PROTOCOL

Developing and evaluating a screening tool to improve pre-operative prediction of absence of endometriosis in people with pelvic pain

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Authors:
Dr Charlotte Reddington, Dr Samantha Mooney, Dr Uri Dior, Dr Keryn Harlow, Dr Lauren Hicks, Dr Claudia Cheng, Dr Lenore Ellett, Dr Emma Readman, Dr Michal Amir, A/Prof Jim Tsaltas, Melissa Parker, Roshan Karri, Dr Jane Girling, Dr Sarah Holdsworth-Carson, Prof Peter Rogers, A/Prof Martin Healey

Sponsor/s:
The Royal Women's Hospital

CONFIDENTIAL

Statement of Compliance

This document is a protocol for a research project. This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

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STUDY SYNOPSIS

Title:	Developing and evaluating a screening tool to improve pre-operative prediction of absence of endometriosis in people with pelvic pain
Short Title:	Predicting absence of endometriosis
Design:	Multicentre prospective cohort study
Study Centres:	• Endosurgery Units A & B, The Mercy Hospital for Women • Gynaecology Units 1 & 2, The Royal Women's Hospital • The Endometriosis Centre, Hadassah-Hebrew University Medical Centre, Israel • Private Practices in metropolitan Melbourne
Hospitals:	• Mercy Hospital for Women, Heidelberg, Victoria • The Royal Women's Hospital, Parkville, Victoria • Hadassah-Hebrew University Medical Centre, Jerusalem, Israel • Epworth Hospitals, East Melbourne & Richmond, Victoria • Ramsay Health, Frances Perry House, Parkville, Victoria • Warringal Private Hospital, Heidelberg, Victoria • Western Health, St Albans, Victoria • St Vincent's Private, Fitzroy, Victoria • Holmesglen Private, Moorabbin, Victoria • Cabrini, Malvern, Victoria
Study Question:	Can we improve prediction of absence of endometriosis in people with pelvic pain and a negative pelvic ultrasound who are planned for a laparoscopy?
Study Objectives:	To develop and evaluate a screening tool/s to predict absence of endometriosis in women with pelvic pain.
Inclusion Criteria:	• Women aged 18 – 45 years • Planned laparoscopy for investigation and/or management of pelvic pain • Pre-operative pelvic ultrasound with no evidence of endometrioma/s and/or deep infiltrating endometriosis
Exclusion Criteria:	• Unable to give consent • Previous participation in the same study • Post-menopausal
Number of Planned Subjects:	333 for "model training" sample set + 333 for "validation" set Total = 666
Statistical Methods:	Logistic regression models and machine learning algorithms will be developed using variables of interest from the "model training" sample set. The 'tool/s' developed will be prospectively applied to the independent validation set to reassess sensitivity, specificity, positive predictive value and negative predictive value.
Subgroups:	Algorithms/tools will be developed and validated for - The entire cohort - Those with a negative specialist quality ultrasound - Those with a negative community quality ultrasound

1. GLOSSARY OF ABBREVIATIONS & TERMS

Abbreviation	Description (using lay language)
USS	Ultrasound scan
rASRM	The revised American Society for Reproductive Medicine classification of endometriosis
DIE	Deep infiltrating endometriosis (infiltrating deeper than 5mm under the peritoneum)
COGU	Certificate in Obstetric and Gynaecological Ultrasound (a sub-specialty qualification obtained by a certified Gynaecologist)
RANZCOG/AGES surgical level	The Royal Australian and New Zealand College of Obstetricians and Gynaecologists and the Australasian Gynaecological Endoscopy and Surgery Society agreed level of laparoscopic surgical expertise
AGD	Anogential Distance (the distance between the vagina and the anus). *Refer to diagram in Section 5 c.*
AGD AC (or AGD anterior)	AGD from anterior clitoral surface to the anus
AGD AF (or AGD posterior)	AGD from posterior fourchette (base of the vaginal entrance) to the anus

2. STUDY SITES

a. STUDY LOCATIONS

Site	Address	Contact Person	Phone	Email
Mercy Hospital for Women (MHW)	163 Studley Rd, Heidelberg, VIC 3084, Australia	Charlotte Reddington	+61 413296553	c.reddington@gmail.com
The Royal Women's Hospital (RWH)	20 Flemington Rd, Parkville,	Charlotte Reddington	+61 413296553	c.reddington@gmail.com

	VIC 3052, Australia			
Epworth Freemasons	320 Victoria Pde, East Melbourne, VIC 3002, Australia	Jim Tsaltas	+613 9416 1172	jtsaltas@icloud.com
Hadassah-Hebrew University Medical Centre	Hadassah Ein-Kerem. POB 12000. Jerusalem 91200. Israel	Uri Dior	+972 50-517-2642	uri.dior@gmail.com
Frances Perry House	20 Flemington Rd, Parkville, VIC 3052, Australia	Charlotte Reddington	+61 413296553	c.reddington@gmail.com
Epworth Richmond	89 Bridge Rd, Richmond, VIC 3121, Australia	Martin Healey	+61 488334519	kathandmutt@bigpond.com
Warringal Private Hospital	216 Burgundy St, Heidelberg, VIC 3084 Australia	Lenore Ellett	+61 401360974	lenore@crosbie.com.au
Western Health (Joan Kirner)	176 Furlong Rd, St Albans, VIC 3021 Australia	Samantha Mooney	+61 402923861	samantha.mooney39@gmail.com
St Vincent's Private Hospital	41 Victoria Pde, Fitzroy, VIC 3065 Australia	Emma Readman	+61 438788854	ereadman@melbpc.org.au
Holmesglen Private	490 South Rd, Moorabbin VIC 3189 Australia	Michal Amir	+61 403274870	Dr.amirmichal@gmail.com
Cabrini Malvern	181-183 Wattletree Rd, Malvern VIC 3144 Australia	Michal Amir	+61 403274870	Dr.amirmichal@gmail.com
Northpark Private Hospital	135 Plenty Rd, Bundoora VIC 3083 Australia	Caroline Hoggenmueller	+61 410861434	caroline.hoggenmueller@gmail.com
Peninsula Private Hospital	525 McClelland Dr, Frankston VIC 3199 Australia	Brett Marshall	+61 397766411	Brett.Marshall@thewomens.org.au

Beleura Private Hospital	925 Nepean Hwy, Mornington VIC 3931 Australia	Brett Marshall	+61 397766411	Brett.Marshall@thewomens.org.au

3. INTRODUCTION/BACKGROUND INFORMATION

a. LAY SUMMARY

Pelvic pain is a very common issue. Endometriosis is a common cause of pelvic pain but currently, in most cases, in order to diagnose endometriosis a person needs to have a laparoscopy (key-hole surgery). While ultrasound can usually pick up endometriosis cysts on ovaries (endometriomas) and larger areas of deep endometriosis, it cannot see superficial (surface) endometriosis which is the most common type. When laparoscopies are undertaken to look for endometriosis in people with pelvic pain, approximately one third will not have endometriosis. That means one third of people having a laparoscopy for this reason will have put themselves through surgery without the possible benefits.

We plan to make an 'endometriosis calculator' that uses questions about a person's symptoms and medical history and their anogenital distance (AGD – the distance from the vagina to the anus which is associated with chance of endometriosis), to give them a better idea about their chance of having endometriosis before they have an operation. This could hopefully be used as a tool that women could use to help decide if they want to go on and have a laparoscopy or not. It might result in fewer women having unnecessary surgery and getting more appropriate treatment for their pain instead.

In this study we will look at people already planning to have a laparoscopy for investigation of their pelvic pain. We will ask them to fill in a questionnaire about their symptoms and medical history before their operation and then we will check if they had endometriosis at surgery or not. We will also measure their anogenital distance while they are asleep under the anaesthetic for their surgery. We will use this information to develop a questionnaire that can predict if a person is less likely to have endometriosis.

b. BACKGROUND INFORMATION

This study is one of nine projects being run as part of a program of endometriosis research recently funded by MRFF (MRF9911715 'Improving diagnosis and treatment of endometriosis' $3.94 million over 5 years). The program is being run through the University of Melbourne Department of Obstetrics and Gynaecology and contains a mixture of clinical trials and laboratory-based studies. Subjects will be recruited for the research program from the Departments' teaching hospitals (primary sites are RWH and Mercy) as well as from listed hospitals where clinicians who are part of each project undertake public and private sessions.

Core datasets for all subjects will be collected using the National Endometriosis Clinical and Scientific Trials (NECST) Network Registry. The NECST Registry is a MRFF funded initiative to create a nationally co-ordinated database containing securely held patient details, clinical history, diagnostic results, treatment details and health outcomes, for patients who have given informed consent for their details to be included, to support research into endometriosis. This national database will underpin a comprehensive national program of clinical, basic science and translational research relevant to the needs of Australians with endometriosis, consistent with the research objectives in the National Action Plan for Endometriosis. The NECST Registry is currently in final stages of developmental testing and has conditional HREC approval from Monash Health (Study Title: Establishment of the National Endometriosis Clinical and Scientific Trials (NECST) Network Registry. ERM Reference Number: 62508. Monash Health Reference: RES-20-0000-258A). The project was reviewed by the Monash Health Human Research Ethics Committee at its meeting on 07 May 2020 and was approved subject to conditions. The responses are to be reviewed outside of the Committee by the Medical Administrator and Research Support Services staff. We will not commence recruitment for our program of research until the Monash HREC approval for NECST is finalised and Site Specific Approvals have been obtained from our participating hospitals

Subjects recruited to projects in our program will need to be consented for both NECST and the specific project(s) they are taking part in. We are not seeking HREC approval for patients to enter data into NECST as that will fall under the Monash approval. However, as part of the current HREC application we require approval to access the relevant core data for each of our subjects collected in NECST for our research program. This will allow us to use NECST as a facility to collect core data that supports our program as well as contributes to growing the National Endometriosis Registry.

In addition to the NECST core dataset, we will collect project-specific data for each of our projects. Project-specific data may be relevant to 1 or more of our projects. To assist evaluation of our projects by the Austin HREC, we have compiled a full list of all the NECST and project specific questions that we will use, accompanied by a 'road map' indicating which questions this project (and all of our other projects) will ask of its participants. Participants will only complete questions for the project(s) that they have consented to participate in.

Pelvic pain including dysmenorrhoea is a common health issue with significant personal and socio-economic burden [1]. Endometriosis is an important and common cause for pelvic pain [2] for which laparoscopy provides definitive diagnosis and often symptom relief [3, 4]. There are however many people with pelvic pain who do not have endometriosis [5] in whom laparoscopy poses potential risks and costs without the same possibility for symptom benefit. Long-term data from the Gynaecology Unit 2 (Pelvic Pain and Endometriosis Unit) at the Royal Women's Hospital shows that endometriosis is absent in approximately 30% of people who have a laparoscopy for investigation and/or management of pelvic pain.

Community ultrasound provides accurate pre-operative diagnosis of endometriomas [6] and increasingly specialist ultrasound can diagnose deeply infiltrating endometriosis [7]. However, ultrasound is not currently able to distinguish absence of endometriosis from superficial disease. In addition, the accuracy of ultrasound is operator dependent and access to specialist quality ultrasound is not universally available. Other studies have tried to ascertain risk factors on history and demographic information and to develop tools to predict endometriosis. As yet, there are no validated, symptom-based, patient-reported questionnaires for endometriosis screening [8].

The anogenital distance (AGD) has been shown to be linked to oestrogen exposure [9,10,11]. There is growing evidence that a shorter AGD is associated with an increased risk of endometriosis [12,13], an oestrogen-dependent disease. The AGD can be measured as part of a non-invasive gynaecological examination. A recent prospective study has shown surgically and histologically proven endometriosis is associated with a shorter AGD [14]. The association was not correlated to severity or location of disease, suggesting that AGD may be a useful non-invasive clinical marker for women with endometriosis which cannot be detected with ultrasound or clinical examination. Combined with patient reported symptom and demographic variables, the AGD may further improve pre-operative prediction of presence or absence of endometriosis.

Laparoscopy remains the gold standard diagnostic test for endometriosis [15] and is required for diagnosis of superficial endometriosis. Ideally, a non-invasive screening tool would exist to provide people with a preoperative likelihood of endometriosis being present or absent. This would serve to reduce the number of diagnostic laparoscopies and their associated risks and costs in people without endometriosis. Additionally, increased suspicion of the presence of endometriosis without the need for laparoscopy may reduce time to diagnosis and accessing effective treatment, which may or may not include surgical management.

Developing and evaluating a non-invasive screening tool to improve prediction of absence of endometriosis that applies to all women with pelvic pain is difficult as in order to definitively exclude endometriosis a laparoscopy must be performed. Although investigating only people who are planned to undergo laparoscopy for pelvic pain creates a selection bias, it does provide a group in which presence or absence of endometriosis can be confirmed. It also targets people who have the most to gain from knowledge that endometriosis is absent – those who would otherwise have surgery.

Developing a non-invasive screening tool aims to reduce the risks and burdens of surgery in women who are less likely to have endometriosis by avoiding a laparoscopy, which will result in a more appropriate medical approach to manage their pain. It may also reduce the total number of laparoscopies performed in this group of women resulting in significant health economic benefit. In women who still pursue laparoscopy it may provide more adequate pre-operative consent and expectation setting regarding the likelihood of diagnosing endometriosis.

4. STUDY OBJECTIVES

a. HYPOTHESIS

It will be possible to develop a clinically useful non-invasive screening tool to determine the preoperative likelihood of endometriosis being present or absent.

b. STUDY AIMS

- To develop and validate non-invasive screening tool/s to predict absence of endometriosis in women planned for laparoscopy for investigation and/or management of pelvic pain with a negative pre-operative pelvic ultrasound.

- To develop and validate non-invasive screening tool/s to predict absence of endometriosis in women planned for laparoscopy for investigation and/or management of pelvic pain with a negative *specialist quality* pre-operative pelvic ultrasound.

- To develop and validate non-invasive screening tool/s to predict absence of endometriosis in women planned for laparoscopy for investigation and/or management of pelvic pain with a negative *community quality* pre-operative pelvic ultrasound.

c. OUTCOME MEASURES

Using laparoscopic diagnosis of presence and absence of endometriosis (where possible confirmed with histological confirmation) as the 'gold standard' (see table in study methodology below) we will report for the developed screening tool/s:

- Sensitivity
- Specificity
- Positive Predictive Value (PPV)
- Negative Predictive Value (NPV)
- Area Under the Receiver Operating Characteristic (ROC) Curve

5. Study Design

a. Study Type & Design & Schedule

Study type
International multi-centre prospective cohort study

Study Table

	Assessment/Procedure	Recruitment/ Pre-operative	Day of Surgery	Post-operative	
	Informed Consent	**x**			
	Pre-operative Participant Questionnaire filled	**x**			
	Measurement of AGD (under anaesthetic)		**x**		
	Laparoscopy		**x**		
	Surgeon Report filled		**x**		
	Histology results obtained			**x**	

b. Standard Care and Additional to Standard Care Procedures

Standard Care Procedures		
Procedure	**Time/Visit**	
Pelvic Ultrasound	Prior to consultation	
Consultation to book laparoscopy	Prior to recruitment	
Laparoscopy +/- treatment of endometriosis if present	As planned by treating gynaecologist	

Additional To Standard Care		
Procedure	**Time/Visit**	
Questionnaire	At recruitment/pre-operative	
Measurement of AGD	At start of operation	
Operation questionnaire for surgeon	At operation	
Obtain histology report (if biopsy taken)	When available after operation	

c. Study Methodology

Upon consenting, participants will complete the study questionnaire pre-operatively. The study questionnaire will be available electronically and in hard copy form if requested.

The study specific questions for this project in the pre-operative questionnaire have been purpose-built, encompassing a large number of variables that are potentially

associated with presence and/or absence of endometriosis. Our analysis will involve developing tools using subsets of variables from the larger study questionnaire and the AGD measurements. The study specific questions have been developed by the research team, informed by the following:

1. Pilot study conducted with secondary analysis of prospectively collected data from 7 cohort studies including 1548 women undergoing laparoscopy for pelvic pain. Significant variables were identified from 518 different pre-operative demographic and symptomatology variables collected across the 7 studies. Logistic regression and machine learning algorithms were generated, including
    a. 25 variable machine learning algorithm: a 'Scikit-learn' machine learning library with an 'ensemble' model yielded the best results, with a Support Vector Machine, Random Forest and Logistic Regression classifiers consolidated using a 'majority vote' method.
        i. In those predicted to have a negative community quality USS: sensitivity 0.91, specificity 0.28, NPV 0.64, Accuracy 0.65
        ii. In those predicted to have a negative specialist quality USS: sensitivity 0.88, specificity 0.42, NPV 0.70, Accuracy 0.64
    b. 10 variable logistic regression model
        i. In those predicted to have a negative community quality USS: sensitivity 0.83, specificity 0.49, PPV 0.71, NPV 0.67
        ii. In those predicted to have a negative specialist quality USS: sensitivity 0.74, specificity 0.42, PPV 0.73, NPV 0.64

    Variables from these models and other analyses are included in our questionnaire
2. Survey of subject matter experts comprising consultant gynaecologists working in the Endosurgery A Unit at the Mercy Hospital for Women and Gynaecology Unit 2 at the Royal Women's Hospital (both are Pelvic Pain and Endometriosis Gynaecology Units) and an expert nurse/researcher from the Canberra Endometriosis Centre. The survey asked subject matter experts to identify factors on history or demographics that would make that expert think a patient did or did not have endometriosis if findings from ultrasound and clinical examination were not available. The results were collated and variables of interest added to the questionnaire.
3. Comprehensive literature review conducted using the PubMed-NCBI database. The following terms were searched "epidemiology endometriosis", "risk factors endometriosis", "prediction endometriosis". No time limits were placed on the searches. Only studies in the English language were reviewed. References of selected studies were also examined for additional relevant literature not found by the initial database searches. A summary of variables with possible associations with presence or absence of endometriosis was formulated and assessed by a panel of subject matter experts for inclusion in the questionnaire.

Measurement and recording of AGD

AGD will be measured after the participant is anesthetised, and before the beginning of surgery by a member of the gynaecology treating team as an additional part of the usual process of examination under anaesthesia prior to gynaecological surgery.

Participants will be positioned on the operating table in the lithotomy position, with thighs at a 45 degree angle to the examination table and the end of the table removed.

Two measurements will be taken using a disposable paper ruler with millimetre accuracy.

- From the anterior clitoral surface (the anterior aspect of the clitoral hood, at the anterior part of the fusion of the labia minora) to the anterior edge of the anus (AGD-AC)
- From the posterior fourchette to the anterior edge of the anus (AGD-AF)

Measurements will be assisted by a diagram illustrating measurement points below [14]. This will be provided to clinicians performing the measurement to allow for uniform collection of measurements.

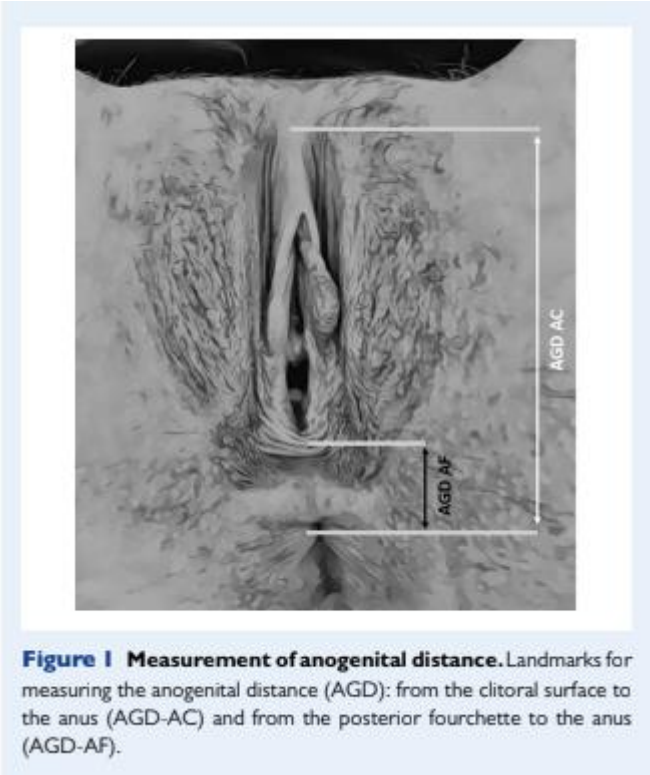


Figure 1 Measurement of anogenital distance. Landmarks for measuring the anogenital distance (AGD): from the clitoral surface to the anus (AGD-AC) and from the posterior fourchette to the anus (AGD-AF).

The measurement will be recorded in the research operation report form.
The measurement of AGD is expected to take approximately 1 minute.

Surgery will then take place as per the patient's needs and the surgeon's usual practice. If endometriosis or possible endometriosis is visualised it will be excised or biopsied and sent for histopathology as long as the surgeon deems it safe and appropriate to do so. Method of treatment of endometriosis following biopsy will be at the discretion of the treating surgeon (eg by ablation or excision) with documentation of treatment method and any residual disease. Surgery and post-operative care will be unaffected by participation in the study. The RANZCOG/AGES level of the surgeon(s) and their years of experience will be documented.

Surgeons will complete a dedicated operation report on surgical findings immediately after surgery including the following:

- Presence/absence of visual endometriosis
- Presence/absence of visual superficial endometriosis
- Presence/absence of visual deeply infiltrating endometriosis
- Location of endometriosis (superficial and deep)
- Presence/absence of adhesions and their locations
- Presence/absence of ovarian cysts, their type and size
- The revised American Society for Reproductive Medicine classification of endometriosis (rASRM) score and stage

The pre-operative USS report will be reviewed and will be classified as either specialist quality USS (performed and/or reported by a known expert at scanning DIE) or community quality USS. The list of specialist quality expert DIE scanners will be developed and periodically reviewed and updated by the clinicians involved in the study. Review of this list will take place every 6 months and will also receive input from members of the specialist quality USS craft group. COGU or equivalent training is not sufficient alone to be classified as specialist quality endometriosis scanner.

The results of the histopathology will be recorded once results are available.
The following table shows how endometriosis will be diagnosed. Cases of inconclusive diagnosis will be excluded from the final analysis. Data pertaining to inconclusive (and thus excluded) cases will be kept for further analysis to see if altered definitions of positive/negative endometriosis would affect study results. Deeply infiltrating endometriosis is defined as endometriosis infiltrating deeper than 5mm under the peritoneum.

VISUAL APPEARANCE	HISTOPATHOLOGY	ENDOMETRIOSIS DIAGNOSIS	INCLUDED/EXCLUDED for final analysis
Positive	Positive	Positive	Included
Positive	Negative	Negative	Included
Positive	Not taken (eg superficial ovarian endometriosis, not appropriate to biopsy OR severe disease not treated at that surgery)	Positive	Included
Positive	Inconclusive	Inconclusive	Excluded
Unsure/possible	Positive	Positive	Included
Unsure/possible	Negative	Negative	Included
Unsure/possible	Not taken (eg ? superficial ovarian endometriosis, not	Inconclusive	Excluded

	appropriate to biopsy)		
Unsure/possible	Inconclusive	Inconclusive	Excluded
Negative	Positive (eg sample still taken for other research study)	Inconclusive	Excluded
Negative	Negative (eg sample still taken for other research study)	Negative	Included
Negative	Not taken	Negative	Included
Negative	Inconclusive (eg sample still taken for other research study)	Inconclusive	Excluded

Data will be entered into a central database (REDcap) shared across sites from which analysis will take place.

Study Timeframe

Allowing for average surgical volumes of laparoscopy for pelvic pain with negative pelvic ultrasounds and accounting for a 30% non-participation rate in eligible participants each site predicts they can aim to recruit

- Mercy Hospital for Women: 60 participants/year
- Royal Women's Hospital Gynaecology Unit 2: 90 participants/year
- Hadassah-Hebrew University Medical Centre: 30 participants/year
- Private Practices in metropolitan Melbourne: 30 participants/year
- TOTAL = approximately 210 participants/year

Recruitment should therefore take approximately 3.5 years.

6. STUDY POPULATION

a. RECRUITMENT PROCEDURE

As this clinical trial is part of a suite of projects under the umbrella of 'Improving diagnosis and treatment of endometriosis', resources for recruitment will be streamlined together. Eligible participants will be identified to be approached and recruited in a number of ways (Figure 1). Advertising poster, flyer and booklet describing all nine projects (of which this clinical trial is one) will be available in waiting rooms of participating hospital clinics and private gynaecologists' rooms. A website will also be set up through Jean Hailes for Women's Health, a national not-for-profit organisation dedicated to improving women's health.

Participants may be approached to be recruited by a gynaecologist, gynaecology trainee/resident or appointed research nurse/assistant associated with the participating unit. Eligible participants could be approached in the gynaecology outpatient clinic; surgical preadmission clinic; preoperatively on the day of surgery or preoperatively over the phone; over the phone after suitable participants are identified via medical records or if patients have provided their details on the flyer to be contacted.

b. INCLUSION CRITERIA

- Women aged 18 – 45 planned to undergo laparoscopy for investigation and/or management of pelvic pain
- Pelvic ultrasound performed within 12 months of recruitment with no evidence of endometrioma/s and/or deep infiltrating endometriosis
    - Both specialist quality and community quality ultrasound included
- Women with a previous laparoscopy for investigation of pelvic pain and women with a previous diagnosis of endometriosis remain eligible
- Women with both current and previous hormone use remain eligible

c. EXCLUSION CRITERIA

- Unable to provide consent
- Previous participation in the same study
- Post-menopausal
- Pelvic ultrasound showing another likely cause for pain that would independently warrant laparoscopy (eg evidence of tubo-ovarian abscess, hydrosalpinx, other ovarian cyst, fibroid warranting myomectomy).
- Evidence on ultrasound of endometriosis (endometrioma or DIE)
- Unable to obtain report of pelvic ultrasound

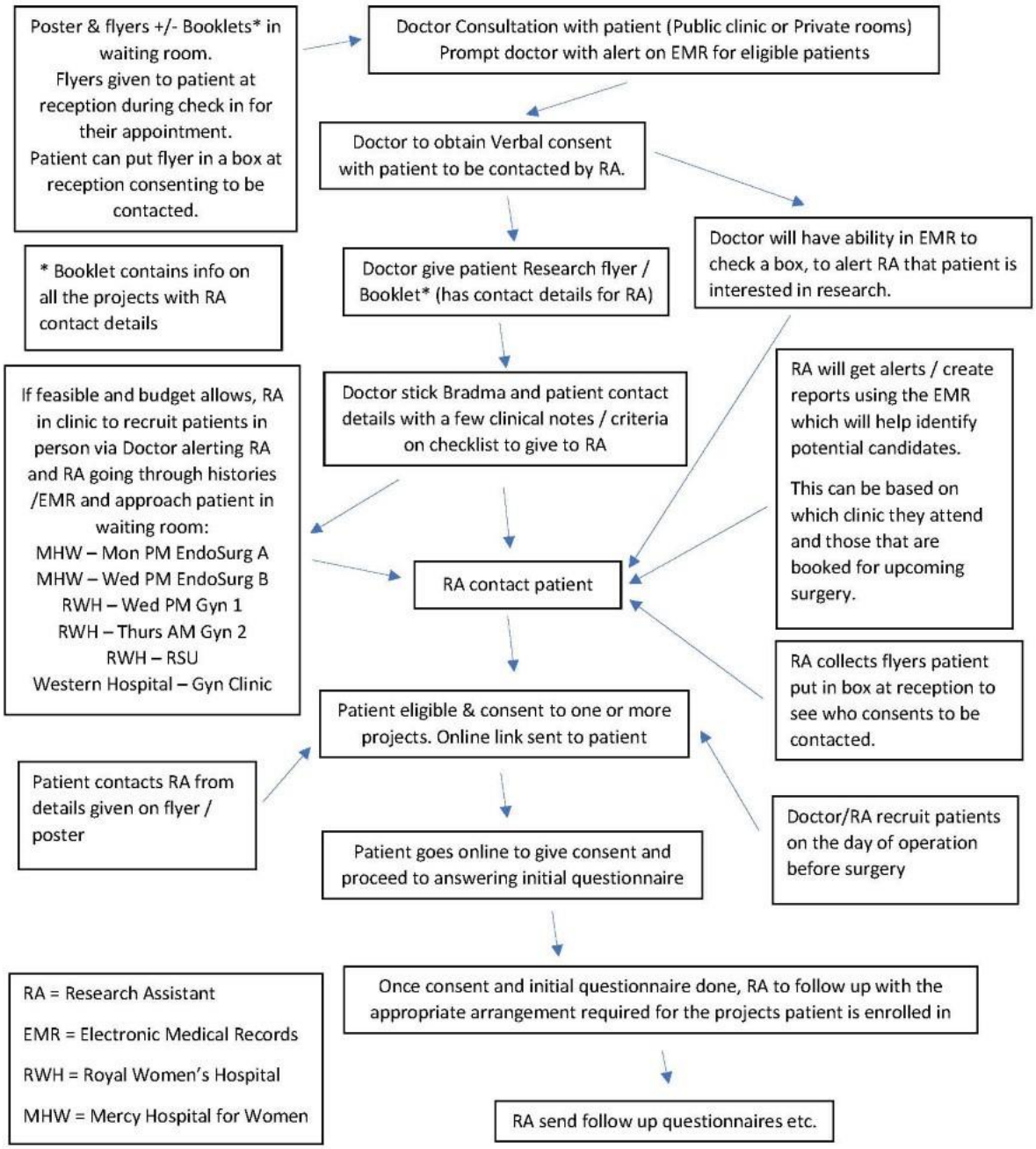
Note participants with sonographic features of polycystic ovaries, possible adenomyosis, fibroids that are not warranting myomectomy, possible pelvic congestion syndrome and possible adhesions remain eligible.

d. CONSENT

The recruiting member of the research team will explain the study to the potential participant, answer questions and provide the Participant Information and Consent

Form either in hardcopy or electronically as per the participant's preference. Consenting participants will be allocated a unique trial number.

Figure 1: Recruitment Procedure



7. PARTICIPANT SAFETY AND WITHDRAWAL

a. RISK MANAGEMENT AND SAFETY

We recognize that the study questionnaire addresses some questions of a sensitive nature regarding fertility and sexual intercourse that may cause distress for some participants. Therefore, we have in place the following actions:

1. In the Patient Information and Consent Form (PICF) participants will be directed to contact a clinical member of the research team) if they identify that they are experiencing distress as a result of participation in the study. The contact for Lifeline is also provided in this document.

2. This member of the research team will identify the nature and severity of the distress and will determine further action(s) which may include:
    a. Review in the gynaecology clinic or with the involved consultant gynaecologist
    b. Referral to psychology/psychiatry services at the Mercy Hospital for Women, Royal Women's Hospital or in the local community, as appropriate
    c. Linking the participant with the hospital consumer advocate
    d. Linking the patient into appropriate care at their home hospital site if not from the Mercy Hospital for Women or the Royal Women's Hospital
    e. Organise acute mental health assessment by the Crisis Assessment and Treatment (CAT) team

b. HANDLING OF WITHDRAWALS

Should a participant choose to withdraw from the study no further information will be collected. The participant will be asked if the data collected prior to their withdrawal is able to be used. Should they decline, the data will be removed from the database and stored in a separate folder to ensure it is not included in the final analysis.

c. REPLACEMENTS

We will continue to recruit until we have 666 participants completed the pre-operative questionnaire and had their laparoscopy who remain eligible for inclusion after their histopathology results are known (per table in methodology above). At this point data collection will be complete. Any withdrawals after this point will not be replaced. At this point withdrawals would be expected to be minimal and therefore not impact the statistical significance.

8. STATISTICAL METHODS

a. SAMPLE SIZE ESTIMATION & JUSTIFICATION

To be powered to perform logistic regression the required sample size = 10 x number of covariates/proportion [16]. In other studies carried out by the Gynaecology 2 Unit at The Royal Women's Hospital studying populations of women planned to undergo laparoscopy for investigation and treatment of pelvic pain our rate of diagnosis of absence of endometriosis has been approximately 30%. Assuming a proportion of 30%, and up to 10 covariates in the final model, the sample size required for the first "model training" sample set is 10x10/0.3 = 333. The "confirmation" set will be of equal size to the "model training" set at 333. Therefore, the final sample size will be 333 + 333 = 666.

b. STATISTICAL METHODS TO BE UNDERTAKEN

Initial analysis will involve examining associations between categorical variables using chi-squared tests. For continuous variables, comparisons between subgroups will be conducted using t-tests or their nonparametric analogues. ROC curves will be used to assess best cut-off points. To build the final discriminatory tool/s we will use machine learning and regression modelling to assess the interactions of potential variables of interest associated with presence and absence of endometriosis. P value of <0.05 will be considered significant. We will experiment with different types and models of machine learning algorithms. The final "tool" will be presented with measures of sensitivity, specificity, positive predictive value & negative predictive value. This analysis will be performed on 50% of cases, a "model training" set, then the tool will be applied to the 2nd 50% of cases, a "confirmation" set, to reassess its sensitivity, specificity, positive predictive value & negative predictive value. This is to avoid "overfitting". All cases will be used to calculate confidence intervals on the diagnostic measures.

9. DATA SECURITY & HANDLING

a. DETAILS OF WHERE RECORDS WILL BE KEPT & HOW LONG WILL THEY BE STORED

Paperwork and data from this project will be kept in a locked room at The Royal Women's and Mercy Hospitals. All computerized information will be kept in a database that is password protected. Only researchers named on this project will have access. All project-specific information will be kept for a period of 7 years after the project is completed, at which time hard copy records will be shredded and computer files deleted.

b. CONFIDENTIALITY AND SECURITY

Each subject will be provided with a unique study identification number (study ID). Identifiable information that is collected in this study will only be accessible by research staff for this project with security as described above. This information will only be used within the requirements of the study: (a) to obtain and document the findings of pre-operative ultrasound and of surgery, (b) to follow-up subjects where data is missing. All data analysis and any publications will use de-identified data involving only the study ID.

10. REFERENCES

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