Psychological Impact of Pregnancy of Unknown Location (SOUL)

12th September 2021

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Sponsor

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Funding

The fellows are funded by the Imperial College NHS Healthcare Trust. The research is performed and funded within the Tommy's National Centre for Miscarriage Research at Imperial.

This protocol describes the study and provides information about procedures for entry. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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1. Study Summary

Title

Psychology of pregnancy of unknown location (SOUL)

Design

Prospective cohort observational study

Primary aim

To assess the psychological impact of pregnancy of unknown location (PUL) classification pending a final diagnosis.

Secondary aims

To assess psychological burden of PUL on patients and their partners.
To assess if shortening time to providing patients classified with PUL with results and advice using point-of-care beta human chorionic gonadotrophin (BhCG) testing reduces psychological burden.

Hypothesis

1) PUL causes significant psychological distress to patients and their partners which can be assessed using a validated psychological tool.
2) Increasing the efficiency of PUL management will reduce anxiety and depression symptoms in patients and their partners.

Outcome measures

Psychological morbidity will be assessed using the HADS on time of PUL classification, 48 hours from PUL classification and following final diagnosis and management.

Eligibility

Pregnant women attending the Early Pregnancy Unit in the first trimester (up to 14 weeks gestation) with a pregnancy of unknown who are over 18 years old and are able to give consent.

Duration

The study will be conducted over a minimum period of two years.

Keywords

Pregnancy of unknown location, beta-human chorionic gonadotrophin, depression, anxiety.

2. Introduction

2.1 Background and study rationale

a. Pregnancy of unknown location and Ectopic pregnancy

Pregnancy of unknown location (PUL) is a syndrome of early pregnancy composed of a positive urine pregnancy test without the visualisation of a pregnancy on trans-vaginal ultrasound (TVUS). There are four possible final diagnoses from PUL: intrauterine pregnancy (IUP); failing pregnancy of unknown location (FPUL); persistent pregnancy of unknown location (PPUL); and ectopic pregnancy (EP) [1].

The initial investigation that is currently performed with TVUS is serum beta human chorionic gonadotrophin (BhCG) testing. Previous studies however have highlighted that the traditional single serum hCG testing following TVUS is a poor predictor of outcome, viability and location of PUL [3].

b. BhCG monitoring and modelling

hCG (a glycoprotein produced by syncytiotrophoblast cells responsible for maintaining the corpus luteum in early pregnancy). hCG is hetrodimeric and consists of an alpha and beta subunit. The beta subunit is unique to hCG and is therefore clinically useful in pregnancy. The use of beta hCG (BhCG) and progesterone levels in the management of PUL is commonplace [4-5]. However, interpretation of the results can be subjective [6-7].

A statistical logistical regression model which utilised initial BhCG levels and BhCG ratio (48-hour BhCG divided by 0 hour BhCG) was created by a research group with the aim of allowing PUL to be safely risk stratified [8-14]. This has been validated and found to be superior to isolated progesterone and BhCG protocols, although unclear how applicable this may be to populations such as the United States [14-15]. A modified and validated model has since been trialled and used in a multi-centre study across North West London in order to optimise PUL risk stratification into ‘low risk’ (encompassing IUP and FPUL) and ‘high risk’ (encompassing PPUL and EP) [2]. This was part of the Assessment of Biomarkers and Ultrasound in Pregnancy of Unknown Location and Ectopic Pregnancy study (ABPEP) which utilised serial BhCG observation (at 0 hours and 48 hours from diagnosis of PUL), BhCG ratio along with progesterone testing [2].

This model has come to be known as the ‘M6 model’ and was developed from a cohort of 2753 cases of PUL. It classified 62.1% PUL as ‘low risk’ with a negative predictive value of 98.6% [2]. This the model which we currently adopt in our unit.

c. Point of care BhCG testing

BhCG measurements require serum samples sent to hospital laboratories in order to assess levels in a standardised manner. However, point of care (POC) BhCG testing is now available that uses whole blood to provide lab-quality, quantitative results in minutes. This could lead to a reduction in time waiting for results as well as a reduction in the associated psychological distress to patients and their partners [16]. The only food and drug agency approved quantitative test is the i-STAT BhCG (Abbott POC) test that could play a role in providing quick results that are comparable to hospital laboratory analysis. This could therefore be used to risk stratify within a risk prediction model [17]. The Abbott POC test is CE marked, confirm its conformity with European standards for health and safety of products sold within the European Economic area.

d. Anxiety and Depression related to Early Pregnancy Loss

Anxiety, depression and post-traumatic stress disorder (PTSD) are recognised complications following early pregnancy loss. A systematic review of 27 papers exploring the psychological impact of early pregnancy loss identified significant depression and anxiety within the first month, with 8-20% moderate depression and 18-32% anxiety reported at 4-6 weeks [18]. A Cochrane review of six studies involving 1001 women demonstrated no single beneficial method of managing the psychological impact of early pregnancy loss, but that counselling may be beneficial [19]

A UK study of 160 women demonstrated that uncertainty in diagnosis, rather than the negative or positive connotations of the diagnosis itself, was a greater contributing factor in women's feelings of anxiety and depression in relation to PUL [20]. Furthermore, a local pilot study demonstrated women experiencing both miscarriage and ectopic pregnancy fulfilled criteria for PTSD, with many suffering from moderate-to-severe anxiety and depression, with psychological morbidity persisting at least 3 months following pregnancy loss [21].

e. The Hospital and Anxiety Depression Scale

The Hospital Anxiety and Depression Scale is a 14-part questionnaire with 7 questions exploring symptoms of anxiety and depression respectively. Each question is answered with a scale of 0-3 to represent severity of symptoms, with an independent maximum score of 21 for depression or anxiety. A score $\geq$11 is deemed moderate, whilst $\geq$16 represents severe symptoms [22].

No single validated psychological tool is recommended for evaluation of these symptoms in the context of early pregnancy loss, and existing literature has relied on existing scoring

systems, self-reported symptoms or structured interview [18, 19]. The HADS tool has been previously utilised in our unit for the psychological impact of early pregnancy loss in women experiencing miscarriage or ectopic pregnancy [21].

A 2002 review of 747 papers identified HADS has a Cronbach's alpha coefficient of 0.83 (0.68-0.93) for internal consistency of anxiety symptoms and 0.82 (0.67-0.90) for depression. It was found to perform well in symptom assessment in a range of clinical settings including in primary care, the general population and in somatic and psychiatric forms of depression and anxiety [23].

2.2 Study rationale and study hypothesis

a. Study rationale

PUL is a syndrome of early pregnancy composed of a positive urine pregnancy test without the visualisation of a pregnancy on trans-vaginal ultrasound (TVUS). The current method for risk stratifying a PUL is via serum BhCG levels at the time of identification of PUL and after 48 hours, in order to ascertain the viability of the pregnancy. Patients and their partners need to wait for this result before a management plan can be adopted, taking at least 2-3 hours.

There is a clear need for the patient care pathway to evolve in order to aid and improve the management of women classified with a PUL. By using point-of-care BhCG testing, we would shorten the time to management. We propose that shortening the time interval would reduce psychological morbidity.

b. Study hypothesis

1) PUL causes significant psychological distress to patients and their partners which can be assessed using a validated psychological tool.
2) Increasing the efficiency of PUL management will reduce anxiety and depression symptoms in patients and their partners.

3. Study Objectives

This study aims to improve the pathway of care to this cohort of women by:

- Assessing the psychological impact of pregnancy of unknown location (PUL) classification pending a final diagnosis.
- Assessing psychological burden of PUL on patients and their partners.

- Assessing if shortening time to providing patients classified with PUL with results and advice using point-of-care beta human chorionic gonadotrophin (BhCG) testing reduces psychological burden.

4. Methodology and Design

4.1 Study centre

The primary centre for the study will be Queen Charlotte's and Chelsea Hospital, part of Imperial Healthcare NHS Trust).
Secondary centres will include St Mary's Hospital (part of Imperial College Healthcare NHS Trust).

There will be:

- A named individual (clinical research fellow - CRF) in the primary study centre who will be responsible for co-ordinating the project, reporting to the chief investigator and co-ordinating the study at the secondary study centres;
- Regular inspection by the named individual under the supervision of the chief investigator in order to ensure both the service (literature, communication, documentation, supervision and logistics) and facilities (ultrasound, equipment, space) are of a high standard;
- Assurances that those who contribute to the study are experienced and trained in the management of patients presenting to an Early Pregnancy Unit (e.g. specialist nurse, research nurse, sonographer, gynaecologist);
- A PhD thesis documenting the outcome.

4.2 Design and links to previous studies

a. Design

SOUL is prospective cohort observational study focussing on psychological assessment of patients and their partners with PUL.

b. Links to previous studies

Pilot study undertaken in the unit in 2016 by Farren J et al [21], led by Chief Investigator Professor Bourne, explored the severity and type of emotional distress in women after early pregnancy loss compared with women with ongoing pregnancies (REC 11/SW/0052). This group implemented HADS.

4.3 Duration

The study will be conducted over a minimum of one year to ensure adequate recruitment and follow up.

4.4 Inclusion criteria

Pregnant women attending the Early Pregnancy Unit in the first trimester (up to 14 weeks gestation) with a pregnancy of unknown who are over 18 years old and are able to give consent.

4.5 Exclusion criteria

Presence diagnosed with cancer, the presence of an acute medical condition, patients/partners aged less than 18 years, patients or partners who cannot give fully informed study consent (language or learning impairment), presence of a viable intrauterine pregnancy, ectopic pregnancy and miscarriage.

4.6 Withdrawal criteria

Patients and/or their partners may withdraw from the study at any stage and all data captured in relation to their participation may be destroyed at their request.

4.7 Consent and information leaflet

Regarding written consent, participants will be given sufficient time to consider recruitment and consent to participate so long as they are clinically stable and that the time taken does not compromise safety and management.

Patients who wish to participate in the study will be provided with a patient information sheet and they will be given a minimum of 15 minutes without the research team present to consider whether they wish to participate. There will be separate patient information sheets for women and their partners. They will be made aware that participation is voluntary and that they can withdraw from the study at any point without affecting their usual care. They will have then have time to formulate and ask questions and time to discuss the study with a relative or personal doctor. If the patient or partner wishes to enter the study, this will be documented on the ultrasound scan notes and the consent form will be completed.

Three copies will be taken, one to the participant, one with health records, one kept by the Chief Investigator within the study file. Good Clinical Practice (GCP) training is mandatory for training in consent for research purposes.

4.8 Recruitment Process

The recruitment process will be undertaken within EPU. The participants could potentially be any woman who is referred or who presents to the early pregnancy assessment unit (EPAU) and requires a trans-vaginal ultrasound scan and will be identified by a member of the clinical care team on EPAU who is scanning, who has signed the delegation log and who is certified with Good Clinical Practice (GCP).

Those that will be invited to participate in the study will include patients and their partners attending the Early Pregnancy Unit in the first trimester (up to 14 weeks gestation) classified with a PUL on trans-vaginal ultrasound scan over the age of 18.

All patients and partners will first be approached by members of the direct care team before being invited to the study once a PUL has been classified using TVUS. Members of the direct care team (if not part of the research team) will ask patients if they can them refer them to a member of the research team.

Advertising using posters in the EPU will be used in order for patients and partners to view the research being offered in the unit and any interest will be referred to the research team where they can ask questions and discuss the study further. The poster that will be on the walls of the early pregnancy unit (EPU) located on the second floor of Hammersmith Hospital, part of Imperial College Healthcare NHS Trust, Block D, Du Cane Road, W12 0HS. Contact details on the poster will allow participants to contact the team through email or over the phone in order to ask questions. There will be separate posters for phases one and two of the study.

Written consent will be required for all aspects of the study. Participants will be made aware that participation is voluntary and that they can withdraw from the study at any point without giving any reason and without affecting their usual care.

Patients and partners will first be approached by members of the direct care team. If they are not part of the research team, they will refer the patient and partner to a member of the research team if the patient and partner give them verbal consent to do so. Patients and partners will then be seen by a member of the research team.

Patients and partners that approach through advertising will be referred to a member of the research team. This may be face to face, or via the contact details available on the poster. If

the patient meets the inclusion criteria, they will be invited to the EPU if not present in the unit already.

4.9 Method of study

This is a cohort study and will recruit patients in the first trimester (less than 14 weeks gestation) and their partners who meet the inclusion criteria attending the Early Pregnancy Unit. There will be two phases of the study, each with a minimum duration of 4 months. Phase 1 aims to establish the psychological burden of PUL under the existing care pathway, whilst phase 2 introduces point of care BhCG testing in clinical practice. The phases of the study are described in more detail below.

An information leaflet detailing the purpose of the study will be provided, and separate patient information sheets will be used for each phase of the study. A minimum of 15 minutes will be provided for patients to read the study information with the research team not present. Patients will then have opportunity to elicit further information or clarification from the research team. There are no significant ethical, legal or management issues. Women who both verbally consent and consent in writing will follow a well-defined pathway (see flowchart appendix).

The phases of the study are

- Group 1: Assessing the psychological impact of pregnancy of unknown location (PUL) classification pending a final diagnosis. Confirming the reliability of point of care testing in correlation with laboratory BhCG levels (gold standard).
- Group 2: To assess if shortening time to providing patients classified with PUL with results and advice using point-of-care beta human chorionic gonadotrophin (BhCG) testing reduces psychological burden.

Women with symptoms in the first trimester are routinely seen in the Early Pregnancy Unit (EPU). A clerking proforma is completed, urine is tested and a transvaginal ultrasound scan is performed. Blood testing and follow up arrangements are made if required with blood results inputted into a validated statistical model if a patient is classified with a PUL.

Participants in phase one of the study will not be provided with the POC BhCG result. They will await the laboratory result. Simultaneously we will ascertain reliability of POC in clinical practice during this time.

Patients in phase two will be provided with the POC test result, which will reduce the time to which they receive the result. Prior to transfer from phase 1 to phase 2 of research, correlation between POC and laboratory BhCG levels will be calculated in order to confirm its reliability by creating a correlation curve using the data.

Patients and partners will be asked to complete the questionnaire at three time points: 1) On classification of PUL at time zero once blood is taken, 2) at the 48-hour time point after blood is taken (if 48-hour bloods are required for the patient); and 3) after definitive diagnosis and management.

The maximum number of questionnaires that will be completed will be 6: 1 for each time point for the patient and 1 for each time point for the partner.

The questionnaires for the first two time points will be offered electronically whilst the patient is having their blood sample taken via use of a quick response matrix barcode (QR code). The third time point HADS will be texted through the encrypted system Accurx. We will contact the patient a maximum of 3 times to complete the questionnaire at the third time point to reduce loss of follow up.

The results will be submitted electronically each time. The results will be reviewed on a weekly-biweekly basis by the research team.
If patients score for moderate to severe anxiety or depression at any time point, we will call the patient. If they are struggling with their PUL classification or diagnosis, we will advise them to make an appointment to see their GP as soon as possible to arrange appropriate follow up, whilst clarifying any ongoing follow up at the early pregnancy unit.
If patients score for moderate to severe anxiety or depression at any time point where no further follow up at the unit is indicated, we will also ask permission to send a text over Accurx that will list information relating to local miscarriage support groups, Tommy's Miscarriage charity, Petals Baby Loss Counselling Charity, the Ectopic Pregnancy Trust, the Miscarriage Association and Improving Access to Psychological Therapists (IAPT). If further support is required, they will be advised to contact their GP as soon as possible.

a. Symptoms

Patients will be asked to complete the standard clerking proforma used within the unit, including demographic data and information regarding previous obstetric, medical and gynaecological history and questions regarding symptoms.

b. Ultrasound

Trans-vaginal ultrasound is then performed as part of standard practice. Women with a PUL will be identified as eligible for the study

Any ultrasound abnormality detected will be managed in accordance with local and national guidance. Follow up trans-vaginal ultrasound for all will be arranged as per routine clinical practice if required.

c. Assessment of psychological symptoms

Patients diagnosed with PUL and their partners will be offered to take part in the study. Participants will be asked for written consent prior to point-of-care BhCG testing and completion of the HADS tool. The HADS tool takes 2-5 minutes to complete [22].

d. Clinical intervention

Performed in EPU as part of PUL classification:

- Transvaginal ultrasound
- 20ml venous blood sample

Performed in EPU or on the gynaecology ward following consent to participate in study:

- HADS tool
- 1ml sample of blood for point-of-care BhCG testing

e. Cataloguing

All data collection will be compliant with the Data Protection Act. The pseudonymised details will be logged onto a protected database with access restricted to only those personnel involved in the study. The data will be archived for secondary analysis.

Patients will be followed up for the duration of their care in the Early Pregnancy Unit. There will be no additional visits planned for research purposes.

Patients would remain in the study for a maximum of 2 months allowing time for final diagnosis and relevant follow up following intervention.

4.9 Study closure

We aimed to recruit approximately 250 participants in total (at least 62 patients and 47 partners per phase) with a minimum study duration of two years. The end of the study will be following the analysis of the patients' questionnaires.

However, in light of the SARS-CoV-2 pandemic, partners cannot attend early pregnancy units. It is likely that data from patients only will be possible to be collected as we will not be able to make up the difference regarding partners as patient recruitment is already under way. The total we will be able to recruit will therefore be at least 124 (at least 62 patients per phase). Although this reduces the scope of the study, we will still be able to meet the vast majority of our objectives.

4.10 Documentation and communication

Clinical data, patient demographics and ultrasound findings will be recorded on the standard clerking proforma filled in by each patient and on a computer software programme (Astraia). This data will be prospectively collated into a master database with raw data relevant to the study. All potential identifiable patient data that requires electronic storage will be stored electronically on NHS approved computers, accessible by members of the research team or the patients direct care team via secure password in the Early Pregnancy Unit, Queen Charlotte's & Chelsea Hospital, Imperial College Healthcare NHS Trust, Hammersmith Hospital. No patient identifiable information will leave the hospital premises nor be subject to access or viewing by anyone other than those directly involved with this research study. Data will be stored for a minimum of 10 years after completion of the study.

5. Study Outcome measures

Psychological morbidity will be assessed using the HADS on time of PUL classification, 48 hours from PUL classification and following final diagnosis and management.

6. Study population and sample size

6.1 Statistics and data analysis

Recruitment will commence upon ethical approval of the study. The infrastructure, research fellow and nurses, questionnaires, BhCG machines and database are already in place, which ensure that the study can start promptly upon approval, without affecting or compromising routine clinical service provision. We aim to recruit 250 participants. As the early pregnancy unit assesses approximately 4200 women per annum, this aim is achievable over the course of two years. We will also be recruiting in two centres within Imperial College Healthcare NHS Trust to ensure there is generalizability in the results.

The calculated sample size follows from the pilot study performed by Farren et al [21] as well as the associated study focussing on partners [24]. Data from the pilot study suggests that 32% of those suffering early pregnancy complications had moderate to severe anxiety compared with 10% in the control group [21]. As this will initially be performed as a pilot study, at least 62 women will be required in both phase 1 and phase 2 where recruitment ratio is 1:1 with type 1 error of 0.05 and power of 80% [25]. Data from the partner study highlighted that the 30% of women reported moderate to severe anxiety compared with 6% of partners [24]. Again, as this will be performed as a pilot study, at least 47 partners will be required in both phase 1 and phase 2 where recruitment ratio is 1:1, with type 1 error of 0.05 and power of 80% [25]. However, due to the SARS-CoV-2 pandemic, it is likely we will only be able to assess patients and not partners.

7. Study Supervision and Monitoring

a. Risk assessment

In summary, there is no significant increase in time spent within the unit or of risk of complications to the patient:

- Trans-vaginal ultrasound is performed routinely in EPU and so does not add to the burden or risk of the patient;
- All research blood samples will be taken/arranged for patients who attend routine EPU appointments only or following admission to the gynaecology ward. All blood samples will therefore be taken at the same time as blood taken as part of routine clinical care, preventing risk and burden as no further venepuncture will be required. These will be taken by highly skilled and trained clinical fellows and research midwives who are medically trained in phlebotomy, reducing potential for discomfort;

Taking part in the study will allow the assessment of the psychological impact of pregnancy of unknown location (PUL) classification pending a final diagnosis. It will also allow the assessment of psychological burden of PUL on their partners. Finally, we hope to establish if shortening time to providing patients classified with PUL with results and advice using point-of-care BhCG testing reduces psychological burden.

The results will not impact patient care negatively, and we in fact hope patients in the future will benefit from the information gained in this study.

b. Central and local supervision

The chief investigator at Imperial College London will be responsible for the protocol, quality control, interim analyses of the data, advice on progress and final analysis and reporting of the study.

8. Regulatory Issues

8.1 Ethical approval

The Chief Investigator has obtained approval from the Health Research Authority and Research Ethics Committee. The study must also receive confirmation of capacity and capability from Imperial College Healthcare NHS Trust before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

No human samples will be stored after they are taken for this study.

8.2 Consent

Consent to enter the study will be sought from each participant only after a full explanation has been given, an information leaflet offered, and time allowed for consideration. Sufficient time will be given to ask any questions about the study. Signed participant consent will be obtained for the collection of research blood samples and completion of a validated psychological tool. The right of the participant to refuse to participate without giving reasons will be respected.

After the participant has entered the study, the clinician remains free to deviate from the outlined pathway at any stage if he/she feels it is in the participants' best interest, but the reasons for doing so will be recorded. In these cases, the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving a reason and without prejudicing further treatment.

8.3 Confidentiality

All patient derived data will be collected onto a paper proforma - primarily consent forms with a case report form (CRF). Patient identifiable data will at no point leave the hospital premises or be subject to access or viewing by anyone not involved with research being carried out. Code in the form of a three-digit number (e.g. 001) will be assigned to participants.

The study number will then be attached to the sheet as well as to the samples taken. The Clinical Research Fellow, Dr Christopher Kyriacou, will keep a log which enables the matching of sample numbers to patient details. This log and all copies of all versions of the consent forms and the CRF will be stored within the study file. This is kept safely within the locked research filing area in the Early Pregnancy Unit, second floor, block D, Queen Charlotte's & Chelsea Hospital, Imperial College London, Hammersmith Campus, Du Cane Road, London W12 0TR and will only accessed when required by researchers directly involved in this study.

All potential identifiable participant data that requires electronic storage will be stored electronically on NHS approved computers, accessible only by a member of the study team or patients direct care team involved in the study via secure password.

All hard copies of data to be stored long term after the study has ended will remain filed securely within the Early Pregnancy Unit at Queen Charlotte's and Chelsea Hospital. All data stored electronically will be kept on an NHS approved computer's hard drive accessible only by responsible personnel involved in the study and will be password protected. This will be in the Early Pregnancy Unit, Queen Charlotte's & Chelsea Hospital, Imperial College Healthcare NHS Trust, Hammersmith Campus. At the end of the study, data will be archived at an Imperial College London archiving facility.

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

8.4 Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.5 Sponsor

Imperial College London and Tommy's National Centre for Miscarriage Research at Imperial act as the main sponsors for this study. Funding for the fellows is provided by Imperial College Healthcare NHS Trust.

8.6 Adverse events

a. Definitions:

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical study subject.
Serious Adverse Event (SAE): Any untoward and unexpected medical occurrence or effect that:

- Results in death
- Is life-threatening – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical judgement will be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, will also be considered serious.

There are no additional risks to the patients participating in this study.

b. Reporting Procedures

All adverse events will be reported. Depending on the nature of the event the reporting procedures below will be followed. Any questions concerning adverse event reporting will be directed to the Chief Investigator in the first instance.

c. Non-serious AEs

All such events, whether expected or not, will be recorded.

d. Serious AEs

A SAE form will be completed and faxed to the Chief Investigator within 24 hours. However, relapse, death and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.
All SAEs will be reported to the Chief Investigator who will determine if the event was:

- Related- resulted from the administration of any of the research procedures
- Unexpected- an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs will be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator will also notify the Sponsor of all SAEs.
Local investigators will report any SAEs as required by their Local Research Ethics

Committee, Sponsor and/or Research & Development Office.

Contact details for reporting adverse events:
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8.7 Audits and Inspections

The study may be subject to inspection and audit by the Joint Research Compliance Office under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research. Direct access to source data/documents as requested will be permitted.

9. Study Management

The day-to-day management of the trial will be co-ordinated through the Early Pregnancy Unit at Queen Charlotte's and Chelsea Hospital by Dr Margaret Pikovsky.

10. Publication Policy

All publications and presentations relating to the study will be authorised by the Study Management Group. The investigators will therefore be responsible for publication of the data. As such they are co-authors in all resulting clinically relevant papers to which they made significant contributions. Co-authors will be included according to their contribution in the study and depending on the journals' publication guidelines.

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12. Appendix

12.1 Flow chart outlining patient pathway and summary of investigations

12.2 Consent forms

12.3 Patient information sheet

12.4 QR code shown to patients