by post or email. Therefore, no face-to-face contact is required.

Pregnancy testing
For women randomised to surgery, a pregnancy test will be performed as part of routine care prior to the procedure. Appropriate COVID precautions will be taken during this process (for example, PPE, social distancing, and hand hygiene). For women randomised to GnRHa with addback HRT, a pregnancy test will be performed by the participant in their own home. Therefore, no face-to-face contact is required.

Qualitative component
Qualitative consent, recording of consultations and interviews will continue remotely. Interviews will be audio recorded as per protocol.