A multi-centre randomised controlled trial to determine the effectiveness of laparoscopic removal of isolated superficial peritoneal endometriosis for the management of chronic pelvic pain in women

Trial Protocol

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PROTOCOL APPROVAL

ESPriT2 - A multi-centre randomised controlled trial to determine the effectiveness of laparoscopic removal of isolated superficial peritoneal endometriosis for the management of chronic pelvic pain in women

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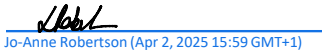
Jo-Anne Robertson, Sponsor Representative	 Jo-Anne Robertson (Apr 2, 2025 15:59 GMT+1)	Apr 2, 2025

I confirm that I have read this protocol and will perform all trial duties as specified within this. This can be an electronic/typed signature.

Principal Investigator	Signature	Date

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Trial Title	A multi-centre randomised controlled trial to determine the effectiveness of laparoscopic removal of isolated superficial peritoneal endometriosis for the management of chronic pelvic pain in women*
Study Acronym	ESPriT2
Clinical Phase	Phase IV
Trial Design	A multi-centre, participant-blind, parallel-group randomised controlled clinical and cost effectiveness trial with internal pilot
Trial Participants	Women with suspected superficial peritoneal endometriosis (SPE) undergoing diagnostic laparoscopy
Planned Number of Participants	400
Planned Number of Sites	Approximately 70 sites
Total Planned Trial Duration	54 months
Primary Objective	To compare laparoscopic removal versus diagnostic laparoscopy alone in terms of participants' pain at 12 months post randomisation
Secondary Objectives	To compare laparoscopic removal versus diagnostic laparoscopy alone in terms of: • physical and emotional functioning • surgical complications • pregnancy events • requirement for future intervention • occupational outcomes • cost utility and effectiveness • adverse events
Primary Outcome	Participants' pain at 12 months post randomisation as defined by the 'pain domain' of the EHP-30 questionnaire
Secondary Outcomes	To compare laparoscopic removal versus diagnostic laparoscopy alone in terms of • time off work and presenteeism defined by the WPAIQ at 12 months • need for hormonal medication for endometriosis related symptoms at 3, 6 and 12 months • need for analgesics for endometriosis related symptoms at 3, 6 and 12 months • pain domain of the EHP-30 at 3 and 6 months • total score of EHP-30 at 3, 6 and 12 months • fatigue symptoms defined by the BFI at 12 months • neuropathic pain symptoms defined by PainDETECT™ at 12 months • urinary symptoms defined by PUF 12 months • irritable bowel symptoms defined by the ROME IV criteria at 12 months • pain catastrophizing defined by PCQ at 12 months • fibromyalgia defined by FS at 12 months • specific patient reported symptoms defined by MYMOP2 • post operative pain and analgesic requirements by patient reported diary • length of hospital stay • surgical complications at 30 days • adverse events related to surgery at 30 days • need for further surgery for endometriosis related symptoms at 12 months • pregnancy events at 3, 6 and 12 months
Economic Outcomes	• quality of life defined by EQ5D-5L at 3, 6, and 12 months • general wellbeing defined by ICECAP-A at 3, 6 and 12 months • costs and resource use at 3, 6 and 12 months (primary and secondary care) • impacts on employment, caregiving, and other usual activities (e.g. education)

ESPriT+ Objectives	• To determine whether blood biomarker panels can predict SPE • To explore the potential of blood markers to act as either a diagnostic or triage tool • To determine if biomarker panels are affected by stage of cycle, concomitant hormone use, volume of SPE and lesion type • To determine whether we can detect SPE on transvaginal ultrasound scan. • To see if the combination of ultrasound and serum markers can improve the diagnosis of SPE
ESPriT+ Outcomes	• The sensitivity and specificity of biomarker panels for diagnosing SPE • To explore which biomarkers are of greatest accuracy impact in combination • To determine the potential use of the biomarker as a diagnostic or triage tool • To explore whether the sensitivity and/or specificity is affected by hormone use, volume of SPE, lesion type and cycle stage • Correlation between presence and site of SPE on scan and laparoscopy • Utility of serum markers when TV scan is negative

*Women refers to those assigned female at birth

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
AE	Adverse event
CI	Chief Investigator
DCF	Data Collection Form
DEPCAT	Deprivation category
DMEC	Data Monitoring and Ethics Committee
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
PI	Principal Investigator
QA	Quality Assurance
QALY	Quality-adjusted life year
QoL	Quality of Life
RCT	Randomised controlled trial
REC	Research Ethics Committee
SAE	Serious adverse event
SOP	Standard Operating Procedure
SPE	Superficial peritoneal endometriosis
TMG	Trial Management Group
TSC	Trial Steering Committee

INTRODUCTION

1.1 BACKGROUND AND RATIONALE FOR THE ESPriT2 MAIN STUDY

Summary

Endometriosis (where cells similar to the womb-lining are found outside the womb) affects~176 million women worldwide and can lead to debilitating pelvic pain. Three subtypes of endometriosis exist, with ~80% of women having 'superficial peritoneal' endometriosis (SPE). Endometriosis is diagnosed by keyhole surgery (laparoscopy) and, if SPE is found, gynaecologists usually remove it surgically. However, many women get limited pain relief from surgical removal of SPE. We therefore plan to undertake a multi-centre trial across the UK where women who have only SPE found at laparoscopy are randomly allocated to have surgical removal or not to have it removed. We want to determine whether surgical removal improves overall SPE symptoms and quality of life, or whether surgery is of no benefit, exacerbates symptoms, or even causes harm.

The clinical problem

Endometriosis is a chronic oestrogen-dependent condition that affects an estimated 176 million women worldwide (1-3). It is defined by the presence of endometrial-like tissue ('lesions') outside the uterus. It is now generally accepted that there are three endometriosis subtypes ('superficial peritoneal' or 'SPE', 'ovarian' and 'deep'). Endometriosis is associated with debilitating pelvic pain and/or infertility and the socioeconomic costs of endometriosis in the UK are ~£8.2 billion per year and direct healthcare costs amount to an ~£2315 per woman per year (based on 2009 prices), similar to those of diabetes mellitus (4).

Current treatment options

Management options in current national and international endometriosis guidelines for women with endometriosis-associated pelvic pain include surgical removal of endometriosis and medical treatment with analgesics, ovarian suppressive drugs and neuromodulators (1-3). 'Surgical removal' involves laparoscopic excision and/or ablation of the endometriosis, often undertaken at the time of initial laparoscopy to investigate pelvic pain. Establishing whether treating isolated SPE in women with chronic pelvic pain is cost-effective is important because this forms a large part of the workload in gynaecology, and uses considerable resources. Around 30% of the direct health care costs of endometriosis are attributable to the cost of surgical treatment. Data from Scotland (population: 5.3 million, 51% women), indicate that 101,137 pelvic laparoscopies were performed in women from 1981 to 2010 (5). An estimated 91,023 (90%) of these procedures were for investigation of chronic pelvic pain and, of these, 17,834 (20%) revealed a new diagnosis of endometriosis. Half of the women with endometriosis in this population underwent a further surgical procedure by five years.

Evidence base

There is little scientific evidence to demonstrate whether surgical removal of isolated SPE (accounting for ~80% of the subtypes) improves overall symptoms and quality of life more than not surgically treating the endometriosis, or whether surgery could exacerbate symptoms (or even cause harm). In the most recent Cochrane review of 'laparoscopic surgery for endometriosis' (published in 2014), the authors conclude that laparoscopic treatment improves 'condition-associated pain' (cited as 'better' or improved') compared to diagnostic laparoscopy alone at six months (OR 6.58, 95% CI 3.31 to 13.10) (6). Yet, this conclusion is based on data from only three randomised controlled trials (RCT) with a total of just 171 participants and an amalgam of different subtypes of endometriosis. Furthermore, only one RCT included in the analysis (just 69 participants) has follow-up data to 12 months showing benefit of surgery (OR 10.00, 95% CI 3.21 to 31.17), leading the authors to define the strength of the evidence as of moderate and low quality, respectively, for the two timepoints, using GRADE criteria (6). The uncertainty around surgical management of SPE is also compounded by the limited evidence to allow an informed selection of specific surgical modalities to remove SPE e.g. laparoscopic 'ablation' versus laparoscopic 'excision' (6, 7).

Research recommendation from NICE
Consequently, the 2017 NICE Endometriosis Guidelines recommend further research into the effectiveness of laparoscopic removal of SPE in isolation to manage endometriosis associated pain (2). This research recommendation is also supported by the results of a recent UK and Ireland, James Lind Alliance Priority Setting Partnership (PSP) Initiative for Endometriosis established to identify the key research questions that were most important to both women with endometriosis and health-care practitioners involved in their care (8).

Risks and benefits
If this trial research demonstrates that surgery is not effective for the treatment of pain associated with isolated superficial peritoneal disease, it is possible that this group of women could be spared an invasive surgical procedure, in particular if their pelvic imaging does not reveal any pathology (pelvic ultrasound or MRI, interpreted by an experienced operator, will diagnose ovarian and deep endometriosis subtypes). Instead of potentially subjecting this group of chronic pelvic pain patients to unnecessary surgical procedures, they could be offered investigations for other known causes of pelvic pain and early pain management (e.g. neuromodulator drugs, physiotherapy, and psychological approaches) (10). It is conceivable that this research may demonstrate that surgery for superficial peritoneal endometriosis in isolation is not only ineffective, but also aggravates the symptoms of pain, or even causes harm. It is therefore crucial that policy makers, funding bodies, researchers, clinicians, and women with endometriosis work together in a 'precision medicine ecosystem' to build a knowledge base that can determine whether superficial peritoneal endometriosis is better suited to surgical, conservative, or multimodal treatment to ultimately guide individualised patient care.

Research question to be addressed
The aim of this randomised study (ESPriT2) is to determine whether laparoscopic excision/ablation is of clinical benefit to women with chronic pelvic pain where the only finding is SPE.

1.2 RATIONALE FOR EMBEDDED BIOMARKER SUB-STUDY (ESPriT+)

Women wait for an average of seven years from developing symptoms to having a diagnosis of endometriosis (11) SPE is particularly difficult to diagnose because it often cannot be seen on imaging (e.g. ultrasound) and women usually require a laparoscopy to make (or exclude) the diagnosis of SPE. Many blood tests (so called 'biomarkers') have been investigated to see if they are predictive of endometriosis but none so far have been shown to be helpful (12-14). A significant challenge for the validation of endometriosis biomarkers has been the lack of sufficiently large well-phenotyped cohorts to offset heterogeneity of disease. However, we have identified a panel of biomarkers, in collaboration with the University of Singapore and Roche Diagnostics, that we believe may have clinical utility that we wish to validate in women who have agreed to participate in ESPriT+:

The aim of this sub-study, called ESPriT+, is to determine if these new blood tests can improve diagnosis of SPE, either as a triage test to exclude SPE or identify those more likely to have SPE, or to replace laparoscopy as the diagnostic test and assess the accuracy of a "targeted ultrasound" for the pre-operative diagnosis of SPE. We will ask all of the women who agree to take part in ESPriT2 (an estimated 1200 women) if they wish to take part in this additional study (ESPriT+). If a woman chooses to participate in ESPriT+, we will take a small blood sample before surgery and before anesthesia takes place, and at the 6- month follow up visit for participants who are randomised. The results of the blood test will be compared to findings at laparoscopy to tell us how accurate the test is at predicting SPE. If we can show that our blood test is accurate enough then in the future women with symptoms

of endometriosis will have the option to avoid a laparoscopy (and its risks) to diagnose endometriosis. The follow up sample will be used to explore the biomarker levels in the two study treatment arms considering the outcome data.

Women (an estimated 100) in selected sites who have experienced clinicians who have been trained in ESPriT+ scanning protocols will also be asked if they are willing to undergo a targeted transvaginal ultrasound scan to assess the presence of SPE pre-surgery and the findings will be confirmed post-surgery.

Part of the blood sample and pseudonymised study data collected pre surgery and in follow up will be sent to Roche Diagnostics for use in future research and product development in the area of endometriosis and women's health.

Once the randomisation target has been reached and ESPriT2 participants are in follow-up for 12 months, we will continue to consent participants to the sub-studies until the main ESPriT2 study has completed follow up.

2 STUDY OBJECTIVES

2.1 ESPriT2 OBJECTIVES

2.1.1 Primary Objective

To compare laparoscopic removal versus diagnostic laparoscopy alone in terms of participants' pain at 12 months post randomisation.

2.1.2 Secondary Objectives

To compare laparoscopic removal versus diagnostic laparoscopy alone in terms of:

- **requirement for future intervention***
- **occupational outcomes***
- physical and emotional functioning
- post-operative pain scores
- surgical complications
- pregnancy events
- cost utility and effectiveness
- adverse events

*Key secondary objectives

2.2 ESPriT+ OBJECTIVES

- To determine whether blood biomarker panels can predict presence of SPE
- To explore the potential of blood biomarkers to act as either a diagnostic or triage tool
- To determine if biomarker panels are affected by stage of cycle, concomitant hormone use, volume of SPE and lesion type
- To determine whether we can detect SPE on transvaginal ultrasound scan
- To see if the combination of ultrasound and serum markers can improve the diagnosis of SPE

2.3 OUTCOMES OF ESPriT2

2.3.1 Primary Outcome

Participants' pain at 12 months post randomisation as defined by the 'pain domain' of the EHP-30 questionnaire.

2.3.2 Secondary Outcomes

To compare laparoscopic removal versus diagnostic laparoscopy alone in terms of

- **time off work and presenteeism defined by the WPAIQ at 12 months***
- **need for hormonal medication for endometriosis related symptoms at 3, 6 and 12 months***
- **need for analgesics for endometriosis related symptoms at 3, 6 and 12 months***
- pain domain of the EHP-30 at 3 and 6 months
- total score of EHP-30 at 3, 6 and 12 months
- fatigue symptoms defined by the BFI at 12 months
- neuropathic pain symptoms defined by PainDETECT™ at 12 months
- urinary symptoms defined by PUF 12 months
- irritable bowel symptoms defined by the ROME IV criteria at 12 months
- pain catastrophizing defined by PCQ at 12 months
- fibromyalgia defined by FS at 12 months
- specific patient reported symptoms defined by MYMOP2
- post-operative pain and analgesic requirements by patient reported diary
- length of hospital stay
- adverse events related to surgery at 30 days
- surgical complications at 30 days
- surgical operating time
- need for further surgery for endometriosis related symptoms at 12 months
- pregnancy events at 3, 6 and 12 months

*Key secondary outcomes

2.3.3 Economic Outcomes

- quality of life defined by EQ5D-5L at baseline, 3, 6, and 12 months
- general wellbeing defined by ICECAP-A at baseline, 3, 6 and 12 months
- costs and resource use at baseline, 3, 6 and 12 months (primary and secondary care use)
- impacts on employment, caregiving, and other usual activities (e.g. education)

2.3.4 Other Outcome Data

For those allocated to surgical removal, the following data will also be reported:

- Operative technique for removal of endometriosis (excision, ablation or combination)
- Adequacy of removal of endometriosis (subjective and independent)

2.3.5 Longer Term Outcomes

Subject to further funding the following outcomes will be compared:

- need for further surgery (data linkage)
- EHP30, ROME IV, PUF, EQ5D-5L, PainDETECT™, ICECAP-A, hormonal and analgesic use and fertility intervention and pregnancy events measured at 2 and 5 years post randomisation.

2.3.6 OUTCOMES OF ESPriT+

- The sensitivity and specificity of biomarker panels for diagnosing SPE.
- To explore which biomarkers are of greatest accuracy in combination
- To determine the potential use of the biomarker(s) as a diagnostic or triage tool
- To explore whether the sensitivity and/or specificity is affected by hormone use, volume of SPE, lesion type and cycle stage
- Correlation between presence and site of SPE on scan and laparoscopy
- Utility of serum markers when TV scan is negative

3 STUDY DESIGN

3.1 Type of study

This is a multi-centre, participant-blind, parallel-group randomised, controlled clinical and cost effectiveness trial with internal pilot (ESPriT2) and embedded biomarker sub-study (ESPriT+).

Participants undergoing laparoscopy for suspected SPE will be invited to take part in ESPriT2. If they consent to ESPriT2, they will also be invited to take part in ESPriT+. If they consent to ESPriT+, they will be asked for a venous blood sample before surgery (pre anaesthesia). A subset of these participants will also be asked to have a targeted transvaginal ultrasound scan. At the time of laparoscopy, if SPE is found, the participant will be randomised 1:1 to diagnostic laparoscopy alone, or surgical removal (excision and/or ablation of SPE, depending on operating surgeon's preference).

3.2 Blinding

This will be a participant blind trial. All surgeons will be asked to insert two accessory ports in addition to the optical (usually umbilical) port (Palmers point entry is also acceptable if required).

One 5mm accessory abdominal wall port is always required for a diagnostic laparoscopy but in the event of uncomplicated anatomy and sufficient trendelenberg a second accessory port may not be required for a diagnostic procedure alone. A second accessory port is always required for excision of endometriosis lesions. As a result if standardisation of number of ports used was not performed, a participant may be able to guess which group they had been allocated to on the basis of the number of port site incisions. Two 5mm accessory ports will therefore be inserted in order to maintain patient blinding in addition to the optical port. This means that all participants will have three ports inserted.

Historic rates of port site complications following conventional laparoscopic surgery is about 21 per 100,000 cases (9), though may be higher depending on co-existing morbidity, obesity and surgical procedure (10,15) .

Serious complications relating to accessory port insertion include inferior epigastric artery (IEA) injury and port site hernia. The true incidence of IEA injury is unclear: historic incidences of IEA injury during operative laparoscopy range from 0.3% to 2.5%, (11-13). but in a more recent case series of 4721 women undergoing laparoscopic endometriosis surgery the incidence of IEA was less 0.1% (14).

Overall port site hernia incidence ranges from 0.2% to 3.1% (15) but when only 5mm ports are used this risk's incidence is around 0.1%

Less serious complications related to accessory port insertion include pain, haematoma, infection, and scarring. IEA injury will be collected as a specific complication and reported to the DMEC, as will port site infection and hernia.

All intra-operative findings, and the patient's participation in the trial, will be documented in the medical notes (as is routine). If the participant is randomised, the treatment allocation and method of removal (if applicable) will not be recorded in the medical notes. This information will instead be transcribed onto the trial Surgical Form and uploaded onto the trial database. If the participant is not eligible for randomisation, they will follow standard care pathways and usual surgical documentation.

Following surgery and randomisation, the participant will be informed of the diagnosis of endometriosis, but not informed as to whether or not surgical removal was carried out to maintain participant blinding.

All attempts will be made to minimise the inadvertent unblinding of all trial participants. This will include providing templates for operative findings and standardised discharge letters. Where feasible, the member of the research team who attends theatre will not be the individual who captures follow-up data. The importance of maintaining the blind will be emphasised to all members of the surgical care team e.g. anaesthetic staff, theatre and recovery staff, etc.

After the participant has been in the trial for 12 months and after primary outcome follow up data has been collected, the participant can request to be unblinded. The treatment allocation and method of removal (if applicable) will be transferred into their medical notes.

If full details of the surgical procedure are required in an emergency to inform clinical management, this information will be available from the trial database (24 hour emergency access) or by contacting the surgeon who performed the operation. Permission should be sought from the local PI before emergency unblinding.

If a participant is unblinded in an emergency, this will be recorded on the 'Change of status form' within the DCF by the local research team.

3.3 Follow-up

Participants will be followed up from time of randomisation until twelve months post laparoscopy (i.e. completion of follow-up trial and outcome questionnaires at three, six and twelve months). Participants will be also asked for permission for us to look at their medical records in the future to track their fertility and pregnancy outcomes and need for further surgery (related to removal of endometriosis) following their participation in the trial. In addition they will also be asked for their permission to be contacted to complete outcome questionnaires at two and five years (subject to future funding).

At the end of follow-up, participants will be given the option of being un-blinded, and if allocated to the diagnostic laparoscopy alone group, they will have the opportunity to discuss whether they wish to have surgical removal as part of their routine clinical follow-up following their diagnosis.

Each ESPriT+ participant with confirmed SPE and randomised to ESPriT2 will be asked to give a venous blood sample at six months post randomisation (±2 weeks).

3.4 Internal pilot

Participants will be recruited from approximately 70 sites across the UK, with the aim to set these up at an average rate of 3 sites per month over the first 24 months of the trial.

For the internal pilot we will use a stop-go criteria based on a Green-Amber-Red statistical approach including sites recruiting over the first 18 months. Assuming each centre month follows an independent identically distributed Poisson distribution with mean 0.33 and an expected randomisation of 54 participants by the end of month 18. 'Green' will be within 1 standard deviations of 54 i.e. if we have randomised 46 or more with an average rate per centre per month of 0.28 we will continue unchanged. 'Amber' will be within 1-4 standard deviations i.e. if we randomise between 24 and 46 with an average rate per centre per month of 0.12 then we will modify (export identified best practice from best recruiting sites; and/or more sites; and/or more recruitment time). 'Red' will be if we randomise less than 24 then consideration will be given stopping the trial dialogue with the HTA as funder.

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

We will randomise 400 women (200 per trial group) to ESPriT2. In order to achieve this total of randomised participants, we anticipate that we will have to consent approximately 1200 women. We aim to approach and consent the participants who have consented to ESPriT2 to ESPriT+ (up to 1200 women). A subset of approximately 100 women will be recruited to undergo a targeted transvaginal ultrasound scan.

4.2 INCLUSION CRITERIA

- Aged over 16
- Undergoing laparoscopy for the investigation of chronic pelvic pain
- In order to be randomised, isolated superficial peritoneal endometriosis (SPE) must be identified at laparoscopy (macroscopically)
- Able to give informed consent

4.3 EXCLUSION CRITERIA

- Previous surgical diagnosis of endometriosis
- Pregnant
- Women who have undergone hysterectomy and or bilateral oophorectomy
- Women who are undergoing the following concurrent procedures at the time of laparoscopy
    - salpingectomy
    - ovarian cystectomy
    - oophorectomy
    - division of dense adhesions
    - endometrial ablation
- Ovarian cyst on imaging that is the indication for surgery
- Deep endometriosis on imaging or at time of laparoscopy

- Endometrioma observed at the time of laparoscopy
- Peritoneal ‘pockets’ only noted at laparoscopy

4.4 CO-ENROLMENT

Participants will be permitted to take part in non-interventional studies such as questionnaire studies and bio banking (with the exception of peritoneal biopsies). Participants will not be permitted to co-enrol in other drug (CTIMPs for treatment of pain or surgical trials. Similarly, those enrolled in active intervention phase of another gynaecological trial will be excluded but eligible for inclusion if in long term follow up phase of other gynaecological trials. This in line with POL008 v1.0 which is the sponsor’s co-enrolment policy.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Participants will be recruited from gynaecology out-patient departments including fertility clinics following a clinical decision to perform a diagnostic laparoscopy for the investigation of chronic pelvic pain. Potentially eligible women will be referred, with permission, by their attending clinician to a member of the Clinical Research Team. They will be given a patient information sheet and the opportunity to discuss the trial. A letter of invitation may also be sent to potential participants from the women’s direct clinical care team.

5.2 CONSENTING PARTICIPANTS

Informed consent to participate in the trial only to be taken by a member of the research team once the patient has had ample time to read the patient information sheet, have their questions answered and consider whether they wish to participate in the study. They will be given at least 24 hours to consider participation.

Initial contact may be face-to-face during a routine clinic appointment or may be via a telephone/video call via an approved NHS platform to the participant by a member of the research team.

Those patients who are approached to take part over a call will have the option to attend the hospital to discuss the trial and provide written informed consent in person or provide informed consent verbally over the call. As all mandatory baseline procedures can be performed over during a call, this will minimise participant burden but leave the option of attending for the baseline visit if preferred. Those who give verbal consent will have the consent form signed by the researcher and a copy of this signed form will be sent to the patient with contact details of the research team should they decide to withdraw consent. Prior to either written or verbal consent, participants will receive the full patient information sheet and have all opportunities to discuss the study with the research team or others. All participants will be asked to re-confirm consent at the time of their laparoscopy and will be asked to wet ink sign the study consent form before any further research activities are carried out although questionnaires may be completed before this signature is obtained.

Information about the trial will always be sent to the participant prior to their surgery day but as this can often change at short notice, they may be consented to the trial on the day of surgery, although all efforts will be made to carry out trial consent and the baseline questionnaires etc before this. The research staff will ensure that the participant has had ample time to think about the trial and has had time to ask any questions.

At the time of consent, the participant will be reminded that they will be given a diagnosis post-operatively of the findings at the time of laparoscopy but will not be told if any removal was carried out. They will be told that the details of any surgical removal will not be disclosed to their GP. Details of trial participation and diagnosis will be disclosed to the GP as well any recommended treatment from their attending physician. However, there will be a process by which they can be unblinded at their request or in case of an emergency. All findings and surgical removal will be available in the research notes. The clinical findings as well as information about the participation in the trial and the importance of maintaining the participant blind will be documented in the medical notes.

All participants consented to the study will be informed of other options for the management of endometriosis-associated pain available to them throughout the trial, as part of routine clinical care, including analgesics, ovarian suppressive drugs and neuromodulators.

5.3 SCREENING FOR ELIGIBILITY

A screening log will be maintained (for at least the period of the internal pilot) and the following anonymised information will be monitored and collected for all approached potential participants*:

- Year of birth
- Initials
- Ethnicity (if given)
- Location of approach e.g. clinic, postal invitation
- Date of approach
- Reason not approached/non-participation/ineligibility
- Whether they have been given a PIS
- Outcome of approach (recruited or declined)
- Reason declined (if given)

Following consent to the trial, initial eligibility will be assessed by the clinical research team. Confirmation of initial eligibility will be recorded within the participants' medical records.

All data will be stored on a secure database.

5.4 INELIGIBLE AND NON-RECRUITED PARTICPANTS

They will be offered routine NHS gynaecological care.

5.5 RANDOMISATION

5.5.1 **Randomisation Procedure**

Eligibility will be confirmed at the time of laparoscopy following a finding of SPE only.

The participant's intraoperative data will be entered into a 24-hour computerised central randomisation service by means of a secure web interface or by a telephone call to the trial management team. The randomisation service determines the treatment allocation and will be given to the operating surgeon.

Participants will be randomised in 1:1 ratio to either diagnostic laparoscopy alone or to concurrent surgical removal (ablation/excision) using a remote randomisation system provided independently by ECTU.

Randomisation will use a computer-based randomisation system stratified using permuted blocks by the following important prognostic variables and:

- Presence of dysmenorrhoea (yes/no)
- Pre-operative hormone treatment (yes/no)
- Presence of dyspareunia (yes/no)

A detailed description of the randomisation system including details on block size is held by ECTU.

5.5.2 **Emergency randomisation**

In the event that the database is not available, emergency randomisations will be performed by simple randomisation using a computer-generated random number list provided independently by ECTU. The allocation sequence will be enclosed in sequentially numbered, opaque, sealed envelopes. Envelopes are opened by the research team only after the enrolled participant has eligibility confirmed, and the treatment allocation will be given to the operating surgeon. Contact the trial management team who will facilitate this.

5.5.3 **Treatment allocation**

Participants will be randomised to diagnostic laparoscopy alone or surgical removal of SPE. The operating surgeon can choose to remove either by excision, ablation or a combination of the two at their own discretion. Details of the extent of SPE and type of surgery will be recorded.

As part their routine clinical care, all participants consented to ESPriT2 will be informed of all the treatment options for the management of endometriosis-associated pain throughout the trial, including oral analgesics, ovarian suppressive (e.g. long-acting reversible contraceptives, combined oral contraceptives, GnRH agonists) and neuromodulators (e.g. amitriptyline, gabapentin. Attending clinicians will be encouraged by the trial team to offer these options to all participants who present with recurrent symptoms) a letter detailing these options will also be sent from the trial team to the participants' GPs).

5.5.4 **Unblinding**

An unblinding facility will be available on the database. If a clinician needs to unblind a participant (e.g. at the participant's request or for emergency purposes), they will need to contact the local PI and local research team who will follow the unblinding procedure on the trial database. This will be documented on the database with the reason why the unblinding has taken place and the date of the unblinding (on the Change of Status Form within the DCF).

To reduce the risk of accidental unblinding the participant's GP will not be informed if surgical removal has been performed but they will be told of the diagnosis and there will be clear information on participant's medical and electronic notes that this is a study participant and they should not be told if removal of endometriosis was carried out. At the end of participation, their GP will be informed if surgical removal of endometriosis was performed. If endometriosis lesions are removed and sent for histological examination, these results will be filed in the research notes. At the end of their participation these results will be conveyed to the GP, filed in the medical notes, and sent to the participant (if wishing to be unblinded). The only exception to this is if malignancy is identified in which case the GP and participant

will be unblinded and the operating surgeon informed. Subsequent referral will be the responsibility of the operating surgeon.

5.6 WITHDRAWAL OF STUDY PARTICIPANTS

Participation in the study is voluntary. A patient has the right to completely withdraw from the study at any time for any reason.

Consent is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation.

The participant will have the option to withdraw from any or all of the following:

- ESPriT2 prior to randomisation (this may not affect participant in ESPriT+)
- postal follow-up questionnaires
- follow-up conducted by telephone
- ESPriT+ follow up

The details of withdrawal (date, reason and type of withdrawal) should be clearly documented in the source data.

If a participant withdraws, no data will be destroyed. It will remain in the Trial Master File for any future audit or regulatory purposes.

If the participant becomes (or wishes) to be unblinded then follow-up will continue as per the timelines.

If a participant withdraws this will not affect their clinical care and they will return to standard care.

All the above will be documented on a change of status form within the database.

6 STUDY ASSESSMENTS

6.1 STUDY ASSESSMENTS

6.1.1 **Baseline**

- Consent and initial eligibility criteria confirmed
- Demographics
- Medical History
- Targeted transvaginal ultrasound scan (ESPriT+ only – London only).
    - This scan should be within 3 months of the date of laparoscopy.

6.1.2 **Randomisation – day of surgery**

- Baseline QoL questionnaire (completed by participant on the day or week before surgery)
- eDCF completed by member of trial team to include
    - Current analgesic use
    - Current hormone use

    - Visits to primary and secondary care providers
    - Postcode to calculate the Depcat score
    - Clinical pregnancy test result
    - Future fertility intent
    - Occupation and education
    - Presence of dysmenorrhoea (yes/no)
    - Presence of dyspareunia (yes/no)
    - Presence of cyclical pain outwith menses (yes/no)
- Venous blood sample (approx. 60mls) (ESPriT+ only) - can also be taken at any visit up to 8 weeks before surgery

- Laparoscopy performed
- Eligibility confirmed – superficial peritoneal endometriosis (SPE) found
- Randomised
- Surgical case report form completed
- Immediate post-operative analgesic requirements will be recorded on this form, obtained from medical records (e.g. drug kardex).
- Give participant post-operative pain diary

6.1.3 Day 30 following surgery (±1 week)

- Postoperative complications form (completed by trial team via telephone)
- Collection of postoperative pain diary
- Recording of any AEs

6.1.4 3 months post laparoscopy (+/-2 weeks)

- Follow-up QoL questionnaires (completed by participant on-line or on paper returned to local site, this can be outwith the +/-2 week window).
- Three-month follow-up outcome form documenting analgesic use, hormonal medication, pregnancy events and use of healthcare services (completed over the telephone)

6.1.5 6 months post laparoscopy (±2 weeks)

- Follow-up QoL questionnaires (completed by participant on-line or on paper returned to local site, this can be outwith the +/-2 week window).
- Six-month follow-up outcome form including analgesic use, hormonal medication, pregnancy events and use of healthcare services (completed over the telephone)
- ESPriT+ venous blood sample (about 60mls) (if consented to sub-study).

6.1.6 12 months post laparoscopy (+/- 2 weeks)

- Follow-up QoL questionnaires (completed by participant on-line or on paper returned to local site, this can be outwith the +/-2 week window).
- Twelve-month follow-up outcome form documenting analgesic use, hormonal medication, fertility interventions and pregnancy events, use of healthcare services (completed over the telephone) and details on blinding status.

6.1.7 **2 and 5 year follow up (+/- 3months)**

Subject to further funding the following outcomes will be collected:

- need for further surgery, hormonal and analgesic use, fertility intervention and pregnancy events, measured at 2 and 5 years post randomisation (via data linkage or asked directly)
- EHP30, ROME IV, PUF, EQ5D-5L, PainDETECT™, ICECAP-A questionnaires

This follow up data will be collected centrally by the research team in NHS Lothian and will be saved on a REDcap database that is stored in the University of Edinburgh.

6.1.8 **Independent review**

A Surgical Adjudication Form will be completed by independent specialist endometriosis surgeons for all randomised participants. The surgeons will review the images obtained at laparoscopy (images including those of the uterovesical fold, Pouch of Douglas and right and left ovarian fossa). This is to provide independent adjudication of the extent of endometriosis. This will not affect participation but will be reported descriptively in the results. If randomised to surgical removal an assessment from photographs of treated areas will also be performed, this is to confirm the surgeon's finding that they record on the surgical report form. It will not be recorded as a deviation if photographs cannot be obtained as this may not be available at every surgical list/operating theatre. The images will be either printed off or saved on a memory stick. These will be anonymised and only identified by the participant's unique PIN number. These will then be transferred to a secure online database which will be password protected and will have limited access. The independent assessors will be given a unique login to access these files.

6.2 BASELINE AND FOLLOW UP QoL QUESTIONNAIRES

Our trial questionnaire comprises of a range of validated patient-reported questionnaires. These will be collected pre-operatively and then at three, six and twelve months post-surgery. All permissions will be sought as needed for the use of these by the trial management team. Note the baseline and follow-up trial questionnaires differ only in that:

1. The baseline questionnaire contains text prior to the EHP-30 as follows "This questionnaire asks about 'symptoms due to endometriosis.' We realise that you do not know whether or not you have endometriosis so please try and ignore the references to endometriosis and simply answer the questions focusing on the symptoms."
2. The questions in the MYMOP2 questionnaire are adapted in the follow-up questionnaires to account for the fact that the participant needs to remember how they answered this questionnaire at baseline.

The trial questionnaire will include:

- **Endometriosis Health Profile-30 (EHP-30)**
  - Questionnaire with 30 items and five scales: pain, control and powerlessness, emotional well-being, social support, and self-image to address dimensions of health-related questions
- **Rome IV Criteria**
  - Three questions to rule out irritable bowel syndrome
- **Pelvic Pain and Urgency/Frequency Patient (PUF) Symptom Scale**
  - 8-point scale about urinary patterns and pain
- **PainDETECT ™**
  - Questionnaire with 14 items to identify those with neuropathic pain
- **Brief Fatigue Inventory (BFI)**

    - Questionnaire with six items that correlate with standard quality of life measures. It assesses severity of fatigue and impact of fatigue on functioning over the previous 24 hour
- **Pain Catastrophising Questionnaire (PCQ)**
    - 13 item scale, with each item rated on a 5-point scale. The PCQ is broken into three subscales being magnification, rumination, and helplessness. The scale was developed as a self-report measurement tool that provided a valid index of catastrophising
- **Fibromyalgia Scale (FS)**
    - Seven questions related to fibromyalgia symptoms
- **Measure Yourself Medical Outcome Profile 2 (MYMOP 2)**
    - Patient generated outcome questionnaire
- **Working Productivity and Activity Impairment Questionnaire (WPAIQ)**
    - Questions related to the effect your health issues have on work and regular activities
- **EuroQol 5 Dimensions 5 Level Questionnaire (EQ-5D)**
    - Two-part questionnaire with the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS) to assess patients' health state in five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression
- **Capability Questionnaire (ICECAP-A)**
    - Capability instrument for individuals with depression.

The above QoL questionnaires can be completed, in person, via telephone, via post or via online link (online link is the preferred option). If a participant becomes distressed whilst completing the questionnaires, we have a specialist research nurse who they can contact for support. This number can be given to them from their local research team.

6.2.1 Three, Six and Twelve Month Follow-Up Outcome Forms

At three, six and twelve months post randomisation, participants will be asked questions (outcome form) about analgesic use, hormonal medication, pregnancy events and use of healthcare services. This will be via a telephone call with the research team.

6.2.2 Surgical Case Report Form

Following laparoscopy the surgeon will complete a "Surgical Case Report Form" (SCRF) detailing information from the operation:

For all participants this will be:

- Grade of surgeon and whether they are an advanced laparoscopic surgeon
- If surgeon has completed iLEARN module on laparascopic surgery
- Diagnosis of endometriosis subtype (SPE, ovarian endometrioma, deep)
- Ovarian cyst present that requires removal
- Confirmation of eligibility to be randomised
- Details of SPE (location and appearance of lesions)
- Details of other findings (fibroids, adhesions, peritoneal pockets)
- Hysteroscopy/cystoscopy taking place during laparoscopy (yes/no)
- Pathology results if endometriosis is removed or deep disease or endometrioma found

For randomised participants this will be:

- Details of any tubal dye tests performed
- Duration of surgery
- Concurrent IUS insertion
- Number and location of accessory ports, not including optical port.
- Intraoperative complications (e.g. uterine perforation, anaesthetic complication, injury to surrounding anatomy, haemorrhage, and laparotomy)
- Details of images captured for diagnosis

If allocated to surgical removal

- Type of removal will be recorded (excision, ablation or combined), if allocated to this arm
- Details of images captured showing any removal, if allocated to this arm
- Subjective assessment of whether or not complete removal was achieved
- Histological result if SPE excised and sent for histological assessment

The SCRF includes a specific set of pre-determined images. For the diagnostic laparoscopy this is a standard panel of images of the pelvis which include the UV fold, Pouch of Douglas and right and left ovarian fossa. If allocated to surgical removal the type of surgical removal will be documented, an assessment of the adequacy of removal and images of treated areas. Two independent clinicians will assess these images, blind to initial classification, to reduce the likelihood of misclassification.

6.2.3 Post-operative form

A post-operative form (part of the eDCF) will be completed detailing complication up to 30 days post-op. This will be completed by the clinical research team, utilising information gained by a phone-call to the patient, and correlated with the participant's hospital record.

Specific complications include urinary retention, unintended overnight stay, haemorrhage, transfusion pelvic haematoma, visceral injury (bowel, bladder, ureteric), infection (urinary, chest, wound, pelvic abscess, other), venous thromboembolism, fistula, hernia, return to theatre, readmission, ITU admission and death.

Any reportable adverse events will be collected up to 30 days.

6.2.4 Post-operative pain diary

Participants will be asked to complete a diary of analgesic use and NRS score for worst and average pelvic pain (day 1 to 7 post op).

6.2.5 Schedule of events

Phase	Baseline	Randomisation	Days 1 – 7 post op	30 days post op	3 months post op	6 months post op	12 months post op
Consent to demographics	x						
Consent to trial	x	X***					
Eligibility	x	x					
Medical history	x						
Ultrasound (ESPriT+ only)	x						
Venous blood sample (ESPriT + only)	x					x	
Post op pain diary			x				
Post op phone call (complications)				x			
Baseline QoL questionnaires	x						
Follow-up outcome form*					x	x	x
Follow-up QoL questionnaires**					x	x	x

Adverse events				x			

*Follow-up outcome questions are completed via a telephone call

**QoL questionnaires can be completed in person, via telephone, via email, via post or via online link.

*** Consent confirmed if initial consent was via telephone

NB longer term follow-up not shown in this table as not funded at time of writing

6.3 LONG TERM FOLLOW UP ASSESSMENTS

We will seek consent for further follow-up of participants for up to 2 years and 5 years (questionnaires). This longer term follow up will be carried out centrally by the trial team in Edinburgh. We will also seek permission to look at participants' medical records to track their fertility/pregnancy outcomes and further surgeries related to endometriosis (via data linkage or asked directly).

6.4 STORAGE AND ANALYSIS OF SAMPLES (ESPriT+ only)

Standard processes regarding collection and processing of the samples will be written and sent to each participating site. Blood samples (serum and plasma) will be frozen and stored locally and then sent via a specialised courier to the trial management team within the University of Edinburgh. Part of the blood samples will be sent with consent to Roche Diagnostics, Penzberg, Germany and potential other collaborators and part of the blood samples will be retained by the University of Edinburgh. All samples will be coded and will only be identifiable via a unique participant number.

7 DATA COLLECTION

7.1 Source Data Documentation

Source documents will be screening log, clinical notes, outcome questionnaires and participant completed QoL questionnaires. Some source data may be captured straight into the database and a source data plan will be put in place.

7.2 Data collection forms

Screening and identification logs: The clinical research team will keep an anonymised electronic log of women who are invited to participate in the study but declined and women recruited. Reasons will be collected for non-participation from women who decline to take part after previously providing contact details.

The clinical research team will keep an electronic log of all women consented to the trial. During the course of the study we will document reasons for non-randomisation (withdrawal prior to surgery, ineligible at time of surgery). Reasons for withdrawal from the study and loss to follow-up will be documented, if available. A paper ID log will be kept in the ISF, this will be the detachable front cover of the data collection form with patient details documented.

Data Collection Form: All data may be recorded on a paper data capture form or inputted directly onto the secure web interface to the trial database. Eligibility will be signed off on the notes and recorded on the database. The data will include questions to capture the baseline demographics and clinical characteristics of the participants. Data will be collected as it becomes available – i.e. at, or shortly after, each patient visit by members of the clinical team supported by research staff. The eDCF will be seen as source data for this trial.

Surgical Case Report Form: At the time of surgery a paper SCRF will be completed and transferred to a secure database. Information included in this is described in section 6.1. The digital images will be anonymised and uploaded. If print out images are only available these will be scanned and then uploaded via the secure web interface.

For participants who are not randomised, the data collected for these participants will be kept in anonymised form on the secure database. Sections of this data will be required for analysis e.g. demographics of the population consented to the trial. No data will be destroyed for consented participants as this may be required for audit or regulatory reasons to ensure the safe running of the trial.

Surgical Adjudication Form: An electronic surgical verification form will be completed by the independent reviewers as to the extent of endometriosis and adequacy of removal (if carried out).

Post Operative Diary: A post-operative diary to be completed in the first week detailing worst, average pain and analgesic use.

Post Operative Form (± 1 week):

Post operative data will be completed after 30 days post-surgery by the clinical research team (either online or on paper), following contact with the participant and cross referenced if required with the hospital records, and stored on a secure database. Information included in this is described in section 6.1.

QoL Questionnaires:

Questionnaires will be anonymised and completed in private, at baseline (before surgery) and after 3, 6 and 12 months post-surgery (this is the ideal time for these to be completed but attempts will be made to obtain these throughout the trial if they are missing). The QoL questionnaires can be completed, in person, via telephone, via email, via post or via online link (online link is the preferred research option).

Follow-Up Outcome Forms (±2 weeks):

At three, six and twelve months post randomisation, participants will be asked questions (outcome form) about analgesic use, hormonal medication, pregnancy events and use of healthcare services. They will also be asked about any impacts associated with their condition on their work any other and caring responsibilities. This will be via a telephone call with the research team. This is stored on a secure database.

Longer term follow up 2 and 5 years post laparoscopy (±3 months)
At 2 and 5 years post laparoscopy (subject to further funding), participants and will be asked to repeat questionnaires (online or on paper returned to NHS Lothian) and we will follow-up fertility and further treatments needed via data linkage or by a telephone call.

7.3 DATA MANAGEMENT

7.3.1 Personal Data

The following personal data will be collected as part of the research:

- Name, CHI number (Scotland only), unique hospital number, email address, telephone number, address, ethnicity and year of birth of a participant.

Personal data will be stored by the research team in a locked cabinet with limited access in research offices in all centres. Electronic data collection will be stored on University of Edinburgh secure server. The participant's email address will be kept securely on the trial database for the purposes for follow-up.

Personal data will be stored for minimum of 5 years.

7.3.2 **Transfer of Data**

Data collected or generated by the study) will be shared in an anonymised form with ESPriT+ collaborators (Roche Diagnostics). Written consent will be gained for data transfer on the ICF.

7.3.3 **Data Controller**

The University of Edinburgh and NHS Lothian are joint data controllers.

7.3.4 **Data Breaches**

Any data breaches will be reported to the University of Edinburgh and NHS Lothian Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

8 STATISTICS AND DATA ANALYSIS

8.1 SAMPLE SIZE CALCULATION

An 8 point different of the EHP-30 pain domain is equivalent to a standardized different of 0.37 and reduction in pain (and associated quality of life) of this magnitude is considered clinically significant (17). Data from a current NIHR-funded endometriosis trial (PRE-EMPT HTA 11/114/01 internal pilot) shows a standard deviation (SD) of 19 (95% CI 16-22) on baseline EHP-30 scores. Assuming an 8-point difference and a SD of 22, 160 participants are required in each treatment arm to detect that difference with 90% power with a 2-sided 5% significance level. Assuming a maximum of 20% loss of primary outcome data, 400 randomised participants will be required. We acknowledge that the variability in our outcome may be different to that observed in the PRE-EMPT trial due to differences in the intervention, therefore the ESPriT2 TSC will review blinded data and update the sample size if necessary.

8.2 PROPOSED ANALYSES FOR ESPriT2

Analyses will primarily be intention-to-treat where all randomised participants will be included in the analysis retained in the group to which they were allocated (i.e. ''as-randomised'') and for whom outcome data are available. All results will be presented as point estimates, 95% confidence intervals with associated p-values. A sensitivity analysis using imputation of missing values will be considered only if the proportion of cases with missing values is sufficiently large.

We will specify all analyses to be undertaken in a statistical analysis plan to be finalised before database lock.

8.2.1 Primary outcome analysis

The primary outcome, pain domain of the EHP-30 at 12 months, will be compared using a linear regression model to estimate the mean difference in outcome, including fixed effect terms for surgical removal group, baseline pain score and stratification variables.

Unadjusted results will also be presented to support the findings of the primary analysis. Secondary analyses will include using repeated-measures (multi-level) models incorporating outcome data from other follow-up time points.

8.2.2 Secondary outcome analysis

A similar approach to the primary analysis will be used for analyses of the other secondary outcomes, using an appropriate (depending on outcome type) regression model.

8.2.3 Subgroup analyses

We will perform the following sub-group analysis of the primary outcome, and test for sub-group interactions if appropriate:

- dysmenorrhoea (yes/no)
- dyspareunia (yes/no)
- use of hormones (yes/no)
- extent of disease (<1 cm^2, 1-3 cm^2 and >3 cm^2)
- neuropathic pain (PainDETECT™) defined by a score of ≥19.

8.3 ECONOMIC ANALYSIS FOR ESPriT2

A full economic evaluation will be conducted using trial data based on the primary outcome of cost per QALY gained, with a secondary analysis of cost per clinically significant change in symptom score at 12 months. The primary perspective adopted will be a NHS and personal social services perspective, but a wider societal perspective will also be pursued using trial data about impact on work productivity. The NHS resource use collected will include secondary care costs related to surgery, length of stay and complications/readmissions as well as primary care and other healthcare costs. If the trial demonstrates that laparoscopy removal is effective in the management of SPE, longer term costs and outcomes will be assessed as part of a decision-analytic model.

The primary analysis will be in the form of a cost-utility analysis using the EQ5D-5L instrument– this will use the results of the EQ5D-5L instrument and plus data on costs and resource use collected in the trial. For the cost-utility analysis we will evaluate the cost per QALY gained at 12 months. We will collect data via the EQ5D-5L questionnaire at baseline, 3 months, 6 months and 12 months.

The secondary analysis will use the EHP-30 instrument (using the same approach as adopted for the clinical analysis), and evaluate the cost per clinically significant change in symptom scores at 12 months, using the results from the EHP-30 instrument (we will use the same definition of clinically significant change as the clinical trial).

For those allocated to surgical removal, the primary outcome data will be summarised by the surgical approach (excision, ablation, or combined).

8.4 PROPOSED ANALYSES FOR ESPriT+

The sensitivity and specificity of the biomarker(s) will be calculated from the 400 patients recruited from ESPriT2 plus the patients without SPE who agree to ESPriT+. As the biomarker is a score on a continuum, it will be possible to adjust the threshold whereby a 'positive' case is defined. Sensitivity and specificity of the biomarker will be reported thus:
1) Point of maximum utility – where the greatest sensitivity is balanced with the point of greatest specificity (maximum Youden's score)
2) Does the threshold at which 94% sensitivity is achieved give a specificity of 70% or greater (diagnostic test)
3) If the diagnostic test fails, the data will be assessed for use as a triage test.

- If at the point of 95% sensitivity, the specificity is >50%, then it may be utilised as a triage-out test.
- If at the point of 95% specificity, the sensitivity is >50%, then it may be utilised as a triage-in test

The addition of other biomarkers to the primary biomarkers will be explored to see if there is any improvement to the sensitivity and/or specificity without any detriment to the overall accuracy.

Logistic and ROC analysis will explore whether the sensitivity and specificity are impacted by demographic factors, hormone use, volume of SPE, lesion type and cycle stage. This is likely to be exploratory only, to inform future research.

9 ADVERSE EVENTS

Participants will be asked about the occurrence of AEs related to their surgery or related to any new medical therapies taken for treatment of their pelvic pain started from the day of laparoscopy. These will be recorded by the research teams during the 30-day follow-up phone call. No adverse events will be recorded for any pre-existing or unrelated conditions. No adverse events will be collected after 30 days post-operative. No SAEs will be reported to the sponsor. Any common anticipated events e.g. surgical complications, which are collected as data on the DCF do not need to be recorded as AEs to reduce duplication of data.

10 OVERSIGHT ARRANGEMENTS

10.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor (including Roche Diagnostics) direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

10.2 STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and, if so, at what frequency.

Risk assessment, if required, will determine if audit by the ACCORD QA group is required. Should audit be required, details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

10.3 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The TSC provides independent supervision for the trial, providing advice to the Chief and Co- Investigators and the Sponsor on all aspects of the trial and affording protection for patients by ensuring the trial is conducted according to the International Committee on Harmonisation Guidelines for Good Clinical Practice in Clinical Trials.

If the Chief and Co-Investigators are unable to resolve any concern satisfactorily, Principal Investigators, and all others associated with the study, may write through the Trial Office to the chairman of the TSC, drawing attention to any concerns they may have about the possibility of particular side-effects, or of particular categories of patient requiring special study, or about any other matters thought relevant.

The Trial office will forward TSC meeting minutes to the Sponsor and funder. Terms of reference of the Trial Steering Committee and the draft template for reporting will be agreed at the inaugural meeting.

10.4 DATA MONITORING AND ETHICS COMMITTEE

An independent Data Monitoring and Ethics Committee (DMEC) will be established to oversee the safety of participants in the trial. If one treatment really is substantially better or worse than any other with respect to the primary outcome, then this may become apparent before the target recruitment has been reached. Alternatively, new evidence might emerge from other sources that any one treatment is definitely more, or less, effective than any other. The DMEC will regularly review data on the outcomes and adverse events along with updates on results of other related studies, and any other analyses that the DMEC may request. The DMEC will advise the chair of the TSC if, in their view, any of the randomised comparisons in the trial have provided both:

(a) “proof beyond reasonable doubt”1 that for all, or for some, types of patient one particular treatment is definitely indicated or definitely contraindicated in terms of a net difference in the major endpoints, and

(b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results. The TSC can then decide whether to close or modify any part of the trial. Unless this happens, however, the TMG, TSC, the investigators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results.

The Trial office will forward DMEC open meeting minutes to the Sponsor and funder. Terms of reference of the Data Monitoring and Ethics Committee and the draft template for reporting will be agreed at the inaugural meeting.

11 GOOD CLINICAL PRACTICE

11.1 ETHICAL CONDUCT

1 Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least 3 standard errors p<0.001 (similar to a Haybittle-Peto stopping boundary) in an interim analysis of a major endpoint may be needed to justify halting, or modifying, the study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed.

- The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).
- Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

11.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

11.3 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form. The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s).

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes (if applicable).

11.3.1 Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

11.3.2 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the DCF at each Investigator Site.

11.3.3 Investigator Documentation

The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs.

11.3.4 GCP Training

Researchers may have commensurate GCP training according to tasks performed for the study which will be updated according to their local trust policy. The trial management team

will hold evidence of GCP training along with a signed CV. Clinicians carrying out their clinical role (e.g. performing the laparoscopy and giving details of the operation on the Surgical Form) will not require GCP training.

11.3.5 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

11.3.6 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) with regard to the collection, storage, processing and disclosure of personal information.

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

Published results will not contain any personal data and be of a form where individuals are not identified and re-identification is not likely to take place.

12 STUDY CONDUCT RESPONSIBILITIES

12.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC and local R&D for approval prior to participants being enrolled into an amended protocol.

12.2 MANAGEMENT OF PROTOCOL NON-COMPLIANCE

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot.

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An

alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

12.3 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

12.4 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

12.5 END OF STUDY

The end of the trial will be the collection of the last participant's 12-month follow-up questionnaire.

The Investigators or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R&D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot

A summary report of the study will be provided to the REC within 1 year of the end of the study.

12.6 CONTINUATION OF TREATMENT FOLLOWING THE END OF STUDY

There is no continuation of treatment.

12.7 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.
The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.

- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.

- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.

13 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

13.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the trial team.

14 REFERENCES

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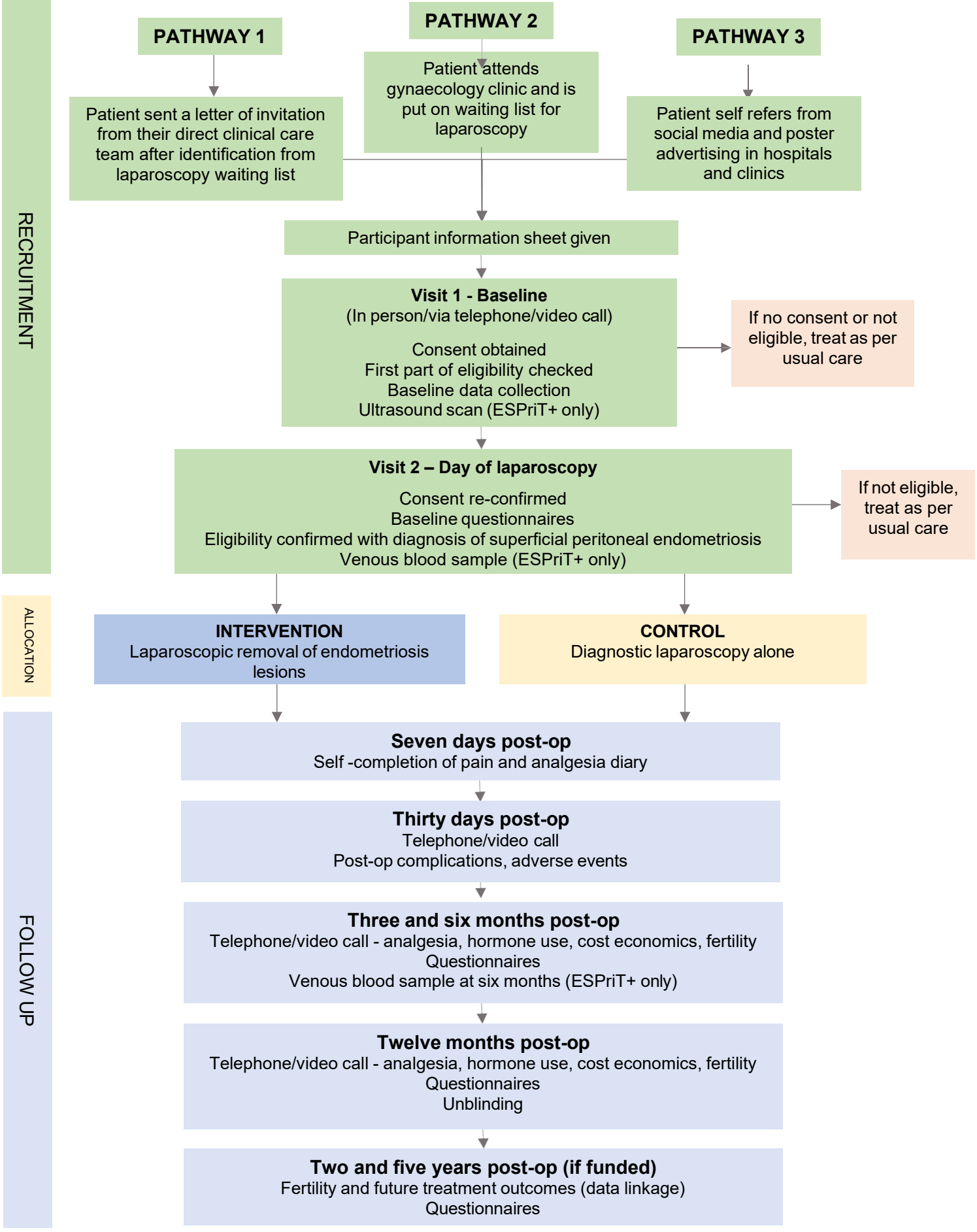
15 FLOWCHART



ESPriT2 Protocol Version 5 21Feb2025

Final Audit Report 2025-04-09

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By:	Lauren Sutherland (Lauren.Sutherland@ed.ac.uk)
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"ESPriT2 Protocol Version 5 21Feb2025" History

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Signer lucy.whitaker@ed.ac.uk entered name at signing as Lucy Whitaker

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Agreement completed.

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