PRISM

Progesterone In Spontaneous Miscarriage

The effectiveness of progesterone to prevent miscarriage in women with early pregnancy bleeding

A randomised placebo-controlled trial

Protocol Version 2.0 (29th January 2015)

CONTENTS

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1 INTRODUCTION

The PRISM trial is a large, double blind, placebo-controlled trial to test the hypothesis that in women presenting with vaginal bleeding in the first trimester, progesterone (400 mg vaginal capsules, twice daily), started as soon as possible after a scan has demonstrated a visible intrauterine gestation sac and continued to 16 completed weeks of gestation, compared with placebo, increases maternities with live births beyond 34 completed weeks by at least 5%. We will also explore the effects of progesterone in prognostic subgroups, according to maternal age, fetal heart activity, gestation at presentation, amount of bleeding and body mass index.

Should the PRISM trial demonstrate a significant benefit from the intervention, it would represent a major breakthrough in the treatment of a common and distressing condition. Given that progesterone treatment is cheap, safe and convenient, and the financial impact of miscarriage substantial, even a small improvement in outcome is likely to be cost-effective.

In order to recruit the large number of participants needed to provide statistically reliable answers, and to maximise the clinical relevance of the findings, the trial is designed to fit in with routine hospital practice as far as possible, imposing minimal additional workload by keeping extra clinic-based tests and evaluations to a minimum.

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Summary and Declarations

Protocol Version	2.0 (29th January 2015)
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Funding Body	NIHR Health Technology Assessment (HTA) Programme grant number 12/167/26
Sponsor	University of Birmingham
Chief Investigator	Professor Arri Coomarasamy

The University of Birmingham is responsible for obtaining the necessary regulatory approvals and for pharmacovigilance. The Trial Management Group (TMG) is jointly responsible for overseeing Good Clinical Practice (GCP). The investigators are responsible for obtaining informed consent and care of the participants.

1.1.4 Chief Investigator's signature

The investigators and the Trial Sponsor have discussed this protocol. The investigators agree to perform the investigation and to abide by this protocol except in case of medical emergency or where departures from it are mutually agreed in writing.

Professor Arri Coomarasamy

Chief Investigator on behalf of the Trial Management Group Date 29th January 2015

1.1.5 Principal Investigator's signature

Site:

Principal Investigator:

Title: Progesterone in Spontaneous Miscarriage Trial (PRISM)

Version: 2.0

I confirm I have received, read and understood the aforementioned version of the trial protocol. I confirm my team and I will adhere to this version of the protocol following receipt of the required local approvals.

Principal Investigator's name: _____

Signature: _____

Date: DD / MM / YYYY

The Principal Investigator should sign this page and return a copy of this page to the PRISM Trial Office

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1.2 Abbreviations

AE	Adverse Event
APGAR	Appearance, Pulse, Grimace, Activity, Respiration
AR	Adverse Reaction
BCTU	Birmingham Clinical Trials Unit at the University of Birmingham
BMI	Body Mass Index
CI	Chief Investigator
CTA	Clinical Trial Authorisation
DMC	Data Monitoring Committee
EPAU	Early Pregnancy Assessment Unit
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GP	General Practitioner
HTA	Health Technology Assessment
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
LCRN	Local Clinical Research Network
MHRA	Medicines and Healthcare Products Regulatory Authority
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
ONS	Office of National Statistics
PBAC	Pictorial Bleeding Assessment Chart
PI	Principal Investigator (leading local investigator for the PRISM study)
PIS	Participant Information Sheet
RCOG	Royal College of Obstetricians and Gynaecologists
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

1.3 Trial Synopsis

Title	**Effectiveness of progesterone to prevent miscarriage in women with early pregnancy bleeding: A randomised placebo-controlled trial**
Acronym	**PRISM**
Short Title	**Progesterone In Spontaneous Miscarriage Trial**
Objectives	**Primary objective:** 1. To test the hypothesis that in women presenting with vaginal bleeding in the first trimester, progesterone (400mg vaginal capsules, twice daily), started as soon as possible after a scan has demonstrated a visible intrauterine gestation sac and continued to 16 completed weeks of gestation, compared with placebo, increases maternities with live births beyond 34 completed weeks by at least 5%. **Secondary objectives:** 2. To test the hypothesis that progesterone improves other pregnancy and neonatal outcomes, including gestation at birth and survival at 28 days of neonatal life. 3. To test the hypothesis that progesterone, compared with placebo, is not associated with serious adverse effects to the mother or the neonate, including chromosomal anomalies in the newborn. 4. To explore differential or subgroup effects of progesterone in prognostic subgroups, including age, fetal heart activity, gestation at presentation, amount of bleeding and body mass index. 5. To perform a cost-effectiveness analysis, with cost per additional birth over 34 weeks' gestation from an NHS and Personal Social Services perspective as the primary analysis. We will also model longer term outcomes to the extent the data permit.
Trial Design	A randomised, double-blind, placebo-controlled multicentre study, with health economic evaluation.
Setting	Early pregnancy units and gynaecology departments.
Number of Participants	We plan to randomise 4,150 women in total (2075 participants each in the progesterone and placebo arms).
Main Eligibility Criteria	**Inclusion Criteria:** · Presentation with early pregnancy bleeding in the first 12 weeks of pregnancy. · Intrauterine gestation sac visible on ultrasonography (women should still be offered the trial in the absence of a visible fetal pole). · Age 16 - 39 years at randomisation. · Willing and able to give informed consent. **Exclusion Criteria:** · A crown-rump length measuring 7mm or more with no visible heartbeat; or, a mean gestational sac of 25mm or more with no visible fetal pole on ultrasonography. · Women presenting with life-threatening bleeding.

	• Recent or current use of progesterone supplementation. • Contra-indications to progesterone therapy • Participation in any other blinded, placebo-controlled trials of investigational medicinal products in pregnancy.
Study Interventions	Progesterone (Utrogestan) vaginal capsules 400mg twice daily from confirmation of an intrauterine gestation sac visible on ultrasonography, to 16 completed weeks of pregnancy or until miscarriage is confirmed, will be compared with placebo vaginal capsules of identical appearance and weight.
Duration of Study	It is anticipated that the trial will last for three years.
Randomisation	Participants will be randomised on-line via a secure internet facility in a 1:1 ratio through a third party independent Integrated Trial Management System (MedSciNet Clinical Trial Framework). A "minimisation" procedure using a computer-based algorithm will be used to avoid chance imbalances in important stratification variables. Stratification variables will be age (<35, ≥35 years), BMI (<30, ≥30), fetal heart activity (present, absent), estimated gestation at presentation, and amount of bleeding (PBAC [Pictorial Bleeding Assessment Chart] score ≤2; ≥3).
Outcome Measures	**Primary Outcome:** Live births beyond 34 completed weeks of gestation, as a proportion of all women randomised. **Secondary Outcomes:** Gestation at delivery; ongoing pregnancy at 12 weeks (range 11 - 13 weeks) gestation; miscarriage rate; survival at 28 days of neonatal life; chromosomal and congenital abnormalities; adverse events; antenatal complications (such as pre-eclampsia, growth restriction); birth weight; arterial and venous cord pH and base excess; APGAR (Appearance, Pulse, Grimace, Activity, Respiration) scores; need for resuscitation; neonatal surfactant use; neonatal ventilation support (days on ventilation, discharge on oxygen); and other neonatal complications (such as infection, respiratory distress syndrome, necrotising enterocolitis). **Resource Use Outcomes:** Antenatal, outpatient or emergency visits; inpatient admissions (nights in hospital); maternal admissions to a High Dependency Unit or Intensive Therapy Unit (nights); and neonatal admissions to a Special Care Baby Unit or Neonatal Unit (nights). **Outcomes For Future Studies:** We will obtain women's consent for future evaluation of themselves, their child and the health records of both, and babies will be flagged with the Office of National Statistics (ONS) or equivalent. Although long-term follow-up will remain outside the scope of this trial, we plan to conduct further studies on outcomes such as the composite endpoint of death or neurodevelopmental impairment at two years of age, the Bailey III cognitive scale cognitive scale standardised score at two years of chronological age, and disability classified into domains according to professional consensus. The NHS number of each baby will be recorded to facilitate future follow-up studies.

2 BACKGROUND

2.1 Clinical Background

Miscarriage, the loss of a pregnancy before 24 weeks of gestation, affects one in five women who conceive, making it the most prevalent complication of pregnancy. It substantially impacts on physical and psychological wellbeing: research shows that the level of distress associated with miscarriage can be equivalent to that of a stillbirth of a term baby. An estimated 140,000 women per year miscarry in the UK, costing the NHS over £350 million each year.

The 2012 NICE (National Institute for Health and Care Excellence) Guideline on "Ectopic Pregnancy and Miscarriage" (Clinical Guideline 154, December 2012) has called for a key clinical trial on the effects of progesterone in preventing miscarriage in women with early pregnancy bleeding, stating "a very large multicentre randomised controlled trial of women treated with either progesterone/progestogen or placebo should be conducted."[1] In response to this, the Association of Early Pregnancy Units, the RCOG Early Pregnancy Clinical Studies Group, the Miscarriage Association and a national team of researchers and clinicians from across the UK have formed a research team to address this question robustly using a well-established early pregnancy research network.

2.1.1 Existing Evidence

Effectiveness of Progesterone Treatment

We conducted a systematic review of trials of the use of progestogens in women with early pregnancy bleeding, and identified seven studies[2-8], including the four studies[3, 4, 7, 8] cited by the NICE guideline[1]. These studies are listed in **Table 1**.

The seven studies included a total of 744 women. These studies were small and of poor quality, with none reporting the method of allocation concealment. Only three out of seven studies were placebo-controlled and five out of seven studies were not blinded. The modified Jadad quality score varied from 1/6 to 3/6.

Outcome data were available for miscarriage rates. Individual studies were too small to show an effect, but a meta-analysis of these seven studies (**Figure 1**) showed a statistically significant reduction in miscarriage rate with progestogen use (RR 0.53, 95% CI: 0.39 to 0.73). There was no heterogeneity across the studies (I^2=0%), suggesting consistency across the studies.

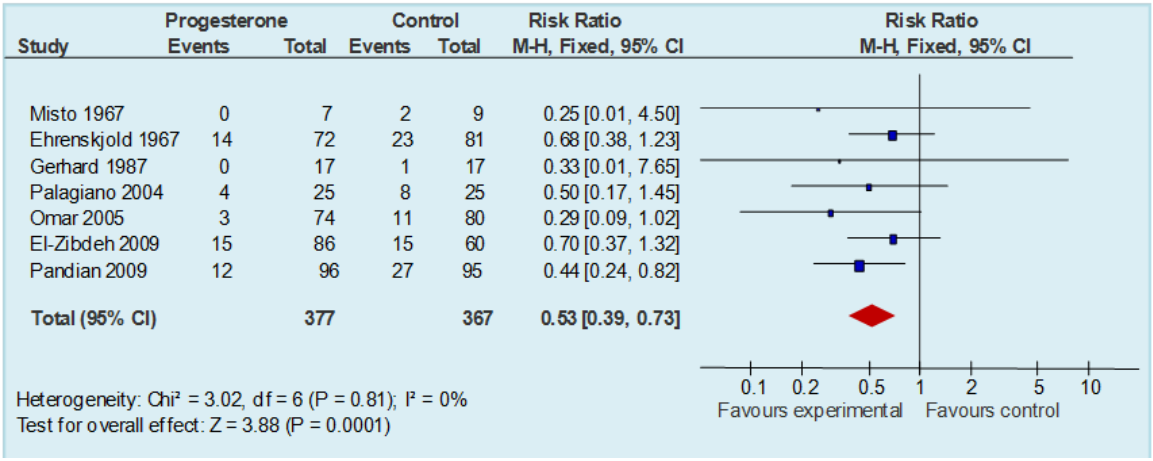
Safety of Progesterone Supplementation in Pregnancy

There is substantial evidence from In Vitro Fertilisation (IVF) practice that progestogen supplementation is safe to the mother and fetus (at the proposed dose for the PRISM trial of 400 mg twice daily)[9-11]. To further explore the question of safety, we conducted a systematic review of observational studies (both cohort and case-control studies) of first trimester sex hormone exposure. We identified 14 studies of relevance to the question, consisting of 65,567 women[12]. The sex hormone in several of these studies was progestogens alone or with other steroids. No harm, particularly any external genital malformation, was found in this review. However, another case-control study has suggested an association between hypospadias and progestogen use[13]. Although the findings of a single case-control study offer weaker evidence than the results of multiple large cohort studies which do not substantiate any association, all effects of progesterone will be documented in this trial. More specifically, all neonates will be examined for genital abnormalities.

Table 1 Randomised trials of progestogens versus placebo or no treatment

Study	Intervention	Duration of Treatment	Comparison	Risk of Bias
Misto 1967 *n*=25	20-40 mg oral dydrogesterone	Once daily for six to 15 days, sometimes for longer periods and for several cycles.	Placebo	Method of randomisation unclear; allocation concealment adequate; blinding of patients and study personnel adequate.
Ehrenskjold 1967 *n*=153	20 mg oral dydrogesterone	20 mg then tapering (20 mg after 12 hours/20 mg every eight hours until symptoms ceased/10 mg twice daily for five days/5 mg twice daily for at least seven days).	No treatment	Method of randomisation unclear; allocation concealment adequate; blinding of patients and study personnel adequate.
Gerhard 1987 *n*=34	25 mg progesterone vaginal suppositories twice daily	Until miscarriage or for 14 days after bleeding stopped.	Placebo	Method of randomisation unclear; allocation concealment unclear; no blinding for participants or study personnel.
Palagiano 2004 *n*=50	90 mg progesterone (Crinone 8%) vaginal suppositories	Once daily for five days.	Placebo	Method of randomisation unclear; allocation concealment adequate; no blinding for participants or study personnel.
Omar 2005 *n*=154	dydrogesterone	40 mg dydrogesterone followed by 10 mg twice daily until bleeding stopped.	No treatment	Method of randomisation unclear; no allocation concealment; no blinding of patients and study personnel.
El-Zibdeh 2009 *n*=146	10 mg oral dydrogesterone twice daily.	From enrolment until one week after bleeding stopped.	No treatment	Quasi-randomised (allocated according to day of the week); no allocation concealment; no blinding for participants or study personnel.
Pandian 2009 *n*=191	oral dydrogesterone	40 mg oral dydrogesterone followed by 10 mg dydrogesterone twice daily, until 16 weeks of gestation.	No treatment	Method of randomisation and allocation concealment adequate; no blinding of participants or study personnel.

Figure 1 Meta-analysis of studies of progesterone in women with early pregnancy bleeding



Outcome: miscarriage

Effects of Progesterone on Maternal Health

Meta-analyses of progesterone use in recurrent miscarriage, in miscarriage[14], and in the prevention of preterm birth[15] have not shown any evidence of short-term safety concerns in the mothers. However, it is not clear whether these trials sought to document maternal side-effects prospectively. In one study, intramuscular 17-Hydroxyprogesterone (17-OHP) caused maternal adverse events in 50% of women, largely due to injection site reactions[16]. However, this risk is not applicable to the PRISM trial, which stipulates vaginal administration. Side-effects were not reported in recent studies of *vaginal* progesterone in the context of prevention of preterm births[17, 18].

Effects of Progesterone on Chromosomally Non-viable Neonates

The available evidence does not suggest that progesterone will support a pregnancy with a chromosomally abnormal fetus. In 38 trials (including a total of 5,110 women) using progesterone or its analogues ("progestogens") in early pregnancy for various indications, there has not been any report of an excess of chromosomally abnormal neonates[19, 20].

Nevertheless, the organisers of the PRISM trial acknowledge the theoretical possibility of the continuation of pregnancies with usually unviable chromosomally abnormal fetuses. Therefore the independent Data Monitoring Committee will review observations of chromosomal and other abnormalities. Chromosomally abnormal fetuses can often be detected by routine antenatal screening at 11 to 14 weeks and 20 weeks of gestation, as well as at birth. For example, combined screening (now routinely offered in the UK) can identify up to 90% of all cases with trisomy 21 (Down's syndrome). Congenital abnormality including chromosomal abnormality in the neonate is a secondary outcome of the PRISM trial.

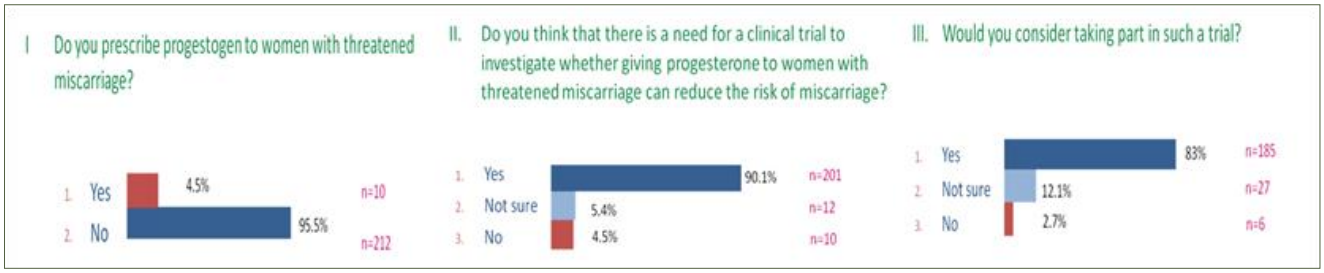
2.1.2 Support for the PRISM Trial

To understand how the existing evidence is viewed by clinicians, we conducted national and international surveys of clinicians. The findings are provided below.

UK and International Clinician Surveys

We conducted a UK clinician survey (n=222) in October 2012. In the UK, the vast majority of clinicians (212 out of 222, 95.5%) do not use progesterone to prevent miscarriage in women with early pregnancy bleeding. The key reason for non-use is the lack of robust evidence. It is therefore not surprising that *the majority (201 out of 222, 91%) called for a definitive trial*.

We also conducted a survey of international practitioners at the FIGO (International Federation of Gynecology and Obstetrics) 2012 Conference, Rome. Surprisingly, this survey found the majority of clinicians (61 out of 68, 90%) already use progesterone in women with early pregnancy bleeding, although the vast majority (56 out of 66, 85%) were willing to recruit into a randomised trial, presumably indicating lack of confidence in the available evidence.



UK Patient Survey

In December 2012 we conducted a survey of women seen in the Early Pregnancy Unit (n=79) at the Birmingham Women's Hospital. The majority of women (57 out of 79, 72%) said they would consider taking part in the trial, and 70% (55 out of 79) considered the vaginal route of administration acceptable. The Miscarriage Association has conducted a survey to identify women's opinions on a double blind placebo-controlled trial in early pregnancy and the acceptability of administering vaginal or rectal medications. The findings of this survey of 128 women showed that 91% (116/128) would enter or consider entering the trial. The vaginal route of administration of medicines was acceptable to 100/111 (90%) of women, and the rectal route acceptable to 91/111 (82%) of women.

Evidence Explaining Why PRISM is Needed Now

- A recent Guideline by the National Institute of Clinical Excellence (NICE) has called for a definitive trial to evaluate this research question: "A very large multicentre randomised controlled trial of women treated with either progesterone/progestogen or placebo should be conducted"[1].
- The Association of Early Pregnancy Units, the RCOG Early Pregnancy Clinical Studies Group, the Miscarriage Association and a national team of researchers and clinicians from across the UK have prioritised this as an urgent question to address.
- The existing trials, although small and of poor quality, suggest benefit in a highly prevalent condition with substantial morbidity and costs. If benefit is confirmed in the PRISM trial, women and NHS stand to gain substantially. On the other hand, if progesterone is found to be ineffective (or indeed harmful), treatment with progesterone can be avoided. This is relevant given the common use of progesterone for this indication outside the UK.
- Progesterone treatment is cheap (£0.68 per 400 mg capsule), safe, and if benefit is confirmed, we expect the intervention to be taken up rapidly.
- There is support for the study among UK and international clinicians. In a UK survey of 212 practitioners, 91% believed that a clinical trial is needed to investigate whether giving progesterone to women with threatened miscarriage can reduce the risk of miscarriage. In the international survey, 56 out of 66 (85%) respondents were willing to recruit into a randomised trial on this question.
- A patient survey supports the study. A patient survey (n=79) showed that 72% of women would consider taking part in this study.
- The study is supported by: the Miscarriage Association (a patient support organisation), the SEPN (Scottish Early Pregnancy Network), INVOLVE (a national advisory group that supports greater public involvement in health research, PRIME (Public and Researchers Involvement in Maternity and Early Pregnancy), CHARM (Charity for Research into Miscarriage) and Tommy's Charity.

2.1.3 Aims and Objectives

The primary aim of the PRISM trial is:

1. To test the hypothesis that in women presenting with vaginal bleeding in the first trimester, progesterone (400 mg vaginal capsules, twice daily), started as soon as possible after a scan has demonstrated a visible intrauterine gestation sac, and continued to 16 completed weeks of gestation, compared with placebo, increases maternities with live births beyond 34 completed weeks by at least 5%.

Additional secondary aims are:

2. To test the hypothesis that progesterone improves other pregnancy and neonatal outcomes, including gestation at birth and survival at 28 days of neonatal life.
3. To test the hypothesis that progesterone, compared with placebo, is not associated with serious adverse effects to the mother or the neonate, including chromosomal anomalies in the newborn.

4. To explore differential or subgroup effects of progesterone in prognostic subgroups, including age, fetal heart activity, gestation at presentation, amount of bleeding and body mass index.
5. To perform a cost-effectiveness analysis, with cost per additional birth over 34 weeks of gestation from an NHS and Personal Social Services perspective as the primary analysis. We will also model longer term outcomes to the extent the data permit.

3 TRIAL DESIGN

3.1 Design

A randomised, double blind, placebo-controlled multicentre study, with health economic evaluation.

3.2 Eligibility

The PRISM trial will recruit women who present with vaginal bleeding in the first 12 weeks of pregnancy with an intrauterine gestation sac visible on ultrasonography.

3.2.1 Source of Potential Participants

Potential participants will be identified and approached by clinic doctors, nurses, and research nurses in the Early Pregnancy Assessment Units (EPAUs) of participating centres. They will be clearly advised that participation in the study is entirely voluntary with the option of withdrawing from the study at any stage, and that participation or non-participation will not affect their usual care. Potential participants will be provided with a Study Participant Information Sheet (PIS) and given time to consider their involvement. Women who give consent will proceed to randomisation if they are eligible to participate in the trial. Consent will be recorded on the approved consent form, which must be retained in the site file with a copy given to the participant and a copy sent to the PRISM Trial Office.

3.2.2 Eligibility for Inclusion

Inclusion Criteria

- Presentation with early pregnancy bleeding in the first 12 weeks of pregnancy.
- Intrauterine gestation sac visible on ultrasonography (women should still be offered the trial in the absence of a visible fetal pole).
- Age 16 - 39 years at randomisation.
- Willing and able to give informed consent.

Exclusion Criteria

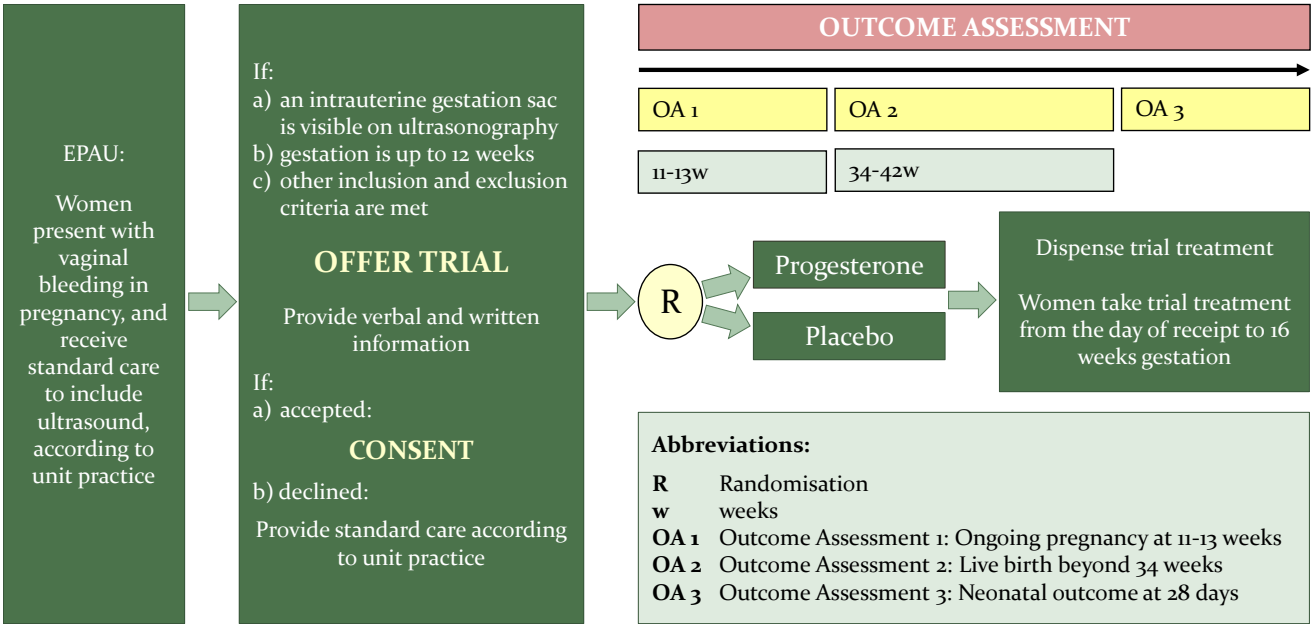
- A crown-rump length measuring 7mm or more with no visible heartbeat; or, a mean gestational sac of 25mm or more with no visible fetal pole on ultrasonography.
- Evidence of ectopic pregnancy.
- Women presenting with life-threatening bleeding.
- Current or recent use of progesterone supplementation.
- Contra-indications to progesterone therapy (progestogens should be avoided in patients with a history of liver tumours; they are also contra-indicated in those with genital or breast cancer unless progestogens are being used in the management of these conditions, severe arterial disease, acute porphyria, or a history during pregnancy of idiopathic jaundice, severe pruritus, or pemphigoid gestationis).
- Participation in any other blinded, placebo-controlled trials of investigational medicinal products in pregnancy.

Ineligible and Declining Patients

All women who are ineligible for the trial, or decline participation, should have the reasons for non-recruitment recorded on the screening log, along with parity and ethnic group. The investigator should record all the reasons for ineligibility according to the codes on the screening log. This information will describe the representativeness of the trial population.

3.2.3 PRISM Trial Flowchart

Figure 2 PRISM trial of progesterone in women with vaginal bleeding in early pregnancy



3.3 Randomisation

3.3.1 The Randomisation Process

Immediately after all eligibility criteria have been confirmed, consent has been obtained and all baseline prognostic factors gathered, a patient will be randomised into the trial. Participants will be randomised into the trial by a secure online randomisation system which is available via the MedSciNet Clinical Trial Framework. Each participating centre and each authorised member of the research team will be provided with a unique log-in username and password for this purpose. Online randomisation will be available 24 hours a day, seven days a week apart from short periods of scheduled maintenance. As a back-up, authorised members of the research team will be able to make one telephone call per participant to the toll-free randomisation service (0800 953 0274). Telephone randomisations will be available Monday to Friday, between 09:00 and 17:00.

Randomisation Notepads (a sample document is available separately) will be provided to investigators and may be used to collate the necessary information prior to randomisation. All the questions and data items on the Randomisation Notepad must be answered before a trial number and pack number may be given. If some data items are missing, randomisation will be suspended but may be resumed once the information is available. Only when all the eligibility criteria and baseline data items have been provided, will the trial and pack numbers be given and a confirmatory email sent to the randomising investigator, the local PI and the research midwife/nurse. The trial number will be linked to a treatment pack number that will be available in the local hospital pharmacy, and the pharmacy will also receive notification of the randomisation by email.

3.3.2 Randomisation Methods and Stratification Variables

Participants will be randomised online via a secure internet facility in a 1:1 ratio through an Integrated Trial Management System. A "minimisation" procedure using a computer-based algorithm will be used to avoid chance imbalances in important stratification variables. Strata used in the minimisation will be:

- Age (<35, ≥35 years).
- Body Mass Index (BMI) (<30, ≥30).
- Fetal heart activity (present, absent).
- Estimated gestation at presentation (<42, ≥42 days).
- Amount of bleeding (PBAC [Pictorial Bleeding Assessment Chart] score ≤2; ≥3).

3.3.3 Informing the Participant's GP

The participant's General Practitioner (GP) will be notified, with the participant's consent.

4 TREATMENT

4.1 Trial treatment

4.1.1 Investigational Medicinal Product: Progesterone and Placebo

The Investigational Medicinal Product (IMP) is progesterone at a dose of 400 mg (i.e. two capsules of Utrogestan 200 mg®) to be taken vaginally twice daily from confirmation of an intrauterine gestation sac visible on ultrasonography, to 16 completed weeks of pregnancy or until miscarriage is confirmed. The up-to-date Investigator's Brochure for progesterone is available to all participating units.

The placebo will be a vaginal capsule, encapsulated in the same form as the IMP, and identical in colour, shape and weight.

4.1.2 Dose and Route of Administration

Dose

The ideal dose of progesterone to potentially prevent miscarriage is unknown. Our choice of 400 mg twice daily was made after a) a careful review of the existing literature, b) an extensive survey of UK clinicians, c) a review of clinical practice and d) a review of other related evidence. The SmPC and the British National Formulary suggest a dose up to 400 mg twice daily. Progesterone vaginal capsules are commonly used for luteal support in Assisted Conception at a treatment dose of 400 mg twice daily, with no specific concerns on safety raised on this dose. Moreover, the PROMISE trial (HTA 08/38/01), that has already randomised over 810 women to 400 mg of progesterone or placebo twice daily, has not identified any acceptability or adverse effect issues. Hence we consider the dosage of 400 mg twice daily of vaginal progesterone to be the optimal choice in order to ensure a clinically effective dose, and to minimise the risk of a negative trial result from therapy with a suboptimal dose.

Route

An immuno-modulatory effect of progesterone within the uterus is the key presumed mechanism for preventing miscarriage. The vaginal route is therefore rational since it delivers a greater proportion of the drug to the uterus. Furthermore, existing miscarriage studies and preterm birth studies have shown effectiveness when given via the vaginal route. For instance, 14 of 36 studies of second/third trimester progesterone to prevent preterm birth (identified by a recent systematic review) used vaginal progesterone, with significant improvements being observed for various clinical outcomes, confirming the biological effects of vaginal progesterone[21]. Finally, a survey of women has found very high acceptability for the vaginal route.

Two vaginal capsules must be inserted vaginally (or rectally if preferred by the participant) twice daily. The first dose should be taken the evening following randomisation and subsequently every morning and evening until 16 completed weeks of pregnancy or until miscarriage is confirmed.

4.1.3 Packaging, Formulation and Supply

Investigational medicinal products will be procured, assembled, packed and quality assured by Besins Healthcare, a global clinical services company with whom we have worked in previous clinical trials. Besins Healthcare holds a Manufacturers' Licence for tablets and capsules under the Good Manufacturing Practice requirements (EU Directive 2003/94/EC) and in compliance with Good Clinical Practice (GCP; Clinical Trials Directive 2001/20/EC) Annex 13 requirements. Besins Healthcare will over-encapsulate the IMP and placebo and dispense into containers accordingly.

At study initiation, the Trial Office will arrange an initial supply of progesterone and placebo to be delivered by Besins Healthcare to the pharmacist of each study site. Local pharmacists will check the amount and condition of the supply, and confirm these details in a Proof of Receipt form.

The SmPC for progesterone states that progesterone should be stored below 25^{o}C in a dry place. Shipments from Besins Healthcare will be temperature-monitored. Participants will be advised to keep their trial treatment packs away from extremes of temperature and out of the reach of children.

All the details of trial drug supply, labelling, storage and preparation will be as per the requirements of the Medicines for Human Use (Clinical Trials) Regulations 2004. Besins Healthcare will provide the Qualified Person for release of trial drug (QP) batch release service under the requirements of the Medicines for Human Use (Clinical Trials) Regulations 2004.

4.1.4 Dispensing and Accountability

At randomisation, the trial treatment number will be provided and this reference will correspond to a trial treatment pack available in the local hospital pharmacy. The pharmacist will receive notification of the name and trial number of the randomised woman and will prepare the trial treatment pack for dispensing. The trial treatment pack will contain between five and 12 weeks' supply, as appropriate to the duration from gestation at presentation until 16 weeks of gestation, for use by each participant.

The local pharmacist should keep accurate records of trial drugs dispensed using a pharmacy log provided by the PRISM Trial Office. Trial drugs must be kept in the packaging supplied and under no circumstances used for other participants or non-participants.

4.1.5 Treatment Duration

The treatment period will be determined by the gestational age at randomisation, ranging from five weeks (for women presenting at 12 weeks of gestation) to 12 weeks (for women presenting at five weeks of gestation). Trial treatment will be stopped at 16 weeks of gestation or if a miscarriage occurs.

4.1.6 Resupply to Centres

The computer program underpinning the randomisation process will automatically notify Besins Healthcare when a local study centre supply is low, to enable the IMP provider to issue another batch of trial drugs to the pharmacy. However, if the local pharmacist notices that supplies are becoming depleted and additional supplies could be needed, the site should contact the PRISM Trial Office, who will be able to initiate an additional supply.

4.2 Compliance Monitoring

The dispensing of the PRISM trial drug will be recorded in the pharmacy drug accountability log. The Trial Coordinator will periodically monitor the trial drug chart to verify that the dispensing system is being followed, to note any deviations from the quarterly schedule, and notify local PIs of any problems or deviations.

Participants will be asked to return completed, partially used and unused treatment packs to the trial centres. The research nurse at each local centre will receive the empty/partially used/unused treatment packs, and record the information for each trial participant, in the database. In an effort to improve compliance, women who fail to return the treatment packs, whether empty or not, will be contacted by telephone or email by the research nurse

for advice and support. Non-compliance is defined as less than 80% usage of the appropriate number of vaginal capsules for the gestational age at randomisation.

4.3 Excluded Medications or Interactions

Progesterone may interfere with the effects of bromocriptine and could raise the plasma concentration of ciclosporin. The metabolism of progesterone is accelerated by rifamycin, an antibacterial agent. Ketoconazole may increase the bioavailability of progesterone.

With participants' consent, the GPs of all the women recruited to the PRISM study will be informed of their participation. Moreover, all the participants will be given a small information card with contact details of the local PRISM investigator (a sample card is available separately), to carry these particulars for the purpose of directing clinicians to information regarding potential drug interactions. Concomitant therapy will be at the discretion of the care-providing clinicians.

Other than the above drugs and other progestogen preparations, the initiation of treatment for another indication will not necessitate withdrawal from the PRISM study.

4.4 Withdrawal of Treatment

A participant may be withdrawn from trial treatment if it becomes medically necessary in the opinion of the investigator(s) or clinician(s) providing patient care. In the event of such premature treatment cessation, PRISM study personnel will make every effort to obtain and record information about the reasons for discontinuation and any adverse events, and to follow up all safety and efficacy outcomes as appropriate.

A participant may voluntarily decide to cease taking the PRISM study treatment at any time. If a participant does not return for a scheduled visit, attempts will be made to contact her and (where possible) to review compliance and adverse events. If a woman decides after randomisation that she does not wish to continue her pregnancy, she may withdraw herself from the trial. We will aim to document the reason(s) for self-withdrawal.

Clear distinction will be made between withdrawals from trial treatments whilst allowing further follow-up, and any participants who refuse any follow-up. If a participant explicitly withdraws consent to any further data recording then this decision will be respected and recorded on the electronic data capture system. All communications surrounding the withdrawal will be noted in the participant's records and no further data will be collected for the participant.

4.4.1 Unblinding

Participants, investigators, research midwives/nurses and other attending clinicians will remain blind to the trial drug allocation throughout the duration of the trial.

Should any Serious Adverse Event occur, the management and care of the participant will be initiated as though the woman is taking progesterone. Cases that are considered serious, unexpected and possibly, probably or definitely related (please refer to section 5.1) will be unblinded only at the Trial Office by the PRISM Trial Coordinator, for reporting purposes. The attending clinician and local PI will not be made aware of the actual trial drug.

In all other circumstances, investigators and research midwives/nurses will remain blind to drug allocation whilst the participant remains in the trial. However, if a participant is withdrawn from the trial and only if the drug allocation is required for the continued medical management of the withdrawn participant, clinicians should contact the PRISM Trial Office or use the online PRISM code-break system. This service will be available 24 hours a day, seven days a week.

5 SAFETY MONITORING PROCEDURES

A recent review showed no clear or consistent evidence of serious adverse effects on the mother or the baby as a result of progesterone treatment during pregnancy (please refer to section 2.1.1). There is moreover substantial

evidence to indicate that progestogen supplementation is safe to the mother and the fetus (at the proposed dose for the PRISM trial of 400 mg twice daily)[9-11]. The unknown risk of fetal abnormalities should be weighed against the risk of miscarriage.

There may yet be unexpected serious adverse reactions associated with progesterone when used in pregnant women. Progesterone has been prescribed to pregnant women in the PROMISE trial, to evaluate its effectiveness in preventing miscarriage. The Investigator's Brochure lists some rare but serious adverse reactions (available separately).

The Medicines for Human Use (Clinical Trials) Regulations 2004 define categories of adverse events, the responsibilities of the investigators to notify adverse events to the Trial Sponsor and the responsibilities of the Trial Sponsor to report to the regulatory authority and ethics committee. It will therefore be imperative for all investigators to maintain a thorough understanding of anticipated adverse events and the process for reporting such events.

5.1 General Definitions

5.1.1 Adverse Events (AEs)

An AE is:

- Any unintentional, unfavourable clinical sign or symptom, including complications of miscarriages (but not miscarriage itself).
- Any new illness or disease or the deterioration of existing disease or illness.
- Any clinically significant deterioration in any laboratory assessments or clinical tests.

The following are not AEs:

- Miscarriage or intrauterine death.
- A pre-existing condition (unless it worsens significantly during treatment).
- Diagnostic and therapeutic procedures likely in a normal pregnancy, such as ultrasound.

5.1.2 Adverse Reactions (ARs)

An AR is an Adverse Event that is considered to have a "reasonable causal relationship" with the trial drug.

5.1.3 Serious Adverse Events (SAEs)

An SAE is an untoward event which:

- Results in death of the mother or a stillbirth.
- Immediately threatens the life of participant*.
- Results in hospitalisation or a longer than anticipated stay in hospital.
- Results in a persistent or significant disability.
- Results in any congenital anomaly or birth defect in this pregnancy.

A Serious Adverse Reaction (SAR) is a Serious Adverse Event that is considered to have a "reasonable causal relationship" with the trial drug.

**Life-threatening in the definition of a Serious Adverse Event or Serious Adverse Reaction refers to an event in which the participant 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. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.*

Events NOT considered to be SAEs are hospitalisations for events that are expected. These events will be recorded on the electronic Case Report Form (e-CRF) and reported to the Data Monitoring Committee (DMC) as part of the safety review. They include:

- Routine treatment or monitoring of miscarriage or threatened preterm birth, not associated with any deterioration in condition, including Premature Rupture of Membranes (PROM) or suspected PROM.

- Treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study, and did not worsen, including elective caesarean section.
- Admission to a hospital or other institution for general care, not associated with any deterioration in condition including:
    - Hospitalisation for rest.
    - Hospitalisation for observation or monitoring of pregnancy.
    - Hospitalisation for maternal discomfort.
    - Hyperemesis which is quickly resolved.
    - Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.
    - Hospital admission for complications of pregnancy unlikely to be related to progesterone use (e.g. pre-eclampsia, UTI, pyelonephritis).

Expected SAEs

Expected SAEs are those listed in the Investigator's Brochure for progesterone (available separately). These events do not meet the criteria for classification as Suspected Unexpected Serious Adverse Reactions (SUSARs) unless for reason of their severity. An up-to-date Investigator's Brochure will be made available to all participating units and the Trial Office will ensure that any updates are circulated to all investigators.

5.1.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

A SUSAR is a Serious Adverse Event suspected to be related to a product, which is of a type or severity NOT consistent with the up-to-date Investigator's Brochure for Utrogestan.

5.1.5 Reporting AEs

Specific AEs, from the first administration of trial treatment until the end of the pregnancy, whether observed directly or reported by the participant, will be collected and recorded. It will not be necessary to report non-serious adverse reactions or events that are not recorded on the data collection forms.

5.1.6 Reporting SAEs

All SAEs must be recorded on the SAE Form (a sample document is available separately) and submitted to the Trial Office via fax (0121 415 9136) or email (prism@trials.bham.ac.uk) within 24 hours of the research staff becoming aware of the event. The local Principal Investigator (PI) (or other nominated clinician) must assign seriousness, causality and expectedness to the SAE before reporting. All SAEs should be assessed for seriousness, causality and expectedness as though the participant is prescribed progesterone.

For each SAE, the following information will be collected:

- Full details in medical terms with a diagnosis, if possible.
- Duration (start and end dates; times, if applicable).
- Action taken.
- Outcome.
- Causality, in the opinion of the investigator.
- Whether the event would be considered to be expected or unexpected (refer to the most recent and relevant Investigator's Brochure).

Assessment of causality and expectedness must be made by a doctor. If a doctor is unavailable, initial reports without causality and expectedness assessment must be submitted to the Trial Office by a healthcare professional within 24 hours, and followed up by medical assessment as soon as possible thereafter, ideally within the following 24 hours. Any SAE which is assessed as possibly, probably or definitely related to trial treatment will be classified as a Serious Adverse Reaction (SAR).

The local investigator and others responsible for patient care should institute any supplementary investigations of SAEs based on their clinical judgement of the likely causative factors. They should also provide further follow-up

information as soon as available. If a participant dies, the causative factors identified in any post-mortem findings must be provided to the Trial Office.

Any SAE that is outstanding at the end of the trial treatment period must be followed up at least until the final outcome is determined, even if this provision necessitates continued follow-up beyond the end of pregnancy.

The Trial Office will report all SAEs to the DMC approximately six-monthly. The DMC will view data blinded to treatment but will be able to review unblinded data if necessary. The Trial Office will also report all SAEs to the Research Ethics Committee (REC) and Medicines and Healthcare Products Regulatory Authority (MHRA) annually, and to the Trial Steering Committee (TSC) approximately six-monthly. The REC, MHRA and TSC will only view data blinded to trial treatment. Local investigators will be responsible for reporting SAEs to their host institutions, according to local regulations.

5.1.7 Reporting SUSARs

Any SAE that is categorised by the local investigator as both (a) suspected to be related to the PRISM trial drug and (b) unexpected will be classified as a SUSAR, and subject to expedited reporting, irrespective of trial arm (progesterone or placebo).

All SUSARs must be recorded on the SAE Form (a sample document is available separately) and submitted to the Trial Office via fax (0121 415 9136) or email (prism@trials.bham.ac.uk) immediately or within 24 hours of the research staff becoming aware of the event. The Chief Investigator (CI) or nominated individual will undertake an urgent review of SUSARs within 24 hours of reporting and may request further information immediately from the local clinical team. The CI will not overrule the causality, expectedness or seriousness assessment of the local investigator. If the CI disagrees with assessment of the local investigator, further clarification and discussion should take place to reach a consensus. If a consensus cannot be reached, both the opinion of the local investigator and the CI should be provided in reports to the REC and MHRA.

The Trial Office will report all SUSARs to the Sponsor, REC and MHRA. The treatment allocation will be unblinded. If any SUSAR results in death or is life-threatening then the report will be made within seven days of the initial report being received, or within 15 days for any other SUSAR.

If information is incomplete at the time of initial reporting, or the event is ongoing, the Trial Office will request follow-up information, including information for categorisation of causality, from the local investigator, and send the follow-up information to the Sponsor, REC and MHRA within an additional 8 days for fatal or life-threatening SUSARs and as soon as possible for any other events.

5.1.8 Notification of Deaths

All maternal and neonatal deaths will be reported to the Trial Office on the SAE Form (a sample document is available separately) irrespective of whether the death is related to the trial drug or an unrelated event. If a participant dies, any post-mortem findings must be provided to the Trial Office with the SAE form. The Trial Office will report all deaths to the DMC for continuous safety review.

5.2 Pharmacovigilance

5.2.1 Local Principal Investigator (PI) (or nominated individual)

- To sign an Investigator's Agreement accepting the responsibilities below:
- To record specified AE/ARs occurring in the trial participants.
- To report all serious, serious, expected or unexpected adverse events or reactions, in the appropriate timescale.
- To provide medical judgement in assigning seriousness, expectedness and causality to AEs.
- To fax SAE forms to the Trial Office within 24 hours of becoming aware, and to provide further follow-up information as soon as available.
- To report SAEs to local committees if required, in line with local arrangements.

5.2.2 Chief Investigator (CI) (or nominated individual)

- To assign causality and the expected nature of SAEs if it is not possible to obtain local assessment.
- To review all events assessed as SAEs in the opinion of the local investigator.
- To review all events assessed as SUSARs in the opinion of the local investigator.

5.2.3 PRISM Trial Office

- To report SUSARs, unblinded to treatment, to the REC and MHRA within required timelines as detailed above.
- To prepare annual safety reports, blinded to treatment, to the REC, MHRA and TSC.
- To prepare SAE safety reports for the DMC at six-monthly intervals (data will be presented blinded to treatment, but the DMC will be able to review unblinded data if necessary).
- To report all fatal SAEs to the DMC for continuous safety review.
- To notify investigators of SUSARs which compromise participant safety.

5.2.4 Trial Steering Committee (TSC)

- To provide independent supervision of the scientific and ethical conduct of the trial on behalf of the Trial Sponsor and funding bodies.
- To review data, participant compliance, completion rates, adverse events (during treatment and up to end of follow-up).
- To receive and consider any recommendations from the DMC on protocol modifications.

5.2.5 Data Monitoring Committee (DMC)

- To review (initially at intervals of six months) overall safety and morbidity data to identify safety issues that may not be apparent on a case-by-case basis.
- To recommend to the TSC whether the trial should continue unchanged, continue with protocol modifications, or stop.

6 FOLLOW-UP AND OUTCOME MEASURES

6.1 Primary Outcome Measures

- Live births beyond 34 completed weeks of gestation, as a proportion of all women randomised.

6.2 Secondary Outcome Measures

- Gestation at delivery.
- Ongoing pregnancy at 12 weeks (range 11 to 13 weeks) of gestation.
- Miscarriage rate (delivery before 24 weeks of gestation).
- Survival at 28 days of neonatal life.
- Chromosomal and congenital abnormalities.
- Adverse events.
- Antenatal complications (such as pre-eclampsia, growth restriction).
- If delivery ≥24 weeks, mode of delivery, birth weight, arterial and venous cord pH, APGAR scores, and resuscitation data.
- Neonatal outcomes: ventilation support and neonatal complications (such as infection, retinopathy of prematurity, necrotising enterocolitis and intraventricular haemorrhage).

6.3 Health Economic Evaluation

If progesterone is shown to be an effective intervention to reduce the risk of miscarriage in pregnant women with early pregnancy bleeding, then it is likely that important cost implications will be seen for the healthcare sector. For example, progesterone may help to maintain the pregnancy for a longer period, avoiding miscarriage but

possibly instead leading to an increase in the number of cases of preterm birth. Preterm birth is associated with high costs both in the short-term (neonatal care) and longer-term; for instance, the potential impact on neurological development may lead to requirements for special needs assistance through early childhood, schooling and even adulthood. Given this situation, the economic evaluation will take the NHS and Personal Social Services (PSS) perspective of the societal costs.

6.3.1 Resource Use Outcomes

Resource use data will be collected to estimate the costs associated with the provision of progesterone in pregnancy. We shall therefore prospectively collect data on NHS resource use on a random sample of women from both arms of the trial and follow-up care.

The items to be monitored include:

- Administration of progesterone.
- Resource use associated with antenatal care in both arms of the trial including antenatal visits to clinic and the GP, contacts with healthcare services that are related to the pregnancy, and knock-on costs associated with other medication and any additional monitoring.
- Additional resources associated with preterm birth and neonatal medication as required.
- Duration of stay in neonatal intensive care, and inpatient days.
- Maternal and neonatal admissions after discharge.

Unit costs or prices will then be required to calculate an overall cost per infant. Cost data will be collected from two principal sources. First, the trial itself will provide the time (staff and resources such as drug dispensing and equipment) and other resource use data to estimate the costs incurred in administering progesterone and associated antenatal care. Many costs of routine antenatal care resources have been previously researched, so the main focus of the PRISM study will be any differences in resource use between the different arms of the trial. We will not estimate the costs of interventions that are the same in both arms. Primary cost data for many other resources will be collected from participating hospital sites. Where possible, additional cost data will be collected from routine sources, including Curtis 2011 and hospital finance departments. Many cost data are already available in recently published sources. A study to investigate the costs of different levels of neonatal intensive care has already been carried out[22] and other studies of costs associated with preterm delivery are available to supplement these[23].

6.3.2 Economic Analysis

The main component to the analysis will be a within-study analysis, but a model-based analysis beyond the end point of the trial will also be conducted.

6.3.3 Within-Study Analysis

Our within-study analysis will use data collected within the trial, so estimates of costs and benefits will relate only to the initial period and assessment of live births with and without disability at 34 weeks (based on the primary outcome of the trial). The data available for this analysis will be study-specific resource use and costs, and the analysis will be based on cost per additional live birth (with and without disability) at 34 weeks. A further analysis based on all data up to infants reaching two years of age is planned, and the outcome of this second analysis will be based on parent reports and neurodevelopment at two years. If sufficient data are available based on a pragmatic literature search, and justifiable according to the second analysis, it may be possible to model beyond the end point of the trial with appropriate emphasis on the limitations of the data.

6.3.4 Model-Based Analysis

We have previously developed a model-based economic analysis to model the tests and interventions to prevent preterm birth[24-26]. If there is no clinically detectable impact on outcomes as a result of this trial (for example, either because progesterone has no effect, or because it does lead to an increase in live births beyond 34 weeks but the rate of preterm birth is no higher than the national average and the increase relates only to term births) then it may be deemed unnecessary to model beyond the outcome of the trial because progesterone may not

cause any harm. However, if the intervention leads to an increase in preterm birth or infants with chromosomal abnormalities, then it will be necessary to assess the cost-effectiveness of the intervention in the longer term, to take account of adverse outcomes, such as cerebral palsy and Down's syndrome. Therefore, if justifiable according to the outcome of the trial, we will model the longer term impact (potentially the lifetime impact if data allow). We will use these data to extend the economic evaluation beyond the end point of the trial. If available data allow, this analysis will be conducted both from NHS and societal perspectives.

Given the skewness inherent in most cost data and the concern of economic analyses with mean costs, a bootstrapping approach will be used to calculate confidence intervals around any difference in mean costs. Initially, the base-case analysis of the within-study analysis will be framed in terms of cost consequences, reporting disaggregated data on the incremental cost and the important consequences as assessed in the trial. An incremental economic analysis will be conducted on the primary outcome and other secondary outcomes.

6.3.5 Presentation of Results and Sensitivity Analyses

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. We shall also use both simple and probabilistic sensitivity analyses to explore the robustness of the 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.

For the longer term model-based analysis, discounting adjustments will be made to reflect differential timing. The base-case analysis will follow both Treasury and NICE recommendations for public sector projects.

6.4 Outcomes for Future Studies

Each participant in the PRISM study will be asked to consent for the future evaluation of themselves, the child that is born and the health records of both, and babies will be flagged with the Office of National Statistics (ONS) or equivalent. Although long-term follow-up will remain outside the scope of this trial, we plan to conduct further studies on outcomes such as the composite endpoint of death or neurodevelopmental impairment at two years of age, the Bailey III cognitive scale cognitive scale standardised score at two years of chronological age, and disability classified into domains according to professional consensus. The NHS number of each baby will be recorded to facilitate future follow-up studies.

6.5 Outcome Assessment

6.5.1 Format

Relevant trial data will be transcribed directly into the web-based database. Source data will comprise the research clinic notes, hospital notes, hand-held pregnancy notes and laboratory results.

Women will be encouraged to report miscarriages, deliveries and adverse events, and any additional visits to non-participating hospitals to the research midwife. Self-reports will be verified against clinical notes by the research team.

6.5.2 Frequency

The trial pathway fits within the current standard care pathway for women presenting with early pregnancy bleeding. Women who experience early pregnancy bleeding usually attend an Early Pregnancy Assessment Unit (EPAU), and are offered a transvaginal ultrasound scan as part of standard care. Potential participants in the PRISM study will be identified, approached and invited to participate in the trial by clinic doctors, research nurses and midwives in EPAUs. Randomisation and prescribing of study medications will take place in the EPAUs. The outcome assessments are detailed in **Table 2** below.

Table 2 Outcome assessment details

What? *Outcome*	**When?** *Timepoint*	**How?** *Methods*	**Why?** *Practice*
Ongoing pregnancy	11 to 13 weeks	Ultrasound	Standard practice
Final pregnancy outcomes including: ▪ Miscarriage ▪ Live birth ▪ Gestation at delivery ▪ Congenital anomalies	At or after the end of pregnancy	Clinical records Individual telephonic or face to face interview with participant Outcome "post card"	Standard practice AND Protocol driven
Neonatal outcomes	Up to 28 days of neonatal life	Neonatal records Individual interview with participant	Standard practice AND Protocol driven
Resource use outcomes	At any time during the PRISM study	Clinical records Individual interview with participant	Protocol driven

The first outcome assessment will be an ultrasound scan performed at about 12 weeks of gestation, which is routine practice. After delivery, information about obstetrical and perinatal outcomes will be gathered, mostly from patient records (with limited inconvenience to the study participants).

Neonatal survival data will be collected by flagging all babies with the NHS Information Centre to receive death certificates. Consent will also be obtained to use NHS records to trace babies for future long-term follow-up studies. These studies will be conducted under separate protocols.

6.6 Data Management and Validation

6.6.1 Loss to Follow-Up

To reduce loss to follow-up, the local research team will record the NHS numbers of participants, to trace the participants via local GP practices.

6.6.2 Withdrawal of Consent for Further Data Collection

Withdrawal from follow-up will be the decision of each participant in the PRISM study (please refer to section 4.4). However, the exclusion of withdrawn participants in data analysis could bias clinical trial results and reduce the power of the study to detect important differences, so women will be encouraged to allow data collection to continue even if trial treatment ceases. If a participant wishes to withdraw from treatment and/or follow-up, there will be a checklist to guide investigators as to what to do with data and trial treatment packs.

6.6.3 Long-Term Follow-Up

The development of the infants born to participants in the PRISM trial is of interest to investigators but outside the scope and time-frame for the trial. Should further funding become available, a new observational protocol will be developed, approval gained and participants traced through the randomising centre and the NHS numbers of mothers and babies.

6.6.4 Definition of the End of the Trial

The interventional phase of the trial will end when the last participant recruited has taken her last dose of the trial treatment. The observational phase of the trial will cease when the 28-day follow-up has been completed for the baby of the last participant recruited.

7 ACCRUAL AND ANALYSIS

7.1 Sample size

We plan to randomise 4,150 women in total (2075 participants each in the progesterone and placebo arms). To detect a Minimally Important Difference (MID) of 5% in live birth beyond 34 weeks (from 60% baseline live birth rate to 65%), for an alpha error rate of 5% and 90% power), it will be necessary to randomise a total of 3940 women to the intervention and placebo groups. However, assuming and adjusting for a 5% attrition rate, the total number of participants required will be 4,150.

The Minimally Important Difference of 5% was defined following consultations amongst healthcare practitioners, patients and representatives of patient bodies as well as through a survey of clinicians. However, it should be noted, this difference is much smaller than what could be expected from the existing literature (please refer to section 2.1.1 and particularly to **Figure 1**), which has shown that the risk of miscarriage is halved with progesterone therapy (RR 0.53, 95% CI: 0.39, 0.73). If the actual difference in live birth is greater than 5%, then the study will have a power greater than 90% to detect that difference; if this is the situation, the DMC and TSC will be able to consider an early finish to recruitment.

The 60% baseline (control) event rate is derived from audits from 2 of the participating units (Imperial College London, and the Royal Infirmary Edinburgh). However, because there is previously published evidence to suggest a higher control event rate, we have provided sample size (**Table 3**) and power (**Table 4**) calculations in the tables below for higher control event rates. We believe it is prudent to work on the assumption of a lower control event rate for power calculation, because this in fact represents a worse-case scenario. The sample size requirements of the lower event rate provide sufficient (and in fact higher) power for a higher control event rate. All the power calculations noted above use two-sided binominal testing.

Table 3 Sample sizes with varying levels of control event rate, all assuming a 5% absolute difference, 5% attrition rate, 90% power and p=0.05

Control rate (%)	Intervention rate (%)	Total sample size required
55	60	4,320
60	65	4,150
65	70	3,880
70	75	3,520
75	80	3,090
80	85	2,550

Table 4 Power with varying levels of control event rate, if sample size is fixed at 4,150, all assuming 5% absolute difference, 5% attrition rate and p=0.05

Control rate (%)	Intervention rate (%)	Power (%)
55	60	89
60	65	90
65	70	92
70	75	94
75	80	96
80	85	99

7.2 Projected Accrual and Attrition Rates

Participants will be recruited from participating centres across the UK. At least 22 hospital units in England and Scotland will contribute to the total, with more sites joining the study if required to randomise 4,150 women within one year. Thus it will be necessary for the trial to achieve a mean recruitment rate of 189 women per centre (approximately 16 participants at each site per month), but local numbers will also be affected by the size of the unit and local population coverage.

7.3 Statistical Analyses

The analysis will be by intention to treat. Every attempt will be made to gather data on all women randomised, irrespective of compliance with the treatment protocol. Point estimates, 95% confidence intervals and p-values

from two-sided tests will be calculated for the outcome measures. A Statistical Analysis Plan will be drawn up prior to any analysis and reviewed by the independent Data Monitoring Committee (DMC).

7.3.1 Interim Analyses

Interim analyses will be conducted on behalf of the DMC (please refer to section 8.4). These will be considered together with a report of the Serious Adverse Events. The DMC will meet before recruitment commences, and thereafter at least annually. Effectiveness and futility criteria will be ratified by the DMC. The DAMOCLES charter will be adopted by the DMC and will include a specific remit for reviewing emerging data from other trials.

7.3.2 Primary Endpoint Analysis

The primary endpoint will be the proportion of women randomised who experience a live birth beyond 34 weeks. The denominator of this proportion will be all women randomised, and the numerator will be those women who proceed to have a live birth beyond 34 weeks. We will use a log-binomial regression model to calculate the relative risk and 95% confidence intervals. Minimisation variables (maternal age, BMI, fetal heart activity, gestation at presentation, and amount of bleeding) will be included as covariates. The p-value from the associated chi-squared test will be produced and used to determine statistical significance.

7.3.3 Secondary Endpoint Analyses

Dichotomous secondary outcomes (e.g. miscarriage rate, survival at 28 days) will be analysed in the same fashion as the primary outcome. Time from randomisation to live birth will be analysed by log-rank test with a Cox Proportional Hazard (PH) model also built if the assumptions of proportionality are met. Fetuses/babies will be censored at the last time-point known to be alive if the final outcome is not known. Standard methods will be used to analyse other outcomes (e.g. t-tests for continuous outcomes such as birth weights). Appropriate summary statistics split by group will be presented for each outcome (e.g. proportions/percentages, mean/standard deviation or median/interquartile range).

7.3.4 Handling Missing Data

Every attempt will be made to collect full follow-up data on all women (unless a woman withdraws consent for follow up data collection). In particular, participants will continue to be followed up even after any protocol treatment deviation or violation. It is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis. This presents a risk of bias, and secondary sensitivity analyses will be undertaken to assess the possible impact of the risk, including the assumption that all participants lost to follow-up were treatment failures (i.e. subsequent miscarriage or preterm birth [<34 weeks of gestation]). Other sensitivity analyses will involve simulating missing responses using a multiple imputation (MI).

7.3.5 Subgroup Analyses

Subgroup analyses will be limited to the same variables used as minimisation variables (please refer to section 3.3.2). Tests for statistical heterogeneity (e.g. by including treatment group by subgroup interaction parameter in the regression model) will be performed prior to any examination of effect estimate within subgroups. Sensitivity analyses will be performed on the primary outcome to investigate the impact of any missing data. This will include the assumption that missing responses are negative (i.e. not a live birth beyond 34 weeks) and a worst-case scenario (all missing data are negative in the progesterone group and positive in the placebo group). Missing responses will also be simulated using a multiple imputation (MI) approach as a sensitivity analysis. In each case, an interaction test will first be used to determine whether there is a basis for treating the groups separately. The results of subgroup analyses will be treated with caution, and used for the purposes of hypothesis generation only.

7.3.6 Final Analysis

The primary analysis for the study will occur after all randomised women have complete primary and major secondary outcomes (up to 28 days of neonatal life).

8 DATA ACCESS AND QUALITY ASSURANCE

8.1 Confidentiality of Personal Data

Personal data and sensitive information required for the PRISM trial will be collected directly from trial participants and hospital notes. Participants will be informed about the transfer of this information to the PRISM Trial Office and asked for their consent. The data will be entered onto a secure computer database, directly via the internet using secure socket layer encryption technology or indirectly from paper Serious Adverse Event (SAE) forms by members of the research team.

Any trial-related personal information received in paper format will be held securely and treated as strictly confidential according to the Standard Operating Procedure (SOP) of the Birmingham Clinical Trials Unit (BCTU). All the staff involved in the PRISM trial (clinical, academic and support personnel) will share the same duty of care to prevent any unauthorised disclosure of personal information. No data that could be used to identify an individual will be published. Data will be stored on a secure server under the provisions of the Data Protection Act and/or applicable laws and regulations.

8.2 In-House Data Quality Assurance

The PRISM Trial Coordinator will perform hospital site visits as part of the trial monitoring plan, as agreed and reviewed by the TMG, TSC and DMC. This may involve source data verification.

8.2.1 Monitoring and Audit

Investigators and their host institutions will be required to permit trial-related monitoring and audits by the PRISM Trial Coordinator, providing direct access to source data and documents as requested. NHS Trusts may also be subject to inspection by the MHRA and/or internal Research and Development Managers, and should do everything requested by the CI in order to prepare and contribute to any inspection or audit. Study participants will be made aware by the PIS of the possibility of external audits of the data they provide.

8.2.2 Trial Drug Quality Assurance

To verify the integrity of the randomisation list and labelling process, a sample of vaginal capsules will be destruction- tested from each batch of treatment packs produced.

8.2.3 Statistical Monitoring Throughout the Trial

The trial will also adopt a centralised approach to monitoring data quality and compliance. Within the MedSciNet Clinical Trial Framework, a computer database will be constructed and tailored specifically to the PRISM trial, with range and logic checks to prevent erroneous data entry. Independent checks of data entry will be periodically undertaken on small subsamples. The Trial Statistician will regularly check the balance of allocations by the stratification variables.

8.3 Independent Trial Steering Committee (TSC)

The TSC will provide independent supervision for the trial, providing advice to the Chief and Co-Investigators and the Trial Sponsor, and affording protection for participants by ensuring the study is conducted according to the International Conference on Harmonisation (ICH) of Good Clinical Practice (GCP) guidelines.

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

8.4 Data Monitoring Committee (DMC)

The DMC will adopt the DAMOCLES charter to define its terms of reference and operation in relation to oversight of the PRISM trial. If progesterone is overwhelmingly better or worse than placebo with respect to reducing the risk of miscarriage and/or preterm birth, then this effect may become apparent before the target recruitment has been reached. Alternatively, new evidence could emerge from other sources to suggest that progesterone is definitely more, or less, effective than placebo. To protect against any unnecessary continuance of the trial in this event, interim analyses of major endpoints will be supplied during the period of recruitment to the study, in strict confidence, to the DMC along with updates on results of other related studies, and any other analyses that the DMC may request.

The DMC will advise the chair of the TSC if, in their view, any of the randomised comparisons in the trial have provided both (a) proof beyond reasonable doubt that for all, or for some, types of participant one particular treatment is definitely indicated or definitely contra-indicated in terms of a net difference in the primary outcome, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results. Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least $p<0.001$ (similar to a Haybittle-Peto stopping boundary) in an interim analysis of the primary outcome may be required to justify halting, or modifying, the study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed. The TSC will then be able to decide whether to close or modify any part of the trial. Unless this happens, however, the TMG, TSC, the investigators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results.

8.5 Long-Term Data Storage

On completion of data collection and in accordance with the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (sections 18 and 28)., all the study data will be securely stored for 25 years to allow adequate time for review and reappraisal, to enable the resolution of any queries or concerns about the results, and to facilitate further follow-up research.

After the closure of the trial, the site files from each centre will be securely archived at the sites. Electronic trial data will be securely stored within the MedSciNet Clinical Trial Framework. The remainder of the trial master file documentation will be securely stored by the PRISM Trial Office at the University of Birmingham. Long-term legacy archiving for electronic data will be considered for continued storage after 15 years.

8.6 Data Sharing

Anonymous data will be made available to other researchers, for example for individual participant data meta-analysis, if the aim is to answer further resolved questions in a scientifically rigorous study design, following review by the TMG or Chief Investigator or nominated data custodian.

9 ORGANISATION AND RESPONSIBILITIES

To ensure the smooth running of the trial and to minimise the overall procedural workload, each participating centre will designate appropriately trained and qualified local individuals to be responsible for the institutional coordination of clinical and administrative arrangements.

All PRISM investigators will be responsible for (a) maintaining the protocol of the trial as described in this document, (b) helping healthcare professionals to ensure the study participants receive appropriate care throughout the period of research enrolment, (c) protecting the integrity and confidentiality of clinical and other records and data that may be generated by the research, and (d) reporting any failures in these respects, adverse drug reactions and other events or suspected misconduct through the appropriate systems.

As part of the BCTU, which is a fully registered UK Clinical Research Collaboration clinical trials unit, the PRISM Trial Office will benefit from accumulated experience in the management of studies with a focus on pregnancy. The BCTU will provide a robust quality management system to ensure good practice in the conduct and statistical analysis of the project.

9.1 Centre Eligibility

Participating centres will be NHS hospitals, with at least one of the following:

- Dedicated EPAU where suspected miscarriages are managed.
- Gynaecology ward.

Each study centre must use an onsite pharmacy to dispense medications to participants, and be able to offer appointments for the women in a dedicated clinical setting.

9.2 Local Coordinators

9.2.1 Local Principal Investigators

Every study centre will nominate a local Principal Investigator (PI) to oversee the conduct of PRISM research at the particular institution. Every PI must sign a declaration to acknowledge these responsibilities. It will be important to ensure close collaboration between clinical teams, in order to identify eligible participants sufficiently early for entry. The responsibilities of local PIs will include ensuring that all medical, nursing and midwifery staff who may be involved in the care of miscarriages and infertility services remain well-informed about the study and trained in trial procedures, such as obtaining informed consent and other aspects of GCP. The local PIs will also liaise with the Trial Coordinator to manage the logistic and administrative arrangements of the trial.

9.2.2 Nursing or Midwifery Coordinators

Each participating centre should also designate a local nurse or midwife to ensure that all eligible patients are considered for the study, provided with a PIS, and offered an opportunity to discuss the study if required. This person may be responsible for collecting baseline data, assessing eligibility, performing randomisation and coordinating follow-up evaluations. They will receive updates and newsletters from the Trial Office, provided with appropriate training and invited to progress meetings.

9.3 The PRISM Trial Office

The PRISM Trial Office will be responsible for providing study materials such as folders with printed and promotional literature, and for supplying these documents to collaborating centres after any relevant ethical approvals are obtained. The Trial Office will also supply additional printed materials on request, provide a central randomisation service, and take responsibility for data collection and verification (including reports of SAEs thought to be due to trial treatment), to notify SUSARs to the Trial Sponsor and/or regulatory authorities and for analyses. The Trial Office will additionally help resolve any local problems that may be encountered in trial participation.

9.4 Research Governance

The trial will be conducted according to the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments, and the principles of GCP guidelines.

Investigators at all the participating centres will be required to sign an Investigator's Agreement to confirm their commitments to accrual, compliance, GCP, confidentiality and publication. Deviations from the Investigator's Agreement will be monitored and the TSC will decide whether any action needs to be taken, e.g. withdrawal of funding or the suspension of study activities at the site.

The Trial Office will ensure that any researchers not employed by an NHS organisation who may be in position to influence the care of participants, or require access to participant notes, obtain a research passport or letter of access.

9.4.1 Regulatory and Ethical Approvals

Ethical and Trust Management Approval

A favourable ethical opinion was granted from the South Central- Oxford C Research Ethics Committee (REC reference number 14/SC/1345).

The Local Clinical Research Network (LCRN) will conduct governance checks and assess the facilities and resources needed to run the trial, in order to give permission for host sites to become involved in the study. The Trial Office will be able to help PIs in the process of obtaining any local research governance approvals that may be required, by answering many of the Site Specific Information questions within the standard IRAS (Integrated Research Application System) form. Local PIs will be responsible for liaison with administrative and managerial representatives of their institutions, with respect to locality issues and obtaining the necessary signatures at their Trust.

When each individual participating centre obtains Trust approval, the Trial Office will send a folder containing all trial materials to the local PI. Potential trial participants may then start to be approached.

Clinical Trial Authorisation

The Trial Office has obtained a unique EudraCT number for the trial (2014-002348-42), and has Clinical Trials Authorisation (CTA) from the Medicines and Healthcare Regulatory Authority (MHRA).

9.5 Funding and Finance

The research costs of the PRISM trial are funded by a grant from the NIHR Health Technology Assessment programme awarded to the University of Birmingham.

9.6 Indemnity

There are no special arrangements for compensation for non-negligent harm suffered by participants as a result of participating in the study. The study will not be sponsored by industry and therefore the indemnity guidelines of the Association of the British Pharmaceutical Industry (ABPI) and Association of British Healthcare Industries (ABHI) will not apply. The standard NHS indemnity liability arrangements for research detailed in Health and Safety Guidance (HSG) 96 (48) will operate in this case.

However, it should be stressed that in terms of negligent liability, NHS Trusts will retain a duty of care to all their patients, whether or not the patients are participating in a clinical trial. Apart from defective products, legal liability will not arise where there is non-negligent harm. NHS Trusts may not offer advance indemnities, nor take out commercial insurance for non-negligent harm.

9.7 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 will depend entirely on the wholehearted collaboration of a large number of doctors, nurses and others across the country. For this reason, the chief credit for the main results will be given not only to the central supervisory committees and/or organisers, but to all those who have collaborated in the trial.

9.8 Ancillary Studies

Any proposals for formal additional studies of the effects of trial treatments on some participants (e.g. special investigations in selected hospitals) will be referred to the TMG for consideration. In general, it will be preferable for the trial to be kept as simple as possible, and add-on studies will need to be fully justified.

10 DISSEMINATION AND PROJECTED OUTPUTS

The impact of the trial question is intrinsically high, as confirmed by the NICE guideline and clinical and patient surveys about the topic. However, we have also prioritised methods to maximise impact from an early stage in the study design.

Guidelines: The information is expected to be rapidly incorporated into professional guidelines by the Association of Early Pregnancy Units (AEPU), the RCOG and NICE, and disseminated to Early Pregnancy Units nationally for implementation.

Patient information resources: The findings will inform lay resources, e.g. via patient organisations such as the Miscarriage Association and the Ectopic Pregnancy Trust. Lay information will also highlight the need for treatment, if found beneficial, to be medically prescribed and supervised. Any negative findings will be equally disseminated to patients and the public to avoid unnecessary or potentially harmful intervention.

Conferences: The findings will be presented and disseminated via national and international conferences of AEPU and other relevant organisations.

Peer reviewed publications: We will aim to publish the findings in a prestigious peer reviewed journal with a high impact factor. We will disseminate the completed paper to the Department of Health, the Scientific Advisory Committees of the RCOG, the Royal College of Nurses (RCN) and the AEPU.

NIHR Journals Library: If funded, the NIHR Journals Library will help to disseminate the findings and provide an important, permanent and comprehensive record of the study.

Media: In consultation with the investigators and appropriate journal representatives, a press release will be issued to the media upon publication of the results.

Book: Effective Care in Early Pregnancy and Emergency Gynaecology: At the conclusion of the study, the findings will contribute to a clinical textbook that will be published in paper format and as an online book. The Chief Investigator of the trial has just published a book of similar format on the subject of infertility (ISBN: 978-1-4443-3555-2, Wiley-Blackwell).

We will share the results of the study with trial participants, staff members at research sites and other related research groups in the area. We will also submit a formal notification to the REC and the Department of Health. We anticipate additional outreach to other stakeholders (trial networks, healthcare advocates).

The trial team includes individuals with considerable previous experience of optimising research dissemination, including the Chairs of the RCOG Early Pregnancy Clinical Study Group (CSG) and AEPU, and the Director of the Miscarriage Association. The charity Ammalife (UK registered: 1120236) brings expertise in projecting information to communities in low- and middle-income countries, and will be involved in the dissemination of trial findings and recommendations.

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