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PROMISE: first-trimester progesterone therapy in women with a history of unexplained recurrent miscarriages – a randomised, double-blind, placebo-controlled, international multicentre trial and economic evaluation

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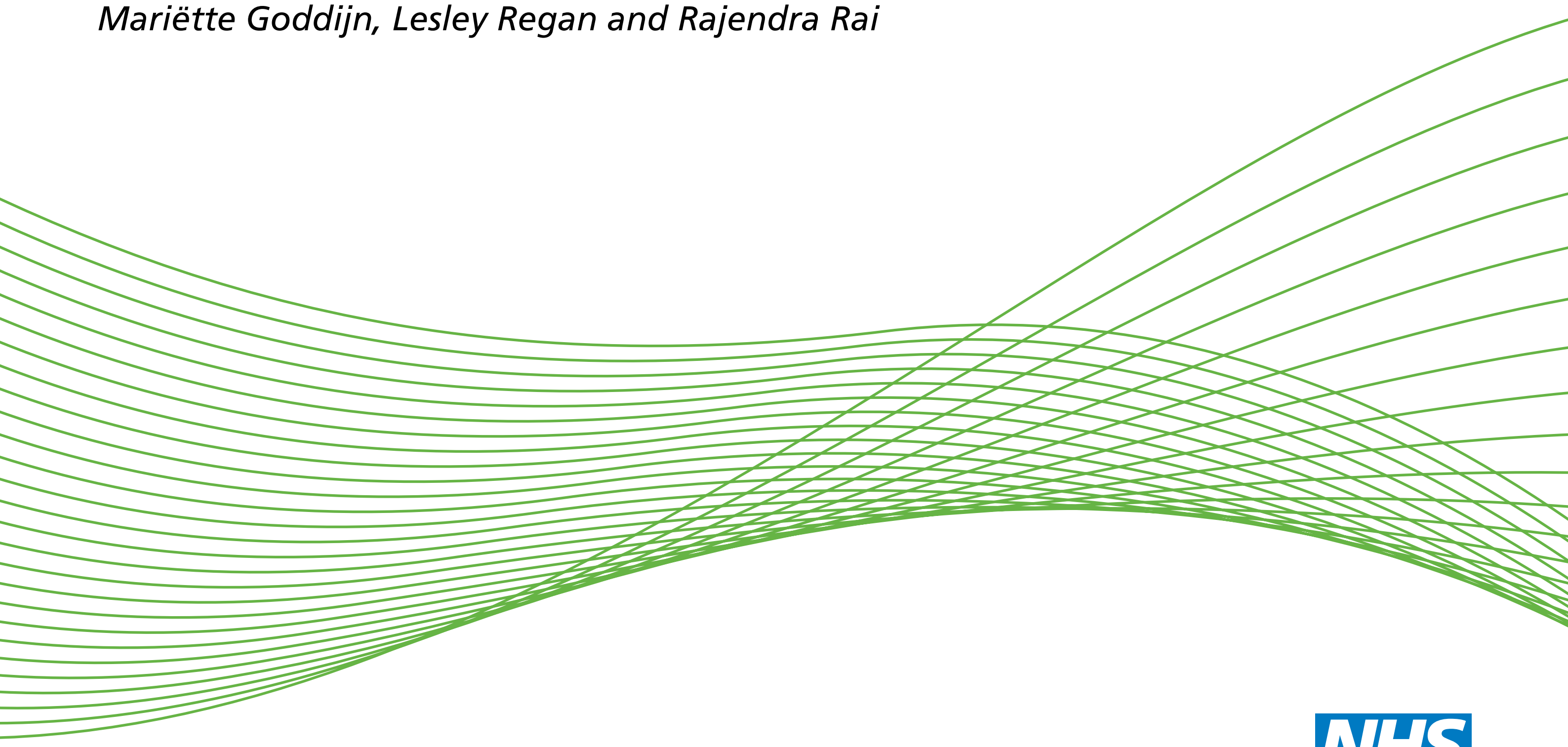

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PROMISE: first-trimester progesterone therapy in women with a history of unexplained recurrent miscarriages – a randomised, double-blind, placebo-controlled, international multicentre trial and economic evaluation

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Abstract

PROMISE: first-trimester progesterone therapy in women with a history of unexplained recurrent miscarriages – a randomised, double-blind, placebo-controlled, international multicentre trial and economic evaluation

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Background and objectives: Progesterone is essential to maintain a healthy pregnancy. Guidance from the Royal College of Obstetricians and Gynaecologists and a Cochrane review called for a definitive trial to test whether or not progesterone therapy in the first trimester could reduce the risk of miscarriage in women with a history of unexplained recurrent miscarriage (RM). The PROMISE trial was conducted to answer this question. A concurrent cost-effectiveness analysis was conducted.

Design and setting: A randomised, double-blind, placebo-controlled, international multicentre study, with economic evaluation, conducted in hospital settings across the UK (36 sites) and in the Netherlands (nine sites).

Participants and interventions: Women with unexplained RM (three or more first-trimester losses), aged between 18 and 39 years at randomisation, conceiving naturally and giving informed consent, received either micronised progesterone (Utrogestan®, Besins Healthcare) at a dose of 400 mg (two vaginal capsules of 200 mg) or placebo vaginal capsules twice daily, administered vaginally from soon after a positive urinary pregnancy test (and no later than 6 weeks of gestation) until 12 completed weeks of gestation (or earlier if the pregnancy ended before 12 weeks).

Main outcome measures: Live birth beyond 24 completed weeks of gestation (primary outcome), clinical pregnancy at 6–8 weeks, ongoing pregnancy at 12 weeks, miscarriage, gestation at delivery, neonatal survival at 28 days of life, congenital abnormalities and resource use.

Methods: Participants were randomised after confirmation of pregnancy. Randomisation was performed online via a secure internet facility. Data were collected on four occasions of outcome assessment after randomisation, up to 28 days after birth.

Results: A total of 1568 participants were screened for eligibility. Of the 836 women randomised between 2010 and 2013, 404 received progesterone and 432 received placebo. The baseline data (age, body mass index, maternal ethnicity, smoking status and parity) of the participants were comparable in the two arms of the trial. The follow-up rate to primary outcome was 826 out of 836 (98.8%). The live birth rate in the progesterone group was 65.8% (262/398) and in the placebo group it was 63.3% (271/428), giving a relative risk of 1.04 (95% confidence interval 0.94 to 1.15; $p = 0.45$). There was no evidence of a significant difference between the groups for any of the secondary outcomes. Economic analysis suggested a favourable incremental cost-effectiveness ratio for decision-making but wide confidence intervals indicated a high level of uncertainty in the health benefits. Additional sensitivity analysis suggested the probability that progesterone would fall within the National Institute for Health and Care Excellence's threshold of £20,000–30,000 per quality-adjusted life-year as between 0.7145 and 0.7341.

Conclusions: There is no evidence that first-trimester progesterone therapy improves outcomes in women with a history of unexplained RM.

Limitations: This study did not explore the effect of treatment with other progesterone preparations or treatment during the luteal phase of the menstrual cycle.

Future work: Future research could explore the efficacy of progesterone supplementation administered during the luteal phase of the menstrual cycle in women attempting natural conception despite a history of RM.

Trial registration: Current Controlled Trials ISRCTN92644181; EudraCT 2009-011208-42; Research Ethics Committee 09/H1208/44.

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List of abbreviations

AE	adverse event
APGAR	appearance, pulse, grimace, activity, respiration
BMI	body mass index
BNF	*British National Formulary*
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
DMC	Data Monitoring Committee
GCP	good clinical practice
HDU	high-dependency unit
HRG	Healthcare Resource Group
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IMP	investigational medicinal product
IQR	interquartile range
ITMS	integrated trial management system
IVF	in vitro fertilisation
MHRA	Medicines and Healthcare products Regulatory Agency
MID	minimally important difference
NICE	National Institute for Health and Care Excellence
NNU	neonatal unit
PI	principal investigator
PIS	participant information sheet
PPI	patient and public involvement
QALY	quality-adjusted life-year
R&D	research and development
RCOG	Royal College of Obstetricians and Gynaecologists
REC	Research Ethics Committee
RM	recurrent miscarriage
RR	relative risk
SAE	serious adverse event
SCBU	special care baby unit
SD	standard deviation
SmPC	summary of product characteristics
SUSAR	suspected unexpected serious adverse reaction
TCC	Trial Co-ordinating Centre
TMG	Trial Management Group
TSC	Trial Steering Committee

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Plain English summary

Progesterone is a natural hormone that is essential to maintain a healthy pregnancy, and previous research has suggested an association between lower levels of progesterone and higher rates of miscarriage. This trial was undertaken to test whether or not progesterone given to pregnant women with a history of repeated (three or more, consecutive or non-consecutive) unexplained early pregnancy losses would increase the number of pregnancies leading to live births after at least 24 weeks of gestation, when compared with placebo (a dummy drug). A pregnancy loss is considered to be unexplained if conditions known to increase the risk of miscarriage are absent.

The treatment that each participant in the study received was decided at random by a computer; one group received progesterone (400 mg twice daily as vaginal capsules) and the other group received placebo with an identical appearance, from soon after a positive urinary pregnancy test, and no later than 6 weeks of pregnancy, until 12 completed weeks of pregnancy (or earlier if the pregnancy ended before 12 weeks).

In total, 836 women received the treatment. Altogether, 533 women experienced a live birth after at least 24 weeks of pregnancy. The live birth rate in the progesterone group was 65.8%, compared with 63.3% in the placebo group (women who took the dummy treatment). The difference between these live birth rates is not statistically significant, which suggests that progesterone therapy in the first trimester is of no benefit for women with unexplained repeated pregnancy loss.

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Scientific summary

Background

Progesterone is essential to maintain a healthy pregnancy. As progesterone plays an important role in maintaining the lining of the uterus and fetal development, some researchers have hypothesised that maternal levels of progesterone could play a role in the pathogenesis of miscarriage. Hence it has been hypothesised that progesterone supplementation in the first trimester of pregnancy may reduce the miscarriage rate and increase the live birth rate among women at high risk of miscarriage, for example women with a history of recurrent miscarriage (RM). The evidence achieved in four controlled clinical trials conducted before the PROMISE trial suggested a benefit from progesterone therapy, but without sufficient certainty to usefully guide clinical practice. Therefore, a Royal College of Obstetricians and Gynaecologists guideline and a Cochrane review called for a definitive trial to evaluate this research question.

Objectives

The PROMISE study was designed to test the hypothesis that in women with unexplained RM, progesterone (400-mg vaginal capsules, twice daily), started as soon as practicable after a positive urinary pregnancy test (and no later than 6 weeks of gestation) and continued to 12 weeks of gestation, compared with placebo, would increase live births beyond 24 completed weeks of pregnancy by at least 10%. A concurrent economic evaluation for cost-effectiveness was conducted.

Design

The trial was a randomised, double-blind, placebo-controlled, international multicentre study, with health economic evaluation.

Setting

The study was conducted in hospital settings across the UK (36 sites) and in the Netherlands (nine sites).

Participants

Participants were women with unexplained RM (three or more consecutive or non-consecutive first-trimester losses), aged between 18 and 39 years at randomisation, conceiving naturally, and willing and able to give informed consent.

Interventions

Each participant in the PROMISE trial received either micronised progesterone at a dose of 400 mg (two vaginal capsules of 200 mg) or placebo vaginal capsules twice daily, administered vaginally from the date of randomisation soon after a positive urinary pregnancy test (and no later than 6 weeks of gestation) until 12 completed weeks of gestation (or earlier if the pregnancy ended before 12 weeks).

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Main outcome measures

Outcome measures included live birth beyond 24 completed weeks of gestation (primary outcome), clinical pregnancy at 6–8 weeks, ongoing pregnancy at 12 weeks, miscarriage, gestation at delivery, neonatal survival at 28 days of life, congenital abnormalities, various exploratory outcomes and resource use.

Methods

Participants were randomised after receiving confirmation of pregnancy. Third-party randomisation was performed online via a secure internet facility, and treatment commenced as soon as practicable after randomisation. Data were collected on four occasions of outcome assessment after randomisation, up to 28 days after birth. The primary analysis was by intention to treat. The primary heath economic analysis was to estimate the incremental cost-effectiveness ratio (ICER) for additional live births beyond 24 weeks.

Results

A total of 1568 participants were screened for eligibility. Of the 836 women randomised, 404 participants received progesterone therapy and 432 received placebo. The baseline data (age, body mass index, maternal ethnicity, smoking status and parity) of the participants were comparable between the two arms of the trial.

The follow-up rate for the primary outcome was 826 out of 836 (98.8%). The live birth rate in the progesterone group was 65.8% (262/398), and in the placebo group it was 63.3% (271/428), giving a relative risk (RR) of 1.04 [95% confidence interval (CI) 0.94 to 1.15; $p = 0.45$].

There was no evidence of a significant difference between the groups for any of the secondary outcomes:

- clinical pregnancy at between 6 and 8 weeks of gestation [progesterone group 81.9% (326/398) vs. placebo group 78.0% (334/428); RR 1.05, 95% CI 0.98 to 1.12; $p = 0.16$]
- ongoing pregnancy at 12 weeks of gestation [progesterone group 67.1% (267/398) vs. placebo group 64.7% (277/428); RR 1.04, 95% CI 0.94 to 1.14; $p = 0.47$]
- miscarriage [progesterone group 32.2% (128/398) vs. placebo group 33.4% (143/428); RR 0.96, 95% CI 0.79 to 1.17; $p = 0.70$]
- ectopic pregnancy [progesterone group 1.5% (6/398) vs. placebo group 1.6% (7/428); RR 0.92, 95% CI 0.31 to 2.72; $p = 0.88$]
- stillbirth [progesterone group 0.3% (1/398) vs. placebo group 0.5% (2/428); RR 0.54, 95% CI 0.05 to 5.92; $p = 0.61$]
- neonatal survival at 28 days of life [progesterone group 99.6% (260/261) vs. placebo group 100% (269/269); RR 1.00, 95% CI 0.99 to 1.00; $p = 0.32$]
- neonatal congenital anomalies [progesterone group 3.0% (8/266) vs. placebo group 4.0% (11/276); RR 0.75, 95% CI 0.31 to 1.85; $p = 0.54$].

In the health economic evaluation, the ICER associated with progesterone therapy was £18,053 per live birth beyond 24 weeks of gestation. However, this analysis should be interpreted with caution given the high level of uncertainty in the health benefits. Additional sensitivity analysis [extrapolating health gains in terms of quality-adjusted life-years (QALYs)] suggested the probability that progesterone would fall within the National Institute for Health and Care Excellence's threshold (£20,000–30,000 per QALY) as between 0.7145 and 0.7341.

Conclusions

The PROMISE trial is the largest clinical trial ever conducted on the subject of recurrent pregnancy loss. The trial was adequately sized and methodologically robust to conclude that vaginal progesterone therapy in the first trimester of pregnancy in women with RM is of no benefit and, therefore, should not be used in clinical settings. Future work could investigate the effectiveness of progesterone therapy during the luteal phase of the menstrual cycle, or for patients who have threatened miscarriage.

Trial registration

This trial is registered as ISRCTN92644181; EudraCT 2009-011208-42; and Research Ethics Committee 09/H1208/44.

Funding

This study was funded by the Health Technology Assessment programme of the National Institute for Health Research.

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Chapter 1 Introduction

This chapter outlines the physiological importance of progesterone in pregnancy, the individual and societal burdens of pregnancy loss, and the rationale to infer a role for progesterone in reducing the risk of miscarriage.

Existing knowledge

Progesterone in pregnancy

Progesterone is essential to achieve and maintain a healthy pregnancy. It is an endogenous hormone, secreted naturally by the corpus luteum (the remnants of the ovarian follicle that enclosed a developing ovum) during the second half of the menstrual cycle, and by the corpus luteum and placenta during early pregnancy. Progesterone prepares the tissue lining of the womb (endometrium) to allow implantation, and stimulates glands in the endometrium to secrete nutrients for the early embryo. During the first 8 weeks of pregnancy, progesterone is produced by the corpus luteum, but between 8 and 12 weeks the placenta takes over this role and maintains the pregnancy thereafter.

The importance of progesterone in pregnancy has prompted many clinicians to infer that progesterone deficiency may be aetiologically linked to recurrent miscarriage (RM), and that progesterone therapy in the first trimester of pregnancy may reduce the risk of miscarriage. In 2003 a Royal College of Obstetricians and Gynaecologists (RCOG) guideline[1] and a Cochrane review[2] called for a definitive trial to test whether or not progesterone therapy in the first trimester could reduce the risk of miscarriage in women with a history of unexplained RM.

Burden of disease

Miscarriage is the commonest complication of pregnancy: one in six clinically recognised pregnancies ends in a miscarriage.[3] RM, the loss of three or more pregnancies, is a distinct clinical entity. The prevalence of RM (1%) is significantly higher than that expected by chance alone (0.4%). Even after comprehensive investigations, a cause for RM is identified in fewer than 50% of cases.[3] The majority of couples are, therefore, labelled as having unexplained RM.

Recurrent miscarriages affect over 6000 couples in the UK every year, and frequently result in substantial adverse physical and psychological consequences for women as well as impacting their families. For example, miscarriage has the potential to cause physical harm, including severe haemorrhage, infection, perforation of the womb during surgery for miscarriage and, rarely, maternal death. The eighth triennial Confidential Enquiry into Maternal Deaths identified several women who had died from complications related to miscarriage.[4] Moreover, qualitative studies have shown the level of distress and the bereavement reaction associated with miscarriage to be equivalent to the impact of the stillbirth of a term baby.[3]

Costs to the NHS

It is estimated that RM costs the NHS £28M per year. This value includes the costs of diagnosis (blood tests and ultrasonography), management of miscarriages (expectant, medical or surgical), investigations for causes of miscarriages (e.g. antiphospholipid syndrome, parental karyotype and uterine cavity tests) and hospital inpatient costs. However, it does not include the management of the complications following treatment of miscarriages (such as uterine perforation, infection, bleeding or visceral damage) or any long-term health consequences of miscarriages or miscarriage management (including complications of intrauterine infections and adhesions). Thus, the true NHS perspective costs are likely to be higher than the estimated £28M per year. The societal costs, including days lost from work and out-of-pocket expenses for patients and partners, can be expected to be far greater.

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Progesterone in clinical use for recurrent miscarriages

The PROMISE study was conceived to address the possibility that progesterone therapy in the first trimester of pregnancy may reduce the risk of RM. In 2007 we conducted a clinician survey in the UK ($n = 114$; response rate 102/114; 89.5%), and found that 2% (2/102) of clinicians use progesterone routinely and 3% (3/102) use it selectively in pregnant women with a history of RM. Over 95% (97/102) reported that they do not use progesterone for this indication and the vast majority of these (92/102; 90.2%) were willing to recruit to a trial evaluating the role of progesterone treatment for the prevention of RM.

We also carried out separate systematic reviews to examine (a) the effectiveness of progesterone in RM[5] and (b) the safety of progesterone in pregnancy.

Effectiveness of progesterone in recurrent miscarriages

Two previously conducted systematic reviews[2,6] had examined the role of progesterone therapy in RM, but, since these reviews were published and at the time of designing the PROMISE trial, new evidence[7] had emerged. Therefore, we conducted a fresh systematic review with a meta-analysis.

We searched the Cochrane Controlled Trials Register, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, ISI Web of Science Proceedings, International Standard Randomised Controlled Trial Number Register, *meta*Register of Controlled Trials database, MEDLINE and EMBASE resources, from database inception to January 2008, for the following search terms: ('progesterone' OR 'progestagen' OR 'progestogen' OR 'progestin' OR 'progestational [hormone or agent] ' OR 'progest$'). We considered outcomes of miscarriage (as defined by the primary authors), live birth, gestation at delivery, pregnancy and neonatal outcomes.

Four randomised trials[7–10] were identified. There were 14 trials assessing the effects of progesterone in miscarriages including spontaneous (one-time) events[2] but these trials should not be confused with trials assessing the effects of progesterone in RM. The quality of the four trials was poor (modified Jadad quality scores between 0/5 and 2/5; *Table 1*), and participant numbers were small even when the trials were combined in meta-analysis, with only 132 women actively treated with progestogens.

Our review and a subsequent review conducted for Cochrane in 2013[11] found that all four trials showed a trend towards benefit of progesterone, but confidence intervals (CIs) were wide and differences were not statistically significant for all but one of the four trials. A meta-analysis showed a statistically significant reduction in miscarriages (odds ratio 0.39, 95% CI 0.21 to 0.72; *Figure 1*). There was no evidence of statistical heterogeneity in the results (heterogeneity p-value 0.98).

Although this evidence would be graded level 1a in the evidence hierarchy (because it is a systematic review of randomised trials), our survey of clinicians showed that it did not result in the use of progesterone for RM by clinical practitioners, owing to the weak methods and small sample sizes employed in the four published trials. One example of weak methodology was in lack of concealment, which has been shown to exaggerate effect sizes by up to 41%,[12] although there is some evidence that this exaggeration may not be a concern when the outcome is objective.[13] Small sample sizes increase the likelihood of random error (generating the wide CIs in *Figure 1*). Nonetheless, the existing evidence presented a powerful reason to proceed with a trial of progesterone in RM, especially in consideration of the size of the effect observed and the low cost, widespread availability and convenience of the intervention, in addition to its safety profile.

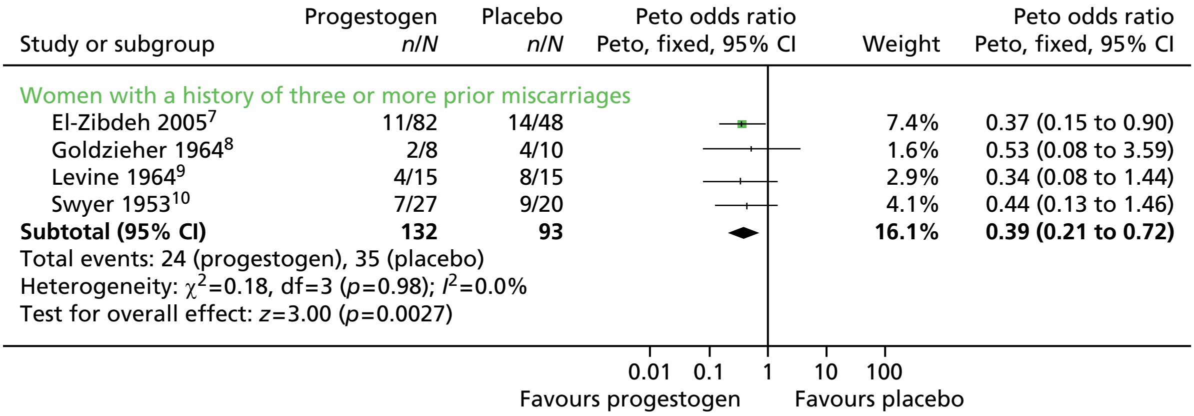
Safety of progesterone supplementation in pregnancy

At the time of designing this study there was substantial evidence from in vitro fertilisation (IVF) practice that progestogen supplementation is safe to the mother and the fetus (at the proposed dose for the trial of 400 mg twice daily).[14–16]

TABLE 1 Characteristics of the four pre-existing trials of progestogen use in RM

Features	El-Zibdeh 2005[7] (*n* = 130)	Goldzieher 1964[8] (*n* = 18)	Levine 1964[9] (*n* = 30)	Swyer and Daley 1953[10] (*n* = 47)
Population	Unexplained RM (three consecutive miscarriages, and conditions such as antiphospholipid syndrome excluded)	Analysis restricted to those with a history of three or more miscarriages	History of three consecutive miscarriages	Analysis restricted to those with a history of three or more miscarriages
Intervention	Dydrogesterone 10 mg twice daily (oral)	Medroxyprogesterone 10 mg daily (oral)	Hydroxyprogesterone caproate 500 mg per week (intramuscular)	Progesterone pellets 6 × 25 mg inserted into gluteal muscle
Comparison	No treatment	Placebo	Placebo	No treatment
Duration of treatment	From diagnosis of pregnancy to 12 weeks	Unclear	Until miscarriage or 36 weeks	Unclear
Randomisation method	'Randomised'; method not given	'Sequentially numbered bottles'	Alternation	Alternation
Allocation concealment	Unclear	Unclear	Unclear	Inadequate
Blinding	No	Double	Double	No
ITT analysis	Yes	Unreported	No	Unreported
Follow-up rates	100%	100%	54% (26/56 excluded)	100%
Jadad score	0/5	2/5	0/5	1/5

ITT, intention to treat.



Study or subgroup	Progestogen *n*/*N*	Placebo *n*/*N*	Weight	Peto odds ratio Peto, fixed, 95% CI
Women with a history of three or more prior miscarriages				
El-Zibdeh 2005[7]	11/82	14/48	7.4%	0.37 (0.15 to 0.90)
Goldzieher 1964[8]	2/8	4/10	1.6%	0.53 (0.08 to 3.59)
Levine 1964[9]	4/15	8/15	2.9%	0.34 (0.08 to 1.44)
Swyer 1953[10]	7/27	9/20	4.1%	0.44 (0.13 to 1.46)
Subtotal (95% CI)	**132**	**93**	**16.1%**	**0.39 (0.21 to 0.72)**

Total events: 24 (progestogen), 35 (placebo)

Heterogeneity: χ^2=0.18, df=3 (p=0.98); I^2=0.0%

Test for overall effect: z=3.00 (p=0.0027)

FIGURE 1 Meta-analysis of the four pre-existing trials of progestogen use in RM (outcome: miscarriage). df, degrees of freedom.

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To further explore the question of safety, we conducted a review using the following search terms in MEDLINE (1966–2007) and EMBASE (1988–2007): ('progesterone' OR 'progestational agents' OR 'progest$') AND ('adverse effects' OR 'complications' OR 'side effects' OR 'harm') AND 'pregnancy'. A systematic review of observational studies (both cohort and case–control studies) of first-trimester sex hormone exposure identified 14 studies, comprising 65,567 women.[17] The sex hormone in several of these studies was progestogens alone or with other steroids.

Most of the evidence in our review did not show harm, particularly any external genital malformation in the offspring, but one case–control study suggested an association between hypospadias and progestogen use.[18] Although findings from a case–control study represented weaker evidence than the better-quality evidence from larger cohort studies which did not substantiate this association, we decided to document all of the effects of progesterone in the PROMISE trial. More specifically, we decided to collect information about any neonatal genital abnormalities.

Meta-analyses of progesterone use in RM, in miscarriage[2] and in the prevention of preterm birth[19] did not identify any evidence of short-term safety concerns in women. However, it was not clear if these trials sought to document maternal side effects prospectively. In one study, intramuscular 17-OHP (hydroxyprogesterone) caused maternal adverse events (AEs) in 50% of women, largely due to injection site reactions.[20] This concern did not apply to the PROMISE trial, in which the route of administration was vaginal. Side effects were not reported in studies of vaginal progesterone in the context of prevention of preterm births.[21,22]

Rationale

A trial of progesterone therapy in the treatment of unexplained RM was required for the following reasons:

- The existing trials, although small and of poor quality, suggested a large benefit in a condition with substantial morbidity and costs.
- A guideline by the RCOG and a Cochrane review called for a definitive trial to evaluate this research question.[12]
- Participants in two unpublished surveys [one of women with RM ($n = 88$) and the other of gynaecologists ($n = 102$) treating women with RM] demonstrated an interest in progesterone therapy and a willingness to participate in a potential trial (Arri Coomarasamy, University of Birmingham, 2008, unpublished data).
- If proven to be effective, the intervention would represent a low-cost, safe and easily deliverable therapy.

Specific objectives

Primary objective

- To test the hypothesis that, in women with unexplained RM, progesterone (400-mg vaginal capsules, twice daily), started as soon as possible after a positive urinary pregnancy test (and no later than 6 weeks of gestation) and continued to 12 weeks of gestation, compared with placebo, would increase live births beyond 24 completed weeks of pregnancy by at least 10%.

Secondary objectives

- To test the hypothesis that progesterone would improve various pregnancy and neonatal outcomes (such as reduced miscarriage rates and improvements in survival at 28 days of neonatal life).
- To test the hypothesis that progesterone, compared with placebo, would not incur serious adverse events (SAEs) in either the mother or the neonate (such as genital abnormalities in the neonate).
- To explore differential or subgroup effects of progesterone in various prognostic subgroups, including subgroups of:
    - maternal age ($\leq$ 35 years or $>$ 35 years)
    - number of previous miscarriages (3 or $\geq$ 4)
    - presence or absence of polycystic ovaries.
- To perform an economic evaluation for cost-effectiveness.

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Chapter 2 Methods

This chapter reports the methods used to conduct the PROMISE trial. It describes the study design and protocol to progress potential participants from enrolment to completion of treatment, data analysis plans, quality assurance and governance.

Design

The PROMISE trial was conducted as a randomised, double-blind, placebo-controlled, international multicentre study, with health economic evaluation. Participants were randomised to receive progesterone or placebo in a 1 : 1 ratio.

Participants

The participants in the PROMISE trial were recruited in hospital settings located across the UK (36 sites) and in the Netherlands (nine sites). These sites (*Figure 2*) included RM clinics and early pregnancy units in secondary or tertiary care hospitals.

All sites in the UK and the Netherlands with local investigators of appropriate capability and experience in conducting clinical trials were eligible to take part. Primary care settings were not utilised as either research sites or patient identification centres.

Participant eligibility for the trial was assessed according to the criteria listed below.

Inclusion criteria

In order to be eligible for the study, it was necessary for participants to meet all of the following criteria:

- having a diagnosis of unexplained RM (three or more consecutive or non-consecutive first-trimester losses)
- being aged 18–39 years at randomisation (the likelihood of miscarriages due to random chromosomal aberrations is higher in older women[3,25] and such miscarriages are unlikely to be prevented by progesterone therapy)
- trying to conceive naturally
- willing and able to give informed consent.

Exclusion criteria

Participants could not be included in the study if any of the following criteria were applicable:

- they were unable to conceive naturally (as confirmed by urinary pregnancy tests) within 1 year of recruitment or before the end of the randomisation period in the trial, whichever came earlier
- they had antiphospholipid syndrome [lupus anticoagulant and/or anticardiolipin antibodies (immunoglobulin G or immunoglobulin M)]; other recognised thrombophilic conditions (testing according to usual clinic practice)
- they had uterine cavity abnormalities (as assessed by ultrasound, hysterosonography, hysterosalpingogram or hysteroscopy)
- they had abnormal parental karyotype
- they had other identifiable causes of RM (tests initiated only if clinically indicated) such as diabetes, thyroid disease or systemic lupus erythematosus
- they were on current heparin therapy
- they had any contraindications to progesterone use (see the following section).

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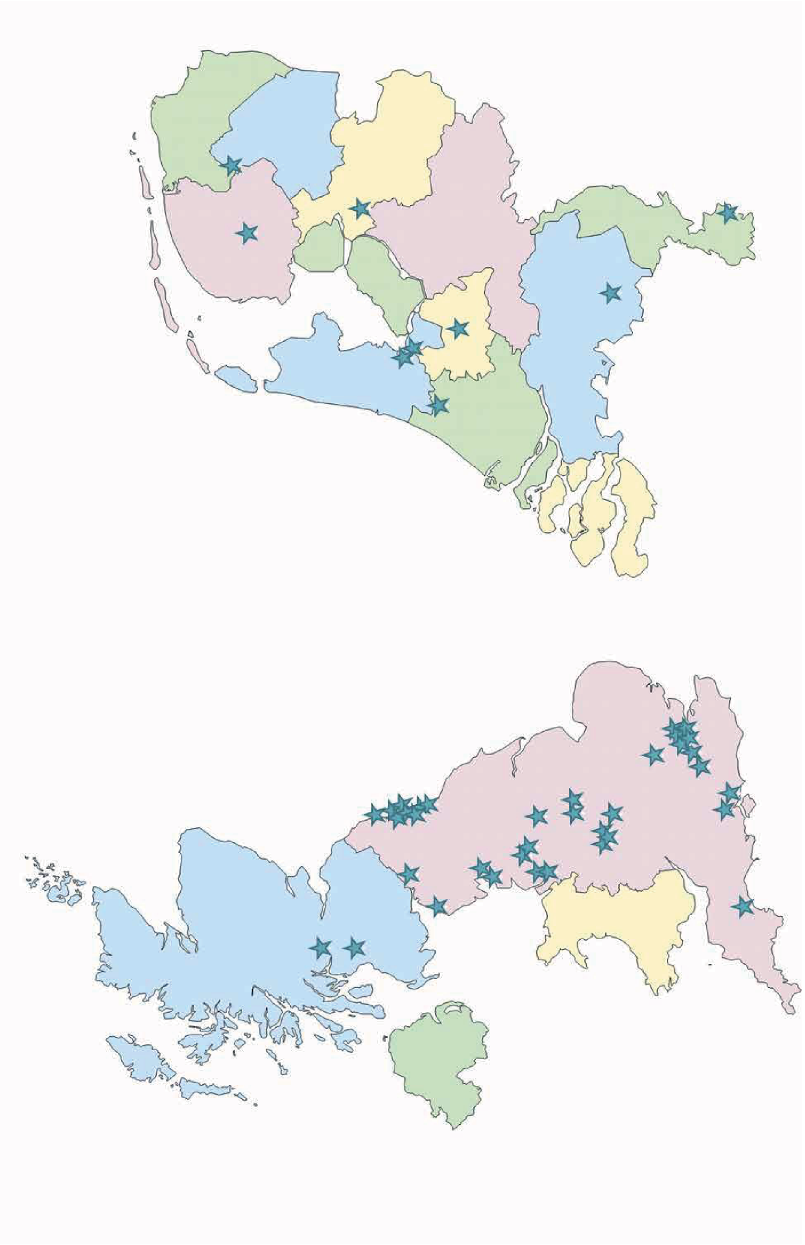

FIGURE 2 PROMISE trial sites in the UK[23] and the Netherlands.[24]

Contraindications to progesterone use

Women to whom any of the following applied were not eligible to take part in the trial:

- they had a history of liver tumours
- they had severe liver impairment
- they had genital tract or breast cancer
- they had severe arterial disease
- they had undiagnosed vaginal bleeding
- they had acute porphyria
- they had a history during pregnancy of:
    - idiopathic jaundice
    - severe pruritus
    - pemphigoid gestationis
- they were taking any of the following drugs, because these products interact with progesterone:
    - bromocriptine
    - cyclosporine
    - rifamycin
    - ketoconazole.

Recruitment

Potential participants were identified from dedicated RM clinics, or other hospital clinics in which the caseload included a substantial number of women with RM. Potential participants were identified and approached by clinic doctors, research nurses and midwives, after having received appropriate training relating to the trial. This training included the development of sensitivity in answering questions about the risks of pregnancy loss, and the importance of attention to early signs of possible miscarriage such as spotting or discharge.

The participant eligibility pathway to recruitment and randomisation is illustrated by *Figure 3*. Eligible women were given verbal and written explanations about the trial. They were informed clearly that participation in the trial was entirely voluntary, with the option of withdrawing at any stage, and that participation or non-participation would not affect their usual care. They were provided with a participant information sheet (PIS) (see *Appendix 1*). Eligible women were then given the opportunity to decide if they wished to participate, or if they needed more time to consider their decision, or if they did not wish to participate. In all three scenarios, the decision of the woman was respected. If a woman needed more time to consider her potential involvement, she was asked to call the research nurse or midwife when she had decided. If an undecided woman had not called within 14 days, the research nurse or midwife contacted her. If an initially undecided woman decided to participate later, the research nurse or midwife arranged a mutually convenient opportunity for the woman to be consented.

A written consent form (see *Appendix 2*) was provided to each woman who agreed to participate in the trial. The investigator and the participant both signed the consent form. The original copy was kept in the investigator site file, one copy was given to the participant and one copy was retained in the woman's hospital records. Baseline demographic and medical data were collected, anonymised and stored in an electronic integrated trial management system (ITMS). Any identifying information was collected and stored in a password-protected local database on a secure computer with restricted access.

The first PROMISE participant was enrolled in June 2010 and randomised in October 2010. The last PROMISE participant was recruited and randomised in October 2013 (see *Chapter 3, Recruitment*).

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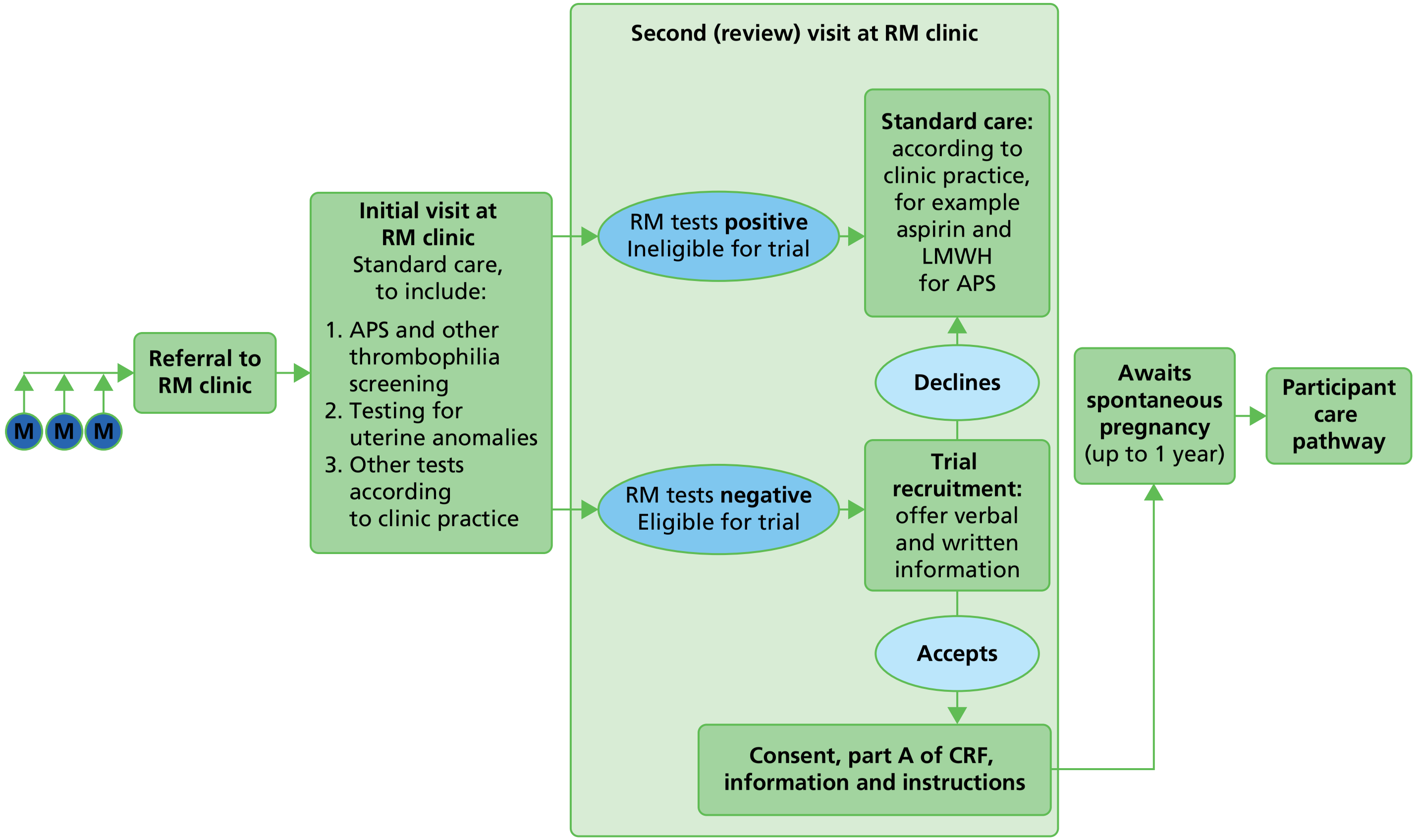
M
M
M
Referral to RM clinic
Initial visit at RM clinic
Standard care, to include:
1. APS and other thrombophilia screening
2. Testing for uterine anomalies
3. Other tests according to clinic practice
Second (review) visit at RM clinic
RM tests positive
Ineligible for trial
Standard care: according to clinic practice, for example aspirin and LMWH for APS
Declines
RM tests negative
Eligible for trial
Trial recruitment: offer verbal and written information
Accepts
Consent, part A of CRF, information and instructions
Awaits spontaneous pregnancy (up to 1 year)
Participant care pathway

FIGURE 3 Eligibility pathway to recruitment and randomisation. APS, antiphospholipid syndrome; CRF, case report form; LMWH, low-molecular-weight heparin; M, miscarriage.

Non-English speakers

We made provision for translation, if necessary, to communicate with non-English speakers and accommodate any special communications requirements of potential study participants. The PISs and consent forms (see *Appendices 1* and *2*) were translated from English into Dutch for use in the Netherlands.

Randomisation

Each woman consenting in advance of pregnancy was given instructions to notify the local research nurse or midwife by telephone as soon as she experienced a positive urinary pregnancy test. We expected most pre-consenting participants to notify us early in pregnancy, at approximately 4 weeks of gestation (4 weeks from their last menstrual period).

On receiving notification of pregnancy and confirming the woman's willingness to participate in the trial (in either order of occurrence), the local research nurse or midwife reverified other aspects of eligibility according to inclusion and exclusion criteria, and obtained details of gestational age. Participants were randomised online to receive the trial intervention (either progesterone or placebo), via a purpose-designed ITMS. Each authorised member of the research team was provided with a unique username and password to the ITMS for this purpose. Online randomisation was available 24 hours per day, 7 days per week, apart from during short periods of scheduled maintenance.

Sequence generation

Computer-generated random numbers were used, and participants were randomised online via a secure internet facility. This third-party independent ITMS was designed, developed and delivered by MedSciNet® (Stockholm, Sweden) according to standards of the International Organisation for Standardisation 9001:2000 and the requirements of the US Food and Drug Administration CFR21:11.[26]

Participants were randomised to receive progesterone or placebo in a 1 : 1 ratio. A 'minimisation' procedure using a computer-based algorithm was used to avoid chance imbalances in important stratification variables. The stratification variables used for minimisation were as follows:

- number of previous miscarriages (3 or > 3)
- maternal age (≤ 35 or > 35 years)
- polycystic ovaries or not
- body mass index (BMI) (≤ 30.0 or > 30.0 kg/m^2).

Allocation and minimisation

After all of the eligibility criteria and baseline data items were entered online, the ITMS generated a code number which took into account the minimisation variables recorded for the individual, and which was linked to a specific trial intervention pack. The code number was advised via e-mail to the local principal investigator (PI), the relevant trial pharmacist (see *Distribution* and *Investigational medicinal product supply, Storage, dispensing and return*) and the research nurse or midwife performing the randomisation.

Blinding

Participants, investigators, research nurses, midwives and other attending clinicians remained unaware of the trial drug allocation throughout the duration of the trial.

In the case of any SAE, the general recommendation was to initiate management and care of the participant as though the woman was taking progesterone. If the drug allocation was specifically requested to assist the medical management of a participant, clinicians could contact the trial manager or the trial co-ordinator for this purpose, 24 hours per day, 7 days per week (see *Safety monitoring, Adverse events*). Cases that were considered serious, unexpected and possibly, probably or definitely related to the trial intervention (see *Appendix 3*) were unblinded as appropriate. In any other circumstances, investigators

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and research nurses and midwives remained blind to drug allocation while the participant remained in the trial.

Distribution

On randomisation, the research nurse or midwife arranged the dispatch of a trial intervention pack to the local participating centre or the home address of the participant within 72 hours of receiving the telephone call informing of pregnancy. Nurses in the UK contacted the trial pharmacy at St Mary's Hospital in London and nurses in the Netherlands contacted the trial pharmacy in Utrecht (see *Investigational medicinal product supply*, *Storage, dispensing and return*). Each trial intervention pack contained either progesterone or placebo.

Instructions to participants

The research nurse or midwife also provided the participant with instructions. In cases of delivery directly to the home address, the research nurse or midwife contacted the participant to ensure receipt and understanding of how to use the supplied capsules.

Each participant was expected to commence the trial intervention on the day it was received, and continue until it was finished, at around 12 completed weeks of gestation, unless the pregnancy ended before this time. The research nurse or midwife also telephoned each woman in the days immediately after the trial medicine was supplied, to ensure that the participant had started taking the medicine. In the event of the capsules being mislaid, the participant was instructed to telephone the research nurse or midwife, who would liaise with trial manager or the trial co-ordinator to arrange a further supply of the same type of intervention.

Each participant was asked for consent to notify the primary care provider (in the UK, the general practitioner) by letter that she was participating in the trial (see *Appendix 4*). Moreover, each participant was given a business card and a fridge magnet with contact details of local PROMISE investigators and the central Trial Co-ordinating Centre (TCC), to inform any directing clinicians, in case of potential drug interactions.

Interventions

Each participant in the PROMISE trial received either micronised progesterone or placebo capsules, to be administered vaginally. Both products were supplied by Besins Healthcare (Mountrouge, France), a global pharmaceutical company with a manufacturer's licence for tablets and capsules, in compliance with good manufacturing practice standards[27] and good clinical practice (GCP) requirements.[28,29]

Progesterone capsules

The investigational medicinal product (IMP) was micronised progesterone at a dose of 400 mg (that is, two capsules of Utrogestan® 200 mg) taken vaginally twice daily (every morning and every evening) for the duration of treatment.

The anatomical therapeutic chemical classification code for the pharmacotherapeutic group of the IMP was G03D and the chemical abstract service number was 57-83-0. The product had all the properties of endogenous progesterone, with induction of a full secretory endometrium and in particular gestagenic, antiestrogenic, slightly antiandrogenic and antialdosterone effects.

Besins Healthcare held the manufacturing authorisation (France) for Utrogestan®, including for the indication of threatened miscarriage or prevention of habitual miscarriage due to luteal phase deficiency up until the 12th week of pregnancy.

Placebo capsules

Placebo capsules were vaginal capsules, composed of sunflower oil, soybean lecithin, gelatin, glycerol, titanium dioxide and purified water, encapsulated in the same form as the IMP, and identical in colour, shape and weight, for use in the control arm of the PROMISE trial. The dose, route and timing of administration were also identical to those in the active progesterone arm of the study.

Dose

The ideal dose of progesterone for the potential prevention of RM was unknown. The biologically effective dosage of micronised progesterone capsules ranged from 200 mg once daily to 400 mg twice daily according to the summary of product characteristics (SmPC)[30] and the *British National Formulary* (BNF).[31] Our choice of 400 mg twice daily was made after a careful review of the existing literature and an extensive survey of clinicians in the UK (see *Chapter 1, Existing knowledge, Progesterone in clinical use for recurrent miscarriages*). We also reviewed other related evidence. For example, progesterone vaginal capsules are commonly used for luteal support in assisted conception at a treatment dose of 400 mg twice daily, with no specific safety concerns raised on this dose.[16,32]

After evaluating the evidence, we considered the dosage of 400-mg vaginal progesterone twice daily to be an acceptable regimen to ensure a clinically effective dose, and to minimise the risk of a negative trial result from therapy with a suboptimal dose.

Route

An immunomodulatory effect of progesterone at the trophoblastic–decidual interface is the key presumed mechanism for preventing RM.[3,33–35] Our choice to use the vaginal route of administration was, therefore, rational to deliver a greater proportion of drug to the relevant site (the uterus) using the 'first uterine pass' effect.[36,37] Furthermore, studies that have used vaginal progesterone in the prevention of preterm birth have reported its effectiveness when given via this route.[19,21,22] For example, 14 out of 36 studies of second- and/or 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.[38]

The acceptability and availability of interventional drugs were also important considerations supporting the vaginal route of drug delivery. Our discussions with consumer representatives confirmed that a vaginal formulation would be more acceptable to women than an intramuscular preparation. These findings were further supported by a study in which 12% of participants were unable to tolerate the intramuscular progesterone preparation and declined participation or withdrew from that trial.[20] Of those who did continue, 34% complained of localised soreness around the injection site. Finally, in our survey of women with RM conducted at St Mary's Hospital and Guy's and St Thomas' Hospitals in London, a very high acceptability of the vaginal route (81/88; 92%) was identified (Arri Coomarasamy, University of Birmingham, 2008, unpublished data).

The capsule formulation of the PROMISE trial is widely available in the UK and worldwide.

Timing

Treatment commenced as soon as possible after a positive pregnancy test and no later than 6 weeks of pregnancy, and continued until the gestational age of 12 weeks. Our rationale to discontinue the treatment at 12 weeks was that production of progesterone by the corpus luteum becomes less important than the placental production of progesterone after 12 weeks of gestation. Furthermore, in the only clinical trial of progesterone treatment for RM to have shown a statistically significant reduction in miscarriage rates, progesterone was given until 12 weeks of gestation (odds ratio 0.37, 95% CI 0.15 to 0.90).[7]

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Compliance assessment

Our previous experience of research and clinical care for women with RM demonstrated that they would be highly motivated and compliant with therapy advice. However, compliance in the PROMISE trial was evaluated by 'pill-counting'.

Participants were asked to return completed, partially used and unused treatment packs to the trial centres. The research nurses and midwives at each study centre documented the capsules returned by each participant, while the trial pharmacists kept their own accountability logs.

In an effort to improve compliance, women who failed to return the blister packs from the previous 4 weeks, whether or not these were empty, using the envelope provided were contacted by the local research nurse or midwife by telephone or e-mail to be offered advice and support.

Non-compliance was defined as missing more than 20% of trial medicines for the gestational age at randomisation. Non-compliant participants were interviewed (face to face or via telephone) in an attempt to establish the reason(s) for their non-compliance.

Investigational medicinal product supply

Manufacture, packaging and labelling

All arrangements for trial drug supply, labelling, storage and preparation were undertaken as per the requirements of the Medicines for Human Use (Clinical Trials) Regulations 2004.[39,40]

Active (Utrogestan® vaginal 200 mg) and placebo capsules were manufactured and packaged (assembled) by Besins Healthcare, in compliance with good manufacturing practice (EU Directive 2003/94/EC)[27] and GCP (Clinical Trials Directive 2001/20/EC)[28] requirements. Besins Healthcare also provided qualified person release of the trial drug under the requirements of the Medicines for Human Use (Clinical Trials) Regulations 2004.[39,40]

Each trial intervention pack contained the entire supply required for the treatment period of up to 8 weeks. As the treatment regimen was two Utrogestan® 200 mg or placebo capsules twice daily, the drug package for each participant contained 224 capsules: 2 (capsules) × 2 (twice daily) × 7 (7 days per week) × 8 (8 weeks) = 224.

The drug packages were labelled in compliance with the UK Medicines for Human Use (Clinical Trials) Regulations 2004,[39,40] ensuring the protection of each participant, traceability and proper identification of the IMP and trial.

Storage, dispensing and return

At study initiation, supplies of progesterone and placebo capsules were delivered by Besins Healthcare to two study pharmacies, where the products were stored and whence they were dispensed to all participants.

The pharmacies were located at St Mary's Hospital in London and the University Medical Centre of Utrecht. Both sites complied with the relevant guidelines and regulations, including (in the UK) the Duthie report[41] and the Royal Pharmaceutical Society of Great Britain's practice guidance on pharmacy services for clinical trials[42] as well as the appropriate standard operating procedures of Imperial College London.[43]

At the pharmacies, the PROMISE trial medications were stored separately from other stock, in areas with restricted access. Drugs expired or returned by participants were stored separately from unallocated trial medicines. Dispensing was undertaken against prescription forms, each entitled 'The PROMISE trial, EudraCT Number 2009-011208-42' and labelled with the name, date of birth and study identification number of the relevant participant and a unique code number provided by the ITMS for randomisation (see *Randomisation*, *Allocation and minimisation*). Each trial pharmacy kept detailed dispensing records including participant study numbers and names, code numbers, batch numbers, expiry dates, doses and dates of dispensing.

The trial co-ordinator monitored the quantity of supplies held by each dispensing pharmacy in comparison with the number and rate of randomisations undertaken, and liaised with Besins Healthcare to ensure adequate supplies of the IMP in the UK and the Netherlands.

Each participant in the PROMISE trial was provided with freepost envelopes to return the unused or used packets to the local study centre. All unused study drugs, including undispensed supplies and supplies returned by participants, were returned to the trial pharmacies for accountability and destruction. Both dispensing pharmacies were involved in the reconciliation of medicines returned by trial participants and the disposal of unused medication, in compliance with appropriate regulatory guidance.

Outcomes

Primary outcome

Live birth beyond 24 completed weeks of gestation.

Secondary outcomes

- Clinical pregnancy at 6–8 weeks (defined as the presence of a gestational sac, with or without a yolk sac or fetal pole).
- Ongoing pregnancy at 12 weeks (range 11–13 weeks) (defined as the presence of a fetal heartbeat).
- Miscarriage (defined as loss of pregnancy before 24 weeks of gestation).
- Gestation at delivery.
- Survival at 28 days of neonatal life.
- Congenital anomalies, and specifically genital abnormalities.

Exploratory outcomes

- Antenatal complications such as pre-eclampsia, small for gestational age (< 10th birthweight centile), preterm prelabour rupture of membranes and antepartum haemorrhage.
- For live births at beyond 24 completed weeks of gestation: mode of delivery, birthweight, arterial and venous cord pH, APGAR (appearance, pulse, grimace, activity, respiration) score and resuscitation.
- For neonates: surfactant use, ventilation support (days on intermittent positive pressure ventilation, continuous positive airway pressure and oxygen, and discharge on oxygen) and neonatal complications (such as infection, respiratory distress syndrome, necrotising enterocolitis, intraventricular haemorrhages and pneumothorax).

Resource use outcomes

The resource use data listed below were collected to estimate the costs associated with the provision of progesterone for RM:

- antenatal, outpatient or emergency visits
- inpatient admissions (nights in hospital)
- maternal admissions to high-dependency units (HDUs) or intensive care units (ICUs) (nights)
- neonatal admissions to special care baby units (SCBUs) or neonatal units (NNUs) (nights).

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Future outcomes

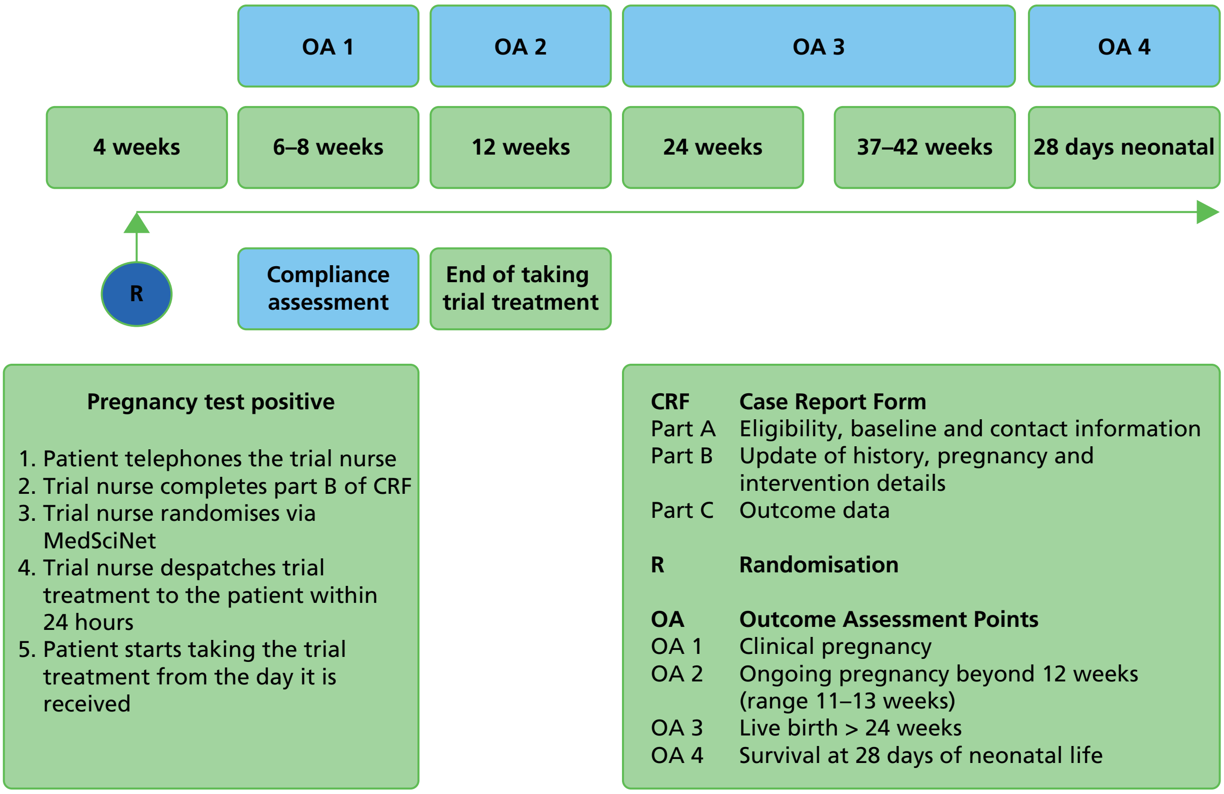
Women were asked to consent for future evaluation of themselves and their child and the health records of both. Although long-term follow-up was outside the scope of the PROMISE trial, we recognised the value of data collected in this study to inform further studies on outcomes such as the composite end point of death or neurodevelopmental impairment at 2 years of age, cognitive scale scores at 2 years of chronological age, and disability classified into domains according to professional consensus. The hospital number and (in the UK) NHS number of each baby within the PROMISE trial were recorded to facilitate future follow-up studies.

Outcome assessment

The ITMS was utilised to capture baseline and outcome data, for contemporaneous data cleaning, to produce reports for the independent Data Monitoring Committee (DMC) and to maintain an audit trail. Relevant trial data were transcribed directly into the ITMS. Source data comprised the research clinic notes, hospital notes, hand-held pregnancy notes, laboratory results and self-reports.

First outcome assessment (6–8 weeks of pregnancy)

The research nurse or midwife at each study site telephoned every participant at between 6 and 7 weeks of gestation, to ensure there were arrangements for an ultrasound appointment with her usual carers, before 8 weeks of gestation (*Figure 4*). If an appointment had not been booked, the research nurse or midwife assisted with booking. The research nurse or midwife telephoned each participant again between 3 and 5 days after the scheduled date of the ultrasound appointment, to obtain details of the observations of a gestational sac.



Pregnancy test positive

1. Patient telephones the trial nurse
2. Trial nurse completes part B of CRF
3. Trial nurse randomises via MedSciNet
4. Trial nurse despatches trial treatment to the patient within 24 hours
5. Patient starts taking the trial treatment from the day it is received

CRF	**Case Report Form**
Part A	Eligibility, baseline and contact information
Part B	Update of history, pregnancy and intervention details
Part C	Outcome data
R	**Randomisation**
OA	**Outcome Assessment Points**
OA 1	Clinical pregnancy
OA 2	Ongoing pregnancy beyond 12 weeks (range 11–13 weeks)
OA 3	Live birth > 24 weeks
OA 4	Survival at 28 days of neonatal life

FIGURE 4 Participant care pathway and outcome assessment.

Second outcome assessment (12 weeks of pregnancy)

The research nurse or midwife at each study site telephoned each participant between 10 and 12 weeks of gestation, to ensure there were arrangements for an ultrasound appointment with her usual carers, at between 12 and 14 weeks of gestation (see *Figure 4*). As previously, the research nurse or midwife assisted with booking an appointment if necessary, and telephoned the participant afterwards to obtain details of variables such as fetal heartbeat. The research nurse or midwife also recorded the expected date of delivery at this stage.

Third outcome assessment

The third outcome assessment was conducted at or after birth (see *Figure 4*). The research nurse or midwife at each study site telephoned every participant 2 weeks after the expected date of delivery to obtain pregnancy outcome data such as the mode of delivery, gestation, weight and APGAR score at birth. The ITMS generated automated prompts to alert the research nurse or midwife at the time of expected date of delivery. The research nurse or midwife also checked birth registers and inpatient records to track hospital admissions and pregnancy outcomes.

Fourth outcome assessment

The fourth and final outcome assessment was conducted to gather neonatal outcomes at 28 days after birth (see *Figure 4*). The research nurse or midwife at each study site telephoned every participant to obtain postnatal and neonatal outcome data including any nights of hospital admission or requirements for ventilation support, and complications such as early infection. The ITMS generated automated prompts to alert the research nurse or midwife at the appropriate time. Using the full repertoire of evidence-based methods to maximise data collection,[44] the research nurse or midwife also checked birth registers and inpatient records to track hospital admissions and pregnancy outcomes.

Continuity

From previous experience of research and clinical care for women with RM, we expected high rates of compliance with therapy advice. Moreover, the time interval between randomisation and final outcome assessment in the PROMISE trial was short (e.g. if delivery occurred at 40 weeks of gestation, the interval was 40 weeks), so we expected loss to follow-up to be minimal. Participants in the study continued to be managed by their clinical teams throughout their pregnancies, according to local protocols.

Withdrawal

Following discussion with the Trial Management Group (TMG), participants in the PROMISE trial could be withdrawn from trial treatment if it became medically necessary in the opinion of the investigator(s) or clinician(s) providing patient care. In the event of such premature treatment cessation, study nurses and midwives made every effort to obtain and record information about the reasons for discontinuation, and to follow up all safety and efficacy outcomes as appropriate.

Participants in the PROMISE trial could voluntarily decide to cease taking the study treatment at any time. If a participant did not return for a scheduled visit, attempts were made to contact her and (where possible) to review compliance and AEs. We documented the reason(s) for self-withdrawal where possible. Each woman remained able to change her mind about withdrawal, and reconsent to participate in the trial, at any time. Clear distinction was made between withdrawals from trial treatments while allowing further follow-up, and any participants who refused any follow-up. If a woman withdrew from taking the trial treatment but permitted further data collection, she was followed up and outcome assessments were undertaken for the remainder of the study.

If a participant explicitly withdrew consent to any further data recording, this decision was respected and recorded via the ITMS. All communications surrounding the withdrawal were noted in the study records and no further data were collected for such participants.

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Concomitant non-trial treatments

Concomitant therapy was provided at the discretion of the care-providing clinicians, and all concomitant treatment and medications were documented via the ITMS. Post-randomisation use of heparin was discouraged unless there was a clear and recognised indication for it (heparin therapy at the time of randomisation made a woman ineligible to participate in the trial). Other than identified contraindicated drugs (see *Participants*, *Exclusion criteria*) and other progestogen preparations, the initiation of treatment for another indication did not necessitate withdrawal from the PROMISE study.

Safety monitoring

A review conducted in 2007, before the PROMISE trial commenced, showed no clear or consistent evidence of SAEs on the mother or the baby as a result of progesterone treatment during pregnancy (see *Chapter 1*, *Existing knowledge*, *Progesterone in clinical use for recurrent miscarriages*). Moreover, there is substantial evidence from other studies to indicate that progestogen supplementation at the dose administered in the PROMISE trial is safe to the mother and the fetus.[14–16]

The SmPC for progesterone (vaginal capsules)[30] states that 'preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology and toxicity' (© Datapharm).

Known side effects

The SmPC for progesterone (vaginal capsules)[30] also states that 'local intolerance (burning, pruritus or fatty discharge) has been observed during the different clinical trials and reported in the literature but incidences were extremely low' (© Datapharm).

Overdose

The symptoms of progesterone overdose may include somnolence, dizziness and euphoria. In case of overdose, the care-providing clinicians of the PROMISE trial were prepared to undertake observation and reporting, and provide symptomatic and supportive measures, as required.

Dose modification for toxicity

The PROMISE trial included provision that, for participants experiencing non-serious side effects, the dosage could be reduced to 200 mg twice daily (one capsule in the morning and one at bedtime) at the discretion of the care-providing clinician, without unblinding treatment allocation (see the following section). The dose modification was noted on the case report form, along with the gestational age and the date on which such change was implemented.

Adverse events

The pharmacovigilance procedures of the PROMISE trial, including documentation, validation, evaluation and reporting, and responsibilities for the performance of these requirements, were based on the contemporaneously available literature to guide good practice.[28,45–47]

Assessment

All of the trial participants were asked to report any hospitalisations, consultations with other medical practitioners, disability, incapacity or any other AEs to their local research team; if the local study nurse or midwife was unavailable for any reason, they were able to report the events to the trial manager or trial co-ordinator via telephone at any time. Moreover, at the time of each outcome assessment, investigators, research nurses and midwives at each study centre proactively asked each participant about any AEs in the preceding weeks. AEs were assessed by clinical investigators and further reported as appropriate, and in any case recorded in the ITMS for scheduled interim analyses to standard formats[47] by the independent DMC. If a local clinical investigator was unavailable, initial AE reports without causality and expectedness assessment were submitted to the TCC by a health-care professional within 24 hours, and followed up by medical assessment as soon as possible thereafter, ideally within the following 24 hours.

Regardless of treatment allocation, the expectedness, seriousness and causality of AEs were assessed according to standardised definitions (see *Appendix 3*) as though the participant had received the active drug (progesterone).

Reporting

Adverse events were reported by local clinical investigators to the TCC, and thence to the sponsor (Imperial College London/Imperial College Healthcare NHS Trust Joint Research Compliance Office). The sponsor (or the chief investigator on behalf of the sponsor) reported to the Medicines and Healthcare products Regulatory Agency (MHRA). The sponsor (or the trial co-ordinator on behalf of the sponsor) also reported to the Research Ethics Committee (REC), and equivalent bodies in the Netherlands, as appropriate. If information was incomplete at the time of initial reporting, or if the event was ongoing, local investigators forwarded follow-up information as soon as possible. If there was a difference between the expectedness, seriousness and causality assessments of the local investigator, the TCC and the sponsor, then the worst-case assessment was used for reporting.

Serious adverse events and serious adverse reactions were recorded on a purpose-designed SAE form and notified by local investigators to the TCC within 24 hours of the local investigators becoming aware of these events. Local investigators were responsible for additionally reporting SAEs to their host institutions, according to local regulations, and instituting supplementary investigations as appropriate based on clinical judgement of the causative factors. Any SAE or serious adverse reaction that was outstanding at the end of the trial treatment period was followed up at least until the final outcome was determined, even if this provision necessitated follow-up beyond 28 days postpartum. The TCC reported all SAEs to the independent DMC approximately 6-monthly. The DMC viewed data blinded to treatment, but was able to review unblinded data if necessary.

Suspected unexpected serious adverse reactions (SUSARs) were unblinded, as appropriate, reviewed by the trial manager within 24 hours of reporting, and further reported to the MHRA and the REC, or the equivalent bodies in the Netherlands, by the TCC as soon as possible, and in any event within 15 days (or 7 days in the case of fatal or life-threatening SUSARs).

Unblinding

Unblinding was undertaken only in the event of a medical emergency requiring knowledge of the drug received. In the event that an investigator or the care-providing clinician required disclosure of the treatment allocation, the ITMS allowed the trial manager or the trial pharmacy to break the randomisation code. For this purpose, the TCC could be contacted between 09.00 and 16.00 every weekday; otherwise, the trial manager or designee could be contacted directly via a 24-hour trial mobile phone. The investigator or care-providing clinician communicating the alert was asked to provide the date of the requirement, the name of person requesting unblinding, the reason for unblinding and any other relevant information.

Sample size

The PROMISE trial investigators believed that it was important to ensure that the study was large enough to detect reliably moderate but clinically important treatment effects. Our calculations indicated that, to detect a minimally important difference (MID) of 10% in rates of live birth after at least 24 weeks (from 60% to 70%, odds ratio 1.56), for an alpha error rate of 5% and beta error rate of 20% (i.e. 80% power), it would be necessary to randomise 376 participants to the intervention arm and 376 participants to the control arm (752 participants in total). However, assuming and adjusting for a worst-case scenario of a loss to follow-up rate of 5%, the total number of participants required would be 790 (395 each in the progesterone and placebo arms). The sample size of the study was planned accordingly.

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The MID of 10% was defined following consultations among health-care practitioners, patients and representatives of patient bodies. However, we noted that this difference was much smaller than that expected from the contemporaneously existing literature (see *Chapter 1, Existing knowledge, Progesterone in clinical use for recurrent miscarriages*), which showed that the odds of miscarriage could be more than halved with progesterone therapy (odds ratio 0.39, 95% CI 0.21 to 0.72). Hence, assuming a conservative actual absolute difference of 15% in rates of live birth beyond 24 weeks, 790 participants (after accounting for 5% attrition) provided a power of 99%.

The 60% baseline (control) event rate was derived from a comprehensive audit carried out at the largest RM unit in the UK (St Mary's Hospital in London) covering the period between 1998 and 2005, that showed the chances of live birth to be 61.8% (698/1129) after three miscarriages, 60.3% (350/580) after four miscarriages, 47.6% (109/229) after five miscarriages and 42.3% (82/194) after at least six miscarriages. However, because we had identified previously published evidence[48] to suggest a higher control event rate, we performed a sensitivity analysis on the power calculations in which we assumed a higher control event rate of 70%. For a 10% absolute difference in rates of live birth after at least 24 weeks, and for an alpha error rate of 5%, 790 participants (after accounting for 5% attrition) gave a power of 89% (higher than 80% power when the control event rate was estimated to be 60%). We prudently adopted a lower control event rate for power calculation, to make provision for a worst-case scenario. All the power calculations noted above used two-sided binominal testing.

Statistical methods

Our data analysis plan was drawn up by the trial statistician and the study team, and approved by the Trial Steering Committee (TSC) and independent DMC prior to any analysis. The analysis was undertaken, using Stata® software, version 12 or later (StataCorp LP, College Station, TX, USA), based on treatment code and following the intention-to-treat principle. Only after the analysis was completed were the actual treatment arms corresponding to the treatment codes revealed. The components of analysis comprised (a) summarising baseline data, (b) intergroup comparisons, (c) subgroup analysis, and (d) adjustments and sensitivity analyses, such as to recognise the implications of missing data. The authors of this report had full access to all data collected in the study.

Summarising trial data

We planned to summarise the recruitment numbers, those lost to follow-up, protocol violations and other relevant data, using a Consolidated Standards Of Reporting Trials (CONSORT) diagram. Baseline data and outcome data were separately summarised. For categorical data, we planned to provide proportions (or percentages). For continuous variables, we planned to examine the distribution of the observations and, if normally distributed, we planned to summarise them as means with standard deviations (SDs). If they were not normally distributed, we planned to report medians and interquartile ranges (IQRs); additionally, we planned to use geometric means and SDs for data where distributions appeared to be log-normal.

We planned to use diagnostic plots to assess the severity of deviations from normality, using log-transformations where necessary, assessing results as estimates with 95% CIs, and using bootstrapping with bias correction and acceleration where non-parametric methods were indicated.

Following previously published CONSORT recommendations,[49–51] significance tests were not given between randomised treatment arms.

Intergroup comparisons

The primary analysis was undertaken on the basis of intention to treat. This approach was intended to avoid any potentially misleading artefacts of the study (such as non-random attrition). Every attempt was made to collect a complete data set about each pregnancy and women were encouraged to allow continued data collection even if withdrawing from trial treatment, because the exclusion of withdrawn participants from data analysis could bias results and reduce the power of the study to detect important differences. In particular, participants were followed up even after any protocol treatment deviation or violation. However, if a participant explicitly withdrew consent to any further data recording then all communications surrounding the withdrawal were noted and no further data were collected for such participants (see *Outcomes*, *Withdrawal*).

Participants were analysed according to the original randomised allocation, irrespective of compliance and crossovers. Binary regression with a log-link was used to assess relative risks (RRs) for the primary outcomes and for other binary outcomes such as clinical pregnancy at 6–8 weeks; ongoing pregnancy at 12 weeks (range 11–13 weeks), miscarriage rate and survival at 28 days of neonatal life, adjusting for minimisation variables.

Significance tests were, in general, carried out only for estimates of treatment effects, as separate tests for changes over time in the two groups might have resulted in entirely false and misleading conclusions about the differences between the groups when comparing *p*-values.

Notwithstanding our best efforts to collect a complete data set about each pregnancy, in a small number of cases it was not possible to determine the primary outcome of the study (see *Chapter 3*, *Numbers analysed*). We conducted an analysis whereby participants with missing primary outcome data were not included in the primary analysis. This presented a risk of bias, and secondary sensitivity analyses were undertaken to assess the possible impact of the risk, considering alternative assumptions both in favour and against the effect of the intervention. Other sensitivity analyses involved simulating missing responses using multiple imputation, using those baseline variables that are significantly related to the outcome as predictors.

Subgroup analysis

Three subgroup analyses were planned:

- number of previous miscarriages (3 or ≥ 4)
- maternal age (≤ 35 or > 35 years)
- polycystic ovaries or not.

Subgroup analyses were conducted only for the primary end point, and multivariate logistic regression was used. In each case, a test for interaction was first used to determine whether or not treatment was particularly effective in individual subgroups; our performance of subgroup analyses was dependent on sufficient data. Because of the well-known risk of false positives, both main effects and tests for interaction were performed and assessed before we considered results for subgroups. In addition, post-hoc subgroup analysis was performed only for the purpose of hypothesis generation.

Adjustments and sensitivity analyses

The process of randomisation with minimisation is designed to result in comparison groups that are highly similar at baseline, even more so than would be expected by chance. However, if randomisation failed to achieve balanced groups, we planned linear or logistic regression to adjust for the imbalance. We planned to adjust for missing data using multiple imputation. In cases of difference, we planned to give greater weighting to the primary analysis of intergroup comparisons than to sensitivity analyses.

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Interim analyses

Interim analyses of principal safety and effectiveness end points were conducted on behalf of the independent DMC. These were considered together with scheduled reports of SAEs. The trial statistician was unblinded to the level of groups 'A' and 'B'. The meaning of 'A' and 'B' was made known to the DMC separately. The first interim analysis was undertaken after the primary outcome data became available for the first 100 participants, and thereafter at annual intervals.

We were prepared to consider early termination of the PROMISE trial in case of interim analyses showing overwhelming evidence of effectiveness or significant harm (see *Termination*). Effectiveness and futility criteria were defined by the DMC (see *Governance*, *Trial oversight bodies*) with regard to the Peto principle that a trial should be stopped only when there is overwhelming evidence against one treatment or another[52,53] with a nominal interim alpha set at 0.001 using O'Brien and Fleming alpha spending rules.[54] Under these conditions, no adjustment to the overall level of significance was needed.[55,56]

Long-term analyses

Although the development of the babies born to participants in the PROMISE trial was of interest to the investigators, this was outside the scope and time frame of the study. Nevertheless, we recognised the value of data collected in this study to inform further studies on outcomes such as the composite end point of death or neurodevelopmental impairment at 2 years of age, cognitive scale scores at 2 years of chronological age, and disability classified into domains according to professional consensus. Women were asked to consent to future evaluation of themselves and their child and the health records of both, and could be traced through NHS Strategic Tracing Services. The hospital number and NHS number of each baby in the PROMISE trial were also recorded to facilitate future follow-up studies.

Health economic methods (see also Chapter 4)

An economic evaluation was conducted alongside the PROMISE trial, pragmatically comparing the costs and consequences of treatment using progesterone versus those of usual care. To examine the effect of treatment of each woman (and baby) on health resource use, data were collected from enrolment until the trial end point (hospital discharge). The analysis considered the number of days that treatment was received and three categories of heath service resources [antenatal contacts, how the pregnancy ended (preterm pregnancy loss management or mode of delivery) and postnatal admissions]. This perspective assumed the most salient costs to be those accrued by perinatal services; the assumption was tested by model-based extrapolation and a sensitivity analysis.

The primary outcome of our economic analysis was incremental cost per additional live birth after at least 24 weeks of gestation, with data collected up to 28 days of neonatal life. In order to provide additional information about the wider resource implications to the NHS and longer-term implications to health status, a systematic search identified models employed previously in similar trial-based economic evaluations to extend the time horizon of the cost and generic health gains of the two arms of the PROMISE trial end point. Furthermore, strategies were identified to attribute variation relating to the surrogate outcome of intervention (gestational age) to estimate health-care costs and associated generic health gains in the longer term.

Data access and quality assurance

Data management

The trial was designed and conducted to meet the requirements of:

- the Data Protection Act 1998[57]
- the NHS Code of Confidentiality[58]
- the Caldicott Principles.[59]

Information about participants in the PROMISE trial was collected directly from trial participants and hospital notes, and was considered confidential. The trial manager was responsible for overseeing data custody, but all of the staff involved in the study (clinical, academic and support personnel) shared the same duty of care to prevent any unauthorised disclosure of personal information. For this purpose, each trial participant was allocated a unique study number at recruitment, and all study documents used this reference as the identifier. Personal data and contact details were held in separate NHS or university password-protected databases at local sites (in compliance with local and national confidentiality and data protection standards), which were linked to the secure ITMS via the unique study number. All data were analysed and reported in summary format (individuals remaining unidentifiable).

Data were collected and stored on secure NHS or university computers. Access to data was restricted by usernames and passwords at two levels (to gain access to NHS and university computers and then to access the ITMS). Only when strictly necessary and after anonymisation were trial data encrypted and transmitted outside the NHS or university settings (e.g. to the DMC). No study data were retained in handheld media, laptops, personal computers or other similar media.

The online ITMS was maintained according to the security policies of the Women's Health Unit of King's College London. These policies included provision for password assignment, encryption, immediate back-up, off-site back-up and disaster recovery processes. Electronic data were backed up to both local and remote media in encrypted format every 24 hours. Paper-based data (such as signed consent forms) were kept in locked filing cabinets at each site.

The data generated during the trial were available for inspection on request by the participating physicians, representatives of the sponsor, the REC, host institutions and the regulatory authorities. These data-handling arrangements were clearly conveyed to participants in the PIS (see *Appendix 1*), and permission was obtained in the consent form (see *Appendix 2*).

On completion of data collection, the site files from each study centre were to be securely archived at the sites. Electronic study data remained securely stored within the ITMS. The trial master file was to be securely stored by the sponsor when all study activities were completed. In accordance with the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (sections 18 and 28),[40] all the study data will remain securely stored for 25 years, to enable review, reappraisal and resolution of any queries or concerns and to facilitate further follow-up research. After this time the data will be securely destroyed.

Data quality assurance

The PROMISE trial co-ordinator performed hospital site visits as part of trial monitoring activities (see *Governance*, *Trial monitoring*). This quality assurance activity occasionally involved source data verification. The research and development (R&D) departments of participating study centres also performed routine monitoring audits at least annually. The PROMISE trial was additionally selected for MHRA inspection at two locations (Liverpool Women's Hospital and Luton and Dunstable Hospital).

The trial also adopted a centralised approach to monitoring data quality and compliance, using the ITMS.

Governance

At all times during the study, the PROMISE trial was conducted strictly in accordance with the most recent version of the authorised PROMISE trial protocol. The PROMISE trial protocol was developed in accordance with the ethical principles originating in the Declaration of Helsinki,[60] the principles of GCP, the Medicines for Human Use Regulations 2004 and its subsequent amendments[39,40] and the Department of Health's 2005 Research Governance Framework for Health and Social Care.[61]

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Ethical implications

In designing the PROMISE trial and considering the ethical implications of the study, the issues indicated below were considered and resolved or safeguarded.

Administration of a drug without full knowledge of its effects (although the existing evidence suggested a large potential benefit)

Existing evidence suggested a potential benefit in reducing the risk of miscarriage but the clinical community was in equipoise (see *Chapter 1, Existing knowledge, Progesterone for clinical use for recurrent miscarriages*). There was overwhelming support for the study from clinicians, patients and representatives of patient bodies (see *Chapter 1, Rationale*).

Furthermore, we identified substantial evidence of the safety of progesterone in pregnancy (see *Chapter 1, Existing knowledge, Progesterone for clinical use for recurrent miscarriages*), from widespread use in pregnancy for other indications such as IVF practice[16] and prevention of preterm birth.[19]

Moreover, we put in place robust mechanisms to address potential AEs (see *Safety monitoring, Adverse events*), in an effort to minimise harm. Overall, the balance of potential benefit versus harm was felt to be ethically acceptable to proceed with the trial.

Potential for distress, discomfort and inconvenience to trial participants

During our interviews and consultations with patients and representatives of patient societies at the time of designing the trial, it emerged that any distress or discomfort to the participants would be limited, and of an acceptable level to most women. We also designed the study to reduce any potential inconvenience to the participants, and put in place accommodating provisions wherever possible.

Face-to-face interviews at the time of recruitment could prolong a hospital visit by approximately 30 minutes, but patients and patient society representatives felt that this delay was well within an acceptable time frame. Furthermore, although five or more telephone interviews could be viewed as intrusive, precautions were incorporated into the study protocol to minimise inconvenience to participants.

These precautions included:

- enquiring at the beginning of the telephone call if it was a convenient time to conduct the interview and, if not, arranging to call at an alternative time
- specifying the purpose and the expected duration of the call
- not leaving any messages if the telephone was answered by an automated machine or anyone other than the index patient
- not telephoning a participant at her place of work if this could be avoided.

Interestingly, most patients and patient society representatives welcomed the telephone calls because the research nurse or midwife was likely to be able to assist standard care (e.g. by helping to arrange ultrasound scans).

Ethical governance

Following a favourable opinion of the National Research Ethics Service via the West Midlands REC and before recruitment commenced at each participating centre, the TCC obtained favourable site-specific assessments and R&D approvals as required.

The PI of each participating study site was responsible for liaison with administrative and managerial representatives of the local institution, and obtaining any necessary permissions from trust authorities. On behalf of the local institution, the PI was also required to sign an Investigator's Agreement in respect of accrual, compliance, GCP, confidentiality and publication. Deviations from the Investigator's Agreement were monitored and remedial action taken as appropriate by the TMG.

In addition, and in compliance with the International Conference on the Harmonisation of Good Clinical Practice, all institutions participating in the trial completed a delegation log and supplied this document to the TCC. The delegation log listed the responsibilities of each member of the local study team, and an up-to-date copy was stored in the site file at the institution and also at the TCC. A curriculum vitae of the PI, and confirmation of GCP training and honorary or substantive employment with the participating trust, was also verified by the trial manager and retained.

Clinical trial authorisation

Clinical trial authorisation for the PROMISE trial was obtained from the MHRA before recruitment started.

Changes to the protocol

It was agreed that if any amendments to the study protocol required regulatory approval (from the MHRA, REC or local R&D offices), these changes would not be instituted until the amendment had been reviewed and received favourable opinion from the relevant bodies. However, a protocol amendment intended to eliminate an apparent immediate hazard to participants would be implemented immediately, with notification and request for approval to the MHRA, REC and R&D offices as soon as possible.

There were no significant changes to the methods after trial commencement. All amendments to the study protocol were in the domain of clarifications to wording and intentions (see *Appendix 5*, *Table 16*).

Trial monitoring

The PROMISE trial was monitored according to the standard operating procedures of Imperial College London/Imperial College Healthcare NHS Trust Joint Research Compliance Office.[43]

The purpose of monitoring was to:

- protect the rights and well-being of trial participants
- ensure that the reported trial data were accurate, complete and verifiable from source documents
- ensure that the trial remained compliant with GCP and other regulatory and good practice guidance.

Participating centres were monitored by the TCC by checking incoming electronic forms for compliance with the protocol, consistency of data and missing data. The trial co-ordinator and trial manager remained in regular telephone or e-mail contact with centre personnel to check on progress and resolve any queries. In addition, periodic site monitoring was undertaken as required by the TCC or the sponsor to:

- review understanding of the protocol and trial procedures by the trial staff
- verify that the trial staff had access to the necessary documents
- verify the existence of participants against clinic records and other sources
- verify selected data items and SAEs recorded, compared with data in clinical records, to identify errors of omission as well as inaccuracies.

Monitoring visits were followed by a monitoring report, summarising the findings of the visit and recommending remedial actions as necessary. Investigator meetings were held at least annually for the purpose of learning, updating and sharing.

Trial oversight bodies

The PROMISE trial was overseen by the TMG, the DMC and the TSC (*Figure 5*).

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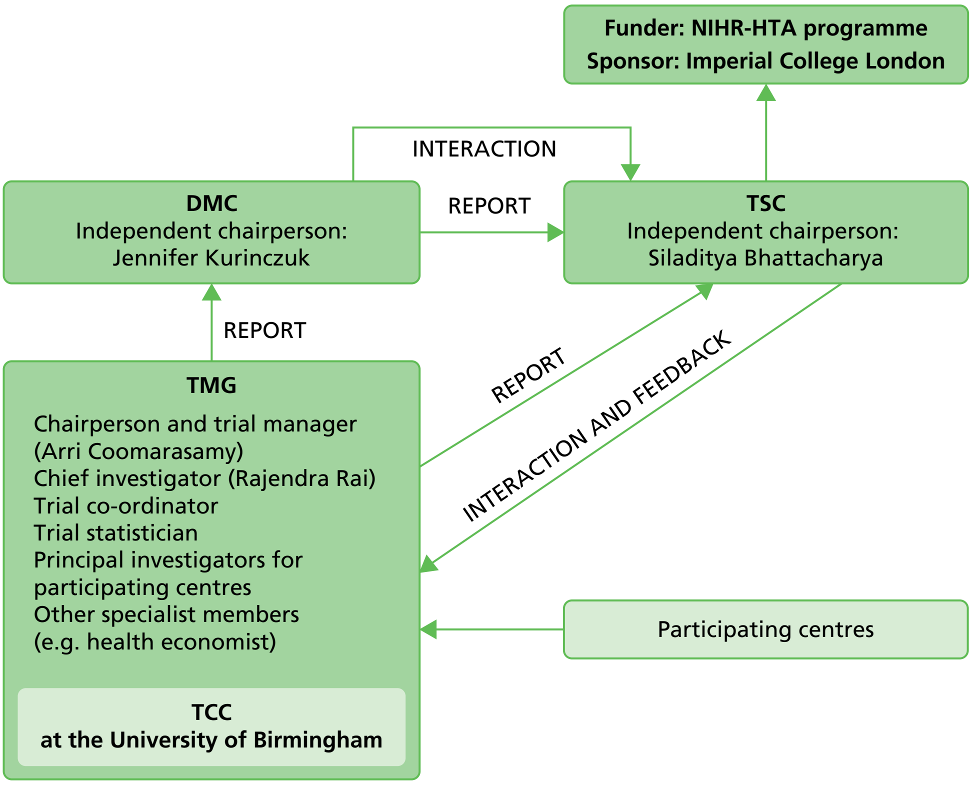
Funder: NIHR-HTA programme
Sponsor: Imperial College London
INTERACTION
REPORT
DMC
Independent chairperson:
Jennifer Kurinczuk
TSC
Independent chairperson:
Siladitya Bhattacharya
REPORT
TMG
Chairperson and trial manager (Arri Coomarasamy)
Chief investigator (Rajendra Rai)
Trial co-ordinator
Trial statistician
Principal investigators for participating centres
Other specialist members (e.g. health economist)
TCC
at the University of Birmingham
REPORT
INTERACTION AND FEEDBACK
Participating centres

FIGURE 5 Reporting relationships of trial oversight bodies. HTA, Health Technology Assessment; NIHR, National Institute for Health Research.

Trial Management Group

The TMG directed the management of the trial from the TCC, which was located in a secure office in the University of Birmingham. The TCC comprised the trial manager, trial co-ordinator and a research nurse, with support from the trial statistician, data manager, health economist and trial advisors. The day-to-day co-ordination of the trial was the responsibility of the trial manager (Professor Arri Coomarasamy) and the trial co-ordinator (Dr Ewa Truchanowicz), who maintained regular contact with local collaborators, research nurses and midwives at participating study sites. The trial manager and the trial co-ordinator reported to the TMG, and the TMG reported to the TSC (or directly to the DMC if necessary) any issues relating to the monitoring and auditing of the research (see *Figure 5*).

The TMG conducted meetings face to face or via teleconference, and action points were implemented via the TCC. The meetings were held on a weekly basis during the early stages of the trial, and regularly as required thereafter, but at least monthly. The TMG disseminated any relevant feedback to investigators and other stakeholders through various approaches, including investigator meetings.

Trial Steering Committee

The TSC provided overall supervision of the trial, affording protection for participants by ensuring that it was conducted in accordance with International Conference on the Harmonisation of Good Clinical Practice guidelines and other relevant regulations. The TSC agreed and authorised the trial protocol and subsequent (minor) amendments (see *Appendix 5*, *Table 16*), and provided advice to investigators on all aspects of the trial. The role of the TSC also included reviewing recruitment, protocol deviations and recommendations from the DMC.

The TSC was chaired by an independent representative (Professor Siladitya Bhattacharya) and conducted meetings face to face or via teleconference on a 6-monthly basis, or more often if required.

Independent Data Monitoring Committee (see also *Safety monitoring*, *Adverse events*, and *Statistical methods*, *Interim analyses*)

The primary role of the PROMISE DMC consisted of periodic reviews of accruing data and assessments of safety, to make recommendations to the TSC about whether the trial should continue, or be modified or terminated. The DMC also reviewed interim analyses of major end points in addition to emerging data from other trials using progesterone in RM patients, to ensure that the continuation of the trial remained ethical.

The DMC additionally examined rates of recruitment, loss to follow-up, compliance and protocol violation data to ensure that the continuation of the trial was not futile.

The membership of the PROMISE DMC (chaired by Professor Jennifer Kurinczuk, and including Professor Javier Zamora and Professor Nick Raine-Fenning) was independent (none of the members had any financial or intellectual conflict of interest). The initiation meeting of the DMC, to review the study protocol and operating procedures, was conducted face to face and subsequent meetings were held either face to face or via teleconference.

Each DMC meeting comprised four consecutive components:

1. For DMC members only, to review rates of recruitment, baseline characteristics, effectiveness, safety, missing data and protocol violations; these data were prepared by the trial statistician, blinded to treatment allocation (identified only as ‘A’ and ‘B’).
2. For DMC members and the chairperson of the TSC, chief investigator, trial manager, sponsor or funder, as appropriate, to access relevant information.
3. For DMC members only, to review the issues arising from the open component above.
4. Discussions of the DMC with the chairperson of the TSC, the chief investigator and/or the trial manager, to convey the results and recommendations of the meeting.

The minutes from each open meeting were made available to all investigators and relevant stakeholders. The minutes from each closed meeting were archived by the DMC chairperson and the trial statistician.

Site responsibilities

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

Local principal investigators

Each participating study centre nominated a local PI to oversee the conduct of PROMISE research at the particular institution. Each PI signed an Investigator’s Agreement to acknowledge these responsibilities, including:

- adherence to the protocol of the trial
- helping local colleagues to ensure that study participants received appropriate care throughout the period of research enrolment
- protecting the integrity and confidentiality of clinical and other records generated by the research
- reporting any failures in these respects, adverse drug reactions and other events or suspected misconduct through the appropriate systems.

Local nursing co-ordinators

Each participating centre also designated a local nurse or midwife to ensure that all eligible patients were considered for the study, provided with a PIS and offered an opportunity to discuss the study if required. This person also took responsibility for the collection of baseline and outcome data and the co-ordination of follow-up evaluations.

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Patient and public involvement

Patient and public involvement (PPI) in research is not only a moral imperative (in consideration of the rights of service users and taxpayers to be involved in activities commissioned for them by government) but also a practical opportunity to ensure relevance, feasibility and accuracy.[62,63] Recognition of the importance of PPI at all stages of the research process and across the clinical spectrum is increasing[64] but the emotive implications of pregnancy and miscarriage particularly heighten the importance of PPI in ensuring a sensitive study design. Therefore, the PROMISE trial team sought and drew extensively on the contributions of lay stakeholders to conceive and develop the project.

The nature of PPI may be described as consultation, collaboration or user-controlled research,[65] and the participants may be existing or potential patients or recipients of health services, informal or unpaid carers, family members, disabled people, members of the public, groups asking for research because they believe they have been exposed to potential harm or denied potential benefit from health services, and/or organisations to represent any of these people.[65] The PROMISE trial team undertook PPI primarily as consultation, with RM service users and organisations representing a wider public.

Information

From the RM clinics at St Mary's Hospital and Guy's and St Thomas' Hospitals in London, 88 women with a history of RM were surveyed with a set of structured and semi-structured questions to identify their opinions regarding the rationale for the trial and its ethical implications (see *Governance*, *Ethical implications*), the route of progesterone administration (vaginal, rectal or intramuscular), the duration of therapy, the suitability of courier transport to deliver study medications directly to study participants, and the relative importance of different outcomes assessed in the PROMISE trial. The interviews were conducted on a one-to-one basis by physicians with experience in early pregnancy care and training in listening to patient concerns. The information collected enabled the PROMISE trial team to understand that self-administration of vaginal progesterone twice daily would be acceptable to most potential participants in the study, and to select meaningful and important outcomes for data collection.

Communication

Five champions from among the participants in our survey volunteered to help the central organisers of the study to develop clear and concise literature for participants (see *Appendices 1* and *2*). During the development, the provisional documents were reviewed by other patients with a history of RM, as well as the independent service user representatives listed below:

- Ms Ruth Bender Atik (National Director of the Miscarriage Association)
- Ms Liz Campbell (Director of the Wellbeing of Women research charity)
- Officers of the RCOG consumers' forum.

These members of the group were selected to represent professional and charitable communities with an interest in pregnancy and miscarriage. They brought experience of working with not only women who had previously suffered RM, but also stakeholders such as women trying to conceive, women in pregnancy and women who had previously suffered miscarriage, and their family members, from across the UK.

All of the lay stakeholders expressed appreciation for their involvement in PROMISE activities and enthusiasm for ongoing involvement in the PROMISE trial, whether as a result of inherent personal interest in the topic under investigation or the value they placed on empowerment to influence service improvements. They expressed opinions about their previous experiences of clinical consultations and identified strategies to improve existing services. Their views were valued by researchers and directly informed the development of literature for participants (see *Appendices 1* and *2*).

Oversight

Ms Ruth Bender Atik, the National Director of the Miscarriage Association, was also involved in overseeing the PROMISE trial as a member of the TSC throughout the duration of the study (see *Governance*, *Trial oversight bodies*). Although Ms Bender Atik was enthusiastic and dedicated, it is important to note that her voluntary contribution to the PROMISE trial took her time and attention away from competing commitments; in retrospect, it would have been helpful to ensure that such a time requirement was recognised financially.

Dissemination

During the years of recruitment and follow-up, various research team members facilitated peer group sessions and seminars, and delivered presentations about study activities and developmental concepts of the intervention. The composition of these groups varied, for example from closed meetings of senior clinical practitioners at each of the participating study centres to a large public audience for an inaugural lecture that was also shown online. The contents of the presentations were tailored accordingly.

Monthly newsletters were circulated to boost the morale of the trial staff at study sites, highlight important tasks and encourage recruitment. When recruitment was complete, the newsletters were no longer disseminated, but targeted, site-specific communications were used instead.

Timelines and targets

The duration of the PROMISE trial was anticipated as 3 years, commencing in February 2010. Audits of RM clinics at the seven study sites originally anticipated to participate in the PROMISE trial showed that over 2200 new RM patients per year were seen in these centres, and that over half of these women would be found to be eligible for the trial (i.e. they had a diagnosis of unexplained RM). Based on our previous experience, we expected up to 75% of eligible women to agree to participate, but we adopted a conservative target recruitment rate of only 50% of eligible patients. Recruitment targets were carefully scrutinised by local PIs and their teams to ensure the anticipated numbers were feasible within the anticipated timeline of the trial. However, owing to a delay in procuring placebo capsules, the trial commenced later than expected, incurring a ‘no-cost’ time-only extension by approximately 1 year.

Termination

The interventional phase of the trial ended when the last recruited participant had taken her last dose of the trial intervention. The observational phase of the trial ceased when the 28-day follow-up was completed for the baby of the last participant recruited.

However, we were prepared to consider early termination of the PROMISE trial in case of:

- interim analysis (see *Statistical methods*, *Interim analyses*) showing overwhelming evidence of effectiveness or significant harm with a nominal interim alpha likely to be set at 0.001 using O’Brien and Fleming alpha spending rules[54] and with regard to the Peto principle that a trial should be stopped only when there is overwhelming evidence against one treatment or another[52,53]
- major safety concerns
- insurmountable issues with IMP supply
- a change in the opinion of the REC
- a regulatory decision or sponsor withdrawal.

We were prepared to terminate recruitment at a particular study site for reasons of low recruitment or compliance issues. The sponsor also reserved the right, only after taking advice from the TSC and the independent DMC, to discontinue the PROMISE trial at any time for safety, overwhelming evidence of effectiveness or significant harm or any other reasonable reasons.

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Chapter 3 Results

This chapter commences with a CONSORT diagram that describes the flow of participants through each stage of the trial (see *Figure 6*). This is followed by demographic information, primary and secondary outcomes, ancillary analyses and AEs.

Participant flow

Participant flow is illustrated by *Figure 6*. A total of 1568 participants were screened for eligibility and consented to take part in the PROMISE trial. Of these, 732 participants were excluded from randomisation, the most common reasons being that they did not conceive naturally within 1 year (515 women) or that they subsequently decided to withdraw from the study before conceiving a pregnancy (202 women). Of those participants who conceived naturally within 1 year and remained willing to participate in the trial, the gestational age of 10 pregnancies could not be confirmed to ensure eligibility, and a further four women were not eligible for other reasons when reassessed. These women were excluded. The remaining participants were randomised to receive either progesterone (404 women) or placebo (432 women).

Recruitment

Recruitment and randomisation took place over 41 months (*Figure 7*). A total of 836 participants were randomised, exceeding the planned target of 790 participants, from 45 active centres (36 in the UK and nine in the Netherlands). Four centres contributed more than 100 enrolled participants each (*Table 2*). Rates of conversion from enrolment to randomisation varied between 0% and 100%.

Baseline data

The randomised participants in the PROMISE trial were aged between 18 and 39 years at the time of randomisation, with a median age of 32.7 years (IQR 29.1–36.1 years). The mean BMI at the time of randomisation was 25.4 kg/m^2 (SD 5.1 kg/m^2). Of the 823 (98.4%) randomised participants who provided ethnic group data, 682 (82.9%) were white, 35 (4.3%) were black, 68 (8.3%) were Asian and 38 (4.6%) were from other ethnic groups. Most of the participants were non-smokers (702/836; 84.0%).

Of the 836 randomised participants, 375 (44.9%) had experienced more than three previous miscarriages and 55 (6.6%) had previously experienced ectopic pregnancy. The median number of preceding miscarriages was 3.0. Women with previous live births constituted 346 (41.4%) of the 836 participants randomised. Cases of comorbidities included 58 (6.9%) participants with polycystic ovarian syndrome, 29 (3.5%) with a fibroid uterus, 19 (2.3%) with endometriosis and 49 (5.9%) with an arcuate uterus. Furthermore, 29 (3.5%) participants had previously undergone large loop excision of the cervical transformation zone, five (0.6%) had previously undergone myomectomy, seven (0.8%) had previously undergone endometriosis surgery, 32 (3.8%) had previously undergone tubal surgery and 14 (1.7%) had previously undergone ovarian cystectomy. Study records of concurrent medications showed that six (0.7%) of the randomised participants were taking metformin at the time of participation, and 75 (9.0%) were taking low-dose aspirin.

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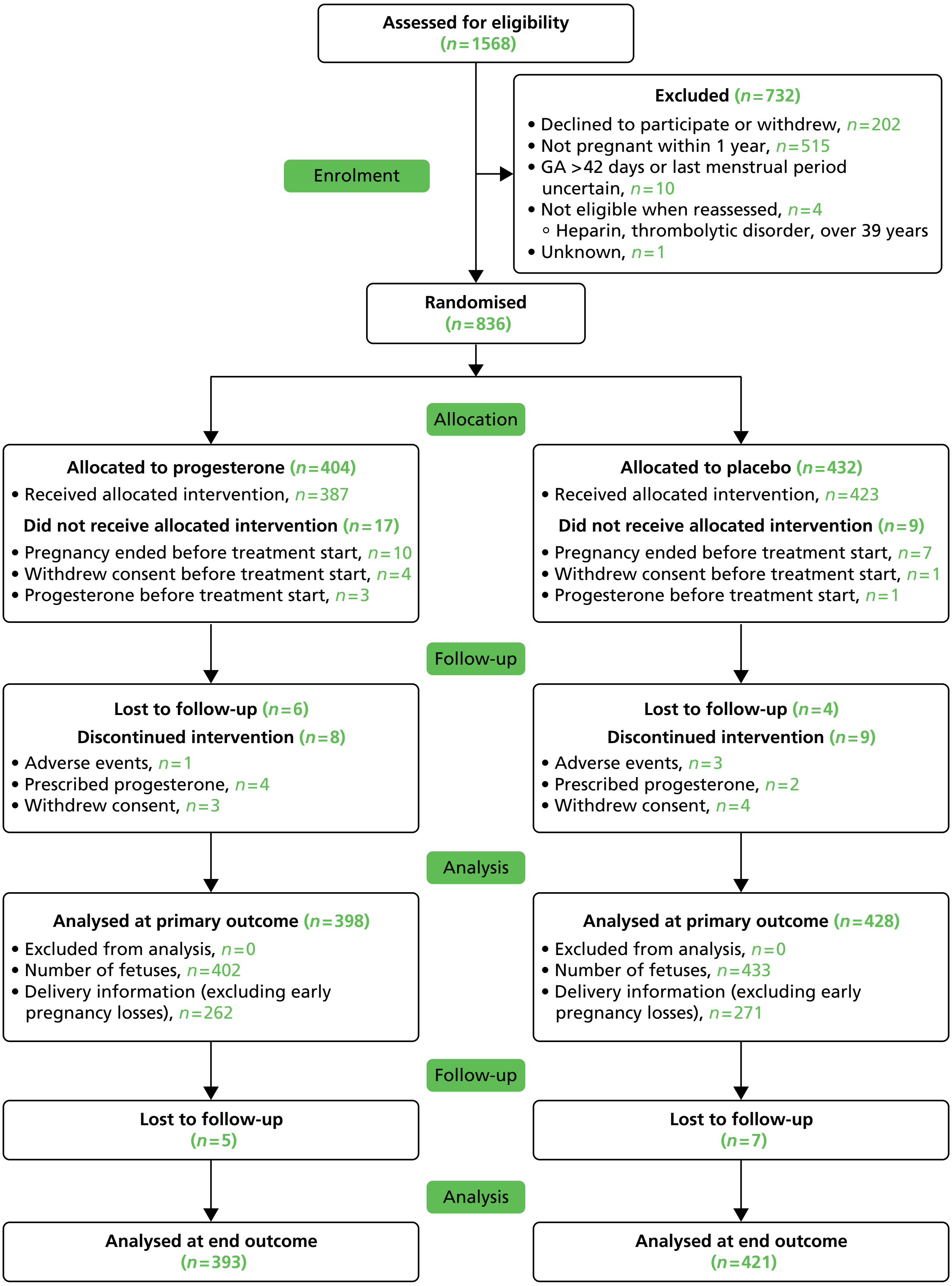
Assessed for eligibility (n=1568)
Excluded (n=732)
• Declined to participate or withdrew, n=202
• Not pregnant within 1 year, n=515
• GA >42 days or last menstrual period uncertain, n=10
• Not eligible when reassessed, n=4
◦ Heparin, thrombolytic disorder, over 39 years
• Unknown, n=1
Enrolment
Randomised (n=836)
Allocation
Allocated to progesterone (n=404)
• Received allocated intervention, n=387
Did not receive allocated intervention (n=17)
• Pregnancy ended before treatment start, n=10
• Withdrew consent before treatment start, n=4
• Progesterone before treatment start, n=3
Allocated to placebo (n=432)
• Received allocated intervention, n=423
Did not receive allocated intervention (n=9)
• Pregnancy ended before treatment start, n=7
• Withdrew consent before treatment start, n=1
• Progesterone before treatment start, n=1
Follow-up
Lost to follow-up (n=6)
Discontinued intervention (n=8)
• Adverse events, n=1
• Prescribed progesterone, n=4
• Withdrew consent, n=3
Lost to follow-up (n=4)
Discontinued intervention (n=9)
• Adverse events, n=3
• Prescribed progesterone, n=2
• Withdrew consent, n=4
Analysis
Analysed at primary outcome (n=398)
• Excluded from analysis, n=0
• Number of fetuses, n=402
• Delivery information (excluding early pregnancy losses), n=262
Analysed at primary outcome (n=428)
• Excluded from analysis, n=0
• Number of fetuses, n=433
• Delivery information (excluding early pregnancy losses), n=271
Follow-up
Lost to follow-up (n=5)
Lost to follow-up (n=7)
Analysis
Analysed at end outcome (n=393)
Analysed at end outcome (n=421)

FIGURE 6 Flow of participants through the PROMISE trial. GA, gestational age.

TABLE 2 Contributions to recruitment and randomisation

Institution	Site	PI	Recruited ($N = 1568$), n (%)	Randomised ($N = 836$), n (%)
UK				
Imperial College Healthcare NHS Trust	St Mary's Hospital	Dr Rajendra Rai	232 (14.8)	137 (16.4)
Heart of England NHS Foundation Trust	Birmingham Heartlands Hospital	Professor Siobhan Quenby and Dr Pratima Gupta	148 (9.4)	64 (7.7)
University Hospital Southampton NHS Foundation Trust	Princess Anne Hospital	Dr Ying Cheong	87 (5.5)	61 (7.3)
Liverpool Women's NHS Foundation Trust	Liverpool Women's Hospital	Dr Feroza Dawood	115 (7.3)	53 (6.3)
Birmingham Women's NHS Foundation Trust	Birmingham Women's Hospital	Professor Mark Kilby	105 (6.7)	48 (5.7)
University Hospitals Coventry and Warwickshire NHS Trust	University Hospital (Coventry)	Professor Siobhan Quenby	71 (4.5)	42 (5.0)
Sheffield Teaching Hospitals NHS Foundation Trust	Sheffield Royal Hallamshire Hospital	Professor Tin-Chiu Li and Dr Shehnaz Jivraj	75 (4.8)	37 (4.4)
Guy's and St Thomas' NHS Foundation Trust	St Thomas' Hospital	Mr Yacoub Khalaf	64 (4.1)	23 (2.8)
Portsmouth Hospitals NHS Trust	Queen Alexandra Hospital	Dr Nirmala Vaithilingam	39 (2.5)	23 (2.8)
Sandwell and West Birmingham Hospitals NHS Teaching Trust	Birmingham City Hospital	Mr Ayman Ewies	38 (2.4)	21 (2.5)
Newcastle upon Tyne Hospitals NHS Foundation Trust	Royal Victoria Infirmary	Dr Jane Stewart	26 (1.7)	20 (2.4)
NHS Ayrshire and Arran	Ayrshire Maternity Unit	Dr Marjory MacLean	30 (1.9)	19 (2.3)
Nottingham University Hospitals NHS Trust	Queen's Medical Centre	Dr Judith Moore	42 (2.7)	18 (2.2)
King's College Hospital NHS Foundation Trust	King's College Hospital	Dr Jackie Ross	30 (1.9)	16 (1.9)
South Tees Hospitals NHS Foundation Trust	James Cook University Hospital	Dr Gamal Sayed and Dr Padma Manda	15 (1.0)	10 (1.2)
Central Manchester University Hospitals NHS Foundation Trust	St Mary's Hospital Manchester	Dr Edmond Edi-Osagie	17 (1.1)	9 (1.1)
City Hospitals Sunderland NHS Foundation Trust	Sunderland Royal Hospital	Dr Amna Ahmed	10 (0.6)	8 (1.0)
Northumbria Healthcare NHS Foundation Trust	Wansbeck Hospital	Dr Shonag Mackenzie	13 (0.8)	7 (0.8)
Luton and Dunstable NHS Foundation Trust	Luton and Dunstable University Hospital	Dr Neela Mukhopadhaya	12 (0.8)	7 (0.8)
South Tyneside NHS Foundation Trust	South Tyneside District Hospital	Dr Shamma Al-Inizi	11 (0.7)	6 (0.7)
Frimley Park Hospital NHS Foundation Trust	Frimley Park Hospital	Dr Manisha Chandra	9 (0.6)	6 (0.7)

continued

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TABLE 2 Contributions to recruitment and randomisation (*continued*)

Institution	Site	PI	Recruited (*N* = 1568), *n* (%)	Randomised (*N* = 836), *n* (%)
Royal Devon and Exeter Hospitals NHS Trust	Royal Devon and Exeter Hospital	Dr Lisa Joels	9 (0.6)	5 (0.6)
Blackpool Teaching Hospitals NHS Foundation Trust	Blackpool Victoria Hospital	Dr Elizabeth Haslett	5 (0.3)	4 (0.5)
Derby Hospitals NHS Foundation Trust	Royal Derby Hospital	Dr Gillian Scothern and Mr Jayaprakasan Kanna	5 (0.3)	4 (0.5)
Chelsea and Westminster Hospital NHS Foundation Trust	Chelsea and Westminster Hospital	Mr Guy Thorpe-Beeston	12 (0.8)	3 (0.4)
Bolton NHS Foundation Trust	Royal Bolton Hospital	Dr Sangeeta Das	3 (0.2)	3 (0.4)
Homerton University Hospital NHS Foundation Trust	Homerton University Hospital	Dr Sandra Watson	7 (0.4)	2 (0.2)
West Middlesex University Hospital NHS Trust	West Middlesex University Hospital	Dr Maysoon Backos	9 (0.6)	2 (0.2)
Countess of Chester Hospital NHS Foundation Trust	Countess of Chester Hospital	Mr Simon Wood	8 (0.5)	2 (0.2)
North Tees and Hartlepool NHS Foundation Trust	University Hospital of North Tees	Dr Iona MacLeod	5 (0.3)	2 (0.2)
NHS Greater Glasgow and Clyde	Southern General Hospital	Dr Judith Roberts	7 (0.4)	1 (0.1)
North Cumbria University Hospitals NHS Trust	Cumberland Infirmary	Professor Nalini Munjuluri	6 (0.4)	1 (0.1)
University Hospitals of Morecambe Bay NHS Foundation Trust	Royal Lancaster Infirmary	Mr Faisal Basama	4 (0.3)	1 (0.1)
North Cumbria University Hospitals NHS Trust	West Cumberland Hospital, Whitehaven	Mr Steve Bober	2 (0.1)	1 (0.1)
County Durham and Darlington Foundation Trust	University Hospital of North Durham	Dr Seema Sen	4 (0.3)	0 (0.0)
Gateshead Health NHS Foundation Trust	Queen Elizabeth Hospital	Dr Isaac Evbuomwan	2 (0.1)	0 (0.0)
Netherlands				
University Medical Centre Utrecht		Dr Yvonne Koot	60 (3.8)	43 (5.1)
Leiden University Medical Centre		Dr Kitty Bloemenkamp	85 (5.4)	41 (4.9)
Academic Medical Centre (Amsterdam)		Dr Mariette Goddijn	58 (3.7)	24 (2.9)
Maxima Medical Centre (Veldhoven)		Dr Carolien Koks	26 (1.7)	20 (2.4)
Onze Lieve Vrouwe Gasthuis (Amsterdam)		Dr Eugenie Kaaijk	23 (1.5)	13 (1.6)
University Medical Centre Groningen		Dr Annemieke Hoek	19 (1.2)	13 (1.6)
Medical Centre Leeuwarden		Dr Denise Perquin	9 (0.6)	8 (1.0)
Isala Klinieken Zwolle		Dr Walter Kuchenbecker	8 (0.5)	8 (1.0)
Atrium Medical Centre (Heerlen)		Dr Patricia Mercelina	3 (0.2)	0 (0.0)

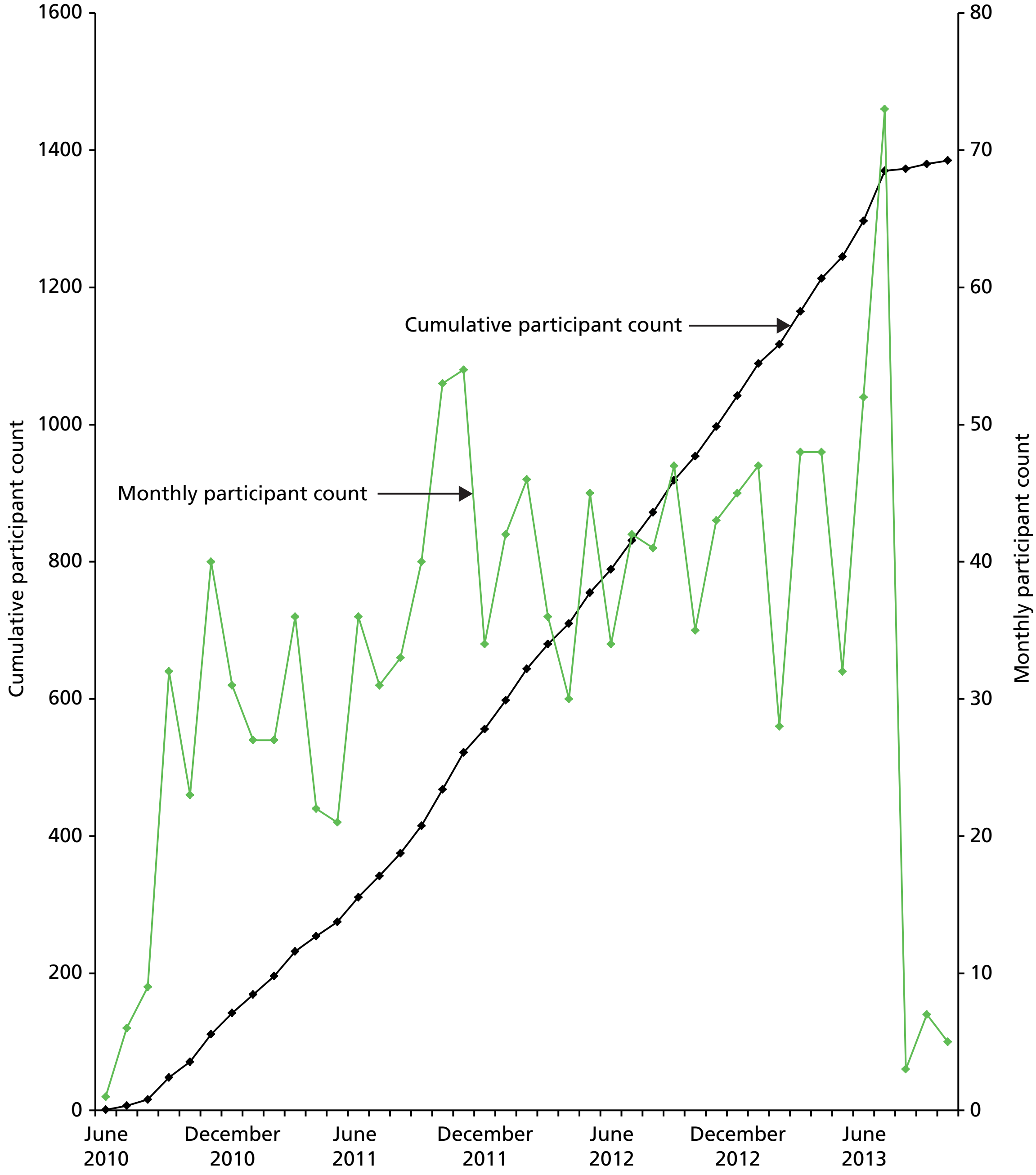

FIGURE 7 Rates of recruitment to the PROMISE trial.

The baseline demographic characteristics of participants in the progesterone and placebo groups were comparable (*Table 3*).

Numbers analysed

A total of 836 participants were randomised, of whom 404 were randomised to progesterone and 432 were randomised to placebo. However, some of these participants (17 women receiving progesterone and nine women receiving placebo) did not receive the allocated intervention (most often as a result of pregnancy loss before treatment could commence), and 10 participants (six women receiving progesterone and four women receiving placebo) were lost to follow-up. Primary outcome data were available for 826 out of 836 (98.8%) participants [398 out of 404 (98.5%) randomised to progesterone, and 428 out of 432 (99.1%) randomised to placebo].

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TABLE 3 Participants at baseline by randomised treatment

Descriptive characteristic	Progesterone	Placebo	All
Maternal age[a] 18 to 35 years,[b] *n*/*N* (%)	261/404 (64.6)	294/432 (68.1)	555/836 (66.4)
Maternal age[a] > 35 years,[b] *n*/*N* (%)	143/404 (35.4)	138/432 (31.9)	281/836 (33.6)
Median age (years) (IQR)[b]	32.9 (29.3–36.3)	32.5 (28.9–35.9)	32.7 (29.1–36.1)
Mean maternal height (m) (SD)	164.4 (7.4)	165.3 (7.1)	164.9 (7.2)
Mean maternal weight (kg) (SD)	68.9 (14.2)	69.2 (14.4)	69.0 (14.3)
Mean maternal BMI (kg/m^2) (SD)[b]	25.5 (5.1)	25.3 (5.1)	25.4 (5.1)
Maternal BMI > 30.0 kg/m^2[b]	63 (15.6)	65 (15.0)	128 (15.3)
Maternal ethnicity, *n*/*N* (%)			
White	316/399 (79.2)	366/424 (86.3)	682/823 (82.9)
Black	16/399 (4.0)	19/424 (4.5)	35/823 (4.3)
Asian	39/399 (9.8)	29/424 (6.8)	68/823 (8.3)
Other, including mixed	28/399 (7.0)	10/424 (2.4)	38/823 (4.6)
Partner's ethnicity, *n*/*N* (%)			
White	293/371 (79.0)	327/395 (82.8)	620/766 (80.9)
Black	24/371 (6.5)	18/395 (4.6)	42/766 (5.5)
Asian	39/371 (10.5)	33/395 (8.4)	72/766 (9.4)
Other, including mixed	15/371 (4.0)	17/395 (4.3)	32/766 (4.2)
Maternal smoking (cigarettes per day), *n*/*N* (%)			
Non-smoker	339/404 (83.9)	363/432 (84.0)	702/836 (84.0)
< 10	28/404 (6.9)	34/432 (7.9)	62/836 (7.4)
10–19	31/404 (7.7)	27/432 (6.3)	58/836 (6.9)
≥ 20	6/404 (1.5)	8/432 (1.9)	14/836 (1.7)
Partner smoking (cigarettes per day), *n*/*N* (%)			
Non-smoker	318/404 (78.7)	348/432 (80.6)	666/836 (79.7)
< 10	30/404 (7.4)	32/432 (7.4)	62/836 (7.4)
10–19	41/404 (10.1)	33/432 (7.6)	74/836 (8.9)
≥ 20	15/404 (3.7)	19/432 (4.4)	34/836 (4.1)
Alcohol (units per day), *n*/*N* (%)			
None	229/404 (56.7)	260/432 (60.2)	489/836 (58.5)
≤ 3	92/404 (22.8)	89/432 (20.6)	181/836 (21.7)
> 3 and ≤ 20	82/404 (20.3)	83/432 (19.2)	165/836 (19.7)
> 20	1/404 (0.2)	0/432 (0.0)	1/836 (0.1)
Parity, *n*/*N* (%)			
Previous live birth	167/404 (41.3)	179/432 (41.4)	346/836 (41.4)
≥ 4 previous miscarriages[b]	183/404 (45.3)	192/432 (44.4)	375/836 (44.9)
Previous ectopic pregnancy	26/402 (6.5)	29/431 (6.7)	55/833 (6.6)
Median number of preceding losses (IQR)	3.0 (3.0–5.0)	3.0 (3.0–4.0)	3.0 (3.0–4.0)

TABLE 3 Participants at baseline by randomised treatment (*continued*)

Descriptive characteristic	Progesterone	Placebo	All
Clinical risk factors, *n*/*N* (%)			
Polycystic ovaries[b]	30/404 (7.4)	28/432 (6.5)	58/836 (6.9)
Fibroids	15/404 (3.7)	14/432 (3.2)	29/836 (3.5)
Endometriosis	8/404 (2.0)	11/432 (2.5)	19/836 (2.3)
Arcuate uterus	24/404 (5.9)	25/432 (5.8)	49/836 (5.9)
Gynaecological surgeries, *n*/*N* (%)			
LLETZ	10/404 (2.5)	19/432 (4.4)	29/836 (3.5)
Myomectomy	1/404 (0.2)	4/432 (0.9)	5/836 (0.6)
Endometriosis surgery	4/404 (1.0)	3/432 (0.7)	7/836 (0.8)
Tubal surgery	17/404 (4.2)	15/432 (3.5)	32/836 (3.8)
Ovarian cystectomy	6/404 (1.5)	8/432 (1.9)	14/836 (1.7)
Family history of RM	55/368 (14.9)	63/391 (16.1)	118/759 (15.5)
Concurrent medications, *n*/*N* (%)			
Metformin	4/404 (1.0)	2/432 (0.5)	6/836 (0.7)
Aspirin	38/404 (9.4)	37/432 (8.6)	75/836 (9.0)

LLETZ, large loop excision of the cervical transformation zone.

a Maternal age at the time of randomisation.

b Treatment allocation was balanced by minimisation on previous miscarriages, maternal age, polycystic ovaries and obesity (BMI $\leq 30.0\,\text{kg/m}^2$ or $> 30.0\,\text{kg/m}^2$).

Outcomes and estimation

The PROMISE trial found no evidence of significant differences in the rates of primary or secondary outcomes between the group randomised to receive progesterone and the group randomised to placebo during the study.

Primary outcome

Overall, 533 out of 826 women (64.5%) experienced a live birth after at least 24 weeks of gestation. *Table 4* shows that the live birth rate in the progesterone group was 65.8% (262/398), and in the placebo group it was 63.3% (271/428), giving a RR of 1.04 (95% CI 0.94 to 1.15; $p = 0.45$).

Of the 533 pregnancies that proceeded to live birth beyond 24 weeks, 524 (98.3%) were singleton pregnancies and nine (1.7%) were twin pregnancies. None of the women participating in the PROMISE trial delivered more than two babies, and, overall, 1.1% of the trial participants [1.0% (4/398) in the progesterone group and 1.2% (5/428) in the placebo group] experienced a twin birth.

Secondary outcomes

Clinical pregnancy at 6–8 weeks

During the study, we were able to confirm that 660 (79.9%) out of all the randomised participants for whom primary outcome data were available experienced a clinical pregnancy (defined as the presence of a gestational sac) at 6–8 weeks. The clinical pregnancy rates observed were not significantly different between the two arms of the trial; we recorded 326 out of 398 (81.9%) clinical pregnancies in the

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progesterone group, versus 334 out of 428 (78.0%) clinical pregnancies in the placebo group. We observed a RR of 1.05 (95% CI 0.98 to 1.12) between the progesterone and placebo groups, with a *p*-value of 0.16 (see *Table 4*).

Ongoing pregnancy at 12 weeks

We were also able to confirm the ongoing pregnancy (defined as the presence of a fetal heartbeat at 12 weeks) of 544 (65.9%) out of all the randomised participants for whom primary outcome data were available. The ongoing pregnancy rates observed were not significantly different between the two groups; we were able to confirm the ongoing pregnancy of 267 out of 398 (67.1%) women in the progesterone group, versus 277 out of 428 (64.7%) women in the placebo group. We observed a RR of 1.04 (95% CI 0.94 to 1.14) between the progesterone and placebo groups, with a *p*-value of 0.47 (see *Table 4*).

Miscarriage

The rates of miscarriage in each study group (progesterone 128/398, 32.2%, vs. placebo 143/428, 33.4%) are given in *Table 4*. Rates of miscarriage were not significantly different between the groups randomised to receive progesterone or placebo. We observed a RR of 0.96 (95% CI 0.79 to 1.17) between the progesterone and placebo groups, with a *p*-value of 0.70.

Of the 128 pregnancies that were lost among participants receiving progesterone, the median age of gestation at miscarriage diagnosis was 7.3 weeks (IQR 6.0–8.7 weeks). Of the 143 pregnancies that were lost among participants receiving placebo, the median gestational age was 7.1 weeks (IQR 6.0–8.5 weeks) (see *Table 4*). We observed a RR of 0.00 (95% CI –0.6 to 0.4) between the progesterone and placebo groups, with a *p*-value of 0.87.

TABLE 4 Primary and secondary outcomes

Outcome	Progesterone, *n*/*N* (%)	Placebo, *n*/*N* (%)	Comparisons, RR (95% CI)	Significance
Clinical pregnancy 6–8 weeks (presence of gestational sac)[a]	326/398 (81.9)	334/428 (78.0)	1.05 (0.98 to 1.12)	$p = 0.16$
Ongoing pregnancy 12 weeks (presence of fetal heartbeat)[a]	267/398 (67.1)	277/428 (64.7)	1.04 (0.94 to 1.14)	$p = 0.47$
Ectopic pregnancy[a]	6/398 (1.5)	7/428 (1.6)	0.92 (0.31 to 2.72)	$p = 0.88$
Miscarriage[a]	128/398 (32.2)	143/428 (33.4)	0.96 (0.79 to 1.17)	$p = 0.70$
Stillbirth[a]	1/398 (0.3)	2/428 (0.5)	0.54 (0.05 to 5.92)	$p = 0.61$
Median gestational age at miscarriage (IQR)[a]	7.3 (6.0 to 8.7)	7.1 (6.0 to 8.5)	0.0 (–0.6 to 0.4)	$p = 0.87$
Live births (≥ 24 + 0 weeks)[a]	262/398 (65.8)	271/428 (63.3)	1.04 (0.94 to 1.15)	$p = 0.45$
Gestation at delivery of live birth[a]				
< 28 + 0 weeks	1/262 (0.4)	1/271 (0.4)	1.03 (0.06 to 16.49)	$p = 0.98$
< 30 + 0 weeks	1/262 (0.4)	2/271 (0.7)	0.52 (0.05 to 5.68)	$p = 0.59$
< 34 + 0 weeks	10/262 (3.8)	10/271 (3.7)	1.03 (0.44 to 2.45)	$p = 0.94$
< 37 + 0 weeks	27/262 (10.3)	25/271 (9.2)	1.12 (0.67 to 1.87)	$p = 0.68$
Twin live births (≥ 24 + 0 weeks)[a]	4/398 (1.0)	5/428 (1.2)	0.86 (0.23 to 3.18)	$p = 0.82$
Survival to 28 days[b]	260/261 (99.6)	269/269 (100.0)	1.00 (0.99 to 1.00)	$p = 0.32$

a End point per trial participant: for women with twin pregnancies, one or two live births counted as a positive outcome.
b End point per neonate [an additional 12 (five progesterone and seven placebo) were lost to follow-up].

Ectopic pregnancy

The rates of ectopic pregnancy in each study group (progesterone 6/398, 1.5%, vs. placebo 7/428, 1.6%) are given in *Table 4*. We observed a RR of 0.92 (95% CI 0.31 to 2.72) between the progesterone and placebo groups, with a *p*-value of 0.88.

Stillbirth

The rates of stillbirth in each study group (progesterone 1/398, 0.3% vs. placebo 2/428, 0.5%) are given in *Table 4*. We observed a RR of 0.54 (95% CI 0.05 to 5.92) between the progesterone and placebo groups, with a *p*-value of 0.61.

Gestational age at live birth

The distributions of gestational age at delivery for the progesterone and placebo groups are illustrated by *Figure 8*. They show a hazard ratio of 1.04 (95% CI 0.91 to 1.19; $p = 0.59$).

Preterm birth: < 28 weeks

Of the 533 pregnancies continuing to live birth after at least 24 weeks, two participants (0.4%, one woman in each arm of the trial) were delivered at < 28 weeks. We observed a RR of 1.03 (95% CI 0.06 to 16.49) between the progesterone and placebo groups, with a *p*-value of 0.98 (see *Table 4*).

Preterm birth: < 30 weeks

Of the 533 pregnancies continuing to live birth after at least 24 weeks, three participants (0.6%) were delivered at < 30 weeks. The rates of delivery at < 30 weeks were not significantly different between the groups randomised to receive progesterone (1/262, 0.4%) or placebo (2/271, 0.7%). We observed a RR of 0.52 (95% CI 0.05 to 5.68) between the progesterone and placebo groups, with a *p*-value of 0.59 (see *Table 4*).

Preterm birth: < 34 weeks

Of the 533 pregnancies continuing to live birth after at least 24 weeks, 20 participants (3.8%, 10 women in each arm of the trial) were delivered at < 34 weeks. Between the progesterone and placebo groups, we observed a RR of 1.03 (95% CI 0.44 to 2.45), with a *p*-value of 0.94 (see *Table 4*).

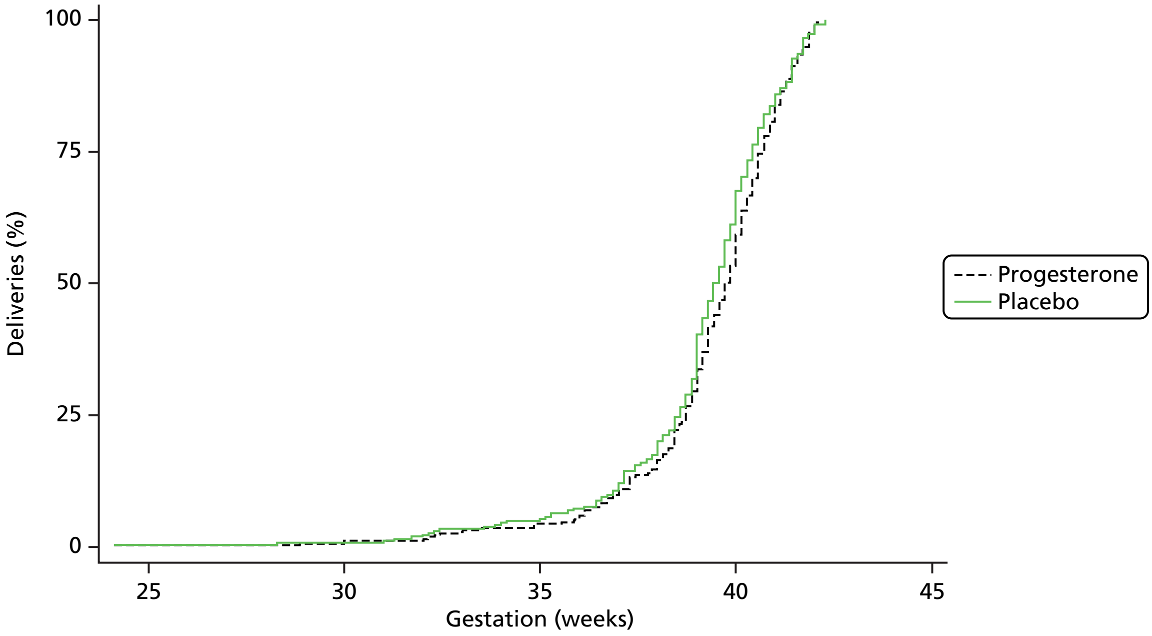

FIGURE 8 Distribution of gestational age by randomised treatment: pregnancies continuing beyond 24 weeks only. Hazard ratio 1.04 (95% CI 0.91 to 1.19; $p = 0.59$).

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Preterm birth: < 37 weeks

Of the 533 pregnancies continuing to live birth after at least 24 weeks, 52 participants (9.8%) were delivered at < 37 weeks. Rates of delivery at < 37 weeks were not significantly different between the groups randomised to receive progesterone (27/262, 10.3%) or placebo (25/271, 9.2%). We observed a RR of 1.12 (95% CI 0.67 to 1.87) between the progesterone and placebo groups, with a *p*-value of 0.68 (see *Table 4*).

Neonatal survival

We were able to collect neonatal survival data from 530 of the 542 babies born alive to 533 women after at least 24 weeks of gestation. The rates of neonatal survival in each study group (progesterone 260/261, 99.6%, vs. placebo 269/269, 100.0%) are given in *Table 4*.

Congenital anomalies

Congenital anomalies observed in babies born to PROMISE participants are listed in *Table 5*. These outcomes were rare, both overall and in each arm of the trial, so our power to identify truly significant rates of difference between the groups is low. Among the pregnancies randomised to receive active treatment, we observed two cases of talipes, two heart anomalies (one ventricular septal defect and one transposition of great arteries), one case of tongue tie, one case of hernia, two chromosomal anomalies (one case of Pierre Robin syndrome and one case of Down syndrome duodenal atresia) and one genital abnormality (hypospadias). Among those randomised to placebo, we observed one case of talipes, three heart anomalies (all ventricular septal defects), two cases of ventriculomegaly, two cases of tongue tie, one case of hernia, one chromosomal anomaly (Turner syndrome) and one genital abnormality (urachal cyst). Overall, 8 out of 266 (3.0%) babies in the progesterone group and 11 out of 276 (4.0%) babies in the placebo group were affected by congenital anomalies, giving a RR of 0.75 (95% CI 0.31 to 1.85), with a *p*-value of 0.54.

TABLE 5 Congenital anomalies

Type of abnormality	Progesterone (*N* = 266), *n* (%)	Placebo (*N* = 276), *n* (%)	All (*N* = 542), *n* (%)
No congenital abnormalities	258 (97.0)	265 (96.0)	523 (96.5)
Talipes	2 (0.8)	1 (0.4)	3 (0.6)
Heart anomaly	2 (0.8)	3 (1.1)	5 (0.9)
Ventriculomegaly	0 (0.0)	2 (0.7)	2 (0.4)
Tongue tie	1 (0.4)	2 (0.7)	3 (0.6)
Hernia	1 (0.4)	1 (0.4)	2 (0.4)
Chromosomal anomaly	2 (0.8)	1 (0.4)	3 (0.6)
Genital abnormality	1 (0.4)	1 (0.4)	2 (0.4)

Note
One baby in the progesterone group was affected by two congenital anomalies.

Ancillary analyses

Subgroup analyses

We planned a priori to conduct subgroup analyses by maternal age (≤ 35 or > 35 years at recruitment), number of previous miscarriages (3 or > 3) and the presence (or not) of polycystic ovaries (*Table 6*). At the end of the trial, we performed additional post-hoc comparisons between the outcomes of women commencing treatment at earlier and later stages of the first trimester, and between women in the UK and in the Netherlands.

TABLE 6 Subgroup analyses of primary end point

Subgroup	Progesterone, *n*/*N* (%)	Placebo, *n*/*N* (%)	Comparisons, RR (95% CI)	Significance
Age				
≤ 35 years[a]	171/258 (66.3)	191/300 (63.7)	1.04 (0.92 to 1.18)	$p = 0.52$
> 35 years[a]	91/140 (65.0)	80/128 (62.5)	1.04 (0.87 to 1.25)	$p = 0.67$
Chi-squared test for interaction			0.00	$p = 0.98$[b]
Previous miscarriages				
3	148/218 (67.9)	159/236 (67.4)	1.01 (0.89 to 1.14)	$p = 0.91$
≥ 4	114/180 (63.3)	112/192 (58.3)	1.09 (0.92 to 1.28)	$p = 0.32$
Chi-squared test for interaction			0.41	$p = 0.52$[b]
Polycystic ovaries				
Absent	245/369 (66.4)	252/401 (62.8)	1.06 (0.95 to 1.17)	$p = 0.30$
Present	17/29 (58.6)	19/27 (70.4)	0.83 (0.56 to 1.23)	$p = 0.36$
Chi-squared test for interaction			1.34	$p = 0.25$[b]
Gestation at treatment start[c,d]				
$< 5 + 0$ weeks	120/182 (65.9)	144/212 (67.9)	0.97 (0.84 to 1.12)	$p = 0.68$
$\geq 5 + 0$ weeks	122/176 (69.3)	113/184 (61.4)	1.13 (0.97 to 1.31)	$p = 0.12$
Chi-squared test for interaction			2.03	$p = 0.15$[b]
Geographical location[d]				
UK	212/312 (67.9)	207/326 (63.5)	1.07 (0.96 to 1.20)	$p = 0.24$
Netherlands	50/86 (58.1)	64/102 (62.7)	0.93 (0.73 to 1.17)	$p = 0.52$
Chi-squared test for interaction			1.20	$p = 0.27$[b]

[a] Maternal age at the time of recruitment.
[b] Non-significant test suggests that considering results separately by group is unsound.
[c] Not including women never commencing treatment, women commencing treatment at unknown gestational age and women commencing treatment later than protocol (total 72, of whom 40 were in the progesterone group and 32 were in the placebo group).
[d] Post-hoc analysis.

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Maternal age

For the purposes of a subgroup analysis, we evaluated the effects of progesterone in women aged ≤ 35 years at the time of recruitment, compared with women who were > 35 years of age (see *Table 6*). We observed that women aged ≤ 35 years experienced a rate of live birth after at least 24 weeks (362/558, 64.9%) similar to older women (171/268, 63.8%). This trend was common to both the progesterone and placebo groups. In the subgroup of women aged ≤ 35 years, the RR of live birth after at least 24 weeks was 1.04 (95% CI 0.92 to 1.18) when progesterone was compared with placebo. In the subgroup of women who were > 35 years of age, the RR of live birth after at least 24 weeks was 1.04 (95% CI 0.87 to 1.25). A chi-squared test for interaction did not find a significant subgroup effect ($\chi^2 = 0.00$; $p = 0.98$).

Previous miscarriages

Our study population was divided into groups of women with a history of three miscarriages and women with a history of more than three miscarriages (see *Table 6*). We observed that women who had experienced three previous miscarriages experienced a higher rate of live birth after at least 24 weeks (307/454, 67.6%) than women who had experienced more than three previous miscarriages (226/372, 60.8%). This trend was observed among women randomised to receive progesterone and women randomised to receive placebo. In the subgroup of women with three previous miscarriages, the RR of live birth after at least 24 weeks was 1.01 (95% CI 0.89 to 1.14) when progesterone was compared with placebo. In the subgroup of women with more than three previous miscarriages, the RR of live birth after at least 24 weeks was 1.09 (95% CI 0.92 to 1.28) when progesterone was compared with placebo. A chi-squared test for interaction was not significant ($\chi^2 = 0.41$; $p = 0.52$).

Polycystic ovaries

Another subgroup analysis was performed by dividing our population into those women with polycystic ovaries and those without (see *Table 6*). We observed that women without polycystic ovaries who received progesterone experienced a higher rate of live birth after at least 24 weeks (245/369, 66.4%) than those with polycystic ovaries who received progesterone (17/29, 58.6%). However, we observed that women without polycystic ovaries who received placebo experienced a lower rate of live birth after at least 24 weeks (252/401, 62.8%) than those with polycystic ovaries who received placebo (19/27, 70.4%). In the subgroup of women without polycystic ovaries, the RR of live birth after at least 24 weeks was 1.06 (95% CI 0.95 to 1.17) when progesterone was compared with placebo. In the subgroup of women with polycystic ovaries, the RR of live birth after at least 24 weeks was 0.83 (95% CI 0.56 to 1.23) when progesterone was compared with placebo. A chi-squared interaction test for interaction was not significant ($\chi^2 = 1.34$; $p = 0.25$).

Gestation at treatment start

In order to explore any possible effect of gestational age at the time of commencing treatment, we conducted a post-hoc analysis comparing the outcomes of participants randomised at < 5 weeks with those of participants randomised at ≥ 5 weeks (see *Table 6*). We found no significant indication that women commencing treatment in the earlier stages of the first trimester experienced higher or lower rates of live birth after at least 24 weeks than those commencing treatment in the later stages. In the subgroup of women randomised at < 5 weeks, the RR of live birth after at least 24 weeks was 0.97 (95% CI 0.84 to 1.12) when progesterone was compared with placebo. In the subgroup of women randomised at ≥ 5 weeks, the RR of live birth after at least 24 weeks was 1.13 (95% CI 0.97 to 1.31) when progesterone was compared with placebo. A chi-squared test for interaction was not significant ($\chi^2 = 2.03$; $p = 0.15$).

Geographical location

We observed (see *Table 6*) that women in the UK experienced a slightly higher rate of live birth after at least 24 weeks (419/638, 65.7%) than those in the Netherlands (114/188, 60.6%). This trend was particularly observed in women randomised to receive progesterone [212/312 (67.9%) live births after at least 24 weeks vs. 50/86 (58.1%) live births after at least 24 weeks]. However, no significant subgroup effects were found (chi-squared test for interaction 1.20; $p = 0.27$).

Exploratory analyses

Maternal complications

Most of the PROMISE trial participants did not experience any antenatal or obstetric complications (*Table 7*). Overall, 17 women (2.1%) were diagnosed with pre-eclampsia. The rate observed in the progesterone group was 1.8% (7/398) and in the placebo group was 2.3% (10/428), giving a RR of 0.75 (95% CI 0.29 to 1.96), with a *p*-value of 0.56.

TABLE 7 Exploratory analyses

Indicator	Progesterone	Placebo	Comparisons	Significance
Maternal complications[a]				
Pre-eclampsia	7/398 (1.8)	10/428 (2.3)	0.75 (0.29 to 1.96)	$p = 0.56$
Antepartum haemorrhage	9/398 (2.3)	14/428 (3.3)	0.69 (0.30 to 1.58)	$p = 0.38$
PPROM	11/398 (2.8)	9/428 (2.1)	1.31 (0.55 to 3.14)	$p = 0.54$
Mode of birth[b]				
Unassisted vaginal	126/262 (48.1)	158/274 (57.7)	0.83 (0.71 to 0.98)	$p = 0.03$
Instrumental vaginal	44/262 (16.8)	32/274 (11.7)	1.43 (0.94 to 2.19)	$p = 0.09$
Elective caesarean	41/262 (15.6)	36/274 (13.1)	1.19 (0.79 to 1.80)	$p = 0.41$
Emergency caesarean	51/262 (19.5)	48/274 (17.5)	1.11 (0.78 to 1.59)	$p = 0.56$
Birthweight[b]				
Live birthweight (g), mean (SD)[c]	($n = 260$) 3213.65 (707.11)	($n = 274$) 3328.87 (635.40)	Mean difference –115.23 (–229.71 to –0.74)	$p = 0.05$
Adjusted live birthweight centile, mean (SD)[c]	($n = 260$) 44.08 (30.58)	($n = 274$) 46.58 (28.91)	Mean difference –2.50 (–7.57 to 2.56)	$p = 0.33$
Small for gestational age[b]				
Small for gestational age[d]	45/260 (17.3)	35/274 (12.8)	1.35 (0.90 to 2.04)	$p = 0.14$
Very small for gestational age[e]	24/260 (9.2)	18/274 (6.6)	1.41 (0.78 to 2.53)	$p = 0.26$
Other neonatal outcomes[b]				
Arterial cord pH of < 7.00	2/58 (3.4)	1/54 (1.9)	1.86 (0.17 to 20.0)	$p = 0.61$
Venous card pH of < 7.00	1/55 (1.8)	0/51 (0.0)	–	–
APGAR score at 1 minute < 7	22/257 (8.6)	15/270 (5.6)	1.54 (0.82 to 2.90)	$p = 0.18$
APGAR score at 5 minutes < 7	3/257 (1.2)	4/271 (1.5)	0.79 (0.18 to 3.50)	$p = 0.76$
Early infection	9/260 (3.5)	8/269 (3.0)	1.16 (0.46 to 2.97)	$p = 0.75$
Necrotising enterocolitis	0/261 (0.0)	0/270 (0.0)	–	–
Intraventraventricular haemorrhage (level 2)	0/261 (0.0)	1/270 (0.4)	–	–
Pneumothorax	0/261 (0.0)	3/270 (1.1)	–	–

continued

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TABLE 7 Exploratory analyses (*continued*)

Indicator	Progesterone	Placebo	Comparisons	Significance
Additional neonatal support required[b]				
Surfactant	2/260 (0.8)	3/269 (1.1)	0.69 (0.12 to 4.09)	$p = 0.68$
Ventilator support	8/260 (3.1)	8/269 (3.0)	1.03 (0.39 to 2.72)	$p = 0.94$
Discharge on oxygen	0/260 (0.0)	1/269 (0.4)	–	–
Median days of additional neonatal support required (if any)[b]				
IPPV	($n = 3$)	($n = 3$)	–	–
	2.0 (IQR 1.0–3.0)	3.0 (IQR 1.0–30.0)		
CPAP	($n = 5$)	($n = 8$)	–	–
	2.0 (IQR 2.0–3.0)	2.5 (IQR 1.0–4.0)		
Oxygen	($n = 6$)	($n = 7$)	–	–
	1.0 (IQR 1.0–3.0)	30.0 (IQR 1.0–80.0)		

– not applicable; CPAP, continuous positive airway pressure; IPPV, intermittent positive pressure ventilation; PPROM, preterm prelabour rupture of membrane.

a End point per trial participant with follow-up to primary outcome.

b End point per neonate born alive after at least 24 weeks of gestation subject to data availability (additional losses to follow-up from total 266 in progesterone arm and 276 in placebo arm as indicated).

c Live birthweight centiles adjusted for maternal height, weight (within healthy range of BMI 18.5–30.0 kg/m^2), ethnicity, parity and neonatal gender and gestational age at delivery.[66]

d < 10th adjusted birthweight centile.

e < 5th adjusted birthweight centile.

Results are given as *n*/*N* (%) unless otherwise stated; comparisons are RR (95% CI) unless otherwise stated.

Antepartum haemorrhage was similarly observed; the rate ocurring in the progesterone group was 2.3% (9/398) and in the placebo group was 3.3% (14/428), giving a RR of 0.69 (95% CI 0.30 to 1.58), with a *p*-value of 0.38 (see *Table 7*).

Overall, 20 (2.4%) cases were diagnosed with preterm prelabour rupture of membrane. The rate observed in the progesterone group was 2.8% (11/398) and in the placebo group was 2.1% (9/428), giving a RR of 1.31 (95% CI 0.55 to 3.14), with a *p*-value of 0.54 (see *Table 7*).

Mode of delivery

Table 7 shows that, overall, more than half of the babies born alive after at least 24 weeks were delivered vaginally without instrumental assistance (284/536, 53.0%). In the group randomised to receive progesterone, 126 out of 262 (48.1%) were delivered in this way. The corresponding proportion in the placebo group was 57.7% (158/274). We observed a RR of 0.83 (95% CI 0.71 to 0.98) between the progesterone and placebo groups ($p = 0.03$).

A higher proportion (44/262, 16.8%) of the babies born to women receiving progesterone than to those receiving placebo (32/274, 11.7%) underwent an instrumental vaginal delivery. We observed a RR of 1.43 (95% CI 0.94 to 2.19) between the progesterone and placebo groups ($p = 0.09$).

Among 536 babies born alive after at least 24 weeks and for whom appropriate delivery data were collected, 77 (14.4%) were delivered by elective caesarean section. In the progesterone group, 41 out of 262 (15.6%) were delivered by elective caesarean section. In the placebo group, 36 out of 274 (13.1%) were delivered by elective caesarean section. We observed a RR of 1.19 (95% CI 0.79 to 1.80) between the progesterone and placebo groups ($p = 0.41$).

In the progesterone group, 51 out of 262 (19.5%) babies were born by emergency caesarean section, while in the placebo group 48 out of 274 (17.5%) babies were delivered in this way. The RR between the progesterone and placebo groups experiencing emergency caesarean section was 1.11 (95% CI 0.78 to 1.59; $p = 0.56$).

Birthweight and small for gestational age

Table 7 shows that among 260 babies born alive after at least 24 weeks of gestation to participants who were randomised to receive progesterone in the PROMISE trial, the mean birthweight was 3214 g (SD 707 g). Among 274 babies born to participants who were randomised to receive placebo, we observed a mean birthweight of 3329 g (SD 635 g). After adjustment for maternal height, weight (within the healthy range of BMI 18.5–30.0 kg/m^2), ethnicity, parity and neonatal gender and gestational age at delivery,[66] there were no significant differences between the mean birthweights of babies born in the different arms of the study.

Among the 534 neonates from whom appropriate data were collected, 80 (15.0%) were small for gestational age (see *Table 7*). The rate observed in the progesterone group was 17.3% (45/260) and in the placebo group was 12.8% (35/274), giving a RR of 1.35 (95% CI 0.90 to 2.04), with a *p*-value of 0.14. Across the same cohort, 42 (7.9%) were very small for gestational age. The proportion observed in the progesterone group was 9.2% (24/260) and in the placebo group was 6.6% (18/274), giving a RR of 1.41 (95% CI 0.78 to 2.53), with a *p*-value of 0.26.

Neonatal outcomes

Other neonatal outcomes of babies born during the PROMISE trial, including arterial and venous cord pH measurements and APGAR scores, are listed in *Table 7*. Outcomes of clinical concern were rare, both overall and within each arm of the trial.

Among the babies from whom neonatal data were immediately collected, the rate of arterial cord pH of < 7 was 3.4% (2/58) in the progesterone group and 1.9% (1/54) in the placebo group, giving a RR of 1.86 (95% CI 0.17 to 20.0), with a *p*-value of 0.61.

Among the same cohort, the proportion of babies with venous cord pH of < 7 was 1.8% (1/55) in the progesterone group and 0.0% (0/51) in the placebo group.

Among the live babies born to PROMISE participants receiving progesterone and from whom APGAR scores were collected, the rate of APGAR score < 7 at 1 minute was 8.6% (22/257). The rate of APGAR score < 7 at 1 minute observed in the placebo group was 5.6% (15/270), giving a RR of 1.54 (95% CI 0.82 to 2.90), with a *p*-value of 0.18.

Among the live babies born to PROMISE participants receiving progesterone and from whom APGAR scores were collected, the rate of APGAR score < 7 at 5 minutes was 1.2% (3/257). The rate observed in the placebo group was 1.5% (4/271), giving a RR of 0.79 (95% CI 0.18 to 3.50), with a *p*-value of 0.76.

Neonatal complications

We did not observe any significant differences in the rates of early infection or other complications experienced by neonates born to PROMISE participants who received progesterone compared with neonates born to those who received placebo (see *Table 7*). In the former group, 9 out of 260 (3.5%) babies from whom data were available acquired early infection, and no babies were diagnosed with necrotising enterocolitis, intraventraventricular haemorrhage (level 2) or pneumothorax. In the latter group, 8 out of 269 (3.0%) babies from whom data were available acquired early infection, no babies (out of 270) were diagnosed with necrotising enterocolitis, 1 baby out of 270 (0.4%) was diagnosed with intraventraventricular haemorrhage (level 2) and 3 out of 270 babies (1.1%) suffered pneumothorax. When considering early infection, we observed a RR between the progesterone and placebo groups of 1.16 (95% CI 0.46 to 2.97), with a *p*-value of 0.75.

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There were few requirements for neonatal support among our study population (see *Table 7*). From the trial arm allocated to receive progesterone, 2 out of 260 (0.8%) babies required surfactant. From the trial arm allocated to receive placebo, 1.1% (3/269) babies required this support. Thus, we calculated a RR of 0.69 (95% CI 0.12 to 4.09), with a *p*-value of 0.68.

Among the same cohort of neonates, 16 (3.0%, eight babies in each group) required ventilator support. We calculated a RR of 1.03 (95% CI 0.39 to 2.72; $p = 0.94$).

Altogether, six babies born to participants in the PROMISE trial required intermittent positive pressure ventilation support. Among the three infants in the progesterone group, the median duration of the requirement was 2 days (IQR 1.0–3.0 days). Among the three infants in the placebo group, the median duration of the requirement was 3 days (IQR 1.0–30.0 days). Altogether, 13 babies born to participants in the PROMISE trial required continuous positive airway pressure support: among the five babies born to women allocated to receive progesterone, the median duration of the requirement was 2 days (IQR 2.0–3.0 days); among the eight babies born to women allocated to receive placebo, the median duration of the requirement was 2.5 days (IQR 1.0–4.0 days). We also observed that 13 babies born to participants in the PROMISE trial required oxygen support: among the six infants in the progesterone group, the median duration of the requirement was a single day (IQR 1.0–3.0 days); among the seven infants in the placebo group, the median duration of the requirement was 30 days (IQR 1.0–80.0 days). One baby in the placebo group was also discharged on oxygen.

Harms

The PROMISE trial incurred only one SUSAR, namely development of a rash by a single participant for whom study medication was discontinued and antihistamines were prescribed. The event was reported to regulatory authorities as appropriate and the rash subsided within 48 hours. Otherwise, AEs were few in both arms of the trial and not in excess of expected complications of pregnancy among women with a history of RM. Based on these records (*Table 8*), it would appear that progesterone in the form of vaginal capsules and at the dose level of 400 mg twice daily is a safe drug to use in early pregnancy.

TABLE 8 Adverse events

Category	Progesterone ($N = 404$), n (%)	Placebo ($N = 432$), n (%)
Allergy	2 (0.5)	0 (0.0)
Dermatological	1 (0.2)	3 (0.7)
Gastrointestinal	20 (5.0)	14 (3.2)
Haematological	0 (0.0)	1 (0.2)
Neurological	7 (1.7)	4 (0.9)
Urological	3 (0.7)	4 (0.9)
Miscellaneous	8 (2.0)	4 (0.9)

Chapter 4 Health economics

This chapter reports the health economic evaluation that was conducted alongside the PROMISE trial.

To ascertain the total financial cost associated with treatment, an economic analysis was conducted alongside the PROMISE trial, with data to show the number of days that treatment (progesterone) was received, and three categories of heath service resource use captured within the trial (antenatal contacts, pregnancy loss management for pregnancies ending before 24 weeks of gestation and mode of delivery for pregnancies proceeding beyond 24 weeks).

Following randomisation, women in the first trimester (and with a history of unexplained RM) were allocated either progesterone therapy (400-mg capsules twice daily) or placebo. The initiation of treatment was intended to occur following a positive pregnancy test (and no later than 6 weeks of gestation), to be continued until 12 weeks of gestation. The number of days of receiving capsules (progesterone or placebo) was calculated as the difference between the trial intervention start date and the trial intervention end date per participant.

Resource usage by treatment group was recorded during the gestation period, at labour and for postnatal admissions in the trial records. At gestational age 6–8 weeks, a standard ultrasound scan to confirm clinical pregnancy was undertaken. At circa 12 weeks, a specialised ‘booking’ ultrasound scan recorded viability and other variables. Other specific types of service contact were captured during the gestation period, including antenatal visits, day assessments and emergency visits (additional ultrasound scans, routine observation and diagnostic procedures, respectively). Participants’ total numbers of antenatal inpatient admissions and total antenatal lengths of stay were also recorded.

Before 24 weeks of gestation, the management of pregnancy loss was categorised as spontaneous resolution, expectant management, medical management or surgical management. After 24 weeks of gestation, the end of each pregnancy was recorded with a mode of delivery as either unassisted vaginal, instrumental vaginal, elective caesarean or emergency caesarean. The onset of delivery was recorded as spontaneous, induced, augmented or pre-labour caesarean. Other variables indicated whether or not there were any intrapartum complications, which for the purpose of this analysis were treated as a binary outcome to indicate whether or not there were any complications. To reflect modes of birth reported in the NHS Reference Costs,[67] mode of delivery, onset of delivery and intrapartum complications were utilised to form 12 categories of Healthcare Resource Groups (HRGs) of modes of birth (see *Valuation of resource use*).

Our analysis of HRGs related to mode of delivery included costs of general postnatal admissions. Therefore, more specific information about general postnatal admissions was not considered necessary. However, above general admissions, we considered maternal admissions into critical care, recorded as admissions to HDUs or ICUs. Neonatal admissions were calculated as nights recorded in SCBUs or NNUs by each pregnancy.

The average resource requirements across the items considered for the economic analysis (such as days receiving treatment, antenatal contacts, pregnancy loss management and mode of delivery) are reported in *Table 9*. Outcome collection was expected at 6–8 weeks of gestation and at 12 weeks of gestation but, for various reasons (such as variation in date of enrolment and miscarriage before these contacts), the table shows the proportions reported as receiving these contacts.

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TABLE 9 Average resource use compared between treatment groups

	Progesterone		Placebo	
Resource items	Mean (SD)	*n*	Mean (SD)	*n*
Days receiving capsules (progesterone or placebo)	39.2 (20.0)	397	39.3 (20.9)	423
Outcome point 1 (6–8 weeks)	0.8 (0.4)	397	0.8 (0.4)	423
Outcome point 2 (12 weeks)	0.7 (0.5)	397	0.7 (0.5)	423
Antenatal visits	6.9 (6.7)	397	6.5 (6.4)	423
Day assessments	0.8 (2.0)	397	0.9 (2.6)	423
Emergency visits	0.4 (0.9)	397	0.4 (1.1)	423
Number of antenatal admissions	0.3 (0.6)	397	0.2 (0.7)	423
Antenatal length of stay (nights)	0.8 (2.8)	397	0.7 (2.6)	423
Miscarriage management				
Spontaneous resolution	0.6 (0.5)	134	0.7 (0.5)	152
Expectant management	0.0 (0.1)	134	0.0 (0.1)	152
Medical management	0.1 (0.3)	134	0.1 (0.3)	152
Surgical management	0.2 (0.4)	134	0.2 (0.4)	152
Mode of delivery				
Normal delivery with CC	0.0 (0.2)	259	0.1 (0.3)	271
Normal delivery without CC	0.3 (0.5)	259	0.3 (0.5)	271
Normal delivery with induction, with CC	0.0 (0.2)	259	0.0 (0.2)	271
Normal delivery with induction, without CC	0.1 (0.3)	259	0.1 (0.4)	271
Assisted delivery with CC	0.0 (0.2)	259	0.0 (0.2)	271
Assisted delivery without CC	0.0 (0.2)	259	0.0 (0.2)	271
Assisted delivery with induction, with CC	0.0 (0.2)	259	0.0 (0.2)	271
Assisted delivery with induction, without CC	0.0 (0.2)	259	0.0 (0.2)	271
Planned lower-uterine caesarean with CC	0.2 (0.4)	259	0.1 (0.3)	271
Planned lower-uterine caesarean without CC	0.0 (0.2)	259	0.0 (0.2)	271
Emergency or upper-uterine caesarean with CC	0.0 (0.1)	259	0.0 (0.1)	271
Emergency or upper-uterine caesarean without CC	0.1 (0.3)	259	0.1 (0.3)	271
Postnatal emergency admissions				
Maternal admission to HDU (nights)	0.1 (1.0)	393	0.1 (0.4)	420
Maternal admission to ICU (nights)	0.0 (0.0)	393	0.0 (0.6)	420
NNU or SCBU admission (nights)	0.8 (4.4)	394	0.8 (4.8)	421

CC, complications during birth.

Valuation of resource use

Table 10 provides the unit costs identified to attribute values to items of resource use as observed within the PROMISE trial.

The costs of treatment using progesterone (Utrogestan®) capsules were identified in the BNF[31] as £21.00 for progesterone 200 mg, 21 vaginal capsules (or £1.00 per 200 mg capsule). The PROMISE treatment protocol stated that two capsules of 200 mg (400 mg) were to be taken twice daily. The cost per participant per day was, therefore, £4.00.

TABLE 10 Unit costs

Resource items	Unit cost (£)	Reference
Progesterone (Utrogestan®) 200 mg, 21 vaginal capsules	21.00	BNF 2014[31]
Antenatal contacts		
Standard ultrasound scan (6–8 weeks)	109.00	NHS reference costs 2011–12 (NZ21Z)[67]
Specialised ultrasound scan (12 weeks)	121.00	NHS reference costs 2011–12 (NZ22Z)[67]
Antenatal visits (standard ultrasound scan)	109.00	NHS reference costs 2011–12 (NZ21Z)[67]
Day assessments (routine observation)	571.00	NHS reference costs 2011–12 (NZ16Z)[67]
Emergency visits (antenatal diagnostic procedures)	133.00	NHS reference costs 2011–12 (NZ23Z)[67]
Antenatal inpatient admissions (per night)	264.00	NHS reference costs 2011–12 (extra bed-day)[67]
Miscarriage management		
Spontaneous resolution	554.00	NHS reference costs 2011–12 (MB08Z)[67]
Expectant management	1033.97	[a]NICE guidelines 2012[68]
Medical management	1421.88	[a]NICE guidelines 2012[68]
Surgical management	1706.82	[a]NICE guidelines 2012[68]
No details available	554.00	Assumed spontaneous resolution
HRG mode of birth		
Normal delivery with CC	1603.03	NHS reference costs 2011–12 (NZ11A)[67]
Normal delivery without CC	1292.04	NHS reference costs 2011–12 (NZ11B)[67]
Normal delivery with induction, with CC	2315.42	NHS reference costs 2011–12 (NZ11E)[67]
Normal delivery with induction, without CC	1750.61	NHS reference costs 2011–12 (NZ11F)[67]
Assisted delivery with CC	2233.05	NHS reference costs 2011–12 (NZ12A)[67]
Assisted delivery without CC	1762.08	NHS reference costs 2011–12 (NZ12B)[67]
Assisted delivery with induction, with CC	2924.16	NHS reference costs 2011–12 (NZ12E)[67]
Assisted delivery with induction, without CC	2293.84	NHS reference costs 2011–12 (NZ12F)[67]
Planned lower-uterine caesarean with CC	3041.26	NHS reference costs 2011–12 (NZ13A)[67]
Planned lower-uterine caesarean without CC	2596.22	NHS reference costs 2011–12 (NZ13B)[67]
Emergency or upper-uterine caesarean with CC	3789.24	NHS reference costs 2011–12 (NZ14A)[67]
Emergency or upper-uterine caesarean without CC	3288.24	NHS reference costs 2011–12 (NZ14B)[67]
Postnatal emergency admissions		
Maternal admission to HDU	629.91	NHS reference costs 2011–12 (XC07Z)[67]
Maternal admission to ICU	1209.28	NHS reference costs 2011–12 (XC06Z to XXC01Z[b])[67]
Neonatal admission (NNU/SCBU)	440.00	NHS reference costs 2011–12 (XA05Z)[67]

CC, complications during birth; NICE, National Institute for Health and Care Excellence.

a Guidelines[68–70] for 2001–2 price year, discounted for 2011–12 values at 3.5%.

b Weighted average across six HRGs for critical care, one or more organ(s) supported.

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The costs of antenatal contacts were obtained from the NHS Reference Costs 2011–12, and for the cost of each antenatal admission night, the average cost of an excess bed-day was provided in a summary report by the NHS Reference Costs 2011–12.[67]

Costs of pregnancy-loss management were not provided in the NHS Reference Costs 2011–12,[67] with the exception of spontaneous resolution. Therefore, the other costs of pregnancy-loss management were identified from other sources.[68] Specifically, costs for expectant management, medical management and surgical management in the UK for the price year 2001–2 were estimated by another study in 2006, and a 3.5% time discount rate was adopted to estimate values for the 2011–12 price year.[69]

Modes of delivery in the NHS Reference Costs 2011–12 were covered by 12 HRGs, broadly categorising each birth as a normal vaginal delivery, an assisted vaginal delivery or a caesarean section, with each category further divided by whether or not there were complications. Normal and assisted vaginal deliveries were further divided by whether or not pregnancy was induced.

As postnatal maternal admissions were recorded as either to HDU or to ICU, together amalgamated into the single entity of ‘critical care’,[71] assumptions were required to associate correct types of service use with these new HRGs. HDU was proxied by the HRG ‘adult critical care, zero organs supported’ and for ICU a weighted average was taken across the six higher-intensity ‘adult critical care’ HRGs, where one or more organs were supported.

Table 11 provides (for each treatment group) mean costs of all items of resource use, with the subtotal costs for each of five categories of resources (treatment, antenatal contacts, miscarriage management, mode of delivery and postnatal emergency admissions) and the average total cost per group.

Based on the average number of days for which participants received treatment with progesterone capsules, the average cost of care was calculated to be £156.82 per pregnancy. Treatment according to the study protocol commenced at no later than 6 weeks’ gestation and continued until 12 weeks of gestation unless miscarriage occurred before this time, which would equate to 42 days and an expected cost of £168.00 per continuing pregnancy. The mean cost indicated by our trial data is lower because it is a calculation of the cost up to either 12 weeks or the time of miscarriage. Although this provides an accurate indication of the consumption cost of treatment, in a real-world setting capsules could be allocated for the expected treatment period (from 4–6 weeks until 12 weeks) and therefore prescription costs could be considered fixed; such scenarios are explored later in this chapter using a sensitivity analysis.

Costs associated with antenatal contacts appeared marginally higher overall among women receiving progesterone than among women receiving placebo. For all items (except day assessments and emergency visits) mean costs were higher in the progesterone group than in the placebo group.

Miscarriage management was, except in the case of surgical management, less expensive in the progesterone group. Surgical miscarriage of management showed a significantly higher average cost in the progesterone group. Costs associated with HRG modes of delivery were, overall, comparable, but with some notable variations by individual HRGs.

Few emergency admissions for mothers were observed, but each of these cases did incur a high tariff. There were no significant differences between treatment groups in the rates of neonatal admissions (progesterone 9.74% vs. placebo 9.73%), although newborns in the progesterone group experienced slightly higher lengths of stay in hospital than those in the placebo group.

Overall, mean total costs were higher in the progesterone group than in the placebo group (progesterone £4062.26 vs. placebo £3730.10). The incremental costs of treatment using progesterone were calculated to be £332.17, which represents 8.9% higher costs than usual care.

TABLE 11 Mean resource costs and total costs by treatment group

	Progesterone		Placebo	
Resource items	**Mean (£)**	***n***	**Mean (£)**	***n***
Treatment using vaginal capsules	156.88	397	0.00	423
Antenatal contacts				
Outcome point 1 (6–8 weeks)	87.86	397	84.00	423
Outcome point 2 (12 weeks)	84.12	397	82.10	423
Antenatal visits	752.02	397	703.48	423
Day assessments	474.63	397	517.00	423
Emergency visits	52.93	397	54.39	423
Antenatal admissions	208.14	397	181.62	423
Subtotal for all antenatal contacts	1659.71	397	1622.59	423
Miscarriage management				
Spontaneous resolution	359.69	134	379.05	152
Expectant management	15.43	134	20.41	152
Medical management	159.17	134	177.74	152
Surgical management	382.13	134	291.96	152
Subtotal for all miscarriage management	916.41	134	869.15	152
HRG mode of birth				
Normal delivery with CC	61.89	259	130.14	271
Normal delivery without CC	389.11	259	414.79	271
Normal delivery with induction, with CC	53.64	259	93.98	271
Normal delivery with induction, without CC	223.05	259	245.47	271
Assisted delivery with CC	103.46	259	90.64	271
Assisted delivery without CC	68.03	259	39.01	271
Assisted delivery with induction, with CC	124.19	259	75.53	271
Assisted delivery with induction, without CC	88.57	259	59.25	271
Planned lower-uterine caesarean with CC	504.92	259	404.01	271
Planned lower-uterine caesarean without CC	70.17	259	95.80	271
Emergency or upper-uterine caesarean with CC	73.15	259	55.93	271
Emergency or upper-uterine caesarean without CC	431.66	259	388.28	271
Subtotal for all HRG modes of delivery	2191.84	259	2092.83	271
Postnatal emergency admissions				
Cost of maternity HDU	120.00	393	63.34	420
Cost of maternity ICU	0.00	393	28.50	420
Cost of neonatal (NNU or SCBU) admissions	357.36	394	345.94	421
Total cost	4062.26	393	3730.10	420

CC, complications during birth.

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Health benefits: measure of effectiveness

The primary health outcome adopted by the economic analysis of the PROMISE trial was live birth after at least 24 weeks of gestation. The incremental effect was, therefore, the incremental probability of an additional live birth after at least 24 weeks of gestation. *Table 12* summarises the expected number of live births beyond 24 weeks by treatment group. To estimate cost-effectiveness from the joint distributions of individuals' total costs and outcomes, the health benefits were estimated in individuals where total cost was not missing.

$$\Delta \mathrm{E} = \bar{\mathrm{E}}_{\mathrm{I}} - \bar{\mathrm{E}}_{\mathrm{C}} \tag{1}$$

$$\Delta \mathrm{E} = 0.6381 - 0.6565 \tag{2}$$

$$\Delta \mathrm{E} = 0.0184, \tag{3}$$

where Δ represents change, E represents the effects, and subscripts I and C refer to the intervention and control arms, respectively.

The adjusted incremental difference in the mean probability of a live birth beyond 24 weeks of gestation was 0.0184.

Logistic regression indicated that the adjusted ΔE had a *p*-value of 0.583 (illustrating substantial uncertainty in the expected incremental benefit); this highlights the importance of referring to the analysis of uncertainty [such as with a cost-effectiveness acceptability curve (CEAC)] while interpreting estimates of cost-effectiveness (see the following section).

TABLE 12 Live birth beyond 24 weeks

Treatment group	Mean	Median	SD	Minimum	Maximum	*n*
Unadjusted primary outcome						
Placebo	0.633	1	0.483	0	1	428
Progesterone	0.658	1	0.475	0	1	398
Adjusted primary outcome for complete-case analysis[a]						
Placebo (E_{C})	0.638	1	0.481	0	1	420
Progesterone (E_{I})	0.657	1	0.476	0	1	393

a Health benefits utilised in the cost-effectiveness analysis are based on individuals where both total cost and outcome were complete.

Cost-effectiveness and uncertainty

The primary cost-effectiveness outcome of the PROMISE study was cost per additional live birth after at least 24 weeks of gestation. To inform the decision-maker, the incremental cost-effectiveness ratio (ICER) is the ratio of the difference in cost (C) to the differences in difference in effect (E), denoted by the formula:

$$\mathrm{ICER} = \frac{\Delta C}{\Delta E} = \frac{\bar{C}_I - \bar{C}_C}{\bar{E}_I - \bar{E}_C} \tag{4}$$

$$\mathrm{ICER} = \frac{£4062.26 - £3735.10}{0.6565 - 0.6381} \tag{5}$$

$$\mathrm{ICER} = \frac{£332.17}{0.0184} \tag{6}$$

$$\mathrm{ICER} = £18{,}053, \tag{7}$$

where Δ represents change, C represents the costs, E represents the effects, and subscripts I and C refer to the intervention and control arms, respectively.

The cost to achieve an additional live birth after at least 24 weeks was calculated to be £18,053. In the UK, a value of £20,000–30,000 per quality-adjusted life-year (QALY) is considered to be an acceptable value for adopting a health-care technology.[70] However, there remains unsettled debate about the valuation of prenatal life in economic evaluations.[72] The generic health gains in terms of QALYs are reported in *Sensitivity analyses*, *Estimation of quality-adjusted life-years and costs beyond the trial end point*.

Uncertainty around the mean statistic for both costs and outcomes is a commonplace feature of economic evaluations. A key component of any evaluation is to demonstrate this uncertainty and the robustness of the cost-effectiveness ratio calculated from the initial main trial analysis. A non-parametric bootstrap (with 50,000 replications) was performed to demonstrate uncertainty in the joint distribution of cost and effects in the PROMISE trial. *Figure 9* provides a visual representation of the degree of uncertainty in the ICER on a cost-effectiveness plane.

The bootstrap estimates that the 95% CI of the incremental probability of an additional live birth beyond 24 weeks of gestation ranges from –0.0477 to 0.0845. Based on the current level of uncertainty, it might also be concluded that there is a 29.30% chance that progesterone may result in a decrease in the probability of a live birth beyond 24 weeks of gestation, compared with usual care. Nevertheless, 17.16% of the bootstrap replications fell within the bottom-left quadrant, where less effect also resulted in lower cost.

The top-right quadrant of the cost-effectiveness plane contained 59.31% of all replications. Although overall there is substantial uncertainty, this may suggest that treatment was most likely to cost more and have some additional benefit.

Given the uncertainty in the current estimates of the cost per additional live birth beyond 24 weeks of gestation, a decision-maker may wish to examine how the probability that progesterone would be the most cost-effective option will vary with an increasing willingness to pay.

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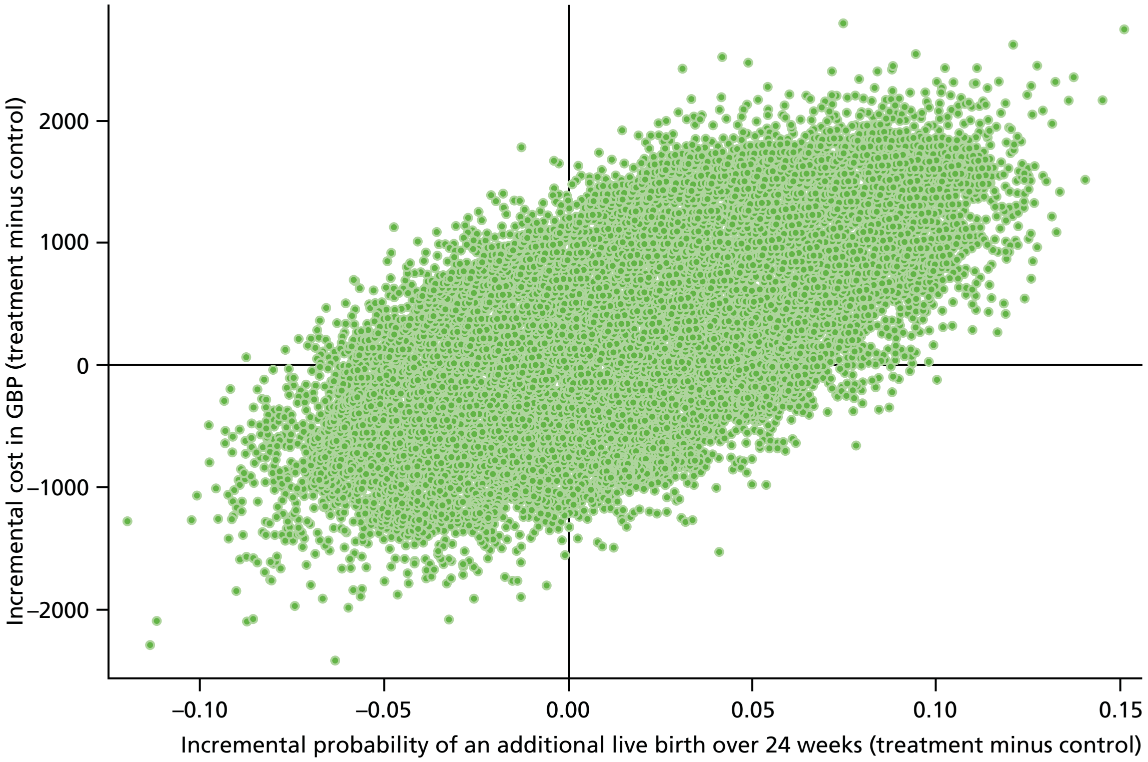

FIGURE 9 Cost-effectiveness plane (50,000 bootstrap replications). GBP, Great British pound.

Figure 10 presents the CEAC to illustrate how the probability of treatment being cost-effective changes as the willingness to pay increases.

At a willingness to pay of £100,000 per additional live birth beyond 24 weeks of gestation, the probability that treatment would be cost-effective asymptotes [p(ICER $< 100{,}000) = 0.7203$]. This raises the question as to what society would be willing to pay to increase the likelihood of an additional live birth beyond 24 weeks of gestation.

Sensitivity analyses

Fixed treatment cost until 12 weeks

In the base-case cost-effectiveness analysis, the direct cost of treatment with progesterone accurately accounted for the total number of days of treatment received by individuals (assuming, as was the case during the trial, that surplus capsules would be returned either at 12 weeks or in the event of miscarriage). *Figure 11* illustrates trends in the variation of stages of pregnancy that treatment started and stopped. The variable trialstop illustrates a bimodal distribution relating to whether pregnancy proceeded beyond 12 weeks or treatment was withdrawn as a result of miscarriage.

If this trial was to be replicated in a real-world setting, it is unlikely that surplus medication prescribed up to an anticipated treatment end point (12 weeks) would be returned and reused. Our sensitivity analysis illustrates the implications that treatment would be prescribed up to a fixed end point (12 weeks of gestation) while still allowing the observed variation in treatment initiation (trialstart).

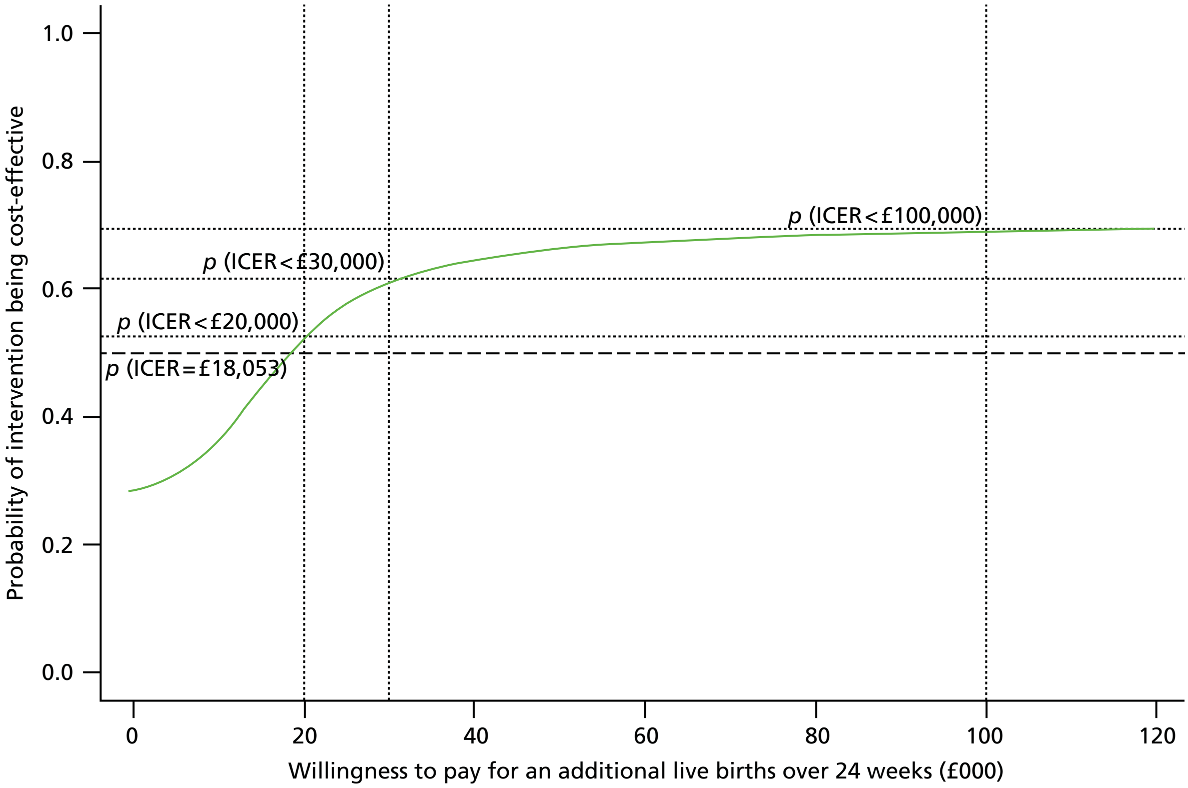

FIGURE 10 Cost-effectiveness acceptability curve.

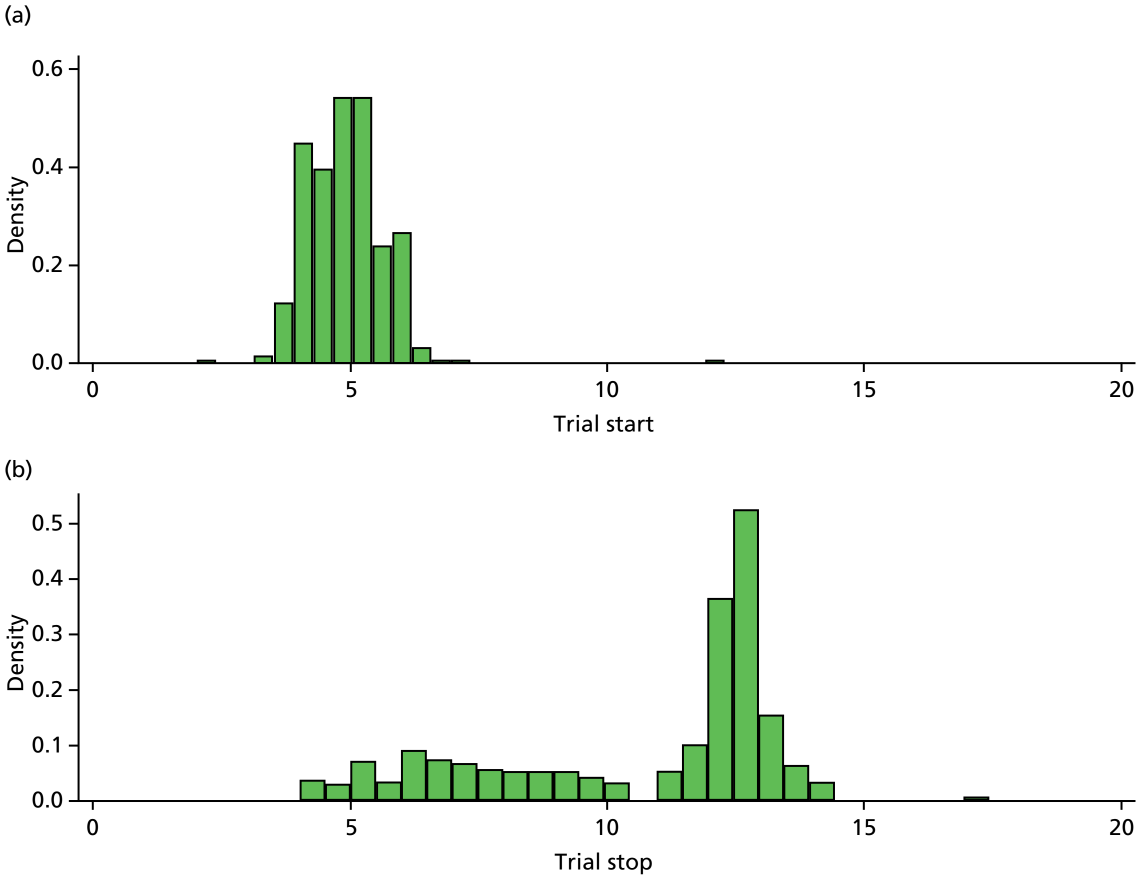

FIGURE 11 Distribution in points of gestation where treatment (a) started; and (b) stopped.

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Repeating the non-parametric bootstrap procedure to re-estimate the ICER and CEAC with respect to this change in the expected cost of treatment generated a predictable increase in the ICER to £22,256 per additional live birth beyond 24 weeks of gestation. *Figure 12* illustrates a marginal decrease in the likelihood that treatment would be cost-effective as willingness to pay increases.

Estimation of quality-adjusted life-years and costs beyond the trial end point

The base-case analysis adopted a condition-specific end point to inform clinical choices of alternative strategies intended to increase the likelihood of a viable birth (live birth beyond 24 weeks of gestation). However, there are limitations of condition-specific outcomes to inform health-care policy. Furthermore, it could be argued that the binary outcome of live birth (or not) beyond 24 weeks of gestation, although providing some indication of life-years gained, does not provide any information on the quality of life achieved from treatment.

Expressing the health benefits in terms of QALYs provides more information to guide the allocation of a limited pool of health-care resources based on explicit monetary values per QALY. To explore methods by which the clinical outcomes might be translated into generic health benefits (such as QALYs), a systematic search was undertaken to identify and project the longer-term costs and consequences, and several potential modelling strategies were explored.

A Finnish study provided the most suitable basis for a strategy to express gains in generic health terms (such as QALYs);[73] to our knowledge this is the only study to date to evaluate the effects of gestational age on QALYs. It estimated QALYs up to 4 years of age using the 17-dimension parental questionnaire, reported with expected variations in the 4-year QALY by gestational age at birth.[74]

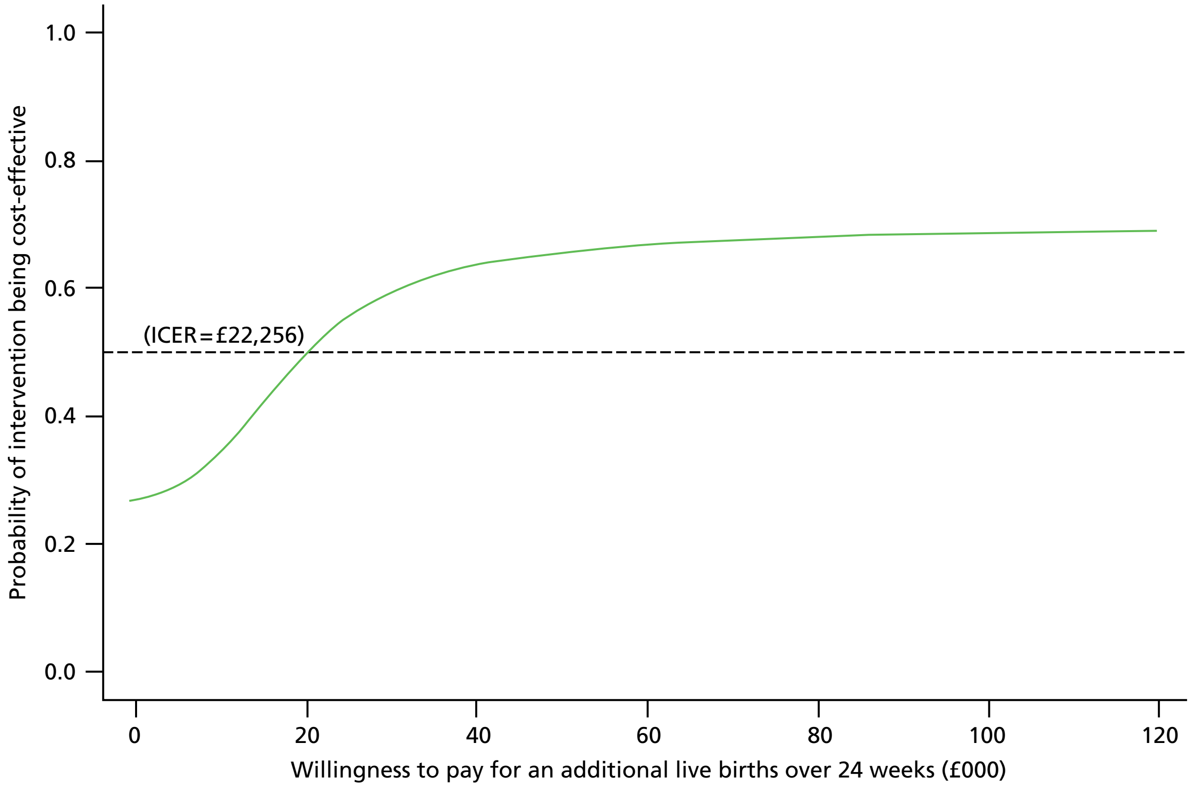

FIGURE 12 Cost-effectiveness acceptability curve: treatment costs fixed until 12 weeks.

By utilising gestational age at delivery within the PROMISE trial to serve as a surrogate outcome for QALYs, QALYs per participant were deduced. However, the estimates of QALYs reported by the Finnish study truncated QALYs at 32 weeks of gestation. Consultation with clinical content experts suggested that generic health gains (QALYs) could be most reasonably assumed to linearly increase up to a gestational age of 34 weeks at birth and, based on this assumption, linear predictors of the expected QALYs for weeks 24–34 were estimated using an ordinary least squares regression. QALYs after 34 weeks showed no additional increase. *Table 13* summarises the data on expected QALYs that were used to inform projected health gains up to 4 years of age by gestational age at birth.

The expected QALYs were applied to PROMISE records of gestational age at birth. In a situation of postnatal infant mortality (up to 28 days), the trial captured mortality date and adjusted individual QALYs to the date of mortality.

Costs beyond initial hospitalisation (at birth) were projected by utilising a data set of individual records supplied from the Oxford Records Linkage Study by Dr Stavros Petrou.[75] This data set provided a sample of 95,635 births in the UK, and their associated costs for the first year after initial hospitalisation (excluding costs associated with the initial admission related to pregnancy). Price years recorded in the data set ranged between 1979 and 1988; a time discount rate of 3.5% was applied to obtain 2011 values. Dummy variables representing weeks of gestation at birth from 23 to 44 weeks were generated. The cost for the first year after initial hospitalisation was regressed against these variables to estimate the magnitude of first year costs by gestational age at birth.

TABLE 13 Expected QALYs up to 4 years of age, by gestational age at birth, estimated from Korvenranta *et al.*[73]

Gestational age at birth (weeks)	Linear predictor of QALYs up to 4 years of age
22	3.6058
23	3.6250
24	3.6441
25	3.6633
26	3.6824
27	3.7016
28	3.7207
29	3.7399
30	3.7590
31	3.7782
32	3.7973
33	3.8165
34	3.8356
35	3.8356
36	3.8356
37	3.8356
38	3.8356
39	3.8356
40	3.8356

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Table 14 provides regression outputs in which coefficients of each gestational age at birth show the expected additional costs following initial hospitalisation.

Gestational age at delivery served as a surrogate outcome to estimate QALYs (over 4 years) and additional health-care costs (over the first year), allowing the treatment effect to be estimated using regression analysis. Cost and QALY distributions were jointly estimated using Zellner's seemingly unrelated regression,[76] thereby allowing analysis to also account for correlation in the residuals. *Table 15* presents the output of the regression.

First, examining the regression coefficients for progesterone indicated the incremental cost to be £366.53 and incremental QALY to be 0.0987, generating an ICER of £3712 per QALY. Subject to certain assumptions required to estimate the utility function (discussed below), this ICER could be considered to be highly cost-effective with respect to explicit decision rules for the reimbursement of health technologies in the UK; it falls well below the benchmark of between £20,000 and £30,000 that is suggested as an appropriate threshold by the National Institute for Health and Care Excellence (NICE).[70]

TABLE 14 Output of regression to estimate costs for the first year after initial hospitalisation by gestational age at birth

Gestation at birth (weeks)	Coefficient	95% CI	Standard error	*p*-value
23	121,636.10	18,538.74 to 798,077.00	116,746.20	< 0.001
24	39,776.66	21,247.04 to 74,466.03	12,725.98	< 0.001
25	57,774.52	36,609.02 to 91,176.86	13,449.13	< 0.001
26	55,784.84	39,094.91 to 79,599.82	10,118.58	< 0.001
27	61,814.74	47,116.21 to 81,098.68	8563.54	< 0.001
28	46,018.71	36,168.45 to 58,551.65	5655.27	< 0.001
29	44,602.67	36,281.46 to 54,832.37	4699.00	< 0.001
30	34,573.18	28,697.57 to 41,651.77	3285.67	< 0.001
31	29,243.02	24,680.64 to 34,648.79	2530.79	< 0.001
32	25,121.59	22,007.13 to 28,676.80	1696.52	< 0.001
33	21,830.22	19,561.84 to 24,361.64	1222.01	< 0.001
34	15,688.96	14,354.70 to 17,147.23	711.46	< 0.001
35	12,204.82	11,321.47 to 13,157.09	467.84	< 0.001
36	10,072.11	9397.77 to 10,794.83	356.11	< 0.001
37	7851.10	7419.87 to 8307.40	226.29	< 0.001
38	7303.05	6994.23 to 7625.50	160.99	< 0.001
39	5793.92	5585.30 to 6010.33	108.41	< 0.001
40	5766.30	5575.62 to 5963.5	98.93	< 0.001
41	5456.47	5246.34 to 5675.02	109.33	< 0.001
42	6446.60	6046.69 to 6872.95	210.64	< 0.001
43	6927.92	6199.75 to 7741.61	392.53	< 0.001
44	6077.39	5260.80 to 7020.73	447.42	< 0.001
			$n = 95{,}635$	$R^2 = 0.2130$

Source: Petrou 2005.[75]

TABLE 15 Outputs of Zellner's[76] seemingly unrelated regression

Variables	Coefficient	95% CI	Standard error	*p*-value
Total cost				
Progesterone	366.532	–960.663 to 1693.728	677.153	0.588
Constant	8185.186	7257.909 to 9112.462	473.109	< 0.001
QALY				
Progesterone	0.099	–0.176 to 0.374	0.140	0.482
Constant	2.246	2.053 to 2.438	0.098	< 0.001
Correlation matrix of residuals			**Total cost**	**QALY**
Total cost			1.000	
QALY			0.649	1.000

Breusch–Pagan test of independence: $\chi^2 = 295.456$; $p = \leq 0.0001$.
Source: Zellner 2012.[76]

Furthermore, significant correlation was observed between cost and QALY distribution within the estimated utility function (0.6487; $p < 0.0001$). To an extent, this correlation could be attributed to the common surrogate outcome of gestational age at delivery; lower gestational age would decrease neonatal health status and that would be correlated to higher health-care costs.

Figure 13 illustrates changes in probability that treatment may be cost-effective as the willingness to pay increases. The CEAC indicates a probability of between 0.7145 and 0.7341 to express the likelihood that prescription progesterone therapy in women with a history of unexplained RM falls within the NICE threshold.

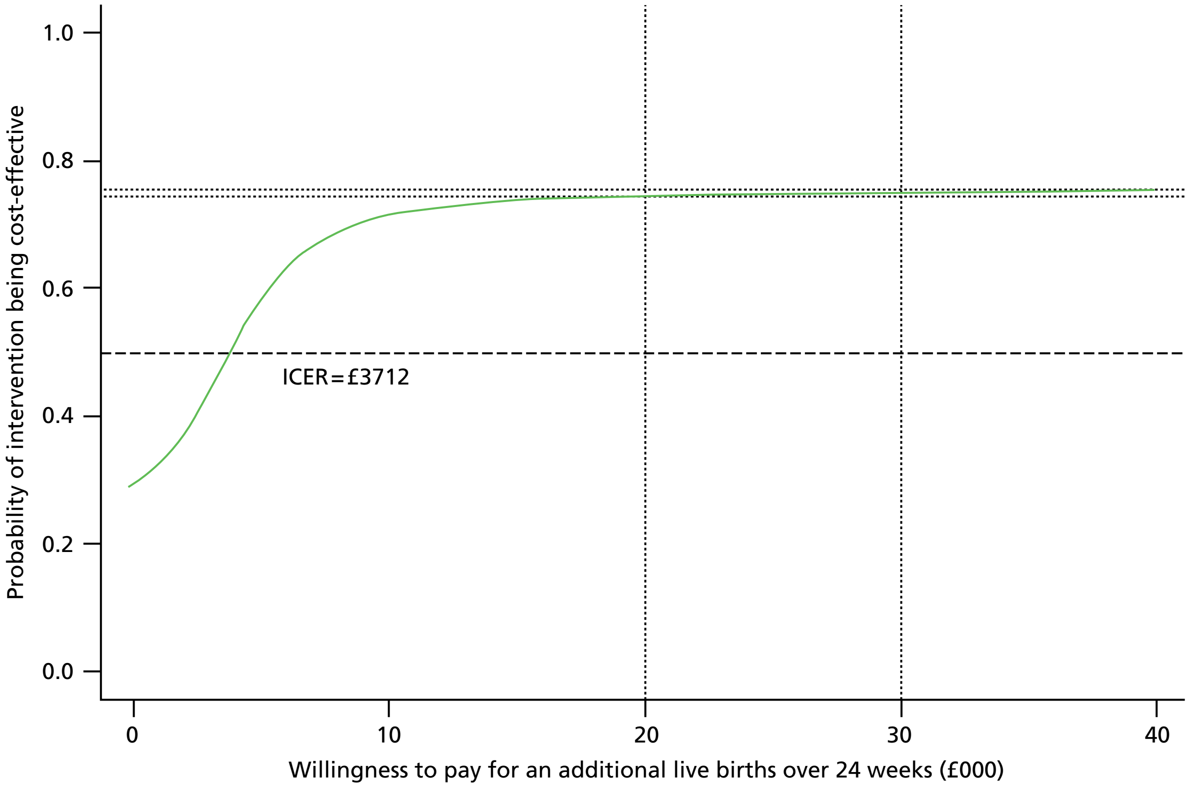

FIGURE 13 Cost-effectiveness acceptability curve: QALYs and cost projected beyond the trial end point.

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Although the estimation of QALYs and first-year cost consequences to the NHS may be useful to policy-makers and decision-makers allocating global health-care budgets,[77] it should be noted that there are several unavoidable limitations to consider when interpreting these results. First, the extrapolation of QALYs utilised data from Finland without accounting for any variation in the preferences for health state that may exist between countries. Second, incorporation of QALYs into the utility function essentially places values on prenatal life (zero QALYs for miscarriage) that may raise moral and ethical debates. Finally, no reliable method was identified to model the implications of miscarriage on individual health, or indeed health-care, utilisation.

Summary

- The average total cost in the progesterone group was higher than in the placebo group (progesterone £4062.26 vs. placebo £3730.10), representing an incremental cost of £332.17 (8.9% higher costs than usual care).
- The incremental difference in the mean probability of a live birth beyond 24 weeks of gestation (adjusted for complete case cost-effectiveness analysis) was 0.0184 ($p = 0.583$).
- The ICER for the base case was £18,053 per additional live birth beyond 24 weeks of gestation.
- Estimates of cost-effectiveness are highly uncertain (the probability of treatment being cost-effective should the decision-maker be willing to pay £100,000 per additional live birth beyond 24 weeks of gestation is 0.7203).
- Using external data sources, the treatment ICER was estimated in terms of QALYs to be £3679 per QALY. This analysis suggests the probability that progesterone would fall within the NICE threshold (£20,000–30,000 per QALY) as between 0.7145 and 0.7341.

Chapter 5 Discussion

In the following discussion, we focus on the findings of the trial, highlighting the strengths and weaknesses of the study and generalisability of the findings in the context of available evidence. We conclude with our recommendations for clinical practice and further research.

Study strengths

This study is the largest-ever randomised placebo-controlled clinical trial to report on the treatment effects of first-trimester progesterone therapy for pregnant women with a history of unexplained RM. It is, in fact, the largest randomised clinical trial ever conducted on the subject of recurrent pregnancy loss. It has demonstrated that a large, high-quality, randomised trial of IMP can be successfully conducted in the challenging and emotive context of RM, with the help of hospital teams and patients from maternity services reflecting a wide range of clinical practice and research experience across the UK and in the Netherlands.

Internal validity

Randomisation and minimisation were effective in achieving balanced treatment allocations at baseline. Thus, the PROMISE trial optimised statistical power and eliminated selection and allocation bias.[78] A computer-generated allocation sequence, allocation concealment and blinding prevented investigators from knowing the assignment of the next participant based on prior treatment assignments. Possible confounding factors such as the number of previous miscarriages, maternal age and polycystic ovaries were similarly distributed between treatment groups. As a study with allocations blinded to participants and care providers, the PROMISE trial also avoided performance bias.

The research team believed that it was important to ensure that the study was large enough to detect clinically important treatment effects, and, therefore, the target sample size of the study was calculated to enable detection of a MID of 10% in rates of live birth after at least 24 weeks of gestation. We planned to randomise 790 women in total (395 participants in each of the progesterone and placebo arms) and we actually exceeded this number. Consequently, we consider the findings of this trial to be methodologically and statistically robust.

Our trial design offered a number of other strengths with respect to data collection and analysis. The treatment of participants by a large number of study centres and practitioners allowed intervention impact to be evaluated without confounding by individual variance in clinical practice and local technology. The outcome indicators that we measured were variables of routine familiarity in pregnancy care, so they were well understood and easily recorded by clinical researchers. Almost all of the outcome data recorded during the PROMISE study were objective outcomes (rather than subjective descriptions), and the study was blinded, so there was no risk of incurring assessor bias.

Contextual suitability

The PROMISE trial was built on a plausible biological basis and encouraging preliminary trial data, and directly answered calls from national bodies to address the possibility that progesterone therapy in early pregnancy could be beneficial to women with a history of unexplained RM. Although clinical equipoise existed, the lack of definitive knowledge or policy guidance for health services practitioners allowed considerable variations in care. The PROMISE trial answered an important question.

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Other strengths

There is increasing recognition of the need for clinical research to embrace the views of both lay and professional stakeholders.[64] In the PROMISE trial, PPI occurred at stages of design, development and monitoring. For example, patients were surveyed to assess the acceptability of the intervention, and engaged in the development of literature for participants, and the TSC included representatives of patient advocacy organisations. We believe these roles were important to ensure appropriate communication with study participants and project oversight throughout the duration of the research.

The trial intervention was deliverable within the context of customary care without major impacts on health service structure. The mode of administration of IMP was designed to reflect the preferences expressed by patients, and most of our data collection could be performed during routine antenatal and postnatal appointments of the study participants.

Limitations and critique

This study is the largest randomised, placebo-controlled trial of progesterone ever conducted in RM, and we consider the trial to be methodologically robust. Nevertheless, it remains possible to observe some limitations.

The potential criticisms of our trial include (1) non-measurement of serum progesterone levels at the time of randomisation, (2) possibly suboptimal dose, (3) possible mistiming of treatment, (4) possibly insufficient duration of treatment, (5) possibly inappropriate pharmacological preparation or route of administration, (6) dilution of treatment effect by factors such as breaches of protocol and loss to follow-up, and (7) narrow and uncertain economic analyses. We examine these issues individually below.

1. Our collection of baseline data for the study population did not include serum progesterone levels at the time of randomisation. None of the existing four trials of first-trimester progesterone therapy for pregnant women with a history of unexplained RM had checked progesterone levels before treatment. Furthermore, serum or salivary progesterone measurements may not accurately reflect progesterone levels and effects at the feto–maternal interface. Finally, PROMISE investigators believed that it would be important to know whether or not progesterone therapy could assist women with RM regardless of their progesterone levels before commencing therapy.

2. The dosage of vaginal progesterone that was adopted by the PROMISE trial (400 mg twice daily) sits at the higher end of the spectrum of biological effect according to the SmPC and the BNF. Our choice was made after a careful review of the existing literature, an extensive survey of clinicians in the UK (see *Chapter 1, Existing knowledge, Progesterone in clinical use for recurrent miscarriages*) and other related evidence such as recommended dosages for luteal support in assisted conception.[16] Therefore, we believe that the outcome of the study is unlikely to be affected by the possibility of suboptimal dosage.

3. Some have suggested that progesterone supplementation could be more effective in reducing the risk of miscarriage if it is administered during the luteal phase of reproduction, prior to confirmation of pregnancy.[6,79–81] Although plausible, this was not the research question that the PROMISE trial set out to address. When the research question for the PROMISE trial was being discussed and debated, the evidence overwhelmingly suggested that the most useful question to answer would be on the effects of progesterone in the first trimester (not during the luteal phase). The evidence was summarised by a review from Cochrane[82] and our update of this review,[5] which identified four trials of progesterone supplementation during the first trimester, but **none** during the luteal phase. All four first-trimester trials suggested promising beneficial effects on miscarriage reduction (see *Chapter 1, Existing knowledge, Progesterone in clinical use for recurrent miscarriages*). Thus, the pursuit of this question was the most rational option, endorsed by a wide body of clinicians, patients and other stakeholders.

4. As many as 80% of miscarriages occur before 12 weeks,[83] and pregnancies that continue beyond 12 weeks rarely miscarry, as observed in the PROMISE trial itself (see *Chapter 3, Outcomes and estimation, Secondary outcomes*). Corpus luteal function is replaced by placental production of progesterone before the end of the first trimester. Therefore, we consider that progesterone supplementation beyond the first trimester of pregnancy is unlikely to be associated with any further clinical benefit than may be postulated during this early stage. Moreover, the median age of gestation among PROMISE participants who experienced miscarriage was < 8 weeks (7.3 weeks in the progesterone group and 7.1 weeks in the placebo group).

5. An immunomodulatory effect of progesterone at the trophoblastic–decidual interface is the key presumed mechanism for preventing RM.[3,33–35] Our choice of administration via the vaginal route was, therefore, rational to deliver a greater proportion of drug to the relevant site (the uterus) using the 'first uterine pass' effect.[36,37] Furthermore, studies of vaginal progesterone in the prevention of preterm birth have shown its effectiveness when given via this route.[19,21,22] Therefore, we believe that any alternative preparation or route of administration is unlikely to result in a greater effect.

6. We recruited and followed up to completion more PROMISE participants than were calculated as necessary to detect a MID between the study treatment groups. Moreover, although we found pill counting to be a poor tool for compliance assessment, deviations were insufficient to compromise the validity of the study findings. The pragmatic nature of the trial intervention was also important to test its effect in everyday clinical practice.

7. The economic analysis has two main limitations. First, it could be suggested that the perspective taken on costs was narrow by solely focusing on perinatal resource use. Second, the economic modelling utilised to estimate wider costs and QALYs related to treatment rested on underlying assumptions, so the results should be interpreted with caution.

Interpretation

Our findings show that women with a history of unexplained RM do not benefit from first-trimester progesterone therapy for any of the key clinical outcomes that we observed. Importantly, our findings are not consistent with the findings of several smaller and poor-quality controlled studies that reported benefit from progesterone supplementation during the first trimester of pregnancy.

An updated review[11] from Cochrane recognised the weaknesses of the trials that pre-dated the PROMISE trial. The review reported that the four trials in which participants had a previous history of three or more miscarriages (the same as participants in the PROMISE trial) 'were of poorer methodological quality', and called for further research.

The PROMISE trial has added to the available safety data regarding the use of progesterone during early pregnancy. The low rate of AEs observed among mothers and neonates of the PROMISE trial, consistent with the background rate, suggests that progesterone therapy in early pregnancy is safe. This is an important evidence finding because progesterone therapy is commonly used as part of assisted conception treatment.

Generalisability

Centres participating in the study were geographically spread across the UK and in the Netherlands, improving the generalisability of the results for women suffering RM. In PROMISE, exclusion criteria were kept to a minimum and the heterogeneity of the RM population was well reflected by trial participants. The study is, therefore, better applied to assess effectiveness than efficacy.

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Chapter 6 Conclusions

In this chapter, we address considerations for the delivery of clinical services and recommendations for future research.

Implications for health care

The key findings of the PROMISE trial are clear and sufficiently generalisable to inform clinical practice. On the basis of the results of this study, first-trimester progesterone therapy does not appear to have clinically significant benefits in pregnant women with a history of unexplained RM. However, it is evident that progesterone at a dose of 400 mg twice daily appears safe to the mother and the fetus. This reassuring information is useful to women who may be taking progesterone for other reasons, for example as part of assisted conception treatment. Indeed, our finding that progesterone does not reduce the risk of miscarriage in pregnant women with a history of RM should not be construed as evidence of the performance of progesterone for other indications such as IVF treatment.

Our economic analysis indicated that prescribing progesterone increases mean total costs by £327.64. This may suggest that the marginal benefit observed justifies the marginal cost. However, the uncertainties must be considered. For example, should a decision-maker be willing to pay £100,000 to increase the chances of an additional live birth after at least 24 weeks of gestation, the probability that this strategy would be cost-effective is < 70%. Alternatively, extrapolating health gains in terms of QALYs suggests the probability that progesterone would fall within the NICE threshold of £20,000–£30,000 per QALY as between 0.7145 and 0.7341. As the magnitude of health gain seems much lower than previously anticipated and remains uncertain, further research may be advised.

Recommendations for research

In our opinion, no further research is necessary to evaluate the role of first-trimester progesterone in the prevention of miscarriage for women with a history of unexplained RM. The PROMISE trial has not addressed questions such as the effectiveness of progesterone therapy during the luteal phase of the menstrual cycle, or whether or not progesterone therapy for patients who have **threatened** miscarriage could be beneficial.[68] Future large randomised controlled trials, specifically designed to answer these questions, are required.

Our economic analysis demonstrated uncertainty in the expected gains of treatment, given the available sample. However, the magnitude of the estimated health benefits, although non-significant and lower than previously anticipated, may raise an empirical question of the value that the NHS or society might associate with decreasing the level of statistical uncertainty surrounding the current point estimate. Future research might also consider estimating the value of further research using value of information analysis.[84,85]

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All of the following named authors contributed substantially to the development of the research question and study design, implementation, analysis and/or interpretation of data and submission of the final report.

Particular contributions are denoted below:

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Miss Helen Williams (Research Associate, Women's Health) was responsible for completion of data gathering, providing data quality assurance, co-ordination of the analysis and the writing groups, and preparation of the initial draft of the final report.

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Other contributors to programme development and implementation

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Data sharing statement

Non-identifiable data will be made available as appropriate for research purposes following an application to the corresponding author.

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Appendix 1 Sample participant information sheet

[local hospital header]

PROMISE – PROGESTERONE IN RECURRENT MISCARRIAGE STUDY

Participant Information Sheet

We would like to invite you to take part in a research study. Whether you take part or not is entirely your choice. You do not have to take part, nor give a reason why you decide not to. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully.

We want to see whether progesterone hormone pessaries reduce the chance of a miscarriage in women who have previously had three or more miscarriages. This study is called the PROMISE trial; "PRO" referring to Progesterone and "MISE" referring to Miscarriage.

- Part One of this information sheet tells you the purpose of this study and what will happen to you if you take part.
- Part Two of this information sheet gives you more detailed information about the conduct of the study.

Please ask us if there is anything that is not clear or if you would like more information.

PART ONE

What is the purpose of the study?

The purpose of this study is to find out whether treating women with history of recurrent miscarriage with progesterone, a natural pregnancy hormone, from the time of a positive pregnancy test until 12 weeks of pregnancy decreases their chance of miscarrying.

Why have I been invited?

You have been invited to take part in the study as you have a history of recurrent miscarriage for which no underlying cause has been found.

Do I have to take part?

No. It is up to you whether or not you take part. If you wish to take part, you will be given this information sheet to keep and will be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect your medical care or maternity care in any way.

What will happen to me if I take part?

If you decide to take part in the study, and have signed the consent form, you don't need to do anything until you become pregnant (and have a positive urine or blood pregnancy test). Once this happens, we want you to let the research nurse know, by telephone as soon as possible. The phone number to call is given on the last page of this information sheet. You will probably be about 4 weeks pregnant (four weeks from the last menstrual period) at this time. When the

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research nurse receives your call, she will ask you some details about this pregnancy and recheck your clinical history to make sure you are still eligible to take part in the study.

If you remain eligible, the nurse will arrange the study pessaries to be dispensed to you. You will be asked to take two pessaries – either vaginally or rectally – twice daily (in the morning and at bedtime), from the time you receive them from us to 12 weeks of pregnancy (We will let you know when you need to stop taking the pessaries). These pessaries will either be progesterone or identical looking dummy pessaries. We do not know if progesterone will help reduce the risk of miscarriage at all, and that is why we need to compare women who take progesterone with others who take the dummy pessaries.

Whether you get the progesterone or dummy pessaries will be decided by a computer. The computer will allocate treatment randomly, like tossing a coin, to decide whether you should receive progesterone or dummy pessaries. You will have an equal chance of receiving progesterone or the dummy pessaries. You will not know which, and neither will the doctors, nurses or researchers looking after you (although they will be able to find out if they need to).

The research nurse will be able to get most of your pregnancy outcome data from your hospital notes. But she may need to contact you to complete the outcome data if these are not available in your or your baby's notes. We may ask you to come and see us so we can get all the information we need. We would also like your permission to follow up your baby's long-term health. At the conclusion of the study, we will let you know of the findings through your preferred method of contact.

What will I have to do?

All you have to do is to keep the pessaries in a safe place, and take two pessaries in the morning and two pessaries in the evening. It is not necessary to take the pessaries at exactly the same time every day. If you forget to take the pessaries, don't worry. If it has been less than six hours from when you would have normally taken it, please take the pessaries as soon as possible, and continue the rest of the pessaries as usual. If it has been more than six hours from when you would have normally taken the pessaries, please omit these pessaries, and take the next lot of pessaries at the usual time.

In the event of you losing the pessaries, please let us know, and we will get you a further supply of the same type of pessaries as soon as possible.

You will be given enough vaginal pessaries to last you until 12 weeks of pregnancy. Each packet will contain enough pessaries for four weeks (112 pessaries). At the end of each 4 weeks, please post back the packet, either empty or with any unused pessaries. You will be given free-post envelopes to post the packets back to your hospital. Your research nurse will contact you by telephone to make sure everything is okay if you do not return the packets. If you lose your envelopes, please use another and write the freepost address, making sure your study number is on the envelope. That way you won't need a stamp.

What is the drug being tested?

We are testing progesterone hormone pessaries (versus a dummy pessaries), at a dose of 400mg (two pessaries at 200mg each), twice daily. Progesterone is a naturally occurring female hormone. It is commonly used in IVF (test-tube baby) practice and to prevent preterm birth.

What are the other possible disadvantages and risks of taking part?

Side effects with progesterone pessaries are rare or minor. Previous studies on natural progesterone treatment did not report any serious side-effects to the mother or the baby. However, reported side effects of progesterone include fluid retention, bloating, headache, sleeplessness, diarrhoea and jaundice. We do not anticipate any problems for those taking part in this study. If you have any concerns, please contact the research nurse (details on the last page of this information sheet). If you become unwell, please contact your general practitioner, accident and emergency services, or ambulance services, as appropriate.

What are the possible benefits of taking part?

We do not know if the study will help you personally, but the information we will get may help improve the pregnancy outcome for women in the future.

How is progesterone administered?

Both the progesterone and the placebo (inactive drug) are in the form of pessaries (capsules). We would ask you to give yourself two capsules twice a day ideally by placing them in the vagina – rather like using a tampon. Alternatively, you can use the capsules as suppositories – inserting them into the rectum.

What if there is a problem? What if something goes wrong?

If you have a complaint about the way you have been treated during the study or any other matter, you can make a complaint. There is more detailed information in Part Two of this leaflet.

Will my taking part in this study be kept confidential?

Yes. The study will follow ethical and legal practice and all the information about your participation in this study will be kept confidential. Details about this are included in Part Two of this leaflet.

This completes Part One of the information sheet.

If the information in Part One has interested you and you are considering participating, please read the additional information in Part Two before making any decision.

PART TWO

What if relevant new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, we will tell you and discuss whether you should continue in the study. If you decide not to carry on, we will make arrangements for your care to continue. If you decide to continue in the study we may ask you to sign an updated consent form.

If the study is stopped for any other reason, we will tell you and arrange your continuing care.

What will happen if I do not want to carry on with the study?

If you decide to take part and then change your mind you are free to withdraw at any time without giving a reason (although it would be useful to know why). Your treatment will not be affected in any way.

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If you withdraw from the study, we will ask your permission to keep in touch with you to know the outcome of your pregnancy and to use such information in our analysis.

Keeping in contact

Until 12 weeks of pregnancy, you will be seen at your normal early pregnancy unit at regular intervals according to local policy. After this time, the research nurse will contact you by telephone at 20, 26, 34 and 38 weeks of pregnancy. The purpose of these telephone calls is to maintain contact and to enquire regarding the progress of your pregnancy. Such questions, which would have been routinely asked at your antenatal visits, may include specific enquires as to whether you have experienced any complications such as issues regarding blood pressure and growth of the baby. It is important to state that at all times the management of your pregnancy rests with the obstetricians and midwives at the hospital at which you have booked for antenatal care and delivery.

After delivery

After delivery, we will ask your permission to contact the hospital at which you delivered to obtain data on the outcome of your pregnancy (including any complications you may have had); the gestation at delivery; mode of delivery; baby's sex and birthweight and any complications the baby may have had after delivery.

What if there is a problem?

Complaints

If you have a concern about any aspect of this study, you should ask to speak to the local research nurse or doctor who will do their best to answer your questions (contact details can be found at the end of this information sheet). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from your hospital. You can contact the Patients Advisory and Liaison Service (PALS) or you can write to the Chief Executive of the hospital. You have the same rights whether or not you take part in this study.

Harm

Imperial College London holds insurance policies which apply to this study. If you experience harm as a result of taking part in this study, you may be eligible to claim compensation without having to prove that Imperial College is at fault. Adverse pregnancy outcomes (for example miscarriage or stillbirth) not directly related to study medication or conduct will not be eligible for compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator (Mr Raj Rai, Imperial College London). The normal National Health Service complaints mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial College Clinical Research Governance Office.

Will my taking part in this study be kept confidential?

Yes. All information collected from you for the purposes of this study will be kept strictly confidential in the same way as your medical records. Any information used outside the hospital or university will have any identifying details removed so that your data remains completely anonymous. All information will be held securely and in strict confidence. You will not be identified in any publication of results from this study. Occasionally, inspections of clinical study data are undertaken to ensure that, for example, all participants have given consent to take part. But apart from this, only study organisers will have access to the data.

Involvement of your General Practitioner

We will inform your general practitioner of your participation in the study if you agree.

What will happen to the results of the research study?

When the results of the PROMISE study are known, we will inform you of the overall results of the study as well as which pessaries you were taking (through your preferred method of contact). We will also publish the results of the study in medical journal(s). We will make the information available on our website for the general public.

Who is organising the research?

The research is organised by Imperial College, London, UK, and managed and coordinated by the University of Birmingham, UK. No private or commercial companies are involved in the organisation or management of this study.

Who is funding the research?

The National Institute for Health Research (NIHR) has funded this study. The research nurses working on this project have their salaries paid by this organisation. The other nurses and doctors do not receive any payment if you help with this research.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable ethical opinion by West Midlands Research Ethics Committee.

Do you have any further questions?

Having read this leaflet and discussed with the research nurse or doctor, we hope that you will choose to take part in the PROMISE study. If you have any questions about the study now or later, please feel free to ask your nurse or doctor, or contact the research nurse at [research nurse name and contact details], or the trial manager at [redacted].

The UK Clinical Research Collaboration has produced a guide entitled, 'Understanding Clinical Trials'. This can be downloaded from their website: www.ukcrn.org.uk and could be useful if you require general information about research.

You will be given a copy of the information sheet and a signed consent form to keep.

Thank you for taking time to read this sheet and for considering taking part in the study.

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Appendix 2 Sample consent form

[local hospital header]

PROMISE – Progesterone in Recurrent Miscarriage Study

Chief Investigator: Dr Raj Rai, Imperial College, London

CONSENT FORM

Please initial the boxes below:

I have read the information sheet for the PROMISE study (version [], dated 14/10/2009) and have had the opportunity to consider the information, ask questions, and have these answered satisfactorily.

I understand that participation in this study is entirely voluntary and that I am free to withdraw at any time, without giving a reason and without my medical care being affected.

I understand that my medical notes will be looked at by members of the research team, and by regulatory bodies auditing research practice.

I consent to taking part in the PROMISE study, which will require me taking the study pessaries vaginally or rectally.

I agree to face-to-face and telephone interviews to gather the outcome data from the study.

I consent to gathering of data from my baby following his/her birth.

I agree to my baby being followed up in the future, and understand this may involve tracing through NHS databases and GP records.

I agree to my GP being informed of my participation in the study.

Name [name]

Date of Birth [DoB]
Hospital ID [Pt ID]

Address [address]

Signed (participant) [signature]
Date [date]

Signed (research nurse/midwife/doctor) [signature]
Date [date]

Print name (research nurse/midwife/doctor) [signature]
Date [date]

Signed (witness, where appropriate) [signature]
Date [date]

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Appendix 3 Definitions of adverse events, seriousness and causality

Adverse event

Any untoward medical occurrence in a participant, which does not necessarily have a causal relationship with the trial intervention.

In the context of the PROMISE trial, an AE was considered to be:

- any unintentional, unfavourable clinical sign or symptom, including complications of miscarriage (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.

In the context of the PROMISE trial, the circumstances listed below were NOT considered to be AEs:

- miscarriage or intrauterine death
- a pre-existing condition (unless it worsened significantly during treatment)
- routine diagnostic and therapeutic procedures likely in a normal pregnancy.

Adverse reaction

Any untoward and unintended responses to the trial intervention, at any dose administered, including all AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to the trial intervention.

Unexpected adverse reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information.

Seriousness

Any AE, adverse reaction or unexpected adverse reaction that at any dose:

- results in death or immediately threatens life (NOT an event which hypothetically might have caused death if it were more severe)
- results in hospitalisation or longer than anticipated stay in hospital
- results in persistent or significant disability or incapacity
- results in a congenital anomaly or birth defect.

Medical judgement may be exercised in deciding seriousness in other situations. Important AEs or reactions that are not immediately life-threatening or do not result in death or hospitalisation may be considered serious if they jeopardise the subject or require intervention to prevent one of the other outcomes listed in the definition above.

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In the context of the PROMISE trial, events NOT considered to be SAEs were hospitalisations for events that were expected, such as:

- routine treatment or monitoring of miscarriage or threatened preterm birth, not associated with any deterioration in condition
- elective or pre-planned treatment for a pre-existing condition that was 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
- outpatient treatment 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 (such as pre-eclampsia, urinary tract infection, pyelonephritis).

Unrelated causality

No evidence of any causal relationship with the trial intervention.

Unlikely causal relationship

Little evidence to suggest a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication) or another reasonable explanation for the event (e.g. another clinical condition or other concomitant treatment).

Possible causal relationship

Some evidence to suggest a causal relationship (e.g. occurrence within a reasonable time after administration of the trial medication), but other factors may have contributed to the event (e.g. another clinical condition or other concomitant treatment).

Probable causal relationship

Evidence to suggest a causal relationship; the influence of other factors is unlikely.

Definite causal relationship

Some evidence to suggest a causal relationship (e.g. occurrence within a reasonable time after administration of the trial medication), but other factors may have contributed to the event (e.g. another clinical condition or other concomitant treatment).

Causal relationship not assessable

Insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

Appendix 4 Sample general practitioner letter

Dr [name]

[address]

Date: [date]

Re: [patient identifier]

Dear Dr [name],

This lady has kindly agreed to participate in the PROMISE trial (A multi-centre randomised placebo-controlled trial of progesterone in spontaneously conceived women with a history of unexplained recurrent miscarriages). The study is funded by the NIHR HTA programme, and has an ethical approval from the West Midlands Research Ethics Committee.

Your patient will be randomised to take either progesterone pessaries (400mg twice daily) or identical placebo, from the time of diagnosis of pregnancy to 12 completed weeks of pregnancy. Since this is a double-blind study, neither the participant, nor the investigators will know which treatment your patient has been allocated to. Your patient has the contact details of the research nurse in case of difficulties.

We do not anticipate that your patient's participation in the study will impact on your care of her, and we will not ask you to carry out any study related investigations or interventions.

This letter is for information only.

If you wish any further details, please feel free to contact either myself or the research nurse for the study [research nurse name and contact details]. A copy of the Participant Information Sheet for the PROMISE trial is enclosed.

Thank you for your support,

Yours sincerely,

Dr Arri Coomarasamy, MBChB, MD, MRCOG

Trial manager for the PROMISE study

Consultant Gynaecologist and Subspecialist in Reproductive Medicine

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Appendix 5 Other information

This appendix provides miscellaneous details of study registration and development, to ensure transparent identification and adherence of the PROMISE trial to appropriate governance.

Registration

Current Controlled Trials ISRCTN92644181; EudraCT number: 2009-011208-42; REC 09/H1208/44.

Funding

This study was funded by the National Institute for Health Research Health Technology Assessment programme, in a research award to Imperial College London/Imperial College Healthcare NHS Trust. No commercial funding was sought for this trial. Participants were not paid to take part in the trial, nor did they receive any incentives or other benefits. The funders of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the report.

Insurance and indemnity

Imperial College London provided negligent and non-negligent harm insurance for the trial, and arranged insurance and/or indemnity to meet the potential legal liability of the sponsor for harm to participants arising from the design, conduct and management of the research. Imperial College London held a policy with Zurich Municipal in case of harm with no legal liability.

Protocol versions

Table 16 demonstrates the development of the PROMISE trial protocol.

TABLE 16 Previous protocol documents

Version	Description
1.0	Circulation for internal and external peer-review before submission to the Medical Research Council
2.0	Outline submission to Medical Research Council (which was shortlisted by Medical Research Council and handed over to the NIHR HTA programme for processing)
3.0	Submission to the NIHR HTA (incorporating recommendations of Medical Research Council and NIHR HTA reviewers)
4.0	Submission to the REC (dated 15 July 2009)
5.0	Acceptance by the REC (dated 28 September 2009)
6.0	Addition and amendment of research sites (dated 26 November 2010)
6.1	Clarification that 'delivery to participant' included 'delivery to participants' home addresses' added (dated 15 April 2011)
6.2	Amendment of the date to end recruitment to 31 July 2013 (dated 1 November 2012; URL: www.nets.nihr.ac.uk/__data/assets/pdf_file/0018/52911/PRO-08–38–01.pdf)
6.3	Clarification that recruited participants will not be eligible for randomisation if they are unable to conceive within a year of recruitment or before the end of randomisation period, whichever comes earlier (dated 30 May 2013)

HTA, Health Technology Assessment; NIHR, National Institute for Health Research.

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