Deep infiltrating endometriosis: management by medical treatment versus early surgery: DIAMOND

PROTOCOL

A UK Collaborative Trial funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme (project number NIHR 130310)

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

Sponsor/Co-Sponsors

Name:	University of Aberdeen
Address:	Polwarth Rm: 1.126 Foresterhill Aberdeen AB25 2ZD
Email:	researchgovernance@abdn.ac.uk

Name:	Grampian Health Board
Address:	Research and Development Office, Foresterhill House Annexe, Foresterhill, Aberdeen AB25 2ZB
Email:	grampian.randd@nhs.net
Co-Sponsor number:	3-001-20

Chief-Investigator (CI)

Name:	Professor Kevin Cooper
Address:	Aberdeen Royal Infirmary
Telephone:	01224 554800
E-mail:	Kevin.Cooper@nhs.scot

Deputy Chief-Investigator and Joint Lead Applicant

Name:	Professor Justin Clark
Address:	Birmingham Women's NHS Foundation Trust
Telephone:	0044 1214721377
E-mail:	t.j.clark@doctors.org.uk

Trial Office

Address:	DIAMOND Trial Office Centre for Healthcare Randomised Trials (CHaRT) 3rd Floor, Health Sciences Building University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD
Telephone:	01224 43xxxx
Fax:	01224 438165
E-mail:	diamond@abdn.ac.uk
Website:	https://w3.abdn.ac.uk/hsru/Diamond

Funder

Name:	NIHR Health Technology Assessment (HTA) Programme
Funder number:	HTA: NIHR127280
Funding start date:	1 January 2021
Funding end date:	30 April 2025

Other

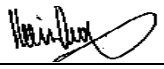
IRAS number	298771
ISRCTN	94462049
REC number	21-WS-0136

Signatures

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigators agree to conduct the trial in compliance with the approved, 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.

Kevin Cooper:	
Date:	17/5/23
Lorna Aucott:	lorna Aucott
Date:	17/5/23

VERSION HISTORY

Amendment no.	Protocol version no.	Description of changes (*incl. author(s) of changes*)	Date of document
	Version 1	New Document	
	Version 2	Updated with the REC reference number (pg 2), the name of the REC (Section 15), and addition of sentence to Appendix 1 to clarify audio recordings will be held securely for 10 years in accordance with Sponsor requirements. Signatures dates also updated. (*Lynda Constable*)	06 Jan 2022
AM-01	Version 3	• To aid clarity, 'Have used or currently using GnRH analogues without satisfactory relief of pain symptoms' added to the exclusion criteria (GnRH is a last line treatment and those already on this treatment would not be eligible for DIAMOND). • To aid clarity, updated inclusion criteria to 'Laparoscopically confirmed deep endometriosis +/- radiological imaging'. • Removal of 'and health status using EQ5D5L' from the trial summary as listed in error as a primary outcome (this is a secondary outcome). • Change of 'patient' to 'participant' throughout when referring to the PIL. • For clarity, added 'pre-menopausal' in the flow diagram. • Removed paragraph on 'monitoring compliance' as not a CTIMP (will still be collected from participant questionnaires) *(Lynda Constable)*	20 Jan 2022
AM-08	Version 4	• To reflect changed name of NIHR, name was updated to National Institute of health and Care Research • To clarify how sexual function outcome is collected, 'EHP-30 + Section C' was added after 'sexual function' throughout • To reflect when which outcome data are collected as noted in Table 2, flow diagram (Figure 1) was updated • To clarify when outcome data are collected and how, footnotes of table 2 were updated • Under Chapter 9. Embedded qualitative work Appendix number was updated to 'Appendix 1' after error. (*Christine Kennedy*)	17 Nov 2022
AM-09	Version 5	• Updated inclusion criteria to allow the use of MRI to confirm deep endometriosis, in line with updated European Society of Human Reproduction and Embryology (ESHRE) guidelines, and to reflect current practice *(Christine Kennedy)*	09 Dec 2022
AM-11	Version 6	• Deleting the exclusion criterion 'Planning to conceive in the next 18 months' and adding the exclusion criterion 'actively trying to conceive as anyone who does become pregnant during the study will be followed up as per protocol and not excluded	10 Feb 2023

		• Deleting ‘Pregnancy or Lactation' from the exclusion criteria in Figure 1 Flow Diagram as this is already captured under ‘Current pregnancy or breast feeding’ in the exclusion criteria. *(Lynda Constable)*	
AM-14	Version 7	• Updated the definition of deep endometriosis in line with current terminology guidelines published in 2021. • Updated inclusion criteria for confirming deep endometriosis to allow the use of laparoscopy or other routinely used investigative radiology technique, in line with the updated ESHRE guidelines and to reflect current routine practice. • Addition of provisional BSGE centres as recruiting sites. • Updated references to include the new terminology and updated ESHRE guidelines papers *(Lynda Constable)*	09 May 2023

Table of contents

Trial Summary

Trial Title	Deep infiltrating endometriosis: management by medical treatment versus early surgery: DIAMOND
Short title	DIAMOND
Rationale	Endometriosis affects up to 10% of women of reproductive age[1,2] and involves the growth of endometrial tissue in sites other than the uterine cavity, causing inflammation and adhesions, leading to pain and infertility. Deep endometriosis is its most severe form affecting up to 2% of women[3]. It is characterised by the presence of endometrium-like tissue lesions in the abdomen, extending on or under the peritoneal surface. They are usually nodular, able to invade adjacent structures, and associated with fibrosis and disruption of normal anatomy.[4] Women with endometriosis have been shown to have significantly impaired quality of life. A global survey in 2013 revealed that endometriosis affected work, relationships and education in 51%, 50% and 16% women respectively.[5] There is very little evidence in the literature to inform decision making in the management of deep endometriosis. An overview of 17 Cochrane reviews[6] assessed the effectiveness of treatments for endometriosis but was unable to comment specifically on women with deep endometriosis. Ovarian suppression by gonadotrophin-releasing hormone (GnRH) analogues, the levonorgestrel releasing intrauterine system (LNG-IUS) and danazol was found to be effective in terms of alleviating pain but unsuitable for women wishing to conceive. Laparoscopic surgery improved pain symptoms in women with endometriosis, but there were no head-to-head trials of medical versus surgical interventions. NICE and the European Society for Human Reproduction and Embryology[1, 7 2] suggest that both medical and surgical treatments can be used for deep endometriosis but highlight the lack of evidence to guide practice and the need for a large, multi-centre, adequately powered, randomised trial comparing the two strategies.
Trial design	This is a multi-centre randomised controlled trial, with an internal pilot phase, to compare medical management alone versus early planned laparoscopic surgery (first attempt at definitive surgery) with or without adjuvant medical treatment) in women with deep endometriosis. The internal pilot phase will monitor recruitment and assess the willingness of patients to participate in DIAMOND.
Eligibility criteria	***Inclusion criteria:*** • Women aged 18–49 years old seeking treatment for pain • Confirmed deep endometriosis (laparoscopic or other routinely used investigative radiology technique) • Suitable for either medical or surgical management. Able and willing to give informed consent to participate and to comply with study procedures (*There 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*)

	Exclusion criteria: • Unfit for laparoscopic surgery • Have used or currently using GnRH analogues without satisfactory relief of pain symptoms • Previous bilateral oophorectomy • Previous surgery for deep endometriosis • Actively trying to conceive • Confirmed bowel stenosis • Hydronephrosis or hydroureter caused by ureteric stenosis • Endometrioma > 5cm in diameter • Women with preference for hormonal medical or surgical treatment • Current pregnancy or breast feeding
Interventions	**Medical management** This will involve hormonal treatment for 18 months. The choice of hormonal medication will be at the discretion of the treating clinician in discussion with the participating woman, avoiding any treatment which has either failed or caused unacceptable side effects in the past. Any of the following preparations can be used: the combined contraceptive pill/patch (COCP), progestogen only preparations (oral tablets, depot injections, subcutaneous implants or intrauterine systems), danazol and gonadotrophin releasing hormone (GnRH) analogues with add back hormone replacement therapy (HRT). Women on hormonal treatment can receive additional neuromodulator drugs, analgesics and other interventions for pain relief. Medical treatment will be prescribed as per normal and accepted clinical practice in the UK. **Early laparoscopic surgery (with or without adjuvant medical treatment** A laparoscopic approach will be used to treat deep endometriosis but the choice of energy modalities and the need for concomitant hysterectomy and/or oophorectomy will be left to the discretion of the surgeon in consultation with their patient. Surgery will involve division of dense adhesions to separate affected pelvic structures, restore normal anatomy and removal of all endometriotic deposits, including deep nodules. Excision of deep endometriosis is achieved using laparoscopic instruments such as scissors, hooks and ultrasonic scalpels along with a variety of energy modalities including electricity, laser and ultrasound. If adjuvant medical management is needed, the same medical options used in the medical treatment arm (see above) will be utilised including hormones, neuromodulators and pain relief medication.
Randomisation and blinding	Eligible and consenting participants will be randomised to one of two groups using the well-established 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	Primary outcome data is required on 320 women at 18 months to detect an 8-point difference on the Endometriosis Health Profile-30 (EHP-30) pain domain for 90% power (two-sided alpha 0.05) assuming a standard deviation of 22 points. We have assumed an attrition rate of 20% for the primary outcome, which requires us to randomise 400 women in total.
Duration of study	52 months
	Objectives
Primary	The primary clinical objective is to compare medical (hormonal) treatment with laparoscopic surgery for deep endometriosis (with or without adjuvant medical treatment) in terms of condition specific quality of life measured using the pain domain of the EHP-30 at 18 months after randomisation. The primary economic objective is to assess the cost-effectiveness of medical (hormonal) treatment versus laparoscopic surgery (with or without adjuvant medical treatment) for deep endometriosis in terms of the incremental cost per QALY gained at 18 months post randomisation and modelled up to time of menopause.
Secondary	To compare medical (hormonal) treatment with laparoscopic surgery (with or without adjuvant medical treatment) for deep endometriosis in terms of: • satisfaction; • pain; • condition specific quality of life (EHP-30 and core domains) at 12 weeks and 12- and 18-months post-randomisation); • generic quality of life; • need for further medical treatment and gynaecological surgery; • serious adverse events and major surgical complications; • discontinuation of randomised treatment (with reasons for change); • sexual function (EHP-30 + Section C questionnaire); • occupational outcomes; • reproductive outcomes (pregnancy, live birth and other obstetric outcomes); • indirect costs due to loss productivity; • number of women in the medical treatment arm who go on to have surgery
Statistical methods	All analyses will be based on the intention-to-treat principle. 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 design covariates, and baseline measure of the primary outcome. Treatment effects will be estimated at each time-point by time-by-treatment interaction. Using EHP-30 scores from

	each time point will increase precision of estimates. Secondary outcomes will be analysed in a similar way with generalised linear models appropriate for the distribution of the outcome (i.e. logistic regression for binary data). Sensitivities of all treatment effect estimates to missing outcome data will be explored using multiple imputation methods, and pattern mixture modelling to assess the robustness of estimates to that missing at random (MAR) assumption. The primary aim of the trial is to compare two management strategies. However, we propose to use Casual Inference Methods to estimate the "efficacy" of receiving surgery. Because receiving surgery in the medical arm will be a time-dependent confounder we will use a marginal structural model (using inverse probability weights) for repeated measures data that will remove the effect of surgery in the medical arm, allowing us to estimate the treatment effects comparing surgery to medical management without cross-over. Full details of the statistical analyses will be documented in the Statistical Analysis Plan.
Co-ordination	Local: by local research teams Central: by Trial Office in Aberdeen (Telephone 01224 43xxxx). Overall: by the Project Management Group and overseen by the Trial Steering Committee and the Data Monitoring Committee.

Lay Summary

Endometriosis is a common condition affecting 1 in 10 women, which can cause severe pain. It happens when cells similar to those lining the womb grow outside the womb, generally on surfaces and organs within the pelvic cavity, causing bleeding, scarring and inflammation. Occasionally, rather than growing on or very near the surface, the endometriosis cells can grow deeper into tissues and organs, such as the bowel, bladder and the vagina causing a painful condition which is called deep endometriosis.

Deep endometriosis is treated in one of two ways:
• by taking hormones which can shrink areas of existing endometriosis and prevent new areas forming by stopping the growth of abnormal cells
• by using keyhole (laparoscopic) surgery to remove areas of endometriosis

Each treatment has its own benefits and potential drawbacks. Hormones can produce side effects and are not suitable for women who want to get pregnant. They may also not provide sufficient pain relief in some women who may need to have surgery. Keyhole surgery for deep endometriosis can reduce pain in many, but not all women, but the procedure is complex with a risk of damage to surrounding organs like bowel and the bladder.

The limited research that has been done in this area suggests that, for women with deep endometriosis who are not considering immediate pregnancy, hormonal treatment over many months could be just as effective as surgery in relieving pain, as long as the bowel or ureters (tubes that carry urine and connect the kidneys to the bladder), are not narrowed by endometriosis. Clinical guidelines state that either hormones or surgery can both be used but are unable to recommend one over the other in the absence of research directly comparing them. As a result, doctors' decisions are often based on their personal preferences, resulting in major differences in clinical practice across the NHS. There is an urgent need for a research trial to compare medical (hormonal) management versus surgery for deep endometriosis, to provide a clear and evidence-based answer to this important question.

We are proposing a large UK-wide study to compare the benefits and risks of medical (hormonal) management versus surgery as treatments for deep endometriosis. We will ask patients who have deep endometriosis which is not causing narrowing of the bowel or ureters to opt into this research project. All women who agree to take part will have an equal chance of getting hormonal medical treatment or surgery, and we will monitor their symptoms for 18 months via questionnaires at 3, 12 and 18 months. Women in either group can also receive additional pain relief and if the medical treatment is not working, they can opt to have surgery, but we still want to know about their symptoms.

Our team of experts include gynaecologists, GPs, researchers, and patient representatives. Involvement of patients and the public has been achieved by working with the University of Aberdeen's Public Interest Research Group and Endometriosis UK and carrying out an online survey of women with endometriosis and clinicians. We have a clear plan to share the results of this research 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, the media and the website of the national charity, Endometriosis UK.

Glossary of Abbreviations

AE	Adverse Event
BSGE	British Society of Gynaecology Endoscopy
CHaRT	Centre for Healthcare Randomised Trials
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTU	Clinical Trial Unit
DMC	Data Monitoring Committee
EHP-30	Endometriosis Health Profile-30
EQ-5D-5L	EuroQol Group's 5 dimension health status questionnaire
GCP	Good Clinical Practice
GnRH	Gonadotrophin-Releasing Hormone
GP	General Practitioner
HRT	Hormone Replacement Therapy
HSRU	Health Services Research Unit
HTA	Health Technology Assessment
ISD	Information Statistics Division
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
LNG-IUS	Levonorgesterol-releasing Intrauterine system
NHS	National Health Service
NHSG	National Health Service Grampian
NICE	National Institute for Health and Care Excellence
NIHR	National Institute Health and Care Research
NRES	National Research Ethics Service
PI	Principal Investigator
PIL	Participant Information Leaflet
PMG	Project Management Group
PPI	Patient and Public Involvement
PQ	Participant Questionnaire
QA	Quality Assurance
QALY	Quality Adjusted Life Year
QP	Qualified Person
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TMF	Trial Master File
TSC	Trial Steering Committee
UK	United Kingdom
UoA	University of Aberdeen

Trial Personnel

Chief Investigator

Professor Kevin Cooper

Deputy Chief Investigator and Joint lead applicant

Professor Justin T Clark

Grant Holders

Professor Kevin Cooper
NHS Grampian
kevin.cooper@nhs.scot

Professor T. Justin Clark
Birmingham Women's NHS Foundation Trust
t.j.clark@doctors.org.uk

Associate Professor Saad Amer
University of Nottingham
saad.amer@nottingham.ac.uk

Professor Graeme MacLennan
University of Aberdeen
g.maclennan@abdn.ac.uk

Dr Katie Gillies
University of Aberdeen
k.gillies@abdn.ac.uk

Professor Peter Murchie
University of Aberdeen
p.murchie@abdn.ac.uk

Professor Siladitya Bhattacharya
University of Aberdeen
s.bhattacharya@abdn.ac.uk

Dr Dominic Byrne
Royal Cornwall Hospitals NHS Trust
dominic.byrne@me.com

Dr Paul Smith
Birmingham Women's NHS Foundation Trust
paul.smith@doctors.org.uk

Emma Cox
Endometriosis UK
ceo@endometriosis-uk.org

Dr Islam Gamaleldin
North Bristol NHS Foundation Trust
islammostafa83@gmail.com

Dr Graham Scotland
University of Aberdeen
g.scotland@abdn.ac.uk

Mr Arvind Vashisht
University College London
arvindvash@gmail.com

Professor Andrew Horne
University of Edinburgh
Andrew.Horne@ed.ac.uk

Trial Office Team

Chief Investigator

Deputy Chief Investigator

CHaRT Director

Trial Manager

Data Co-ordinator

Senior Trial Manager

Senior IT Manager

Trial statistician

Qualitative Researcher

Project Management Group (PMG)

This Group is comprised of the grant holders along with representatives from the Trial Office 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 Investigators (CIs) Kevin Cooper and T Justin Clark, or a nominated delegate. The other

DIAMOND grant-holders and key members of the Trial Office team (e.g. the trial manager) may attend TSC meetings.

Data Monitoring Committee (DMC) Members
This Committee is comprised of independent members, and the trial statistician contributes as appropriate. The CIs 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 affects up to 10% of women of reproductive age[1,2] and involves the growth of endometrial tissue in sites other than the uterine cavity, causing inflammation and adhesions, leading to pain and infertility. Deep endometriosis (DE) which affects up to 2% of women[3], is its most severe form. It is characterised by the presence of endometrium-like tissue lesions in the abdomen, extending on or under the peritoneal surface. They are usually nodular, able to invade adjacent structures, and associated with fibrosis and disruption of normal anatomy.[4]

Women with endometriosis have been shown to have significantly impaired quality of life. A global survey in 2013 revealed that endometriosis affected work, relationships and education in 51%, 50% and 16% of women respectively.[5]

The need for randomised trials comparing surgery with medical treatment in women with DE has been highlighted in an overview of Cochrane reviews[6], while the James Lind Alliance Priority Setting Partnership have identified effective non-surgical treatment for endometriosis-related pain as a top ten research priority.[8]

Endometriosis is difficult to treat successfully[9] and poses a significant public health burden. It compromises quality of life, causes severe social and psychological distress[10, 11] and has major occupational consequences. The average annual worldwide cost associated with endometriosis has been estimated at €9579 per woman – costs comparable to those associated with diabetes, inflammatory bowel disease and rheumatoid arthritis.[12]

Of an estimated 176 million women of reproductive age worldwide who have endometriosis, a total of 18 million (10%) with DE have received little attention from researchers.[13] This is because the current approach – i.e. initial medical treatment followed by surgery has been the generally accepted modality but access to specialist surgery is variable, and there are few comparative data on surgical outcomes. With the establishment of centralised, specialist BSGE Endometriosis Surgery Centres and publication of their results, these problems have been overcome in the UK[13], making it possible to conduct clinical trials comparing surgery with contemporary medical treatments. Operations for DE are complex and associated with potentially serious complications.[13] Medical treatments are less invasive, and, if shown to be effective, could transform women's lives and NHS treatment pathways.

In a recent survey of 66 women with endometriosis undertaken by the applicants in conjunction with Endometriosis UK, 47% of responders stated that they were willing to be randomised to either medical or surgical treatment and most (74%) felt that relief of pain and quality of life were the most important outcomes. The best time point for the assessment of symptoms was felt to be 6, 12 or 24 months after starting treatment by 42%, 35% and 17% women respectively, while 6% felt that outcomes should be assessed at several points in time.

Of 79 specialist clinicians surveyed by the British Society for Gynaecological Endoscopy, 43% felt there was insufficient evidence to inform decision making in DE management and 94% were willing to randomise their patients to either a surgical or medical pathway. Most (64%) considered both pain and quality of life to be the most important outcome measures; with 3% prioritising pain and 34% quality of life. Post treatment, the optimal follow-up period was felt to be 12 and 24 months by 44% and 36% respectively, while 20% of respondents favoured measurements at multiple time points.

The current clinical pathway for management of women with pain due to DE involves initial medical management using a variety of hormonal agents, but ultimately many women go on to have surgery. Laparoscopic excision of endometriosis has been shown to improve pain symptoms in DE[13] and surgery has been the traditional approach favoured by many clinicians who believe that medical treatment cannot reverse pelvic scarring caused by the condition. [14-16] While surgery is the only option in women with mechanical obstruction of the bowel or ureters, long-term hormonal treatment with the aim of shrinking areas of endometriosis have been

shown to relieve symptoms in other cases.[17-19] Surgery for DE is very invasive and can lead to bowel injury, septic peritonitis, rectovaginal fistula formation, stenosis, and functional bowel or bladder problems in about one in 14 patients.[13] Some women undergoing surgery will also request concomitant hysterectomy and or bilateral oophorectomy if they have completed their family and it is felt that this would reduce the need for further treatment. Hormonal treatment is less invasive, but can cause side-effects that may impact on compliance and is not suitable for women trying to conceive. A recent review of observational studies suggests that long-term hormonal treatment could be a viable alternative to surgery for DE[20], but there are no randomised controlled trials to provide conclusive comparative evidence on clinical and cost effectiveness.

1.2 Rationale for the trial

There is very little evidence in the literature to inform decision making in DE. An overview of 17 Cochrane reviews assessed the effectiveness of treatments for endometriosis but was unable to comment specifically on women with DE.[6] Ovarian suppression by gonadotrophin-releasing hormone (GnRH) analogues, the levonorgestrel releasing intrauterine system (LNG-IUS) and danazol was found to be effective in terms of alleviating pain but unsuitable for women wishing to conceive. Laparoscopic surgery improved pain symptoms in women with endometriosis, but there were no head-to-head trials of medical versus surgical interventions.

In a small trial of 60 women with DE affecting the rectum[21], conservative surgery (shaving or disc excision) versus rectal resection offered similar functional outcomes. A search of ClinicalTrials.gov identified a single ongoing trial (MEdical Versus SUrgical Treatments of Rectal Endometriosis), comparing oral cyproterone acetate (unlicensed for endometriosis in the UK) with percutaneous estradiol versus surgery (rectal shaving; rectal disc excision; colorectal resection) in 78 women aged 35–50 years with deep endometriosis with bowel symptoms. The population and interventions in this trial are different to our proposed trial where the entry criteria are much wider and include all women with DE (without narrowing of the bowel or ureter) who will be randomised to either surgery or a variety of hormonal treatments. Our search of the relevant databases has not revealed any other randomised trials (either completed or in progress) comparing medical versus surgical treatment in women with DE.

Observational data from 87 women with colorectal endometriosis show that, at 12 months, 78% of those who chose hormonal medical treatment were satisfied with the level of their symptoms compared with 76% of those who chose surgery.[20] In a UK cohort study of 5162 women with rectovaginal endometriosis, improvement in pain, bowel symptoms and quality of life was reported by 4721 women who had had laparoscopic excision.[13] In a review of 8 case series (N = 420) of women with colorectal endometriosis, treatment with the combined oral pill, progestogens, GnRH analogues and aromatase inhibitors was able to control most symptoms in the absence of bowel obstruction.[22] Two thirds of all women were satisfied with the level of their symptoms, regardless of the drug used, suggesting that long-term hormone use could be an alternative to surgery for DE in women for whom fertility is not a priority.

In terms of hormonal treatment for endometriosis, NICE favours the combined contraceptive pill and Danazol over GnRH analogues, which are as effective, but more costly. As hormones can affect ovarian function, leading to side effects, they are incompatible with concurrent plans for pregnancy. On the other hand, surgery is invasive and associated with substantial intra- and postoperative complication rates. [23-25]

NICE and the European Society for Human Reproduction and Embryology suggest that both medical and surgical treatments can be used for DE but highlight the lack of evidence to guide practice and highlight the need for a large, multi-centre, adequately powered, randomised trial comparing the two strategies. [1, 7]

1.3 Assessment and management of risk

The co-CIs will ensure, through the TSC, that adequate systems are in place for monitoring the quality of the study (compliance with GCP) and appropriate expedited and routine reports of adverse events, to a level appropriate to the risk assessment of the study.

Women will be informed of possible benefits and known risks (including known complications) of both treatment policies in the trial by means of a Participant Information Leaflet, discussion with the local Research Nurses and their own Consultant Gynaecologist. Both treatment policies (medical and surgery treatment) are routinely used within the NHS. We do not anticipate that participants will run additional risks by participating in DIAMOND. They will sign a consent form approved by the Ethics Committee. They will be consented to participating in the study with follow up, being randomised, being contacted in the future about this and other research including electronic tracing using NHS data, and data linkage with computerised NHS data sources. Women who are not able or not willing to be randomised will not be recruited.

2. Trial Aims and Objectives

The primary aim of the trial is to compare the clinical and cost-effectiveness of medical treatment versus laparoscopic surgery for the management of deep endometriosis.

The research question to be addressed is: What is the clinical and cost-effectiveness of medical management alone versus laparoscopic surgery (with or without adjuvant medical treatment) in women with deep endometriosis?

2.1 Primary objectives

The primary objectives are:

- To compare medical (hormonal) treatment with laparoscopic surgery for deep endometriosis (with or without adjuvant medical treatment) in terms of condition specific quality of life measured using the pain domain of the Endometriosis Health Profile-30 (EHP-30) and health status using EQ-5D-5L at 18 months after randomisation.
- To assess the cost-effectiveness of medical (hormonal) treatment with laparoscopic surgery (with or without adjuvant medical treatment) for deep endometriosis in terms of the incremental cost to the health service per QALY gained at 18 months post randomisation and modelled up to the time of menopause (QALYs derived from participant responses to the EQ-5D-5L).

2.2 Secondary objectives

To compare medical (hormonal) treatment with laparoscopic surgery for deep endometriosis (with or without adjuvant medical treatment) in terms of:

- satisfaction;
- pain;
- condition specific quality of life and participants' functional health and well-being (EHP-30 and core domains at 12 weeks and 12- and 18-months post-randomisation);
- generic quality of life;
- need for further medical treatment and gynaecological surgery;
- serious adverse events and major surgical complications (Clavien Dindo grades 3-5 [26]);
- discontinuation of randomised treatment (with reasons for change);
- sexual function (EHP-30 + Section C questionnaire);
- occupational outcomes;
- reproductive outcomes (pregnancy, live birth and other obstetric outcomes);
- indirect costs due to loss of productivity.
- number of women in the medical treatment arm who go on to have surgery and vice versa

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

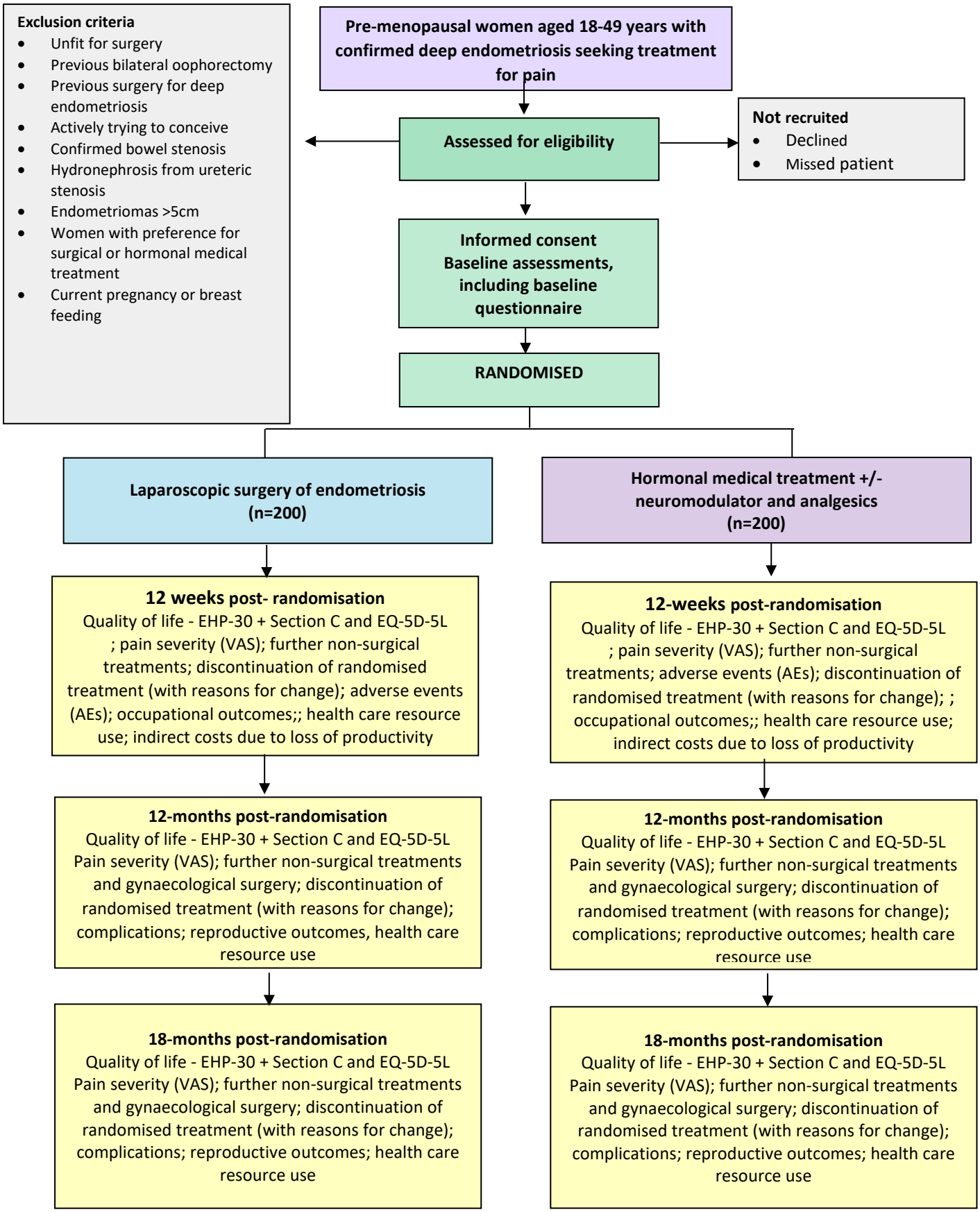
2.3 Qualitative sub-study

There is an embedded qualitative sub-study in DIAMOND (see Appendix 1). One to one interviews (either face to face or via telephone or video call) with women and staff from recruiting centres will be conducted to explore the patient experience of both the trial and the interventions. The aim of the qualitative sub-study is to inform delivery of the study and facilitate problem solving during an internal pilot as well as the main phase of the trial and to provide timely feedback and improve successful recruitment and delivery of the DIAMOND trial. Qualitative data will also be used to explore the experiences of women randomised to different pathways of care. In sites where recruitment is problematic, we will audio record consultations to identify how recruitment consultations are framed.

3. Trial Design

This is a multi-centre randomised controlled trial, with an internal pilot phase, to compare medical management alone versus planned laparoscopic surgery (first attempt at definitive surgery) with or without adjuvant medical treatment) in women with deep endometriosis. The trial structure is shown in Figure 1 (Flow Diagram). The internal pilot will monitor recruitment and assess the willingness of patients to participate in DIAMOND. The embedded qualitative sub-study is described in Appendix 2.

Figure 1 Flow diagram



3.1 Interventions to be evaluated

i) Medical management:

This will involve hormonal treatment for 18 months. The choice of hormonal medication will be at the discretion of the treating clinician in discussion with the participating woman, avoiding any treatment which has either failed or caused unacceptable side effects in the past. Any of the following preparations can be used: the combined contraceptive pill/patch (COCP), progestogen only preparations (oral tablets), depot injections (depot medroxyprogesterone acetate (DMPA), subcutaneous implants (e.g. Nexplanon) or intrauterine systems (levonorgestrel intrauterine systems (LNG-IUS)), danazol and gonadotrophin releasing hormone (GnRH) analogues with add back hormone replacement therapy (HRT). Women on hormonal treatment can receive additional neuromodulator drugs, analgesics and other interventions for pain relief. Medical treatment will be prescribed in line with normal and accepted clinical practice, as recommended by NICE guidelines on management of endometriosis[7] in the UK

ii) Laparoscopic Surgery (with or without adjuvant medical treatment):

A laparoscopic approach will be used to treat DE but the choice of energy modalities and the need for concomitant hysterectomy and/or oophorectomy will be left to the discretion of the surgeon in consultation with their patient. Surgery will involve division of dense adhesions to separate affected pelvic structures, restore normal anatomy and removal of all endometriotic deposits, including deep nodules. Excision of DE is achieved using laparoscopic instruments such as scissors, hooks and ultrasonic scalpels along with a variety of energy modalities including electricity and ultrasound. If adjuvant medical management is needed, the same medical options used in the medical treatment arm (see below) will be utilised including hormones, neuromodulators and pain relief medication. For pragmatic reasons, changes to medical treatment used prior to surgery will be accepted, in line with NICE guiedlines[7].

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 18-49 years presenting with pelvic pain associated with DE who are suitable for either medical or surgical management.

4.2 Setting

This trial will take place in British Society for Gynaecology Endoscopy (BSGE) accredited and provisional UK Endometriosis centres where all operations will be performed. This will allow comparison of optimal surgery by endometriosis specialists with those allocated medical treatment.

4.3 Inclusion and exclusion criteria

Inclusion criteria:

- Women aged 18–49 years old seeking treatment for pain
- Confirmed deep endometriosis (laparoscopic or other routinely used investigative radiology technique)
- Suitable for either medical or surgical management
- Able and willing to give informed consent to participate and to participate in study procedures (*There 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*)

Exclusion criteria:

- Unfit for laparoscopic surgery
- Have used or currently using GnRH analogues without satisfactory relief of pain symptoms
- Previous bilateral oophorectomy
- Previous surgery for deep endometriosis
- Actively trying to conceive
- Confirmed bowel stenosis
- Hydronephrosis or hydroureter caused by ureteric stenosis
- Endometrioma > 5cm in diameter
- Women with preference for hormonal medical or surgical treatment
- Current pregnancy or breast feeding

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 are 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 meet the eligibility criteria can be considered 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 and provisional endometriosis centres, although peripheral hospitals referring women with confirmed DE to endometriosis centres (accredited and provisional) for further assessment and discussion about medical and/or surgical treatment, can approach potential participants about the study. Restricting recruitment to BSGE accredited and provisional endometriosis centres has several advantages including:

- Access to dedicated weekly endometriosis clinics run by gynaecologists who are likely to be able to access a large pool of eligible participants (>5 per centre per month);
- The ability to offer optimal surgery performed by specialists thus ensuring standardisation of the comparator arm;
- The presence of endometriosis nurse(s) in each centre, who along with research nurse(s) can monitor compliance with medical management, promote recruitment and provide patient support.

Eligible women who are referred with pelvic pain associated with DE may be identified by the DIAMOND 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 Participant Information Leaflet (PIL) describing the study and will have the opportunity to read this before deciding 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. 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 if they will take part in the study. Women may decide to participate during an initial (or subsequent) 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 may send their completed documents (consent form and baseline questionnaire) through the post to the local team at their treating hospital. All women will have the option to complete the consent form electronically rather than completing a hard copy. Details of the consent discussion, including discussion date, will be recorded.

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 the principles of Good Clinical Practice (GCP). 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. Consent may be documented using a hard copy consent form during a face to face 'in person' informed consent consultation, or documented by post (following an informed consent in person or telephone discussion), or documented electronically (following an informed consent in person or telephone discussion).

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 of withdrawal cannot be erased and will be used in the final analyses.

Participants who cannot give informed consent (e.g. due to impaired cognition) 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 to which the patient has access to facilitate their participation in the study (e.g. 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 to be 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. The countersignature will only be recorded after discussion has taken place with the participant about the study and any questions have been answered. Only once both patient and person receiving consent signatures are present will informed consent be considered to have been obtained. Participants will be sent a copy of the completed consent form for their own records and a copy will be retained in the investigator site file and TMF.

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

4.7.1 Obtaining e-Consent

To cater for participant preference and COVID adaptations, participants may opt to consent using an e-consent form via the secure web-based trial management system provided by CHaRT. If this option is preferred, participants will be asked to provide their email address which will be entered into the secure web-based trial management system. Participants will be sent a verification email with a link to verify their email. Once the email address is verified, participants will be automatically emailed the PIL and a link to the participant e-consent form for their unique study number. The e-consent form will be identical to the approved paper version of consent form, with the approved PIL version number and date automatically populated. The participant will be asked to provide their signature online via a signature box using a finger tracing via a touch screen or using a mouse. Completed e-consent forms will be checked, and electronically counter-signed by someone listed on the delegation log with appropriate delegated responsibilities. The countersignature will only be recorded after discussion has taken place with the participant about the study and any questions have been answered. Only once both patient and person receiving consent signatures are present will informed consent be considered to have been obtained. Any e-consent obtained will be verbally confirmed by the site at any future communication. Participants will be sent a copy of the e-consent form for their own records and a copy will be retained in the investigator site file and TMF.

Should participants who are sent the study information choose not to take part in the study their email address will be deleted from the trial management system after 3 months.

The trial management system used to record e-consent has a clear audit trail with tracking of all inserts or updates made. Database interactions logged against a user and date/time and the audit trail can be downloaded and analysed at any time by authorised users.

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 (18-30; 31-40; 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. Patient screening

identification initials and recruiting site will be entered into the web-based system which will return the allocation status. 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, (but can take medical treatment whilst waiting, see section 5.2)
- For those randomised to medical management, arrangements for the medical management should be made (for example commence treatment, provide a prescription or ask the GP to prescribe/administer the treatment)
- 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

The current clinical pathway for management of women with pain due to DE involves medical management which may end up with surgery at a later stage.

Women will be offered a choice of hormonal treatments including progestogens, combined contraceptive pill or patch, danazol and GnRH analogues (with add back hormone replacement therapy to reduce menopausal symptoms).

Women with DE randomised to the surgical arm will be offered surgery, after which women who are not trying to conceive may be offered hormonal treatment to reduce the risk of recurrence according to local centre practice/women's choice.

Women in both randomised arms (treated medically or surgically) can be offered analgesics or neuromodulators for additional pain relief. Trial participants randomised to medical management will aim to remain on their allocated medication for 18 months, alterations in medical treatment regime will be allowed but if adequate symptom relief is not achieved then surgery can be offered.

5.1 Medical management

This will involve hormonal treatment for 18 months. The choice of hormonal medication will be at the discretion of the treating clinician in discussion with the participating woman, avoiding any treatment which has either failed or caused unacceptable side effects in the past. The treating clinician will avoid prescribing medication for which the woman has contraindications. Any of the following preparations can be used: the combined contraceptive pill/patch (COCP), progestogen only preparations (oral tablets), depot injections (DMPA), subcutaneous implants or intrauterine systems (LNG-IUS)), danazol and gonadotrophin releasing hormone (GnRH) analogues with add back hormone replacement therapy (HRT). Women on hormonal treatment can receive additional neuromodulator drugs, analgesics and other interventions for pain relief. Medical treatment will be prescribed in line with normal and accepted clinical practice, as recommended by NICE guidelines on management of endometriosis[7] in the UK.

Women may switch between various forms of medical management, depending on their preference and tolerance of various preparations. However, hormonal treatment should continue for 18 months post-randomisation unless:

- A serious adverse reaction to hormonal treatment occurs and in the opinion of the investigator or clinician that it is medically necessary to stop all hormonal treatment.
- A participant wishes to become pregnant.

- The participant declines to start or declines to continue taking hormonal treatment for any reason.

Women in the medical management arm may go on to have surgery, after which they may be offered hormonal contraception to reduce the risk of recurrence according to local centre practice/women's choice.

Regardless of the compliance to medical management women will continue to be followed up within the study.

The medical treatments offered within DIAMOND will not be specifically manufactured or labelled for use within the DIAMOND trial. The trial will use routine stocks prescribed by the clinical team or their GP and dispensed by hospital or local community pharmacy.

5.1.2 Prescription of DIAMOND hormonal treatment

Any hormonal treatment (used as standard of care) may be used. The administration of hormonal treatment will depend on the local policy. The intention would be to initiate the allocated treatment as soon as possible to minimise non-compliance and for the convenience of the participant. The administration of hormonal treatment will usually be in primary care but can be initiated in secondary care or initiated and continued in secondary care. If it is to be administered in primary care, a letter will be sent to the GP specifying the name, dose and duration of hormonal treatment that is being recommended (based on the preference of the participants and their secondary care clinicians) asking the GP to prescribe and initiate treatment. If it is to be initiated in secondary care but ongoing administration is in primary care, a letter will be sent to the GP specifying the name, dose and duration of hormonal treatment that is being recommended (based on the preference of the participants and their secondary care clinicians) asking the GP to continue treatment. If the treatment will be administered purely in secondary care, a letter will be sent to the GP specifying the treatment (for information only).

If the GP does not prescribe/ initiate the hormonal treatment that is recommended this is NOT considered to be a breach of protocol within this pragmatic study and the women will be followed up within the study.

At each follow-up questionnaire, we will ask women to report all treatments that they are receiving. At final follow up, the prescription record for each participant will be requested directly from GP practices or by linking to patient prescribing data (e.g. NHS Digital Data Access Request Service (digital.nhs.uk/data-and-information/data-insights-and-statistics/prescribing-and-medicines-team, www.nhsresearchscotland.org.uk/research-in-scotland/data/health-informatics, in Scotland, or equivalent), to accurately establish medicinal use during the trial. We will seek consent for such linkage at the outset of the study.

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 5.1.2, women randomised to the medical management arm will have a letter 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. Women will be asked in their 12 week follow up questionnaire whether or not they have initiated treatment.

5.1.4 Drug accountability

Routine stocks of hormonal treatment 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 Surgery (with or without adjuvant medical treatment)

A laparoscopic approach will be used to treat DE but the choice of energy modalities and the need for concomitant hysterectomy and/or oophorectomy will be left to the discretion of the surgeon in consultation with their patient. Rarely a laparotomy may be required to complete the procedure safely

Surgery will involve division of dense adhesions to separate affected pelvic structures, restore normal anatomy and removal of all endometriotic deposits, including deep nodules.

Excision of DE is achieved using laparoscopic instruments such as scissors, hooks and ultrasonic scalpels along with a variety of energy modalities including electricity and ultrasound. If adjuvant medical management is needed, the same medical options used in the medical treatment arm will be utilised including hormones, neuromodulators and pain relief medication.

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; and thereafter to confirm that surgery has taken place. 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. If the woman is already taking hormonal treatment to supress endometriosis symptoms, they will be advised to continue using this until their surgery. For pragmatic reasons, any changes to medical treatment used prior to surgery will be accepted, in line with NICE guiedlines[7].

Excised material will be sent for pathological examination. Women in the surgical arm can use any medical (hormonal) treatment available to those randomised to the medical arm, either for contraception or to prevent recurrence of endometriosis. This will be recorded in each follow up questionnaire.

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 both randomised arms can be offered analgesics or neuromodulators for additional pain relief. Women in the surgical arm can also be offered hormonal treatment if felt this would be beneficial to the patient's well-being.

6. Outcome Measures

6.1 Primary outcome measure

Primary patient outcome: The primary clinical outcome is the pain domain of the condition-specific Endometriosis Health Profile-30 (EHP-30) measured at 18 months post-randomisation.

Primary economic outcome**:** incremental cost per quality adjusted life year (QALY) gained from a health service perspective at 18 months and modelled over the reproductive life of women (QALYs derived from participant responses to the EQ-5D-5L).

6.2 Secondary outcome measures

Clinical:

- Surgical complications

Patient reported:

- Condition specific quality of life [EHP 30], four core domains (control, emotional aspects, social support and self-image) measured at 12 weeks, 12 months and 18 months post-randomisation;
- Satisfaction;
- Pain domain of the condition-specific Endometriosis Health Profile-30 (EHP-30) measured at 12 weeks and 12 months post-randomisation;
- Pain (measured on a visual analogue scale) measured at 12 weeks, 12 months and 18 months post-randomisation;
- Further medical treatments (hormones, analgesics, alternative therapies, physiotherapy, TENS etc.);
- Further related surgery;
- Sexual function (EHP-30 + Section C questionnaire);
- Discontinuation of randomised treatment (with reasons for change);
- Serious adverse events and complications;
- Occupational outcome measured by Work Productivity and Activity Impairment questionnaire;
- Indirect costs due to loss productivity;
- Reproductive outcomes (pregnancy, live birth and other obstetric outcomes);
- number of women in the medical treatment arm who go on to have surgery

Economic:

- Indirect costs based on time lost from productive activity measured over the follow-up period (assessed via patient questionnaires).

6.3 Long term outcomes (beyond 18 month horizon)

Data on long-term outcomes (beyond 18 months) 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, 12 weeks, 12 months and 18 months post-randomisation using questionnaires.

Table 2 Measurement of outcomes: components and timing

	Baseline	**Surgery**	**12 weeks post-randomisation**	**12 months post-randomisation**	**18 months post-randomisation**
Baseline CRF[1]	x				
Surgical details CRF[2]		x			
EHP-30 + Section C[3]	x		x	x	x
EQ-5D-5L[3]	x		x	x	x
Satisfaction				x	x
Pain (VAS)[3]	x		x	x	x
Initiation of medical management (for those in the medical management arm only)			x		
Further medical treatments[4]			x	x	x

	Baseline	Surgery	12 weeks post-randomisation	12 months post-randomisation	18 months post-randomisation
Further healthcare resource use			x	x	x
Gynaecological surgery	x			x	x
Discontinuation of randomised treatment (with reasons for change) [4]			x	x	x
SAEs / complications		x[2]	x	x[3]	x[3]
Occupational outcome measured by Work Productivity and Activity Impairment questionnaire[4]			x	x	x
Reproductive outcomes[3]				x	x
Indirect costs due to loss of productivity[4]			x	x	x
Case-note review for further treatment[5]					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 medical management and having surgery)
[3] completed by participant at recruitment and at 12 weeks, 12 months and 18 months post randomisation; combined into a single questionnaire with other participant completed outcomes at same time-points
[4] completed by participant at 12 weeks, 12 months and 18 months post randomisation; combined into a single questionnaire with other participant completed outcomes at same time-points or CRF completed by site research team
[5] completed by site research team at 18 months post-randomisation

7.2 Baseline

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

The site research team will complete the baseline CRF including information on parity; age, ethnicity, current and previous treatments used for endometriosis associated pain.

At baseline, we will also collect contact details of participants (including postal address, email, home and mobile number) and their contact preferences (see section 7.4) along with details of their GP.

7.3 Surgery

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

7.4 Follow-up

Patient reported outcomes will be collected at 12 weeks, 12 months and 18 months post-randomisation using questionnaires completed by women at home. The questionnaires will include EHP-30 + Section C, EQ-5D-5L, symptoms, and questions about current and recent treatment (including analgesic use), satisfaction with treatment, serious adverse events/complications, 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 or have discontinued medical management 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

The secondary care medical notes of all participants will be reviewed at 18 months after randomisation and any relevant data on further treatment (and outcome of pregnancy, where relevant) will be captured. The prescription record for each participant will also be requested directly from GP practices or by linking to patient prescribing data (e.g. NHS Digital Data Access Request Service (https://digital.nhs.uk/data-and-information/data-insights-and-statistics/prescribing-and-medicines-team, www.nhsresearchscotland.org.uk/research-in-scotland/data/health-informatics, in Scotland, or equivalent) to accurately establish medicinal use during the trial .

7.6 Change of Status/Withdrawal procedures

Participants remain in the trial unless they choose to withdraw consent. Participants are free to withdraw from the trial at any timepoint. 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.

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.

Participants who do not receive their allocated treatment, receive the non-randomised treatment or discontinue their medical management 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 questionnaires 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.

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 DIAMOND trial involves two different policies for treating deep endometriosis: medical management or surgical management (with or without adjuvant medical treatment). The MHRA has confirmed that DIAMOND is not a CTIMP and therefore the safety reporting within DIAMOND will follow guidance for safety reporting in research other than CTIMPs.

Medical management will involve hormonal treatment for 18 months. The choice of hormonal medication will be at the discretion of the treating clinician in discussion with the participating woman (in line with current accepted UK prescribing practice), avoiding any treatment which has either failed or caused unacceptable side effects in the past. Surgical management (laparoscopic ablation or excision of endometriosis/endometrioma) is well established in current NHS clinical practice. Women in both trial arms can receive additional neuromodulator drugs, analgesics and other interventions for pain relief, as required.

Adverse events (AEs) in DIAMOND may occur during or after any type of surgery for endometriosis or may be related to the use of hormonal treatment or may be related to other treatment for endometriosis.

At each follow-up questionnaire, we will ask women about serious adverse events and complications and these will be reported as a secondary outcome. Women may not be able to distinguish between serious adverse events/complications that occur as a result of their hormonal treatment from those that occur from other treatment and therefore we will ask about side effects as a result of treatment for endometriosis. Those meeting the criteria for serious will be reported as SAEs 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.
Serious Adverse Event (SAE)	Where an AE • 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 overnight 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

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).

In this trial, all serious and related AEs will be recorded as SAEs (see definition of "related" in section 8.3.2 below).

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 DIAMOND. 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.

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 (e.g. further surgery) will be recorded as an outcome measure but will not be reported as SAEs.

Complications occurring during endometriosis surgery will be considered, recorded and reported as a SAE, if appropriate.

Any SAEs related to the participants' endometriosis treatment that are not further interventions (e.g. 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 18 months) will be recorded on the serious adverse event form.

8.2 Trial specific expected adverse events

Within DIAMOND, AEs that meet the criteria for serious will be assessed to determine if they are related and expected or not. In this trial, the events listed in the sections below are potentially expected.

8.2.1 Adverse events related to medical management (Hormonal treatments)

In this trial the following events are potentially expected with hormonal treatment:

- Change in mood
- Vasomotor symptoms
- Altered libido
- Fatigue / lack of energy
- Nausea
- Weight increase
- Headaches

For less common events please refer to the appropriate SmPC (SmPC section 4.8) to confirm if they are potentially expected.

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 (Clavien Dindo grades 3-5 [26]):

- Bleeding intraoperative or postoperative >500ml
- Blood transfusion
- Injury to abdominal viscera, including bowel, bladder, ureters and blood vessels
- Laparotomy
- Colostomy
- Ileostomy
- Emergency hysterectomy
- Unplanned organ removal
- 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/abscess/haematoma
- Return to theatre
- Any other complication not covered requiring surgical, endoscopic or radiological intervention

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.

8.2.3 Other medications

Women may be taking other medication to reduce pain and if they report adverse events that meet the criteria for a serious adverse event, consideration will be given to the side effect profile of these other drugs.

8.3 Procedures for detecting, recording, evaluating & reporting AEs and SAEs

8.3.1 Detecting AEs

All SAEs meeting the criteria for recording within the DIAMOND trial (see section 8.1) are recorded from the time a participant consents to join the trial until the last trial follow-up. The

Investigator asks about the occurrence of relevant SAEs and complications (i.e. those that meet the criteria for recording within the DIAMOND trial) within follow-up questionnaires.

AEs that occur during or immediately after surgery for endometriosis will be captured on the surgical CRF. At 18 months, a case note review will identify any other hospitalisations for endometriosis treatment, complications of treatment etc.

8.3.2 Evaluating AEs

When a potential SAE 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 assess seriousness as defined in Section 8.1.

Assessment of Relatedness (causality)

The Investigator will make an assessment of whether the SAE is likely to be related to research procedures according to the following definitions:

- **Related**: resulted from administration of any of the research procedures required by the protocol, whether or not it is either a) the specific intervention under investigation or b) it is administered outside the study as part of normal care.
- **Unrelated**: where an event is not considered to have resulted from any of the research procedures.

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 are considered.

Assessment of Expectedness

Expectedness will be assessed for events that meet the criteria for serious outlined in Section 8.1.

8.3.3 Recording SAEs

Notification and reporting SAEs

Site staff are responsible for notifying the trial office of any SAEs meeting the criteria for recording within the DIAMOND trial.

When an SAE form is uploaded onto the trial website, the Trial Manager is automatically notified. If, in the opinion of the local PI and/or the CI, the event is confirmed as being *serious* and *related* and *unexpected*, the CI or Trial Manager notifies the Sponsor within 24 hours of receiving the signed SAE notification; a CI cannot downgrade an assessment from the PI. The Sponsor provides an assessment of the SAE; the Sponsor cannot downgrade an assessment from the PI or CI. Any disparity is resolved by further discussion between these parties.

If, in the opinion of the local PI and/or the CI, the event is confirmed as being serious but not related or serious and expected, expedited reporting to Sponsor is not required. Rather these will be summarised and reported to Sponsor, REC, Funder, TSC and DMC in their regular progress reports.

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.

8.3.5 Regulatory reporting requirements

The CI or delegate reports any SAEs that are related to any of the research procedures and unexpected to the REC within 15 days of the CI becoming aware of it using the HRA SAE form.

The CI is responsible for submitting annual reports to the REC on the anniversary of the approval.

All related SAEs are summarised and reported to the Ethics Committee, the Funder, the Trial Steering Committee and the Data Monitoring Committee in their regular reports.

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. Relevant follow up information on a SAE should be reported to the trial office as described above in the section above. The trial office will notify the Sponsor about any relevant follow-up information.

8.4 Pregnancy

Pregnancy is not considered an AE or SAE, however we will collect pregnancy information for trial subjects as part of the follow up questionnaires. Participants who become pregnant will be treated in line with local clinical practice.

9. Embedded qualitative work

See Appendix 1 for details

10. Sample size and proposed recruitment rate

10.1 Sample size

We need primary outcome data on 320 women at 18 months to detect an 8-point difference for the EHP-30 pain domain for 90% power (two-sided alpha 0.05) assuming a standard deviation of 22 points. The 8-point improvement was decided as a clinically important difference for the Pre-Empt trial[25] and has now been accepted for use by all new endometriosis trials to allow consistency and comparison of results and future metanalysis. We have assumed an attrition rate of 20% for the primary outcome, which requires us to randomise 400 women in total. The anticipated attrition rate is based on follow up data from BSGE accredited Units which have a dedicated endometriosis nurse and work to a consistent protocol which includes patient completed post-operative questionnaires at 6 and 12 months. As women with DE are all referred for treatment to dedicated endometriosis centres, they are unlikely to be lost to follow-up or choose to seek treatment elsewhere.

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.

10.2 Recruitment rates

Our surveys show that approximately 30 women per centre will undergo surgery for DE annually and at least 40% will be willing to be randomised. The recruitment projection is based on an estimate of 40 active centres contributing 0.8 participants per month over 22 months. This allows for staggered centre set-up and 50% reduced recruitment during the first month of site set up and 50% during the holiday months of June/July, December and April. The first 23

patients will be recruited by month 12 (recruitment month 6), 145 patients by month 18, 289 patients by month 24 and the remaining 111 by month 28, making a total of 401 participants.

The projected recruitment is modelled below in Figure 2.

10.2.1 Internal pilot study

An internal pilot stage has been included in the proposal. This 9-month pilot stage will commence in July 2021 (study month 7) and run to end April 2022 (study month 15). During this phase 28 sites will be opened and, in accordance with recruitment projections, we expect to randomise 76 subjects by the end of April 2022. The area of uncertainty we are addressing in the internal pilot is the willingness of patients to participate. Due to COVID-19, these milestones have slipped, and we anticipate recruitment commencing in month 10. Figures 2 and 3 will be updated (at the next protocol amendment) once we have established recruitment and the revised timelines are clearer.

10.2.2 Stop/go criteria

The proposed stop/go criteria are at 9 months, if we recruit:

- At least 68 participants (90% or more): We will continue without modification;
- 45–68 participants (60–90%): We will need to modify recruitment approach and continue to monitor recruitment carefully to ensure recovery manoeuvres worked.
- Less than 45 (<60%): 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.

10.2.3 Project timetable and milestones

The projected timetable start date for the study was 1 January 2021: the study duration will be 52 months. Milestones: prefunding: Research Ethics Committee (REC) and HRA approvals; month 1–6, set-up, authorisations; months 7–28: patient recruitment; months 29–46: patient follow-up to 18 months post randomisation; months 47–52: data analysis, interpretation of results, report writing and dissemination. A Gantt chart is shown below (Figure 3). Due to COVID-19, these milestones have slipped, and we anticipate recruitment commencing in month 10. Figures 2 and 3 will be updated (at the next protocol amendment) once we have established recruitment and the revised timelines are clearer.

Figure 2 Recruitment Projections

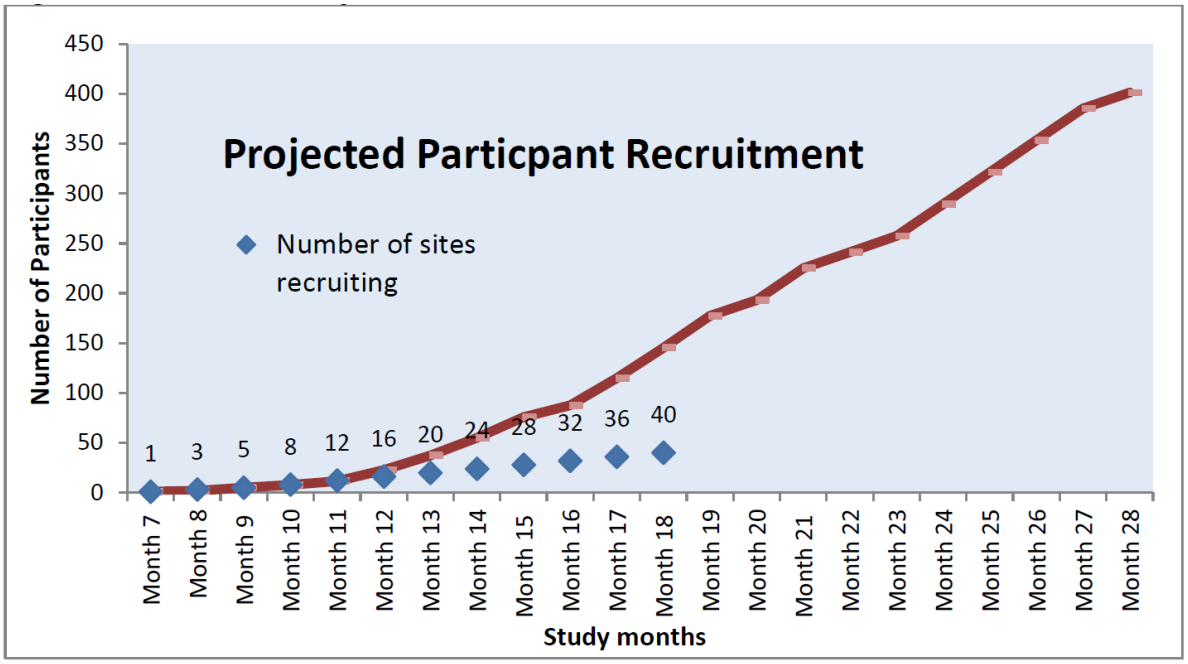
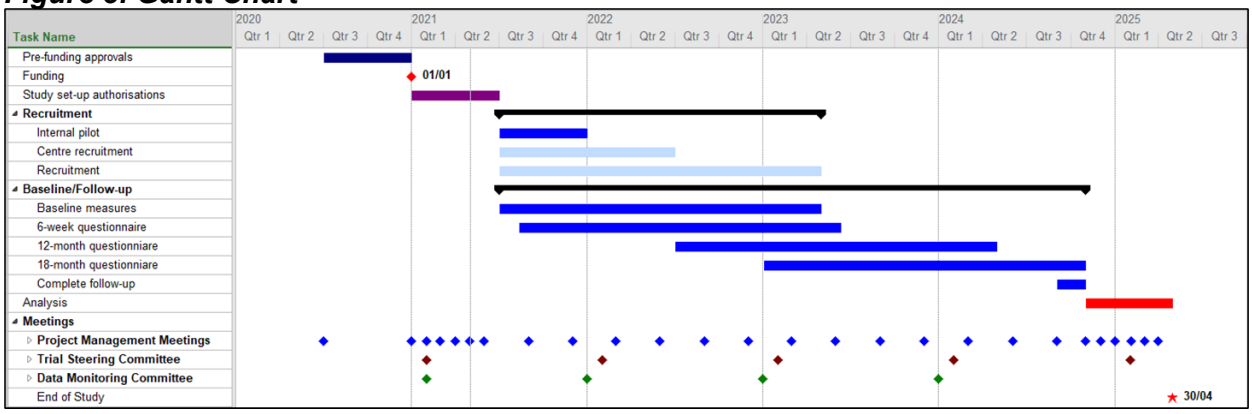


Figure 3: Gantt Chart



11. Statistical analysis

All primary analyses will be based on the intention-to-treat principle. 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 design covariates, and baseline measure of the primary outcome. Treatment effects will be estimated at each time-point by time-by-treatment interaction. Using EHP-30 scores from each time point will increase precision of estimates. Secondary outcomes will be analysed in a similar way with generalised linear models appropriate for the distribution of the outcome (i.e. logistic regression for binary data). Sensitivities of all treatment effect estimates to missing outcome data will be explored using multiple imputation methods, and pattern mixture modelling to assess the robustness of estimates to that MAR assumption.

A secondary analysis will estimate the direct effect of receiving surgery using Casual Inference Methods. Because receiving surgery in the medical arm will be a time-dependent confounder we will use a marginal structural model (using inverse probability weights) for repeated measures data that will remove the effect of surgery in the medical arm, allowing us

to estimate the treatment effects comparing surgery to medical management without cross-over.

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

11.1 Planned subgroup analyses

We will undertake subgroup analyses by age and presence of recto-vaginal endometriosis. The potential moderating effects of subgroup will be modelled using treatment-by-subgroup interactions. Treatment effects and interactions will be reported with stricter confidence intervals at the 99% level to reflect the exploratory nature of these analyses.

11.2 Proposed frequency of analyses

There will be a single analysis at the end of the trial. Safety data will be examined by an independent Data Monitoring Committee (DMC) at least every 12 months.

12. Economic evaluation

The economic evaluation will include a within-trial analysis using patient level data on costs and quality adjusted life years, and a model-based analysis to inform longer-term cost effectiveness. The trial-based analysis will use participant level data on health care costs and QALYs at 18 months post-randomisation. Data on resources required to deliver the surgical intervention will be collected in the surgical details CRF. Patient questionnaires at 12 weeks and 12- and 18-months post-randomisation will be used to gauge adherence to and switching between medical treatments. Any subsequent surgery related to endometriosis will also be captured in both arms via the patient questionnaires, with more details collected from centres using a case note review at 18 months. The patient questionnaires will also capture health related quality of life (EQ-5D-5L), the use of primary care services, subsequent outpatient referrals, and indirect costs resulting from lost productivity.

For the surgical intervention, data on procedures, complications, time in theatre, and length of stay will be combined with unit cost data to calculate patient level episode costs. It is anticipated that bottom-up costing will be used for the primary analysis, but the use of reference costs by health care resource group will also be explored (NHS Improvement Reference Costs). Data on health service resource use during follow-up will be combined with published unit cost data to capture total health service costs per participant.[27-30] Quality adjusted life years for the within trial analysis will be derived from participant responses to the EQ-5D-5L at baseline, 12 weeks, 12 months and 18-months post-randomisation, using an area under the curve approach. The cost-effectiveness analysis will take a health service perspective, but indirect costs associated with time lost from productive actives over the follow-up period will also be estimated for comparison alongside the cost-effectiveness findings.

For the analysis of participant level costs and QALYs, between group differences will be estimated using generalised linear models appropriate for the distribution of the outcome. Uncertainty surrounding the incremental cost-effectiveness ratio at 18 months will be presented graphically on the cost-effectiveness plane and summarised using cost-effectiveness acceptability curves.

Since further treatment beyond 18 months may be an important driver of cost-effectiveness, we will use decision modelling techniques to extrapolate the trial cost-effectiveness data. It is anticipated that the model will incorporate effects of the alternative interventions on endometriosis pain, associated quality of life, and subsequent treatment pathways. Trial data will be used as far as possible to inform the model inputs, but external evidence may be required to help inform longer term risks of recurrence and further treatment.[31] The model time horizon will likely be up to the age of menopause, but a lifetime horizon will be considered if evidence suggests potential for important differences in post-menopausal outcomes between treatment arms. An appropriate sampling distribution will be assigned to each model input parameter, and Monte Carlo simulation will be used to run the model many

times, with input values drawn at random from the assigned input distributions.[32] The uncertainty surrounding the estimated joint difference in costs and effects will be summarised using cost-effectiveness scatter plots and acceptability curves, indicating the probability of each strategy being cost-effective at increasing thresholds of willingness-to-pay per QALY. Further deterministic sensitivity analysis will be used to assess the robustness of the model findings to variation in key input values and assumptions.

All women in the trial will also be asked to consent to long-term follow-up to determine the need for subsequent gynaecological surgery using routine HES data (England and Wales) or ISD data (Scotland). This will enable the model to be updated with observed data on future surgery (funding to be sought separately).

13. Organisation: trial management and oversight arrangements

13.1 Trial office in Aberdeen

The Trial Office is in the Centre for Healthcare Randomised Trials (CHaRT) based within the Health Services Research Unit (HSRU), 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 trial to ensure smooth running and troubleshooting.

13.2 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).

13.3 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.

13.4 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).

13.5 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.

13.6 Patient and Public Involvement (PPI)

Emma Cox, who facilitated our PPI survey through Endometriosis UK, has agreed to be 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 Chief Executive Officer (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. Emma has affirmed the importance of the research question, provided comments on the proposal, and examined our plain English language summary.

Emily Rumbles, a patient, is a member of our independent PPI panel which will contribute to the delivery of the trial and dissemination of results. Our PPI group will be generated by identifying interested women via Endometriosis UK and local patients to contribute to the delivery of the trial and dissemination of results. 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. Emma Cox and members of the TSC will liaise with the PPI group and facilitate communication between the two (TSC and PPI).

14. Research governance, data protection and sponsorship

14.1 Research Governance

CHaRT is a fully registered Clinical Trials Unit with 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 CIs 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.

14.2 Data protection

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

The CIs 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 usernames and passwords.

Remote access to the network will be subject to robust authentication, and VPN (Virtual Private Network) connections to the network are only permitted for authorised users, ensuring that use is authenticated, and data is encrypted during transit across the network. No personal data will be downloaded or stored on laptop local hard drives. All data input/access will be via the VPN/secure website.

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.

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

15. Ethics and regulatory approvals
The West of Scotland Research Ethics Committee 4 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 West of Scotland REC 4 within the timelines defined in the regulations.

15.1 Protocol compliance and amendment
The Investigators will conduct the trial in compliance with the Protocol given favourable opinion by the Ethics Committee. Any amendment to the Protocol or other approved documents will be reviewed by Sponsor (and funder where appropriate) before application to REC, 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.

16. 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.

16.1 Risk assessment
An independent risk assessment has been carried out by the Sponsor.

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 and REC 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 and REC 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 or surgery. Continuation of hormonal treatment and referral for surgery 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 10 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 2 (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.

21. References

1 Dunselman GA, Vermeulen N, Becker C, et al. ESHRE guideline: management of women with endometriosis. *Hum Reprod* 2014;29:400-12 doi:10.1093/humrep/det457.

2 Becker CM, Bokor A, Heikinheimo O, et al. ESHRE guideline: endometriosis. *Hum Reprod Open* 2022;2022:hoac009 doi:10.1093/hropen/hoac009.

3 Koninckx PR, Martin D. Treatment of deeply infiltrating endometriosis. *Curr Opin Obstet Gynecol* 1994;6:231-41.

4 International Working Group of AAGL E, Tomassetti C, Johnson NP, et al. An international terminology for endometriosis, 2021. *Hum Reprod Open* 2021;2021:hoab029 doi:10.1093/hropen/hoab029.

5 De Graaff AA, D'Hooghe TM, Dunselman GA, et al. The significant effect of endometriosis on physical, mental and social wellbeing: results from an international cross-sectional survey. *Hum Reprod* 2013;28:2677-85 doi:10.1093/humrep/det284.

6 Brown J, Farquhar C. Endometriosis: an overview of Cochrane Reviews. *Cochrane Database Syst Rev* 2014;2014:CD009590 doi:10.1002/14651858.CD009590.pub2.

7 National Institute for Health and Care Excellence. Endometriosis: diagnosis and management (NICE guideline 73).
Available from www.nice.org.uk/guidance/ng73. 2017.

8 Horne AW, Saunders PTK, Abokhrais IM, et al. Top ten endometriosis research priorities in the UK and Ireland. *Lancet* 2017;389:2191-2 doi:S0140-6736(17)31344-2 [pii].

9 Saraswat L, Ayansina D, Cooper KG, et al. Impact of endometriosis on risk of further gynaecological surgery and cancer: a national cohort study. *BJOG* 2018;125:64-72 doi:10.1111/1471-0528.14793.

10 Moradi M, Parker M, Sneddon A, et al. Impact of endometriosis on women's lives: a qualitative study. *BMC Womens Health* 2014;14:123- doi:10.1186/1472-6874-14-123.

11 Nnoaham KE, Hummelshoj L, Webster P, et al. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. *Fertil Steril* 2011;96:366,373.e8 doi:10.1016/j.fertnstert.2011.05.090.

12 Simoens S, Dunselman G, Dirksen C, et al. The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres. *Hum Reprod* 2012;27:1292-9 doi:10.1093/humrep/des073.

13 Byrne D, Curnow T, Smith P, et al. Laparoscopic excision of deep rectovaginal endometriosis in BSGE endometriosis centres: a multicentre prospective cohort study. *BMJ Open* 2018;8:e018924-018924 doi:10.1136/bmjopen-2017-018924.

14 Abrão MS, Petraglia F, Falcone T, et al. Deep endometriosis infiltrating the recto-sigmoid: critical factors to consider before management. *Hum Reprod Update* 2015;21:329-39 doi:10.1093/humupd/dmv003.

15 Remorgida V, Ferrero S, Fulcheri E, et al. Bowel endometriosis: presentation, diagnosis, and treatment. *Obstet Gynecol Surv* 2007;62:461-70 doi:0006254-200707000-00022 [pii].

16 Minelli L, Fanfani F, Fagotti A, et al. Laparoscopic colorectal resection for bowel endometriosis: feasibility, complications, and clinical outcome. *Arch Surg* 2009;144:234,9; discussion 239 doi:10.1001/archsurg.2008.555.

17 Ferrero S, Camerini G, Ragni N, et al. Triptorelin improves intestinal symptoms among patients with colorectal endometriosis. *Int J Gynaecol Obstet* 2010;108:250-1 doi:10.1016/j.ijgo.2009.09.028.

18 Ferrero S, Camerini G, Ragni N, et al. Norethisterone acetate in the treatment of colorectal endometriosis: a pilot study. *Hum Reprod* 2010;25:94-100 doi:10.1093/humrep/dep361.

19 Ferrari S, Persico P, DI Puppo F, et al. Continuous low-dose oral contraceptive in the treatment of colorectal endometriosis evaluated by rectal endoscopic ultrasonography. *Acta Obstet Gynecol Scand* 2012;91:699-703 doi:10.1111/j.1600-0412.2012.01366.x.

20 Vercellini P, Facchin F, Buggio L, et al. Management of Endometriosis: Toward Value-Based, Cost-Effective, Affordable Care. *J Obstet Gynaecol Can* 2018;40:726,749.e10 doi:S1701-2163(17)30684-9 [pii].

21 Roman H, Darwish B, Bridoux V, et al. Functional outcomes after disc excision in deep endometriosis of the rectum using transanal staplers: a series of 111 consecutive patients. *Fertil Steril* 2017;107:977,986.e2 doi:S0015-0282(17)30002-X [pii].

22 Vercellini P. Are combined hormonal contraceptives the neglected treatment for symptomatic endometriosis?. *Fertil Steril* 2018;110:61-2 doi:S0015-0282(18)30293-0 [pii].

23 Vercellini P, Somigliana E, Vigano P, et al. Surgery for endometriosis-associated infertility: a pragmatic approach. *Hum Reprod* 2009;24:254-69 doi:10.1093/humrep/den379.

24 De Cicco C, Corona R, Schonman R, et al. Bowel resection for deep endometriosis: a systematic review. *BJOG* 2011;118:285-91 doi:10.1111/j.1471-0528.2010.02744.x.

25 Kondo W, Bourdel N, Tamburro S, et al. Complications after surgery for deeply infiltrating pelvic endometriosis. *BJOG* 2011;118:292-8 doi:10.1111/j.1471-0528.2010.02774.x.

26 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240:205-13 doi:00000658-200408000-00003 [pii].

27 Information Services Division. ISD Unit Costs.

28 Curtis LA, Burns A. Unit Costs of Health & Social Care 2020. 2020 doi:10.22024/UniKent/01.02.84818.

29 Joint Formulae Committee. British National Formulary. *BNF*.

30 NHS. NHS Improvement Reference Costs .

31 Ianieri MM, Mautone D, Ceccaroni M. Recurrence in Deep Infiltrating Endometriosis: A Systematic Review of the Literature. *J Minim Invasive Gynecol* 2018;25:786-93 doi:S1553-4650(18)30037-2 [pii].

32 Briggs A, Claxton K, Sculpher M. Decision modelling for health economic evaluation. *Oxford, University Press* 2006.

33 Donovan J, Mills N, Smith M, et al. Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. Commentary: presenting unbiased information to patients can be difficult. *BMJ* 2002;325:766-70 doi:10.1136/bmj.325.7367.766.

34 Donovan JL, Rooshenas L, Jepson M, et al. Optimising recruitment and informed consent in randomised controlled trials: the development and implementation of the Quintet Recruitment Intervention (QRI). *Trials* 2016;17:283-4 doi:10.1186/s13063-016-1391-4.

35 Wilson C, Rooshenas L, Paramasivan S, et al. Development of a framework to improve the process of recruitment to randomised controlled trials (RCTs): the SEAR (Screened, Eligible, Approached, Randomised) framework. *Trials* 2018;19:50-6 doi:10.1186/s13063-017-2413-6.

36 Francis JJ, Johnston M, Robertson C, et al. What is an adequate sample size? Operationalising data saturation for theory-based interview studies. *Psychol Health* 2010;25:1229-45 doi:10.1080/08870440903194015.

37 ICMJE. 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 2019) 2019.

38 Huth EJ. Guidelines on authorship of medical papers. *Ann Intern Med* 1986;104:269-74 doi:10.7326/0003-4819-104-2-269.

39 Glass RM. New information for authors and readers. Group authorship, acknowledgements and rejected manuscripts. *Journal of the American Medical Association (JAMA)* 1992.

Appendix 1: Embedded Process Evaluation

Background

DIAMOND will compare two different treatments, medical management and laparoscopic surgery (with or without adjuvant medical treatment). 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.[33-35]

Interviews with women and staff from recruiting centres will be conducted to explore the patient experience of both the trial and the interventions. The aim of these interviews is to understand how surgery and/or hormone treatments are experienced by women with deep endometriosis, investigating trade-offs between fertility and pain with regard to treatment choices. Findings will help interpret overall trial results regarding satisfaction of treatment received. The additional aim of the interviews is to explore aspects of decision making with regard to trial involvement by both clinical teams and patients.

We will also audio-record consultations at trial sites (when recruitment is problematic) to identify how recruitment consultations are framed or requirements for staff training. Analysis of these recordings will only be triggered if recruitment at a site is poor and the participant flow data (SEAR – see below) identifies the approached to randomised rate to be low. Much of this work will be modelled on the Quintet Recruitment Intervention and adapted for efficient application.[34]

Methods

1. Participant invitation and informed consent

1A. Audio-recording of recruitment consultations

Sites will be made aware at study start-up of the potential for audio recording of recruitment consultations in order to assist the local study team to develop recruitment strategies (if required). This component of the process evaluation will only be implemented at trial sites where recruitment is problematic. 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 DIAMOND 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 component of the process evaluation will only be activated should sites drop below the expected recruitment rate. If recruitment continues at a steady state, and within target, this element of this study will not be required to be implemented.

If, and when this component is implemented at a site, as part of the DIAMOND trial, potential participants will receive a participant information leaflet (PIL) explaining the trial in detail. 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 DIAMOND. Similarly, patients may agree to take part in the audio-recording study but then decline to take part in the main DIAMOND trial.

Recruitment consultations will be 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 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. The audio recordings and anonymised transcripts will be held securely for 10 years in accordance with Sponsor requirements and data legislation. 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 eligible for the RCT but who decline trial participation (n=15);
2. Participants who intentionally withdraw or fail to complete data collection (n=15) from the trial; and
3. Participants who have completed the trial (n=16, 8 from each arm).

Potential participants of the interview study (which includes those that have consented to the main DIAMOND trial and those that have refused consent) will be provided with a separate PIL in the clinic or by post or email if conducted remotely. Enclosed with the PIL will be a 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 the reply 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 DIAMOND. 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. 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.

For the participants who consent to participate in the DIAMOND trial and consent to the interview study, a second interview will be scheduled following completion of the trial shortly after the 18 month follow up. 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 sites (4 staff from 5 sites, n=20) 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. Staff at five recruiting sites (sampled using a positive-negative deviant approach) 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.

2. Data collection

2A. Audio-recording of recruitment consultation
If, and when the audio-recording component is implemented at a site, recruitment consultations will be audio-recorded for those participants who consent to the audio-recording. Only conversations related to the DIAMOND trial (where recruiters explain the design and details of the DIAMOND 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 Sponsor approved third party professional transcription service or an HSRU member of staff. 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. [36] To provide 15 participants for the patient group who have refused consent to the DIAMOND trial, it is anticipated that a total of 60 interview study PILs will require to be distributed (anticipate participation rate of ~20%).

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, and whether there were specific aspects of trial design or conduct that led to decision to terminate their involvement. Topic guides will be informed by the Theoretical Domains Framework (TDF) for questions focussing on recruitment to, and continuation in, the trial. For those interviews focussing on patient experience, topic guides will explore past treatment experiences (e.g. reasons for decision, what were expectations), views on treatments offered in the trial (e.g. acceptability, views on effectiveness), and how they experienced trial treatment (e.g. what were expectations and were they met, what was better/worse than anticipated).

All interviews will last approximately 30-60 minutes and will be audio-recorded and transcribed verbatim using a third party professional transcription service or an HSRU member of staff.

3. Data Analysis

3A. Audio-recording of recruitment consultation

Analysis of transcripts will only be initiated if there is a problem with recruitment at a site. Once 10 recordings (which will include conversations with consenters and non-consenters) have been collected for a site, the analysis will be conducted. 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'. 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 at these sites, the analysis of these will be triggered based on key diagnostics identified using the SEAR framework.

3B. Interviews

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 15 per group) is collected before full analysis is conducted and feedback based on the results provided. 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. Both an inductive and a deductive approach to analysis will be carried out. The inductive approach will follow a thematic analysis using constant comparison across the data set and guided by the Framework approach. The TDF will guide the deductive analysis and will be used to develop a coding guide developed based on the published definitions and constructs of the TDF domains and agreed for the purpose of consistent coding.

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 [35] 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

DIAMOND-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 DIAMOND-QUAL study folder) by a research nurse.

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 key milestones. 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.

Timeline
Following ethical approval, the invitation of potential trial participants and staff interviews will align with the internal pilot.

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 DIAMOND 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.

References
1. Donovan J, Mills N, Smith M, Brindle L, Jacoby A, Peters T, et al. Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. Commentary: presenting unbiased information to patients can be difficult. BMJ 2002 Oct 5;325(7367):766770.
2. Donovan JL, Rooshenas L, Jepson M, Elliott D, Wade J, Avery K, et al. Optimising recruitment and informed consent in randomised controlled trials: the development and implementation of the Quintet Recruitment Intervention (QRI). Trials 2016 Jun 8;17(1):283016-1391-4.
3. Wilson C, Rooshenas L, Paramasivan S, Elliott D, Jepson M, Strong S, et al. Development of a framework to improve the process of recruitment to randomised controlled trials (RCTs): the SEAR (Screened, Eligible, Approached, Randomised) framework. Trials 2018 Jan 19;19(1):50-017-2413-6.
4. Francis JJ, Johnston M, Robertson C, Glidewell L, Entwistle V, Eccles MP, et al. What is an adequate sample size? Operationalising data saturation for theory-based interview studies. *Psychol Health* 2010;**25:**1229-45.

Appendix 2: Authorship Policy

AUTHORSHIP POLICY FOR THE DIAMOND TRIAL

1. DEFINING AUTHORSHIP

Authorship of published or presented papers is based on the following criteria.[37]

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[38, 39] and are in accordance with the rules of the International Committee of Medical Journal Editors (ICMJE).[37]

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.[37] Those persons may be acknowledged and their contribution described. See section 3: ACKNOWLEDGEMENTS.

a. Preferred CHaRT authorship

Where possible, all CHaRT trials 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 such as “The DIAMOND trial group” or “Jane Doe, John Doe, John Smith, Ann Other and the DIAMOND 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')[38]. 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[37].

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 trial's data and conclusions, authors are advised to obtain written permission to be acknowledged from all acknowledged individuals [37].

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 trial funder's disclaimer: refer to the funder's 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 DIAMOND trial, including conference abstracts, outputs describing methodological aspects of the trial, and any outputs describing results from the trial, 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 trial 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 2019) is available at (www.icmje.org/#authors)
2. Huth EJ (1986). Guidelines on authorship of medical papers. *Annals of Internal Medicine*, **104**, 269-274.
3. Glass RM (1992). New information for authors and readers. Group authorship, acknowledgements and rejected manuscripts. *Journal of the American Medical Association*, **268**, 99.

Appendix 3: COVID-19 Mitigation

These arrangements are put in place to minimise risk to participants and research staff during the COVID-19 pandemic to ensure the DIAMOND study can proceed.

The pragmatic approach used in the DIAMOND study, will continue during the COVID-19 pandemic. The main protocol will be followed as far as possible, in line with the approved remote procedures, during any restrictions due to the pandemic.

1. Interactions with COVID-19 vaccinations
No known / reported interactions between the trial interventions and the COVID-19 vaccines.

2. Recruitment
If the woman agrees to be contacted at home after reading the PIL, she will receive a telephone or video call from the local Research Nurse, a member of the local clinical team or a clinical member of the central research team to discuss any queries. Women may make a decision to participate at home following this telephone / video counselling, or during a subsequent visit to hospital (e.g. a clinic appointment or a pre-assessment visit).

Telephone, postal and e-consenting procedures approved for DIAMOND (described in section 4.7) can continue to be used in line with current COVID-19 restrictions, allowing remote consent of participants to the study as far as possible. Remote consent options will remain in place for the duration of the project.

3. Interventions

Medical (hormonal) treatment.
Those randomised to hormonal treatment will receive their prescription and medication in line with local procedures during the pandemic.

Surgery
Those randomised to surgical intervention, will receive their surgery in line with local procedures during the pandemic. The pandemic may result in some delays to the waiting list if restrictions are in place. In saying that, grade 4 endometriosis is a category 1 priority due to level of symptoms and risk to bowel and renal tract. As such, advanced endometriosis surgical lists in endometriosis centres are all running at normal pre-covid levels. The research nurse will monitor the surgical lists to identify when surgery has been booked; and thereafter to confirm that surgery has taken place. 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. If the woman is already taking hormonal treatment to supress endometriosis symptoms, they will be advised to continue using this until their surgery. For pragmatic reasons, any changes to medical treatment used prior to surgery will be accepted, in line with NICE guiedlines[7].

Follow up
Follow up will continue to be managed remotely as outlined in the main protocol, in line with current guidelines.

Qualitative component

It is anticipated that the qualitative component will be completed remotely; if and when current restrictions on social distancing are lifted, face to face activity may commence.