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# **PROTOCOL**

## **MEDAL: MRI to Establish Diagnosis Against Laparoscopy**

**Can magnetic resonance imaging scan replace or triage the use of laparoscopy in establishing a diagnosis amongst women presenting in secondary care with chronic pelvic pain?**



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Queen Mary, University of London is the principal sponsor. Professor Khalid Khan, Consultant Obstetrics, Gynaecology and Clinical Epidemiology, is the Chief Investigator.

The Queen Mary, University of London is responsible for the design of the protocol, obtaining necessary approvals and for safety monitoring. The coordinating centre at the University of Birmingham Clinical Trials Unit is responsible for the management and analysis of the study. The Study Management Committee is jointly responsible for overseeing good clinical practice and the Investigators are responsible for obtaining informed consent and care of the participants.

## **Chief Investigator Agreement Page**

The clinical study as detailed within this research protocol (**Version 3.0, dated 12<sup>th</sup> August 2013**), or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

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# 1. BACKGROUND

## 1.1. Clinical Context

Chronic Pelvic Pain (CPP) is defined as pain in the pelvic and lower abdominal region, that lasts 6 months or longer (1). In primary care, the annual prevalence of CPP is 38/1000 in women aged 15-73, a rate comparable to that of asthma (37/1000) and chronic back pain (41/1000) (2) (3). No effective management policy exists for CPP. Only 20-25% of patients respond to conservative treatment (4). CPP remains the single most common indication for referral to a gynaecology clinic accounting for 20% of all outpatient appointments (5). Five percent of all new gynaecological appointments are for CPP (6).

The pathogenesis of CPP is poorly understood. There are several underlying aetiological factors which may overlap. Possible pathological causes for CPP include endometriosis, chronic pelvic inflammatory infection, adhesions (7), irritable bowel syndrome, interstitial cystitis, and pelvic congestion syndrome (8). Pain may also arise from musculoskeletal conditions, from pelvic organ prolapse, or from adaptive posture as a result of lower back pain. The condition is perhaps best seen from a biopsychosocial perspective; organic pathology, beliefs, coping skills, and social interactions all contribute to the woman's experience of pain (7).

Given that the symptoms experienced are varied and non-specific, a differential diagnosis in CPP can be hard to establish. It is a chronic condition and women present repeatedly over several years. It is important that at every new encounter in the GP surgery or gynaecology clinic, whether first or repeat, the whole range of possible causes are considered, keeping in mind the biopsychosocial perspective. It is possible that a previously diagnosed condition (e.g. endometriosis) has recurred or a new condition has developed (e.g. interstitial cystitis or depression in a previously diagnosed endometriosis or idiopathic CPP case). A multidisciplinary approach is ideal for achieving this. As diagnoses emerge through careful history and examination and directed investigation, so do treatment strategies. These should be tailored to the needs of individual patients as, whatever the cause chronic symptoms need long term management and a multimodal approach.

Pain affects the daily activities of women with CPP. Around 18% of employed women take at least a day off work each year due to the chronic pain (9). The economic burden to healthcare systems is difficult to establish and no recent data exist. Hospital episode data estimated the direct cost of healthcare provision for CPP at £158 million and incurring a further £24 million in indirect costs in 1992 (10).

At present there is wide variation in clinical practice concerning diagnosis and management of CPP (11). There is a significant disease burden due to CPP in both primary and secondary care (12). Patients virtually go from pillar to post seeing several health professionals before eventually having their underlying condition identified. This wastes both the patients' time and NHS resources. The diagnosis of endometriosis may be delayed by over 8 years after first presentation with CPP symptoms (13;14;15), potentially demoralising the patient and missing the opportunity to improve their life quality through early effective treatment and may provoke women to seek having a hysterectomy with its inherent risks and consequences. Using the biopsychosocial approach demands a multidisciplinary approach to management and there is some evidence that this may result in improved quality of life, if not reduced pain (16).

A troublesome clinical issue is the lack of an accurate tool to efficiently diagnose and direct cases of patients (17). The Royal College of Obstetricians and Gynaecologists (RCOG) guidelines provide a number of suggested initial investigations, including history,

microbiological screening and vaginal examination, all with weak evidence (levels B or C) for utility (11). If no cause of the pain is found, the first port of call would be to perform a diagnostic laparoscopy.

## **1.2. The role of laparoscopy in the differential diagnosis of CPP**

One reason for the diagnostic delay is the reluctance to undertake a laparoscopy in secondary care after first presentation with CPP symptoms. There is a perception that diagnostic laparoscopy, an invasive, expensive and potentially risky procedure, is used far too frequently in the NHS as a significant proportion of patients have no pathology identified (18). There were approximately 24,000 laparoscopies performed in England 2006/07, at a cost of £1274 per procedure (19). The procedure is associated with about a 3% risk of minor complications (e.g. nausea and vomiting, shoulder tip pain), a 0.24% risk of unanticipated injury causing major complications (e.g. bowel perforation), of which two-thirds require laparotomy (20-22). There is an estimated risk of death of 3.3-8 per 100,000, (23;24) and payments in medical negligence cases totalling £24.3m in a one survey from 2000 (25)

The value of laparoscopy as a diagnostic tool for CPP has been considered in several papers (26-28), including a semi-systematic review of published reports of laparoscopically diagnosable conditions, in which an average of 61% of women undergoing laparoscopy for CPP had an identifiable pathology, compared with pathology in 28% of those without CPP.(26) Over 40% of laparoscopies are done solely for the diagnosis of the causes of CPP (28).

## **1.3. Target conditions**

Possible pathological conditions include endometriosis, chronic pelvic inflammatory infection, adhesions, irritable bowel syndrome, adenomyosis, ovarian cysts, interstitial cystitis, and pelvic congestion syndrome, although many other potential diagnoses exist (29).

Endometriosis, pelvic adhesions, chronic pelvic inflammatory disease, and ovarian cysts were the pathologies most frequently observed at laparoscopy in women with CPP (26). CPP is seldom caused by a single factor alone and psychological symptoms may be both causative and associative. A diagnosis of idiopathic CPP is arrived at once all other organic causes of pain are excluded by various diagnostic technologies or empirical treatment. That is not to say that idiopathic CPP is a psychogenic condition, nor that severity of pain is related to severity of underlying pathology, as illustrated by endometriosis where stage of disease is poorly correlated with reported pain (30). In a cohort of 487 women recruited into a trial of neuroablation (31), 54% of women had no identifiable pathology at laparoscopy, whilst 31% had endometriosis, 5% had PID and 17% had adhesions. Approximately 11% had more than one finding. Those with moderate to significant pathology were excluded from this trial. This is in broad agreement with other surveys, where findings were that 35% had no visible pathology, 33% endometriosis, 5% PID and 24% adhesions (26).

## **1.4. Evidence on the accuracy of diagnostic tests for CPP**

Few systematic reviews of the diagnostic accuracy of laparoscopy and MRI for each of the target conditions were identified following a thorough search of the literature. Evidence for

the accuracy of diagnosis of each specific condition by MRI and laparoscopy is summarised in Table 2.

**Table 2 Summary of the evidence for accuracy for MRI and laparoscopy in the investigation of CPP**

| <b>Some specific target conditions</b> | <b>Diagnostic criteria</b>   | <b>Diagnosis by MRI</b>   | <b>Diagnosis by laparoscopy</b>  |
|--|--|---|--|
| Endometriosis                          | Visual. Laparoscopy is discriminative for negative findings but less so for positive findings against biopsy (32). | Uncertain. Evidence for deep infiltrating endometriosis (33) and ovarian endometrioma (34)  | Gold standard. Negative laparoscopy accurate for excluding endometriosis (pooled LR- 0.06; 95%CI 0.01-0.47) compared to biopsy but positive findings not as accurate (pooled LR+ 4.30; 95%CI 2.45-7.55) (35) |
| Adhesions                              | Visual, directly or by absence of movement between adjacent organs.  | Evidence from single trial PPV 55% NPV 96% (36)   | Gold standard  |
| Pelvic inflammatory disease (chronic)  | Laparoscopic visualisation or histology from fimbrial minibiopsy.  | Ultrasonography represents preferable initial non-invasive diagnostic method.   | May fail to detect early disease or those with endosalpingitis only (37)   |
| Adenomyosis                            | Presence of diffuse endometrial tissue in myometrium at post-hysterectomy biopsy.                                  | MRI had a pooled sensitivity, specificity, LR+, and LR- of 71% (95% CI 63%-78%), 90% (86%-92%), 5.90 (4.30–8.09) and 0.29 (0.15-0.58) respectively (38) | Uncertain – may observe bulky uterus   |

Thus MRI may be useful diagnostic tools for adenomyosis, deep infiltrating endometriosis and ovarian endometriomas. However, its use for the differential diagnosis of other pathological causes of CPP has not yet been fully investigated. (39) (40). Existing research does not tell us whether MRI can replace laparoscopy in the differential diagnosis of underlying conditions. Compared to laparoscopy, MRI may be more or equally accurate, is less invasive, carries fewer risks, is easier to do, does not require a general anaesthetic, is less uncomfortable for patients, has shorter waiting times and is cheaper at £173 (19) MRI findings may also assist in patient management for example referral could be to a

gynaecologist specialising in the particular problem discovered, rather than a general gynaecologist.

This study will delineate the accuracy of MRI against a reference diagnosis derived from an expert independent panel and examine the cost-effectiveness of the alternative pathways to diagnosis.

### **1.5. Evidence on cost effectiveness of MRI in the differential diagnosis of CPP**

A scoping electronic search conducted in Medline, Embase, and EED, (from database inception to the July 2009) revealed no studies of cost-effectiveness of MRI in the diagnosis of CPP. There is an international collaboration aiming to estimate direct and indirect cost of endometriosis with a view to determine the overall socio-economic impact of endometriosis ([www.mh-hannover.de/endocoststudy.html](http://www.mh-hannover.de/endocoststudy.html)), which may provide important data for the economic evaluation.

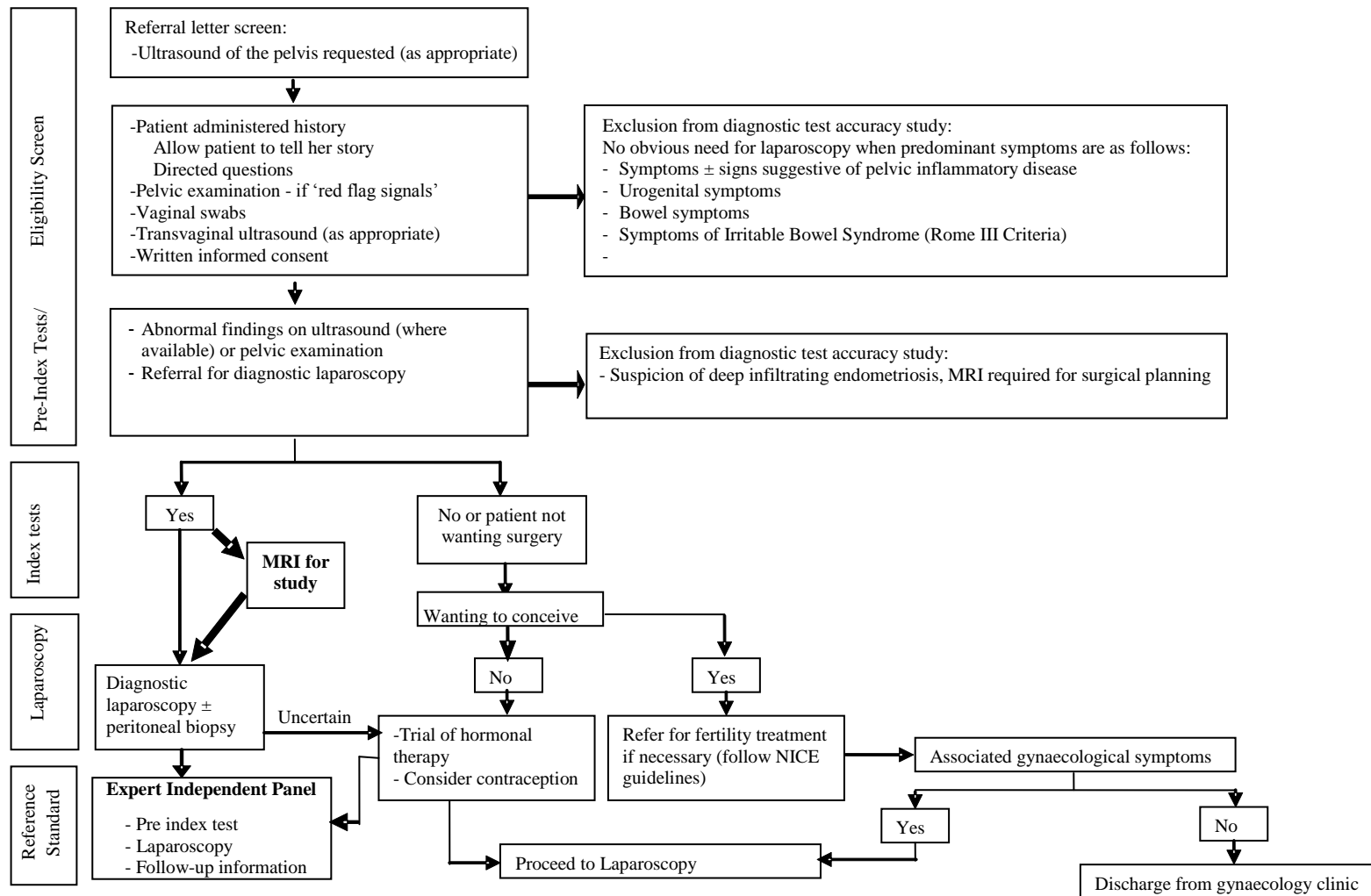
### **1.6. The place of MRI in the diagnostic path**

The order of tests in current practice can vary between clinician and according to presentation, but will follow the RCOG clinical guidelines:

1. Non-invasive tests [initial, pre-index test, testing used routinely]
  - a. Clinical history
  - b. Vaginal examination
  - c. Appropriate test for Chlamydia and Gonorrhoea where there is suspicion of PID or opportunistic screening for women under the age of 25 years
  - d. Transvaginal ultrasound (TVUS)
2. Invasive tests
  - a. Laparoscopy under general anaesthetic
  - b. Conscious pain mapping (rarely used)

Figure 1 shows the patient pathway for the initial triage diagnosis of the causes CPP (adapted from the Royal College of Obstetricians and Gynaecologists Clinical Guideline “Initial Management of Chronic Pelvic Pain”).

**Figure 1 Flow chart of study organisation**





## 1.7. Aim and Objectives of the MEDAL Study

**Aim** is to assess if MRI can replace or triage the need for laparoscopy in women presenting with Chronic Pelvic Pain (CPP). We will determine the proportion of women for whom MRI is sufficiently accurate to replace laparoscopy following evaluation of presenting characteristics. This will be completed by ascertaining if the “post-laparoscopy diagnoses” has added any clinical benefit to the “post MRI diagnoses” (i.e. whether it has diagnosed substantially more pathological conditions) or whether it could have been avoided.

### Objectives:

1. To compare the diagnostic accuracy of the post-MRI diagnoses and the post-laparoscopy diagnoses for a) the absence of any pathological cause (i.e. idiopathic) and b) the main pathological causes of CPP
2. To determine the added value of laparoscopy over MRI and both tests over information collected at baseline (history/clinical examination/ultrasound)
3. To quantify the impact that MRI and laparoscopy have on diagnostic decision-making, and to compare the certainty of the post-MRI diagnoses and the post-laparoscopy diagnoses
3. Estimate the proportion of women for whom a diagnostic and/or therapeutic laparoscopy is indicated
4. To determine, using multiple logistic regression, the presenting characteristics which identify the subgroups who would benefit most from MRI and conversely, those who would not benefit
6. To perform a decision-analytic model based economic evaluation determining the cost-effectiveness of MRI in reducing the need for laparoscopy

We have framed our project around the following components of a research question:

**Population:** women aged 16 and over with chronic pelvic pain of at least 6 months duration.

**Index test(s):** pelvic MRI, diagnostic laparoscopy, baseline information (patient history/ clinical examination and ultrasound where clinically indicated/ available).

**Reference standard:** a composite of history, examination, ultrasound (clinically indicated/ available laparoscopic findings and response to treatment, with a reference diagnosis agreed by an Expert Independent Panel.

## 2. STUDY DESIGN

### 2.1. Brief summary

An outline of the test accuracy study is shown in Figure 2. MRI will be undertaken before laparoscopy but the resulting report will not be provided to the gynaecologist, unless there is a critical finding such as suspected malignancy, in order not to distort clinical practice and avoid verification bias arising from knowledge of the index test. A diagnostic laparoscopy will also be performed and together with information from the history, examination and ultrasound, produce a post-laparoscopy diagnosis. Information will also be collected from those who are not eligible for the test accuracy study. Follow-up at 6 months, involving response to treatment and results of additional tests will also be obtained, and will be used according to an a priori algorithm for panel evaluation to determine the reference diagnosis to minimise the risk of incorporation bias (see Sections 2.2 and 4.4) An economic evaluation will be performed to establish the relative cost-effectiveness of MRI as a replacement or in combination with laparoscopy for the various target conditions. If accurate and cost-effective, MRI will be placed after the non-invasive tests, leading to more selective use of invasive tests.

In order to understand the relative impact of MRI versus laparoscopy on diagnostic thinking, a nested comparison of gynaecologists' diagnostic certainty will be undertaken using subjective estimates recorded at the time of diagnostic decision-making.

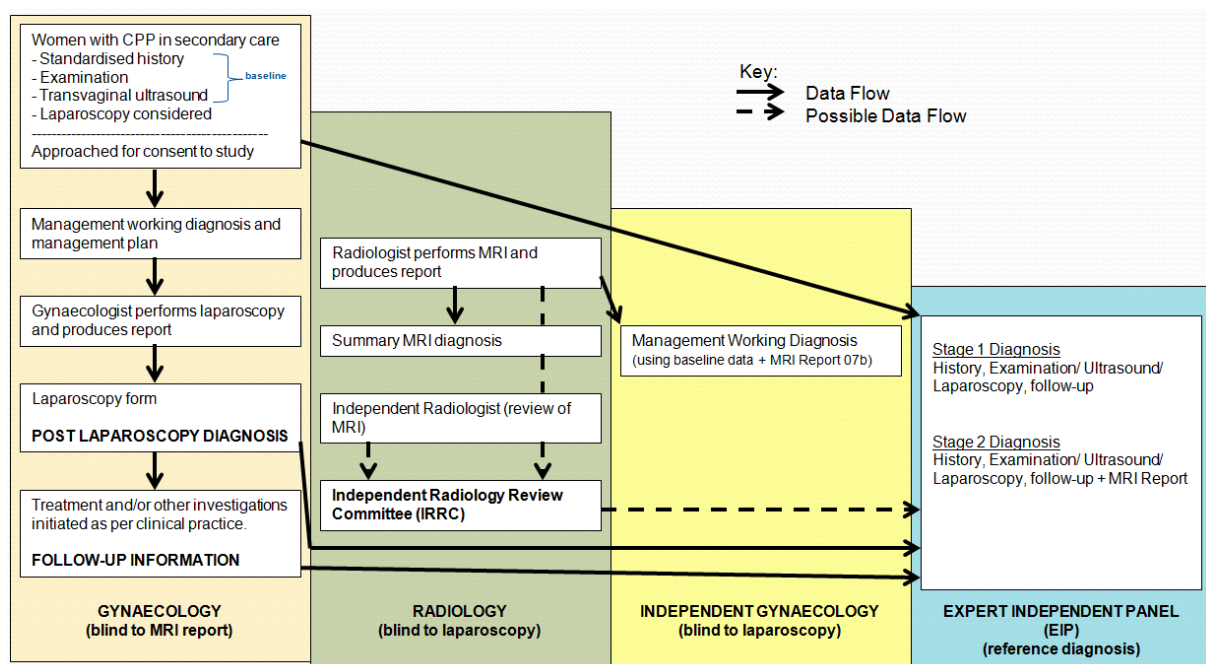


Figure 2. MEDAL study flow of data

### 2.2. The choice of study design

Test accuracy studies are designed to generate measures of accuracy by comparison of the index test with a reference standard, a test that confirms or refutes

the presence or absence of disease beyond reasonable doubt. Classical test accuracy studies require that the target condition is independently verified by the reference test, which must provide a definitive diagnosis, be applicable in all cases and preferably performed alongside the index test. Complete verification of the presence or absence of target condition is essential to reduce bias and to maximise statistical power of the study. By comparing the index test with the reference standard, the result of the index test can be categorised as a true positive, false positive, true negative or false negative. Measures of index test accuracy, including sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratios can be computed (41).

MRI visualises the various pathologies with different degrees of accuracy (Table 2). To determine the sensitivity of MRI for each pathology would require a large number of participants, to accommodate the low prevalence of some conditions. Furthermore, some pathologies are not independent of each other and could frequently be concurrently observed, for example endometriosis can give rise to adhesions from fibrotic tissue. Therefore, the principal research question is to ascertain how many women could have avoided laparoscopy if MRI was used in practice. From a cost effectiveness perspective, the cost per laparoscopy avoided is the most pertinent question. Diagnostic accuracy of MRI and laparoscopy for each pathological condition will be a secondary aim.

In the context of the MEDAL study, there are a number of target conditions to be considered, not all of which have a perfect reference standard of identification against which to make a differential diagnosis. There is a risk of partial or differential verification of the underlying causes, with the inherent bias. There are several proposed study designs that overcome the problems of an imperfect reference diagnosis (42) In the absence of a single “gold standard” test, the results of several imperfect tests or observations can be combined to create a composite reference standard. These can be combined according to a pre-defined algorithm or a consensus diagnosis obtained from considering all the information.

We will employ an expert independent panel (consensus) diagnosis in which a group of experts will determine the presence or absence of the target condition based on several sources of information, namely the pre-index tests, the post-laparoscopy report and any follow-up information. This is an acceptable way of addressing the problem of achieving a diagnosis from multiple sources of information and of subjective assessment of that information, as a diagnosis is achieved by consensus (42). A final diagnosis is obtained for all patients and the panel method reflects the clinical reality, where several items of information are synthesised by the clinician. The results of this methodology can be viewed generalisable to clinical practice.

The aim of the study is to determine the proportion of women for whom MRI could remove the need for a laparoscopy, or in other words, where MRI is a replacement for laparoscopy. This would be attractive as MRI is less invasive and cheaper. There will also be circumstances where MRI adds benefit to the laparoscopy, so that the combination of both tests gives rise to a more accurate diagnosis. There are different study designs to address these two scenarios.

To establish whether MRI can replace laparoscopy, a paired design is employed, where both tests are compared with the reference standard. As sensitivity and specificity can vary across sub-groups, the two tests and reference standard are best performed in the same population (43). It is feasible to perform MRI and laparoscopy

in women with CPP, and whilst MRI does not interfere with the laparoscopy, the paired design is preferable to a randomised trial (44). As MRI would precede laparoscopy, it can also be viewed as a triage test, directing only patients with a specific condition towards a laparoscopic confirmation or operative laparoscopic procedure. A fully paired study design is also appropriate for this type of diagnostic situation.

## **2.3. Setting**

This will be a multicentre study with recruitment from up to 26 gynaecology outpatient clinics in the UK. These units serve a large, socio-economically and ethnically diverse population, which will aid generalisability of findings. The units also represent the spectrum of settings, from a busy district general hospital to a specialised tertiary referral centre. Existing referral networks to hospitals with MRI facilities will be exploited.

### **2.3.1 Risks and benefits for the participants**

Risks of MRI are rare, but mainly revolve around changing radiofrequencies and magnetic fields which can theoretically produce heat, which is absorbed by the body tissue, but this is not known to produce any side effects at all. Like any surgery, a laparoscopy is not without its risks. However, since a laparoscopy involves minimal damage to body tissues, it is on the whole safer than 'open' operations such as laparotomy. Possible complications of laparoscopies include damage to organs inside the abdomen and wound infections. Women having a laparoscopy will have to have a general anaesthetic, as with all anaesthetics, there is a risk of adverse events, particularly in obese women. All these risks are extremely rare, and unlikely to occur, as we will only allow experienced surgeons/ radiologists to take part.

By having an additional MRI scan prior to the laparoscopy, any abnormalities such as malignancies have a high likelihood of being detected. These may be picked up during the laparoscopy, but if detected earlier (in the MRI scan), treatment can be initiated prior to the laparoscopy being conducted.

## **3. ELIGIBILITY**

### **3.1. The following inclusion / exclusion criteria will be used to initially identify potential participants: Inclusion criteria**

#### **3.1.1 Inclusion criteria**

- Women aged 16 and over
- Women referred to a gynaecologist with CPP
- Women who have given written informed consent

#### **3.1.2 Exclusion criteria**

- Women who have had a hysterectomy

- Women who are pregnant
- Women unable to give consent through incapacity or inability to speak English and lack of suitable interpreter

Women who meet the above criteria will be invited to participate in the study. To take part in the diagnostic test accuracy study, the following *additional* inclusion and exclusion criteria will apply:

### **3.2. Additional eligibility criteria for diagnostic test accuracy study**

#### **3.2.1 Inclusion criteria**

- Need for a laparoscopy is established and the patient wishes to proceed with it

#### **3.2.2 Exclusion criteria**

- Women who are considered to definitely require an MRI, based on examination, history, ultrasound (where available).
- Women with an identifiable cause of CPP for which treatment can be initiated

#### **3.2.3 Transition from Data Collection Only to Diagnostic Study**

Women who met the inclusion criteria (and do not meet any of the exclusion criteria) but the need for laparoscopy is not yet established may be consented into the data collection only arm of the study. Examples of data collection participants include women who are prescribed the Combined oral contraceptive pill (COCP) and/ or those prescribed Gonadotrophin hormone (GnRH). Participants who see no improvement in their pain from medication or through the referral process to another other specialist(s) maybe consented into the diagnostic study at a later visit to clinic.

#### **3.2.4 Transition from Diagnostic Study to Data Collection Only**

In some cases, women who consented into the diagnostic study may transfer to the data collection only arm of the study. Examples of participants who may transfer from diagnostic study to data collection only arm include those who changed their mind about undergoing the MRI scan or if a radiology department were unable to perform the MRI scan before laparoscopy (e.g. if the date of laparoscopy was moved forward).

The inclusion / exclusion criteria shown in Figure 3

#### Inclusion Criteria:

- Women aged 16 and over
- Women referred to a gynaecologist with CPP
- Women who have given written informed consent
- Need for a laparoscopy is established and the patient wishes to proceed with it (Diagnostic Study)

#### Exclusion criteria:

- Women who have had a hysterectomy
- Women who are pregnant
- Women unable to give consent through incapacity or inability to speak English and lack of suitable interpreter
- Women who are considered to definitely require an MRI, based on examination, history, ultrasound.
- Women with an identifiable cause of CPP for which treatment can be initiated

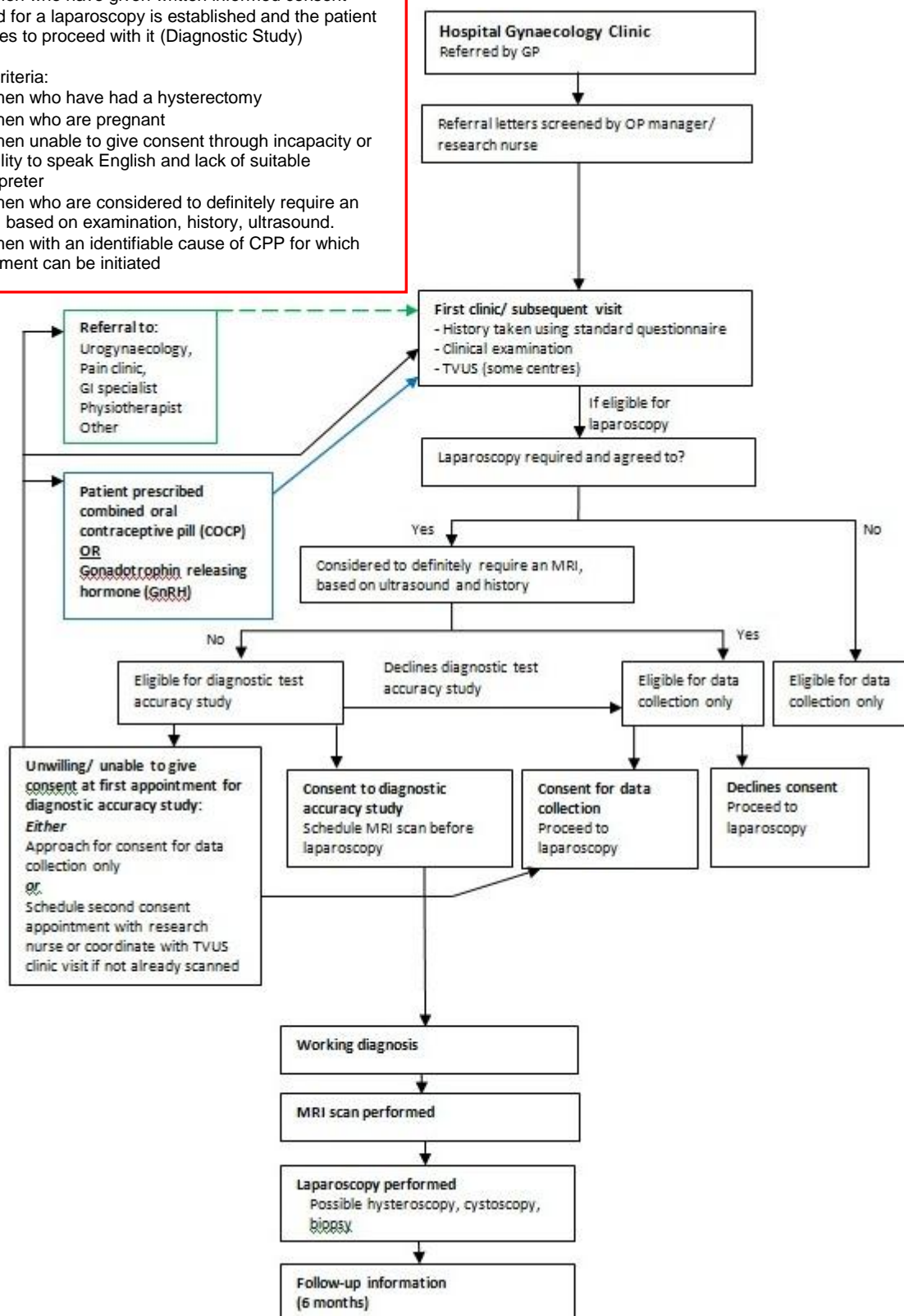


Figure 3. MEDAL study Patient Consent and Pathway Diagram

### 3.3. Recruitment of participants and consent

**Ideally consent is sought under unhurried circumstances, when entry criteria are fulfilled. Consent will be sought in stages:**

- A patient information leaflet will be sent to all women who are referred with chronic pelvic pain to the participating clinics along with their appointment letters to attend gynaecology out-patient clinics, to enable women to have an understanding of the study before they see their gynaecologist. An information leaflet about MRI scans, developed by the Pelvic Pain Support Network and certified by The Information Standard will also be sent.
- When women are seen in the clinic, their history will be taken using a standardised proforma, and a clinical examination and ultrasound scan performed. If they fulfil the inclusion criteria and do not have any exclusion criteria, they will be invited to join the diagnostic test accuracy study. They will be counselled regarding the process of referral for an MRI and scheduling of the laparoscopy and the risks of both investigations discussed.
- If they are eligible and agree to provide consent for the diagnostic test accuracy study, they will be asked to sign a study consent form. If they are eligible for the diagnostic accuracy study, they will be sent an appointment for a MRI scan. If they are not eligible for the diagnostic test accuracy study, due to a finding from the history, examination or ultrasound, they will be asked for consent to provide the baseline data only (Data Collection Only), but subsequent investigations and treatments will be provided as appropriate.
- To provide enough time for consideration and to provide opportunities to ask questions, obtaining consent from the woman can be deferred to the next appointment when the pre-operative assessment and/ or transvaginal ultrasound is undertaken. However, the MRI cannot be scheduled until consent to participation in the diagnostic test accuracy is provided by the woman.

Wherever necessary, appropriate interpreters will be asked to aid clinician-patient discussion relating to study participation. It is anticipated that willingness to participate in the study may potentially vary between ethnic groups.

Feedback from service users indicates women do not always appreciate the difference between a diagnostic and operative laparoscopy. Thus by suggesting that MRI might avoid “surgery” this may leave the impression that an operative procedure is not available to her. We will be clear about the difference and reassure women that should the diagnostic process point to a condition treatable by laparoscopic surgery, then this will be available to her. The decision to perform a strictly diagnostic laparoscopy, or to intervene if laparoscopic interventions e.g. ablation of endometrial deposits, are considered appropriate will be left to individual clinicians.

### **3.4. Organisation of Recruitment**

Recruitment will be organised and supported by dedicated clinical principal investigators. Documentation will be provided by the MEDAL Study Office and the clinical research fellow will be available to support clinics in some centres. We believe that the following strategy is likely to be successful in achieving maximum recruitment.

- Appointment or nomination of a dedicated nurse at each centre with responsibility for overseeing identification of potential participants referred to the gynaecologists at that centre, for consent, for appointment scheduling, for data collection and problem resolution. Resources for this post may be available from the Trust's R&D support allocation or via the local comprehensive research network. (see Section 7.7)
- Appointment of a clinical research fellow, based at the Royal London Hospital, who will liaise with all the local principal investigators at each centre, provide training and trouble-shoot recruitment and testing problems.
- Provision of simple written study information, supported by face to face discussion with gynaecologists and nurses.
- Engagement of outpatient, radiology and theatre managers to assist in the screening of referral letters, provision of the study information and scheduling of appointments so that MRI scans and laparoscopies for study participants are not delayed.
- Provision of regular feedback on progress in study recruitment, including individual hospital teams' performance and progress against targets.
- Regular newsletters to all relevant staff involved in the study.

All gynaecology outpatient nurses and junior doctors will receive training regarding the introduction of information about the study and instruction on their roles from the local coordinating clinicians. This will occur during team meetings and the information provided will be reinforced periodically throughout the study by further meetings and newsletters from the MEDAL Study Office.

#### **3.4.1 Declining and Ineligible Women**

Any women declining participation will have this recorded in the outpatient notes and centres will be asked to keep a log of the number of decliners. We will record anonymous baseline demographic (age, parity, ethnicity) information from all women invited to take part who decline to take part. This will establish the take-up rate of the study.

We will seek consent to collect the same information on those who are identified as ineligible for the diagnostic test accuracy part of the study for clinical reasons, whether excluded on the basis of history, examination, ultrasound or MRI findings, as for those in the diagnostic accuracy study. This will establish the incidence and reasons why women with CPP do not undergo diagnostic laparoscopy.



## **4. TESTS AND PROCEDURES**

All information will be collected on standard proformas. Information will be collated on paper forms and then either copied and sent to the coordinating centre for input or entered directly into the study database via a web interface. We aim to collect a minimal demographic dataset including age, ethnicity, parity and significant medical/surgical history. We aim to use the NHS number as the primary identifier and to track individuals throughout the NHS.

### **4.1. Pre-index tests and information**

A structured assessment template for use by gynaecologists will be agreed in each participating centre. This will collect relevant medical, obstetric and surgical history and require the gynaecologist to designate a working diagnosis, a management plan and the degree to which they anticipate the laparoscopy will be diagnostic or therapeutic. This is to quantify the propensity of the gynaecologist to adopt a “see and treat” laparoscopic strategy rather than a purely diagnostic laparoscopy.

#### **4.1.1 Clinical history assessment**

The assessment is based on standardised questionnaires previously validated in either women with pelvic pain or other clinical symptom groups. There will be some overlap with the Women’s Health Symptom Survey (45).

The assessment will comprise of the following:

- General, gynaecological and obstetric history
- Previous gynaecological tests, treatments and contraceptive use
- Pain symptoms: location, timing and intensity, including visual analogue scales
- General quality of life questionnaires (EuroQoL 5Q-ED) (46) and ICECAP-A (47)
- Pelvic pain and urgency/ frequency questionnaire for interstitial cystitis (48)
- Physical and sexual abuse history questionnaire (49)
- Assessment of Sexual Activity (50)
- Endometriosis Health Profile Questionnaire (EHP5) (51)
- Irritable Bowel Syndrome Rome III criteria questionnaire (52)
- Short Form McGill Pain Questionnaire version 2 (SF-MPQ2) (53)
- Pain Catastrophising Scale (54)
- Patient Health Questionnaire – 2 (PHQ-2) assessment of depression (55)
- 10-item Big 5 Personality Inventory (56)

Some questionnaires e.g. Assessment of Sexual Activity, Sexual Experiences Survey ask questions regarding very personal and sensitive information and completion of these questionnaires may be reduced if women do not want their clinician to see their

responses. The front page of the assessment makes it clear that women may leave blank any question they do not wish to answer.

The clinician will offer signposting to services for those women disclosing abuse or are suggestive of possible depression on the PHQ-2.

#### **4.1.2 Investigations and Examinations**

These are all routinely offered and reported to the gynaecologist.

- Appropriate test for Chlamydia and Gonorrhoea (unless declined/ inappropriate)
- Manual vaginal examination, including dermatological assessment
- Transvaginal ultrasound (TVUS) of pelvic organs and bladder

The report generated for the TVUS would depend on the nature of the clinical query but would include as standard an assessment of uterine size, endometrial thickness, myometrial texture, ovarian size and appearance, presence of free fluid in the pelvis and, abnormal masses/fluid collections. Where possible the presence and site of any tenderness or immobility and bladder wall thickness. Strong suspicion of deep infiltrating endometriosis in the rectum or vagina, from the TVUS and other clinical features, where the gynaecologist considers a MRI scan essential for surgical planning, will render the women ineligible for the diagnostic test accuracy part of the study.

### **4.2. Magnetic Resonance Imaging (MRI)**

#### **4.2.1 Timing of the MRI**

Those who are eligible and consent to participation in the diagnostic study will have a MRI scan scheduled before the diagnostic laparoscopy. Women will be asked to fast for 2-4 hours prior to the scan and not to empty their bladder immediately prior to the scan. Sometimes an injection may be needed (Buscopan and/or Gadolinium) which is given into a vein in the arm and helps to clarify the scan. Antiperistaltics should not be given.

Some patients may be prescribed medication such as the combined oral contraceptive pill (COCP), Gonadotrophin releasing hormone (GnRH) or be referred to another specialist before returning for a follow-up gynaecology clinic appointment (consented to data collection). Some returning patients/ participants may have experienced little or no improvement in their pain, and may be consented for the diagnostic study.

#### **4.2.2 MRI sequences**

The MRI protocol will comprise: T1 and T2 axial, T2 sagittal, T2 coronal and T1FS axial, sagittal and coronal sequences using standardised anatomical landmarks, slice thicknesses and Field of VIEW. If unexpected abnormalities are detected, additional sequences, potentially using contrast media, may be added to the protocol. The

protocol has been developed in consultation with the independent radiology review panel.

#### **4.2.3 MRI report**

The MRI proforma report will contain the following data fields:

- Scan quality
- Description of findings
- Uterine size, appearance, junctional zone thickness, adjacent myometrial thickness, endometrial thickness, presence of fibroids
- Ovarian size, presence, size and intensity of cysts
- Other masses
- Free or loculated fluid present
- Adhesions seen/ suspected
- Bladder status, including wall thickness if abnormal
- Presence of small bowel in pelvis, location and description

MRI reports will be provided on a standard proforma by the local radiologist.

#### **4.2.4 MRI review**

The MRI scan will also be independently reported by a radiologist blinded to the initial MRI report. Three experienced radiologists, who are not involved in imaging participants in the study, will share this task. Where the local and independent radiologists agree, the findings will be accepted as a consensus and will constitute the “post-MRI diagnosis”. Lack of agreement between local and independent radiologist will require further review and be referred to an Independent Radiology Review Committee (IRRC).

#### **4.2.5 Unblinding of MRI to gynaecologist**

The MRI reports will not be provided to the gynaecologist unless unexpected significant findings are picked up by the local reporting radiologist. Depending on the significance, the gynaecologist may have to be informed of the findings.

Circumstances necessitating informing the recruiting gynaecologist will include

- unexpected cancer
- abscess
- a non-gynaecological abnormality requiring immediate attention.

In the case of these findings, the participant may need to be excluded from the diagnostic accuracy study and managed appropriately, although could still contribute to the wider study data collection objective. This will be documented and although will

not add to the accuracy estimates, will give an indication of how frequently unexpected findings will be picked up in this population. The use of information collected should be explained to the patient and she should not be deemed as “withdrawn” to avoid confusion. Bowel thickening would not result in a participant being excluded from the study. Unless consent is completely withdrawn by the women, or follow-up is deemed inappropriate by the gynaecologist, she will receive the six-month follow-up questionnaire.

### **4.3. Laparoscopy**

#### **4.3.1 Initial diagnostic laparoscopy**

Routine preparation will be made for a diagnostic laparoscopy with the patient intubated for general anaesthesia. Following pneumoperitonium, a laparoscope will be used to visualise the pelvis. Before embarking on any operative laparoscopy considered necessary e.g. ablation or excision of endometriosis deposits, an anatomical pelvic assessment will be performed to identify pelvic structures and pathology. Laparoscopy will be performed by experienced gynaecologist who will be capable of identifying all potential target conditions. Where possible, still or video clips of specific lesions or anatomical structures will be taken. The gynaecologist will complete a standard proforma to report their observations. This will include specific questions regarding the presence or absence of particular pathological features, location and severity, using accepted rating scales.). The clinician must report their diagnosis and their confidence in the accuracy of their decision.

Where clinically indicated patients who are recruited for the MEDAL study will be invited to undergo a cystoscopy under general anaesthesia at the same time as the laparoscopy. The cystoscopies may be performed on patients with and without urinary symptoms to compare intra-operative findings.

Where clinically indicated peritoneal or bladder biopsies may be taken during the laparoscopy and cystoscopy – this information may be used to confirm or refute any disease that may be present.

#### **4.3.2 Follow-up information**

##### ***Further treatment***

Following the diagnostic laparoscopy, there will be three possible scenarios for management of the pelvic pain:

- No obvious gynaecological pathology – no gynaecological surgery or medical options (beyond analgesia), referral to another specialist or pain management clinic.
- Obvious gynaecological pathology – requiring surgical treatment e.g. ablation or excision of endometriotic lesions and treatment of ovarian cysts, adhesiolysis etc that may be undertaken as part of the diagnostic laparoscopy or as a subsequent procedure.
- Unclear diagnosis – gynaecologist opts for empirical treatment to establish a diagnosis e.g. gonadotrophin releasing hormone agonist for endometriosis or refers the participant to another specialist for further investigation. Should

patients experience little or no improvement in their pain they may be consented for the diagnostic study upon a possible second gynaecology clinic appointment.

Investigators will be asked to report any further tests and investigations employed in this 6 month window. This will be supplemented by questions to the participant to identify or validate further investigations and treatments. These questions will include a repeat administration of the Quality of Life (EHP-5, EuroQoL EQ-5D and ICECAP-A) and pain intensity visual analogue scales that were assessed at baseline.

### ***Preference for order of tests***

The assumption that a MRI scan prior to the laparoscopy would be the natural order of tests may be challenged by the women's experiences. Some simple questions asked at six months post-laparoscopy will help resolve this.

### ***Quality of life and resource usage***

The EuroQoL EQ-5D, ICECAP-A will be administered at baseline and 6 months post-laparoscopy, and will also be used for purposes of health economic evaluation. We will also ask the woman to list any further treatments, tests or surgical procedures they have had, to ensure all further management is captured, as above, and to quantify health resources used.

## **4.4 Reference diagnosis (by Expert Independent Panel)**

As discussed above, there are a number of target conditions to be considered, some of which can be accurately diagnosed by laparoscopy and others by other means. To circumvent this problem, we will employ an expert independent panel (consensus) diagnosis. History, presenting signs and symptoms, questionnaire data and the laparoscopy report will form the bulk of the diagnostic information. Some of the target conditions will respond well to treatment, therefore we will collect information regarding treatment offered and patient reported outcomes at six months post-diagnosis. On others, further tests may reveal a definitive diagnosis. This follow-up information will also be provided to the panel and together with the pre-index and post-laparoscopic information, will determine the reference diagnosis. The reference diagnosis will be assigned an ICD-10 code by the panel. Including both pre and post treatment information strengthens the differential diagnosis rather than undermining it through the treatment paradox.

A panel of three expert independent experts, who are not responsible for recruiting participants into the trial, will be convened (face to face meetings or webcasts) at regular intervals. There is little literature on how panels should be convened or how information should be presented (42). The expert independent panel will be asked to make their diagnosis after consideration of structured summaries of the history, questionnaires, investigations, examinations and the post-laparoscopy report present in a stepwise manner. These will be prepared by the clinical research fellow, who will have resolved any omissions and ambiguities with the investigator prior to the panel. Each panel member will give their immediate diagnosis and where there is disagreement, cases will be resolved by discussion. Inter rater agreement will be

recorded. Results of the MRI scan will not be provided to the expert independent panel at this point to avoid incorporation bias. At the final stage, the panel will be provided with results of the MRI scan and be asked if this alters their diagnostic decision. This will provide a measure of how much weight should be placed on the MRI results.

#### **4.5 Compliance issues**

There is a risk of patients declining participation after having given consent to take part. The key issue for us is the timing of the MRI scan to avoid loss of participation after consent has been obtained. The study has been designed to tackle this issue by ensuring MRI and laparoscopy are both undertaken within NHS waiting time targets.

If a woman requests no further tests or treatments, the clinical team should respect her wishes but seek permission to use the data collected up to that point. Withdrawal of consent to use any information should be reported to the MEDAL study office.

#### **4.6 Other Management, Sub-study, Quality Control, Serious and Unexpected Adverse Events**

##### **4.6.1 Other Management**

The women will be managed for their CPP in the same manner as in current clinical practice. If on MRI, there are any suspicious findings, e.g. concern about cancer, the result will be conveyed to the appropriate clinician. If the clinician decides to proceed with a laparoscopic procedure e.g. ablation of endometriosis, on the basis of the results of diagnostic laparoscopy, this is permitted. All aspects of patient management are entirely at the discretion of the local doctors who will follow the local guidelines for treatment.

##### **4.6.2 Sub-study (Educational Project)**

Using the existing data set, a sub study (educational project) will be performed on patients who present with unexplained chronic pelvic pain and urinary symptoms suggestive of bladder pain syndrome who consent to participate in the diagnostic arm of the MEDAL study. These patients will be offered a cystoscopy under general anaesthesia to investigate their symptoms, at the time of their laparoscopy. A bladder hydrodistension test and bladder biopsies may be taken at the time of cystoscopy, as per the clinician's usual practice. This study will be carried out by the named clinical research fellow as part of a higher educational degree, supervised by the chief investigator. Additional data analysis will be performed on this group of patients.

##### **4.6.3 Quality Control**

Quality assurance of test reporting will begin with a clearly documented acceptance of the reporting proformas by the participating gynaecologists and radiologists. Review of MRI scans will allow differences in interpretation of images to be explored and inter-observer reliability will be calculated.

#### 4.6.4 Serious and unexpected adverse events

There are no foreseeable risks of mortality or significant morbidity associated with testing. Every effort will be made to minimise any risk through training. All **serious adverse events** believed to be associated with the study tests should be reported by fax to the Study Office as soon as possible. This report should be followed within 1 week by a completed SAE form. For the purposes of this study, “serious” adverse events are those occurring in the participants which are fatal, life-threatening, disabling or require or prolong hospitalisation arising from either the MRI or laparoscopy, within one week of having the procedure.

For the purpose of the study, the following are considered anticipated SAEs:

##### ***MRI***

- Reactions to contrast media
- Events caused by metal objects in the magnet room

##### ***Laparoscopy***

- Death
- Conversion to laparotomy
- Repair to damage to bowel, bladder, uterus or major blood vessels
- Blood transfusion
- Hernia at site of entry

Other unanticipated serious adverse events occurring at the time of the MRI or laparoscopy should be considered for causality and reported if thought to be a consequence of the investigation.

## 5. ACCRUAL AND ANALYSIS

### 5.1. Sample size

A pragmatic sample size of 340 women has been chosen to address the primary research question of how many women could have avoided laparoscopy if MRI was routinely used in practice for all women with CPP. This will be based on a comparison of both post-MRI diagnosis and post-laparoscopy diagnosis with the reference diagnosis. The independent panel will determine if the post-laparoscopy diagnosis has added any clinical benefit, i.e. helped to diagnose substantially more pathological conditions.

With this number of women, the study will have over 90% power (at  $p=0.05$ ) to detect a reduction of 10% in the number of laparoscopies needed (i.e. from 100% down to 90%). This difference would be cost-effective if laparoscopy was at least 10 times more expensive than MRI. Current estimates make laparoscopy 7.4 times more expensive than MRI (£1274 versus £173), however these NHS estimates may not

necessarily reflect the true cost of the procedure which will be estimated through primary data collection as part of this study.

340 women will also provide a reasonable number of cases of each of the more common target conditions from which to estimate the sensitivity of MRI for diagnosis. We anticipate a high sensitivity of MRI for detecting common pathological causes of CPP, so have based our calculations around an anticipated sensitivity of 80% for any particular condition (sensitivity of 90% has also been provided for comparison). We then computed the 95% confidence intervals for these sensitivities for a range of prevalences of any particular condition (Table 4). These figures can equally apply to specificity. For a target condition with a prevalence of 30% or more, we will be able reliably rule out a sensitivity or specificity less than 70% if the “true” sensitivity or specificity is >80%.

| Assuming sample size n = 340 |                 | Assumed sensitivity |        |
|------------------------------|-----------------|---------------------|--------|
| Prevalence                   | Number of cases | 80%                 | 90%    |
| 50%                          | 170             | 73-86%              | 84-95% |
| 40%                          | 136             | 72-86%              | 83-94% |
| 30%                          | 102             | 71-87%              | 83-95% |
| 20%                          | 68              | 69-89%              | 80-96% |

**Table 4 Range of 95% confidence intervals for varying prevalences**

It is anticipated some women will need to be excluded from the test accuracy analysis due to the need to unblind the gynaecologist to the results of the MRI or if the laparoscopy is not performed. Recruitment will continue until 340 cases have been registered and both an post-MRI diagnosis and post-laparoscopy diagnosis obtained. Rates of, and reasons for, exclusion from the main analysis will be monitored.

We have commitment to recruit from up to 26 UK centres, 9 of which have a track record of recruitment into the LUNA trial (31).

## **5.2. Projected accrual and attrition rates**

Accrual and attrition rates will be closely monitored against our target, and in the unlikely event that recruitment is insufficient, the Study Management Group have identified other units likely to be able to participate.

## **5.3. Analysis for test accuracy study**

### **5.3.1 Primary analysis**

Comparison of the post-MRI diagnosis and the post-laparoscopy diagnosis with the reference diagnosis will determine in how many cases the post-laparoscopy diagnosis has diagnosed more pathological conditions. We will also determine in how



many women the post-MRI diagnosis has delivered a correct pathological diagnosis when the post-laparoscopy diagnosis did not. These proportions will be reported along with 95% confidence intervals calculated by binomial exact methods.

### **5.3.2 Secondary analyses**

The accuracy of MRI and laparoscopy for each pathological cause of CPP will be made through standard estimates of sensitivity, specificity, predictive values and likelihood ratios. 95% confidence intervals will be calculated as per the primary analysis. We will investigate the value added by laparoscopy compared with MRI and also the value added by either of these tests compared with information already obtained from routinely used initial non-invasive tests (history, questionnaires, ultrasound, etc) (22). These combinations of tests were be assessed using logistic regression models, with the sequential nature of the testing taken into account using the model parameterization of Kottnerus (57).

### **5.3.3 Other analyses**

Using multivariable logistic regression analysis, we will also generate predictive probabilities for various combinations of history, MRI and laparoscopy results. We have experience of undertaking such analysis to estimate predictive probabilities (24). In statistical terms, logistic modelling will aim to derive a diagnostic regression function, i.e. probability of each pathological cause of CPP given test result. The analysis will be performed with an expert independent panel reference diagnosis of the cause of CPP as the outcome variable and MRI or laparoscopy as an explanatory variable. The models will allow a direct estimation of the post-test-combination disease probabilities that we need for decision-making and for decision-analysis. Models of varying complexity may be compared through the familiar receiver operating characteristic (ROC) analyses. More importantly, the clinical situation where some information is already acquired, such as clinical symptoms prior to undertaking MRI, will be mirrored. In this way, for various index test results conditional disease probabilities will be generated directly taking into account any overlap of information that may exist between tests. This approach evaluates the extent to which the findings of the index tests add value to the presentation. Its output is transparent, and is likely to enable production of simple clinical algorithms based on probabilities. The advantages of tackling diagnostic problems with logistic regression modelling are well known (25). The limitation associated with the regression approach lies mainly in its generalisability to other data sets or clinical practices. The recommended techniques, such as bootstrapping to enhance generalisability and estimate the amount of shrinkage will be applied for model validation (26;27). We anticipate that our sample will comfortably meet the recommended events per variable rule to avoid overfitting the models even if some data were missing. In a sensitivity analysis, missing data will be estimated by multiple imputation and maximum-likelihood methods, as appropriate, to explore the potential bias and reduced statistical power associated with list wise deletion.

## 5.4. Handling missing data

Sensitivity analysis will be employed to explore the potential bias and reduced statistical power associated with listwise deletion of missing data, using multiple imputation and maximum-likelihood methods, as appropriate (28).

### 5.4.1 Certainty of diagnosis

The certainty with which gynaecologists have made their diagnoses will be measured and compared as a secondary measure of diagnostic efficacy. In order to be clinically effective, tests should contribute to the diagnostician's decision-making (58), for example by changing a differential diagnosis, strengthening an existing hypothesis or simply reassuring the clinician. Although accuracy is the chief concern, the extent to which clinicians make use of test results also relies on their confidence that the test has contributed usefully to a diagnosis. The MEDAL study will therefore evaluate the diagnostic impact of MRI and of laparoscopy by conducting:

1. Before-after comparison of diagnostic certainty for having diagnosed the cause of CPP
2. Before-after comparison of diagnostic certainty for the leading diagnosis
3. Before-after comparison of the number of differential diagnoses considered per patient
4. Retrospective survey of the test's perceived usefulness

### Impact of laparoscopy

On the basis of clinical history, examination and ultrasound findings only (**Form 6**), treating gynaecologists will be asked state whether a pathological cause for CPP has or has not been identified, and to express their certainty regarding this decision. They will also be asked to list their differential diagnoses, state whether each is thought to be a cause of CPP, and express their certainty regarding these opinions. After the laparoscopy has been performed, clinicians will be asked for a revised differential diagnosis and associated certainty using identical questions (**Form 8**). A comparison between pre- and post-laparoscopy diagnostic certainty will be made to determine the utility of laparoscopy for identifying a pathological cause of CPP, and secondarily to compare changes in the certainty surrounding the leading differential diagnosis. The number of differential diagnoses considered before laparoscopy will also be compared directly with the number considered after test results are known.

### Impact of MRI

An identical process will be followed with independent non-treating gynaecologists who will use MRI to arrive at a diagnosis (blind to the laparoscopy). Pre-MRI diagnoses and associated certainty (**Form 11a**) based on the same clinical history, examination and ultrasound findings (where available), will be compared with post-MRI revised diagnoses and certainties (**Form 11b**). Independent gynaecologists will also be asked whether they believe the patient should require a laparoscopy.

### **Measurement of certainty**

Certainty will be quantified using an eleven-point probabilistic rating scale (59), known to have good validity (60). Clinicians will be asked to rate the certainty of their diagnoses by choosing one of the eleven statements that are ranked from 'certain/practically certain' (rank 10) to 'no chance/almost no chance' (rank 0). Each statement is also associated with a probabilistic descriptor (e.g. 'Very slight possibility' is combined with 'a 1 in 10 chance') to further anchor clinicians' responses, and to facilitate a numerical analysis of these subjective responses. These range from a 1 in 100 chance (equivalent to 1% certainty) to a 99 in 100 chance (or 99% certainty).

### **Perceived usefulness**

The gynaecologist's subjective assessment of the usefulness of MRI or laparoscopy will be evaluated after disclosure of the relevant test results, by asking clinicians to select one of four statements that best reflects their perception of the contribution of the test to each case. These statements were initially drafted with reference to those used in published before-after diagnostic confidence studies (61;62;63), and modified for their relevance to chronic pelvic pain diagnosis following consultation with eight practicing gynaecologists.

### **Analysing the diagnostic impact of MRI vs. Laparoscopy**

The primary question of this nested substudy seeks to address whether the use of laparoscopy is associated with a greater increase in diagnostic certainty than the use of MRI for identifying the cause of CPP. To do this, mean differences in diagnostic certainty as a result of using laparoscopy are compared with mean differences as a result of using MRI. Secondary analyses will perform the same comparison for the certainty of the leading differential diagnosis.

Calculations will use the probabilistic descriptors associated with certainty ratings, for example 'very slight possibility, a 1 in 10 chance' will become 10%. The change in diagnostic certainty is calculated on a per-patient basis as the direct difference between diagnostic probabilities given before clinicians see the results of a particular test (pre-test confidence), and those given with knowledge of the test results (post-test confidence).

Analysis will follow the Tsushima method that takes the accuracy of index diagnoses into account (64). When the gynaecologist's pre or post-test diagnosis is not consistent with the final true diagnosis, as determined by the reference standard, the reported diagnostic certainty will be converted to a negative value to 'penalise' the negative impact incorrect diagnoses could have on decision-making and patient health. Thus a 90% confidence in an false diagnosis will become -90%. The maximum difference will therefore be 198%.

The number of differential diagnoses considered pre- and post-testing will be compared to further clarify how MRI and laparoscopy are used in decision-making.

These continuous data will be presented as means  $\pm$  standard deviation. For statistical analysis the paired t-test will be used, with p-values  $<0.05$  considered significant.

Perceived usefulness responses will be summarised as proportions of clinicians finding the relevant test useful versus of little/no use, with the  $\chi^2$  test for statistical comparison at the 0.05 significance level.

## **5.5 MODEL BASED ECONOMIC ANALYSIS**

The objective of the economic evaluation is to compare the relative cost effectiveness of MRI imaging as a triage tool, an adjunct or replacement to standard practice of laparoscopy in the differential diagnosis of women with CPP.

There will be two components to the analysis: a within study analysis and a model-based analysis. The model-based analysis will allow projection of costs and benefits beyond the immediate test accuracy study data. Data from the follow up assessment carried out at six month will be available from the study. Data will be sought from the women who were ineligible for the diagnostic test accuracy study for any reason and were not further followed up by the study. The accuracy data on screening based on the MRI, and the laparoscopy will be collected directly from the current study.

The model will consider treatment over total duration of the diagnostic accuracy study and will include consideration of medical and/or surgical treatments provided in the longer term. The model-based analysis will adopt a short term outcome of 'cost per correct diagnosis from MRI' and an outcome of cost per laparoscopy avoided by six months to coincide with the final follow up. Depending on the data availability from published sources, the model outcome may be extended beyond the study outcome of six months. A cost utility analysis will also be performed using data from the EuroQol 5Q-ED and ICECAP-A.

### **5.5.1 Perspective and data collection**

If MRI is shown to be an effective adjunct or replacement to the standard practice of laparoscopic examination to investigate CPP in women, then it is likely that important cost implications will be seen for the health care sector. For example, MRI may accurately diagnose a target condition and remove the necessity for a laparoscopy. It is also possible that incidental cases of cancer are detected sooner and more readily than by laparoscopy alone, or at least provide the reassurance women want and improve their perception of their health related quality of life. The additional costs of MRI and resulting treatment may lead to a reduction in costs associated with the more invasive laparoscopy and avoid potential complications. The economic evaluation will be based on outcomes which include cost per QALY, cost per laparoscopy avoided and cost per correct diagnosis. The utility values required to calculate QALYs will be obtained by administering the EuroQol EQ-5D and ICECAP-A questionnaires to all study participants as part of the pre-index tests and at six months post recruitment.

The economic evaluation will take the perspective of the NHS in the base case but a wider societal perspective will also be considered as far as possible.

Based on the NHS best practice tariff system resource use data will be collected to estimate the costs associated with the additional use of MRI in the differential diagnosis of CPP. We shall therefore prospectively collect data on NHS resource use for a purposive sample of the study. The main resources to be monitored include:

1. The time for preparing the scanner, performing the MRI scan and interpretation of the images.
2. The equipment and resources associated with MRI and knock-on costs associated with additional or incidental findings
3. Time and resources associated with the laparoscopy
4. Time and resources associated with complications or adverse events arising from either tests (although given the sample size, it is unlikely we will observe any serious adverse events)

Cost data will be collected from two principal sources. First, the primary MRI test accuracy study will provide the time (staff and equipment) and other resource use data to estimate cost incurred in performing the MRI and the subsequent laparoscopy and a patient cost questionnaire will collect private out of pocket costs to women. Primary cost data for many of these resources will be collected from the participating hospital sites. Where possible other cost data, such as cost of radiologist time etc to carry out the MRI scan will be collected from routine sources, including Netten *et al* (65) and hospital finance departments.

The accuracy data on differential diagnosis, based on the MRI imaging, the laparoscopy and the panel reference diagnosis will be collected directly from the current study.

Additional literature searches will be undertaken to help populate the decision model. The clinical Chief Investigator will work in close liaison with the health economist to identify the model questions. Information to answer these questions will be provided by focused searching of appropriate databases, including reference cost databases, statistical sources and other sources of relevant information.

### **5.5.2 Within study analysis**

This will use only data collected within the accuracy study and so, for example, will draw upon the test performance data. Estimates of costs and benefits will therefore relate only to the period of follow-up, and no predictions for costs and benefits beyond the study will be made. The data available for this analysis will be patient-specific resource use and costs. Given the skewness inherent in most cost data and the concern of economic analyses with mean costs, we shall use a bootstrapping approach in order to calculate confidence intervals around the difference in mean costs (66;67). An incremental economic analysis will be conducted. The base-case analysis will be framed in terms of cost-consequences, reporting data in a disaggregated manner on the incremental cost and the important consequences, including data on the number of correct diagnoses identified by MRI, etc.

Three main strategies will be compared:

- History, examination, ultrasound (where clinically indicated/ available) and laparoscopy
- MRI scans as an adjunct to laparoscopy
- MRI as a replacement for laparoscopy

### **5.5.3 Discounting**

If the outcome of the model coincides with that of the study, i.e. six months, then discounting is not required. But if the model extends beyond the outcome of the study and given the potentially relatively long time horizons being considered in these analyses, many of the costs (and benefits) will be incurred (and experienced) in future years. Using discounting, adjustments will be made to reflect this differential timing. The base-case analysis will follow Treasury recommendations for public sector projects.

### **5.5.4 Presentation of results and sensitivity analysis**

The results of these economic analyses will be presented using cost-effectiveness acceptability curves to reflect sampling variation and uncertainties in the appropriate threshold cost-effectiveness value. Both simple and probabilistic sensitivity analyses will be used to explore the robustness of these results to plausible variations in key assumptions and variations in the analytical methods used, and to consider the broader issue of the generalisability of the results.

## **6. DATA MANAGEMENT AND QUALITY ASSURANCE**

### **6.1. *Data management and validation***

#### **6.1.1 *Confidentiality of personal data***

All participants in the study will be identified to the central organisers by their NHS and/or hospital number and will be given a unique study number. As there is central follow-up by postal questionnaire or an email link to a web form, we will collect personal identifiable information, for which the women will be asked to provide consent.

The study will collect personal data and sensitive information about the participating women. Participants will be informed about the transfer of this information to the MEDAL Study office at the Birmingham Clinical Trials Unit (BCTU), University of Birmingham and will be asked to consent to this. Baseline and follow-up data will be pseudo-anonymised by using study numbers and patient initials. Participant demographic data, test results and questionnaire answers will be stored on a secure server, input where possible via the internet using secure socket layer encryption technology, may be faxed or through NHS.net to NHS.net email system. Remaining data will be returned via a couriered postal service to the BCTU. Only registered study personnel will have access to the database.

All participant data will be processed and stored according to the MRC guidelines of use of personal data. All personal information obtained for the study will be held securely and treated as confidential. All staff, at the hospitals, in the community or at the BCTU, share the same duty of care to prevent unauthorised disclosure of personal information. No data that could be used to identify an individual will be published.

### **6.1.2 Long-term storage of data**

Following the MRC's guide for retention of data, we will keep the data collected for 20 years following the close of the study to allow for verification and any further data sharing e.g. individual patient data meta-analysis. The BCTU has standard operating procedures for legacy archiving. The University of Birmingham will act as custodians of the data.

## **6.2. In-house Data Quality Assurance**

### **6.2.1 Monitoring and Audit**

Investigators and their host Trusts will be required to permit trial-related monitoring and audits to take place by the MEDAL Study Coordinator, providing direct access to source data and documents as requested. Trusts may also be subject to inspection by the Research and Development Manager of their own Trust and should do everything requested by the Chief Investigator in order to prepare and contribute to any inspection or audit. Study participants will be made aware of the possibility of external audit of data they provide in the participant information sheet. Study staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Study staff will check incoming Data Collection Forms for compliance with the protocol, data consistency, missing data and timing. Sites will be contacted to request missing data or clarification of inconsistencies or discrepancies. A sample of test results input in the participating centres will be cross-checked at the MEDAL Study Office with paper or electronic records.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the Data Monitoring Committee. This includes reporting serious breaches of GCP and/or the study protocol to the main Research Ethics Committee (REC).

### **6.2.2 On-site Monitoring**

Monitoring will be carried out as required following a risk assessment. Additional on-site monitoring visits may be triggered for example by poor data collection form return, poor data quality, low SAE reporting rates, excessive number of patient withdrawals or deviations. If a monitoring visit is required the Study Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the MEDAL study staff access to source documents as requested.

### **6.2.3 Statistical monitoring throughout the study**

Real-time reports will be available to staff indicating missing test and questionnaire data for all participants at that centre. This will be supplemented by regular reminders from the MEDAL Study Office for incomplete data. The study statistician will report on recruitment, compliance and completeness of verification to the Steering Committee quarterly.

### **6.3. Independent Supervision of the Study**

The Study Steering Committee provides independent supervision for the study, providing advice to the investigators and the Sponsor on all aspects of the study and affording protection for patients by ensuring the study is conducted as applicable to the MRC Guidelines for Good Clinical Practice in Clinical Trials.

If the clinical co-ordinators are unable to resolve any concern satisfactorily, collaborators, and all others associated with the study, may write through the study office to the chair of the SSC, drawing attention to any concerns they may have about the possibility of distortion of clinical practice, or of particular categories of patient requiring special study, or about any other matters thought relevant. The terms of reference and charter for this committee will be determined at the outset taking into account issues relevant to monitoring of diagnostic test accuracy studies.

The study shall follow and comply with the MRC Guidelines on Good Clinical Practice, although its advice in relation to test accuracy studies is limited. The Study Team has made provisional recommendations regarding the independent supervision and data monitoring of test accuracy studies as a consequence of experiences in previous studies (31). One such recommendation is that, if desirable, the independent Data Monitoring Committee (DMC) should be formed as a sub-committee of the Study Steering Committee (SSC). For the purposes of this study, the SSC shall convene and nominate a three member independent DMC from within its membership, that shall not include study researchers.

### **6.4. Data Monitoring Committee: determining when clear answers have emerged**

If the MRI has acceptable sensitivity and specificity compared with the reference standard, then this may become apparent before the target recruitment has been reached. The assumed prevalence of specific causes of CPP may prove to be inaccurate and require a recalculation of the sample size. Alternatively, the MRI may be found to be unworkable, new evidence of the effectiveness of the test might emerge from other sources or new technologies may be introduced to the market.

To protect against this, at 6 months into recruitment to the study, interim analyses of major endpoints will be supplied to the DMC along with updates on results of other related studies, and any other analyses that the DMC may request. The DMC will determine whether the assumptions underpinning the sample size are correct at 6 months after commencement of recruitment. The interim analysis will also determine if the principal question on index test accuracy has been answered and will monitor adverse events. The combined SSC/ DMC (a) should consider the balance of harms and risks in the context of all available data, and make recommendations on the principle of “proof beyond reasonable doubt” and (b) consider evidence that might reasonably be expected to influence the patient management of many clinicians. The SSC/DMC can then decide whether to close or modify any part of the study. Unless this happens, however, the SSC, the collaborators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results.



## **7. ORGANISATION AND RESPONSIBILITIES**

The Chief Investigator is responsible for the management, central co-ordination of clinical and administrative aspects of the study, compliance with the Research Governance Framework and management of study budget. Relevant ethics committee and Trust research governance approval will be coordinated centrally for efficiency and speed.

All investigators are responsible for ensuring that the research they undertake follows the agreed protocol, for helping care professionals to ensure that participants receive appropriate care while involved in research, for protecting the integrity and confidentiality of clinical and other records and data generated by the research, and for reporting any failures in these respects, adverse reactions and other events or suspected misconduct through the appropriate systems.

### **7.1. Centre eligibility**

Initially, nine hospitals in nine NHS Trusts will recruit women into the study. Per patient payments may be available recruited which can be used to fund a research nurse session to conduct the study in the participating centres. Other centres wishing to participate can do so provided their Trust will support this portfolio study.

### **7.2. Local Co-ordinator at each centre**

Each Trust has a designated Consultant gynaecologist or radiologist to act as Principal Investigator and bear responsibility for the conduct of research at their centre. The responsibilities of the Principal Investigators will be to ensure that all medical and radiography staff involved are well informed about the study. This will involve distributing protocols and patient information sheets to all relevant staff, displaying publicity material where it is likely to be read, and contributing to the regular newsletters. The Principal Investigators should liaise with the MEDAL Study Office on logistic, data collection and administrative matters connected with the study.

### **7.3. Nurse Co-ordinator at each centre**

Each participating centre should have a designated research nurse who will act as Local Nurse Coordinator. This person would be responsible for ensuring that all eligible patients are considered for the study, that patients are provided with study information sheets, and have an opportunity to discuss the study if required. The nurse will be responsible for the organisation of data collection and will be the first point of contact for data queries.

### **7.4. The Study Office**

The Study Office at the University of Birmingham Clinical Trials Unit (BCTU) is responsible for providing all study materials, including the coded stickers and questionnaires. Additional supplies of any printed material can be obtained on request. The Study Office is also responsible for collection and checking of data

(including reports of serious adverse events) and for analyses. The Study Office will help resolve any local problems that may be encountered in study participation and will supply accrual data to the NIHR on behalf of each centre.

## **7.5. Research Governance**

The conduct of the study will be according to the principles of MRC Guidelines for Good Clinical Practice in Clinical Trials (1998) and the appropriate NHS Research Governance Frameworks.

All centres will be required to sign an Investigator's Agreement, detailing their commitment to accrual, compliance, Good Clinical Practice, confidentiality and publication. Deviations from the agreement will be monitored and the SSC will decide whether any action needs to be taken, e.g. withdrawal of funding, suspension of centre. Proof of training in the principles of good clinical practice and informed consent may be required.

The Study Office will ensure researchers not employed by an NHS organisation who interact with individuals in a way that has direct bearing on the quality of their care hold an NHS research passport for that organisation.

## **7.6. Regulatory and Ethical Approval**

The Chief Investigator has obtained a favourable ethical opinion from National Research Ethics Services (NRES) Committee East Midlands – Nottingham 1 for a multi-centre study. Each Trust Research and Development Office will assess each site for "locality issues" relating to their population, the investigators, the facilities and resources and grant site specific approval before recruitment commences. Applications for NHS host approval from each participating Trust will be facilitated by the study coordinator. Training of the study research nurse in the requirements of the study and in the principles of good clinical practice will be provided by the Study Office, who will monitor conduct centrally.

## **7.7. Funding and Cost implications**

The research costs of the study are funded by a grant from the National Institute for Health Research (NIHR) Health Technology Assessment Unit awarded to the Queen Mary, University of London.

The MEDAL trial will automatically be included in the NIHR portfolio, which allows local investigators and their Trust to access additional support for the study, for example regular nurses sessions to support clinics. This may be provided directly from the Trust's service support allocation or via the local comprehensive research network. The MEDAL Study Coordinator will assist local investigators in accessing this support.

The clinical assessment form completed at the initial clinic visit will be photocopied and can either be data entered by the coordinating nurse, which should take only a couple of minutes, or returned to the Study Office for entry. Personal identifiers will be removed before forwarding the form to the Study Office.

The follow-up assessment will be posted to study participants with a postage-paid return envelope and will be data entered at the Study Office.

As the trial will automatically be included in the NIHR CRN, speciality group leads for each CLRN will be approached to provide dedicated research nurse support for the trial. Already, within the Birmingham and Black Country CLRN, provisional agreement has been given for nurse support, for promotion of the trial within referring centres and for facilitating a dedicated pelvic pain clinic, through their REACH (Reproductive Health and Childbirth) Network. The Scottish Universities have funding for the setting up of Clinical Research Facilities to cover Scotland that will include research nurse time as well as infrastructure support to support Clinical Trials. It will be possible to access these facilities.

### **7.8. Indemnity**

There are no special arrangements for compensation for non-negligent harm suffered by patients as a result of participating in the study. The study is not an industry-sponsored study and so ABPI/ABHI guidelines on indemnity do not apply. The normal NHS indemnity liability arrangements for research detailed in HSG96 will operate in this case.

However, it should be stressed that in terms of negligent liability, NHS Trust hospitals have a duty of care to a patient being treated within their hospital, whether or not that patient is participating in a clinical study. Apart from defective products, legal liability does not arise where there is non-negligent harm. NHS Trusts may not offer advance indemnities or take out commercial insurance for non-negligent harm.

### **7.9. Publication**

A meeting will be held after the end of the study to allow discussion of the main results among the collaborators prior to publication. The success of the study depends entirely on the wholehearted collaboration of a large number of doctors, nurses and others. For this reason, chief credit for the main results will be given not to the committees or central organisers but to all those who have collaborated in the study. Collaborators will be permitted to publish data obtained from participants in the MEDAL Study that use study outcome measures but do not relate to the study objectives.

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## APPENDIX A: PARTICIPANT INFORMATION SHEET

### The MEDAL Study: MRI to Establish Diagnosis Against Laparoscopy

- Principal Investigator (name only stated)
- Local staff (contact telephone numbers/ email) who may be contacted by patient listed here (e.g. research nurse)

- MEDAL Study Office  
Birmingham Clinical Trials Unit,  
University of Birmingham

Robert Aitken Institute, University of Birmingham  
Edgbaston, Birmingham, B15 2TT

Tel: 0121 414 6665

Email: [medal-study@trials.bham.ac.uk](mailto:medal-study@trials.bham.ac.uk); Website: [www.birmingham.ac.uk/medal](http://www.birmingham.ac.uk/medal)

**Please note that the MEDAL Study office does not offer advice on clinical queries.**

### **PARTICIPANT INFORMATION SHEET**

We would like to invite you to take part in a research study that will see if magnetic resonance imaging (MRI) scans are useful in investigating the causes of pelvic pain in women. We have included a leaflet that gives you more information about MRI scans. The study is entirely voluntary – you do not have to take part, nor do you have to give a reason if you decide not to participate. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it would involve. Please take your time to read this information sheet carefully and talk to others about the study if you wish. If there is anything that is not clear, or if you would like more information, you should ask your gynaecologist or the research nurse for further advice.

Part One of this leaflet tells you about the purpose of the MEDAL study and what will happen if you take part

Part Two gives you more detailed information about the conduct of the study

### **What is the purpose of the study?**

- Chronic Pelvic Pain (CPP) is defined as pain in the pelvic and lower abdominal region, that lasts 6 months or longer. It is a very common condition.
- Possible causes for CPP include endometriosis, chronic pelvic inflammatory disease, adhesions, irritable bowel syndrome, painful bladder syndrome, and pelvic congestion syndrome. Pain may also arise from musculoskeletal conditions or pelvic organ prolapse.
- Often, a diagnostic laparoscopy (a telescopic examination of the pelvis by keyhole surgery) is performed to look for a cause for the pain. Laparoscopy requires a general anaesthetic and has a small risk of injury to internal organs. However, about a third to a half of women with CPP who undergo laparoscopy have no obvious cause for their pain identified.
- MRI scans of the pelvic region may be able to identify or rule out conditions such as endometriosis, so a laparoscopy can either be avoided or surgical treatment planned as part of the laparoscopy.
- Our aim is to evaluate if a MRI scan can replace laparoscopy in the diagnosis of CPP in women. We will do this by determining whether MRI scans give a correct diagnosis as often as laparoscopy does.

### **Why have I been chosen?**

All women with symptoms of chronic pelvic pain who have been referred to this hospital by their GP are invited to participate.

Your hospital doctor may offer you an ultrasound and a diagnostic laparoscopy to investigate the cause of your pain. It is hoped 340 women from several hospitals who are undergoing a laparoscopy will take part in the study.

If you do not need a laparoscopy, we would still like to ask you for permission to access information in your medical notes so that we can look at the reasons why laparoscopy is, or is not, recommended.

### **Do I have to take part?**

It is up to you to decide whether or not to join the study. Please bring this information sheet and consent form with you when you come to the clinic as you will be asked at your hospital clinic appointment whether you are willing to take part. If you agree, you will be asked to sign the consent form. At the next hospital clinic visit, you will be asked again if you still agree to participate. You are free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to participate, will not affect the standard of care you receive.

### **What will happen to me if I take part?**

If you agree to take part in the study, we would like your permission to use information from your medical notes for the study. This will include the Pelvic Pain Assessment that you filled in either at home and/or when you first attended the clinic.

No payment is available to participants for taking part in the study; however any travel expenses incurred for attending the MRI scan (requested as part of the study) may be reimbursed.

### **What else do I have to do?**

In about 6 months time, we will ask you to fill in a questionnaire about your symptoms and wellbeing. We will post the questionnaire to you with a postage-paid return envelope.

### **What are the possible disadvantages and risks of taking part?**

MRI, which is a widely used and accepted test, is not frequently used to investigate the causes of pelvic pain. We do not expect there to be any problems or risks due to the MRI scan.

The laparoscopy investigation will be identical whether or not you are the MEDAL study. With laparoscopy, there is about a 1 in 30 risk of minor complications (e.g. nausea and vomiting, shoulder tip pain), a 1 in 420 risk of unanticipated injury causing major complications (e.g. bowel perforation). There are also risks from the general anaesthetic.

### **What are the possible benefits of taking part?**

MRI is not frequently used to investigate the causes of pelvic pain. Unless your hospital doctor thinks you have a condition that definitely requires a MRI scan, you would not normally be offered a MRI. If you take part in MEDAL and something unexpected and serious is found on the MRI scan, you will be treated appropriately. Therefore there is the possible benefit of something unexpected being identified which might not have been picked up otherwise. Another way of looking at this is that the MRI may quickly rule out any serious causes of the pain that you may have been worrying about.

Also, of course, the information we get from this study may in the future help us reduce the need for laparoscopy in women with chronic pelvic pain.

Thank you for reading about the MEDAL Study. If you are interested in participation, please read Part Two.

## **PART TWO: more information about the MEDAL Study**

### **What if something goes wrong or I have any concerns?**

Queen Mary University of London has agreed that if you are harmed as a result of your participation in the study, you will be compensated, provided that, on the balance of probabilities, an injury was caused as a direct result of the intervention or procedures you received during the course of the study. These special compensation arrangements apply where an injury is caused to you that would not have occurred if you were not in the trial. These arrangements do not affect your right to pursue a claim through legal action if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you. You contact the Patient Advocacy and Liaison Service (PALS) at your hospital.

### **Will my taking part in this study be kept confidential?**

Yes, all information collected in the study will remain strictly confidential in the same way as your other medical records. If you agree to take part, your nurse or doctor will send information about you to the study's central organisers. This information will be put into a computer and analysed. The information will be identified only by a code number. All information will be held securely and in strict confidence. No named information about you will be published in the study report. Occasionally, inspections of clinical study data are undertaken to ensure that, for example, all participants have given consent to take part. But, apart from this, only the study organisers will have access to the data.

With your consent we will inform your GP of your participation in the MEDAL Study.

### **What will happen to the results of the research study?**

The study will last for around three years, after which we expect to publish the results in scientific journals. We will send you a summary of the results by post.

### **Who is organising and funding the research?**

The MEDAL study is funded by a grant from the NIHR Health Technology Assessment programme. The central study organisers are based at Queen Mary, University of London and the University of Birmingham. This study has been reviewed and given favourable opinion by The Chief Investigator and has obtained a favourable ethical opinion from National Research Ethics Services (NRES) Committee East Midlands – Nottingham 1 for a multi-centre study. The Clinical Trials Unit at the University of Birmingham will collect and analyse the data. The researchers, doctors and nurses involved are not being paid for recruiting women into the study. We cannot pay women to take part either, but we will be very grateful for your participation in the study.

### **Do you have any other questions?**

Having read this leaflet, we hope that you will choose to take part in the MEDAL Study. If you have any questions about the study now or later, feel free to ask the personnel whose names and telephone numbers are given on the front of this leaflet.

## **APPENDIX B1: PATIENT CONSENT FORM – FOR THE DIAGNOSTIC STUDY (FORM 5A)**

### **The MEDAL Study:**

#### **MRI to Establish Diagnosis Against Laparoscopy**

#### **PATIENT CONSENT FORM – FOR THE DIAGNOSTIC STUDY**

I confirm that I have read and understand the participant information sheet (version 3.0, dated 12/08/2013) for the MEDAL study and have had the opportunity to consider the information, to ask questions and these have been answered satisfactorily.

☐ (Please initial)

I understand what is involved in the MEDAL study and agree to participate. I intend to participate in the study, but I understand that I am free to change my mind when I go into hospital without necessarily giving a reason. If I do withdraw, I can continue to expect the highest standard of care from my doctor or nurse.

☐ (Please initial)

I understand that if I require a laparoscopy, I will have a MRI scan before the laparoscopy. I agree to have an MRI scan.

☐ (Please initial)

I understand that my doctors will provide a copy of my consent form and information from my medical notes, in confidence, to the central organisers at Birmingham Clinical Trials Unit (BCTU) for use in the MEDAL Study. I understand that the information held by the NHS may be used to keep in touch with me and follow up my health status.

☐ (Please initial)

I understand that the information will be used for medical research only and that I will not be identified in any way in the analysis and reporting of the results. I understand that sections of any of my medical notes may be looked at by responsible individuals from the University of Birmingham or from regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

☐ (Please initial)

4 copies: Original copy for MEDAL site file, 1 copy for patient, 1 copy to be kept in patient's hospital notes and 1 copy to be sent to MEDAL Study Office.

I consent to my GP being informed that I am participating in the MEDAL study ☐ (Please initial)

I agree to participate in the MEDAL Study (doctor/nurse to indicate here) ☐ (Please initial)

Name of Participant

Date

Signature

Name of Person taking consent

Date

Signature

If applicable:

I have interpreted the information above to the best of my ability and in a way in which the patient can understand.

Name of Interpreter

Date

Signature

4 copies: Original copy for MEDAL site file, 1 copy for patient, 1 copy to be kept in patient's hospital notes and 1 copy to be sent to MEDAL Study Office.

## **APPENDIX B2: PATIENT CONSENT FORM – DATA COLLECTION ONLY (FORM 5B)**

### **The MEDAL Study: MRI to Establish Diagnosis Against Laparoscopy**

#### **PATIENT CONSENT FORM – FOR DATA COLLECTION ONLY**

I confirm that I have read and understand the participant information sheet (version 3.0, dated 12/08/2013) for the MEDAL study and have had the opportunity to consider the information, to ask questions and these have been answered satisfactorily.

☐ (Please initial)

I understand that I am not eligible for the MEDAL diagnostic study. My gynaecologist has explained to me why I am not.

☐ (Please initial)

I do consent for the information already collected to be used alongside information collected for the MEDAL study. This includes the Pelvic Pain assessment form that I completed, information from the gynaecologist, the ultrasound scan, and the MRI scan (if applicable).

☐ (Please initial)

I understand that my doctors will provide a copy of my consent form and personal information, in confidence, to the central organisers at Birmingham Clinical Trials Unit (BCTU) for use in the MEDAL Study.

☐ (Please initial)

I understand that the information will be used for medical research only and that I will not be identified in any way in the analysis and reporting of the results. I understand that sections of any of my medical notes may be looked at by responsible individuals from the University of Birmingham or from regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

☐ (Please initial)

4 copies: Original copy for MEDAL site file, 1 copy for patient, 1 copy to be kept in patient's hospital notes and 1 copy to be sent to MEDAL Study Office.

I consent to my GP being informed that I am contributing information to be used alongside the MEDAL study.

☐

(Please initial)

Name of Participant

Date

Signature

Name of Person taking consent

Date

Signature

If applicable:

I have interpreted the information above to the best of my ability and in a way in which the patient can understand.

Name of Interpreter

Date

Signature

4 copies: Original copy for MEDAL site file, 1 copy for patient, 1 copy to be kept in patient's hospital notes and 1 copy to be sent to MEDAL Study Office.





## APPENDIX C: REGISTRATION FORM

To be completed before registering participant into the Study

Hospital label here

### PART A: IDENTIFICATION DETAILS

Consultant: .....

Hospital:.....

Patient's Surname: .....

Patient's Forenames: .....

Patient's title: Mrs Miss Ms Dr Other:.....

Date of birth (dd/mm/yyyy): ...../...../.....

Patient NHS No.:

Patient hospital no.:

Patient's address: .....

Postcode: .....

Patient's daytime telephone number:.....

Evening telephone number: .....

Mobile telephone number: .....

Patient's email: .....

### PART B: ELIGIBILITY

| B(i)  | Yes                                 | No                                  |
|---|-------------------------------------|-------------------------------------|
| Aged 16 or over   | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |
| Referred to gynaecologist for unexplained Chronic Pelvic Pain | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |
| Has capacity to give consent                                  | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |
| Is able to speak English or has a suitable interpreter        | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |
| Is pregnant   | <input checked="" type="checkbox"/> | <input type="checkbox"/>            |
| Has had a hysterectomy  | <input checked="" type="checkbox"/> | <input type="checkbox"/>            |

If any of the shaded boxes in section B(i) are ticked, the patient is not eligible. If the patient is eligible, proceed to section B(ii) to consider eligibility for the diagnostic test accuracy part of the study

| B(ii)   | Yes                                 | No                                  |
|---|-------------------------------------|-------------------------------------|
| Has identifiable cause of CPP on which treatment can be initiated without laparoscopy | <input checked="" type="checkbox"/> | <input type="checkbox"/>            |
| Referred for laparoscopy  | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |
| Requires MRI based on history and ultrasound  | <input checked="" type="checkbox"/> | <input type="checkbox"/>            |

If all the clear boxes in both Sections B(i) and B(ii) are ticked, the patient is eligible for the diagnostic test accuracy part of the study. If all the clear boxes in section B(i) are ticked but one or more shaded box in B(ii) is ticked, the patient is eligible for data collection only.

Date of participant registration:

--

Yes

No

Has the patient been previously considered and consented for MEDAL (if yes, please use original Study No.)

☐

☐

### PART C: STUDY REGISTRATION (COMPLETE AT THE TIME OF THE PHONE CALL ONLY)

To register please call 0800 953 0274

MEDAL study number:

MEDAL Contact name: .....

Telephone: .....

Date of laparoscopy, if known:

--

## APPENDIX D: LETTER TO GP

*To be printed on centre headed paper*

### The MEDAL Study: MRI to Establish Diagnosis Against Laparoscopy

#### LETTER TO GP

*Doctor*

*Practice*

*Street*

*City*

*Postcode*

*Date*

Dear Dr <gp name>

Name.....D.o.B.....NHS No.....

Your patient, named above, has been referred to <centre> for assessment of pelvic pain symptoms, and is suitable for entry to the MEDAL Study: MRI to Establish Diagnosis Against Laparoscopy

Queen Mary, University of London is acting as sponsor. The University of Birmingham Clinical Trials Unit are acting as coordinating centre. The study is funded NIHR Health Technology Assessment Programme. The study has been approved by the XXX Research Ethics Committee and approvals have been obtained at each participating centre.

*Your patient has been informed about the **MEDAL** study, has consented to take part and will undergo both MRI and diagnostic laparoscopy to establish a differential diagnosis for her chronic pelvic pain. We will inform you of the diagnosis and recommended management in due course.*

OR

*Your patient has been informed about the **MEDAL** study and has consented to take part. Her participation will not alter her clinical care.*

OR

*Your patient had previously consented to take part in the study and following a second clinic visit has now consented to undergo both an MRI and diagnostic laparoscopy to establish a differential diagnosis for her chronic pelvic pain.*

Should the MRI identify any symptoms that warrant further investigation the patient will be referred to the relevant place and withdrawn from the study.

If you have any queries about the patient's management, please feel free to contact me. If you require any further information about the **MEDAL** study, it can be obtained from the **MEDAL** trial office (see address below). Please file this letter in the patient's notes. I would appreciate being notified if they are no longer one of your patients.

Yours sincerely

*Name*

*Position*

MEDAL Study Office, FREEPOST RRKR-JUZR-HZHG, Birmingham Clinical Trials Unit, School of Cancer Sciences, University of Birmingham, Birmingham, B15 2TT

Tel: 0121 414 6665; Fax: 0121 415 9136; Email: [medal-study@trials.bham.ac.uk](mailto:medal-study@trials.bham.ac.uk); Website: [www.birmingham.ac.uk/medal](http://www.birmingham.ac.uk/medal)



Please report any **serious, unexpected** adverse events\* believed to be due to the diagnostic procedures undertaken as part of the MEDAL study by faxing the following details to the Study Office (fax: 0121-415-9136) immediately (and ideally within 24 hours) on becoming aware of the event.

### Patient/ Site Details:

Patient's Initials:    Study No.:

Date of birth:   -    -

Hospital No.:

Site Name: .....

Responsible doctor: .....

### **Reason for Reporting (i.e. seriousness of event)** (please provide an answer to each question)

|   | No                   | Yes                  |
|---|----------------------|----------------------|
| Death:  | <input type="text"/> | <input type="text"/> |
| Life threatening event:                           | <input type="text"/> | <input type="text"/> |
| Prolonged Hospitalisation:                        | <input type="text"/> | <input type="text"/> |
| Persistent or significant disability/ incapacity: | <input type="text"/> | <input type="text"/> |
| Other pertinent medical reason for reporting:     | <input type="text"/> | <input type="text"/> |

Please state.....

### **Description of SAE**

Date event deemed to be serious (i.e. date of onset):   -    -

Details of 'relevant' medical history: .....

.....

.....

Details of Serious Adverse Event (including special investigations, location) (please attach copies of relevant reports)

Date Event Started:  –  –

Date Event Ceased:  –  –

## Treatment

Treatment given:

Date Treatment Started:  –  –

## Outcome of event:

|                                      | No   | Yes                      |
|--------------------------------------|--|--------------------------|
| Death:                               | <input type="checkbox"/>   | <input type="checkbox"/> |
| Recovered:                           | <input type="checkbox"/>   | <input type="checkbox"/> |
| Continuing:                          | <input type="checkbox"/>   | <input type="checkbox"/> |
| If 'yes' please provide details..... |  |                          |
| Resolved:                            | <input type="checkbox"/>   | <input type="checkbox"/> |
| Date of resolution:                  | <input type="text" value="D"/> <input type="text" value="D"/> – <input type="text" value="M"/> <input type="text" value="M"/> <input type="text" value="M"/> – <input type="text" value="Y"/> <input type="text" value="Y"/> <input type="text" value="Y"/> <input type="text" value="Y"/> |                          |
| Other:                               | <input type="checkbox"/>   | <input type="checkbox"/> |
| Please state.....                    |  |                          |

Name of Person Reporting (please print)

Designation.....

Telephone Number: ..... Date:  –  –

\* For the purposes of the study, “**serious**” adverse events are those which occur within a week of the procedure and are fatal, life-threatening, disabling or require or prolong hospitalisation. “**Unexpected**” adverse experiences are defined as those that would not be expected as a result of MRI or laparoscopy. It is not required to report in this way any minor side-effects or events that might reasonably be expected.