STUDY PROTOCOL

Pilot study to investigate the **A**ccuracy and potential clinical application of a non-invasive **D**iagnostic **D**evice, EVG Clinical Decision Tool (Endosure test, EndoSure Inc), in the diagnosis and management of **END**ometriosis.

(**ADDEND** Study)

Final Version 1.0
DATE

IRAS Project ID: 346375

Study Sponsor: Worcestershire Acute Hospitals NHS Trust

ISRCTN Reference:46561

Funders Reference: The British Society for Gynaecological Endoscopy Research Grant/Ref 36

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

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 investigation without the prior written consent of the Sponsor

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

For and on behalf of the Study Sponsor:

Signature: Date: ...../...../.....

.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Signature: Date: 15/07/24

Name: Miss Donna Ghosh

LIST OF CONTENTS

KEY STUDY CONTACTS

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Chief Investigator	Miss Donna Ghosh, Consultant Gynaecologist, Endometriosis Lead 07753 171001 donna.ghosh@nhs.net
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Funder	The British Society for Gynaecological Endoscopy (BSGE)
Key Protocol Contributors	Donna Ghosh, 07753 171001, donna.ghosh@nhs.net Sabrina Butt, 07956 454147, drsabrinabutt@gmail.com Jyoti Sharma, 07914 626755, jyoti.sharma10@nhs.net Zahra Azeem, 07404 659151, zahra.azeem2@nhs.net
Trial Statistician	Alexandra Argyrou, MD, MSC, PHD Master in Biostatistics and Bioinformatics, University of Thessaly, Greece

STUDY SUMMARY

Study Title	Pilot study to investigate the accuracy and potential clinical application of a non-invasive diagnostic device, EVG Clinical Decision Tool (Endosure test, EndoSure Inc), in the diagnosis and management of endometriosis.
Short Title	Study into the Accuracy of a new non-invasive Device (Endosure test, EndoSure, Inc) for the Diagnosis of ENDometriosis
Acronym	ADDEND Study
Study Design	Pilot study
Study Participants	Worcestershire Acute Hospitals NHS Trust patients and healthy volunteers (women aged 18-50 years with no pain)
Planned Size of Sample	78 participants (26 into each group)
Follow up duration	8 weeks
Planned Study Period	6-12 months
Research Question	Can the EVG Clinical Decision Tool be clinically helpful in accurate early diagnosis of endometriosis (presence and severity), to replace laparoscopic surgery as the gold standard diagnostic tool?
Research Aims	- Confirm accuracy of EVG Clinical Decision Tool to detect the presence and severity of endometriosis in subjects undergoing primary surgery. - Confirm accuracy of EVG Clinical Decision Tool to detect absence/ exclude presence and severity of endometriosis following laparoscopic disease excision. - Confirm the accuracy of EVG Clinical Decision Tool to exclude or detect presence and severity of endometriosis in subjects undergoing laparoscopic surgery for other benign indications.

FUNDING

FUNDER	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
The British Society for Gynaecological Endoscopy (BSGE)	BSGE Clinical Research Grant Ref 36 - £2,000

ROLE OF SPONSOR AND FUNDER

The Study Sponsor is Worcestershire Acute Hospitals NHS Trust.

Funds have been secured from BSGE clinical research grant.

The funders have no role or responsibility for study design, conduct, data analysis and interpretation, manuscript writing or dissemination of results.

The Sponsor has provided advice via the Research and Innovation department, assisting in IRAS application.

ROLES AND RESPONSIBILITIES OF STUDY GROUPS

Core Research Group	
Conduct recruitment and data collection as outlined in protocol	Donna Ghosh, Consultant Gyneacologist Jyoti Sharma, Consultant Gyneacologist Zahra Azeem, ST7 O&G Joanna Street, Endometriosis Specialist Nurse
Endometriosis surgeons at Worcestershire Acute Hospitals NHS Trust	
Approval of study aims and protocol	Donna Ghosh, Consultant in Gynaecology Angus Thomson, Consultant Gynaecologist Jon Hughes, Consultant Gynaecologist Natalia Price, Consultant Gynaecologist Jyoti Sharma, Consultant Gynaecologist Zahra Azeem, ST7 O&G, Advanced Laparoscopic and Endometriosis Fellow. Joanna Street, Endometriosis Specialist Nurse
Two surgeons will be named and will review operative image data to confirm or exclude disease	
Public Involvement Group	
Patient focused endometriosis group regularly has a meeting in WAHT. The final version of patient information leaflet was devised after two meetings with them. Meetings were led by Joanna Street (Endometriosis Nurse) and facilitated by Miss Donna Ghosh, Miss Sabrina Butt and Miss Jyoti Sharma.	

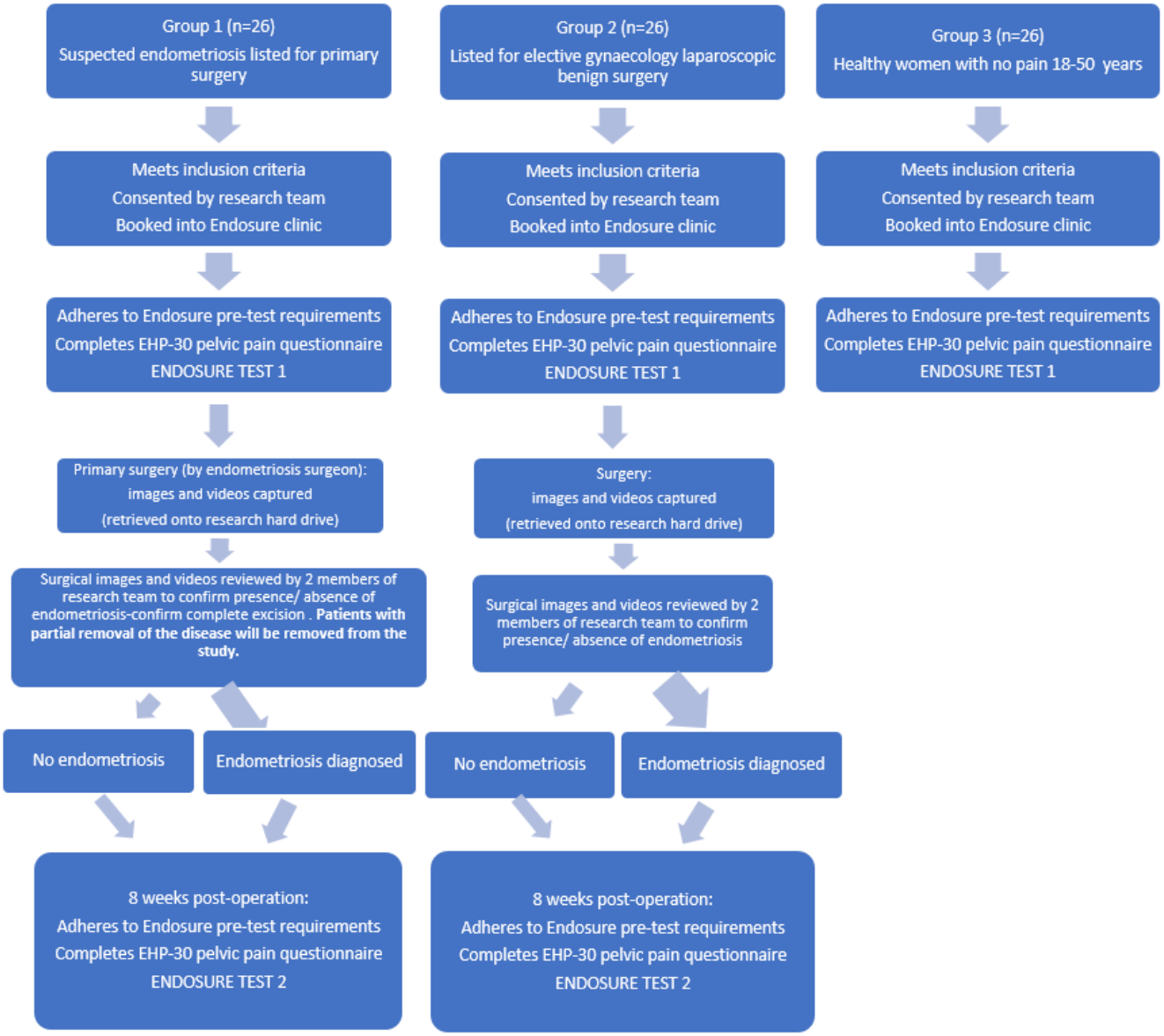
PROTOCOL CONTRIBUTORS

We have a loan agreement for the device with Lawmed Ltd, the company owning the rights to Endosure (EndoSure, Inc), Electroviscerogram System and N532961W Laptop, reducing the expenses for the trial. This will be clearly declared and the device will be independently validated during the study with Lawmed Ltd having no involvement in the study design, protocol, conduct, data analysis or interpretation, manuscript writing or dissemination of results of the trial data. They have no final decision regarding any aspect of the study.

KEY WORDS

Accuracy, diagnosis, endometriosis, non-invasive diagnostic device

STUDY FLOW CHART



1 BACKGROUND

Endometriosis is a chronic inflammatory disease, causing pelvic pain and subfertility to a significant proportion of our society. It is estimated that up to one in ten women of reproductive age are burdened by this chronic condition, starting from menarche in adolescence, and leading to significant impact on quality of life with wider socioeconomic effects.[1]

There is a well-documented non-invasive diagnostic void for endometriosis with associated impact on morbidity of the sufferer, from worsening disease progression and reduced quality of life before a reliable diagnosis is reached (average of 8 years), and from potential complication of surgery to obtain histological diagnosis.[1]

Recent increase in research into non-invasive diagnostic tools have not yielded a positive result, with multiple Cochrane Systematic Reviews failing to recommend a suitable biomarker (or combination of biomarkers) in endometrial tissue, blood, urine, or uterine fluid that meets the accuracy and challenge of clinical practicality within the NHS.[2, 3, 4, 5, 6]

Imaging with ultrasound or MRI, in combination with reviewing the effect of empirical medical treatment (if acceptable to the patient), is now recommended as a diagnostic tool for endometriosis, but definitive laparoscopic confirmation is still often sought, with its associated morbidity.[1]

Imaging modalities, although proven to be highly sensitive and specific in diagnosing ovarian and deeply infiltrating endometriosis, requires expertise and resources not always available, and is poor at detecting superficial peritoneal disease. Transvaginal ultrasound is also not truly non-invasive and may not be acceptable, suitable or tolerable in the significant adolescent cohort of patients.[1]

Urgent exploration of all possible non-invasive diagnostic tools is imperative to reduce the burden of delayed, surgical diagnosis. We present an opportunity to validate claims of a non-invasive test developed in the USA, based on a novel approach to detect disease.[7] Evidence of abnormally high frequency of small bowel motility characteristic of patients with endometriosis was first published in 1998,[8] with non-invasive cutaneous Electroviscerogram (EVG) technique later developed. The Endosure test (EndoSure, Inc) is an EVG clinical decision tool that claims to have 100% detection rate of surgically confirmed endometriosis using gastrointestinal myoelectrical activity (GMA) based artificial intelligence (AI)-derived algorithm of the EVG recording.[9] The Endosure test (EndoSure, Inc) has yet to be validated in the UK with only a limited study performed in the USA that did not include a control group.[9]

We propose to conduct a pilot study of the non-invasive diagnostic device for endometriosis, Endosure test (EndoSure, Inc).

We will recruit 3 patient groups of at least 78 subjects within the Trust: group 1 is patients listed for elective primary laparoscopic surgery due to pelvic pain (suspected endometriosis); group 2 is patients listed for elective laparoscopic surgery for other benign conditions (surgical control group); group 3 is healthy female volunteers (from trust staff) of with no pelvic pain (non-surgical control group). Inclusion criteria for all groups includes: pre-menopausal status; age 18-50 years; no previous surgical detection or treatment of endometriosis; no known malignancy; acceptability to patient of pre-test requirements (omission of opioid medication for 7 days prior to the test, omission of prokinetic or anti-

spasmodic medication for 3 days prior to test, nil by mouth for 8 hours prior to the test). Surgical patients in group 1 and 2 are recruited from clinics and theatre waiting lists; healthy volunteers from group 3 are self-referral from hospital advertisements (weekly electronic staff newsletter and posters).

All participants will be contacted by the research team for information and consent.

All participants will: book into an additional one-hour research clinic; confirm adherence to the pre-test requirements; complete an EHP-30 pelvic pain questionnaire; undertake the Endosure test by trained staff. Results will be stored on a named-only-access computer directory, blinded to surgical team.

Surgery will be performed on patients in groups 1 and 2. Standardised and stipulated captured operative images from diagnostic laparoscopy will be saved onto the laparoscopic stack and retrieved onto a study hard drive. 8 weeks following surgery patients will attend a repeat visit to the research clinic with the same requirements of questionnaire and EndoSure test. Review of captured operative images separately by two endometriosis surgeons will classify disease presence and severity. Unblinding of Endosure test results once all data has been collected will be compared with surgical confirmation or absence of disease. All results will be analysed and the study written up with the endometriosis team at Worcestershire Acute Hospitals NHS Trust approving the final manuscript for publication submission.

2 RATIONALE

We will conduct robust, reproducible, transparent and peer reviewed research into the validity of this device in the UK using a prospective, double blinded study protocol adhering to GCP requirements. We will investigate the manufacturer's claim of 100% detection rate of surgically diagnosed endometriosis.

Despite the prevalence and wide-ranging socioeconomic impact of this chronic inflammatory disease, there is no accurate, non-invasive, diagnostic test for endometriosis currently available in clinical practice. The Endosure test (EndoSure, Inc) has yet to be validated in the UK and we present an opportunity to investigate this different approach, that, if proven accurate, can be tool to reduce the time to reliable diagnosis (average of 8 years). Delayed diagnosis impacts the morbidity of the sufferer, from worsening disease progression and reduced quality of life to potential complication from surgery to obtain histological diagnosis.

Definitive laparoscopic confirmation is still often sought, despite imaging modalities proving to be highly sensitive and specific in detecting ovarian and deeply infiltrating endometriosis. Limitations of expertise and resources, poor detection of peritoneal disease and unacceptability of transvaginal ultrasound in adolescent patients highlights the paramount importance to develop novel, non-invasive diagnostic methods to detect or exclude disease.

3 THEORETICAL FRAMEWORK

A similar study has been reported in the USA (1) assessing the efficacy of GIMA biomarker for diagnosis of Endometriosis. A three group approach and inclusion of healthy patients helps to

determine if the results were particularly related to endometriosis, or if this could be due to the causes.

(1)Noar M, Mathias J, Kolatkar A. Gastrointestinal Myoelectrical Activity (GIMA) Biomarker for Noninvasive Diagnosis of Endometriosis. J. Clin. Med. 2024, 13, 2866. https://doi.org/ 10.3390/jcm13102866

4 RESEARCH QUESTION/AIM(S)

Can the Endosure (EndoSure, Inc) EVG Clinical Decision Tool be clinically helpful in the NHS in accurate early diagnosis of endometriosis (presence and severity), to replace laparoscopic surgery as the gold standard diagnostic tool?

4.1 Objectives

- Assess the accuracy of Endosure (EndoSure, Inc) device to detect the presence and severity of endometriosis in subjects undergoing primary surgery for patients with suspected disease.
- Assess the accuracy of Endosure (EndoSure, Inc) device to detect absence / exclude presence and severity of endometriosis following laparoscopic disease excision.
- Assess the accuracy of Endosure (EndoSure, Inc) device to exclude or detect presence and severity of endometriosis in subjects undergoing laparoscopic surgery for other benign indications.
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4.2 Outcome

GIMA can be adopted as a non-invasive biomarker in NHS in UK with good diagnostic results.

5 STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYSIS

5.1 Study Population and Sample Size

The full study population will be composed of women, aged 18 or older. Subjects will be recruited from an endometriosis clinic, other gynaecology clinics and healthy volunteers into one of three cohorts depending on if the criteria for inclusion is satisfied: Cohort 1 consists of suspected endometriosis patients listed for primary laparoscopy; Cohort 2 consists of subjects listed for elective laparoscopic benign surgery; Cohort 3 Healthy women with no pelvic pain.

Participating clinicians will be blinded to EVG results and EVG technicians will be blinded to surgical results. Subjects found to have endometriosis will be scored by #ENZIAN. Exclusion criteria included: known malignant disease, previous surgical treatment of endometriosis and confirmed menopause for all three groups.

This pilot study is being conducted so that larger studies can be built on it in future. The sample size was calculated on the basis of IBM SPSS version 29. With the power 90%, confidence interval 95% and effect size 90% the sample size is of 26 patients in each group.

5.2 Study Procedures and Protocol

Participants who satisfied exclusion and inclusion criteria will be stratified into one of three main cohorts. They will undergo complete history and physical examinations, complete a standardized pain questionnaire, and will undergo EVG (3CPM Company, Inc., Sparks Glencoe, MD, USA, Software Version 2.09i) with a water load satiety test (WLST).

Electroviscerogram with a WLST Following an overnight fast of 6–8 h:

Subjects will undertake a standardized EVG (3CPM Company, Inc., Sparks Glencoe, MD, USA, Software Version 2.09i) with a WLST study. Subjects will be placed in a 30◦ to 45◦ reclining position, wearing loose-fitting clothing. Following standard protocol, three dry gel electrode pads will be applied to the anterior abdomen halfway between the umbilicus and xiphoid process, and 5 cm below the costal border at the midclavicular line on both left and right sides. A respiratory sensor belt will be placed across the upper chest to distinguish respirations from bowel activity (Figure 1). Initial equipment and calibration testing will be conducted over a 3–5 min period of time after which the subject remained quietly in the same position for a baseline study, lasting 10 min. At the end of the 10 min baseline period, the subject will begin a standardized water load stimulation. The purpose of the WLST will be to cause gastric distention with activation of the gastric pacemaker and subsequent activation of small bowel contractility. This is considered an essential part of any gastrointestinal motility study. The WLST will consist of drinking room-temperature water until the subject indicated that they felt completely full. The WLST usually takes approximately 2 to 5 min, with the subject typically ingesting between 300 to 1000ml of fluid. The amount ingested will be recorded. The ingestion of the fluid will take place in the same position as during the baseline and for the remainder of the study. After the WLST, the subject remains motionless, in a reclining position for a 30-minute period of time at which point the study is completed. Results will then immediately be available. The standardized EVGs will be recorded using an FDA-cleared hand-held EVG device and respiratory belt to distinguish respirations from bowel contractions. Three silver chloride electrodes will be positioned on the abdomen. EVGSAS custom software version 2.09i (3CPM Company, Sparks Glencoe, MD, USA) will be used to perform recording and data analysis of measurements of filtered percent distribution of power at 15–20, 20– 30, 30–40, 40–50, and 50–60 cpm ranges during baseline recording and 10, 20, and 30 min after water load. These are the GIMA biomarker frequency ranges specific to endometriosis. Additionally, a running spectral analysis (RSA) will be created, stratifying frequency over time and AUC measurements at specified frequency ranges to provide visual recognition of disease-state GIMA biomarker abnormal frequencies versus normal range values. The RSA is a visual representation of biomarker activity over time and provides a visual diagnosis of disease. However, for more precise statistical analysis, it is the AUC that is used. The percentage frequency distribution of power of the AUC will be used to determine sensitivity, specificity, positive and negative predictive values as well as the diagnostic predictability.

5.3 Pain/Discomfort Score

Pain will be calculated using a EHP 30 questionnaire a standardized pain questionnaire. Participants will use a 30-point rating scale for categorising the pain associated with menstruation, urination, sexual intercourse, defecation, and otherwise general levels of abdominal and pelvic pain. The calculated score will be the highest single score of reported items.

5.4 Statistical Methods

To compare baseline characteristics among the three cohorts, the appropriate statistical tests will be selected based on the type and distribution of the data*: for normally distributed data*, **One- way analysis of variance (ANOVA**)will be used to compare means across the cohorts. If significant differences are observed, post-hoc analysis, such as Tukey's test will be performed to identify pairwise differences. For non- normally distributed data, the **Kruskal-Wallis test**, a non parametric alternative to ANOVA, will be applied. If significant differences are found, pairwise comparisons with appropriate adjustments (e.g., Bonferroni correction will be conducted. For categorical variables, the **Chi square test** will be employed to compare proportions among the cohorts. In cases where expected are less than five, the **Fisher's Exact test** will be used as an alternative. The normality of continuous variables will be checked by Shapiro- Wilk test, and homogeneity of variances will be evaluated using Levene's test before applying ANOVA. Descriptive statistics, including means and standard deviation or medians and interquartile ranges, will be used to summarize continuous variables, while frequencies and percentages will be reported for categorical variables.

To evaluate the optimal cut- offs sensitivity, specificity, positive predictive value (PPV), Negative predictive value (NPV), and overall diagnostic predictability among the three cohorts, the following statistical methods will be employed. **Receiver Operating Characteristics (ROC)Curve Analysis** will be conducted to determine the optimal cut-off points for diagnostic variables. The **Youden Index** (Sensitivity+ Specificity – 1) will be used to identify the threshold that maximizes diagnostic performance. The diagnostic performance of the test will be summarized using the **area under the ROC curve (AUC).** The AUC provides a measure of the test's ability to distinguish between conditions across all possible thresholds. Additional metrics, such as **Likelihood Ratios** (positive and negative) and the **Diagnostic Odds Ratio** (DOR), will also be reported. ROC Curve will be compared between the cohorts using **DeLong's Test** to evaluate the statistical significance of difference in AUCs. Subgroup analysis will be performed to assess sensitivity, specificity, PPV, NPV and diagnostic accuracy within each cohort.

Any patients who are suspected to have endometriosis surgically but did not have a histological confirmation, will still remain part of the group and we will analyse them separately.

6 STUDY SETTING

The study will be conducted in Worcestershire Acute Hospital NHS Trust. This is one of the largest trusts operating in West Midlands and is a tertiary referral centre for endometriosis.

There is a dedicated endometriosis clinic where patients are referred from across the West Midlands UK. This is supported by an Endometriosis Lead Consultant, nurses and endometriosis special interest registrars

7 SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

Patient groups

1. Pelvic pain patients undergoing first diagnostic laparoscopy- It is anticipated that this will be our diseased group – patients with suspected disease based on symptoms or imaging (pelvic USS or MRI or both) that need and want diagnostic confirmation and subsequent surgical treatment if disease identified. Any patients who are suspected to have endometriosis surgically but did not have a histological confirmation, will still remain part of the group and we will analyse them separately.

2. Surgical control group – patients undergoing elective gynaecology laparoscopic surgery for benign conditions
    a. Laparoscopic sterilisation
    b. Laparoscopic cystectomy for non endometriotic cyst
    c. Laparoscopy for fertility patients
    d. Laparoscopy for preventative BRCA salpingectomy +/- oophorectomy

3. Non-surgical control group – Healthy women with no pain aged 18-50

7.1.1 Inclusion & Exclusion criteria

	Group 1 (undergoing first laparoscopy for pelvic pain)	Group 2 (surgical control group)	Group 3 (non-surgical control group)
Inclusion criteria	Female patients listed for primary laparoscopy for pelvic pain Ages 18 – 50 years Acceptable to patient to omit - opioid medication (eg. Codeine, Morphine, etc) 7 days before test - prokinetic or antispasmodic medication (eg. Erythromycin, Domperidone etc) 3 days before test	Female patients listed for elective gynaecology laparoscopic surgery Ages 18 – 50 years Acceptable to patient to omit - opioid medication (eg. Codeine, Morphine, etc) 7 days before test - prokinetic or antispasmodic medication (eg. Erythromycin, Domperidone, etc) 3 days before test	Healthy women with no pelvic pain Ages 18 – 50 years Acceptable to patient to omit - opioid medication (eg. Codeine, Morphine, etc) 7 days before test - prokinetic or antispasmodic medication (eg. Erythromycin, Domperidone, etc) 3 days before test

Exclusion criteria	Ages < 18 and > 50 years Known malignant disease Previous surgical treatment of endometriosis Confirmed menopause BMI > 35	Ages < 18 and > 50 years Known malignant disease Known surgical diagnosis and/or surgical treatment of endometriosis Confirmed menopause BMI >35	Ages < 18 and > 50 years Known malignant disease Known surgical diagnosis and/or surgical treatment of endometriosis Known pelvic pain Confirmed menopause BMI >35

7.2 Sampling

7.2.1 Size of sample

This is a pilot study being conducted so that larger studies can be built on it in future. The sample size was calculated on the basis of IBM SPSS version 29. With the power 90%, confidence interval 95% and effect size 90% the sample size is of 26 patients in each group.

7.2.2 Sampling technique

Patient groups

1. Pelvic pain patients undergoing first diagnostic laparoscopy
   It is anticipated that this will be our diseased group – patients with suspected disease based on symptoms or imaging (pelvic USS or MRI or both) that need and want diagnostic confirmation and subsequent surgical treatment if disease identified.

2. Surgical control group – patients undergoing elective gynaecology laparoscopic surgery for benign conditions:
   a. Laparoscopic sterilisation
   b. Laparoscopic cystectomy for non endometriotic cyst
   c. Laparoscopy for fertility patients
   d. Laparoscopy for preventative BRCA salpingectomy +/- oophorectomy

   It is anticipated that majority of these patients will not have endometriosis and so will form our surgical control group.

3. Non-surgical control group – Healthy women with no pain aged 18-50.
   As these participants have no pain, an assumption is made that they do not have endometriosis. There is no need for medical or surgical treatment. The exclusion of endometriosis is clinical (the absence of pelvic pain from history and examination, and reflected in the EHP-30 questionnaire results) and not surgical. Therefore, these participants will form our non-surgical control group.

7.3 Recruitment

Recruitment pools

1. Gynaecology clinic
    - Participants will be identified in clinic – this can be performed by any member of the gynaecology team.
    - Posters will be put up in gynaecology clinic waiting room and all gynaecology consultation rooms with contact details of research team.
    - Education of all gynaecology consultants via presentation in gynaecology governance teams meeting re: selection process if listing for benign surgery and study captured images / video recording required (to diagnose and qualify severity of endometriosis using #ENZIAN classification).
    - Education of all gynaecology trainees that attend outpatient clinics, with presentation at teaching and poster in doctor's office of participant inclusion criteria.
    - There will be a secure MS Teams research chat for gynaecology consultants and trainees to add potential participant details so the research team can review patient electronic notes and contact.
    - Patient study information leaflet and FAQ factsheet available within gynaecology clinic to give to potential participants prior to contact by research team.

2. Theatre waiting lists
    - Weekly review of add to theatre waiting list forms to screen for potential participants and contact. This will be conducted by one of the core research team and responsibility will be planned in advance and shared.

3. Self-referral for healthy women with no pain
    - Advertisement via Trust Intranet "The Source" and Trust social media for healthy female volunteers with no pelvic pain between ages of 18 and 50 years inclusive.

Patients identified will be called by one of the core research team and invited to a face to face consultation to ask questions and sign consent form, after they have had adequate time to consider the study information and FAQ factsheet (given to them in clinic or sent by post).

The participants will not be paid any expenses for travel and participation.

7.3.2 Consent

Patients will have a discussion about the trial by the research team, when they attend the clinic. Any potential participants will have the opportunity to discuss this further with the endometriosis nurse specialist and they will be provided with a patient information leaflet. A pro forma has been designed to gain informed consent from the patient and one member of trial team will go through this with patient in detail.

8 ETHICAL AND REGULATORY CONSIDERATION

8.1 Research Ethics Committee (REC) and other Regulatory review & reports

Before the start of the study, a favourable opinion will be sought from a Regional Ethical Committee.

Regulatory Review & Compliance

Before any patient enrolment into the study, the Chief Investigator or designee will ensure that appropriate approvals are in place.

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with the R&I department as well as the study delivery team so they can put the necessary arrangements in place to implement the amendment.

Amendments

If the Sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the Sponsor will submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment within 35 days of receipt of the notice. The sponsor will determine whether an amendment is substantial or non-substantial for the purposes of submission to the REC.

If applicable, other specialist review bodies (e.g. Confidentiality Advisory Group (CAG)) will be notified about substantial amendments in case the amendment affects their opinion of the study.

The Chief investigator will be responsible for the decision to amend the protocol and deciding whether an amendment is substantial or non-substantial. The substantive changes will be communicated to relevant stakeholders e.g. REC, R&D and other regulatory agencies through email.

Amendment history will be tracked and the any amendments will be notified on the front page of the document.

8.3 Peer review

The protocol has been sent to two independent peer reviewers, who have provided feedback. These peer reviewers will not be involved in study in any way.

8.4 Patient & Public Involvement

Endometriosis patient support groups are held four times a year at Worcestershire Royal Hospital. This research was discussed in a support group at the end of 2023 followed by a specific focus group. The final version of the patient information leaflet was devised after these two meetings. Meetings were led by Joanna Street (Endometriosis Specialist Nurse) and facilitated by the Miss Donna Ghosh, Miss Sabrina Butt and Miss Jyoti Sharma.

8.5 Protocol compliance

- Any protocol deviations will be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

- Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

8.6 Data protection and patient confidentiality

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 2018. All the participants will be pseudonymised. The Case Report Form (CRF) will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one-way encryption method).
Information about the trial in the participant's medical records will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

8.7 Indemnity

Insurance and indemnity for participants and staff is covered within the NHS Indemnity Arrangements in the NHS. Device manufacturers will not take on any indemnity.

8.8 Access to the final study dataset

- All the co-investigators will have access to the full dataset.
- Dataset can be used for secondary analysis and will be undertaken with the consent of the participants. All patient documentation will reflect the future use of these data in research.

9 DISSEMINIATION POLICY

9.1 Dissemination policy

The data will be owned by The Worcestershire Endometriosis Research Group, who will analyse the data and prepare the final report. The full study report will be published in scientific journals. The study report will also acknowledge any sponsors.

All the participants will also receive summary of the study findings through a letter sent by post. Any published material will be completely anonymized.

9.2 Authorship eligibility guidelines and any intended use of professional writers

The criteria defined by The International Committee of Medical Journal Editors will defined authorship criteria for the researchers.

10 REFERENCES

1. ESHRE GUIDELINE ENDOMETRIOSIS 2022. *Human Reproduction Open*, Volume 2022, Issue 2, 2022, hoac009, https://doi.org/10.1093/hropen/hoac009
2. Gupta D, Hull ML, Fraser I, Miller L, Bossuyt PMM, Johnson N, Nisenblat V. Endometrial biomarkers for the non-invasive diagnosis of endometriosis. Cochrane Database of Systematic Reviews 2016, Issue 4. Art. No.: CD012165. DOI: 10.1002/14651858.CD012165.
3. Nisenblat V, Prentice L, Bossuyt PMM, Farquhar C, Hull ML, Johnson N. Combination of the non-invasive tests for the diagnosis of endometriosis. Cochrane Database of Systematic Reviews 2016, Issue 7. Art. No.: CD012281. DOI: 10.1002/14651858.CD012281.
4. Nisenblat V, Bossuyt PMM, Farquhar C, Johnson N, Hull ML. Imaging modalities for the non-invasive diagnosis of endometriosis. Cochrane Database of Systematic Reviews 2016, Issue 2. Art. No.: CD009591. DOI: 10.1002/14651858.CD009591.pub2.
5. Nisenblat V, Bossuyt PMM, Shaikh R, Farquhar C, Jordan V, Scheffers CS, Mol BWJ, Johnson N, Hull ML. Blood biomarkers for the non-invasive diagnosis of endometriosis. Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD012179. DOI: 10.1002/14651858.CD012179.
6. Liu E, Nisenblat V, Farquhar C, Fraser I, Bossuyt PMM, Johnson N, Hull ML. Urinary biomarkers for the non-invasive diagnosis of endometriosis. Cochrane Database of Systematic Reviews 2015, Issue 12. Art. No.: CD012019. DOI: 10.1002/14651858.CD012019.
7. https://www.endosure.com/
8. Mathias JR, Franklin R, Quast DC, Fraga N, Loftin CA, Yates L, Harrison V. Relation of endometriosis and neuromuscular disease of the gastrointestinal tract: new insights. Fertil Steril. 1998 Jul;70(1):81-8.
9. Noar M. AI-derived threshold score of intraabdominal myoelectrical activity predicts presence and stage of endometriosis with 100% accuracy. J Minim Invasive Gynecol. 2022 Nov;29(11):S4-S5. DOI:https://doi.org/10.1016/j.jmig.2022.09.026.
10. Keckstein J, Saridogan E, Ulrich U A, et al. The #Enzian classification: A comprehensive non-invasive and surgical description system for endometriosis. Acta Obstet Gynecol Scand. 2021;100:1165–1175. https://doi.org/10.1111/ aogs.14099

11. APPENDICIES

11.1 Appendix 1- Required documentation

Updated CV and Good Clinical Practice (GCP) training certificate for all the researchers will be recorded.

11.2 Appendix 3 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made