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This report

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Abstract

Does progesterone prophylaxis to prevent preterm labour improve outcome? A randomised double-blind placebo-controlled trial (OPPTIMUM)

Jane E Norman,[1]* Neil Marlow,[2] Claudia-Martina Messow,[3] Andrew Shennan,[4] Philip R Bennett,[5] Steven Thornton,[6] Stephen C Robson,[7] Alex McConnachie,[3] Stavros Petrou,[8] Neil J Sebire,[2] Tina Lavender,[9] Sonia Whyte[1] and John Norrie[10] for the OPPTIMUM study group

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Background: Progesterone prophylaxis is widely used to prevent preterm birth but is not licensed and there is little information on long-term outcome.

Objective: To determine the effect of progesterone prophylaxis in women at high risk of preterm birth on obstetric, neonatal and childhood outcomes.

Design: Double-blind, randomised placebo-controlled trial.

Setting: Obstetric units in the UK and Europe between February 2009 and April 2013.

Participants: Women with a singleton pregnancy who are at high risk of preterm birth because of either a positive fibronectin test or a negative fibronectin test, and either previous spontaneous birth at ≤ 34 weeks^{+0} of gestation or a cervical length of ≤ 25 mm.

Interventions: Fibronectin test at 18^{+0} to 23^{+0} weeks of pregnancy to determine risk of preterm birth. Eligible women were allocated (using a web-based randomisation portal) to 200 mg of progesterone or placebo, taken vaginally daily from 22^{+0} to 24^{+0} until 34^{+0} weeks' gestation. Participants, caregivers and those assessing the outcomes were blinded to group assignment until data collection was complete.

Main outcome measures: There were three primary outcomes, as follows: (1) obstetric – fetal death or delivery before 34^{+0} weeks' gestation; (2) neonatal – a composite of death, brain injury on ultrasound scan (according to specific criteria in the protocol) and bronchopulmonary dysplasia; and (3) childhood – the Bayley-III cognitive composite score at 22–26 months of age.

Results: In total, 96 out of 600 (16%) women in the progesterone group and 108 out of 597 (18%) women in the placebo group had the primary obstetric outcome [odds ratio (OR) 0.86, 95% confidence interval (CI) 0.61 to 1.22]. Forty-six out of 589 (8%) babies of women in the progesterone group and 62 out of 587 (11%) babies of women in the placebo group experienced the primary neonatal outcome [OR 0.72, 95% CI 0.44 to 1.17]. The mean Bayley-III cognitive composite score of the children at 2 years of age was 97.3 points [standard deviation (SD) 17.9 points; $n = 430$] in the progesterone group and 97.7 points (SD 17.5 points; $n = 439$) in the placebo group (difference in means –0.48, 95% CI –2.77 to 1.81).

Limitations: Overall compliance with the intervention was 69%.

Harms: There were no major harms, although there was a trend of more deaths from trial entry to 2 years in the progesterone group (20/600) than in the placebo group (16/598) (OR 1.26, 95% CI 0.65 to 2.42).

Conclusions: In this study, progesterone had no significant beneficial or harmful effects on the primary obstetric, neonatal or childhood outcomes.The OPPTIMUM trial is now complete. We intend to participate in a comprehensive individual patient-level data meta-analysis examining women with a singleton pregnancy with a variety of risk factors for preterm birth.

Trial registration: Current Controlled Trials ISRCTN14568373.

Funding: This trial was funded by the Medical Research Council (MRC) and managed by the National Institute for Health Research (NIHR) on behalf of the MRC–NIHR partnership.

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List of abbreviations

17α-OHP	17α-hydroxyprogesterone caproate
BMI	body mass index
CI	confidence interval
eCRF	electronic case report form
EME	Efficacy and Mechanism Evaluation
EQ-5D	EuroQol-5 Dimensions
FDA	Food and Drug Administration
fFN	fetal fibronectin
IDMC	Independent Data Monitoring Committee
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	intention to treat
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
NIHR	National Institute for Health Research
OR	odds ratio
PP	per protocol
PPI	patient and public involvement
RCB	Robertson Centre for Biostatistics
SAE	serious adverse event
SmPC	Summary of Product Characteristics
TSC	Trial Steering Committee

Plain English summary

Progesterone is widely used to prevent preterm birth (birth of the baby before 37 weeks' gestation), but it has not been approved by government bodies for this purpose. Additionally, we do not know how progesterone will affect the baby in the longer term. We wanted to find out what effect progesterone given to women at high risk of preterm birth would have on rates of preterm birth, the health of the newborn baby and the health of the offspring at the age of 2 years.

In total, 1197 women at risk of preterm birth helped with the study. We did a test to look at the risk of preterm birth in those who agreed. We gave half of the women who were at increased risk progesterone and the other half a dummy treatment (placebo). Neither the women nor the researchers knew which treatment the women were getting until the end of the study. We recorded how long pregnancy lasted and the health of the baby shortly after birth and at 2 years of age.

We found that progesterone had no significant benefits or harms on either the rate of preterm birth or the health of the baby. This means that progesterone might not be helpful for women at risk of preterm birth. This information should be considered by expert groups making guidelines and doctors advising pregnant women, and needs to be discussed with pregnant women considering taking it. Potentially, this research could prevent the exposure of large numbers of pregnant women and their babies to unnecessary progesterone.

Scientific summary

Background

Progesterone prophylaxis is widely used to prevent preterm birth, but does not have licensing approval, and there is little information on long-term outcome.

Objective

To determine the effect of progesterone prophylaxis in women at high risk of preterm birth on obstetric, neonatal and childhood outcomes.

Design

Double-blind, randomised placebo-controlled trial.

Setting

Obstetric units in the UK and Europe.

Participants

Women with a singleton pregnancy who were at a high risk of preterm birth.

Interventions

Fibronectin test at 18^{+0} to 23^{+0} weeks of pregnancy to determine the risk of preterm birth. Women with a positive fibronectin test and selected women with a negative fibronectin test were randomised to 200 mg of progesterone or placebo taken vaginally from 22^{+0} to 24^{+0} weeks' until 34^{+0} weeks' gestation.

Main outcome measures

There were three primary outcomes, as follows: (1) obstetric – fetal death or delivery before 34^{+0} weeks' gestation; (2) neonatal – a composite of death, brain injury on ultrasound scan (according to specific criteria in the protocol) and bronchopulmonary dysplasia; and (3) childhood – the Bayley-III cognitive composite score at 22–26 months of age.

Results

In total, 96 out of 600 (16%) women in the progesterone group and 108 out of 597 (18%) women in the placebo group experienced the primary obstetric outcome [odds ratio (OR) 0.86, 95% confidence interval (CI) 0.61 to 1.22]. Forty-six out of 589 (8%) babies of women in the progesterone group and 62 out of 587 (11%) babies of women in the placebo group experienced the primary neonatal outcome [OR 0.72,

95% CI 0.44 to 1.17]. The Bayley-III cognitive composite score at age 2 years for the child was 97.3 points [standard deviation (SD) 17.9 points] in the progesterone group and 97.7 points (SD 17.5 points) in the placebo group (difference in means –0.48, 95% CI –2.77 to 1.81).

Limitations

Overall compliance with the intervention was 69%.

Conclusions

In this study, progesterone had no significant beneficial or harmful effects on the primary obstetric, neonatal or childhood outcome.

Future work

We hope to participate in a comprehensive individual patient-level data meta-analysis examining women with a singleton pregnancy and with a variety of risk factors for preterm birth.

Trial registration

This trial is registered as ISRCTN14568373.

Funding

This trial was funded by the Medical Research Council (MRC) and managed by the National Institute for Health Research (NIHR) on behalf of the MRC–NIHR partnership.

Chapter 1 Introduction

The OPPTIMUM study was conceived in 2007, after two large randomised trials[1,2] suggested that progestogens prevent preterm delivery and may improve neonatal outcomes. At the conception of the study, we firmly believed that understanding the long-term effects of progesterone on the baby (either good or bad) would be important for both women and caregivers in deciding when preterm birth prophylaxis with progesterone would be important.

By the time OPPTIMUM was completed in 2015, the question of the long-term effects of progesterone, when given for preterm birth prophylaxis, remained important. Preterm birth is the single biggest cause of neonatal mortality and morbidity, with rates of 7.6% in the UK in 2015.[3] Although there has been a modest decline in rates of preterm birth in the USA since 2006, to 11.4% in 2013,[4] no such change has been observed in the UK. Worldwide, 15 million babies are born preterm each year, accounting for 2 million deaths within the first month after birth and 77 million disability-adjusted life-years, 3.1% of the global total.[5] The economic burden is huge.

Since starting OPPTIMUM in 2008, further randomised trials have been published examining the efficacy of progestogens to prevent preterm birth. One of two formulations of progestogen are commonly used: (1) a synthetic hormone, 17α-hydroxyprogesterone caproate (17α-OHP), injected intramuscularly; and (2) 'natural' progesterone, usually administered vaginally. Several systematic reviews, the most recent by the Cochrane collaboration,[6] and one individual patient-level data meta-analysis[7] have summarised the effect of progestogens on obstetric and neonatal outcomes. We performed a literature search on 11 July 2016 to identify any randomised trials in which asymptomatic women with a singleton pregnancy were given progesterone or progestogens with the aim of preventing preterm birth that were published since the search date of the Cochrane meta-analysis (January 2013). The only relevant published study was OPPTIMUM,[8] the study described in this report.

The Cochrane review[6] summarises the data by preterm birth risk (e.g. previous preterm birth or cervical shortening). In women with a previous preterm birth, progestogen prophylaxis reduces preterm birth before 34 weeks' gestation, perinatal mortality, birthweight of < 2500 g and rates of neonatal death (*Table 1*).

In women with cervical shortening, progestogens reduce the risk of preterm birth before 34 weeks' gestation, but have no significant effect on perinatal mortality, birthweight of < 2500 g or neonatal death (*Table 2*).

In contrast, in the individual patient-level data meta-analysis[7] restricted to women with cervical shortening, progesterone prophylaxis reduced both rates of preterm birth and composite adverse neonatal outcomes with relative risks of 0.58 and 0.57, respectively (*Table 3*).

TABLE 1 Effects of progestogens compared with placebo on preterm birth and associated complications in women with a previous preterm birth. Data from Dodd *et al.*[6]

Outcome	Progesterone group, *n*/*N*	Placebo group, *n*/*N*	Risk ratio	95% CI
Preterm birth < 34 weeks' gestation	30/302	78/300	0.31	0.14 to 0.69
Perinatal mortality	35/801	59/652	0.50	0.33 to 0.75
Birthweight of < 2500 g	94/418	97/274	0.58	0.42 to 0.79
Neonatal death	21/801	39/652	0.45	0.27 to 0.76

CI, confidence interval.

TABLE 2 Progestogens vs. placebo in women with cervical shortening. Data from Dodd *et al.*[6]

Outcome	Progesterone group, *n*/*N*	Placebo group, *n*/*N*	Risk ratio	95% CI
Preterm birth < 34 weeks' gestation	41/219	64/219	0.64	0.45 to 0.90
Perinatal mortality	21/698	28/691	0.74	0.42 to 1.29
Birthweight of < 2500 g	188/693	202/686	0.92	0.78 to 1.09
Neonatal death	11/791	20/780	0.55	0.26 to 1.13

CI, confidence interval.

TABLE 3 Individual patient-level data meta-analysis on vaginal progesterone in women with a short cervix. Data from Romero *et al.*[7]

Outcome	Relative risk	95% CI
Preterm birth before 33 weeks' gestation	0.58	0.42 to 0.80
Respiratory distress syndrome	0.48	0.30 to 0.76
Composite neonatal morbidity and mortality	0.57	0.40 to 0.81

CI, confidence interval.

The reasons for the discrepancy in results for the outcomes for women with a short cervix are not clear. It is possible that the additional statistical power conferred by analysis of the individual patient-level data is responsible for the significant reduction reported in the Romero *et al.*[7] paper but not the Cochrane review.[6] Alternative explanations are that 17α-OHP is ineffective in women with a short cervix and that inclusion of these data in the Cochrane review,[6] but not in the Romero *et al.*[7] paper, accounts for the difference in results. Regardless, there is a consensus from both these systematic reviews[6,7] that progesterone prevents preterm birth, at least in women with a short cervix, but disagreement about whether or not this reduction in preterm birth is associated with improved outcomes for the baby.

17α-hydroxyprogesterone caproate (Makena®; Amag Pharmaceuticals, Waltham, MA, USA) is the only progestogen licensed for preterm birth prevention in the USA, with the licensing application having been supported by data from the Meis *et al.*[9] trial. The indication for use is to reduce preterm birth in women with a history of spontaneous preterm birth in a previous singleton pregnancy, where the index pregnancy is a singleton pregnancy.[10]

Although 17α-OHP and progesterone are both progestogens, they are somewhat different drugs and may have different effects. A licensing application was submitted to the US Food and Drug Administration (FDA) for progesterone based on data from a large randomised trial of progesterone to prevent preterm birth in women with a short cervix,[11] but the FDA advisory panel voted 13 to 4 against it.[12]

The primary rationale for the OPPTIMUM study was that the long-term effects of progesterone prophylaxis to prevent preterm birth on the child are unknown. It is plausible that preventing preterm birth could be harmful: preterm birth is known to be associated with high rates of intrauterine infection and/or inflammation,[13] and intrauterine infection is known to have deleterious effects on the baby.[14] The absence of adverse effects in the short term does not mean that there will be no long-term harm. For example, in the ORACLE II trial,[15,16] maternal administration of antibiotics to prevent preterm birth had no effect on the baby in the short term, but there was an increase in the rate of cerebral palsy at 7 years of age with each of co-amoxicillin and erythromycin, with some evidence of higher rates when both antibiotics were given together.

Hence, the purpose of the OPPTIMUM study was to determine whether or not, in women at high risk of preterm labour, 200 mg of prophylactic vaginal natural progesterone, inserted once daily from 22 to 34 weeks' gestation, compared with placebo:

i. improves obstetric outcome by lengthening pregnancy and, thus, reduces the incidence of preterm delivery (before 34 weeks' gestation)
ii. improves neonatal outcome by reducing a composite of death and major morbidity
iii. leads to improved childhood cognitive and neurosensory outcomes at age 2 years.

A successful grant application was submitted to the Medical Research Council (MRC) in 2007 to test these hypotheses.

Chapter 2 Methods

The OPPTIMUM study methodology is described in detail in the published protocol[17] and in the 'working' protocol of this paper. An abbreviated version is also described in the main publication[8] summarising the results of the study.

Study design

In summary, this was a randomised controlled double-masked study. The participants were pregnant women at risk of preterm birth, and were approached in, and recruited from, one of 65 antenatal clinics in the UK and one antenatal clinic in Sweden between February 2009 and April 2013. The study was in two phases: (1) a screening phase and (2) a treatment phase.

Inclusion and exclusion criteria

Eligibility for the screening phase was conferred by the inclusion criteria of:

- all women aged ≥ 16 years
- gestational age established by scan at ≤ 16 weeks to ensure that the estimated date of delivery was accurate (or the consultant had to be confident that the gestation dates were accurate)
- signed consent form
- one of the following – history in a previous pregnancy of either previous preterm birth; second trimester loss (at ≥ 16 weeks' or ≤ 37 weeks' gestation); preterm premature rupture of the fetal membranes (≤ 37 weeks' gestation); or, in this pregnancy, a short cervical length (≤ 25 mm) on ultrasound scan at 18^{+0} to 24^{+0} weeks' gestation or a previous history of any cervical procedure to treat abnormal smears (i.e. large loop excision, laser conisation, cold knife conisation or radical diathermy).

Exclusion criteria were:

- known significant congenital structural or chromosomal fetal anomaly
- known sensitivity or contraindication to or intolerance of progesterone (listed contraindications including known allergy or hypersensitivity to progesterone, severe hepatic dysfunction, undiagnosed vaginal bleeding, mammary or genital tract carcinoma, thrombophlebitis, thromboembolic disorders, cerebral haemorrhage and porphyria)
- suspected or proven rupture of the fetal membranes at the time of recruitment
- multiple pregnancy
- prescription or ingestion of medications known to interact with progesterone (e.g. bromocriptine, rifamycin, ketoconazole or ciclosporin)
- women currently prescribed progesterone or who have taken progesterone beyond 18 weeks' gestation.

In the early phases of the study, the excipient of the study drug contained arachis (peanut) oil; hence, those with peanut allergies were excluded. However, midway through the study, the excipient was changed to sunflower oil. Once the supply of a drug containing arachis oil was removed, peanut allergy was removed as a contraindication; hence, two Summary of Product Characteristics (SmPCs) are shown in *Appendix 1*.

Interventions

Women participating in the screening phase had a fibronectin test performed between 18^{+0} and 23^{+6} weeks' gestation inclusive. Initially, eligibility for the treatment phase was conferred only by a positive fibronectin test result. However, as described in the published protocol,[17] these criteria were changed partway through the study, when we realised that we were missing women at medium risk of preterm birth. Thereafter, eligibility for the treatment phase was conferred by eligibility for the screening phase and any of i–iii:

i. a positive fetal fibronectin (fFN) test in combination with a history in a previous pregnancy of any of preterm birth, second trimester loss, premature fetal membrane rupture or a positive fFN test in combination with a history of cervical procedure to treat abnormal smears
ii. history in a previous pregnancy of spontaneous preterm birth at, or before, 34^{+0} weeks' gestation (regardless of the fFN test result)
iii. a cervical length in this pregnancy of ≤ 25 mm (regardless of the fFN test result).

Women recruited into the treatment phase were randomised to treatment with either 200 mg of progesterone inserted (by the participant) vaginally once daily from 22–24 weeks' gestation to 34^{+0} weeks' gestation, or to an identical-appearing placebo. Progesterone and placebo were in the form of a pessary.

The dose used was 200 mg daily. The choice of dose was pragmatic and relied on efficacy and safety outcomes from existing studies, given that the mechanism of action was (and still is) uncertain and the plasma (and/or uterine) concentration of progesterone required to reduce preterm delivery was (and still is) unknown. When the study was planned, the doses of vaginal progesterone used in completed trials were 100 mg ($n = 142$)[2] or 200 mg;[18] 200 mg was the dose that UK obstetricians were using off-label for preterm birth prevention. A variety of doses were used in subsequent large trials, including 90 mg daily[11] and 200 mg daily.[18] With no indication of any safety issue at any dose, we believed it was prudent to use the higher dose to minimise the risk of using a dose lower than the minimal clinically effective dose.

There was no restriction on prior or concomitant therapy, other than women who were currently prescribed or taking progesterone or who had taken progesterone beyond 18 weeks' gestation in the index pregnancy. Administration of other agents or strategies aimed at preventing preterm birth (e.g. cervical cerclage) or improving the outcome (e.g. tocolytics or corticosteroids for fetal lung maturation) were not prohibited. We recorded the number of women who had cervical cerclage.

Governance and oversight

Quality assurance of the data was achieved by following data management procedures at the study data centre [Robertson Centre for Biostatistics (RCB)] and data monitoring at study sites. Data management at the RCB was carried out in accordance with a prespecified management plan. The electronic case report form (eCRF) included point-of-entry validation checks. During the trial, additional data validation checks were carried out periodically, with data queries issued to study sites for resolution. Prior to database lock, final data validation checks were carried out and all queries were resolved, when possible. During the trial, study statisticians produced reports for the Trial Steering Committee (TSC) and Independent Data Monitoring Committee (IDMC). Issues of data quality identified by study statisticians were reported to study data management staff and queried when appropriate, and/or included in future routing data validation checks. TSC and IDMC meetings provided opportunities for external, independent review of summary data, with additional feedback on potential data quality issues being incorporated into ongoing data quality checks.

Data monitoring at study sites consisted of on-site periodic monitoring and site closure visits including a review of 100% consent forms and participant eligibility and a 10% check of primary outcome data against the eCRF. Site initiation visits were conducted at all participating sites. This included a site set-up

visit consisting of protocol, eCRF and procedure training for staff. Further onsite monitoring and closure visits were conducted, each included a review of investigator site files, site delegation logs, staff qualifications and training (Good Clinical Practice, curricula vitae), and pharmacy documentation.

Outcomes

The primary outcomes for the study were obstetric (fetal death or delivery before 34^{+0} weeks' gestation), neonatal [a composite of death, brain injury on ultrasound scan (according to specific criteria in the protocol) and bronchopulmonary dysplasia] and childhood (the Bayley-III cognitive composite score at 22–26 months of age).

Secondary outcomes are as listed in the protocol. Definitions for both primary and secondary outcomes are listed in the protocol. A statistical analysis plan was prepared and finalised before data lock, unblinding and data analysis and is shown in *Appendix 2*. In brief, data were analysed by intention to treat (ITT), with supplementary sensitivity analyses of a per-protocol (PP) data set and with multiple imputation for missing data. Additional exploratory subgroup analyses were performed. Mixed-effects logistic regression or linear regression was used to compare outcomes between the treatment groups, with study centre as a random effect and treatment allocation and previous pregnancy ($\geq$ 14 weeks) as fixed effects. *p*-values for the primary analysis of the primary outcomes were adjusted for multiple comparisons.

This trial is registered as ISRCTN14568373.

A summary of the study was registered on the International Standard Randomised Controlled Trial Number (ISRCTN) register (reference number 14568373). The study was also registered with the Medicines and Healthcare products Regulatory Agency (MHRA) (22931/0009/001-0001, later revised to 01384/0208/001-0007) and received ethics approval from the Scotland A Research Ethics Committee (reference 08/MRE00/6). Oversight of the study was performed by a TSC and a Data Monitoring Committee (see Norman *et al.*[8] for more details).

There was no formal patient and public involvement (PPI) in the design of the study, although the clinicians involved in study design informally consulted the pregnant women they were looking after. PPI in study oversight was achieved through participation of two successive individual patient representatives on the TSC (the second was recruited after the first was unable to continue because of other commitments) and by participation of a charity representative, Jane Brewin. As a chief executive office of Tommy's baby charity, Jane Brewin acted as a 'voice' for women undergoing preterm birth.

We were aware that securing childhood outcome data would be one of the challenges of the study, given the long interval between birth and interaction with the study team, and the invitation to the Bayley-III cognitive composite score test. We used the following strategies to increase contact with participants (i.e. the pregnant woman): sending them a letter immediately after birth, a letter at 6 months, a questionnaire at 12 months, a card and teddy bear gift for the child's first birthday, a further 12-month reminder, a letter at 18 months and a birthday card and a small gift for the child at 2 years of age. Partway through the study we also set up a Facebook (www.facebook.com; Facebook, Inc., Menlo Park, CA, USA) page with pictures of the babies (permission and pictures were supplied by the parents) and began to offer a £50 voucher for participation in the Bayley-III cognitive composite score test. We also asked for details of a third person as a contact point (often the participant's own mother) and we used this strategy to access difficult-to-contact women, including those who had moved after the birth of their child.

The study was reported in accordance with CONSORT (Consolidated Standards of Reporting Trials) guidelines.[19]

Chapter 3 Results

Recruitment and retention

Recruitment and retention to the study is described in the original paper.[8] Briefly, 15,132 patient records were reviewed for eligibility, 5833 women were tested with a fFN test, 1228 women were randomly assigned and 1226 were part of the ITT population. Follow-up data were obtained for 1197 women for the obstetric outcome, 1176 babies for the neonatal outcome and 869 children for the childhood outcome.

Demographic and other baseline characteristics

The baseline characteristics and other demographics of participating women (by treatment allocation) are shown in *Tables 4* and *5*.

TABLE 4 Inclusion criteria at randomisation: ITT population. Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by treatment

		Trial group	
Criterion	All	Placebo	Progesterone
History of delivery/pregnancy loss at ≥ 16 and < 37 weeks' gestation			
N_{obs} (N_{miss})	1225 (1)	610 (0)	615 (1)
No, *n* (%)	118 (9.6)	61 (10.0)	57 (9.3)
Yes, *n* (%)	1107 (90.4)	549 (90.0)	558 (90.7)
Previous preterm premature rupture of fetal membranes before or at 37 weeks' gestation			
N_{obs} (N_{miss})	1225 (1)	610 (0)	615 (1)
No, *n* (%)	581 (47.4)	312 (51.1)	269 (43.7)
Yes, *n* (%)	644 (52.6)	298 (48.9)	346 (56.3)
Cervical length of ≤ 25 mm on ultrasound scan at 18^{+0} to 24^{+0} weeks' gestation			
N_{obs} (N_{miss})	1225 (1)	610 (0)	615 (1)
No, *n* (%)	1000 (81.6)	506 (83.0)	494 (80.3)
Yes, *n* (%)	225 (18.4)	104 (17.0)	121 (19.7)
Any cervical procedure to treat abnormal smears			
N_{obs} (N_{miss})	1196 (30)	594 (16)	602 (14)
No, *n* (%)	1000 (83.6)	502 (84.5)	498 (82.7)
Yes, *n* (%)	196 (16.4)	92 (15.5)	104 (17.3)
Positive fFN test at 22–24 weeks' gestation			
N_{obs} (N_{miss})	1225 (1)	610 (0)	615 (1)
No, *n* (%)	882 (72.0)	430 (70.5)	452 (73.5)
Yes, *n* (%)	343 (28.0)	180 (29.5)	163 (26.5)

continued

TABLE 4 Inclusion criteria at randomisation: ITT population. Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by treatment (*continued*)

Criterion	All	Trial group	
		Placebo	Progesterone
Negative fFN test at 22–24 weeks' gestation and previous spontaneous preterm birth before or at 34 weeks' gestation			
N_{obs} (N_{miss})	1175 (51)	585 (25)	590 (26)
No, *n* (%)	337 (28.7)	179 (30.6)	158 (26.8)
Yes, *n* (%)	838 (71.3)	406 (69.4)	432 (73.2)
Negative fFN test at 22–24 weeks' gestation and cervical length of ≤ 25 mm between 18 and 24 weeks' gestation in index pregnancy			
N_{obs} (N_{miss})	1175 (51)	585 (25)	590 (26)
No, *n* (%)	1057 (90.0)	532 (90.9)	525 (89.0)
Yes, *n* (%)	118 (10.0)	53 (9.1)	65 (11.0)

N_{miss}, number of women with missing data; N_{obs}, number of observations.

TABLE 5 Baseline characteristics at randomisation: ITT population. Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by treatment

Characteristic	All	Trial group	
		Placebo	Progesterone
Age (years)			
N_{obs} (N_{miss})	1225 (1)	610 (0)	615 (1)
Mean (SD)	31.4 (5.7)	31.4 (5.8)	31.5 (5.6)
Median (IQR)	31.5 (27.4–35.7)	31.4 (27.2–35.7)	31.5 (27.6–35.6)
Range	16.8–49.2	17.5–49.2	16.8–45.9
Height (cm)			
N_{obs} (N_{miss})	1221 (5)	607 (3)	614 (2)
Mean (SD)	163.5 (6.6)	163.6 (6.4)	163.5 (6.7)
Median (IQR)	163.0 (159.0–168.0)	163.0 (159.0–168.0)	164.0 (159.0–168.0)
Range	144.0–183.0	144.0–183.0	147.0–183.0
Weight (kg)			
N_{obs} (N_{miss})	1221 (5)	607 (3)	614 (2)
Mean (SD)	71.6 (17.1)	71.4 (16.7)	71.9 (17.5)
Median (IQR)	68.0 (60.0–81.0)	68.0 (59.0–82.0)	68.0 (60.0–80.0)
Range	41.0–186.0	43.0–145.0	41.0–186.0
BMI (kg/m^2)			
N_{obs} (N_{miss})	1221 (5)	607 (3)	614 (2)
Mean (SD)	26.8 (6.3)	26.7 (6.1)	26.9 (6.4)
Median (IQR)	25.5 (22.3–29.8)	25.4 (22.2–29.7)	25.6 (22.5–29.8)
Range	15.2–80.5	15.6–54.4	15.2–80.5

TABLE 5 Baseline characteristics at randomisation: ITT population. Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by treatment (*continued*)

Characteristic	All	Trial group	
		Placebo	Progesterone
Systolic blood pressure (mmHg)			
N_{obs} (N_{miss})	1219 (7)	608 (2)	611 (5)
Mean (SD)	111.9 (12.4)	112.4 (12.2)	111.3 (12.5)
Median (IQR)	110.0 (102.0–120.0)	110.0 (104.0–120.0)	110.0 (100.0–120.0)
Range	78.0–189.0	78.0–159.0	82.0–189.0
Diastolic blood pressure (mmHg)			
N_{obs} (N_{miss})	1219 (7)	608 (2)	611 (5)
Mean (SD)	66.0 (8.6)	66.2 (8.6)	65.7 (8.5)
Median (IQR)	65.0 (60.0–71.0)	66.0 (60.0–71.0)	64.0 (60.0–70.0)
Range	40.0–104.0	41.0–104.0	40.0–98.0
Smoking			
N_{obs} (N_{miss})	1220 (6)	607 (3)	613 (3)
No, *n* (%)	984 (80.7)	482 (79.4)	502 (81.9)
Yes, *n* (%)	236 (19.3)	125 (20.6)	111 (18.1)
Alcohol consumption			
N_{obs} (N_{miss})	1223 (3)	609 (1)	614 (2)
No, *n* (%)	1160 (94.8)	575 (94.4)	585 (95.3)
Yes, *n* (%)	63 (5.2)	34 (5.6)	29 (4.7)
Drug use			
N_{obs} (N_{miss})	1223 (3)	609 (1)	614 (2)
No, *n* (%)	1206 (98.6)	600 (98.5)	606 (98.7)
Yes, *n* (%)	17 (1.4)	9 (1.5)	8 (1.3)
In full-time education			
N_{obs} (N_{miss})	1216 (10)	607 (3)	609 (7)
No, *n* (%)	1175 (96.6)	590 (97.2)	585 (96.1)
Yes, *n* (%)	41 (3.4)	17 (2.8)	24 (3.9)
Years in full-time education			
N_{obs} (N_{miss})	1122 (53)	568 (22)	554 (31)
Mean (SD)	13.5 (3.1)	13.5 (3.0)	13.5 (3.1)
Median (IQR)	13.0 (11.0–16.0)	13.0 (11.0–16.0)	13.0 (11.0–16.0)
Range	1.0–31.0	1.0–30.0	3.0–31.0
Educated in the UK			
N_{obs} (N_{miss})	1206 (20)	602 (8)	604 (12)
No, *n* (%)	211 (17.5)	109 (18.1)	102 (16.9)
Yes, *n* (%)	995 (82.5)	493 (81.9)	502 (83.1)

continued

TABLE 5 Baseline characteristics at randomisation: ITT population. Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by treatment (*continued*)

Characteristic	All	Trial group	
		Placebo	Progesterone
Highest level of education if in the UK			
N_{obs} (N_{miss})	975 (20)	488 (5)	487 (15)
No formal qualifications, *n* (%)	99 (10.2)	56 (11.5)	43 (8.8)
Entry Level Certificate/Foundation Diploma, *n* (%)	13 (1.3)	6 (1.2)	7 (1.4)
GCSE/Standard/O Level, *n* (%)	327 (33.5)	164 (33.6)	163 (33.5)
A Level, AS Level, Highers, BTEC, *n* (%)	137 (14.1)	70 (14.3)	67 (13.8)
Certificate of Higher Education/City & Guilds, *n* (%)	53 (5.4)	25 (5.1)	28 (5.7)
Diploma HE/FE/HND/HNC, *n* (%)	69 (7.1)	33 (6.8)	36 (7.4)
Graduate certificate, diploma, *n* (%)	14 (1.4)	10 (2.0)	4 (0.8)
Degree, *n* (%)	158 (16.2)	72 (14.8)	86 (17.7)
Professional qualifications, *n* (%)	40 (4.1)	19 (3.9)	21 (4.3)
PG certificate, diploma, masters, doctorate, *n* (%)	65 (6.7)	33 (6.8)	32 (6.6)
Ethnic group			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
White, *n* (%)	895 (73.1)	446 (73.2)	449 (73.0)
Chinese, *n* (%)	1 (0.1)	1 (0.2)	0 (0.0)
Other ethnic group, *n* (%)	17 (1.4)	5 (0.8)	12 (2.0)
Mixed			
White/black Caribbean, *n* (%)	17 (1.4)	8 (1.3)	9 (1.5)
White/black African, *n* (%)	3 (0.2)	0 (0.0)	3 (0.5)
White/Asian, *n* (%)	2 (0.2)	1 (0.2)	1 (0.2)
Other mixed background, *n* (%)	6 (0.5)	3 (0.5)	3 (0.5)
Asian			
Indian, *n* (%)	30 (2.5)	16 (2.6)	14 (2.3)
Pakistani, *n* (%)	45 (3.7)	23 (3.8)	22 (3.6)
Bangladeshi, *n* (%)	5 (0.4)	4 (0.7)	1 (0.2)
Other Asian background, *n* (%)	23 (1.9)	7 (1.1)	16 (2.6)
Black			
Caribbean, *n* (%)	47 (3.8)	27 (4.4)	20 (3.3)
African, *n* (%)	119 (9.7)	59 (9.7)	60 (9.8)
Other black background, *n* (%)	14 (1.1)	9 (1.5)	5 (0.8)

TABLE 5 Baseline characteristics at randomisation: ITT population. Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by treatment (*continued*)

Characteristic	All	Trial group	
		Placebo	Progesterone
Ethnic group			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
White, *n* (%)	895 (73.1)	446 (73.2)	449 (73.0)
Black, *n* (%)	180 (14.7)	95 (15.6)	85 (13.8)
Asian, *n* (%)	104 (8.5)	51 (8.4)	53 (8.6)
Mixed, *n* (%)	28 (2.3)	12 (2.0)	16 (2.6)
Other, *n* (%)	17 (1.4)	5 (0.8)	12 (2.0)
Gestation at fFN test, weeks			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
Mean (SD)	22.9 (0.6)	22.9 (0.6)	22.9 (0.6)
Median (IQR)	22.9 (22.4–23.4)	22.9 (22.4–23.4)	22.9 (22.4–23.4)
Range	21.7–27.1	22.0–27.1	21.7–26.6
Fetal anomaly scan done			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
No, *n* (%)	63 (5.1)	34 (5.6)	29 (4.7)
Yes, *n* (%)	1163 (94.9)	576 (94.4)	587 (95.3)
Fetal anomaly scan result			
N_{obs} (N_{miss})	1163 (0)	576 (0)	587 (0)
Normal, *n* (%)	1150 (98.9)	569 (98.8)	581 (99.0)
Defined abnormality, *n* (%)	7 (0.6)	4 (0.7)	3 (0.5)
Uncertain abnormality, *n* (%)	6 (0.5)	3 (0.5)	3 (0.5)
Amniocentesis done			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
No, *n* (%)	1218 (99.3)	607 (99.5)	611 (99.2)
Yes, *n* (%)	8 (0.7)	3 (0.5)	5 (0.8)
Results of amniocentesis			
N_{obs} (N_{miss})	8 (0)	3 (0)	5 (0)
Normal, *n* (%)	8 (100.0)	3 (100.0)	5 (100.0)
Other, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Chorionic villus sampling done			
N_{obs} (N_{miss})	1225 (1)	610 (0)	615 (1)
No, *n* (%)	1216 (99.3)	607 (99.5)	609 (99.0)
Yes, *n* (%)	9 (0.7)	3 (0.5)	6 (1.0)

continued

TABLE 5 Baseline characteristics at randomisation: ITT population. Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by treatment (*continued*)

Characteristic	All	Trial group	
		Placebo	Progesterone
Results of chorionic villus sampling			
N_{obs} (N_{miss})	9 (0)	3 (0)	6 (0)
Normal, *n* (%)	9 (100.0)	3 (100.0)	6 (100.0)
Other, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Cervical length (mm)			
N_{obs} (N_{miss})	712 (514)	351 (259)	361 (255)
Mean (SD)	28.5 (10.8)	28.8 (11.1)	28.2 (10.6)
Median (IQR)	30.0 (22.0–36.0)	30.0 (22.5–36.0)	30.0 (22.0–36.0)
Range	0.0–84.0	0.0–84.0	0.0–58.0
Risk			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
Low, *n* (%)	882 (71.9)	429 (70.3)	453 (73.5)
High, *n* (%)	344 (28.1)	181 (29.7)	163 (26.5)
Any previous pregnancy			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
No, *n* (%)	52 (4.2)	28 (4.6)	24 (3.9)
Yes, *n* (%)	1172 (95.8)	581 (95.4)	591 (96.1)
Number of previous pregnancies			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
Mean (SD)	2.6 (2.0)	2.7 (1.9)	2.6 (2.0)
Median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)
Range	0.0–14.0	0.0–12.0	0.0–14.0
Any previous pregnancy of ≥ 14 weeks' gestation			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
No, *n* (%)	75 (6.1)	38 (6.2)	37 (6.0)
Yes, *n* (%)	1149 (93.9)	571 (93.8)	578 (94.0)
Number of previous pregnancies of ≥ 14 weeks' gestation			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
Mean (SD)	1.9 (1.4)	1.9 (1.4)	1.9 (1.4)
Median (IQR)	2.0 (1.0–2.0)	2.0 (1.0–3.0)	2.0 (1.0–2.0)
Range	0.0–13.0	0.0–10.0	0.0–13.0
Any previous live birth			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
No, *n* (%)	197 (16.1)	97 (15.9)	100 (16.3)
Yes, *n* (%)	1027 (83.9)	512 (84.1)	515 (83.7)

TABLE 5 Baseline characteristics at randomisation: ITT population. Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by treatment (*continued*)

Characteristic	All	Trial group	
		Placebo	Progesterone
Number of previous live births			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
Mean (SD)	1.5 (1.3)	1.6 (1.3)	1.5 (1.3)
Median (IQR)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)
Range	0.0–13.0	0.0–10.0	0.0–13.0
Any previous pregnancy that ended with baby alive and well			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
No, *n* (%)	646 (52.8)	321 (52.7)	325 (52.8)
Yes, *n* (%)	578 (47.2)	288 (47.3)	290 (47.2)
Number of previous pregnancies that ended with baby alive and well			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
Mean (SD)	0.8 (1.2)	0.8 (1.2)	0.8 (1.2)
Median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)
Range	0.0–13.0	0.0–10.0	0.0–13.0
History of induced labour or elective caesarean section			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
No, *n* (%)	1065 (87.0)	524 (86.0)	541 (88.0)
Yes, *n* (%)	159 (13.0)	85 (14.0)	74 (12.0)
History of miscarriage			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
No, *n* (%)	701 (57.3)	335 (55.0)	366 (59.5)
Yes, *n* (%)	523 (42.7)	274 (45.0)	249 (40.5)
History of ectopic pregnancy			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
No, *n* (%)	1193 (97.5)	600 (98.5)	593 (96.4)
Yes, *n* (%)	31 (2.5)	9 (1.5)	22 (3.6)
History of termination of pregnancy			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
No, *n* (%)	1085 (88.6)	542 (89.0)	543 (88.3)
Yes, *n* (%)	139 (11.4)	67 (11.0)	72 (11.7)
History of termination of pregnancy before 14 weeks' gestation			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
No, *n* (%)	1106 (90.2)	554 (90.8)	552 (89.6)
Yes, *n* (%)	120 (9.8)	56 (9.2)	64 (10.4)

continued

TABLE 5 Baseline characteristics at randomisation: ITT population. Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by treatment (*continued*)

Characteristic	All	Trial group	
		Placebo	Progesterone
History of termination of pregnancy at ≥ 14 weeks' gestation			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
No, *n* (%)	1201 (98.0)	596 (97.7)	605 (98.2)
Yes, *n* (%)	25 (2.0)	14 (2.3)	11 (1.8)
History of live birth followed by neonatal death			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
No, *n* (%)	1059 (86.5)	524 (86.0)	535 (87.0)
Yes, *n* (%)	165 (13.5)	85 (14.0)	80 (13.0)
History of live birth followed by death other than neonatal			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
No, *n* (%)	1208 (98.7)	604 (99.2)	604 (98.2)
Yes, *n* (%)	16 (1.3)	5 (0.8)	11 (1.8)
History of stillbirth			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
No, *n* (%)	1129 (92.2)	561 (92.1)	568 (92.4)
Yes, *n* (%)	95 (7.8)	48 (7.9)	47 (7.6)

A Level, Advanced Level; AS Level, Advanced Subsidiary Level; BMI, body mass index; BTEC, Business and Technology Education Council; FE, Further Education; GCSE, General Certificate of Secondary Education; HE, Higher Education; HNC, Higher National Certificate; HND, Higher National Diploma; IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; O Level, ordinary level; PG, postgraduate; SD, standard deviation.

Baseline characteristics of women in each of the treatment groups

The statistical analysis output (see *Appendix 3*) shows demographics of participants for whom information on the obstetric outcome, neonatal outcome, childhood outcome and survival at 2 years of age was and was not available. Smokers and those without formal qualifications were somewhat over-represented among those for whom the outcomes were unavailable (e.g. for obstetric outcome smokers, 25% vs. 19.2%; and, for no formal qualifications, 25.0% vs. 9.8%), but there were no other obvious differences by outcome availability.

Primary outcomes

The primary outcomes for the study (by treatment group) are shown in *Table 6*.

Secondary outcomes

The secondary clinical outcomes for the study (again by treatment group) are shown in *Table 7*. Odds ratios (ORs) and 95% confidence intervals (CIs) for these outcomes are shown in the main paper.[8] For the neonatal outcome, there were outcomes on 587 babies in the placebo group and 589 babies in the progesterone group. Reasons for unavailability of outcomes in the placebo group were consent withdrawn

TABLE 6 Summaries of primary outcome measures for all patients and according to treatment groups

Outcome	All	Trial group		Adjusted OR or difference in means (95% CI)
		Placebo	Progesterone	
Death or delivery before 34 weeks				
N_{obs} (N_{miss})	1197 (29)	597 (13)	600 (16)	
No, *n* (%)	993 (83.0)	489 (81.9)	504 (84.0)	0.86 (0.61 to 1.22)
Yes, *n* (%)	204 (17.0)	108 (18.1)	96 (16.0)	
Death, brain injury or severe chronic lung disease				
N_{obs} (N_{miss})	1176 (50)	587 (23)	589 (27)	
No, *n* (%)	1068 (90.8)	525 (89.5)	543 (92.2)	0.72 (0.44 to 1.17)
Yes, *n* (%)	108 (9.2)	62 (10.6)	46 (7.8)	
Bayley-III cognitive composite score at age 2 years (children who are alive only)				
N_{obs} (N_{miss})	833 (393)	423 (187)	410 (206)	
Mean (SD), points	99.6 (14.9)	99.5 (15.0)	99.7 (14.7)	
Median (IQR), points	100.0 (90.0–105.0)	100.0 (90.0–105.0)	100.0 (90.0–110.0)	
Range, points	55.0–149.0	55.0–149.0	55.0–145.0	
Bayley-III cognitive composite score at age 2 years (scores imputed for deaths)				
N_{obs} (N_{miss})	869 (357)	439 (171)	430 (186)	
Mean (SD), points	97.5 (17.7)	97.7 (17.5)	97.3 (17.9)	–0.48 (–2.77 to 1.81)
Median (IQR), points	100.0 (90.0–105.0)	100.0 (90.0–105.0)	100.0 (90.0–105.0)	
Range, points	49.0–149.0	49.0–149.0	49.0–145.0	

CI, confidence interval; IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; OR, odds ratio; SD, standard deviation.

TABLE 7 Secondary clinical outcomes, by treatment group

Outcome	All	Trial group	
		Placebo	Progesterone
Summaries of secondary outcome measures at delivery and in the neonatal period for all patients and according to treatment groups			
Gestational age at delivery (weeks)			
N_{obs} (N_{miss})	1197 (29)	597 (13)	600 (16)
Mean (SD)	36.9 (4.2)	36.8 (4.2)	36.9 (4.1)
Median (IQR)	38.3 (35.7–39.6)	38.3 (35.4–39.7)	38.1 (36.0–39.4)
Range	22.4–42.7	22.4–42.7	23.0–42.1
Delivery before 34 weeks			
N_{obs} (N_{miss})	1197 (29)	597 (13)	600 (16)
No, *n* (%)	993 (83.0)	489 (81.9)	504 (84.0)
Yes, *n* (%)	204 (17.0)	108 (18.1)	96 (16.0)

continued

TABLE 7 Secondary clinical outcomes, by treatment group (*continued*)

Outcome	All	Trial group	
		Placebo	Progesterone
Fetal death (miscarriage or stillbirth)			
N_{obs} (N_{miss})	1197 (29)	597 (13)	600 (16)
No, *n* (%)	1182 (98.7)	590 (98.8)	592 (98.7)
Yes, *n* (%)	15 (1.3)	7 (1.2)	8 (1.3)
Neonatal death			
N_{obs} (N_{miss})	1197 (29)	597 (13)	600 (16)
No, *n* (%)	1180 (98.6)	589 (98.7)	591 (98.5)
Yes, *n* (%)	17 (1.4)	8 (1.3)	9 (1.5)
Brain injury			
N_{obs} (N_{miss})	1158 (68)	574 (36)	584 (32)
No, *n* (%)	1106 (95.5)	540 (94.1)	566 (96.9)
Yes, *n* (%)	52 (4.5)	34 (5.9)	18 (3.1)
Severe chronic lung disease			
N_{obs} (N_{miss})	1154 (72)	574 (36)	580 (36)
No, *n* (%)	1119 (97.0)	556 (96.9)	563 (97.1)
Yes, *n* (%)	35 (3.0)	18 (3.1)	17 (2.9)
Need for surfactant administration			
N_{obs} (N_{miss})	1156 (70)	573 (37)	583 (33)
No, *n* (%)	1064 (92.0)	528 (92.1)	536 (91.9)
Yes, *n* (%)	92 (8.0)	45 (7.9)	47 (8.1)
Necrotising enterocolitis			
N_{obs} (N_{miss})	1155 (71)	574 (36)	581 (35)
No, *n* (%)	1124 (97.3)	561 (97.7)	563 (96.9)
Yes, suspected, *n* (%)	16 (1.4)	5 (0.9)	11 (1.9)
Yes, medical treatment only, *n* (%)	10 (0.9)	4 (0.7)	6 (1.0)
Yes, required drain or laparotomy, *n* (%)	5 (0.4)	4 (0.7)	1 (0.2)
Infection			
N_{obs} (N_{miss})	1154 (72)	573 (37)	581 (35)
No, *n* (%)	1074 (93.1)	537 (93.7)	537 (92.4)
Yes, *n* (%)	80 (6.9)	36 (6.3)	44 (7.6)
Number of discrete episodes with positive blood culture in those with infection			
N_{obs} (N_{miss})	73 (7)	33 (3)	40 (4)
0, *n* (%)	37 (50.7)	14 (42.4)	23 (57.5)
1, *n* (%)	28 (38.4)	16 (48.5)	12 (30.0)
2, *n* (%)	7 (9.6)	3 (9.1)	4 (10.0)
4, *n* (%)	1 (1.4)	0 (0.0)	1 (2.5)

TABLE 7 Secondary clinical outcomes, by treatment group (*continued*)

Outcome	All	Trial group	
		Placebo	Progesterone
Number of discrete episodes with positive cerebrospinal fluid culture in those with infection			
N_{obs} (N_{miss})	74 (6)	34 (2)	40 (4)
0, *n* (%)	71 (95.9)	34 (100.0)	37 (92.5)
1, *n* (%)	2 (2.7)	0 (0.0)	2 (5.0)
2, *n* (%)	1 (1.4)	0 (0.0)	1 (2.5)
Highest level of care in delivery room			
N_{obs} (N_{miss})	1165 (61)	584 (26)	581 (35)
Minimal (none or tactile stimulation) , *n* (%)	924 (79.3)	456 (78.1)	468 (80.6)
Intubation plus chest compressions and/or adrenaline, *n* (%)	3 (0.3)	0 (0.0)	3 (0.5)
Suction, *n* (%)	7 (0.6)	4 (0.7)	3 (0.5)
Suction and facial O_2 only, *n* (%)	39 (3.3)	19 (3.3)	20 (3.4)
Mask ventilation only, *n* (%)	100 (8.6)	56 (9.6)	44 (7.6)
Intubation, *n* (%)	86 (7.4)	47 (8.0)	39 (6.7)
Intubation plus chest compressions, *n* (%)	6 (0.5)	2 (0.3)	4 (0.7)
Number of days of normal care			
N_{obs} (N_{miss})	1151 (75)	570 (40)	581 (35)
Mean (SD)	1.7 (2.0)	1.7 (2.3)	1.7 (1.6)
Median (IQR)	1.0 (1.0–2.0)	1.0 (0.0–2.0)	1.0 (1.0–2.0)
Range	0.0–28.0	0.0–28.0	0.0–12.0
Number of days of special care			
N_{obs} (N_{miss})	1151 (75)	570 (40)	581 (35)
Mean (SD)	3.5 (9.6)	4.2 (10.6)	2.9 (8.3)
Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–1.0)	0.0 (0.0–0.0)
Range	0.0–92.0	0.0–85.0	0.0–92.0
Number of days of level 2 care			
N_{obs} (N_{miss})	1149 (77)	569 (41)	580 (36)
Mean (SD)	2.2 (9.5)	2.2 (8.4)	2.1 (10.4)
Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Range	0.0–137.0	0.0–74.0	0.0–137.0
Number of days of level 1 care			
N_{obs} (N_{miss})	1149 (77)	569 (41)	580 (36)
Mean (SD)	1.9 (7.7)	1.8 (7.3)	1.9 (8.1)
Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Range	0.0–75.0	0.0–75.0	0.0–64.0
Maternal or child serious adverse events during pregnancy and birth[a]			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
No, *n* (%)	1097 (89.5)	540 (88.5)	557 (90.4)
Yes, *n* (%)	129 (10.5)	70 (11.5)	59 (9.6)

continued

TABLE 7 Secondary clinical outcomes, by treatment group (*continued*)

Outcome	All	Trial group	
		Placebo	Progesterone
Death or moderate/severe neurodevelopmental impairment			
N_{obs} (N_{miss})	818 (408)	419 (191)	399 (217)
No, *n* (%)	700 (85.6)	368 (87.8)	332 (83.2)
Yes, *n* (%)	118 (14.4)	51 (12.2)	67 (16.8)
Moderate/severe neurodevelopmental impairment			
N_{obs} (N_{miss})	782 (444)	403 (207)	379 (237)
No, *n* (%)	700 (89.5)	368 (91.3)	332 (87.6)
Yes, *n* (%)	82 (10.5)	35 (8.7)	47 (12.4)
Components of neurodevelopmental disability			
Motor			
N_{obs} (N_{miss})	917 (309)	456 (154)	461 (155)
No, *n* (%)	909 (99.1)	452 (99.1)	457 (99.1)
Yes, *n* (%)	8 (0.9)	4 (0.9)	4 (0.9)
Cognitive function			
N_{obs} (N_{miss})	913 (313)	452 (158)	461 (155)
No, *n* (%)	876 (95.9)	434 (96.0)	442 (95.9)
Yes, *n* (%)	37 (4.1)	18 (4.0)	19 (4.1)
Hearing			
N_{obs} (N_{miss})	931 (295)	465 (145)	466 (150)
No, *n* (%)	928 (99.7)	463 (99.6)	465 (99.8)
Yes, *n* (%)	3 (0.3)	2 (0.4)	1 (0.2)
Speech and language			
N_{obs} (N_{miss})	891 (335)	446 (164)	445 (171)
No, *n* (%)	859 (96.4)	432 (96.9)	427 (96.0)
Yes, *n* (%)	32 (3.6)	14 (3.1)	18 (4.0)
Vision			
N_{obs} (N_{miss})	913 (313)	466 (144)	447 (169)
No, *n* (%)	909 (99.6)	462 (99.1)	447 (100.0)
Yes, *n* (%)	4 (0.4)	4 (0.9)	0 (0.0)
Respiratory			
N_{obs} (N_{miss})	847 (379)	434 (176)	413 (203)
No, *n* (%)	837 (98.8)	431 (99.3)	406 (98.3)
Yes, *n* (%)	10 (1.2)	3 (0.7)	7 (1.7)
Gastrointestinal			
N_{obs} (N_{miss})	844 (382)	432 (178)	412 (204)
No, *n* (%)	831 (98.5)	428 (99.1)	403 (97.8)
Yes, *n* (%)	13 (1.5)	4 (0.9)	9 (2.2)

TABLE 7 Secondary clinical outcomes, by treatment group (*continued*)

Outcome	All	Trial group	
		Placebo	Progesterone
Renal			
N_{obs} (N_{miss})	848 (378)	434 (176)	414 (202)
No, *n* (%)	844 (99.5)	433 (99.8)	411 (99.3)
Yes, *n* (%)	4 (0.5)	1 (0.2)	3 (0.7)
Admitted to hospital			
N_{obs} (N_{miss})	850 (376)	434 (176)	416 (200)
No, *n* (%)	751 (88.4)	383 (88.2)	368 (88.5)
Yes, *n* (%)	99 (11.6)	51 (11.8)	48 (11.5)
Admitted to hospital for respiratory reason			
N_{obs} (N_{miss})	127 (1099)	63 (547)	64 (552)
No, *n* (%)	79 (62.2)	39 (61.9)	40 (62.5)
Yes, *n* (%)	48 (37.8)	24 (38.1)	24 (37.5)
Admitted to hospital for surgery			
N_{obs} (N_{miss})	118 (1108)	56 (554)	62 (554)
No, *n* (%)	96 (81.4)	49 (87.5)	47 (75.8)
Yes, *n* (%)	22 (18.6)	7 (12.5)	15 (24.2)
Admitted to hospital for other reason			
N_{obs} (N_{miss})	119 (1107)	56 (554)	63 (553)
No, *n* (%)	92 (77.3)	43 (76.8)	49 (77.8)
Yes, *n* (%)	27 (22.7)	13 (23.2)	14 (22.2)
Number of hospitalisations			
N_{obs} (N_{miss})	858 (368)	437 (173)	421 (195)
0, *n* (%)	750 (87.4)	386 (88.3)	364 (86.5)
1, *n* (%)	87 (10.1)	42 (9.6)	45 (10.7)
2, *n* (%)	15 (1.7)	5 (1.1)	10 (2.4)
3, *n* (%)	2 (0.2)	2 (0.5)	0 (0.0)
4, *n* (%)	2 (0.2)	1 (0.2)	1 (0.2)
7, *n* (%)	1 (0.1)	1 (0.2)	0 (0.0)
11, *n* (%)	1 (0.1)	0 (0.0)	1 (0.2)
Summaries of secondary outcome measures at 2-year follow-up for all patients and according to treatment groups: SDQ			
Emotional problems scale			
N_{obs} (N_{miss})	669 (557)	341 (269)	328 (288)
Mean (SD)	1.1 (1.2)	1.1 (1.2)	1.1 (1.2)
Median (IQR)	1.0 (0.0–2.0)	1.0 (0.0–1.0)	1.0 (0.0–2.0)
Range	0.0–10.0	0.0–10.0	0.0–7.0

continued

TABLE 7 Secondary clinical outcomes, by treatment group (*continued*)

Outcome	All	Trial group	
		Placebo	Progesterone
Conduct problems scale			
N_{obs} (N_{miss})	668 (558)	342 (268)	326 (290)
Mean (SD)	2.6 (1.8)	2.7 (1.8)	2.6 (1.8)
Median (IQR)	2.0 (1.0–4.0)	2.0 (1.0–4.0)	2.0 (1.0–3.8)
Range	0.0–10.0	0.0–10.0	0.0–8.0
Hyperactivity scale			
N_{obs} (N_{miss})	649 (577)	334 (276)	315 (301)
Mean (SD)	4.3 (2.3)	4.2 (2.4)	4.5 (2.3)
Median (IQR)	4.0 (3.0–6.0)	4.0 (2.0–6.0)	4.0 (3.0–6.0)
Range	0.0–10.0	0.0–10.0	0.0–10.0
Peer problems scale			
N_{obs} (N_{miss})	663 (563)	345 (265)	318 (298)
Mean (SD)	2.0 (1.6)	2.0 (1.7)	2.1 (1.6)
Median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)
Range	0.0–7.0	0.0–7.0	0.0–7.0
Prosocial scale			
N_{obs} (N_{miss})	659 (567)	339 (271)	320 (296)
Mean (SD)	6.1 (2.2)	6.3 (2.2)	5.9 (2.3)
Median (IQR)	6.0 (5.0–8.0)	6.0 (5.0–8.0)	6.0 (4.0–8.0)
Range	0.0–10.0	0.0–10.0	0.0–10.0
Total difficulties scale			
N_{obs} (N_{miss})	597 (629)	302 (308)	295 (321)
Mean (SD)	10.0 (4.9)	9.8 (4.9)	10.2 (4.9)
Median (IQR)	9.0 (7.0–12.0)	9.0 (6.0–12.0)	9.0 (7.0–13.0)
Range	0.0–30.0	0.0–30.0	0.0–30.0
Impact scale			
N_{obs} (N_{miss})	828 (398)	424 (186)	404 (212)
Mean (SD)	0.2 (1.1)	0.2 (1.0)	0.2 (1.2)
Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Range	0.0–10.0	0.0–10.0	0.0–10.0

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation; SDQ, Strengths and Difficulties Questionnaire.
a Up to and including day 1 after birth.

after initiation of treatment ($n = 18$), lost to follow-up ($n = 3$) and missing data ($n = 2$). In the progesterone group these figures were 13, 6 and 8, respectively; a further two women in the progesterone group withdrew consent before treatment was initiated. For the childhood outcome, there were outcomes on 439 children in the placebo group and 430 children in the progesterone group. Reasons for unavailability in the placebo group were consent withdrawn after initiation of treatment ($n = 42$), lost to follow-up ($n = 100$) and missing data ($n = 29$). In the progesterone group these figures were 45, 116 and 25, respectively, plus the two women in the progesterone group who withdrew before treatment was initiated.

Women's views on treatment were ascertained by questionnaire on two occasions post delivery (3 months and 6 months) and are shown in *Tables 8* and *9*, respectively.

The EuroQol-5 Dimensions (EQ-5D) health utility scores at various time points during the study, with changes between these time points, are shown in *Table 10*.

TABLE 8 Women's views on treatment at a mean of 3 months post delivery

Characteristic or view	All	Trial group	
		Placebo	Progesterone
Age of baby (days)			
N_{obs} (N_{miss})	612 (614)	317 (293)	295 (321)
Mean (SD)	94.6 (163.3)	100.9 (171.8)	87.8 (153.6)
Median (IQR)	17.0 (7.0–91.0)	21.0 (7.0–112.0)	14.0 (7.0–70.0)
Range	0.0–805.0	0.0–805.0	0.0–751.0
Preferred treatment mode			
N_{obs} (N_{miss})	613 (613)	314 (296)	299 (317)
Vaginal pessary, *n* (%)	434 (70.8)	222 (70.7)	212 (70.9)
Rectal pessary, *n* (%)	17 (2.8)	8 (2.5)	9 (3.0)
Injection, *n* (%)	158 (25.8)	82 (26.1)	76 (25.4)
Any, *n* (%)	2 (0.3)	0 (0.0)	2 (0.7)
Pessaries, *n* (%)	2 (0.3)	2 (0.6)	0 (0.0)
Enough information about trial participation			
N_{obs} (N_{miss})	639 (587)	330 (280)	309 (307)
Yes, *n* (%)	624 (97.7)	322 (97.6)	302 (97.7)
No, *n* (%)	15 (2.3)	8 (2.4)	7 (2.3)
Enough information about treatment			
N_{obs} (N_{miss})	640 (586)	331 (279)	309 (307)
Yes, *n* (%)	626 (97.8)	324 (97.9)	302 (97.7)
No, *n* (%)	14 (2.2)	7 (2.1)	7 (2.3)

continued

TABLE 8 Women's views on treatment at a mean of 3 months post delivery (*continued*)

Characteristic or view	All	Trial group	
		Placebo	Progesterone
Satisfaction with treatment			
N_{obs} (N_{miss})	634 (592)	327 (283)	307 (309)
Extremely satisfied, *n* (%)	445 (70.2)	244 (74.6)	201 (65.5)
Fairly satisfied, *n* (%)	163 (25.7)	70 (21.4)	93 (30.3)
Somewhat dissatisfied, *n* (%)	22 (3.5)	10 (3.1)	12 (3.9)
Extremely dissatisfied, *n* (%)	4 (0.6)	3 (0.9)	1 (0.3)
The treatment was messy			
N_{obs} (N_{miss})	628 (598)	325 (285)	303 (313)
Strongly agree and would not repeat treatment, *n* (%)	35 (5.6)	14 (4.3)	21 (6.9)
Agree but would still repeat treatment, *n* (%)	223 (35.5)	110 (33.8)	113 (37.3)
Neither agree nor disagree, *n* (%)	94 (15.0)	48 (14.8)	46 (15.2)
Disagree, *n* (%)	276 (43.9)	153 (47.1)	123 (40.6)
The treatment smelled unpleasant			
N_{obs} (N_{miss})	620 (606)	322 (288)	298 (318)
Strongly agree and would not repeat treatment, *n* (%)	19 (3.1)	9 (2.8)	10 (3.4)
Agree but would still repeat treatment, *n* (%)	40 (6.5)	18 (5.6)	22 (7.4)
Neither agree nor disagree, *n* (%)	75 (12.1)	43 (13.4)	32 (10.7)
Disagree, *n* (%)	486 (78.4)	252 (78.3)	234 (78.5)
The application of treatment was uncomfortable			
N_{obs} (N_{miss})	624 (602)	323 (287)	301 (315)
Strongly agree and would not repeat treatment, *n* (%)	37 (5.9)	19 (5.9)	18 (6.0)
Agree but would still repeat treatment, *n* (%)	125 (20.0)	64 (19.8)	61 (20.3)
Neither agree nor disagree, *n* (%)	121 (19.4)	62 (19.2)	59 (19.6)
Disagree, *n* (%)	341 (54.6)	178 (55.1)	163 (54.2)
The treatment interfered with sexual activity			
N_{obs} (N_{miss})	619 (607)	320 (290)	299 (317)
Strongly agree and would not repeat treatment, *n* (%)	33 (5.3)	16 (5.0)	17 (5.7)
Agree but would still repeat treatment, *n* (%)	154 (24.9)	68 (21.2)	86 (28.8)
Neither agree nor disagree, *n* (%)	145 (23.4)	90 (28.1)	55 (18.4)
Disagree, *n* (%)	287 (46.4)	146 (45.6)	141 (47.2)
The treatment stopped me working			
N_{obs} (N_{miss})	625 (601)	324 (286)	301 (315)
Strongly agree and would not repeat treatment, *n* (%)	17 (2.7)	12 (3.7)	5 (1.7)
Agree but would still repeat treatment, *n* (%)	11 (1.8)	8 (2.5)	3 (1.0)
Neither agree nor disagree, *n* (%)	28 (4.5)	16 (4.9)	12 (4.0)
Disagree, *n* (%)	569 (91.0)	288 (88.9)	281 (93.4)

TABLE 8 Women's views on treatment at a mean of 3 months post delivery (*continued*)

Characteristic or view	All	Trial group	
		Placebo	Progesterone
The treatment made me feel dirty			
N_{obs} (N_{miss})	624 (602)	324 (286)	300 (316)
Strongly agree and would not repeat treatment, *n* (%)	22 (3.5)	11 (3.4)	11 (3.7)
Agree but would still repeat treatment, *n* (%)	70 (11.2)	32 (9.9)	38 (12.7)
Neither agree nor disagree, *n* (%)	65 (10.4)	34 (10.5)	31 (10.3)
Disagree, *n* (%)	467 (74.8)	247 (76.2)	220 (73.3)
The treatment caused irritation			
N_{obs} (N_{miss})	625 (601)	322 (288)	303 (313)
Strongly agree and would not repeat treatment, *n* (%)	27 (4.3)	14 (4.3)	13 (4.3)
Agree but would still repeat treatment, *n* (%)	69 (11.0)	32 (9.9)	37 (12.2)
Neither agree nor disagree, *n* (%)	67 (10.7)	33 (10.2)	34 (11.2)
Disagree, *n* (%)	462 (73.9)	243 (75.5)	219 (72.3)
The treatment made me feel constipated			
N_{obs} (N_{miss})	625 (601)	323 (287)	302 (314)
Strongly agree and would not repeat treatment, *n* (%)	16 (2.6)	10 (3.1)	6 (2.0)
Agree but would still repeat treatment, *n* (%)	26 (4.2)	13 (4.0)	13 (4.3)
Neither agree nor disagree, *n* (%)	47 (7.5)	21 (6.5)	26 (8.6)
Disagree, *n* (%)	536 (85.8)	279 (86.4)	257 (85.1)
The treatment gave me backache			
N_{obs} (N_{miss})	624 (602)	324 (286)	300 (316)
Strongly agree and would not repeat treatment, *n* (%)	15 (2.4)	9 (2.8)	6 (2.0)
Agree but would still repeat treatment, *n* (%)	11 (1.8)	6 (1.9)	5 (1.7)
Neither agree nor disagree, *n* (%)	42 (6.7)	22 (6.8)	20 (6.7)
Disagree, *n* (%)	556 (89.1)	287 (88.6)	269 (89.7)
Panty liners or sanitary towels used?			
N_{obs} (N_{miss})	630 (596)	327 (283)	303 (313)
Yes, *n* (%)	412 (65.4)	212 (64.8)	200 (66.0)
No, *n* (%)	218 (34.6)	115 (35.2)	103 (34.0)
Number of towels used per day			
N_{obs} (N_{miss})	391 (835)	197 (413)	194 (422)
Mean (SD)	2.3 (1.4)	2.3 (1.4)	2.3 (1.3)
Median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)
Range	0.0–10.0	0.0–10.0	0.0–7.0

continued

TABLE 8 Women's views on treatment at a mean of 3 months post delivery (*continued*)

Characteristic or view	All	Trial group	
		Placebo	Progesterone
Did treatment interfere with daily activities?			
N_{obs} (N_{miss})	629 (597)	324 (286)	305 (311)
Yes, *n* (%)	11 (1.7)	8 (2.5)	3 (1.0)
No, *n* (%)	618 (98.3)	316 (97.5)	302 (99.0)
Was the frequency of appointment with health professional . . .			
N_{obs} (N_{miss})	608 (618)	311 (299)	297 (319)
Too often, *n* (%)	3 (0.5)	1 (0.3)	2 (0.7)
Enough, *n* (%)	583 (95.9)	302 (97.1)	281 (94.6)
Not enough, *n* (%)	22 (3.6)	8 (2.6)	14 (4.7)
How would you feel if treatment became normal practice?			
N_{obs} (N_{miss})	623 (603)	320 (290)	303 (313)
Disappointed, *n* (%)	6 (1.0)	3 (0.9)	3 (1.0)
Not sure, *n* (%)	168 (27.0)	89 (27.8)	79 (26.1)
Pleased, *n* (%)	449 (72.1)	228 (71.2)	221 (72.9)
If time went backwards, would you take part again?			
N_{obs} (N_{miss})	635 (591)	327 (283)	308 (308)
Definitely not, *n* (%)	6 (0.9)	4 (1.2)	2 (0.6)
Probably not, *n* (%)	21 (3.3)	9 (2.8)	12 (3.9)
Not sure, *n* (%)	37 (5.8)	19 (5.8)	18 (5.8)
Probably yes, *n* (%)	159 (25.0)	85 (26.0)	74 (24.0)
Definitely yes, *n* (%)	412 (64.9)	210 (64.2)	202 (65.6)
Did you have access to a health professional for medical support?			
N_{obs} (N_{miss})	632 (594)	325 (285)	307 (309)
Yes, *n* (%)	618 (97.8)	319 (98.2)	299 (97.4)
No, *n* (%)	14 (2.2)	6 (1.8)	8 (2.6)
Did you have access to a health professional for emotional support?			
N_{obs} (N_{miss})	623 (603)	321 (289)	302 (314)
Yes, *n* (%)	566 (90.9)	294 (91.6)	272 (90.1)
No, *n* (%)	57 (9.1)	27 (8.4)	30 (9.9)
Did partner have adequate support from care providers?			
N_{obs} (N_{miss})	611 (615)	315 (295)	296 (320)
Yes, *n* (%)	543 (88.9)	281 (89.2)	262 (88.5)
No, *n* (%)	68 (11.1)	34 (10.8)	34 (11.5)

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.

TABLE 9 Women's views on treatment at 6 months post delivery

Woman's view	All	Trial group	
		Placebo	Progesterone
Enough information about treatment			
N_{obs} (N_{miss})	79 (1147)	45 (565)	34 (582)
Yes, *n* (%)	77 (97.5)	44 (97.8)	33 (97.1)
No, *n* (%)	2 (2.5)	1 (2.2)	1 (2.9)
Satisfaction with treatment			
N_{obs} (N_{miss})	78 (1148)	44 (566)	34 (582)
Extremely satisfied, *n* (%)	60 (76.9)	33 (75.0)	27 (79.4)
Fairly satisfied, *n* (%)	18 (23.1)	11 (25.0)	7 (20.6)
Somewhat dissatisfied, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Extremely dissatisfied, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
How would you feel if treatment became normal practice?			
N_{obs} (N_{miss})	78 (1148)	44 (566)	34 (582)
Disappointed, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Not sure, *n* (%)	10 (12.8)	7 (15.9)	3 (8.8)
Pleased, *n* (%)	68 (87.2)	37 (84.1)	31 (91.2)
If time went backwards, would you take part again?			
N_{obs} (N_{miss})	79 (1147)	45 (565)	34 (582)
Definitely not, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Probably not, *n* (%)	1 (1.3)	1 (2.2)	0 (0.0)
Not sure, *n* (%)	4 (5.1)	1 (2.2)	3 (8.8)
Probably yes, *n* (%)	11 (13.9)	5 (11.1)	6 (17.6)
Definitely yes, *n* (%)	63 (79.7)	38 (84.4)	25 (73.5)
Did you have access to health professional for medical support?			
N_{obs} (N_{miss})	79 (1147)	45 (565)	34 (582)
Yes, *n* (%)	76 (96.2)	44 (97.8)	32 (94.1)
No, *n* (%)	3 (3.8)	1 (2.2)	2 (5.9)
Did you have access to health professional for emotional support?			
N_{obs} (N_{miss})	76 (1150)	43 (567)	33 (583)
Yes, *n* (%)	70 (92.1)	41 (95.3)	29 (87.9)
No, *n* (%)	6 (7.9)	2 (4.7)	4 (12.1)
Did partner have adequate support from care providers?			
N_{obs} (N_{miss})	77 (1149)	44 (566)	33 (583)
Yes, *n* (%)	67 (87.0)	41 (93.2)	26 (78.8)
No, *n* (%)	10 (13.0)	3 (6.8)	7 (21.2)
Willing participate in interview			
N_{obs} (N_{miss})	377 (849)	200 (410)	177 (439)
Yes, *n* (%)	301 (79.8)	164 (82.0)	137 (77.4)
No, *n* (%)	76 (20.2)	36 (18.0)	40 (22.6)

N_{miss}, number of women with missing data; N_{obs}, number of observations.

TABLE 10 EuroQol-5 Dimensions health utility scores

EQ-5D scores and time point of measurements	All	Trial group	
		Placebo	Progesterone
Randomisation			
N_{obs} (N_{miss})	1056 (170)	524 (86)	532 (84)
Mean (SD)	0.876 (0.190)	0.874 (0.190)	0.879 (0.190)
Median (IQR)	1.000 (0.796–1.000)	1.000 (0.796–1.000)	1.000 (0.796–1.000)
Range	–0.349 to 1.000	–0.349 to 1.000	–0.074 to 1.000
Birth			
N_{obs} (N_{miss})	394 (832)	202 (408)	192 (424)
Mean (SD)	0.867 (0.198)	0.866 (0.203)	0.868 (0.194)
Median (IQR)	1.000 (0.796–1.000)	1.000 (0.796–1.000)	1.000 (0.796–1.000)
Range	–0.184 to 1.000	–0.184 to 1.000	–0.016 to 1.000
12-month follow-up			
N_{obs} (N_{miss})	616 (610)	307 (303)	309 (307)
Mean (SD)	0.875 (0.194)	0.872 (0.202)	0.878 (0.186)
Median (IQR)	0.883 (0.848–1.000)	0.883 (0.848–1.000)	0.883 (0.848–1.000)
Range	–0.135 to 1.000	–0.135 to 1.000	–0.135 to 1.000
24-month follow-up			
N_{obs} (N_{miss})	5 (1221)	2 (608)	3 (613)
Mean (SD)	0.940 (0.083)	0.925 (0.106)	0.949 (0.088)
Median (IQR)	1.000 (0.850–1.000)	0.925 (0.888–0.962)	1.000 (0.924–1.000)
Range	0.848 to 1.000	0.850 to 1.000	0.848 to 1.000
Change from baseline			
Birth			
N_{obs} (N_{miss})	390 (836)	199 (411)	191 (425)
Mean (SD)	–0.022 (0.214)	–0.023 (0.220)	–0.021 (0.207)
Median (IQR)	0.000 (–0.152 to 0.036)	0.000 (–0.152 to 0.061)	0.000 (–0.114 to 0.000)
Range	–1.032 to 0.970	–1.032 to 0.807	–0.787 to 0.970
12-month follow-up			
N_{obs} (N_{miss})	553 (673)	274 (336)	279 (337)
Mean (SD)	–0.012 (0.217)	–0.015 (0.221)	–0.009 (0.213)
Median (IQR)	0.000 (–0.117 to 0.035)	0.000 (–0.117 to 0.064)	0.000 (–0.117 to 0.000)
Range	–1.135 to 1.128	–1.135 to 1.128	–0.841 to 0.829
24-month follow-up			
N_{obs} (N_{miss})	4 (1222)	1 (609)	3 (613)
Mean (SD)	0.068 (0.136)	0.000 (–)	0.091 (0.158)
Median (IQR)	0.000 (0.000–0.068)	0.000 (0.000–0.000)	0.000 (0.000–0.136)
Range	0.000–0.273	0.000–0.000	0.000–0.273

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.

Chapter 4 Safety evaluation

Treatment compliance (assessed according to the criteria described above) is shown in *Table 11*. We assessed compliance by looking at medication pack returns, patient diaries and asking patients what they had been taking. Prior to unblinding, we defined adequate compliance as women in whom the proportion of actual doses of study medication were 80% of those of expected doses.

Compliance was calculated from the expected number of doses taken and the assumed number of doses taken, based on the number of doses issued (usually 84) and the number returned or reportedly lost. If the number returned or lost was not recorded, this were taken as zero. In some cases, this yields implausibly large values for compliance.

Six women had a derived compliance value of > 120%:

1. compliance = 2100% – expected four doses; number of doses returned or lost not recorded; doses taken calculated as 84
2. compliance = 158% – expected 53 doses; number of doses returned or lost both zero; doses taken calculated as 84
3. compliance = 156% – expected 53 doses; number of doses returned = 1, lost = 0; doses taken calculated as 83
4. compliance = 138% – expected 26 doses; number of doses returned = 48, lost = 0; doses taken calculated as 36
5. compliance = 135% – expected 17 doses; number of doses returned = 61, lost = 0; doses taken calculated as 23
6. compliance = 133% – expected nine doses; number of doses returned = 0, lost = 72; doses taken calculated as 12.

TABLE 11 Treatment compliance in the ITT population

		Trial group	
Treatment compliance	All	Placebo	Progesterone
Percentage of medication taken			
N_{obs} (N_{miss})	1011 (215)	509 (101)	502 (114)
Mean (SD)	78.6 (72.0)	77.9 (32.8)	79.3 (96.7)
Median (IQR)	92.7 (65.0–98.7)	92.3 (71.6–98.7)	92.9 (59.0–98.6)
Range	0.0–2100.0	0.0–138.5	0.0–2100.0
Expected number of doses			
N_{obs} (N_{miss})	1197 (29)	597 (13)	600 (16)
Mean (SD)	71.0 (17.4)	70.6 (17.3)	71.4 (17.6)
Median (IQR)	76.0 (72.0–81.0)	76.0 (72.0–80.0)	76.0 (72.0–81.0)
Range	1.0–86.0	1.0–85.0	2.0–86.0
Compliant			
N_{obs} (N_{miss})	1011 (215)	509 (101)	502 (114)
No, *n* (%)	317 (31.4)	148 (29.1)	169 (33.7)
Yes, *n* (%)	694 (68.6)	361 (70.9)	333 (66.3)

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.

The compliance value for subject 1, listed above, is clearly erroneous, as the participant could not have taken all 84 doses within 4 days. This subject withdrew from study treatment very soon after randomisation, delivered shortly afterwards – at approximately 25 weeks' gestation – and withdrew from the study. The child died within 2 weeks of birth. However, there is no information that indicates that the participant was not compliant with treatment during the time that she was supposedly taking the medication.

Compliance (excluding data from subjects who had missing compliance data) is shown in *Table 12*.

Of the individuals indicated below, the following remain (only the 2100% is removed):

1. compliance = 158% – expected 53 doses; number of doses returned or lost both zero; doses taken calculated as 84
2. compliance = 156% – expected 53 doses; number of doses returned = 1, lost = 0; doses taken calculated as 83
3. compliance = 138% – expected 26 doses; number of doses returned = 48, lost = 0; doses taken calculated as 36
4. compliance = 135% – expected 17 doses; number of doses returned = 61, lost = 0; doses taken calculated as 23
5. compliance = 133% – expected nine doses; number of doses returned = 0, lost = 72; doses taken calculated as 12.

Premature treatment withdrawal is shown in *Table 13*.

Serious adverse events (SAEs) known to occur in the safety population in the reporting window (maximum of end of treatment date + 28 days and date of delivery + 30 days) or where it is unclear whether or not they are in the reporting window are listed in *Table 14*.

Serious adverse events known to occur outside the reporting window and those in which the timing was uncertain are also reported separately in *Appendix 3*.

Other prespecified safety outcomes are shown in *Tables 15–17*.

TABLE 12 Treatment compliance in the ITT population (missing data removed)

Treatment compliance	All	Trial group	
		Placebo	Progesterone
Percentage of medication taken			
N_{obs} (N_{miss})	878 (348)	438 (172)	440 (176)
Mean (SD)	77.2 (33.1)	78.7 (32.1)	75.8 (33.9)
Median (IQR)	92.8 (66.7–98.7)	92.3 (74.7–98.7)	93.2 (59.9–98.6)
Range	0.0–158.5	0.0–138.5	0.0–158.5
Compliant			
N_{obs} (N_{miss})	878 (348)	438 (101)	502 (114)
No, *n* (%)	272 (31.0)	125 (28.5)	147 (33.4)
Yes, *n* (%)	606 (69.0)	313 (71.5)	293 (66.6)

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.

TABLE 13 Premature treatment withdrawal in the ITT population

Trial participation or withdrawal and numbers	All	Trial group	
		Placebo	Progesterone
Trial completed			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
No, *n* (%)	374 (30.5)	176 (28.9)	198 (32.1)
Yes, *n* (%)	852 (69.5)	434 (71.1)	418 (67.9)
Reason for trial termination			
N_{obs} (N_{miss})	374 (852)	176 (434)	198 (418)
Woman unwilling to continue, *n* (%)	56 (15.0)	25 (14.2)	31 (15.7)
Adverse event, *n* (%)	1 (0.3)	1 (0.6)	0 (0.0)
Serious adverse event, *n* (%)	1 (0.3)	1 (0.6)	0 (0.0)
Detection of significant structural chromosomal anomalies after randomisation, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Other, *n* (%)	207 (55.3)	101 (57.4)	106 (53.5)
Physician recommended withdrawal, *n* (%)	1 (0.3)	1 (0.6)	0 (0.0)
Lost to follow-up, *n* (%)	72 (19.3)	31 (17.6)	41 (20.7)
Death, *n* (%)	36 (9.6)	16 (9.1)	20 (10.1)

N_{miss}, number of women with missing data; N_{obs}, number of observations.

TABLE 14 Patients with at least one SAE by System Organ Class and preferred term

Type of SAE	All patients, *n* (%)	Trial group, *n* (%)	
		Placebo	Progesterone
Number of patients, *N*	1183	590	593
Blood and lymphatic system disorders	1 (0.1)	1 (0.2)	0 (0.0)
Thrombocytopenia	1 (0.1)	1 (0.2)	0 (0.0)
Congenital, familial and genetic disorders	19 (1.6)	8 (1.4)	11 (1.9)
Cardiac septal defect	1 (0.1)	1 (0.2)	0 (0.0)
Cleft lip and palate	1 (0.1)	0 (0.0)	1 (0.2)
Congenital central nervous system anomaly	1 (0.1)	0 (0.0)	1 (0.2)
Congenital oesophageal anomaly	1 (0.1)	0 (0.0)	1 (0.2)
Cryptorchism	1 (0.1)	0 (0.0)	1 (0.2)
Cystic fibrosis	1 (0.1)	1 (0.2)	0 (0.0)
Congenital dacryostenosis	1 (0.1)	0 (0.0)	1 (0.2)
Hip dysplasia	1 (0.1)	1 (0.2)	0 (0.0)
Holoprosencephaly	1 (0.1)	0 (0.0)	1 (0.2)
Hydrocele	1 (0.1)	1 (0.2)	0 (0.0)
Hypospadias	2 (0.2)	0 (0.0)	2 (0.3)
Kidney malformation	1 (0.1)	0 (0.0)	1 (0.2)
Oculoauriculovertebral dysplasia	1 (0.1)	1 (0.2)	0 (0.0)

continued

TABLE 14 Patients with at least one SAE by System Organ Class and preferred term (*continued*)

Type of SAE	All patients, *n* (%)	Trial group, *n* (%)	
		Placebo	Progesterone
Patent ductus arteriosus	2 (0.2)	2 (0.3)	0 (0.0)
Polydactyly	2 (0.2)	0 (0.0)	2 (0.3)
Congenital pulmonary artery stenosis	1 (0.1)	1 (0.2)	0 (0.0)
Gastrointestinal disorders	8 (0.7)	8 (1.4)	0 (0.0)
Abdominal pain	2 (0.2)	2 (0.3)	0 (0.01)
Ileus paralytic	1 (0.1)	1 (0.2)	0 (0.0)
Inguinal hernia	1 (0.2)	1 (0.2)	0 (0.0)
Necrotising colitis	2 (0.2)	2 (0.3)	0 (0.0)
Neonatal necrotising enterocolitis	3 (0.3)	3 (0.5)	0 (0.0)
General disorders and administration site conditions	4 (0.3)	2 (0.3)	2 (0.3)
Adverse drug reaction	1 (0.1)	1 (0.2)	0 (0.0)
Death neonatal	17 (1.4)	8 (1.3)	9 (1.5)
Infections and infestations	17 (1.4)	8 (1.4)	9 (1.5)
Appendicitis	1 (0.1)	1 (0.2)	0 (0.0)
Bacterial sepsis	2 (0.2)	0 (0.0)	2 (0.3)
Bronchiolitis	1 (0.1)	0 (0.0)	1 (0.2)
Bronchopneumonia	1 (0.1)	0 (0.0)	1 (0.2)
Infection	1 (0.1)	1 (0.2)	0 (0.0)
Lower respiratory tract infection	1 (0.1)	1 (0.2)	0 (0.0)
Meningitis	1 (0.1)	1 (0.2)	0 (0.0)
Meningitis bacterial	1 (0.1)	1 (0.2)	0 (0.0)
Rash pustular	2 (0.2)	1 (0.2)	1 (0.2)
Sepsis	4 (0.3)	2 (0.3)	2 (0.3)
Urinary tract infection	3 (0.3)	1 (0.2)	2 (0.3)
Wound infection	1 (0.1)	0 (0.0)	1 (0.2)
Injury, poisoning and procedural complications	4 (0.3)	1 (0.2)	3 (0.5)
Post-lumbar puncture syndrome	2 (0.2)	0 (0.0)	2 (0.3)
Post-procedural complication	1 (0.1)	1 (0.2)	0 (0.0)
Uterine rupture	1 (0.1)	0 (0.0)	1 (0.2)
Investigations	5 (0.4)	2 (0.3)	3 (0.5)
Echocardiogram abnormal	1 (0.1)	0 (0.0)	1 (0.2)
Echogram abnormal	1 (0.1)	1 (0.2)	0 (0.0)
Fetal heart rate abnormal	1 (0.1)	0 (0.0)	1 (0.2)
Weight decreased	2 (0.2)	1 (0.2)	1 (0.2)
Metabolism and nutrition disorders	4 (0.3)	3 (0.5)	1 (0.2)
Gestational diabetes	1 (0.1)	1 (0.2)	0 (0.0)
Hypoglycaemia	3 (0.3)	2 (0.3)	1 (0.2)

TABLE 14 Patients with at least one SAE by System Organ Class and preferred term (*continued*)

Type of SAE	All patients, *n* (%)	Trial group, *n* (%)	
		Placebo	Progesterone
Neoplasms benign, malignant and unspecified (including cysts and polyps)	3 (0.3)	1 (0.2)	2 (0.3)
Breast cancer	1 (0.1)	1 (0.2)	0 (0.0)
Haemangioma of skin	1 (0.1)	0 (0.0)	1 (0.2)
Teratoma	1 (0.1)	0 (0.0)	1 (0.2)
Nervous system disorders	4 (0.3)	4 (0.7)	0 (0.0)
Cerebral ventricle dilatation	2 (0.2)	2 (0.3)	0 (0.0)
Hydrocephalus	1 (0.1)	1 (0.2)	0 (0.0)
Migraine	1 (0.1)	1 (0.2)	0 (0.0)
Pregnancy, puerperium and perinatal conditions	83 (7.0)	44 (7.5)	39 (6.6)
Amniorrhexis	3 (0.3)	3 (0.5)	0 (0.0)
Antepartum haemorrhage	9 (0.8)	5 (0.8)	4 (0.7)
Complication of pregnancy	1 (0.1)	1 (0.2)	0 (0.0)
Eclampsia	1 (0.1)	1 (0.2)	0 (0.0)
Fetal growth restriction	1 (0.1)	1 (0.2)	0 (0.0)
Fetal hypokinesia	2 (0.2)	1 (0.2)	1 (0.2)
Intrauterine death	9 (0.8)	4 (0.7)	5 (0.8)
Jaundice neonatal	1 (0.1)	1 (0.2)	0 (0.0)
Oligohydramnios	1 (0.1)	0 (0.0)	1 (0.2)
Placenta praevia haemorrhage	1 (0.1)	0 (0.0)	1 (0.2)
Post-partum haemorrhage	33 (2.8)	17 (2.9)	16 (2.7)
Pre-eclampsia	1 (0.1)	1 (0.2)	0 (0.0)
Premature baby	13 (1.1)	7 (1.2)	6 (1.0)
Premature labour	4 (0.3)	3 (0.5)	1 (0.2)
Premature rupture of membranes	3 (0.3)	1 (0.2)	2 (0.3)
Premature separation of placenta	4 (0.3)	3 (0.5)	1 (0.2)
Retained placenta or membranes	1 (0.1)	0 (0.0)	1 (0.2)
Stillbirth	2 (0.2)	0 (0.0)	2 (0.3)
Threatened labour	4 (0.3)	1 (0.2)	3 (0.5)
Uterine contractions during pregnancy	2 (0.2)	1 (0.2)	1 (0.2)
Renal and urinary disorders	1 (0.1)	1 (0.2)	0 (0.0)
Pyelocaliectasis	1 (0.1)	1 (0.2)	0 (0.0)
Reproductive system and breast disorders	10 (0.8)	6 (1.0)	4 (0.7)
Chordee	1 (0.1)	0 (0.0)	1 (0.2)
Coital bleeding	1 (0.1)	1 (0.2)	0 (0.0)
Uterine atony	1 (0.1)	0 (0.0)	1 (0.2)
Vaginal haemorrhage	7 (0.6)	5 (0.8)	2 (0.3)

continued

TABLE 14 Patients with at least one SAE by System Organ Class and preferred term (*continued*)

Type of SAE	All patients, *n* (%)	Trial group, *n* (%)	
		Placebo	Progesterone
Respiratory, thoracic and mediastinal disorders	6 (0.5)	2 (0.3)	4 (0.7)
Bronchopulmonary dysplasia	1 (0.1)	0 (0.0)	1 (0.2)
Cyanosis neonatal	1 (0.1)	1 (0.2)	0 (0.0)
Grunting	1 (0.1)	0 (0.0)	1 (0.2)
Neonatal asphyxia	1 (0.1)	0 (0.0)	1 (0.2)
Pneumothorax	1 (0.1)	0 (0.0)	1 (0.2)
Transient tachypnoea of the newborn	1 (0.1)	1 (0.2)	0 (0.0)
Skin and subcutaneous tissue disorders	1 (0.1)	1 (0.2)	0 (0.0)
Rash	1 (0.1)	1 (0.2)	0 (0.0)
Surgical and medical procedures	6 (0.5)	5 (0.8)	1 (0.2)
Caesarean section	1 (0.1)	1 (0.2)	0 (0.0)
Mechanical ventilation	1 (0.1)	1 (0.2)	0 (0.0)
Patent ductus arteriosus repair	1 (0.1)	0 (0.0)	1 (0.2)
Spinal decompression	1 (0.1)	1 (0.2)	0 (0.0)
Steroid therapy	1 (0.1)	1 (0.2)	0 (0.0)
Surgery	1 (0.1)	1 (0.2)	0 (0.0)
Vascular disorders	2 (0.2)	1 (0.2)	1 (0.2)
Deep-vein thrombosis	1 (0.1)	1 (0.2)	0 (0.0)
Essential hypertension	1 (0.1)	0 (0.0)	1 (0.2)

TABLE 15 Other preplanned safety outcomes: maternal complications

Maternal complications	All	Trial group	
		Placebo	Progesterone
Obstetric cholestasis			
N_{obs} (N_{miss})	1182 (1)	589 (1)	593 (0)
No, *n* (%)	1172 (99.2)	583 (99.0)	589 (99.3)
Yes, *n* (%)	10 (0.8)	6 (1.0)	4 (0.7)
Hypertension			
N_{obs} (N_{miss})	1183 (0)	590 (0)	593 (0)
No, *n* (%)	1136 (96.0)	566 (95.9)	570 (96.1)
Yes, *n* (%)	47 (4.0)	24 (4.1)	23 (3.9)
Pre-eclampsia			
N_{obs} (N_{miss})	1183 (0)	590 (0)	593 (0)
No, *n* (%)	1162 (98.2)	579 (98.1)	583 (98.3)
Yes, *n* (%)	21 (1.8)	11 (1.9)	10 (1.7)

TABLE 15 Other preplanned safety outcomes: maternal complications (*continued*)

Maternal complications	All	Trial group	
		Placebo	Progesterone
Eclampsia			
N_{obs} (N_{miss})	1183 (0)	590 (0)	593 (0)
No, *n* (%)	1182 (99.9)	589 (99.8)	593 (100.0)
Yes, *n* (%)	1 (0.1)	1 (0.2)	0 (0.0)
Preterm membrane rupture			
N_{obs} (N_{miss})	1183 (0)	590 (0)	593 (0)
No, *n* (%)	1046 (88.4)	518 (87.8)	528 (89.0)
Yes, *n* (%)	137 (11.6)	72 (12.2)	65 (11.0)
Antepartum haemorrhage			
N_{obs} (N_{miss})	1183 (0)	590 (0)	593 (0)
No, *n* (%)	1110 (93.8)	554 (93.9)	556 (93.8)
Yes, *n* (%)	73 (6.2)	36 (6.1)	37 (6.2)
Confirmed deep-vein thrombosis			
N_{obs} (N_{miss})	1183 (0)	590 (0)	593 (0)
No, *n* (%)	1181 (99.8)	588 (99.7)	593 (100.0)
Yes, *n* (%)	2 (0.2)	2 (0.3)	0 (0.0)
Gestational diabetes			
N_{obs} (N_{miss})	1183 (0)	590 (0)	593 (0)
No, *n* (%)	1119 (94.6)	553 (93.7)	566 (95.4)
Yes, *n* (%)	64 (5.4)	37 (6.3)	27 (4.6)
Cerclage			
N_{obs} (N_{miss})	728 (455)	360 (230)	368 (225)
No, *n* (%)	648 (89.0)	321 (89.2)	327 (88.9)
Yes, *n* (%)	80 (11.0)	39 (10.8)	41 (11.1)
Other maternal complication			
N_{obs} (N_{miss})	1183 (0)	590 (0)	593 (0)
No, *n* (%)	853 (72.1)	426 (72.2)	427 (72.0)
Yes, *n* (%)	330 (27.9)	164 (27.8)	166 (28.0)

N_{miss}, number of women with missing data; N_{obs}, number of observations.

TABLE 16 Other preplanned safety outcomes: fetal and neonatal complications

Fetal and neonatal complications	All	Trial group	
		Placebo	Progesterone
Other fetal complication			
N_{obs} (N_{miss})	1183 (0)	590 (0)	593 (0)
No, *n* (%)	1146 (96.9)	572 (96.9)	574 (96.8)
Yes, *n* (%)	37 (3.1)	18 (3.1)	19 (3.2)
Abdominal circumference of < 5th centile			
N_{obs} (N_{miss})	37 (0)	18 (0)	19 (0)
No, *n* (%)	27 (73.0)	14 (77.8)	13 (68.4)
Yes, *n* (%)	10 (27.0)	4 (22.2)	6 (31.6)
Liquor volume reduced			
N_{obs} (N_{miss})	37 (0)	18 (0)	19 (0)
No, *n* (%)	25 (67.6)	12 (66.7)	13 (68.4)
Yes, *n* (%)	12 (32.4)	6 (33.3)	6 (31.6)
Doppler > 95th centile (umbilical artery)			
N_{obs} (N_{miss})	37 (0)	18 (0)	19 (0)
No, *n* (%)	35 (94.6)	17 (94.4)	18 (94.7)
Yes, *n* (%)	2 (5.4)	1 (5.6)	1 (5.3)
Absent end-diastolic flow (umbilical artery)			
N_{obs} (N_{miss})	37 (0)	18 (0)	19 (0)
No, *n* (%)	36 (97.3)	18 (100.0)	18 (94.7)
Yes, *n* (%)	1 (2.7)	0 (0.0)	1 (5.3)
Reversed end-diastolic flow (umbilical artery)			
N_{obs} (N_{miss})	37 (0)	18 (0)	19 (0)
No, *n* (%)	35 (94.6)	17 (94.4)	18 (94.7)
Yes, *n* (%)	2 (5.4)	1 (5.6)	1 (5.3)
Abnormal cardiotocogram			
N_{obs} (N_{miss})	37 (0)	18 (0)	19 (0)
No, *n* (%)	27 (73.0)	11 (61.1)	16 (84.2)
Yes, *n* (%)	10 (27.0)	7 (38.9)	3 (15.8)

N_{miss}, number of women with missing data; N_{obs}, number of observations.

TABLE 17 Further preplanned safety outcomes

Safety outcomes	All	Trial group	
		Placebo	Progesterone
Hospital admissions			
Number of antenatal hospital admissions (per woman)			
N_{obs} (N_{miss})	1160 (23)	581 (9)	579 (14)
Mean (SD)	0.7 (1.2)	0.7 (1.3)	0.6 (1.1)
Median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)
Range	0.0–10.0	0.0–10.0	0.0–8.0
Number of antenatal hospital admissions for threatened preterm labour			
N_{obs} (N_{miss})	1160 (23)	581 (9)	579 (14)
Mean (SD)	0.3 (0.8)	0.4 (0.9)	0.3 (0.7)
Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Range	0.0–9.0	0.0–9.0	0.0–5.0
Number of antenatal hospital admissions for other reasons			
N_{obs} (N_{miss})	1160 (23)	581 (9)	579 (14)
Mean (SD)	0.3 (0.8)	0.4 (0.8)	0.3 (0.8)
Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Range	0.0–7.0	0.0–7.0	0.0–6.0
Total number of days in hospital antenatally (per woman)			
N_{obs} (N_{miss})	1153 (30)	576 (14)	577 (16)
Mean (SD)	2.9 (7.6)	3.0 (7.6)	2.7 (7.7)
Median (IQR)	0.0 (0.0–2.0)	0.0 (0.0–3.0)	0.0 (0.0–2.0)
Range	0.0–97.0	0.0–97.0	0.0–84.0
Total number of days in hospital for threatened preterm labour			
N_{obs} (N_{miss})	1156 (27)	579 (11)	577 (16)
Mean (SD)	1.7 (5.8)	1.8 (6.2)	1.6 (5.3)
Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Range	0.0–97.0	0.0–97.0	0.0–56.0
Total number of days in hospital for other reasons			
N_{obs} (N_{miss})	1157 (26)	578 (12)	579 (14)
Mean (SD)	1.2 (5.0)	1.2 (4.3)	1.1 (5.6)
Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Range	0.0–84.0	0.0–39.0	0.0–84.0
Antenatal hospital admissions: other details of hospital admissions			
Number of hospital admissions with tocolysis, *n* (%)	33 (8.5)	18 (8.1)	15 (8.9)
Type of tocolysis, N_{obs} (N_{miss})	33 (0)	18 (0)	15 (0)
Nifedipine, *n* (%)	17 (51.5)	8 (44.4)	9 (60.0)
Indomethacine, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Atosiban, *n* (%)	15 (45.5)	9 (50.0)	6 (40.0)
Other, *n* (%)	1 (3.0)	1 (5.6)	0 (0.0)

continued

TABLE 17 Further preplanned safety outcomes (*continued*)

Safety outcomes	All	Trial group	
		Placebo	Progesterone
Number of hospital admissions with steroids, *n* (%)	160 (41.0)	77 (34.8)	83 (49.1)
Number of hospital admissions with antibiotics, *n* (%)	94 (24.1)	54 (24.4)	40 (23.7)
Number of hospital admissions with sutures, *n* (%)	18 (4.6)	10 (4.5)	8 (4.7)
Number of hospital admissions with magnesium, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Labour outcomes			
Duration of first stage (hours)			
N_{obs} (N_{miss})	933 (250)	463 (127)	470 (123)
Mean (SD)	4.2 (5.2)	4.1 (5.1)	4.3 (5.3)
Median (IQR)	3.0 (1.2–5.4)	2.8 (1.2–5.3)	3.2 (1.3–5.5)
Range	0.0–70.0	[0.0–56.0	0.0–70.0
Duration of second stage (minutes)			
N_{obs} (N_{miss})	933 (250)	462 (128)	471 (122)
Mean (SD)	44.1 (113.9)	47.0 (132.8)	41.2 (91.6)
Median (IQR)	16.0 (6.0–40.0)	16.0 (6.0–42.8)	16.0 (5.0–39.0)
Range	0.0–1800.0	0.0–1800.0	0.0–1383.0
Duration of third stage (minutes)			
N_{obs} (N_{miss})	942 (241)	465 (125)	477 (116)
Mean (SD)	16.6 (49.0)	17.0 (46.2)	16.1 (51.6)
Median (IQR)	7.0 (4.0–11.0)	6.0 (4.0–11.0)	7.0 (5.0–10.0)
Range	0.0–900.0	0.0–600.0	0.0–900.0
Membranes ruptured			
N_{obs} (N_{miss})	1149 (34)	575 (15)	574 (19)
No, *n* (%)	235 (20.5)	109 (19.0)	126 (22.0)
Yes, *n* (%)	914 (79.5)	466 (81.0)	448 (78.0)
Type of membrane rupture			
N_{obs} (N_{miss})	916 (267)	468 (122)	448 (145)
Artificial, *n* (%)	253 (27.6)	131 (28.0)	122 (27.2)
Spontaneous, *n* (%)	663 (72.4)	337 (72.0)	326 (72.8)
Analgesic			
N_{obs} (N_{miss})	1150 (33)	576 (14)	574 (19)
No, *n* (%)	217 (18.9)	121 (21.0)	96 (16.7)
Yes, *n* (%)	933 (81.1)	455 (79.0)	478 (83.3)
Analgesics used, *n* (%)			
General anaesthetic	28 (2.4)	16 (2.7)	12 (2.0)
Epidural	388 (32.8)	191 (32.4)	197 (33.2)
Opiates	176 (14.9)	88 (14.9)	88 (14.8)
Entonox	572 (48.4)	269 (45.6)	303 (51.1)
Other	65 (5.5)	34 (5.8)	31 (5.2)

TABLE 17 Further preplanned safety outcomes (*continued*)

Safety outcomes	All	Trial group	
		Placebo	Progesterone
Delivery outcomes			
Delivery method, N_{obs} (N_{miss})	1154 (29)	578 (12)	576 (17)
Spontaneous vaginal delivery, *n* (%)	755 (65.4)	380 (65.7)	375 (65.1)
Lower segment caesarean section in labour, *n* (%)	115 (10.0)	58 (10.0)	57 (9.9)
Lower segment caesarean section pre labour, *n* (%)	176 (15.3)	92 (15.9)	84 (14.6)
Forceps, *n* (%)	48 (4.2)	21 (3.6)	27 (4.7)
Ventouse, *n* (%)	38 (3.3)	18 (3.1)	20 (3.5)
Vaginal breech (spontaneous or assisted), *n* (%)	22 (1.9)	9 (1.6)	13 (2.3)
Reason for assisted delivery, *n* (%)			
Abnormal cardiotocogram	89 (7.5)	45 (7.6)	44 (7.4)
Abnormal pH on fetal scalp sampling	1 (0.1)	0 (0.0)	1 (0.2)
Slow stage 1	14 (1.2)	4 (0.7)	10 (1.7)
Slow stage 2	64 (5.4)	29 (4.9)	35 (5.9)
Malpresentation	54 (4.6)	30 (5.1)	24 (4.0)
Suspected maternal compromise	29 (2.5)	18 (3.1)	11 (1.9)
Suspected fetal compromise	60 (5.1)	33 (5.6)	27 (4.6)
Obstetric history	85 (7.2)	39 (6.6)	46 (7.8)
Other	76 (6.4)	37 (6.3)	39 (6.6)
Blood loss (ml)			
N_{obs} (N_{miss})	1144 (39)	572 (18)	572 (21)
Mean (SD)	405.5 (375.8)	387.4 (356.4)	423.7 (393.8)
Median (IQR)	300.0 (200.0–500.0)	300.0 (200.0–450.0)	300.0 (200.0–500.0)
Range	0.0–4000.0	0.0–4000.0	0.0–4000.0
Suture			
N_{obs} (N_{miss})	1151 (32)	578 (12)	573 (20)
No, *n* (%)	793 (68.9)	413 (71.5)	380 (66.3)
Yes, *n* (%)	358 (31.1)	165 (28.5)	193 (33.7)
Reason for suture, *n* (%)			
Episiotomy	98 (8.3)	48 (8.1)	50 (8.4)
Degree 1 tear	46 (3.9)	21 (3.6)	25 (4.2)
Degree 2 tear	201 (17.0)	91 (15.4)	110 (18.5)
Degree 3 tear	23 (1.9)	11 (1.9)	12 (2.0)
Blood transfusion			
N_{obs} (N_{miss})	1152 (31)	578 (12)	574 (19)
No, *n* (%)	1124 (97.6)	568 (98.3)	556 (96.9)
Yes, *n* (%)	28 (2.4)	10 (1.7)	18 (3.1)

continued

TABLE 17 Further preplanned safety outcomes (*continued*)

Safety outcomes	All	Trial group	
		Placebo	Progesterone
Antibiotics during labour and delivery			
N_{obs} (N_{miss})	1151 (32)	578 (12)	573 (20)
No, *n* (%)	963 (83.7)	482 (83.4)	481 (83.9)
Yes, *n* (%)	188 (16.3)	96 (16.6)	92 (16.1)
Surgical procedure required			
N_{obs} (N_{miss})	1153 (30)	578 (12)	575 (18)
No, *n* (%)	1120 (97.1)	563 (97.4)	557 (96.9)
Yes, *n* (%)	33 (2.9)	15 (2.6)	18 (3.1)
Duration of hospital stay (days)			
N_{obs} (N_{miss})	1144 (39)	577 (13)	567 (26)
Mean (SD)	3.3 (3.3)	3.2 (2.2)	3.3 (4.1)
Median (IQR)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)
Range	1.0–86.0	1.0–19.0	1.0–86.0
Placental examination			
Result of placental examination			
N_{obs} (N_{miss})	167 (1016)	84 (506)	83 (510)
None, *n* (%)	113 (67.7)	57 (67.9)	56 (67.5)
Chorioamnionitis, *n* (%)	19 (11.4)	10 (11.9)	9 (10.8)
Chorioamnionitis and funisitis, *n* (%)	35 (21.0)	17 (20.2)	18 (21.7)
Post-partum complications			
Thrombophlebitis			
N_{obs} (N_{miss})	1157 (26)	580 (10)	577 (16)
No, *n* (%)	1155 (99.8)	579 (99.8)	576 (99.8)
Yes, *n* (%)	2 (0.2)	1 (0.2)	1 (0.2)
Deep-vein thrombosis			
N_{obs} (N_{miss})	1157 (26)	580 (10)	577 (16)
No, *n* (%)	1157 (100.0)	580 (100.0)	577 (100.0)
Wound infection			
N_{obs} (N_{miss})	1157 (26)	580 (10)	577 (16)
No, *n* (%)	1144 (98.9)	574 (99.0)	570 (98.8)
Yes, *n* (%)	13 (1.1)	6 (1.0)	7 (1.2)
Urine infection			
N_{obs} (N_{miss})	1157 (26)	580 (10)	577 (16)
No, *n* (%)	1150 (99.4)	574 (99.0)	576 (99.8)
Yes, *n* (%)	7 (0.6)	6 (1.0)	1 (0.2)
Wound breakdown			
N_{obs} (N_{miss})	1157 (26)	580 (10)	577 (16)
No, *n* (%)	1154 (99.7)	579 (99.8)	575 (99.7)
Yes, *n* (%)	3 (0.3)	1 (0.2)	2 (0.3)

TABLE 17 Further preplanned safety outcomes (*continued*)

Safety outcomes	All	Trial group	
		Placebo	Progesterone
Mastitis			
N_{obs} (N_{miss})	1157 (26)	580 (10)	577 (16)
No, *n* (%)	1155 (99.8)	579 (99.8)	576 (99.8)
Yes, *n* (%)	2 (0.2)	1 (0.2)	1 (0.2)
Unknown infection			
N_{obs} (N_{miss})	1157 (26)	580 (10)	577 (16)
No, *n* (%)	1145 (99.0)	574 (99.0)	571 (99.0)
Yes, *n* (%)	12 (1.0)	6 (1.0)	6 (1.0)
Post-partum haemorrhage			
N_{obs} (N_{miss})	1157 (26)	580 (10)	577 (16)
No, *n* (%)	1070 (92.5)	539 (92.9)	531 (92.0)
Yes, *n* (%)	87 (7.5)	41 (7.1)	46 (8.0)
Depression			
N_{obs} (N_{miss})	1157 (26)	580 (10)	577 (16)
No, *n* (%)	1155 (99.8)	579 (99.8)	576 (99.8)
Yes, *n* (%)	2 (0.2)	1 (0.2)	1 (0.2)
Other complication			
N_{obs} (N_{miss})	1157 (26)	580 (10)	577 (16)
No, *n* (%)	1099 (95.0)	553 (95.3)	546 (94.6)
Yes, *n* (%)	58 (5.0)	27 (4.7)	31 (5.4)
No complication			
N_{obs} (N_{miss})	1157 (26)	580 (10)	577 (16)
No, *n* (%)	173 (15.0)	83 (14.3)	90 (15.6)
Yes, *n* (%)	984 (85.0)	497 (85.7)	487 (84.4)
Child assessments at birth			
Sex			
N_{obs} (N_{miss})	1156 (27)	578 (12)	578 (15)
Male, *n* (%)	582 (50.3)	289 (50.0)	293 (50.7)
Female, *n* (%)	573 (49.6)	289 (50.0)	284 (49.1)
Indeterminate, *n* (%)	1 (0.1)	0 (0.0)	1 (0.2)
Birthweight (g)			
N_{obs} (N_{miss})	1154 (29)	577 (13)	577 (16)
Mean (SD)	2849 (866)	2822 (884)	2875 (847)
Median (IQR)	3000 (2470–3448)	2960 (2350–3420)	3040 (2550–3450)
Range	380–6400	455–6400	380–5025

continued

TABLE 17 Further preplanned safety outcomes (*continued*)

Safety outcomes	All	Trial group	
		Placebo	Progesterone
Apgar score at 1 minute			
N_{obs} (N_{miss})	1110 (73)	553 (37)	557 (36)
Mean (SD)	8.1 (1.9)	8.1 (1.8)	8.1 (1.9)
Median (IQR)	9.0 (8.0–9.0)	9.0 (8.0–9.0)	9.0 (8.0–9.0)
Range	0.0, 10.0	0.0, 10.0	0.0, 10.0
Apgar score at 5 minutes			
N_{obs} (N_{miss})	1115 (68)	555 (35)	560 (33)
Mean (SD)	9.1 (1.4)	9.1 (1.3)	9.0 (1.4)
Median (IQR)	9.0 (9.0–10.0)	9.0 (9.0–10.0)	9.0 (9.0–10.0)
Range	0.0, 10.0	0.0, 10.0	0.0, 10.0
Length of hospital stay (days)			
N_{obs} (N_{miss})	1118 (65)	556 (34)	562 (31)
Mean (SD)	9.1 (20.6)	9.8 (20.9)	8.4 (20.2)
Median (IQR)	2.0 (1.0–5.0)	2.0 (1.0–6.0)	2.0 (1.0–4.0)
Range	0.0–220.0	0.0–152.0	0.0–220.0
Child assessments at 2 years			
Weight (kg)			
N_{obs} (N_{miss})	687 (496)	355 (235)	332 (261)
Mean (SD)	13.3 (2.7)	13.2 (2.6)	13.4 (2.7)
Median (IQR)	13.0 (12.0–14.2)	13.0 (11.9–14.2)	13.1 (12.0–14.2)
Range	7.0–45.4	7.0–39.3	9.0–45.4
Height (cm)			
N_{obs} (N_{miss})	716 (467)	369 (221)	347 (246)
Mean (SD)	87.3 (9.5)	87.2 (10.7)	87.4 (7.9)
Median (IQR)	88.0 (85.0–91.0)	88.0 (84.1–91.4)	87.6 (85.0–91.0)
Range	0.9–111.0	0.9–111.0	0.9–109.0
Head circumference (cm)			
N_{obs} (N_{miss})	686 (497)	354 (236)	332 (261)
Mean (SD)	49.2 (5.7)	48.9 (4.6)	49.6 (6.7)
Median (IQR)	49.0 (48.0–50.4)	49.0 (48.0–50.3)	49.1 (48.0–50.5)
Range	0.5–98.0	0.5–84.9	0.5–98.0
Respiration rate (breaths per minute)			
N_{obs} (N_{miss})	76 (1107)	38 (552)	38 (555)
Mean (SD)	23.6 (11.3)	25.2 (14.1)	21.9 (7.3)
Median (IQR)	23.0 (16.0–28.0)	24.0 (20.0–28.0)	22.0 (16.0–27.5)
Range	12.0–98.0	12.0–98.0	12.0–38.0

TABLE 17 Further preplanned safety outcomes (*continued*)

Safety outcomes	All	Trial group	
		Placebo	Progesterone
Heart rate (beats per minute)			
N_{obs} (N_{miss})	73 (1110)	36 (554)	37 (556)
Mean (SD)	109.7 (18.3)	111.4 (17.3)	108.1 (19.3)
Median (IQR)	110.0 (100.0–119.0)	111.0 (102.2–118.0)	110.0 (100.0–120.0)
Range	40.0–170.0	68.0–170.0	40.0–160.0
Systolic blood pressure (mmHg)			
N_{obs} (N_{miss})	46 (1137)	24 (566)	22 (571)
Mean (SD)	98.7 (14.0)	96.6 (13.2)	100.9 (14.7)
Median (IQR)	98.5 (90.2–107.8)	97.0 (89.2–103.5)	103.5 (91.8–108.0)
Range	59.0–128.0	64.0–123.0	59.0–128.0
Diastolic blood pressure (mmHg)			
N_{obs} (N_{miss})	37 (1146)	20 (570)	17 (576)
Mean (SD)	64.2 (12.3)	66.0 (12.9)	62.1 (11.7)
Median (IQR)	64.0 (54.0–70.0)	65.5 (58.5–72.5)	63.0 (54.0–68.0)
Range	42.0–90.0	42.0–90.0	44.0–85.0

N_{miss}, number of women with missing data; N_{obs}, number of observations.

Chapter 5 Subgroup analyses

Subgroup analyses for the subgroups fibronectin positive (yes/no), short cervix (yes/no; ≤ 25 mm and < 15 mm), previous preterm birth and chorioamnionitis are shown in *Tables 18–22*.

TABLE 18 Logistic regression model for the effect of treatment adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to risk group (fibronectin status)

Risk group	OR (progesterone vs. placebo)	95% CI	*p*-value	*p*-value for interaction
Primary obstetric outcome (death or delivery before 34 weeks' gestation). Interaction model ($n = 1197$)				
Low, negative fFN ($n = 859$)	0.88	0.58 to 1.33	0.542	0.907
High, positive fFN ($n = 338$)	0.91	0.57 to 1.46	0.707	
Primary neonatal outcome (death, brain injury or severe chronic lung disease). Interaction model ($n = 1176$)				
Low, negative fFN ($n = 847$)	0.56	0.19 to 1.70	0.310	0.55
High, positive fFN ($n = 329$)	0.87	0.36 to 2.08	0.747	
Risk group	**Expected mean difference (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
Primary childhood outcome (Bayley-III cognitive composite score adjusted for previous pregnancy). Interaction model ($n = 869$)				
Low, negative fFN ($n = 628$)	–0.63	–3.28 to 2.03	0.644	0.858
High, positive fFN ($n = 241$)	–1.09	–5.41 to 3.23	0.621	

TABLE 19 Logistic regression model for the effect of treatment adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to cervical length (≤ 25 mm) at baseline

Cervical length at baseline (mm)	OR (progesterone vs. placebo)	95% CI	*p*-value	*p*-value for interaction
Primary obstetric outcome (death or delivery before 34 weeks' gestation). Interaction model ($n = 696$)				
> 25 ($n = 445$)	0.88	0.50 to 1.57	0.672	0.542
≤ 25 ($n = 251$)	0.69	0.39 to 1.20	0.191	
Primary neonatal outcome (death, brain injury or severe chronic lung disease). Interaction model ($n = 682$)				
> 25 ($n = 436$)	0.86	0.42 to 1.74	0.690	0.38
≤ 25 ($n = 246$)	0.54	0.26 to 1.15	0.112	
Cervical length at baseline (mm)	**Expected mean difference (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
Primary childhood outcome (Bayley-III cognitive composite score adjusted for previous pregnancy). Interaction model ($n = 496$)				
> 25 ($n = 317$)	–2.27	–6.10 to 1.56	0.247	0.971
≤ 25 ($n = 179$)	–2.15	–7.23 to 2.93	0.408	

TABLE 20 Logistic regression model for the effect of treatment adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to cervical length (< 15 mm) at baseline

Cervical length at baseline (mm)	OR (progesterone vs. placebo)	95% CI	*p*-value	*p*-value for interaction
Primary obstetric outcome (death or delivery before 34 weeks' gestation). Interaction model ($n = 696$)				
> 15 ($n = 599$)	0.77	0.48 to 1.23	0.274	0.727
≤ 15 ($n = 97$)	0.91	0.41 to 2.04	0.819	
Primary neonatal outcome (death, brain injury or severe chronic lung disease). Interaction model ($n = 682$)				
> 15 ($n = 588$)	0.82	0.44 to 1.52	0.526	0.39
≤ 15 ($n = 94$)	0.49	0.18 to 1.32	0.158	
Cervical length at baseline (mm)	**Expected mean difference (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
Primary childhood outcome (Bayley-III cognitive composite score adjusted for previous pregnancy). Interaction model ($n = 496$)				
> 15 ($n = 423$)	–2.49	–5.77 to 0.78	0.137	0.680
≤ 15 ($n = 73$)	–0.69	–8.60 to 7.22	0.865	

TABLE 21 Logistic regression model for the effect of treatment adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to history of spontaneous preterm birth

History of spontaneous preterm birth	OR (progesterone vs. placebo)	95% CI	*p*-value	*p*-value for interaction
Primary obstetric outcome (death or delivery before 34 weeks' gestation). Interaction model ($n = 1176$)				
No ($n = 273$)	0.99	0.51 to 1.92	0.972	0.62
Yes ($n = 903$)	0.82	0.58 to 1.16	0.254	
Primary neonatal outcome (death, brain injury or severe chronic lung disease). Interaction model ($n = 1156$)				
No ($n = 270$)	1.23	0.54 to 2.77	0.623	0.15
Yes ($n = 886$)	0.60	0.37 to 0.96	0.033	
History of spontaneous preterm birth	**Expected mean difference (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
Primary childhood outcome (Bayley-III cognitive composite score adjusted for previous pregnancy). Interaction model ($n = 857$)				
No ($n = 201$)	–1.11	–5.96 to 3.73	0.653	0.73
Yes ($n = 656$)	–0.14	–2.79 to 2.52	0.919	

TABLE 22 Logistic regression model for the effect of treatment adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to chorioamnionitis diagnosed on pathology

Chorioamnionitis diagnosed on pathology	OR (progesterone vs. placebo)	95% CI	*p*-value	*p*-value for interaction
Primary obstetric outcome (death or delivery before 34 weeks' gestation). Interaction model ($n = 172$)				
No	1.38	0.55 to 3.45	0.497	0.547
Yes ($n = 57$)	2.17	0.68 to 6.85	0.190	
Primary neonatal outcome (death, brain injury or severe chronic lung disease). Interaction model ($n = 171$)				
No	1.18	0.30 to 4.68	0.810	0.43
Yes ($n = 56$)	2.53	0.71 to 9.06	0.156	
Chorioamnionitis diagnosed on pathology	**Expected mean difference (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
Primary childhood outcome (Bayley-III cognitive composite score adjusted for previous pregnancy). Interaction model ($n = 124$)				
No ($n = 81$)	–2.30	–10.30 to 5.70	0.575	0.859
Yes ($n = 43$)	–1.08	–11.91 to 9.76	0.846	

Chapter 6 Further analysis of factors influencing the childhood outcome

As a further post hoc analysis, we investigated the influence of gestational age at birth and other factors at birth on the childhood outcome.

Figure 1 shows a scatterplot of gestational age at delivery and Bayley-III cognitive composite scores (with deaths imputed).

These data show that, at gestational ages of < 34 weeks, there is a linear relationship between gestation at delivery and the Bayley-III cognitive composite score. The shape of the Lowess line suggests that a quadratic model might fit best, which was confirmed by comparing the quadratic fit to thinplate regression splines and finding a very similar shape.

Table 23 shows the results for unadjusted and adjusted models predicting Bayley-III cognitive composite scores from gestational age as a linear and a quadratic term.

The predicted scores in *Figure 2* are for a woman of average age, education and body mass index (BMI), who has had no previous pregnancy of ≤ 14 weeks, does not smoke and is at a low risk of preterm birth.

Gestational age at delivery has a significant effect on the cognitive outcome. Adjustment alters the effect estimates only slightly. Other significant predictors are maternal age, BMI, the number of previous pregnancies and whether the woman was in the high- or the low-risk group; with higher maternal age, lower BMI, lower number of previous pregnancies and being of a low risk predicting higher Bayley-III cognitive composite scores.

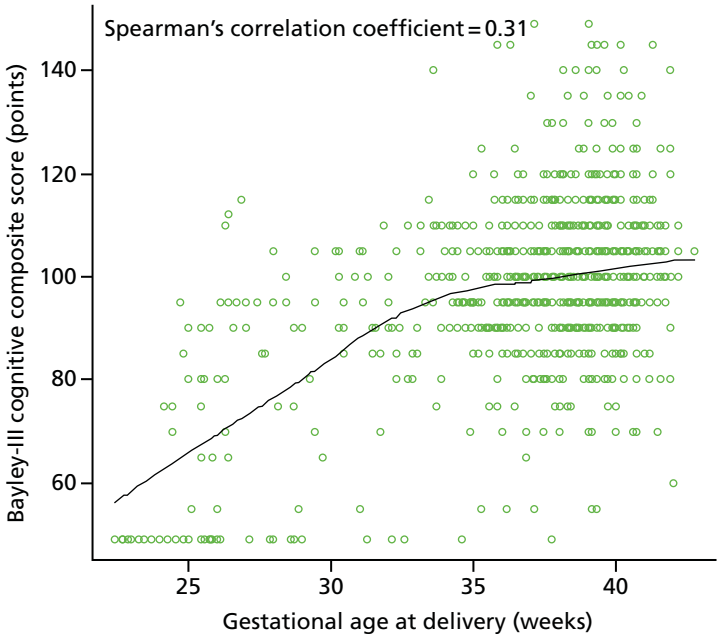

FIGURE 1 Scatterplot of raw values of gestational age at delivery and Bayley-III cognitive composite scores, with a Lowess line.

TABLE 23 Linear regression model predicting Bayley-III cognitive composite score from gestational age at delivery as a linear and a quadratic term

Characteristic adjusted for	Effect	95% CI	*p*-value
Unadjusted			
Gestational age at delivery (linear term)	11.503	8.351 to 14.654	< 0.001
Gestational age at delivery (quadratic term)	–0.140	–0.187 to –0.093	< 0.001
Adjusted			
Gestational age at delivery (linear term)	10.398	7.155 to 13.640	< 0.001
Gestational age at delivery (quadratic term)	–0.126	–0.174 to –0.078	< 0.001
Mother's age	0.283	0.090 to 0.477	0.004
Time in full-time education	0.288	–0.047 to 0.623	0.092
Mother's BMI	–0.212	–0.365 to –0.059	0.007
Smoking	–2.024	–5.025 to 0.976	0.186
Number of previous pregnancies of ≤ 14 weeks	–1.863	–2.638 to –1.089	< 0.001
High risk	–3.150	–5.477 to –0.824	0.008

BMI, body mass index.
Note
The adjusted model adjusts for mother's age, years in full-time education, BMI, smoking, previous pregnancies of ≥ 14 weeks and high/low risk.

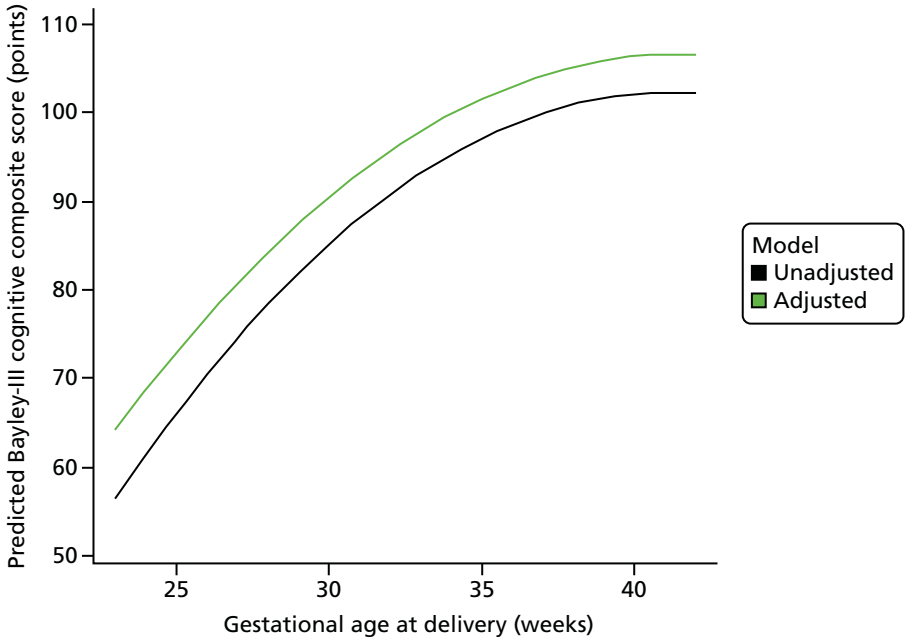

FIGURE 2 Unadjusted and adjusted models predicting Bayley-III cognitive composite scores from gestational age as a linear and a quadratic term.

In addition, the relation between gestational age and Bayley-III cognitive composite scores has been analysed including gestational age as a categorical variable (gestational ages rounded to weeks), with 40 weeks as the reference group. *Figure 3* shows the estimated regression coefficients for each week.

Those results suggest that the lower gestational age, the higher the gain from each additional week of gestation. From week 34 or 36 (weeks 34 and 35 results are unclear) onwards, there seems to be little additional gain from longer gestation.

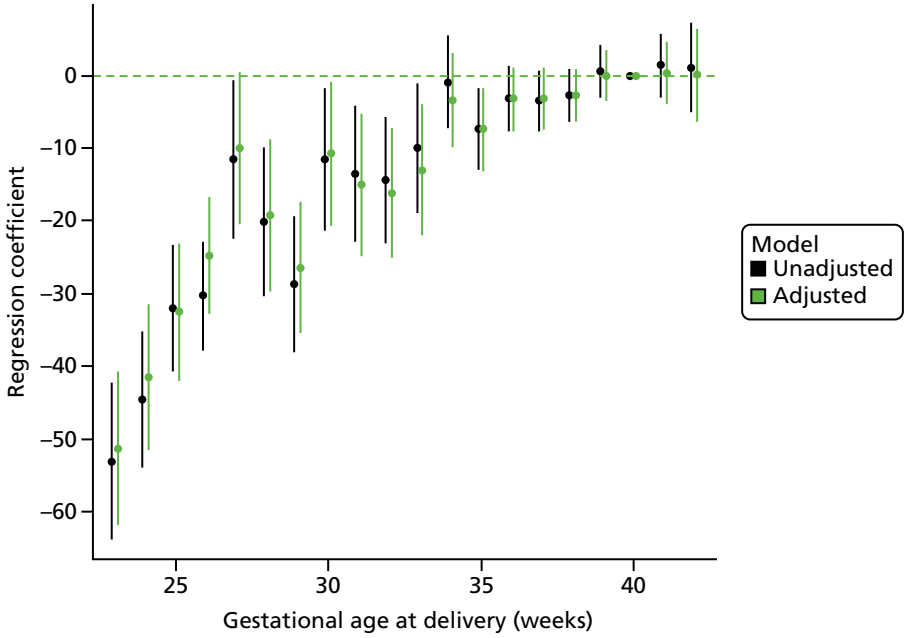

FIGURE 3 Regression coefficients for gestational age at delivery from a linear model predicting Bayley-III cognitive composite scores from gestational age at delivery as a categorical variable, with 95% CIs. Gestational ages of 22 and 23 weeks have been grouped together, as well as gestational ages of 42 and 43 weeks. The reference category is 40 weeks. The adjusted model adjusts for mother's age, years in full-time education, BMI, smoking, previous pregnancies of $\geq$ 14 weeks and high/low risk.

Chapter 7 Discussion and overall conclusions

The OPPTIMUM study aimed to test the hypotheses that progesterone:

- improves obstetric outcome by lengthening pregnancy and reducing the incidence of preterm delivery (before 34 weeks' gestation)
- improves neonatal outcome by reducing a composite of death and major morbidity
- leads to improved childhood cognitive and neurosensory outcomes at age 2 years.

In the OPPTIMUM study, the CI of the OR of treatment effect crossed unity for each of the obstetric, neonatal or childhood outcomes, suggesting that progesterone had no effect on any of these outcomes. These data contrast with the meta-analyses[6,7] on preterm birth prevention (the obstetric outcome) detailed in *Chapter 1*, which found that progesterone prevents preterm birth. The literature is less consistent on whether or not progesterone improves neonatal outcomes. For women with a short cervix, two major meta-analyses[6,7] come to different conclusions for the neonatal outcome, with one[7] showing that progesterone reduces adverse outcomes and the other[6] finding no benefit. For women with a previous preterm birth, the Cochrane meta-analysis[6] suggests that progesterone reduces perinatal death and other adverse neonatal outcomes. OPPTIMUM, the largest single randomised trial, found no effect of progesterone on the composite neonatal outcome. In subgroup analyses, none of the *p*-values of any of the interaction terms approached statistical significance; in other words, we found no evidence that progesterone is any more effective in any subgroup.

The study benefited from participation of PPI in the conduct of the study. Having PPI representatives on the trial steering committee was useful in focusing on what patients would find helpful. Our PPI representatives faced the challenge that many 'pregnancy' PPI representatives face, that of little time to contribute to the study because of the competing demands of their young family.

Reported compliance was 68.6% (95% CI 65.8% to 71.5%). This rate is similar to or better than compliance rates seen when drugs are taken for clinical indications; hence, we believe that efficacy is as good or better as would be achieved in 'real-world' situations.[21] Although other studies[11] have reported higher compliance, this is based on counting returned unused medication, a strategy likely to overestimate compliance.

Some commentators have noted that the ORs for the obstetric and neonatal outcome are in the direction of benefit, and have suggested that OPPTIMUM was underpowered to show benefit. We powered the study carefully as described in the protocol and in the statistical analysis plan (see *Appendix 2*), and we ultimately recruited to the planned sample size. Post hoc, we compared the planned with the actual event rate for the obstetric outcome in the placebo group. In planning our sample size, we calculated that the obstetric outcome event rate would be 40% for those in the fFN-positive group and 10% for those in the fFN-negative group for a study power of 81% (see power calculation in *Appendix 2* and published).[17] We anticipated recruiting 375 women in the fFN-positive group and 750 women in the fFN-negative group in the study as whole. Assuming half of these women were randomised to the placebo group, the number of outcome events in the placebo group would be $0.5 \times [(0.4 \times 375) + (0.1 \times 750)] = 112.5$. Once OPPTIMUM was complete, the event rate in the fFN-positive group was a little lower and the event rate in the fFN-negative group was a little higher than expected, with the actual number of obstetric outcome events in the placebo group being 108. The failure to show an effect of progesterone (at least for the obstetric outcome) was not because the sample size was too small, but because the effect size (an OR of 0.86 for the obstetric outcome) was less than anticipated; in other words, because progesterone was much less effective than anticipated. Hence, OPPTIMUM's failure to demonstrate benefit (at least for the obstetric outcome) is not because it is underpowered.

Progesterone is endorsed for preterm birth prevention in women with a short cervix by several expert guideline groups including the Society for Maternal Fetal Medicine in the USA (that recommend its use in women with a cervical length of ≤ 20 mm)[20] and the National Institute for Health and Care Excellence in the UK (that endorse its use in women with a cervical length of ≤ 25 mm).[21] Both of these guidelines (generated before the publication of OPPTIMUM) are likely to be revisited to take into account the data described here. We believe that a comprehensive individual patient-level data meta-analysis, evaluating the effect of progesterone in a variety of 'at-risk' subgroups, is likely to be helpful in determining the appropriate role of progesterone for preterm birth prevention.

Acknowledgements

Contributions of authors

Jane E Norman, **Neil Marlow**, **Andrew Shennan**, **Philip R Bennett**, **Steven Thornton**, **Stephen C Robson**, **Stavros Petrou**, **Neil J Sebire**, **Tina Lavender** and **John Norrie** contributed to study design.

Jane E Norman, Neil Marlow, Andrew Shennan, Philip R Bennett, Steven Thornton, Stephen C Robson, Stavros Petrou, Neil J Sebire, Tina Lavender, **Sonia Whyte** and the OPPTIMUM study group contributed to data collection.

Claudia-Martina Messow, **Alex McConnachie** and John Norrie did the statistical analysis of the data.

Jane E Norman, Claudia-Martina Messow, Alex McConnachie and John Norrie did the initial data interpretation.

Jane E Norman wrote the first draft of the manuscript.

All authors contributed to final data interpretation and contributed to and approved the final draft of the manuscript.

Publications

Two previous publications describe the protocol for OPPTIMUM and the main study results, respectively, and are listed here:

Norman JE, Shennan A, Bennett P, Thornton S, Robson S, Marlow N, *et al.* Trial protocol OPPTIMUM – does progesterone prophylaxis for the prevention of preterm labour improve outcome? *BMC Pregnancy Childbirth* 2012;**12**:79.

Norman JE, Marlow N, Messow CM, Shennan A, Bennett PR, Thornton S, *et al.* Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial. *Lancet* 2016;**387**:2106–16.

Conference abstracts

Norman JE, Messow CM, Shennan A, Bennett P, Thornton S, Robson SC, et al. Opptimum. *Am J Obstet Gynecol* 2016;**214**:S452–53. Presented at the Society of Maternal and Fetal Medicine Conference, Atlanta, GA, February 2016.

OPPTIMUM was also presented to the Paediatric Academic Societies meeting, Baltimore, MD, April 2016. Abstracts are not published for this meeting.

Data sharing statement

We shall make data available to the scientific community with as few restrictions as feasible, while retaining exclusive use until the publication of major outputs. It is the intention of the authors to deposit the data in a data sharing repository, once the appropriate governance arrangements are secured

(including identification of a suitable repository that will ensure privacy of the participants, and define conditions for use). In the meantime, data can be made available by contacting the corresponding author.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Study drugs

Two SmPCs are shown. The first with arachis oil as the excipient and the second with sunflower oil as the excipient.

(a) (Arachis)

Utrogestan 200mg Capsules
Summary of Product Characteristics

1. NAME OF MEDICINAL PRODUCT

Utrogestan 200mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 200 mg micronised progesterone (INN). For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Capsules, soft
White

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Adjunctive use with estrogen in post-menopausal women with an intact uterus. (HRT)

4.2. Posology and method of administration

Posology

In women receiving estrogen replacement therapy there is an increased risk of endometrial cancer which can be countered by progesterone administration. The recommended dose is 200 mg daily at bedtime, for twelve days in the last half of each therapeutic cycle (beginning on day 15 of the cycle and ending on day 26). Withdrawal bleeding may occur in the following week.
Alternatively 100 mg can be given at bedtime from day 1 to day 25 of each therapeutic cycle, withdrawal bleeding being less with this treatment schedule.
Children: Not applicable.
Elderly: As for adults
Method of Administration: Oral. Utrogestan 200mg Capsules should not be taken with food

4.3. Contraindications

Known allergy or hypersensitivity to progesterone or to any of the excipients. The capsules contain arachis oil (peanut oil) and should never be used by patients allergic to peanuts. Severe hepatic dysfunction. Undiagnosed vaginal bleeding. Mammary or genital tract carcinoma. Thrombophlebitis. Thromboembolic disorders. Cerebral haemorrhage. Porphyria.

4.4. Special warning and precautions for use

Warnings:
Utrogestan 200mg Capsules are not a treatment for premature labour. Prescription of progesterone beyond the first trimester of pregnancy may reveal gravidic cholestasis.
Utrogestan 200mg Capsules are not suitable for use as a contraceptive.
If unexplained, sudden or gradual, partial or complete loss of vision, proptosis or diplopia, papilloedema, retinal vascular lesions or migraine occur during therapy, the drug should be discontinued and appropriate diagnostic and therapeutic measures instituted.
Utrogestan 200mg Capsules are intended to be co-prescribed with an estrogen product as HRT. Epidemiological evidence suggests that the use of HRT is associated with an increased risk of developing deep vein thrombosis (DVT) or pulmonary embolism. The prescribing information for the co-prescribed estrogen product should be referred to for information about the risks of venous thromboembolism.
There is suggestive evidence of a small increased risk of breast cancer with estrogen replacement therapy. It is not known whether concurrent progesterone influences the risk of cancer in post-menopausal women taking hormone replacement therapy. The prescribing information for the coprescribed estrogen product should be referred to for information about the

risks of breast cancer.
Precautions
Prior to taking hormone replacement therapy (and at regular intervals thereafter) each woman should be assessed. A personal and family medical history should be taken and physical examination should be guided by this and by the contraindications and warnings for this product.
Utrogestan 200mg Capsules should not be taken with food and should be taken at bedtime. Concomitant food ingestion increases the bioavailability of Utrogestan 100mg Capsules.
Utrogestan 200mg Capsules should be used cautiously in patients with conditions that might be aggravated by fluid retention (e.g. hypertension, cardiac disease, renal disease, epilepsy, migraine, asthma); in patients with a history of depression, diabetes, mild to moderate hepatic dysfunction, migraine or photosensitivity and in breast-feeding mothers.
Clinical examination of the breasts and pelvic examination should be performed where clinically indicated rather than as a routine procedure.
Women should be encouraged to participate in the national breast cancer screening programme (mammography) and the national cervical cancer screening programme (cervical cytology) as appropriate for their age. Breast awareness should also be encouraged and women advised to report any changes in their breasts to their doctor or nurse.

4.5. Interaction with other medicinal products and other forms of interaction

Utrogestan 200mg Capsules may interfere with the effects of bromocriptine and may raise the plasma concentration of cyclosporine. Utrogestan 200mg Capsules may affect the results of laboratory tests of hepatic and/or endocrine functions.
Metabolism of Utrogestan 200mg Capsules is accelerated by rifamycin an antibacterial agent.
The metabolism of progesterone by human liver microsomes was inhibited by ketoconazole (IC_{50} <0.1 ìM Ketoconazole is a known inhibitor of cytochrome P450 3A4. These data therefore suggest that ketoconazole may increase the bioavailability of progesterone. The clinical relevance of the in vitro findings is unknown.

4.6. Pregnancy and lactation

Pregnancy
Utrogestan 200mg Capsules are not indicated during pregnancy. If pregnancy occurs during medication, Utrogestan 200mg Capsules should be withdrawn immediately.
Lactation
Detectable amounts of progesterone enter the breast milk. There is no indication for prescribing HRT during lactation.

4.7. Effects on ability to drive and use machines

Utrogestan 200mg Capsules may cause drowsiness and/or dizziness in a minority of patients; therefore caution is advised in drivers and users of machines. Taking the capsules at bedtime should reduce these effects during the day.

4.8. Undesirable effects

Somnolence or transient dizziness may occur 1 to 3 hours after intake of the drug. Bedtime dosing and reduction of the dose may reduce these effects.
Shortening of the cycle or breakthrough bleeding may occur. If this occurs, the dose of Utrogestan 200mg Capsules can be reduced and taken at bedtime from day 1 to day 26 of each therapeutic cycle.
Acne, urticaria, rashes, fluid retention, weight changes, gastro-intestinal disturbances, changes in libido, breast discomfort, premenstrual symptoms, menstrual disturbances; also chloasma, depression, pyrexia, insomnia, alopecia, hirsutism; rarely jaundice.
Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and

pulmonary embolism, is more frequent among hormone replacement therapy users than among non-users.

4.9. Overdose

Symptoms of overdosage may include somnolence, dizziness, euphoria or dysmenorrhoea. Treatment is observation and, if necessary, symptomatic and supportive measures should be provided.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group (ATC code: G03D)

Progesterone is a natural progestogen, the main hormone of the corpus luteum and the placenta. It acts on the endometrium by converting the proliferating phase to the secretory phase. Utrogestan 200mg Capsules have all the properties of endogenous progesterone with induction of a full secretory endometrium and in particular gestagenic, antiestrogenic, slightly antiandrogenic and antialdosterone effects.

5.2. Pharmacokinetic properties

Absorption

Micronised progesterone is absorbed by the digestive tract. Pharmacokinetic studies conducted in healthy volunteers have shown that after oral administration of 2 capsules (200mg), plasma progesterone levels increased to reach the Cmax of 13.8ng/ml +/- 2.9ng/ml in 2.2 +/- 1.4 hours. The elimination half-life observed was 16.8+/- 2.3 hours.

Although there were inter-individual variations, the individual pharmacokinetic characteristics were maintained over several months, indicating predictable responses to the drug.

Distribution

Progesterone is approximately 96%-99% bound to serum proteins, primarily to serum albumin (50%-54%) and transcortin (43%-48%).

Elimination

Urinary elimination is observed for 95% in the form of glycuroconjugated metabolites, mainly 3 α, 5 β –pregnanediol (pregnandiol).

Metabolism

Progesterone is metabolised primarily by the liver. The main plasma metabolites are 20 α hydroxy- Δ 4 α- prenolone and 5 α-dihydroprogesterone. Some progesterone metabolites are excreted in the bile and these may be deconjugated and further metabolised in the gut via reduction, dehydroxylation and epimerisation. The main plasma and urinary metabolites are similar to those found during the physiological secretion of the corpus luteum.

5.3. Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology and toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Arachis oil
Soya lecithin
Gelatin
Glycerol
Titanium dioxide

6.2. Incompatibilities

None.

6.3. Shelf-life

3 years.

6.4. Special precautions for storage

No special precautions for storage.

6.5. Nature and contents of container

The product is supplied in PVC/Aluminium blisters contained in cartons.

Pack size: 15 capsules per carton

6.6. Instructions for use and handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Laboratoires BESINS INTERNATIONAL
3, rue du Bourg l'Abbé
75003
Paris
France

8. MARKETING AUTHORISATION NUMBER

PL 16468/0007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23rd February 2006

10. DATE OF REVISION OF THE TEXT

Supprimé : 5
Supprimé : 6
Supprimé : January
Supprimé : 5

(b) (Sunflower)

ANNEXE I

SUMMARY OF THE PRODUCT'S CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

UTROGESTAN 200 mg, oral or vaginal soft capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Progesterone……..200-mg

For one soft capsule

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Oral or vaginal soft capsule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral route

- Pre-menstrual syndrome,
- Menstrual irregularities due to ovulation disorders or anovulation,
- Benign mastopathy,
- Premenopause,
- Hormone replacement therapy for menopause (as an oestrogen complement).

Vaginal route

- Progesterone support during ovarian insufficiency or complete ovarian failure in women lacking ovarian function (oocyte donation).
- Luteal phase supplementation during in vitro fertilization (IVF) cycles,
- Luteal phase supplementation during spontaneous or induced cycles, in cases of hypofertility, in primary or secondary sterility and in particular due to dysovulation,
- Risk of miscarriage or prevention of repeated miscarriage due to luteal phase insufficiency up until the 12th week of pregnancy.
- For all other progesterone indications, the vaginal route represents an alternative to the oral route, in cases of:
- Adverse events due to progesterone (somnolence after absorption by the oral route).

4.2 Posology and method of administration

As in all therapeutic indications, it is important to strictly respect the recommended dose.

Regardless of the indication or the administration route (oral or vaginal), the dosage should not exceed 200-mg per dose.

Oral route

For progesterone insufficiency, the average dosage is 200 to 300-mg of micronized progesterone per day.

It is not recommended to take the medicine close to mealtimes; preferably, it should be taken in the evening before going to bed.

- **In cases of luteal insufficiency** (premenstrual syndrome, benign mastopathies, menstrual irregularities, premenopause) the usual therapeutic programme is 200 to 300-mg per day:
  - either 200-mg taken in one dose before bedtime,
  - or 300-mg taken in two doses, 10 days per cycle, normally from the 17th to the 26th day inclusive.
- **In replacement treatment for the menopause**, oestrogen therapy is not recommended on its own (risk of endometrial hyperplasia): progesterone should be added at a dosage of 200-mg per day:
  - 100-mg taken twice a day,
  - or in a single dose of 200-mg in the evening before going to bed, either for 12 to 14 days per month or during the last two weeks of each therapeutic sequence.

This treatment should be followed by an interruption of any substitutive treatment for roughly one week during which it is normal to experience a deprivation haemorrhage.

For these indications, the vaginal route should be used at the same dosage as the oral

route in the case of side effects due to the progesterone (drowsiness after oral absorption).

Vaginal route

Each capsule should be inserted as far as possible into the vagina.

- Progesterone substitution for ovarian insufficiency or complete deficiency in women without ovaries (oocyte donation).

The therapeutic programme (in complement to an appropriate oestrogenic treatment) is as follows:

- 100-mg of micronized progesterone per day on the 13th and 14th day of the transfer cycle then,
- 200-mg of micronized progesterone per day from the 15th to the 25th day of the cycle, spread over one or two daily doses, then,
- From the 26th day of the cycle and, in the case of the start of pregnancy, this dose can be increased to a maximum of 600-mg/day spread over three doses.

This posology can be followed until the 60th day, or at the latest, until the 12th week of pregnancy.

- **Supplementation of the luteal phase during IVF cycles:**

The recommended posology is 400 to 600-mg per day in two or three doses each day starting from the hCG injection and until the 12th week of pregnancy.

- **Supplementation of the luteal phase during spontaneous or induced cycles**, in cases of hypofertility or primary or secondary sterility, especially by dysovulation: the recommended posology is 200 to 300-mg per day in two doses starting from the 17th day of the cycle for 10 days. The treatment should be started again rapidly should menstruation not occur or pregnancy is diagnosed until the 12th week of pregnancy.
- **Risk of miscarriage or prevention of repeated miscarriages due to luteal insufficiency:** the recommended posology is 200 to 400-mg per day taken in two doses until the 12th week of pregnancy.

4.3 Contraindications

This medicine is contraindicated in the case of serious alterations to the hepatic function.

4.4 Special warnings and precautions for use

Special warnings:

- More than half of all early miscarriages are due to genetic accidents. Furthermore, infectious phenomena and mechanical problems can be responsible for miscarriages. Therefore, the only effect of the administration of progesterone would be to slow down the expulsion of a dead ovum (or the interruption of a non-evolutional pregnancy).
- The use of progesterone should only be reserved to cases where the secretion of the corpus luteum in insufficient.
- Under the recommended conditions of use, this treatment is not contraceptive.
- The use of UTROGESTAN 200-mg during a pregnancy is reserved to the first three months and for the vaginal route. UTROGESTAN 200-mg is not a treatment against the risk of premature birth.
- Cytolytic-type cases of hepatic attack and cases of gravidic cholestase have been reported on extremely rare occasions during the administration of micronized progesterone during 2nd and 3rd thirds of pregnancy.

4.5 Interaction with other medicinal products and other forms of interaction

Not applicable.

4.6 Pregnancy and breast feeding

Numerous epidemiological studies on over one thousand patients have not shown any association between progesterone and foetal malformations.

4.7 Effects on ability to drive and use machines

Attention should be paid, especially for drivers of vehicles and those using machinery of the risks of drowsiness and/or dizziness attached to the use of this medicine when taking it by the oral route.

4.8 Undesirable effects

Oral route

- Drowsiness of transitory dizziness occurring 1 to 3 hours after ingestion of the product. In this case:
- Decrease the posology of each dose,
- Or modify the rhythm of the doses (i.e. for a dosage of 200-mg/day, take the 200-mg in the evening before bedtime in a single dose not close to mealtimes).
- Or adopt the vaginal route.
- Shortening of the menstrual cycle or intercurrent bleeding. Move the start of treatment to later on in the cycle (for example, start on the 19th day of the cycle in stead of the 17th).

In most cases, these effects indicate overdose.
Due to the presence of soya lecithin there is a risk of hypersensitive reactions occurring (anaphylactic shock, urticaria).

Vaginal route

- No local intolerance (burning, pruritus or fatty discharge) has been observed during the different clinical trials.
- No general side effect, in particular, drowsiness or dizziness has been reported during clinical studies at the recommended dosages.

4.9 Overdose

See part 4.8.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PROGESTERONE

(G03DA04: genito-urinary system and sexual hormones).

The properties of UTROGESTAN are comparable to those of natural progesterone, in particular, gestagen, anti-oestrogen, slightly anti-androgen and anti-aldosterone.

5.2 Pharmacokinetic properties

Oral route

Absorption
Micronized progesterone is absorbed by the digestive route.
Progesterone blood level rises during the first hour and the highest plasmatic levels are reached 1 to 3 hours after taking the medicine.
Pharmacokinetic studies carried out on volunteers have shown that after the simultaneous ingestion of two capsules of UTROGESTAN 100-mg, the progesterone blood level on average goes from 0.13-ng/ml to 4.25-ng/ml after one hour, 11.75-ng/ml after 2 hours, 8.37-ng/ml after 4 hours, 2-ng/ml after 6 hours and 1.64-ng/ml after 8 hours.
Given the tissue retention time of the hormone, it would appear necessary in order to obtain an impregnation the length of the nychthemeron, to spread the dosage over two doses roughly 12 hours apart.
There are noticeable individual variations, however, the same individual conserves the same pharmacokinetic characteristics for several months which leads to good individual adaptation to the posology.
Metabolism
In the plasma, the principle metabolites are 20α-hydroxy, _4-pregnanolone and 5α-dihydroprogesterone.
Urinary elimination is 95 % in the form of glycuroconjugated metabolites the principal of which is 3α-5β-pregnandiol. These plasmatic and urinary metabolites are identical to those found during the physiological secretion of the ovarian corpus luteum.

Vaginal route

Absorption
After vaginal insertion, the absorption of the progesterone by the vaginal mucous is rapid, as witnessed by the increase in the plasma progesterone levels one hour after its administration.
The maximum plasmatic concentration is attained 2 to 6 hours after insertion and is maintained at an average concentration over 24 hours of 9.7-ng/ml after administration

of 100-mg in the morning and evening. Therefore, this recommended average dosage brings about stable and physiological plasmatic concentrations of progesterone similar to those observed during the luteal phase of a normal ovulatory menstrual cycle. The low interpersonal variations in the levels of progesterone permit a precise forecast of the effect expected with a standard posology.
At doses above 200-mg per day, the concentrations of progesterone obtained are comparable to those described during the first three months of pregnancy.
Metabolism
The concentration of 5β-pregnanolone is not augmented in the plasma.
Urinary elimination is mainly in the form of 3α, 5β-pregnandiol as is witnessed by the progressive increase in its concentration (until it attains the maximum concentration of 142-ng/ml by the 6th hour).

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sunflower oil, soya lecithin
Capsule shell: gelatine, glycerine and titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

There are no special precautions for storage.

6.5 Nature and contents of container

14, 15, 30 or 60 capsules in blister packs (PVC/aluminium)

6.6 Special precautions for disposal and other handling

No particular requirements.

7. MARKETING AUTHORIZATION HOLDER

LABORATOIRES BESINS INTERNATIONAL
3, rue du Bourg l'Abbé
75003 PARIS – FRANCE

8. MARKETING AUTHORIZATION NUMBERS

- 361 988-1: 14 capsules in a blister pack (PVC/aluminium).
- 348 399-6: 15 capsules in a blister pack (PVC/aluminium).
- 348 400-4: 30 capsules in a blister pack (PVC/aluminium).
- 348 401-0: 60 capsules in a blister pack (PVC/aluminium).

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

(To be completed by the authorization holder)

10. DATE OF REVISION OF THE TEXT

(To be completed by the authorization holder)

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

CONDITIONS FOR PRESCRIPTION AND ISSUE

List I

Appendix 2 Statistical analysis plan

OPPTIMUM

STATISTICAL ANALYSIS PLAN
FINAL ANALYSIS

Study Title:	Does progesterone prophylaxis to prevent preterm labour improve outcome? – a randomised double blind placebo controlled trial.
Short Title:	OPPTIMUM
EudraCT:	2007-007950-77
Funded by:	UK Medical Research Council

SAP Version:	v1.1	Date:	08/09/2015	
Protocol Version	v15.1	Date	01/04/2015	Date
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CONTENTS

1. INTRODUCTION

1.1. STUDY BACKGROUND

(This paragraph on the background to the study was updated in Spring 2015, to summarise the current literature).

Spontaneous preterm birth (PTB) is associated with high morbidity, mortality and high health costs. A systematic review [4]has shown that, in women with a previous history of preterm birth, progestogens reduces the risk of perinatal mortality (risk ratio (RR) 0.50, 95% confidence interval (CI) 0.33 to 0.75), and preterm birth less than 34 weeks (RR 0.31, 95% CI 0.14 to 0.69). Progestogens also reduce the risk of preterm birth before 34 weeks in women with a short cervix (RR 0.64, 95% CI 0.45 to 0.90) . In women with "other" risk factors for preterm birth, progestogens reduce the risk of infant birthweight less than 2500 g (RR 0.48, 95% CI 0.25 to 0.91), but not preterm birth (RR 0.69, 95% CI 0.16 to 3.01). There is no significant effect of different routes of progesterone (a surrogate for different progestogens, since progesterone is normally given vaginally, and 17 hydroxyprogesterone caproate is given intramuscularly) for the majority of outcomes examined. An individual patient level data meta-analysis of vaginal progesterone given to women with a short cervix demonstrates that progesterone reduced the risk of preterm birth before 33 weeks (relative risk 0.58, 95% CI 0.42 to 0.80) and a composite of neonatal mortality and morbidity (relative risk 0.57, 95% CI 0.40 to 0.81. [7]

Despite the overwhelming evidence for the efficacy of progesterone in preterm birth prevention, there is very limited evidence on longer term infant and childhood effects, with the most recent Cochrane review indicating that "the assessment of which remains a priority". OPPTIMUM aims to address this issue.

1.2. STUDY OBJECTIVES

The objective of the study is to assess whether a prophylactic vaginal treatment with natural progesterone (200 mg/day) from 22 to 34 weeks gestation in women at high risk for PTB does, compared to placebo:

- improve obstetric outcome by lengthening pregnancy and thus reducing the incidence of preterm delivery (before 34 weeks gestation)? (Obstetric outcome)

- improve neonatal outcome by reducing a composite of death and major morbidity? (Neonatal outcome)

- lead to improved childhood cognitive and neurosensory outcomes at two years of age? (Early childhood outcome)

1.3. STUDY DESIGN

The study is designed as a UK multicentre double blind, randomised, placebo controlled trial. There are two parallel groups, one treated daily with 200mg vaginal progesterone, the other with an

identical looking placebo from their inclusion between 22 and 24 weeks gestation until week 34 or earlier delivery, elective (preterm) delivery, fetal membrane rupture or low-lying placenta (symptomatic placenta praevia).

Women with singleton pregnancy are invited to a screening visit if they are identified to be at risk of PTB (having either a history in a previous pregnancy of PTB, second trimester loss or premature fetal membrane rupture in a previous pregnancy, a current cervical length <25mm or any cervical procedure to treat abnormal smears) at a routine antenatal appointment between 22^{+0} and 24^{+0} weeks gestation. If they consent, a fetal fibronectin (fFN) test is carried out. Those with a positive result are invited to participate in the study, and comprise the "high risk" group. Those with a negative result are invited to participate if they have had a previous spontaneous preterm birth before 34^{+0} weeks gestation or a cervical length of 25mm or less between 18^{+0} and 24^{+0} weeks gestation in the current pregnancy and together comprise the "low risk" group. Women giving further consent are randomised to receive either 200mg/day vaginal progesterone or identical looking placebo.

A baseline examination is carried out and a formal follow up visit at 34 weeks gestation. Information on labour and delivery is recorded, as well as information on contacts with social care or health professionals from a patient diary.

The women's satisfaction is assessed through two questionnaires, one at one week and one at six months after delivery, and through focus group interviews in a subset of randomised women.

For the babies a neonatal examination is carried out. A cranial ultrasound is performed within one month of birth. At two years of age, the development of the child is assessed in a follow up visit.

1.4. SAMPLE SIZE AND POWER

The study was originally designed to have a sample size of 750 (375 per group). Due to slow recruitment, the inclusion criteria were modified to allow women at lower risk of preterm birth (but still with potential to benefit from the intervention) into the study. This required an increase in sample size. Both sample size calculations are described below.

1.4.1. ORIGINAL CALCULATION

A sample size of 750 (375 per group) gives adequate statistical power to detect clinically important and plausible differences in the three primary measures of outcome. All these power calculations allow for loss to follow up rates (5% at delivery and 10% at 2 years) and suboptimal compliance.

Primary Obstetric Outcome: The primary obstetric outcome is delivery before 34^{+0} weeks gestation. On placebo, this is expected to be 40% (data from an untreated high risk UK population with a positive fFN test at 22 weeks[22]) and 27% on progesterone consistent with the odds ratio of 0.45 for the overall PTB with any progestational agent.[23] With 750 randomised, the study will have 95% power at a 5% level of significance to detect such a reduction from 40% to 27% using a two-sided binomial test. For a more modest reduction from 40% to 30% (odds ratio 0.64) the study would still have 80% power.

Primary Neonatal Outcome: The primary neonatal outcome is a composite of death, severe chronic lung disease, and intraventricular haemorrhage and also includes non-haemorrhagic brain injuries. With n=750 randomised, the OPPTIMUM study would have 80% power at a 5% level of

significance to detect a difference in this composite outcome of death, brain damage, or chronic lung disease from 20 to 12%, using a binomial test.

Primary Childhood Outcome: The primary childhood outcome is the Bayley III Cognitive Scale at 2 years. With 750 randomised, the study will have 93% power at a 5% level of significance to detect a difference in means equivalent to 0.25 of a standard deviation, using a two sample two sided t-test. Based on previous work[24], we estimate the standard deviation will be

about 15 points, enabling us to detect a difference of 4 points in the Bayley Score. In clinical terms, a difference of 4 points is small, thus the power of the study to detect larger, more clinically significant differences, is high.

1.4.2. Revised Calculation

The following calculations are based on recruiting 1250 women, where 400 are classified as high risk (i.e. meet the original entry criteria of having a positive fFN test at 22^{+0}-24^{+0} weeks gestation, plus satisfying the screening phase entry criteria), and 850 are classified as low risk (i.e. a previous spontaneous preterm birth before 34^{+0} weeks gestation or a cervical length of 25mm or less between 18^{+0} and 24^{+0} weeks gestation in the current pregnancy, with a negative fFN test at 22 weeks).

Primary Obstetric Outcome: The following table gives the estimated power for different combinations of sample sizes, all assuming that the proportion of high risk women will be one third of the study population and assuming a relative treatment effect of 32.5%.

Table 1 *Study power for a variety of sample sizes, and a variety of proportions of women at high and low risk*

Event rate		Power for total number of subjects of		
High risk	Low risk	1125	1200	1275
40%	10%	81%	83%	85%
45%	13%	88%	90%	92%
50%	15%	93%	94%	95%

The assumed outcome rates in the placebo group were conservative estimates, based on a blinded data review.

Primary Neonatal Outcome: Assuming that in the placebo group, the primary neonatal outcome (neonatal death, severe chronic lung disease, intraventricular haemorrhage) rate is 25% in the high risk group and 8% in the low risk group, then the overall outcome rate will be 13.67%. A sample size of 1125 women will have 81% power to detect a reduction in this rate to 8.2% (a relative risk of 0.6, as per the original calculation). Under the same assumptions, a sample size of 1200 women will have 83% power and a sample size of 1275 will have 86% power. The assumed outcome rates in the placebo group were also based on a blinded data review, though the data at the time were less mature than for the primary obstetric outcome.

Primary Childhood Outcome: At the time the power calculation was revised there was no data mature on this outcome within OPPTIMUM, as the first babies born had not yet reached two years of age. It is more difficult to assess the power convincingly with a mixture of high and low risk women on a continuous outcome such as the Bayley Score, since the power calculation requires assumptions about not just the anticipated treatment effect but also the assumed variability via the standard deviation. If we assume the same 4 unit difference in the high risk and a 4/3 unit difference in the low risk group (consistent with the pro-rata rate of delivery <34 weeks), with the same 15 unit standard deviation, then the study will have 71%, 73% or 76% power if 1125, 1200 or 1275 women are randomised. However, this is for an unadjusted analysis, and in practice we will adjust

for high and low risk group, and a limited number of other baseline covariates strongly related to Bayley Score at 2 years (eg gender) as specified in the statistical analysis plan, and this will reduce the variability and hence increase the power. For example, if the underlying variability in the lower risk group is lower – say halved, at 7.5 units, consistent with a higher proportion having uniformly high Bayley Scores since they have no disability – then the approximate power would be 93%, 94% or 95%. In practice the reduction in variability by adjusting for both this design variate (high and low risk) and additional baseline covariates may be considerably greater, so we are confident that the original power on the childhood development outcome will be protected at or above the original 90% level by randomising at least 1125 subjects.

1.5. STUDY POPULATION

The study population are pregnant women who meet all inclusion and none of the exclusion criteria listed below and who give written informed consent to participate in the study.

1.5.1. INCLUSION CRITERIA

- Screening phase:
    - At least one of
        - History of PTB or second trimester loss.
        - History of previous preterm premature fetal membrane rupture.
        - Cervical length < 25mm on ultrasound at 18^{+0}-24^{+0} weeks gestation.
        - Any cervical procedure to treat abnormal smears.
    - Gestation established by scan at 16^{+0} weeks or earlier.
    - Signed consent form.
    - Aged 16 years or older.

- Main study: At least one of
    - Positive fetal fibronectin (fFN) test at 22^{+0}-24^{+0} weeks gestation.
    - Previous spontaneous preterm birth before 34^{+0} weeks gestation.
    - Cervical length < 25mm on ultrasound at 18^{+0}-24^{+0} weeks gestation.

Depending on which inclusion criteria are met patients are classified as high or low risk as follows:

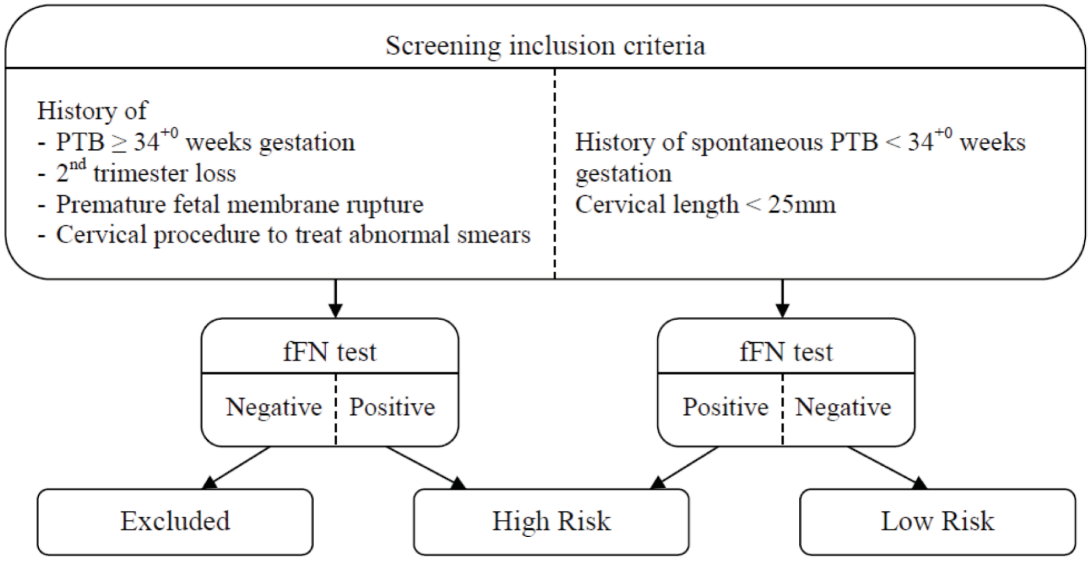

Figure 1 *Screening inclusion criteria, and risk allocation according to fFN status*

1.5.2. Exclusion Criteria

- Known significant structural or chromosomal fetal anomaly.
- Known sensitivity, contraindication or intolerance to progesterone (initially including peanut allergy, but this criterion has been removed later).
- Suspected or proven rupture of the fetal membranes at the time of recruitment.
- Multiple pregnancy.
- Prescription or ingestion of medications known to interact with progesterone.
- Women currently prescribed progesterone or who have taken progesterone beyond 18 weeks gestation.

1.6. Statistical Analysis Plan (SAP)

1.6.1. SAP Objectives

The objective of this SAP is to describe the statistical analyses to be carried out for the final analysis of the OPPTIMUM Study.

Earlier draft versions of the SAP only included analyses relating to birth and neonatal outcomes. It has then been decided to have only one SAP for all efficacy and safety analyses.

1.6.2. Current Protocol

The current study protocol at the time of writing is version 15.1, dated 1st April 2015. Future amendments to the protocol will be reviewed for their impact on this SAP, which will be updated only if necessary. If no changes are required to this SAP following future amendments to the study protocol, this will be documented as part of Robertson Centre Change Impact Assessment processes.

1.6.3. General Principles

For all variables summarised, the number of available measurements and the number of missing values will be given. Continuous variables will be summarised as mean, standard deviation, minimum, 1st quartile, median, 3rd quartile and maximum. For categorical variables, numbers and percentages for all categories will be given.

Baseline characteristics will be compared between patients with and patients without missing primary outcome variables.

The number of observations used and number of missing values will be reported for all analyses. Main analyses will not impute missing values, but multiple imputation strategies will be considered as sensitivity analyses. The following predictors will be considered:

Primary obstetric and neonatal outcomes: Previous pregnancy of at least 14 weeks, high/low risk, maternal age, sex. Gestational age will not be used to predict the primary neonatal outcome since it is assumed to be too closely related.

Primary Childhood outcome: Gestational age, birth weight, Chronic Lung Disease, brain injury, previous pregnancy of at least 14 weeks, high/low risk, maternal age, sex. Multiple imputation will be repeated not using gestational age, since gestational age is likely to be a predictor of the other variables in the model.

As results of generalised linear models, type 3 p-values, effect estimates (in case of a binomially distributed outcome odds ratios) and 95% confidence intervals for the effect estimates will be reported for each variable in the model. For all generalised linear models the canonical link function will be used.

Regression analyses will adjust for previous pregnancy of at least 14 weeks and study centre as a random effect. Continuous variables may be transformed to enhance model fit.

In addition, regression analyses adjusting for baseline covariates that are significantly related to the outcome in question will be carried out as major secondary analyses. All baseline variables will considered for this. The subset of variables related to each outcome will be determined prior to unblinding through LASSO retaining all variables with non-zero coefficients. The results of this blinded analysis and the resulting sets of adjustment variables will be documented and agreed prior to the final unblinded analysis.

The global level of significance is 0.05. The statistical report will present p-values without adjustment for multiple comparisons. Given that more than one primary outcome will be analysed, the results will also be interpreted with adjustment by the Bonferroni-Holm method [Holm 1979]. The analyses of secondary and exploratory outcomes are exploratory, therefore no adjustment will be done. P-values other than for the primary outcomes have to be considered as descriptive measures.

1.6.4. Deviations to the Analyses Specified in Study Protocol

The primary neonatal outcome was defined as death OR (brain injury AND severe chronic lung disease) in the study protocol. It has been agreed that the primary neonatal outcome to be analysed is death OR brain injury OR severe chronic lung disease.

The protocol states that in the subgroup analyses the significance level will be 0.01. This will not be done, as all subgroup analyses are now exploratory.

In the protocol it was planned to use two part models for the analysis of the primary childhood outcome, the Bayley III scale. Over the course of the study it has been decided to analyse death and Bayley III scores separately for the primary analysis, since the interpretation of a combined analysis might be difficult. In addition, analyses of each primary outcome will be carried out using multiple imputation to account for missing values; in these analyses, Bayley III scores of children who died will be imputed as the lowest possible score -1, which is 49.

The protocol mentions that the Child Behavior Check List will be part of the childhood outcomes. However, the Child Behavior Check List is not used and therefore not part of the outcomes in this SAP.

1.6.5. Additional Analyses to those Specified in Study Protocol

Additional analyses are detailed in section 2.7.

1.6.6. Software

Statistical analyses will be carried out with S-Plus for Windows v8.1, SAS v9.3 or R v3.0.1 or higher versions of those programs.

2. Analysis

2.1. Study Populations

All efficacy analyses will be carried out on the intention to treat population. Safety analyses will be carried out on the safety population. Primary analyses will be repeated exploratorily on the per protocol population.

2.1.1. Population Definitions

Screening population: All women who have been screened for the trial and consented to the fFN test.

Safety population: All women and children who were randomised and have been exposed to the study drug at least once according to the patient diary or the number of doses returned. The women will be grouped according to treatment received for the safety analyses.

Intention to treat (ITT) population: All women and children who were randomised and did not fail any inclusion/exclusion criteria.

Per protocol (PP) population: All members of the ITT population without any major protocol violations and for whom there is sufficient evidence of adequate treatment compliance. The following predefined protocol violations will be considered:

- Structural or chromosomal fetal anomaly discovered after inclusion.
- Multiple pregnancy discovered after inclusion.
- Patient has ingested medications known to interact with progesterone.
- Any other reported potential protocol violations.

Other protocol violations may be identified during blinded data reviews prior to the final analyses.

2.1.2. SUBGROUPS

In order to determine whether a reduced or improved response to progesterone can be predicted, subgroups of the ITT population will be formed according to the following factors (ordered from most important to least important):

1. Risk group (high risk / low risk).
2. Cervical length at 18-24 weeks gestation (≤25mm / >25mm and ≤15mm / >15mm).
3. Reason for risk of preterm delivery.
    a. Spontaneous preterm birth (yes / no).
    b. Any preterm birth (yes / no).
4. Chorioamnionitis diagnosed on pathology (yes / no).
5. Previous pregnancy of at least 14 weeks (yes / no).

2.1.3. PATIENT NUMBERS

The number of women in the following groups will be reported for the whole study and separately for each study site:

- Screened women.
- Women in the safety population.
- Women in the ITT population.
- Women in the PP population.

Further, the number of women excluded in each step will be reported according to the different reasons for exclusion.

2.2. INCLUSION CRITERIA

The following inclusion criteria will be summarised for all patients, for subgroups according to treatment groups and for subgroups according to missingness of primary outcome variables for each outcome:

- History of delivery / pregnancy loss at 16 or more and less than 37 weeks gestation.
- Previous preterm premature rupture of fetal membranes before or at 37 weeks gestation.
- Cervical length <25mm on ultrasound at 18+0 to 24+0 gestation.
- Any cervical procedure to treat abnormal smears.
- Positive fetal fibronectin test at 22–24 weeks gestation.
    - Negative fetal fibronectin test at 22+0 to 24+0 weeks gestation and previous spontaneous preterm birth before or at 34 weeks gestation.
    - Negative fetal fibronectin test at 22+0 to 24+0 weeks gestation and cervical length ≤ 25mm between 18 and 24 weeks gestation in index pregnancy.

All other inclusion criteria have to be met by all women in the ITT population and will therefore not be summarised.

2.3. BASELINE CHARACTERISTICS

The following baseline variables will be summarised for all patients, for subgroups according to treatment groups and for subgroups according to missingness of primary outcome variables for each outcome:

- Age at trial entry as (date of trial entry – date of birth)/365.25
- Height
- Weight (earliest recorded during this pregnancy)
- BMI=weight [kg]/(height[m])^2
- Smoking at baseline (yes/no)
- Alcohol at baseline (yes/no)
- Drug use at baseline (yes/no)
- Level of education
- Ethnic group (White / Asian / Afro-Caribbean / Oriental / Mixed / other)
- Systolic blood pressure
- Diastolic blood pressure
- Week of gestation at inclusion calculated from EDD from scan
  - Result of fetal anomaly scan (normal / defined abnormality / uncertain abnormality / not done)
- Amniocentesis (normal / not normal / not done)
- CVS (normal / not normal / not done)
- Cervical length at 18-24 weeks gestation
- Number of live births
- Total number of pregnancies
- History of induced labour or elective caesarean.
- History of miscarriage.
- History of ectopic pregnancy.
- History of TOP before 14 weeks gestation.
- History of TOP at or after 14 weeks gestation.
- History of still birth.
- History of live birth followed by neonatal death.
- History of spontaneous preterm birth with premature membrane rupture.
- History of spontaneous preterm birth without premature membrane rupture.
- History of elective or induced preterm birth.
- EQ-5D

2.4. EFFICACY OUTCOMES

All outcome variables will be summarised for all patients and according to treatment groups.

2.4.1. PRIMARY OUTCOME

OBSTETRIC OUTCOME

The primary obstetric outcome is delivery or fetal death before 34 completed weeks of gestation based on ultrasound (based on the projected date of delivery estimated from scan in the first trimester).

The following null hypothesis will be tested:

There is no difference in the incidence of delivery or fetal death before 34 completed weeks of gestation between the group treated with 200mg / day progesterone and the group treated with placebo from week 22-24 to week 34 of gestation or earlier delivery.

The outcome will be compared between the treatment groups using a logistic regression model including treatment and previous pregnancy of at least 14 weeks. The hypothesis will be tested with a likelihood ratio test.

NEONATAL OUTCOME

The primary neonatal outcome is a binary outcome indicating whether one of the following has occurred:

- Death at any time point, i.e. miscarriage, stillbirth or neonatal death.

- Brain injury (defined as any intraventricular haemorrhage (IVH) (excludes subependymal haemorrhages), parenchymal cystic or haemorrhagic lesion or persistent ventriculomegaly (VI >97th percentile). If no scan has been carried out, it is assumed that there is no brain injury.

- Severe chronic lung disease (defined as need for ≥30% oxygen and/or positive pressure (positive pressure ventilation or nasal continuous positive airway pressure) at 36 weeks post menstrual age or discharge, which ever comes first).

The following null hypothesis will be tested:

There is no difference in the combined incidence of neonatal death, brain injury or severe chronic lung disease between the group treated with 200mg / day progesterone and the group treated with placebo from week 22-24 to week 34 or earlier delivery.

This outcome will also be compared between the treatment groups using a logistic regression model including treatment and previous pregnancy of at least 14 weeks. The hypothesis will be tested with a likelihood ratio test.

CHILDHOOD OUTCOME

The primary childhood outcome is the Bayley III Cognitive Scale standardised score at 2 years (22 to 26 months) of age. As the number of deaths at any point between randomisation and 2 years of age is expected to be sufficiently large as not to be negligible, survival up to 2 years will also be an outcome.

The following null hypotheses will be tested:

There is no difference in Bayley III cognitive scale standardised scores at 2 years of age between the group treated with 200mg / day progesterone and the group treated with placebo from week 22-24 to week 34 or earlier delivery.

There is no difference in survival up to 2 years between the group treated with 200mg / day progesterone and the group treated with placebo from week 22-24 to week 34 or earlier delivery.

The first outcome will be compared between the treatment groups using a linear regression model including treatment and previous pregnancy of at least 14 weeks. The hypothesis will be tested with a likelihood ratio test.

The second outcome will be compared between the treatment groups using a logistic regression model including treatment and previous pregnancy of at least 14 weeks. The hypothesis will be tested with a likelihood ratio test.

2.4.2. Secondary Outcomes

Secondary outcomes are:

- Obstetric:
    - Fetal death, i.e. miscarriage or stillbirth
    - Delivery before 34 completed weeks of pregnancy
- Birth and neonatal:
    - Gestational age at delivery.
    - Neonatal death
    - Incidence of the individual components of the primary neonatal outcome (death, brain injury, severe chronic lung disease).
    - Need for surfactant administration.
    - Incidence of necrosing entercolitis (no and suspected vs. yes, medical treatment only and yes, required drain or laparotomy).
    - Number of discrete episodes of bloodstream or CNS infection (e.g. positive blood or CSF culture).
    - Daily level of care after delivery room (normal / special / level 2 / level 1).
    - Maternal and child serious adverse events during pregnancy and birth. (Yes if either mother or child had at least one serious adverse event, else no)
- Childhood (2 years of age)
    - Composite outcome of death or moderate/severe neurodevelopmental impairment (as defined by BAPM/RCPCH working group, Jan 2008).
    - Moderate/severe neurodevelopmental impairment (as defined by BAPM/RCPCH working group, Jan 2008).
        - Individual components of disability (motor, cognitive function, hearing, speech and language, vision, respiratory, gastrointestinal, renal, as defined by BAPM/RCPCH working group, Jan 2008).
    - Medical events during follow-up
    - Behavioural outcome at 2 years assessed in parent questionnaire
- Change in EQ-5D from baseline
- Women's perception of treatment.

All secondary outcomes will be compared between treatment groups through generalised mixed linear regression analyses including treatment and adjusting for previous pregnancy of at least 14 weeks and a random effect for centre.

2.5. SAFETY OUTCOMES

2.5.1. TREATMENT COMPLIANCE

Patients are supposed to record on what days they took the study medication in the patient diary. In addition, medication packs will be reviewed. The number of doses of study medication taken will be recorded by the midwife in an interview with the patient, based on the information in the diary and the returned medication packs.

One dose of study medication should be taken daily from the date of randomisation until the start of labour or 6 weeks prior to the expected date of delivery (EDD), which ever comes first. The expected number of doses of study medication is then

min(Date of membrane rupture, EDD - 6 weeks) - Date of randomisation

Compliance will be calculated as the ratio of the number of doses of study medication used, divided by the expected number of doses for each patient, expressed as a percentage. Compliance will be summarised for all women and separately for both treatment groups.

Patients are considered to be adequately compliant if they have taken the medication on at least 80% of the days they should have taken it.

2.5.2. PREMATURE WITHDRAWAL

The following details on premature withdrawals will be summarised according to treatment groups:

- Number of women who stopped treatment
- Main reason for discontinuation.
    - Woman unwilling to continue
    - Severe adverse event
    - Detection of significant structural chromosomal anomalies after randomisation
    - Woman violated protocol
    - Sponsor terminated participation
    - Investigator terminated participation
    - Woman withdrawn consent for use of outcome data
    - Elective (preterm) delivery
    - Fetal membrane rupture
    - Symptomatic placenta praevia
    - Other reason

2.5.3. ADVERSE EVENTS

All serious adverse events, including intrauterine infections or chorioamnionitis, occurring during the study will be listed individually. Listings will include the system organ class and preferred term according to the MedDRA system, the date of onset, the date the adverse event ended, the intensity of the adverse event, relationship to study medication, medication taken in relation to the serious adverse event (for details see section on concomitant medications), and the outcome.

Serious adverse events will be summarised as the number and percentage of subjects reporting at least one event by system organ class, preferred term, intensity, and relationship to study medication for each treatment group.

The same serious adverse event recorded by a patient at different visits will count as one event for that patient, with the strongest reported intensity and relationship to study medication.

Data on non-serious adverse events is not collected in this study.

2.5.4. Concomitant Medications

Only medications in relation with serious adverse events are recorded. These will be listed individually, including drug name, start date, stop date, dose, frequency and the SAE they're linked to.

2.5.5. Other Safety Outcomes

The following safety outcomes will be summarised according to treatment groups:

Pregnancy complications

Hospital admissions before Delivery:
- Indication
- Diagnosis
- Duration of hospital stay
- Tocolysis and details thereof
- Steroid therapy
- Antibiotic therapy
- Treatment with magnesium sulphate

Labour
- Type of labour (Spontaneous / Induced) or Elective CS
- Duration of stages of labour
- Details of membrane rupture
- Analgesics

Delivery
- Delivery method
- Reason for assisted delivery
- Blood loss
- Suture
- Reason for suture
- Blood transfusion
- Antibiotics
- Surgical procedure required
- Duration of hospital stay

Results of the placental examination (classified as "normal", "ascending infection" or "other pathology")

Post partum complications

Child assessment at birth
- Sex
- Weight
- Apgar score at 1 minute

- Apgar score at 5 minutes
- Duration of hospital stay

Child assessment at 2 years
- Weight
- Height
- Head circumference
- Respiratory rate
- Heart rate
- Blood pressure

2.6. SUBGROUP ANALYSES

The analyses of the primary outcomes will be repeated on the subgroups of patients defined in section 2.1 in an exploratory manner.

In addition, the effect of the subgroup variables on outcome will be analysed through logistic regression models. Logistic regression will be carried out in one model including the subgroup variable and treatment and a second model additionally including the interaction term of the subgroup variable and treatment.

2.7. ADDITIONAL ANALYSES

Additional analyses to those specified in this SAP based on the results of the primary and secondary analyses may be carried out at a later stage where appropriate. Any additional analyses will be documented separately as appropriate. The following additional analyses are planned at this stage.

2.7.1. SURVIVAL ANALYSIS

The possibility of analysing survival from randomisation up to two years using proportional hazards regression as a supplemental analysis to the primary childhood outcome will be explored.

2.7.2. RISK FACTOR MODEL

The possibility of creating a risk prediction model for the primary obstetric outcome will be explored. Variables considered for the risk prediction model will be those related to the primary obstetric outcome identified as explained in section 1.6.3. Logistic regression will be used in the first place to derive a risk score, but the use of other methods may be explored. The predictive performance of the resulting risk score will be assessed.

3. DOCUMENT HISTORY

This is version 1.1 of the SAP for the OPPTIMUM study, dated 16th November 2011, replacing v1.0, dated 01st September 2010. It is based on version 13 of the study protocol. The following changes have been made:

inclusion criteria have been modified to allow inclusion of women with a negative fFN test at 22 weeks gestation (Section 1.5.1).
Added definition of high/low risk group to inclusion criteria section.
sample size calculations for the modified study have been added (Section 1.4).

more explicit reference has been made to the current protocol version (Section 1.6.2).
Details about adjusted analyses of the primary outcomes added (Section 1.6.3).
Details about imputation of missing values added (Section 1.6.3).
Change of primary neonatal outcome added to deviations section (Section 1.6.4).
Section about primary childhood analysis added to deviations section (Section 1.6.4).
Population definitions updated (Section 2.1.1).
Added hierarchy to subgroup analyses (Section 2.1.2).

Added list of inclusion criteria that will be summarised, i.e. those where not all of them need to be met (section 2.2).
Lists of outcomes updated (Sections 2.4 and 2.5).
Section about additional analyses added (Section 2.7).
Risk factor model has been moved into the additional analyses section.
Sample tables have been removed (Section 4).
Introduction updated to reflect current literature.

4. TABLES

The layout of the tables will be agreed based on tables created using dummy treatment codes prior to database lock.

5. LISTINGS

Listing 1: Serious Adverse Events.
Listing 2: Listing of coconcomitant medications in relation to serious adverse events.

Appendix 3 Statistical analysis output

Part 1: patient numbers

Does progesterone prophylaxis to prevent preterm labour improve outcome?	
OPPTIMUM	
Final report tables	
Part 1: patient numbers	
v1.1	
20 November 2015	
Martina Messow	
Robertson Centre for Biostatistics	
EudraCT number	2007-007950-77
CTA number	22931/0009/001-0001 revised by MHRA to 01384/0208/001
MREC number	08/MRE00/6
ISRCTN	ISRCTN14568373
Co-sponsors	University of Edinburgh/NHS Lothian
Funder	Medical Research Council/NIHR EME
Funding reference number	G0700452, Grant No: 84982 – 09/800/27
Protocol version	15.1 (1 April 2015)
SAP version	1.1 (8 September 2015)

CTA, Clinical Trial Authorisation; EudraCT, European Union Drug Regulating Authorities Clinical Trials; MREC, Multicentre Research Ethics Committee; SAP, statistical analysis plan.

TABLE 24 Number of patients in each population (screening, ITT, safety and PP), overall and by treatment group

Population	All	Placebo	Progesterone
Screening, *n*	15,132	–	–
Randomised (% of screened), *n* (%)	1228 (8.1)	610	618
ITT (% of randomised), *n* (%)	1226 (99.8)	610 (100.0)	616 (99.7)
Safety (% of randomised), *n* (%)	1183 (96.3)	590 (96.7)	593 (96.0)
PP (% of ITT), *n* (%)	687 (56.0)	360 (59.0)	327 (53.1)

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Nov 20 11:25:52 2015.

TABLE 25 Number of patients in each population (screening, ITT, PP and safety), by study site

Site	Population (*n*)			
	Screening	ITT	PP	Safety
Ealing Hospital	77	3	2	3
University Hospital of Coventry, Warwickshire	448	20	5	20
Guy's & St Thomas' Hospital (KCL), London	959	165	71	149
Queen Charlotte's Maternity, London	212	35	11	34
Birmingham Women's Hospital	324	60	32	59
City Hospital, Nottingham	253	23	12	20
St Mary's Hospital, London	138	32	18	29
Wansbeck General Hospital	149	10	4	10
Ninewell's Hospital, Dundee	101	0	0	0
St Mary's Hospital, Manchester	227	14	12	13
Liverpool Women's Hospital	382	23	11	23
Royal Derby Hospital	130	9	5	9
Warrington Hospital	193	14	9	13
Princess Anne Hospital, Southampton	57	16	6	14
Edinburgh Royal Infirmary	259	41	15	41
Pilgrim Hospital	62	7	2	7
Royal Victoria Hospital, Newcastle	558	50	30	49
Aberdeen Maternity Hospital	63	11	7	9
Bradford Royal Infirmary	256	21	14	19
Worcester Royal Hospital	190	14	7	14
Royal Devon and Exeter	303	6	3	5
Pembury Hospital	3	1	1	1
University Hospital Wales/Llandough Hospital, Cardiff	261	23	13	23
University College Hospital, London	587	51	27	48
North Staffordshire Hospital	251	14	7	14
Wirral Hospital Trust	184	31	24	30
Cumberland Infirmary, Carlisle	27	0	0	0
Queen's Medical Centre, Nottingham	357	21	12	21
Brighton & Sussex University Hospitals NHS Trust	12	6	5	6
Heart of England Hospital	122	24	12	23
Lincoln County Hospital	97	2	0	2
Forth Park Hospital, Fife	34	7	5	7
South Tyneside NHS Foundation Trust	115	6	1	6
Royal Preston Hospital	604	44	31	44
Isle of Wight NHS Trust	261	21	17	21

TABLE 25 Number of patients in each population (screening, ITT, PP and safety), by study site (*continued*)

Site	Population (*n*)			
	Screening	ITT	PP	Safety
Calderdale Royal Hospital	50	0	0	0
Royal Hospital	52	7	4	7
Blackpool Victoria Hospital	393	13	10	13
Southport & Ormskirk NHS Trust	355	9	5	9
Burnley General Hospital	615	25	13	25
Queen Elizabeth Hospital, Gateshead	171	3	2	3
Royal Blackburn Hospital	924	9	5	8
Southern General Hospital	185	5	5	5
Derriford Hospital, Plymouth	284	12	6	12
The Ulster Hospital	10	1	0	1
West Cumberland Infirmary	49	6	3	6
Basingstoke & North Hampshire Foundation Trust	70	15	2	14
Lancaster, Morecambe and Furness	245	21	13	21
Chesterfield Royal Hospital	441	10	7	10
Chelsea & Westminster Hospital	53	14	8	14
Royal Cornwall	53	12	10	12
Royal Bolton Hospital	106	7	4	7
Royal Shrewsbury Hospital	182	3	2	3
Wishaw General Hospital	91	18	16	18
Basildon & Thurrock University Hospital	57	12	8	12
St George's Hospital London	177	12	9	11
South Warwickshire NHS Trust	317	5	2	5
West Middlesex University Hospital	172	25	12	25
The Dudley Group of Hospitals	340	14	9	14
Burton Hospitals NHS Foundation Trust	407	35	29	36
Norfolk & Norwich University Hospitals	86	24	15	24
Newham Hospital	14	6	3	5
City Hospitals Sunderland NHS Foundation Trust	663	58	36	57
Leighton Hospital, Mid-Cheshire	306	13	12	13
Sahlgrenska University	8	7	6	7

KCL, King's College London.

Note

OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Nov 20 11:25:53 2015.

Part 2: baseline characteristics

Does progesterone prophylaxis to prevent preterm labour improve outcome?	
OPPTIMUM	
Final report tables	
Part 2: baseline characteristics	
v1.0	
2 October 2015	
Martina Messow	
Robertson Centre for Biostatistics	
EudraCT number	2007-007950-77
CTA number	22931/0009/001-0001 revised by MHRA to 01384/0208/001
MREC number	08/MRE00/6
ISRCTN	ISRCTN14568373
Co-sponsors	University of Edinburgh/NHS Lothian
Funder	Medical Research Council/NIHR EME
Funding reference number	G0700452, Grant No: 84982 – 09/800/27
Protocol version	15.1 (1 April 2015)
SAP version	1.1 (8 September 2015)

CTA, Clinical Trial Authorisation; EudraCT, European Union Drug Regulating Authorities Clinical Trials; MREC, Multicentre Research Ethics Committee; SAP, statistical analysis plan.

TABLE 26 Inclusion criteria at randomisation: ITT population

		Trial group	
Inclusion criteria at randomisation	**All**	**Placebo**	**Progesterone**
History of delivery/pregnancy loss at ≥ 16 and < 37 weeks' gestation			
N_{obs} (N_{miss})	1225 (1)	610 (0)	615 (1)
No, *n* (%)	118 (9.6)	61 (10.0)	57 (9.3)
Yes, *n* (%)	1107 (90.4)	549 (90.0)	558 (90.7)
Previous preterm premature rupture of fetal membranes ≤ 37 weeks' gestation			
N_{obs} (N_{miss})	1225 (1)	610 (0)	615 (1)
No, *n* (%)	581 (47.4)	312 (51.1)	269 (43.7)
Yes, *n* (%)	644 (52.6)	298 (48.9)	346 (56.3)
Cervical length of ≤ 25 mm on ultrasound at 18^{+0}–24^{+0} weeks' gestation			
N_{obs} (N_{miss})	1225 (1)	610 (0)	615 (1)
No, *n* (%)	1000 (81.6)	506 (83.0)	494 (80.3)
Yes, *n* (%)	225 (18.4)	104 (17.0)	121 (19.7)
Any cervical procedure to treat abnormal smears			
N_{obs} (N_{miss})	1196 (30)	594 (16)	602 (14)
No, *n* (%)	1000 (83.6)	502 (84.5)	498 (82.7)
Yes, *n* (%)	196 (16.4)	92 (15.5)	104 (17.3)

TABLE 26 Inclusion criteria at randomisation: ITT population (*continued*)

Inclusion criteria at randomisation	All	Trial group	
		Placebo	Progesterone
Positive fFN test at 22–24 weeks' gestation			
N_{obs} (N_{miss})	1225 (1)	610 (0)	615 (1)
No, *n* (%)	882 (72.0)	430 (70.5)	452 (73.5)
Yes, *n* (%)	343 (28.0)	180 (29.5)	163 (26.5)
Negative fFN test at 22–24 weeks' gestation and previous spontaneous preterm birth before ≤ 34 weeks' gestation			
N_{obs} (N_{miss})	1175 (51)	585 (25)	590 (26)
No, *n* (%)	337 (28.7)	179 (30.6)	158 (26.8)
Yes, *n* (%)	838 (71.3)	406 (69.4)	432 (73.2)
Negative fFN test at 22–24 weeks' gestation and cervical length of ≤ 25 mm between 18 and 24 weeks' gestation in index pregnancy			
N_{obs} (N_{miss})	1175 (51)	585 (25)	590 (26)
No, *n* (%)	1057 (90.0)	532 (90.9)	525 (89.0)
Yes, *n* (%)	118 (10.0)	53 (9.1)	65 (11.0)

N_{miss}, number of women with missing data; N_{obs}, number of observations.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:33:54 2015.

TABLE 27 Baseline characteristics (part 1). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by treatment

Parameter	All	Trial group	
		Placebo	Progesterone
Age (years)			
N_{obs} (N_{miss})	1225 (1)	610 (0)	615 (1)
Mean (SD)	31.4 (5.7)	31.4 (5.8)	31.5 (5.6)
Median (IQR)	31.5 (27.4–35.7)	31.4 (27.2–35.7)	31.5 (27.6–35.6)
Range	16.8–49.2	17.5–49.2	16.8–45.9
Height (cm)			
N_{obs} (N_{miss})	1221 (5)	607 (3)	614 (2)
Mean (SD)	163.5 (6.6)	163.6 (6.4)	163.5 (6.7)
Median (IQR)	163.0 (159.0–168.0)	163.0 (159.0–168.0)	164.0 (159.0–168.0)
Range	144.0–183.0	144.0–183.0	147.0–183.0
Weight (kg)			
N_{obs} (N_{miss})	1221 (5)	607 (3)	614 (2)
Mean (SD)	71.6 (17.1)	71.4 (16.7)	71.9 (17.5)
Median (IQR)	68.0 (60.0–81.0)	68.0 (59.0–82.0)	68.0 (60.0–80.0)
Range	41.0–186.0	43.0–145.0	41.0–186.0

continued

TABLE 27 Baseline characteristics (part 1). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by treatment (*continued*)

Parameter	All	Trial group	
		Placebo	Progesterone
BMI (kg/m^2)			
N_{obs} (N_{miss})	1221 (5)	607 (3)	614 (2)
Mean (SD)	26.8 (6.3)	26.7 (6.1)	26.9 (6.4)
Median (IQR)	25.5 (22.3–29.8)	25.4 (22.2–29.7)	25.6 (22.5–29.8)
Range	15.2–80.5	15.6–54.4	15.2–80.5
Systolic blood pressure (mmHg)			
N_{obs} (N_{miss})	1219 (7)	608 (2)	611 (5)
Mean (SD)	111.9 (12.4)	112.4 (12.2)	111.3 (12.5)
Median (IQR)	110.0 (102.0–120.0)	110.0 (104.0–120.0)	110.0 (100.0–120.0)
Range	78.0–189.0	78.0–159.0	82.0–189.0
Diastolic blood pressure (mmHg)			
N_{obs} (N_{miss})	1219 (7)	608 (2)	611 (5)
Mean (SD)	66.0 (8.6)	66.2 (8.6)	65.7 (8.5)
Median (IQR)	65.0 (60.0–71.0)	66.0 (60.0–71.0)	64.0 (60.0–70.0)
Range	40.0–104.0	41.0–104.0	40.0–98.0

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; O Level, ordinary level; PG, postgraduate; SD, standard deviation.

Note

OPPTIMUM. Output created by OPPTIMUM_main_v2_0.R. Last run on Fri Oct 02 14:33:55 2015.

TABLE 28 Baseline characteristics (part 2). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by treatment

Parameter	All	Trial group	
		Placebo	Progesterone
Smoking			
N_{obs} (N_{miss})	1220 (6)	607 (3)	613 (3)
No, *n* (%)	984 (80.7)	482 (79.4)	502 (81.9)
Yes, *n* (%)	236 (19.3)	125 (20.6)	111 (18.1)
Alcohol consumption			
N_{obs} (N_{miss})	1223 (3)	609 (1)	614 (2)
No, *n* (%)	1160 (94.8)	575 (94.4)	585 (95.3)
Yes, *n* (%)	63 (5.2)	34 (5.6)	29 (4.7)
Drug use			
N_{obs} (N_{miss})	1223 (3)	609 (1)	614 (2)
No, *n* (%)	1206 (98.6)	600 (98.5)	606 (98.7)
Yes, *n* (%)	17 (1.4)	9 (1.5)	8 (1.3)

TABLE 28 Baseline characteristics (part 2). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by treatment (*continued*)

Parameter	All	Trial group	
		Placebo	Progesterone
In full-time education			
N_{obs} (N_{miss})	1216 (10)	607 (3)	609 (7)
No, *n* (%)	1175 (96.6)	590 (97.2)	585 (96.1)
Yes, *n* (%)	41 (3.4)	17 (2.8)	24 (3.9)
Years in full-time education			
N_{obs} (N_{miss})	1122 (53)	568 (22)	554 (31)
Mean (SD)	13.5 (3.1)	13.5 (3.0)	13.5 (3.1)
Median (IQR)	13.0 (11.0–16.0)	13.0 (11.0–16.0)	13.0 (11.0–16.0)
Range	1.0–31.0	1.0–31.0	1.0–31.0
Educated in the UK			
N_{obs} (N_{miss})	1206 (20)	602 (8)	604 (12)
No, *n* (%)	211 (17.5)	109 (18.1)	102 (16.9)
Yes, *n* (%)	995 (82.5)	493 (81.9)	502 (83.1)

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:33:55 2015.

TABLE 29 Baseline characteristics (part 3). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by treatment

Parameter	All	Trial group	
		Placebo	Progesterone
Highest level of education if in the UK			
N_{obs} (N_{miss})	975 (20)	488 (5)	487 (15)
No formal qualifications, *n* (%)	99 (10.2)	56 (11.5)	43 (8.8)
Entry Level Certificate/Foundation Diploma, *n* (%)	13 (1.3)	6 (1.2)	7 (1.4)
GCSE/Standard/O Level, *n* (%)	327 (33.5)	164 (33.6)	163 (33.5)
A Level, AS Level, Highers or BTEC Diploma/Certificate, *n* (%)	137 (14.1)	70 (14.3)	67 (13.8)
Certificate of Higher Education/ City & Guilds, *n* (%)	53 (5.4)	25 (5.1)	28 (5.7)
Diploma HE/FE or HND/HNC, *n* (%)	69 (7.1)	33 (6.8)	36 (7.4)
Graduate certificate or diploma, *n* (%)	14 (1.4)	10 (2.0)	4 (0.8)
Degree, *n* (%)	158 (16.2)	72 (14.8)	86 (17.7)

continued

TABLE 29 Baseline characteristics (part 3). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by treatment (*continued*)

Parameter	All	Trial group	
		Placebo	Progesterone
Professional qualifications, *n* (%)	40 (4.1)	19 (3.9)	21 (4.3)
PG certificate, diploma, masters, doctorate, *n* (%)	65 (6.7)	33 (6.8)	32 (6.6)
Ethnic group			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
White, *n* (%)	895 (73.1)	446 (73.2)	449 (73.0)
Chinese, *n* (%)	1 (0.1)	1 (0.2)	0 (0.0)
Other ethnic group, *n* (%)	17 (1.4)	5 (0.8)	12 (2.0)
Mixed			
White and black Caribbean, *n* (%)	17 (1.4)	8 (1.3)	9 (1.5)
White and black African, *n* (%)	3 (0.2)	0 (0.0)	3 (0.5)
White and Asian, *n* (%)	2 (0.2)	1 (0.2)	1 (0.2)
Other mixed background, *n* (%)	6 (0.5)	3 (0.5)	3 (0.5)
Asian			
Indian, *n* (%)	30 (2.5)	16 (2.6)	14 (2.3)
Pakistani, *n* (%)	45 (3.7)	23 (3.8)	22 (3.6)
Bangladeshi, *n* (%)	5 (0.4)	4 (0.7)	1 (0.2)
Other Asian background, *n* (%)	23 (1.9)	7 (1.1)	16 (2.6)
Black			
Caribbean, *n* (%)	47 (3.8)	27 (4.4)	20 (3.3)
African, *n* (%)	119 (9.7)	59 (9.7)	60 (9.8)
Other black background, *n* (%)	14 (1.1)	9 (1.5)	5 (0.8)
Ethnic group			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
White, *n* (%)	895 (73.1)	446 (73.2)	449 (73.0)
Black, *n* (%)	180 (14.7)	95 (15.6)	85 (13.8)
Asian, *n* (%)	104 (8.5)	51 (8.4)	53 (8.6)
Mixed, *n* (%)	28 (2.3)	12 (2.0)	16 (2.6)
Other, *n* (%)	17 (1.4)	5 (0.8)	12 (2.0)

A Level, Advanced Level; AS Level, Advanced Subsidiary Level; BTEC, Business and Technology Education Council; FE, Further Education; GCSE, General Certificate of Secondary Education; HE, Higher Education; HNC, Higher National Certificate; HND, Higher National Diploma; N_{miss}, number of women with missing data; N_{obs}, number of observations; O Level, ordinary level; PG, postgraduate.

Note

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TABLE 30 Baseline characteristics (part 4): this pregnancy. Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by treatment

Parameter	All	Trial group	
		Placebo	Progesterone
Gestation (weeks) at fFN test			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
Mean (SD)	22.9 (0.6)	22.9 (0.6)	22.9 (0.6)
Median (IQR)	22.9 (22.4–23.4)	22.9 (22.4–23.4)	22.9 (22.4–23.4)
Range	21.7–27.1	22.0–27.1	21.7–26.6
Fetal anomaly scan done			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
No, *n* (%)	63 (5.1)	34 (5.6)	29 (4.7)
Yes, *n* (%)	1163 (94.9)	576 (94.4)	587 (95.3)
Fetal anomaly scan result			
N_{obs} (N_{miss})	1163 (0)	576 (0)	587 (0)
Normal, *n* (%)	1150 (98.9)	569 (98.8)	581 (99.0)
Defined abnormality, *n* (%)	7 (0.6)	4 (0.7)	3 (0.5)
Uncertain abnormality, *n* (%)	6 (0.5)	3 (0.5)	3 (0.5)
Amniocentesis done			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
No, *n* (%)	1218 (99.3)	607 (99.5)	611 (99.2)
Yes, *n* (%)	8 (0.7)	3 (0.5)	5 (0.8)
Results of amniocentesis			
N_{obs} (N_{miss})	8 (0)	3 (0)	5 (0)
Normal, *n* (%)	8 (100.0)	3 (100.0)	5 (100.0)
Other, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Chorionic villus sampling done			
N_{obs} (N_{miss})	1225 (1)	610 (0)	615 (1)
No, *n* (%)	1216 (99.3)	607 (99.5)	609 (99.0)
Yes, *n* (%)	9 (0.7)	3 (0.5)	6 (1.0)
Results of chorionic villus sampling			
N_{obs} (N_{miss})	9 (0)	3 (0)	6 (0)
Normal, *n* (%)	9 (100.0)	3 (100.0)	6 (100.0)
Other, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)

continued

TABLE 30 Baseline characteristics (part 4): this pregnancy. Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by treatment (*continued*)

Parameter	All	Trial group	
		Placebo	Progesterone
Cervical length (mm)			
N_{obs} (N_{miss})	712 (514)	351 (259)	361 (255)
Mean (SD)	28.5 (10.8)	28.8 (11.1)	28.2 (10.6)
Median (IQR)	30.0 (22.0–36.0)	30.0 (22.5–36.0)	30.0 (22.0–36.0)
Range	0.0–84.0	0.0–84.0	0.0–58.0
Risk			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
Low, *n* (%)	882 (71.9)	429 (70.3)	453 (73.5)
High, *n* (%)	344 (28.1)	181 (29.7)	163 (26.5)

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:33:55 2015.

TABLE 31 Previous pregnancies (part 1). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by treatment

Parameter	All	Trial group	
		Placebo	Progesterone
Any previous pregnancy			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
No, *n* (%)	52 (4.2)	28 (4.6)	24 (3.9)
Yes, *n* (%)	1172 (95.8)	581 (95.4)	591 (96.1)
Number of previous pregnancies			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
Mean (SD)	2.6 (2.0)	2.7 (1.9)	2.6 (2.0)
Median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)
Range	0.0–14.0	0.0–12.0	0.0–14.0
Any previous pregnancy of ≥ 14 weeks' gestation			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
No, *n* (%)	75 (6.1)	38 (6.2)	37 (6.0)
Yes, *n* (%)	1149 (93.9)	571 (93.8)	578 (94.0)
Number of previous pregnancies of ≥ 14 weeks' gestation			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
Mean (SD)	1.9 (1.4)	1.9 (1.4)	1.9 (1.4)
Median (IQR)	2.0 (1.0–2.0)	2.0 (1.0–3.0)	2.0 (1.0–2.0)
Range	0.0–13.0	0.0–10.0	0.0–13.0

TABLE 31 Previous pregnancies (part 1). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by treatment (*continued*)

		Trial group	
Parameter	All	Placebo	Progesterone
Any previous live birth			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
No, *n* (%)	197 (16.1)	97 (15.9)	100 (16.3)
Yes, *n* (%)	1027 (83.9)	512 (84.1)	515 (83.7)
Number of previous live births			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
Mean (SD)	1.5 (1.3)	1.6 (1.3)	1.5 (1.3)
Median (IQR)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)
Range	0.0–13.0	0.0–10.0	0.0–13.0
Any previous pregnancy that ended with baby alive and well			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
No, *n* (%)	646 (52.8)	321 (52.7)	325 (52.8)
Yes, *n* (%)	578 (47.2)	288 (47.3)	290 (47.2)
Number of previous pregnancies that ended with baby alive and well			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
Mean (SD)	0.8 (1.2)	0.8 (1.2)	0.8 (1.2)
Median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)
Range	0.0–13.0	0.0–10.0	0.0–13.0

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:33:56 2015.

TABLE 32 Previous pregnancies (part 2). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by treatment

		Trial group	
Parameter	All	Placebo	Progesterone
History of induced labour or elective caesarean section			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
No, *n* (%)	1065 (87.0)	524 (86.0)	541 (88.0)
Yes, *n* (%)	159 (13.0)	85 (14.0)	74 (12.0)
History of miscarriage			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
No, *n* (%)	701 (57.3)	335 (55.0)	366 (59.5)
Yes, *n* (%)	523 (42.7)	274 (45.0)	249 (40.5)

continued

TABLE 32 Previous pregnancies (part 2). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by treatment (*continued*)

Parameter	All	Trial group	
		Placebo	Progesterone
History of ectopic pregnancy			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
No, *n* (%)	1193 (97.5)	600 (98.5)	593 (96.4)
Yes, *n* (%)	31 (2.5)	9 (1.5)	22 (3.6)
History of termination of pregnancy			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
No, *n* (%)	1085 (88.6)	542 (89.0)	543 (88.3)
Yes, *n* (%)	139 (11.4)	67 (11.0)	72 (11.7)
History of termination of pregnancy before 14 weeks' gestation			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
No, *n* (%)	1106 (90.2)	554 (90.8)	552 (89.6)
Yes, *n* (%)	120 (9.8)	56 (9.2)	64 (10.4)
History of termination of pregnancy at ≥ 14 weeks' gestation			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
No, *n* (%)	1201 (98.0)	596 (97.7)	605 (98.2)
Yes, *n* (%)	25 (2.0)	14 (2.3)	11 (1.8)
History of live birth followed by neonatal death			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
No, *n* (%)	1059 (86.5)	524 (86.0)	535 (87.0)
Yes, *n* (%)	165 (13.5)	85 (14.0)	80 (13.0)
History of live birth followed by death other than neonatal			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
No, *n* (%)	1208 (98.7)	604 (99.2)	604 (98.2)
Yes, *n* (%)	16 (1.3)	5 (0.8%)	11 (1.8)
History of stillbirth			
N_{obs} (N_{miss})	1224 (2)	609 (1)	615 (1)
No, *n* (%)	1129 (92.2)	561 (92.1)	568 (92.4)
Yes, *n* (%)	95 (7.8)	48 (7.9)	47 (7.6)

N_{miss}, number of women with missing data; N_{obs}, number of observations.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:33:56 2015.

TABLE 33 Baseline characteristics (part 1). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of obstetric outcome

		Obstetric outcome available	
Parameter	All	No	Yes
Age (years)			
N_{obs} (N_{miss})	1225 (1)	28 (1)	1197 (0)
Mean (SD)	31.4 (5.7)	32.4 (5.2)	31.4 (5.7)
Median (IQR)	31.5 (27.4–35.7)	32.8 (29.1–34.9)	31.4 (27.3–35.7)
Range	16.8–49.2	22.7–41.0	16.8–49.2
Height (cm)			
N_{obs} (N_{miss})	1221 (5)	28 (1)	1193 (4)
Mean (SD)	163.5 (6.6)	165.4 (8.1)	163.5 (6.5)
Median (IQR)	163.0 (159.0–168.0)	166.0 (160.0–170.5)	163.0 (159.0–168.0)
Range	144.0–183.0	147.0–181.0	144.0–183.0
Weight (kg)			
N_{obs} (N_{miss})	1221 (5)	28 (1)	1193 (4)
Mean (SD)	71.6 (17.1)	73.2 (14.5)	71.6 (17.2)
Median (IQR)	68.0 (60.0–81.0)	71.0 (63.5–80.2)	68.0 (59.0–81.0)
Range	41.0–186.0	51.0–113.0	41.0–186.0
BMI (kg/m^2)			
N_{obs} (N_{miss})	1221 (5)	28 (1)	1193 (4)
Mean (SD)	26.8 (6.3)	26.8 (5.2)	26.8 (6.3)
Median (IQR)	25.5 (22.3–29.8)	27.1 (22.4–28.8)	25.5 (22.3–29.8)
Range	15.2–80.5	19.9–45.3	15.2–80.5
Systolic blood pressure (mmHg)			
N_{obs} (N_{miss})	1219 (7)	28 (1)	1191 (6)
Mean (SD)	111.9 (12.4)	113.1 (12.8)	111.8 (12.4)
Median (IQR)	110.0 (102.0–120.0)	110.0 (102.0–119.2)	110.0 (102.0–120.0)
Range	78.0–189.0	92.0–150.0	78.0–189.0
Diastolic blood pressure (mmHg)			
N_{obs} (N_{miss})	1219 (7)	28 (1)	1191 (6)
Mean (SD)	66.0 (8.6)	65.9 (10.6)	66.0 (8.5)
Median (IQR)	65.0 (60.0–71.0)	62.0 (60.0–70.5)	65.0 (60.0–71.0)
Range	40.0–104.0	50.0–98.0	40.0–104.0

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:33:56 2015.

TABLE 34 Baseline characteristics (part 2). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of obstetric outcome

		Obstetric outcome available	
Parameter	All	No	Yes
Smoking			
N_{obs} (N_{miss})	1220 (6)	28 (1)	1192 (5)
No, *n* (%)	984 (80.7)	21 (75.0)	963 (80.8)
Yes, *n* (%)	236 (19.3)	7 (25.0)	229 (19.2)
Alcohol consumption			
N_{obs} (N_{miss})	1223 (3)	28 (1)	1195 (2)
No, *n* (%)	1160 (94.8)	26 (92.9)	1134 (94.9)
Yes, *n* (%)	63 (5.2)	2 (7.1)	61 (5.1)
Drug use			
N_{obs} (N_{miss})	1223 (3)	28 (1)	1195 (2)
No, *n* (%)	1206 (98.6)	28 (100.0)	1178 (98.6)
Yes, *n* (%)	17 (1.4)	0 (0.0)	17 (1.4)
In full-time education			
N_{obs} (N_{miss})	1216 (10)	28 (1)	1188 (9)
No, *n* (%)	1175 (96.6)	28 (100.0)	1147 (96.5)
Yes, *n* (%)	41 (3.4)	0 (0.0)	41 (3.5)
Years in full-time education			
N_{obs} (N_{miss})	1122 (53)	28 (0)	1094 (53)
Mean (SD)	13.5 (3.1)	13.5 (3.1)	13.5 (3.1)
Median (IQR)	13.0 (11.0–16.0)	13.0 (11.0–16.2)	13.0 (11.0–16.0)
Range	1.0–31.0	7.0–19.0	1.0–31.0
Educated in the UK			
N_{obs} (N_{miss})	1206 (20)	28 (1)	1178 (19)
No, *n* (%)	211 (17.5)	8 (28.6)	203 (17.2)
Yes, *n* (%)	995 (82.5)	20 (71.4)	975 (82.8)

N_{miss}, number of women with missing data; N_{obs}, number of observations.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:33:56 2015.

TABLE 35 Baseline characteristics (part 3). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of obstetric outcome

Parameter	All	Obstetric outcome available	
		No	Yes
Highest level of education if in UK			
N_{obs} (N_{miss})	975 (20)	20 (0)	955 (20)
No formal qualifications, *n* (%)	99 (10.2)	5 (25.0)	94 (9.8)
Entry Level Certificate/Foundation Diploma, *n* (%)	13 (1.3)	0 (0.0)	13 (1.4)
GCSE/Standard/O Level, *n* (%)	327 (33.5)	8 (40.0)	319 (33.4)
A Level, AS Level, Highers or BTEC Diploma/Certificate, *n* (%)	137 (14.1)	1 (5.0)	136 (14.2)
Certificate of Higher Education/City & Guilds, *n* (%)	53 (5.4)	0 (0.0)	53 (5.5)
Diploma HE/FE or HND/HNC, *n* (%)	69 (7.1)	2 (10.0)	67 (7.0)
Graduate certificate or diploma, *n* (%)	14 (1.4)	0 (0.0)	14 (1.5)
Degree, *n* (%)	158 (16.2)	4 (20.0)	154 (16.1)
Professional qualifications, *n* (%)	40 (4.1)	0 (0.0)	40 (4.2)
PG certificate, diploma, masters, doctorate, *n* (%)	65 (6.7)	0 (0.0)	65 (6.8)
Ethnic group			
N_{obs} (N_{miss})	1224 (2)	28 (1)	1196 (1)
White, *n* (%)	895 (73.1)	22 (78.6)	873 (73.0)
Chinese, *n* (%)	1 (0.1)	0 (0.0)	1 (0.1)
Other ethnic group, *n* (%)	17 (1.4)	0 (0.0)	17 (1.4)
Mixed			
White and black Caribbean, *n* (%)	17 (1.4)	0 (0.0)	17 (1.4)
White and black African, *n* (%)	3 (0.2)	0 (0.0)	3 (0.3)
White and Asian, *n* (%)	2 (0.2)	0 (0.0)	2 (0.2)
Other mixed background, *n* (%)	6 (0.5)	1 (3.6)	5 (0.4)
Asian			
Indian, *n* (%)	30 (2.5)	1 (3.6)	29 (2.4)
Pakistani, *n* (%)	45 (3.7)	1 (3.6)	44 (3.7)
Bangladeshi, *n* (%)	5 (0.4)	0 (0.0)	5 (0.4)
Other Asian background, *n* (%)	23 (1.9)	0 (0.0)	23 (1.9)
Black			
Caribbean, *n* (%)	47 (3.8)	0 (0.0)	47 (3.9)
African, *n* (%)	119 (9.7)	3 (10.7)	116 (9.7)
Other black background, *n* (%)	14 (1.1)	0 (0.0)	14 (1.2)

continued

TABLE 35 Baseline characteristics (part 3). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of obstetric outcome (*continued*)

		Obstetric outcome available	
Parameter	All	No	Yes
Ethnic group			
N_{obs} (N_{miss})	1224 (2)	28 (1)	1196 (1)
White, *n* (%)	895 (73.1)	22 (78.6)	873 (73.0)
Black, *n* (%)	180 (14.7)	3 (10.7)	177 (14.8)
Asian, *n* (%)	104 (8.5)	2 (7.1)	102 (8.5)
Mixed, *n* (%)	28 (2.3)	1 (3.6)	27 (2.3)
Other, *n* (%)	17 (1.4)	0 (0.0)	17 (1.4)

A Level, Advanced Level; AS Level, Advanced Subsidiary Level; BTEC, Business and Technology Education Council; FE, Further Education; GCSE, General Certificate of Secondary Education; HE, Higher Education; HNC, Higher National Certificate; HND, Higher National Diploma; N_{miss}, number of women with missing data; N_{obs}, number of observations; O Level, ordinary level; PG, postgraduate.

Note

OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:33:56 2015.

TABLE 36 Baseline characteristics (part 4): this pregnancy. Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of obstetric outcome

		Obstetric outcome available	
Parameter	All	No	Yes
Gestation (weeks) at fFN test			
N_{obs} (N_{miss})	1226 (0)	29 (0)	1197 (0)
Mean (SD)	22.9 (0.6)	22.8 (0.6)	22.9 (0.6)
Median (IQR)	22.9 (22.4–23.4)	22.7 (22.3–23.4)	22.9 (22.4–23.4)
Range	21.7–27.1	22.0–23.9	21.7–27.1
Fetal anomaly scan done			
N_{obs} (N_{miss})	1226 (0)	29 (0)	1197 (0)
No, *n* (%)	63 (5.1)	1 (3.4)	62 (5.2)
Yes, *n* (%)	1163 (94.9)	28 (96.6)	1135 (94.8)
Fetal anomaly scan result			
N_{obs} (N_{miss})	1163 (0)	28 (0)	1135 (0)
Normal, *n* (%)	1150 (98.9)	28 (100.0)	1122 (98.9)
Defined abnormality, *n* (%)	7 (0.6)	0 (0.0)	7 (0.6)
Uncertain abnormality, *n* (%)	6 (0.5)	0 (0.0)	6 (0.5)
Amniocentesis done			
N_{obs} (N_{miss})	1226 (0)	29 (0)	1197 (0)
No, *n* (%)	1218 (99.3)	28 (96.6)	1190 (99.4)
Yes, *n* (%)	8 (0.7)	1 (3.4)	7 (0.6)

TABLE 36 Baseline characteristics (part 4): this pregnancy. Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of obstetric outcome (*continued*)

		Obstetric outcome available	
Parameter	All	No	Yes
Results of amniocentesis			
N_{obs} (N_{miss})	8 (0)	1 (0)	7 (0)
Normal, *n* (%)	8 (100.0)	1 (100.0)	7 (100.0)
Other, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Chorionic villus sampling done			
N_{obs} (N_{miss})	1225 (1)	29 (0)	1196 (1)
No, *n* (%)	1216 (99.3)	29 (100.0)	1187 (99.2)
Yes, *n* (%)	9 (0.7)	0 (0.0)	9 (0.8)
Results of chorionic villus sampling			
N_{obs} (N_{miss})	9 (0)	0 (0)	9 (0)
No, *n* (%)	9 (100.0)	0 (–)	9 (100.0)
Yes, *n* (%)	0 (0.0)	0 (–)	0 (0.0)
Cervical length (mm)			
N_{obs} (N_{miss})	712 (514)	16 (13)	696 (501)
Mean (SD)	28.5 (10.8)	31.2 (10.4)	28.5 (10.9)
Median (IQR)	30.0 (22.0–36.0)	32.0 (23.5–38.8)	30.0 (22.0–36.0)
Range	0.0–84.0	12.0–50.0	0.0–84.0
Risk			
N_{obs} (N_{miss})	1226 (0)	29 (0)	1197 (0)
Low, *n* (%)	882 (71.9)	23 (79.3)	859 (71.8)
High, *n* (%)	344 (28.1)	6 (20.7)	338 (28.2)

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:33:57 2015.

TABLE 37 Previous pregnancies (part 1). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of obstetric outcome

		Obstetric outcome available	
Parameter	All	No	Yes
Any previous pregnancy			
N_{obs} (N_{miss})	1224 (2)	27 (2)	1197 (0)
No, *n* (%)	52 (4.2)	0 (0.0)	52 (4.3)
Yes, *n* (%)	1172 (95.8)	27 (100.0)	1145 (95.7)

continued

TABLE 37 Previous pregnancies (part 1). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of obstetric outcome (*continued*)

Parameter	All	Obstetric outcome available	
		No	Yes
Number of previous pregnancies			
N_{obs} (N_{miss})	1224 (2)	27 (2)	1197 (0)
Mean (SD)	2.6 (2.0)	2.7 (1.7)	2.6 (2.0)
Median (IQR)	2.0 (1.0–3.0)	3.0 (1.0–3.5)	2.0 (1.0–3.0)
Range	0.0–14.0	1.0–6.0	0.0–14.0
Any previous pregnancy of ≥ 14 weeks' gestation			
N_{obs} (N_{miss})	1224 (2)	27 (2)	1197 (0)
No, *n* (%)	75 (6.1)	2 (7.4)	73 (6.1)
Yes, *n* (%)	1149 (93.9)	25 (92.6)	1124 (93.9)
Number of previous pregnancies of ≥ 14 weeks' gestation			
N_{obs} (N_{miss})	1224 (2)	27 (2)	1197 (0)
Mean (SD)	1.9 (1.4)	2.0 (1.5)	1.9 (1.4)
Median (IQR)	2.0 (1.0–2.0)	2.0 (1.0–2.5)	2.0 (1.0–2.0)
Range	0.0–13.0	0.0–6.0	0.0–13.0
Any previous live birth			
N_{obs} (N_{miss})	1224 (2)	27 (2)	1197 (0)
No, *n* (%)	197 (16.1)	5 (18.5)	192 (16.0)
Yes, *n* (%)	1027 (83.9)	22 (81.5)	1005 (84.0)
Number of previous live births			
N_{obs} (N_{miss})	1224 (2)	27 (2)	1197 (0)
Mean (SD)	1.5 (1.3)	1.6 (1.3)	1.5 (1.3)
Median (IQR)	1.0 (1.0–2.0)	2.0 (1.0–2.0)	1.0 (1.0–2.0)
Range	0.0–13.0	0.0–6.0	0.0–13.0
Any previous pregnancy that ended with baby alive and well			
N_{obs} (N_{miss})	1224 (2)	27 (2)	1197 (0)
No, *n* (%)	646 (52.8)	12 (44.4)	634 (53.0)
Yes, *n* (%)	578 (47.2)	15 (55.6)	563 (47.0)
Number of previous pregnancies that ended with baby alive and well			
N_{obs} (N_{miss})	1224 (2)	27 (2)	1197 (0)
Mean (SD)	0.8 (1.2)	1.1 (1.3)	0.8 (1.2)
Median (IQR)	0.0 (0.0–1.0)	1.0 (0.0–2.0)	0.0 (0.0–1.0)
Range	0.0–13.0	0.0–5.0	0.0–13.0

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:33:57 2015.

TABLE 38 Previous pregnancies (part 2). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of obstetric outcome

		Obstetric outcome available	
Parameter	All	No	Yes
History of induced labour or elective caesarean section			
N_{obs} (N_{miss})	1224 (2)	27 (2)	1197 (0)
No, *n* (%)	1065 (87.0)	21 (77.8)	1044 (87.2)
Yes, *n* (%)	159 (13.0)	6 (22.2)	153 (12.8)
History of miscarriage			
N_{obs} (N_{miss})	1224 (2)	27 (2)	1197 (0)
No, *n* (%)	701 (57.3)	13 (48.1)	688 (57.5)
Yes, *n* (%)	523 (42.7)	14 (51.9)	509 (42.5)
History of ectopic pregnancy			
N_{obs} (N_{miss})	1224 (2)	27 (2)	1197 (0)
No, *n* (%)	1193 (97.5)	26 (96.3)	1167 (97.5)
Yes, *n* (%)	31 (2.5)	1 (3.7)	30 (2.5)
History of termination of pregnancy			
N_{obs} (N_{miss})	1224 (2)	27 (2)	1197 (0)
No, *n* (%)	1085 (88.6)	24 (88.9)	1061 (88.6)
Yes, *n* (%)	139 (11.4)	3 (11.1)	136 (11.4)
History of termination of pregnancy before 14 weeks' gestation			
N_{obs} (N_{miss})	1226 (0)	29 (0)	1197 (0)
No, *n* (%)	1106 (90.2)	26 (89.7)	1080 (90.2)
Yes, *n* (%)	120 (9.8)	3 (10.3)	117 (9.8)
History of termination of pregnancy at ≥ 14 weeks' gestation			
N_{obs} (N_{miss})	1226 (0)	29 (0)	1197 (0)
No, *n* (%)	1201 (98.0)	29 (100.0)	1172 (97.9)
Yes, *n* (%)	25 (2.0)	0 (0.0)	25 (2.1)
History of live birth followed by neonatal death			
N_{obs} (N_{miss})	1224 (2)	27 (2)	1197 (0)
No, *n* (%)	1059 (86.5)	26 (96.3)	1033 (86.3)
Yes, *n* (%)	165 (13.5)	1 (3.7)	164 (13.7)
History of live birth followed by death other than neonatal			
N_{obs} (N_{miss})	1224 (2)	27 (2)	1197 (0)
No, *n* (%)	1208 (98.7)	26 (96.3)	1182 (98.7)
Yes, *n* (%)	16 (1.3)	1 (3.7)	15 (1.3)
History of stillbirth			
N_{obs} (N_{miss})	1224 (2)	27 (2)	1197 (0)
No, *n* (%)	1129 (92.2)	25 (92.6)	1104 (92.2)
Yes, *n* (%)	95 (7.8)	2 (7.4)	93 (7.8)

N_{miss}, number of women with missing data; N_{obs}, number of observations.

Note

OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:33:57 2015.

TABLE 39 Baseline characteristics (part 1). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of neonatal outcome

		Neonatal outcome available	
Parameter	All	No	Yes
Age (years)			
N_{obs} (N_{miss})	1225 (1)	49 (1)	1176 (0)
Mean (SD)	31.4 (5.7)	31.5 (5.3)	31.4 (5.7)
Median (IQR)	31.5 (27.4–35.7)	31.9 (27.6–35.0)	31.4 (27.4–35.7)
Range	16.8–49.2	20.8–41.0	16.8–49.2
Height (cm)			
N_{obs} (N_{miss})	1221 (5)	48 (2)	1173 (3)
Mean (SD)	163.5 (6.6)	165.1 (7.3)	163.5 (6.6)
Median (IQR)	163.0 (159.0–168.0)	166.0 (160.0–170.0)	163.0 (159.0–168.0)
Range	144.0–183.0	147.0–181.0	144.0–183.0
Weight (kg)			
N_{obs} (N_{miss})	1221 (5)	48 (2)	1173 (3)
Mean (SD)	71.6 (17.1)	75.5 (19.5)	71.5 (17.0)
Median (IQR)	68.0 (60.0–81.0)	71.0 (63.0–84.0)	68.0 (59.0–81.0)
Range	41.0–186.0	51.0–130.0	41.0–186.0
BMI (kg/m^2)			
N_{obs} (N_{miss})	1221 (5)	48 (2)	1173 (3)
Mean (SD)	26.8 (6.3)	27.7 (7.1)	26.8 (6.2)
Median (IQR)	25.5 (22.3–29.8)	26.2 (22.5–30.2)	25.5 (22.3–29.8)
Range	15.2–80.5	18.0–49.5	15.2–80.5
Systolic blood pressure (mmHg)			
N_{obs} (N_{miss})	1219 (7)	49 (1)	1170 (6)
Mean (SD)	111.9 (12.4)	115.9 (13.7)	111.7 (12.3)
Median (IQR)	110.0 (102.0–120.0)	110.0 (109.0–122.0)	110.0 (102.0–120.0)
Range	78.0–189.0	92.0–159.0	78.0–189.0
Diastolic blood pressure (mmHg)			
N_{obs} (N_{miss})	1219 (7)	49 (1)	1170 (6)
Mean (SD)	66.0 (8.6)	66.8 (9.6)	65.9 (8.5)
Median (IQR)	65.0 (60.0–71.0)	67.0 (60.0–70.0)	65.0 (60.0–71.0)
Range	40.0–104.0	50.0–98.0	40.0–104.0

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:33:57 2015.

TABLE 40 Baseline characteristics (part 2). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of neonatal outcome

		Neonatal outcome available	
Parameter	All	No	Yes
Smoking			
N_{obs} (N_{miss})	1220 (6)	48 (2)	1172 (4)
No, *n* (%)	984 (80.7)	38 (79.2)	946 (80.7)
Yes, *n* (%)	236 (19.3)	10 (20.8)	226 (19.3)
Alcohol consumption			
N_{obs} (N_{miss})	1223 (3)	49 (1)	1174 (2)
No, *n* (%)	1160 (94.8)	47 (95.9)	1113 (94.8)
Yes, *n* (%)	63 (5.2)	2 (4.1)	61 (5.2)
Drug use			
N_{obs} (N_{miss})	1223 (3)	49 (1)	1174 (2)
No, *n* (%)	1206 (98.6)	49 (100.0)	1157 (98.6)
Yes, *n* (%)	17 (1.4)	0 (0.0)	17 (1.4)
In full-time education			
N_{obs} (N_{miss})	1216 (10)	49 (1)	1167 (9)
No, *n* (%)	1175 (96.6)	47 (95.9)	1128 (96.7)
Yes, *n* (%)	41 (3.4)	2 (4.1)	39 (3.3)
Years in full-time education			
N_{obs} (N_{miss})	1122 (53)	44 (3)	1078 (50)
Mean (SD)	13.5 (3.1)	13.4 (2.9)	13.5 (3.1)
Median (IQR)	13.0 (11.0–16.0)	13.0 (11.0–15.2)	13.0 (11.0–16.0)
Range	1.0–31.0	7.0–19.0	1.0–31.0
Educated in the UK			
N_{obs} (N_{miss})	1206 (20)	49 (1)	1157 (19)
No, *n* (%)	211 (17.5)	14 (28.6)	197 (17.0)
Yes, *n* (%)	995 (82.5)	35 (71.4)	960 (83.0)

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:33:58 2015.

TABLE 41 Baseline characteristics (part 3). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of neonatal outcome

Parameter	All	Neonatal outcome available	
		No	Yes
Highest level of education if in UK			
N_{obs} (N_{miss})	975 (20)	33 (2)	942 (18)
No formal qualifications, *n* (%)	99 (10.2)	8 (24.2)	91 (9.7)
Entry Level Certificate/Foundation Diploma, *n* (%)	13 (1.3)	0 (0.0)	13 (1.4)
GCSE/Standard/O Level, *n* (%)	327 (33.5)	11 (33.3)	316 (33.5)
A Level, AS Level, Highers or BTEC Diploma/Certificate, *n* (%)	137 (14.1)	2 (6.1)	135 (14.3)
Certificate of Higher Education/City & Guilds, *n* (%)	53 (5.4)	2 (6.1)	51 (5.4)
Diploma HE/FE or HND/HNC, *n* (%)	69 (7.1)	2 (6.1)	67 (7.1)
Graduate certificate or diploma, *n* (%)	14 (1.4)	1 (3.0)	13 (1.4)
Degree, *n* (%)	158 (16.2)	4 (12.1)	154 (16.3)
Professional qualifications, *n* (%)	40 (4.1)	2 (6.1)	38 (4.0)
PG certificate, diploma, masters, doctorate, *n* (%)	65 (6.7)	1 (3.0)	64 (6.8)
Ethnic group			
N_{obs} (N_{miss})	1224 (2)	49 (1)	1175 (1)
White, *n* (%)	895 (73.1)	34 (69.4)	861 (73.3)
Chinese, *n* (%)	1 (0.1)	0 (0.0)	1 (0.1)
Other ethnic group, *n* (%)	17 (1.4)	0 (0.0)	17 (1.4)
Mixed			
White and black Caribbean, *n* (%)	17 (1.4)	0 (0.0)	17 (1.4)
White and black African, *n* (%)	3 (0.2)	0 (0.0)	3 (0.3)
White and Asian, *n* (%)	2 (0.2)	1 (2.0)	1 (0.1)
Other mixed background, *n* (%)	6 (0.5)	1 (2.0)	5 (0.4)
Asian			
Indian, *n* (%)	30 (2.5)	1 (2.0)	29 (2.5)
Pakistani, *n* (%)	45 (3.7)	1 (2.0)	44 (3.7)
Bangladeshi, *n* (%)	5 (0.4)	0 (0.0)	5 (0.4)
Other Asian background, *n* (%)	23 (1.9)	1 (2.0)	22 (1.9)
Black			
Caribbean, *n* (%)	47 (3.8)	0 (0.0)	47 (4.0)
African, *n* (%)	119 (9.7)	9 (18.4)	110 (9.4)
Other black background, *n* (%)	14 (1.1)	1 (2.0)	13 (1.1)

TABLE 41 Baseline characteristics (part 3). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of neonatal outcome (*continued*)

		Neonatal outcome available	
Parameter	All	No	Yes
Ethnic group			
N_{obs} (N_{miss})	1224 (2)	49 (1)	1175 (1)
White, *n* (%)	895 (73.1)	34 (69.4)	861 (73.3)
Black, *n* (%)	180 (14.7)	10 (20.4)	170 (14.5)
Asian, *n* (%)	104 (8.5)	3 (6.1)	101 (8.6)
Mixed, *n* (%)	28 (2.3)	2 (4.1)	26 (2.2)
Other, *n* (%)	17 (1.4)	0 (0.0)	17 (1.4)

A Level, Advanced Level; AS Level, Advanced Subsidiary Level; BTEC, Business and Technology Education Council; FE, Further Education; GCSE, General Certificate of Secondary Education; HE, Higher Education; HNC, Higher National Certificate; HND, Higher National Diploma; N_{miss}, number of women with missing data; N_{obs}, number of observations; O Level, ordinary level; PG, postgraduate.

Note

OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:33:58 2015.

TABLE 42 Baseline characteristics (part 4): this pregnancy. Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of neonatal outcome

		Neonatal outcome available	
Parameter	All	No	Yes
Gestation (weeks) at fFN test			
N_{obs} (N_{miss})	1226 (0)	50 (0)	1176 (0)
Mean (SD)	22.9 (0.6)	22.9 (0.6)	22.9 (0.6)
Median (IQR)	22.9 (22.4–23.4)	22.7 (22.4–23.4)	22.9 (22.4–23.4)
Range	21.7–27.1	22.0–23.9	21.7–27.1
Fetal anomaly scan done			
N_{obs} (N_{miss})	1226 (0)	50 (0)	1176 (0)
No, *n* (%)	63 (5.1)	2 (4.0)	61 (5.2)
Yes, *n* (%)	1163 (94.9)	48 (96.0)	1115 (94.8)
Fetal anomaly scan result			
N_{obs} (N_{miss})	1163 (0)	48 (0)	1115 (0)
Normal, *n* (%)	1150 (98.9)	48 (100.0)	1102 (98.8)
Defined abnormality, *n* (%)	7 (0.6)	0 (0.0)	7 (0.6)
Uncertain abnormality, *n* (%)	6 (0.5)	0 (0.0)	6 (0.5)
Amniocentesis done			
N_{obs} (N_{miss})	1226 (0)	50 (0)	1176 (0)
No, *n* (%)	1218 (99.3)	49 (98.0)	1169 (99.4)
Yes, *n* (%)	8 (0.7)	1 (2.0)	7 (0.6)

continued

TABLE 42 Baseline characteristics (part 4): this pregnancy. Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of neonatal outcome (*continued*)

Parameter	All	Neonatal outcome available	
		No	Yes
Results of amniocentesis			
N_{obs} (N_{miss})	8 (0)	1 (0)	7 (0)
Normal, *n* (%)	8 (100.0)	1 (100.0)	7 (100.0)
Other, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Chorionic villus sampling done			
N_{obs} (N_{miss})	1225 (1)	50 (0)	1175 (1)
No, *n* (%)	1216 (99.3)	50 (100.0)	1166 (99.2)
Yes, *n* (%)	9 (0.7)	0 (0.0)	9 (0.8)
Results of chorionic villus sampling			
N_{obs} (N_{miss})	9 (0)	0 (0)	9 (0)
Normal, *n* (%)	9 (100.0)	0 (–)	9 (100.0)
Other, *n* (%)	0 (0.0)	0 (–)	0 (0.0)
Cervical length (mm)			
N_{obs} (N_{miss})	712 (514)	30 (20)	682 (494)
Mean (SD)	28.5 (10.8)	31.0 (11.4)	28.4 (10.8)
Median (IQR)	30.0 (22.0–36.0)	32.0 (22.2–37.8)	30.0 (22.0–36.0)
Range	0.0–84.0	12.0–58.0	0.0–84.0
Risk			
N_{obs} (N_{miss})	1226 (0)	50 (0)	1176 (0)
Low, *n* (%)	882 (71.9)	35 (70.0)	847 (72.0)
High, *n* (%)	344 (28.1)	15 (30.0)	329 (28.0)

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:33:58 2015.

TABLE 43 Previous pregnancies (part 1). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of neonatal outcome

Parameter	All	Neonatal outcome available	
		No	Yes
Any previous pregnancy			
N_{obs} (N_{miss})	1224 (2)	48 (2)	1176 (0)
No, *n* (%)	52 (4.2)	0 (0.0)	52 (4.4)
Yes, *n* (%)	1172 (95.8)	48 (100.0)	1124 (95.6)

TABLE 43 Previous pregnancies (part 1). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of neonatal outcome (*continued*)

Parameter	All	Neonatal outcome available	
		No	Yes
Number of previous pregnancies			
N_{obs} (N_{miss})	1224 (2)	48 (2)	1176 (0)
Mean (SD)	2.6 (2.0)	2.8 (1.6)	2.6 (2.0)
Median (IQR)	2.0 (1.0–3.0)	3.0 (1.8– 4.0)	2.0 (1.0–3.0)
Range	0.0–14.0	1.0–7.0	0.0–14.0
Any previous pregnancy of ≥ 14 weeks' gestation			
N_{obs} (N_{miss})	1224 (2)	48 (2)	1176 (0)
No, *n* (%)	75 (6.1)	2 (4.2)	73 (6.2)
Yes, *n* (%)	1149 (93.9)	46 (95.8)	1103 (93.8)
Number of previous pregnancies of ≥ 14 weeks' gestation			
N_{obs} (N_{miss})	1224 (2)	48 (2)	1176 (0)
Mean (SD)	1.9 (1.4)	2.0 (1.3)	1.9 (1.4)
Median (IQR)	2.0 (1.0–2.0)	2.0 (1.0–3.0)	2.0 (1.0–2.0)
Range	0.0–13.0	0.0–6.0	0.0–13.0
Any previous live birth			
N_{obs} (N_{miss})	1224 (2)	48 (2)	1176 (0)
No, *n* (%)	197 (16.1)	7 (14.6)	190 (16.2)
Yes, *n* (%)	1027 (83.9)	41 (85.4)	986 (83.8)
Number of previous live births			
N_{obs} (N_{miss})	1224 (2)	48 (2)	1176 (0)
Mean (SD)	1.5 (1.3)	1.5 (1.1)	1.6 (1.3)
Median (IQR)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)
Range	0.0–13.0	0.0–6.0	0.0–13.0
Any previous pregnancy that ended with baby alive and well			
N_{obs} (N_{miss})	1224 (2)	48 (2)	1176 (0)
No, *n* (%)	646 (52.8)	26 (54.2)	620 (52.7)
Yes, *n* (%)	578 (47.2)	22 (45.8)	556 (47.3)
Number of previous pregnancies that ended with baby alive and well			
N_{obs} (N_{miss})	1224 (2)	48 (2)	1176 (0)
Mean (SD)	0.8 (1.2)	0.8 (1.2)	0.8 (1.2)
Median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)
Range	0.0–13.0	0.0–5.0	0.0–13.0

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:33:58 2015.

TABLE 44 Previous pregnancies (part 2). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of neonatal outcome

		Neonatal outcome available	
Parameter	All	No	Yes
History of induced labour or elective caesarean section			
N_{obs} (N_{miss})	1224 (2)	48 (2)	1176 (0)
No, *n* (%)	1065 (87.0)	38 (79.2)	1027 (87.3)
Yes, *n* (%)	159 (13.0)	10 (20.8)	149 (12.7)
History of miscarriage			
N_{obs} (N_{miss})	1224 (2)	48 (2)	1176 (0)
No, *n* (%)	701 (57.3)	24 (50.0)	677 (57.6)
Yes, *n* (%)	523 (42.7)	24 (50.0)	499 (42.4)
History of ectopic pregnancy			
N_{obs} (N_{miss})	1224 (2)	48 (2)	1176 (0)
No, *n* (%)	1193 (97.5)	45 (93.8)	1148 (97.6)
Yes, *n* (%)	31 (2.5)	3 (6.2)	28 (2.4)
History of termination of pregnancy			
N_{obs} (N_{miss})	1224 (2)	48 (2)	1176 (0)
No, *n* (%)	1085 (88.6)	42 (87.5)	1043 (88.7)
Yes, *n* (%)	139 (11.4)	6 (12.5)	133 (11.3)
History of termination of pregnancy before 14 weeks' gestation			
N_{obs} (N_{miss})	1226 (0)	50 (0)	1176 (0)
No, *n* (%)	1106 (90.2)	44 (88.0)	1062 (90.3)
Yes, *n* (%)	120 (9.8)	6 (12.0)	114 (9.7)
History of termination of pregnancy at ≥ 14 weeks' gestation			
N_{obs} (N_{miss})	1226 (0)	50 (0)	1176 (0)
No, *n* (%)	1201 (98.0)	49 (98.0)	1152 (98.0)
Yes, *n* (%)	25 (2.0)	1 (2.0)	24 (2.0)
History of live birth followed by neonatal death			
N_{obs} (N_{miss})	1224 (2)	48 (2)	1176 (0)
No, *n* (%)	1059 (86.5)	45 (93.8)	1014 (86.2)
Yes, *n* (%)	165 (13.5)	3 (6.2)	162 (13.8)
History of live birth followed by death other than neonatal			
N_{obs} (N_{miss})	1224 (2)	48 (2)	1176 (0)
No, *n* (%)	1208 (98.7)	47 (97.9)	1161 (98.7)
Yes, *n* (%)	16 (1.3)	1 (2.1)	15 (1.3)
History of stillbirth			
N_{obs} (N_{miss})	1224 (2)	48 (2)	1176 (0)
No, *n* (%)	1129 (92.2)	44 (91.7)	1085 (92.3)
Yes, *n* (%)	95 (7.8)	4 (8.3)	91 (7.7)

N_{miss}, number of women with missing data; N_{obs}, number of observations.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:33:59 2015.

TABLE 45 Baseline characteristics (part 1). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of Bayley-III cognitive composite score at 2 years

		Bayley-III cognitive composite score at 2 years available	
Parameter	All	No	Yes
Age (years)			
N_{obs} (N_{miss})	1225 (1)	392 (1)	833 (0)
Mean (SD)	31.4 (5.7)	29.8 (5.7)	32.2 (5.5)
Median (IQR)	31.5 (27.4–35.7)	29.4 (26.1–33.8)	32.3 (28.2–36.2)
Range	16.8–49.2	16.8–45.3	17.5–49.2
Height (cm)			
N_{obs} (N_{miss})	1221 (5)	390 (3)	831 (2)
Mean (SD)	163.5 (6.6)	163.5 (6.6)	163.5 (6.6)
Median (IQR)	163.0 (159.0–168.0)	163.0 (159.0–168.0)	164.0 (159.0–168.0)
Range	144.0–183.0	147.0–183.0	144.0–183.0
Weight (kg)			
N_{obs} (N_{miss})	1221 (5)	390 (3)	831 (2)
Mean (SD)	71.6 (17.1)	70.4 (15.8)	72.2 (17.6)
Median (IQR)	68.0 (60.0–81.0)	67.0 (58.0–80.0)	68.0 (60.0–81.0)
Range	41.0–186.0	43.0–130.0	41.0–186.0
BMI (kg/m^2)			
N_{obs} (N_{miss})	1221 (5)	390 (3)	831 (2)
Mean (SD)	26.8 (6.3)	26.3 (5.6)	27.0 (6.5)
Median (IQR)	25.5 (22.3–29.8)	25.2 (22.2–29.6)	25.6 (22.4–30.1)
Range	15.2–80.5	15.2–49.5	15.6–80.5
Systolic blood pressure (mmHg)			
N_{obs} (N_{miss})	1219 (7)	392 (1)	827 (6)
Mean (SD)	111.9 (12.4)	111.2 (12.0)	112.2 (12.5)
Median (IQR)	110.0 (102.0–120.0)	110.0 (102.0–120.0)	110.0 (102.5–120.0)
Range	78.0–189.0	78.0–159.0	80.0–189.0
Diastolic blood pressure (mmHg)			
N_{obs} (N_{miss})	1219 (7)	392 (1)	827 (6)
Mean (SD)	66.0 (8.6)	65.6 (8.9)	66.1 (8.4)
Median (IQR)	65.0 (60.0–71.0)	65.0 (60.0–70.0)	65.0 (60.0–71.0)
Range	40.0–104.0	44.0–98.0	40.0–104.0

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:33:59 2015.

TABLE 46 Baseline characteristics (part 2). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of Bayley-III cognitive composite score at 2 years

		Bayley-III cognitive composite score at 2 years available	
Parameter	All	No	Yes
Smoking			
N_{obs} (N_{miss})	1220 (6)	391 (2)	829 (4)
No, *n* (%)	984 (80.7)	277 (70.8)	707 (85.3)
Yes, *n* (%)	236 (19.3)	114 (29.2)	122 (14.7)
Alcohol consumption			
N_{obs} (N_{miss})	1223 (3)	392 (1)	831 (2)
No, *n* (%)	1160 (94.8)	369 (94.1)	791 (95.2)
Yes, *n* (%)	63 (5.2)	23 (5.9)	40 (4.8)
Drug use			
N_{obs} (N_{miss})	1223 (3)	392 (1)	831 (2)
No, *n* (%)	1206 (98.6)	384 (98.0)	822 (98.9)
Yes, *n* (%)	17 (1.4)	8 (2.0)	9 (1.1)
In full-time education			
N_{obs} (N_{miss})	1216 (10)	388 (5)	828 (5)
No, *n* (%)	1175 (96.6)	371 (95.6)	804 (97.1)
Yes, *n* (%)	41 (3.4)	17 (4.4)	24 (2.9)
Years in full-time education			
N_{obs} (N_{miss})	1122 (53)	345 (26)	777 (27)
Mean (SD)	13.5 (3.1)	12.8 (3.1)	13.8 (3.0)
Median (IQR)	13.0 (11.0–16.0)	12.0 (11.0–14.0)	13.0 (11.0–16.0)
Range	1.0–31.0	1.0–31.0	3.0–24.0
Educated in the UK			
N_{obs} (N_{miss})	1206 (20)	382 (11)	824 (9)
No, *n* (%)	211 (17.5)	69 (18.1)	142 (17.2)
Yes, *n* (%)	995 (82.5)	313 (81.9)	682 (82.8)

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:33:59 2015.

TABLE 47 Baseline characteristics (part 3). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of Bayley-III cognitive composite score at 2 years

Parameter	All	Bayley-III cognitive composite score at 2 years available	
		No	Yes
Highest level of education if in UK			
N_{obs} (N_{miss})	975 (20)	303 (10)	672 (10)
No formal qualifications, *n* (%)	99 (10.2)	58 (19.1)	41 (6.1)
Entry Level Certificate/Foundation Diploma, *n* (%)	13 (1.3)	2 (0.7)	11 (1.6)
GCSE/Standard/O Level, *n* (%)	327 (33.5)	129 (42.6)	198 (29.5)
A Level, AS Level, Highers or BTEC Diploma/Certificate, *n* (%)	137 (14.1)	34 (11.2)	103 (15.3)
Certificate of Higher Education/City & Guilds, *n* (%)	53 (5.4)	10 (3.3)	43 (6.4)
Diploma HE/FE or HND/HNC, *n* (%)	69 (7.1)	21 (6.9)	48 (7.1)
Graduate certificate or diploma, *n* (%)	14 (1.4)	4 (1.3)	10 (1.5)
Degree, *n* (%)	158 (16.2)	29 (9.6)	129 (19.2)
Professional qualifications, *n* (%)	40 (4.1)	7 (2.3)	33 (4.9)
PG certificate, diploma, masters, doctorate, *n* (%)	65 (6.7)	9 (3.0)	56 (8.3)
Ethnic group			
N_{obs} (N_{miss})	1224 (2)	392 (1)	832 (1)
White, *n* (%)	895 (73.1)	276 (70.4)	619 (74.4)
Chinese, *n* (%)	1 (0.1)	0 (0.0)	1 (0.1)
Other ethnic group, *n* (%)	17 (1.4)	7 (1.8)	10 (1.2)
Mixed			
White and black Caribbean, *n* (%)	17 (1.4)	5 (1.3)	12 (1.4)
White and black African, *n* (%)	3 (0.2)	1 (0.3)	2 (0.2)
White and Asian, *n* (%)	2 (0.2)	0 (0.0)	2 (0.2)
Other mixed background, *n* (%)	6 (0.5)	2 (0.5)	4 (0.5)
Asian			
Indian, *n* (%)	30 (2.5)	7 (1.8)	23 (2.8)
Pakistani, *n* (%)	45 (3.7)	13 (3.3)	32 (3.8)
Bangladeshi, *n* (%)	5 (0.4)	3 (0.8)	2 (0.2)
Other Asian background, *n* (%)	23 (1.9)	8 (2.0)	15 (1.8)
Black			
Caribbean, *n* (%)	47 (3.8)	17 (4.3)	30 (3.6)
African, *n* (%)	119 (9.7)	46 (11.7)	73 (8.8)
Other black background, *n* (%)	14 (1.1)	7 (1.8)	7 (0.8)

continued

TABLE 47 Baseline characteristics (part 3). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of Bayley-III cognitive composite score at 2 years (*continued*)

Parameter	All	Bayley-III cognitive composite score at 2 years available	
		No	Yes
Ethnic group			
N_{obs} (N_{miss})	1224 (2)	392 (1)	832 (1)
White, *n* (%)	895 (73.1)	276 (70.4)	619 (74.4)
Black, *n* (%)	180 (14.7)	70 (17.9)	110 (13.2)
Asian, *n* (%)	104 (8.5)	31 (7.9)	73 (8.8)
Mixed, *n* (%)	28 (2.3)	8 (2.0)	20 (2.4)
Other, *n* (%)	17 (1.4)	7 (1.8)	10 (1.2)

A Level, Advanced Level; AS Level, Advanced Subsidiary Level; BTEC, Business and Technology Education Council; FE, Further Education; GCSE, General Certificate of Secondary Education; HE, Higher Education; HNC, Higher National Certificate; HND, Higher National Diploma; N_{miss}, number of women with missing data; N_{obs}, number of observations; O Level, ordinary level; PG, postgraduate.

Note

OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:33:59 2015.

TABLE 48 Baseline characteristics (part 4): this pregnancy. Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of Bayley-III cognitive composite score at 2 years

Parameter	All	Bayley-III cognitive composite score at 2 years available	
		No	Yes
Gestation (weeks) at fFN test			
N_{obs} (N_{miss})	1226 (0)	393 (0)	833 (0)
Mean (SD)	22.9 (0.6)	22.9 (0.6)	22.9 (0.6)
Median (IQR)	22.9 (22.4–23.4)	22.9 (22.4–23.4)	22.9 (22.4–23.4)
Range	21.7–27.1	22.0–24.1	21.7–27.1
Fetal anomaly scan done			
N_{obs} (N_{miss})	1226 (0)	393 (0)	833 (0)
No, *n* (%)	63 (5.1)	25 (6.4)	38 (4.6)
Yes, *n* (%)	1163 (94.9)	368 (93.6)	795 (95.4)
Fetal anomaly scan result			
N_{obs} (N_{miss})	1163 (0)	368 (0)	795 (0)
Normal, *n* (%)	1150 (98.9)	365 (99.2)	785 (98.7)
Defined abnormality, *n* (%)	7 (0.6)	0 (0.0)	7 (0.9)
Uncertain abnormality, *n* (%)	6 (0.5)	3 (0.8)	3 (0.4)
Amniocentesis done			
N_{obs} (N_{miss})	1226 (0)	393 (0)	833 (0)
No, *n* (%)	1218 (99.3)	392 (99.7)	826 (99.2)
Yes, *n* (%)	8 (0.7)	1 (0.3)	7 (0.8)

TABLE 48 Baseline characteristics (part 4): this pregnancy. Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of Bayley-III cognitive composite score at 2 years (*continued*)

		Bayley-III cognitive composite score at 2 years available	
Parameter	All	No	Yes
Results of amniocentesis			
N_{obs} (N_{miss})	8 (0)	1 (0)	7 (0)
Normal, *n* (%)	8 (100.0)	1 (100.0)	7 (100.0)
Other, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Chorionic villus sampling done			
N_{obs} (N_{miss})	1225 (1)	393 (0)	832 (1)
No, *n* (%)	1216 (99.3)	390 (99.2)	826 (99.3)
Yes, *n* (%)	9 (0.7)	3 (0.8)	6 (0.7)
Results of chorionic villus sampling			
N_{obs} (N_{miss})	9 (0)	3 (0)	6 (0)
Normal, *n* (%)	9 (100.0)	3 (100.0)	6 (100.0)
Other, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Cervical length (mm)			
N_{obs} (N_{miss})	712 (514)	234 (159)	478 (355)
Mean (SD)	28.5 (10.8)	28.4 (10.6)	28.6 (11.0)
Median (IQR)	30.0 (22.0–36.0)	30.0 (22.0–36.0)	30.0 (22.0–36.0)
Range	0.0–84.0	0.0–50.0	0.0–84.0
Risk			
N_{obs} (N_{miss})	1226 (0)	393 (0)	833 (0)
Low, *n* (%)	882 (71.9)	268 (68.2)	614 (73.7)
High, *n* (%)	344 (28.1)	125 (31.8)	219 (26.3)

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:33:59 2015.

TABLE 49 Previous pregnancies (part 1). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of Bayley-III cognitive composite score at 2 years

		Bayley-III cognitive composite score at 2 years available	
Parameter	All	No	Yes
Any previous pregnancy			
N_{obs} (N_{miss})	1224 (2)	391 (2)	833 (0)
No, *n* (%)	52 (4.2)	10 (2.6)	42 (5.0)
Yes, *n* (%)	1172 (95.8)	381 (97.4)	791 (95.0)

continued

TABLE 49 Previous pregnancies (part 1). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of Bayley-III cognitive composite score at 2 years (*continued*)

Parameter	All	Bayley-III cognitive composite score at 2 years available	
		No	Yes
Number of previous pregnancies			
N_{obs} (N_{miss})	1224 (2)	391 (2)	833 (0)
Mean (SD)	2.6 (2.0)	2.9 (2.2)	2.5 (1.9)
Median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–4.0)	2.0 (1.0–3.0)
Range	0.0–14.0	0.0–13.0	0.0–14.0
Any previous pregnancy of ≥ 14 weeks' gestation			
N_{obs} (N_{miss})	1224 (2)	391 (2)	833 (0)
No, *n* (%)	75 (6.1)	19 (4.9)	56 (6.7)
Yes, *n* (%)	1149 (93.9)	372 (95.1)	777 (93.3)
Number of previous pregnancies of ≥ 14 weeks' gestation			
N_{obs} (N_{miss})	1224 (2)	391 (2)	833 (0)
Mean (SD)	1.9 (1.4)	2.1 (1.6)	1.8 (1.3)
Median (IQR)	2.0 (1.0–2.0)	2.0 (1.0–3.0)	1.0 (1.0–2.0)
Range	0.0–13.0	0.0–13.0	0.0–10.0
Any previous live birth			
N_{obs} (N_{miss})	1224 (2)	391 (2)	833 (0)
No, *n* (%)	197 (16.1)	61 (15.6)	136 (16.3)
Yes, *n* (%)	1027 (83.9)	330 (84.4)	697 (83.7)
Number of previous live births			
N_{obs} (N_{miss})	1224 (2)	391 (2)	833 (0)
Mean (SD)	1.5 (1.3)	1.7 (1.5)	1.5 (1.2)
Median (IQR)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)
Range	0.0–13.0	0.0–13.0	0.0–10.0
Any previous pregnancy that ended with baby alive and well			
N_{obs} (N_{miss})	1224 (2)	391 (2)	833 (0)
No, *n* (%)	646 (52.8)	210 (53.7)	436 (52.3)
Yes, *n* (%)	578 (47.2)	181 (46.3)	397 (47.7)
Number of previous pregnancies that ended with baby alive and well			
N_{obs} (N_{miss})	1224 (2)	391 (2)	833 (0)
Mean (SD)	0.8 (1.2)	0.9 (1.4)	0.8 (1.1)
Median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)
Range	0.0–13.0	0.0–13.0	0.0–10.0

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:00 2015.

TABLE 50 Previous pregnancies (part 2). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of Bayley-III cognitive composite score at 2 years

		Bayley-III cognitive composite score at 2 years available	
Parameter	All	No	Yes
History of induced labour or elective caesarean section			
N_{obs} (N_{miss})	1224 (2)	391 (2)	833 (0)
No, *n* (%)	1065 (87.0%)	334 (85.4)	731 (87.8)
Yes, *n* (%)	159 (13.0%)	57 (14.6)	102 (12.2)
History of miscarriage			
N_{obs} (N_{miss})	1224 (2)	391 (2)	833 (0)
No, *n* (%)	701 (57.3)	212 (54.2)	489 (58.7)
Yes, *n* (%)	523 (42.7)	179 (45.8)	344 (41.3)
History of ectopic pregnancy			
N_{obs} (N_{miss})	1224 (2)	391 (2)	833 (0)
No, *n* (%)	1193 (97.5)	380 (97.2)	813 (97.6)
Yes, *n* (%)	31 (2.5)	11 (2.8)	20 (2.4)
History of termination of pregnancy			
N_{obs} (N_{miss})	1224 (2)	391 (2)	833 (0)
No, *n* (%)	1085 (88.6)	338 (86.4)	747 (89.7)
Yes, *n* (%)	139 (11.4)	53 (13.6)	86 (10.3)
History of termination of pregnancy before 14 weeks' gestation			
N_{obs} (N_{miss})	1226 (0)	393 (0)	833 (0)
No, *n* (%)	1106 (90.2)	348 (88.5)	758 (91.0)
Yes, *n* (%)	120 (9.8)	45 (11.5)	75 (9.0)
History of termination of pregnancy at ≥ 14 weeks' gestation			
N_{obs} (N_{miss})	1226 (0)	393 (0)	833 (0)
No, *n* (%)	1201 (98.0)	382 (97.2)	819 (98.3)
Yes, *n* (%)	25 (2.0)	11 (2.8)	14 (1.7)
History of live birth followed by neonatal death			
N_{obs} (N_{miss})	1224 (2)	391 (2)	833 (0)
No, *n* (%)	1059 (86.5)	338 (86.4)	721 (86.6)
Yes, *n* (%)	165 (13.5)	53 (13.6)	112 (13.4)
History of live birth followed by death other than neonatal			
N_{obs} (N_{miss})	1224 (2)	391 (2)	833 (0)
No, *n* (%)	1208 (98.7)	383 (98.0)	825 (99.0)
Yes, *n* (%)	16 (1.3)	8 (2.0)	8 (1.0)
History of stillbirth			
N_{obs} (N_{miss})	1224 (2)	391 (2)	833 (0)
No, *n* (%)	1129 (92.2)	359 (91.8)	770 (92.4)
Yes, *n* (%)	95 (7.8)	32 (8.2)	63 (7.6)

N_{miss}, number of women with missing data; N_{obs}, number of observations.

Note

OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:00 2015.

TABLE 51 Baseline characteristics (part 1). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability survival at 2 years

		Survival at 2 years available	
Parameter	All	No	Yes
Age (years)			
N_{obs} (N_{miss})	1225 (1)	216 (1)	1009 (0)
Mean (SD)	31.4 (5.7)	29.4 (5.6)	31.9 (5.6)
Median (IQR)	31.5 (27.4–35.7)	29.2 (25.6–33.0)	32.0 (28.0–36.0)
Range	16.8–49.2	17.6–45.3	16.8–49.2
Height (cm)			
N_{obs} (N_{miss})	1221 (5)	216 (1)	1005 (4)
Mean (SD)	163.5 (6.6)	163.9 (6.9)	163.4 (6.5)
Median (IQR)	163.0 (159.0–168.0)	163.0 (159.0–168.0)	163.0 (159.0–168.0)
Range	144.0–183.0	147.0–182.0	144.0–183.0
Weight (kg)			
N_{obs} (N_{miss})	1221 (5)	216 (1)	1005 (4)
Mean (SD)	71.6 (17.1)	71.5 (16.4)	71.7 (17.2)
Median (IQR)	68.0 (60.0–81.0)	68.0 (59.0–81.0)	68.0 (60.0–81.0)
Range	41.0–186.0	43.0–130.0	41.0–186.0
BMI (kg/m^2)			
N_{obs} (N_{miss})	1221 (5)	216 (1)	1005 (4)
Mean (SD)	26.8 (6.3)	26.6 (5.8)	26.8 (6.3)
Median (IQR)	25.5 (22.3–29.8)	25.5 (22.4–29.7)	25.6 (22.3–29.8)
Range	15.2–80.5	16.4–49.5	15.2–80.5
Systolic blood pressure (mmHg)			
N_{obs} (N_{miss})	1219 (7)	216 (1)	1003 (6)
Mean (SD)	111.9 (12.4)	110.9 (12.1)	112.1 (12.4)
Median (IQR)	110.0 (102.0–120.0)	110.0 (100.8–120.0)	110.0 (103.0–120.0)
Range	78.0–189.0	78.0–159.0	80.0–189.0
Diastolic blood pressure (mmHg)			
N_{obs} (N_{miss})	1219 (7)	216 (1)	1003 (6)
Mean (SD)	66.0 (8.6)	65.2 (8.7)	66.1 (8.5)
Median (IQR)	65.0 (60.0–71.0)	64.0 (60.0–70.0)	65.0 (60.0–71.0)
Range	40.0–104.0	44.0–98.0	40.0–104.0

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:00 2015.

TABLE 52 Baseline characteristics (part 2). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of survival at 2 years

		Survival at 2 years available	
Parameter	All	No	Yes
Smoking			
N_{obs} (N_{miss})	1220 (6)	216 (1)	1004 (5)
No, *n* (%)	984 (80.7)	137 (63.4)	847 (84.4)
Yes, *n* (%)	236 (19.3)	79 (36.6)	157 (15.6)
Alcohol consumption			
N_{obs} (N_{miss})	1223 (3)	216 (1)	1007 (2)
No, *n* (%)	1160 (94.8)	201 (93.1)	959 (95.2)
Yes, *n* (%)	63 (5.2)	15 (6.9)	48 (4.8)
Drug use			
N_{obs} (N_{miss})	1223 (3)	216 (1)	1007 (2)
No, *n* (%)	1206 (98.6)	211 (97.7)	995 (98.8)
Yes, *n* (%)	17 (1.4)	5 (2.3)	12 (1.2)
In full-time education			
N_{obs} (N_{miss})	1216 (10)	215 (2)	1001 (8)
No, *n* (%)	1175 (96.6)	206 (95.8)	969 (96.8)
Yes, *n* (%)	41 (3.4)	9 (4.2)	32 (3.2)
Years in full-time education			
N_{obs} (N_{miss})	1122 (53)	196 (10)	926 (43)
Mean (SD)	13.5 (3.1)	12.7 (2.7)	13.7 (3.1)
Median (IQR)	13.0 (11.0–16.0)	12.0 (11.0–14.0)	13.0 (11.0–16.0)
Range	1.0–31.0	5.0–23.0	1.0–31.0
Educated in the UK			
N_{obs} (N_{miss})	1206 (20)	213 (4)	993 (16)
No, *n* (%)	211 (17.5)	30 (14.1)	181 (18.2)
Yes, *n* (%)	995 (82.5)	183 (85.9)	812 (81.8)

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:01 2015.

TABLE 53 Baseline characteristics (part 3). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of survival at 2 years

Parameter	All	Survival at 2 years available	
		No	Yes
Highest level of education if in UK			
N_{obs} (N_{miss})	975 (20)	176 (7)	799 (13)
No formal qualifications, *n* (%)	99 (10.2)	40 (22.7)	59 (7.4)
Entry Level Certificate/Foundation Diploma, *n* (%)	13 (1.3)	1 (0.6)	12 (1.5)
GCSE/Standard/O Level, *n* (%)	327 (33.5)	74 (42.0)	253 (31.7)
A Level, AS Level, Highers or BTEC Diploma/Certificate, *n* (%)	137 (14.1)	21 (11.9)	116 (14.5)
Certificate of Higher Education/City & Guilds, *n* (%)	53 (5.4)	8 (4.5)	45 (5.6)
Diploma HE/FE or HND/HNC, *n* (%)	69 (7.1)	7 (4.0)	62 (7.8)
Graduate certificate or diploma, *n* (%)	14 (1.4)	3 (1.7)	11 (1.4)
Degree, *n* (%)	158 (16.2)	15 (8.5)	143 (17.9)
Professional qualifications, *n* (%)	40 (4.1)	4 (2.3)	36 (4.5)
PG certificate, diploma, masters, doctorate, *n* (%)	65 (6.7)	3 (1.7)	62 (7.8)
Ethnic group			
N_{obs} (N_{miss})	1224 (2)	216 (1)	1008 (1)
White, *n* (%)	895 (73.1)	154 (71.3)	741 (73.5)
Chinese, *n* (%)	1 (0.1)	0 (0.0)	1 (0.1)
Other ethnic group, *n* (%)	17 (1.4)	2 (0.9)	15 (1.5)
Mixed			
White and black Caribbean, *n* (%)	17 (1.4)	4 (1.9)	13 (1.3)
White and black African, *n* (%)	3 (0.2)	1 (0.5)	2 (0.2)
White and Asian, *n* (%)	2 (0.2)	0 (0.0)	2 (0.2)
Other mixed background, *n* (%)	6 (0.5)	1 (0.5)	5 (0.5)
Asian			
Indian, *n* (%)	30 (2.5)	5 (2.3)	25 (2.5)
Pakistani, *n* (%)	45 (3.7)	7 (3.2)	38 (3.8)
Bangladeshi, *n* (%)	5 (0.4)	2 (0.9)	3 (0.3)
Other Asian background, *n* (%)	23 (1.9)	2 (0.9)	21 (2.1)
Black			
Caribbean, *n* (%)	47 (3.8)	11 (5.1)	36 (3.6)
African, *n* (%)	119 (9.7)	23 (10.6)	96 (9.5)
Other black background, *n* (%)	14 (1.1)	4 (1.9)	10 (1.0)

TABLE 53 Baseline characteristics (part 3). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of survival at 2 years (*continued*)

Parameter	All	Survival at 2 years available	
		No	Yes
Ethnic group			
N_{obs} (N_{miss})	1224 (2)	216 (1)	1008 (1)
White, *n* (%)	895 (73.1)	154 (71.3)	741 (73.5)
Black, *n* (%)	180 (14.7)	38 (17.6)	142 (14.1)
Asian, *n* (%)	104 (8.5)	16 (7.4)	88 (8.7)
Mixed, *n* (%)	28 (2.3)	6 (2.8)	22 (2.2)
Other, *n* (%)	17 (1.4)	2 (0.9)	15 (1.5)

A Level, Advanced Level; AS Level, Advanced Subsidiary Level; BTEC, Business and Technology Education Council; FE, Further Education; GCSE, General Certificate of Secondary Education; HE, Higher Education; HNC, Higher National Certificate; HND, Higher National Diploma; N_{miss}, number of women with missing data; N_{obs}, number of observations; O Level, ordinary level; PG, postgraduate.

Note

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TABLE 54 Baseline characteristics (part 4): this pregnancy. Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of survival at 2 years

Parameter	All	Survival at 2 years available	
		No	Yes
Gestation (weeks) at fFN test			
N_{obs} (N_{miss})	1226 (0)	217 (0)	1009 (0)
Mean (SD)	22.9 (0.6)	22.9 (0.6)	22.9 (0.6)
Median (IQR)	22.9 (22.4–23.4)	22.9 (22.4–23.6)	22.9 (22.4–23.3)
Range	21.7–27.1	22.0–24.1	21.7–27.1
Fetal anomaly scan done			
N_{obs} (N_{miss})	1226 (0)	217 (0)	1009 (0)
No, *n* (%)	63 (5.1)	12 (5.5)	51 (5.1)
Yes, *n* (%)	1163 (94.9)	205 (94.5)	958 (94.9)
Fetal anomaly scan result			
N_{obs} (N_{miss})	1163 (0)	205 (0)	958 (0)
Normal, *n* (%)	1150 (98.9)	205 (100.0)	945 (98.6)
Defined abnormality, *n* (%)	7 (0.6)	0 (0.0)	7 (0.7)
Uncertain abnormality, *n* (%)	6 (0.5)	0 (0.0)	6 (0.6)
Amniocentesis done			
N_{obs} (N_{miss})	1226 (0)	217 (0)	1009 (0)
No, *n* (%)	1218 (99.3)	216 (99.5)	1002 (99.3)
Yes, *n* (%)	8 (0.7)	1 (0.5)	7 (0.7)

continued

TABLE 54 Baseline characteristics (part 4): this pregnancy. Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of survival at 2 years (*continued*)

Parameter	All	Survival at 2 years available	
		No	Yes
Results of amniocentesis			
N_{obs} (N_{miss})	8 (0)	1 (0)	7 (0)
Normal, *n* (%)	8 (100.0)	1 (100.0)	7 (100.0)
Other, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Chorionic villus sampling done			
N_{obs} (N_{miss})	1225 (1)	217 (0)	1008 (1)
No, *n* (%)	1216 (99.3)	214 (98.6)	1002 (99.4)
Yes, *n* (%)	9 (0.7)	3 (1.4)	6 (0.6)
Results of chorionic villus sampling			
N_{obs} (N_{miss})	9 (0)	3 (0)	6 (0)
Normal, *n* (%)	9 (100.0)	3 (100.0)	6 (100.0)
Other, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Cervical length (mm)			
N_{obs} (N_{miss})	712 (514)	129 (88)	583 (426)
Mean (SD)	28.5 (10.8)	29.9 (10.0)	28.2 (11.0)
Median (IQR)	30.0 (22.0–36.0)	32.0 (23.0–37.0)	30.0 (22.0–36.0)
Range	0.0–84.0	4.0–50.0	0.0–84.0
Risk			
N_{obs} (N_{miss})	1226 (0)	217 (0)	1009 (0)
Low, *n* (%)	882 (71.9)	157 (72.4)	725 (71.9)
High, *n* (%)	344 (28.1)	60 (27.6)	284 (28.1)

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:01 2015.

TABLE 55 Previous pregnancies (part 1). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of survival at 2 years

Parameter	All	Survival at 2 years available	
		No	Yes
Any previous pregnancy			
N_{obs} (N_{miss})	1224 (2)	215 (2)	1009 (0)
No, *n* (%)	52 (4.2)	2 (0.9)	50 (5.0)
Yes, *n* (%)	1172 (95.8)	213 (99.1)	959 (95.0)

TABLE 55 Previous pregnancies (part 1). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of survival at 2 years (*continued*)

Parameter	All	Survival at 2 years available	
		No	Yes
Number of previous pregnancies			
N_{obs} (N_{miss})	1224 (2)	215 (2)	1009 (0)
Mean (SD)	2.6 (2.0)	3.1 (2.2)	2.5 (1.9)
Median (IQR)	2.0 (1.0–3.0)	3.0 (1.0–4.0)	2.0 (1.0–3.0)
Range	0.0–14.0	0.0–12.0	0.0–14.0
Any previous pregnancy of ≥ 14 weeks' gestation			
N_{obs} (N_{miss})	1224 (2)	215 (2)	1009 (0)
No, *n* (%)	75 (6.1)	6 (2.8)	69 (6.8)
Yes, *n* (%)	1149 (93.9)	209 (97.2)	940 (93.2)
Number of previous pregnancies of ≥ 14 weeks' gestation			
N_{obs} (N_{miss})	1224 (2)	215 (2)	1009 (0)
Mean (SD)	1.9 (1.4)	2.3 (1.5)	1.8 (1.4)
Median (IQR)	2.0 (1.0–2.0)	2.0 (1.0–3.0)	1.0 (1.0–2.0)
Range	0.0–13.0	0.0–8.0	0.0–13.0
Any previous live birth			
N_{obs} (N_{miss})	1224 (2)	215 (2)	1009 (0)
No, *n* (%)	197 (16.1)	26 (12.1)	171 (16.9)
Yes, *n* (%)	1027 (83.9)	189 (87.9)	838 (83.1)
Number of previous live births			
N_{obs} (N_{miss})	1224 (2)	215 (2)	1009 (0)
Mean (SD)	1.5 (1.3)	1.8 (1.4)	1.5 (1.3)
Median (IQR)	1.0 (1.0–2.0)	2.0 (1.0–2.0)	1.0 (1.0–2.0)
Range	0.0–13.0	0.0–8.0	0.0–13.0
Any previous pregnancy that ended with baby alive and well			
N_{obs} (N_{miss})	1224 (2)	215 (2)	1009 (0)
No, *n* (%)	646 (52.8)	109 (50.7)	537 (53.2)
Yes, *n* (%)	578 (47.2)	106 (49.3)	472 (46.8)
Number of previous pregnancies that ended with baby alive and well			
N_{obs} (N_{miss})	1224 (2)	215 (2)	1009 (0)
Mean (SD)	0.8 (1.2)	0.9 (1.2)	0.8 (1.2)
Median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)
Range	0.0–13.0	0.0–6.0	0.0–13.0

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:01 2015.

TABLE 56 Previous pregnancies (part 2). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of survival at 2 years

		Survival at 2 years available	
Parameter	All	No	Yes
History of induced labour or elective caesarean section			
N_{obs} (N_{miss})	1224 (2)	215 (2)	1009 (0)
No, *n* (%)	1065 (87.0)	178 (82.8)	887 (87.9)
Yes, *n* (%)	159 (13.0)	37 (17.2)	122 (12.1)
History of miscarriage			
N_{obs} (N_{miss})	1224 (2)	215 (2)	1009 (0)
No, *n* (%)	701 (57.3)	114 (53.0)	587 (58.2)
Yes, *n* (%)	523 (42.7)	101 (47.0)	422 (41.8)
History of ectopic pregnancy			
N_{obs} (N_{miss})	1224 (2)	215 (2)	1009 (0)
No, *n* (%)	1193 (97.5)	209 (97.2)	984 (97.5)
Yes, *n* (%)	31 (2.5)	6 (2.8)	25 (2.5)
History of termination of pregnancy			
N_{obs} (N_{miss})	1224 (2)	215 (2)	1009 (0)
No, *n* (%)	1085 (88.6)	183 (85.1)	902 (89.4)
Yes, *n* (%)	139 (11.4)	32 (14.9)	107 (10.6)
History of termination of pregnancy before 14 weeks' gestation			
N_{obs} (N_{miss})	1226 (0)	217 (0)	1009 (0)
No, *n* (%)	1106 (90.2)	190 (87.6)	916 (90.8)
Yes, *n* (%)	120 (9.8)	27 (12.4)	93 (9.2)
History of termination of pregnancy at ≥ 14 weeks' gestation			
N_{obs} (N_{miss})	1226 (0)	217 (0)	1009 (0)
No, *n* (%)	1201 (98.0)	210 (96.8)	991 (98.2)
Yes, *n* (%)	25 (2.0)	7 (3.2)	18 (1.8)
History of live birth followed by neonatal death			
N_{obs} (N_{miss})	1224 (2)	215 (2)	1009 (0)
No, *n* (%)	1059 (86.5)	186 (86.5)	873 (86.5)
Yes, *n* (%)	165 (13.5)	29 (13.5)	136 (13.5)
History of live birth followed by death other than neonatal			
N_{obs} (N_{miss})	1224 (2)	215 (2)	1009 (0)
No, *n* (%)	1208 (98.7)	210 (97.7)	998 (98.9)
Yes, *n* (%)	16 (1.3)	5 (2.3)	11 (1.1)
History of stillbirth			
N_{obs} (N_{miss})	1224 (2)	215 (2)	1009 (0)
No, *n* (%)	1129 (92.2)	195 (90.7)	934 (92.6)
Yes, *n* (%)	95 (7.8)	20 (9.3)	75 (7.4)

N_{miss}, number of women with missing data; N_{obs}, number of observations.

Note

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Part 3: summaries of outcomes

Does progesterone prophylaxis to prevent preterm labour improve outcome?	
OPPTIMUM	
Final report tables	
Part 3: summaries of outcomes	
v1.0	
2 October 2015	
Martina Messow	
Robertson Centre for Biostatistics	
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CTA, Clinical Trial Authorisation; EudraCT, European Union Drug Regulating Authorities Clinical Trials; MREC, Multicentre Research Ethics Committee; SAP, statistical analysis plan.

TABLE 57 Summaries of primary outcome measures for all patients and according to treatment groups

		Trial group	
Parameter	All	Placebo	Progesterone
Death or delivery before 34 weeks' gestation			
N_{obs} (N_{miss})	1197 (29)	597 (13)	600 (16)
No, *n* (%)	993 (83.0)	489 (81.9)	504 (84.0)
Yes, *n* (%)	204 (17.0)	108 (18.1)	96 (16.0)
Death, brain injury or severe chronic lung disease			
N_{obs} (N_{miss})	1176 (50)	587 (23)	589 (27)
No, *n* (%)	1068 (90.8)	525 (89.4)	543 (92.2)
Yes, *n* (%)	108 (9.2)	62 (10.6)	46 (7.8)
Bayley-III cognitive composite score at 2 years			
N_{obs} (N_{miss})	833 (393)	423 (187)	410 (206)
Mean (SD)	99.6 (14.9)	99.5 (15.0)	99.7 (14.7)
Median (IQR)	100.0 (90.0–105.0)	100.0 (90.0–105.0)	100.0 (90.0–110.0)
Range	55.0–149.0	55.0–149.0	55.0–145.0

continued

TABLE 57 Summaries of primary outcome measures for all patients and according to treatment groups (*continued*)

Parameter	All	Trial group	
		Placebo	Progesterone
Bayley-III cognitive composite score at 2 years (imputed)			
N_{obs} (N_{miss})	869 (357)	439 (171)	430 (186)
Mean (SD)	97.5 (17.7)	97.7 (17.5)	97.3 (17.9)
Median (IQR)	100.0 (90.0–105.0)	100.0 (90.0–105.0)	100.0 (90.0–105.0)
Range	49.0–149.0	49.0–149.0	49.0–145.0
Alive at 2 years			
N_{obs} (N_{miss})	1009 (217)	509 (101)	500 (116)
No, *n* (%)	36 (3.6)	16 (3.1)	20 (4.0)
Yes, *n* (%)	973 (96.4)	493 (96.9)	480 (96.0)
Survival (days)			
N_{obs} (N_{miss})	1198 (28)	598 (12)	600 (16)
Deaths, median time	36,756.00	16,759.00	20,751.00
Range	1–1335	1–1331	1–1335

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:02 2015.

TABLE 58 Summaries of secondary outcome measures at delivery/neonatal for all patients and according to treatment groups (part 1)

	All	Trial group	
		Placebo	Progesterone
Gestational age at delivery (weeks)			
N_{obs} (N_{miss})	1197 (29)	597 (13)	600 (16)
Mean (SD)	36.9 (4.2)	36.8 (4.2)	36.9 (4.1)
Median (IQR)	38.3 (35.7–39.6)	38.3 (35.4–39.7)	38.1 (36.0–39.4)
Range	22.4–42.7	22.4–42.7	23.0–42.1
Delivery before 34 weeks' gestation			
N_{obs} (N_{miss})	1197 (29)	597 (13)	600 (16)
No, *n* (%)	993 (83.0)	489 (81.9)	504 (84.0)
Yes, *n* (%)	204 (17.0)	108 (18.1)	96 (16.0)
Fetal death (miscarriage or stillbirth)			
N_{obs} (N_{miss})	1197 (29)	597 (13)	600 (16)
No, *n* (%)	1182 (98.7)	590 (98.8)	592 (98.7)
Yes, *n* (%)	15 (1.3)	7 (1.2)	8 (1.3)
Neonatal death			
N_{obs} (N_{miss})	1197 (29)	597 (13)	600 (16)
No, *n* (%)	1180 (98.6)	589 (98.7)	590 (98.3)
Yes, *n* (%)	17 (1.4)	8 (1.3)	9 (1.5)

TABLE 58 Summaries of secondary outcome measures at delivery/neonatal for all patients and according to treatment groups (part 1) (*continued*)

		Trial group	
	All	Placebo	Progesterone
Brain injury			
N_{obs} (N_{miss})	1158 (68)	574 (36)	584 (32)
No, *n* (%)	1106 (95.5)	540 (94.1)	566 (96.9)
Yes, *n* (%)	52 (4.5)	34 (5.9)	18 (3.1)
Severe chronic lung disease			
N_{obs} (N_{miss})	1154 (72)	574 (36)	580 (36)
No, *n* (%)	1119 (97.0)	556 (96.9)	563 (97.1)
Yes, *n* (%)	35 (3.0)	18 (3.1)	17 (2.9)
Need for surfactant administration			
N_{obs} (N_{miss})	1156 (70)	573 (37)	583 (33)
No, *n* (%)	1064 (92.0)	528 (92.1)	536 (91.9)
Yes, *n* (%)	92 (8.0)	45 (7.9)	47 (8.1)
Necrotising enterocolitis			
N_{obs} (N_{miss})	1155 (71)	574 (36)	581 (35)
No, *n* (%)	1124 (97.3)	561 (97.7)	563 (96.9)
Yes suspected, *n* (%)	16 (1.4)	5 (0.9)	11 (1.9)
Yes medical treatment only, *n* (%)	10 (0.9)	4 (0.7)	6 (1.0)
Yes required drain or laparotomy, *n* (%)	5 (0.4)	4 (0.7)	1 (0.2)
Infection			
N_{obs} (N_{miss})	1154 (72)	573 (37)	581 (35)
No, *n* (%)	1074 (93.1)	537 (93.7)	537 (92.4)
Yes, *n* (%)	80 (6.9)	36 (6.3)	44 (7.6)
Number of discrete episodes with positive blood culture in those with infection			
N_{obs} (N_{miss})	73 (7)	33 (3)	40 (4)
0, *n* (%)	37 (50.7)	14 (42.4)	23 (57.5)
1, *n* (%)	28 (38.4)	16 (48.5)	12 (30.0)
2, *n* (%)	7 (9.6)	3 (9.1)	4 (10.0)
4, *n* (%)	1 (1.4)	0 (0.0)	1 (2.5)
Number of discrete episodes with positive cerebrospinal fluid culture in those with infection			
N_{obs} (N_{miss})	74 (6)	34 (2)	40 (4)
0, *n* (%)	71 (95.9)	34 (100.0)	37 (92.5)
1, *n* (%)	2 (2.7)	0 (0.0)	2 (5.0)
2, *n* (%)	1 (1.4)	0 (0.0)	1 (2.5)

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:02 2015.

TABLE 59 Summaries of secondary outcome measures at delivery/neonatal for all patients and according to treatment groups (part 2)

	All	Trial group	
		Placebo	Progesterone
Highest level of care in delivery room			
N_{obs} (N_{miss})	1165 (61)	584 (26)	581 (35)
Minimal (none required or tactile stimulation), *n* (%)	924 (79.3)	456 (78.1)	468 (80.6)
Intubation plus chest compressions and/or adrenaline, *n* (%)	3 (0.3)	0 (0.0)	3 (0.5)
Suction, *n* (%)	7 (0.6)	4 (0.7)	3 (0.5)
Suction and facial O_2 only, *n* (%)	39 (3.3)	19 (3.3)	20 (3.4)
Mask ventilation only, *n* (%)	100 (8.6)	56 (9.6)	44 (7.6)
Intubation, *n* (%)	86 (7.4)	47 (8.0)	39 (6.7)
Intubation plus chest compressions, *n* (%)	6 (0.5)	2 (0.3)	4 (0.7)
Number of days of normal care			
N_{obs} (N_{miss})	1151 (75)	570 (40)	581 (35)
Mean (SD)	1.7 (2.0)	1.7 (2.3)	1.7 (1.6)
Median (IQR)	1.0 (1.0–2.0)	1.0 (0.0–2.0)	1.0 (1.0–2.0)
Range	0.0–28.0	0.0–28.0	0.0–12.0
Number of days of special care			
N_{obs} (N_{miss})	1151 (75)	570 (40)	581 (35)
Mean (SD)	3.5 (9.6)	4.2 (10.6)	2.9 (8.3)
Median (IQR)	(0.0–0.0)	0.0 (0.0–1.0)	0.0 (0.0–0.0)
Range	0.0–92.0	0.0–85.0	0.0–92.0
Number of days of level 2 care			
N_{obs} (N_{miss})	1149 (77)	569 (41)	580 (36)
Mean (SD)	2.2 (9.5)	2.2 (8.4)	2.1 (10.4)
Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Range	0.0–137.0	0.0–74.0	0.0–137.0
Number of days of level 1 care			
N_{obs} (N_{miss})	1149 (77)	569 (41)	580 (36)
Mean (SD)	1.9 (7.7)	1.8 (7.3)	1.9 (8.1)
Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Range	0.0–75.0	0.0–75.0	0.0–64.0
Maternal or child SAEs during pregnancy and birth[a]			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
No, *n* (%)	1097 (89.5)	540 (88.5)	557 (90.4)
Yes, *n* (%)	129 (10.5)	70 (11.5)	59 (9.6)

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
a Up to and including day 1 after birth.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:03 2015.

TABLE 60 Summaries of secondary outcome measures at 2-year follow-up for all patients and according to treatment groups (part 1)

	All	Trial group	
		Placebo	Progesterone
Death or moderate/severe neurodevelopmental impairment			
N_{obs} (N_{miss})	818 (408)	419 (191)	399 (217)
No, *n* (%)	700 (85.6)	368 (87.8)	332 (83.2)
Yes, *n* (%)	118 (14.4)	51 (12.2)	67 (16.8)
Moderate/severe neurodevelopmental impairment			
N_{obs} (N_{miss})	782 (444)	403 (207)	379 (237)
No, *n* (%)	700 (89.5)	368 (91.3)	332 (87.6)
Yes, *n* (%)	82 (10.5)	35 (8.7)	47 (12.4)
Components of neurodevelopmental disability			
Motor			
N_{obs} (N_{miss})	917 (309)	456 (154)	461 (155)
No, *n* (%)	909 (99.1)	452 (99.1)	457 (99.1)
Yes, *n* (%)	8 (0.9)	4 (0.9)	4 (0.9)
Cognitive function			
N_{obs} (N_{miss})	913 (313)	452 (158)	461 (155)
No, *n* (%)	876 (95.9)	434 (96.0)	442 (95.9)
Yes, *n* (%)	37 (4.1)	18 (4.0)	19 (4.1)
Hearing			
N_{obs} (N_{miss})	931 (295)	465 (145)	466 (150)
No, *n* (%)	928 (99.7)	463 (99.6)	465 (99.8)
Yes, *n* (%)	3 (0.3)	2 (0.4)	1 (0.2)
Speech and language			
N_{obs} (N_{miss})	891 (335)	446 (164)	445 (171)
No, *n* (%)	859 (96.4)	432 (96.9)	427 (96.0)
Yes, *n* (%)	32 (3.6)	14 (3.1)	18 (4.0)
Vision			
N_{obs} (N_{miss})	913 (313)	466 (144)	447 (169)
No, *n* (%)	909 (99.6)	462 (99.1)	447 (100.0)
Yes, *n* (%)	4 (0.4)	4 (0.9)	0 (0.0)
Respiratory			
N_{obs} (N_{miss})	847 (379)	434 (176)	413 (203)
No, *n* (%)	837 (98.8)	431 (99.3)	406 (98.3)
Yes, *n* (%)	10 (1.2)	3 (0.7)	7 (1.7)
Gastrointestinal			
N_{obs} (N_{miss})	844 (382)	432 (178)	412 (204)
No, *n* (%)	831 (98.5)	428 (99.1)	403 (97.8)
Yes, *n* (%)	13 (1.5)	4 (0.9)	9 (2.2)

continued

TABLE 60 Summaries of secondary outcome measures at 2-year follow-up for all patients and according to treatment groups (part 1) (*continued*)

	All	Trial group	
		Placebo	Progesterone
Renal			
N_{obs} (N_{miss})	848 (378)	434 (176)	414 (202)
No, *n* (%)	844 (99.5)	433 (99.8)	411 (99.3)
Yes, *n* (%)	4 (0.5)	1 (0.2)	3 (0.7)

N_{miss}, number of women with missing data; N_{obs}, number of observations.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:03 2015.

TABLE 61 Summaries of secondary outcome measures at 2-year follow-up for all patients and according to treatment groups (part 2): hospitalisations

	All	Trial group	
		Placebo	Progesterone
Admitted to hospital			
N_{obs} (N_{miss})	850 (376)	434 (176)	416 (200)
No, *n* (%)	751 (88.4)	383 (88.2)	368 (88.5)
Yes, *n* (%)	99 (11.6)	51 (11.8)	48 (11.5)
Admitted to hospital for respiratory reason			
N_{obs} (N_{miss})	127 (1099)	63 (547)	64 (552)
No, *n* (%)	79 (62.2)	39 (61.9)	40 (62.5)
Yes, *n* (%)	48 (37.8)	24 (38.1)	24 (37.5)
Admitted to hospital for surgery			
N_{obs} (N_{miss})	118 (1108)	56 (554)	62 (554)
No, *n* (%)	96 (81.4)	49 (87.5)	47 (75.8)
Yes, *n* (%)	22 (18.6)	7 (12.5)	15 (24.2)
Admitted to hospital for other reason			
N_{obs} (N_{miss})	119 (1107)	56 (554)	63 (553)
No, *n* (%)	92 (77.3)	43 (76.8)	49 (77.8)
Yes, *n* (%)	27 (22.7)	13 (23.2)	14 (22.2)
Number of hospitalisations			
N_{obs} (N_{miss})	858 (368)	437 (173)	421 (195)
0, *n* (%)	750 (87.4)	386 (88.3)	364 (86.5)
1, *n* (%)	87 (10.1)	42 (9.6)	45 (10.7)
2, *n* (%)	15 (1.7)	5 (1.1)	10 (2.4)
3, *n* (%)	2 (0.2)	2 (0.5)	0 (0.0)
4, *n* (%)	2 (0.2)	1 (0.2)	1 (0.2)
7, *n* (%)	1 (0.1)	1 (0.2)	0 (0.0)
11, *n* (%)	1 (0.1)	0 (0.0)	1 (0.2)

N_{miss}, number of women with missing data; N_{obs}, number of observations.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:03 2015.

TABLE 62 Summaries of secondary outcome measures at 2-year follow-up for all patients and according to treatment groups (part 3): Strengths and Difficulties Questionnaire

		Trial group	
	All	Placebo	Progesterone
Emotional problems scale			
N_{obs} (N_{miss})	669 (557)	341 (269)	328 (288)
Mean (SD)	1.1 (1.2)	1.1 (1.2)	1.1 (1.2)
Median (IQR)	1.0 (0.0–2.0)	1.0 (0.0–1.0)	1.0 (0.0–2.0)
Range	0.0–10.0	0.0–10.0	0.0–7.0
Conduct problems scale			
N_{obs} (N_{miss})	668 (558)	342 (268)	326 (290)
Mean (SD)	2.6 (1.8)	2.7 (1.8)	2.6 (1.8)
Median (IQR)	2.0 (1.0–4.0)	2.0 (1.0–4.0)	2.0 (1.0–3.8)
Range	0.0–10.0	0.0–10.0	0.0–8.0
Hyperactivity scale			
N_{obs} (N_{miss})	649 (577)	334 (276)	315 (301)
Mean (SD)	4.3 (2.3)	4.2 (2.4)	4.5 (2.3)
Median (IQR)	4.0 (3.0–6.0)	4.0 (2.0–6.0)	4.0 (3.0–6.0)
Range	0.0–10.0	0.0–10.0	0.0–10.0
Peer problems scale			
N_{obs} (N_{miss})	663 (563)	345 (265)	318 (298)
Mean (SD)	2.0 (1.6)	2.0 (1.7)	2.1 (1.6)
Median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)
Range	0.0–7.0	0.0–7.0	0.0–7.0
Prosocial scale			
N_{obs} (N_{miss})	659 (567)	339 (271)	320 (296)
Mean (SD)	6.1 (2.2)	6.3 (2.2)	5.9 (2.3)
Median (IQR)	6.0 (5.0–8.0)	6.0 (5.0–8.0)	6.0 (4.0–8.0)
Range	0.0–10.0	0.0–10.0	0.0–10.0
Total difficulties scale			
N_{obs} (N_{miss})	597 (629)	302 (308)	295 (321)
Mean (SD)	10.0 (4.9)	9.8 (4.9)	10.2 (4.9)
Median (IQR)	9.0 (7.0–12.0)	9.0 (6.0–12.0)	9.0 (7.0–13.0)
Range	0.0–30.0	0.0–30.0	0.0–25.0
Impact scale			
N_{obs} (N_{miss})	828 (398)	424 (186)	404 (212)
Mean (SD)	0.2 (1.1)	0.2 (1.0)	0.2 (1.2)
Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Range	0.0–10.0	0.0–10.0	0.0–10.0

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:03 2015.

TABLE 63 Summaries of secondary outcome measures for all patients and according to treatment groups: women's views at 1 month post delivery (part 1)

		Trial group	
	All	Placebo	Progesterone
Age of baby (days)			
N_{obs} (N_{miss})	612 (614)	317 (293)	295 (321)
Mean (SD)	94.6 (163.3)	100.9 (171.8)	87.8 (153.6)
Median (IQR)	17.0 (7.0–91.0)	21.0 (7.0–112.0)	14.0 (7.0–70.0)
Range	0.0–805.0	0.0–805.0	0.0–751.0
Treatment received to prevent preterm labor			
N_{obs} (N_{miss})	643 (583)	332 (278)	311 (305)
None, *n* (%)	389 (60.5)	197 (59.3)	192 (61.7)
Aspirin, *n* (%)	66 (10.3)	34 (10.2)	32 (10.3)
Antibiotics, *n* (%)	41 (6.4)	22 (6.6)	19 (6.1)
Stitch, *n* (%)	93 (14.5)	51 (15.4)	42 (13.5)
Other, *n* (%)	54 (8.4)	28 (8.4)	26 (8.4)
Progesterone in previous pregnancy			
N_{obs} (N_{miss})	632 (594)	325 (285)	307 (309)
Yes, *n* (%)	67 (10.6)	45 (13.8)	22 (7.2)
No, *n* (%)	565 (89.4)	280 (86.2)	285 (92.8)
Relationship status			
N_{obs} (N_{miss})	639 (587)	331 (279)	308 (308)
Married, *n* (%)	356 (55.7)	181 (54.7)	175 (56.8)
Living with partner, *n* (%)	213 (33.3)	105 (31.7)	108 (35.1)
Single, *n* (%)	70 (11.0)	45 (13.6)	25 (8.1)
Widowed, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Preferred treatment mode			
N_{obs} (N_{miss})	613 (613)	314 (296)	299 (317)
Vaginal pessary, *n* (%)	434 (70.8)	222 (70.7)	212 (70.9)
Rectal pessary, *n* (%)	17 (2.8)	8 (2.5)	9 (3.0)
Injection, *n* (%)	158 (25.8)	82 (26.1)	76 (25.4)
Any, *n* (%)	2 (0.3)	0 (0.0)	2 (0.7)
Pessaries, *n* (%)	2 (0.3)	2 (0.6)	0 (0.0)
Enough information about trial participation			
N_{obs} (N_{miss})	639 (587)	330 (280)	309 (307)
Yes, *n* (%)	624 (97.7)	322 (97.6)	302 (97.7)
No, *n* (%)	15 (2.3)	8 (2.4)	7 (2.3)

TABLE 63 Summaries of secondary outcome measures for all patients and according to treatment groups: women's views at 1 month post delivery (part 1) (*continued*)

	All	Trial group	
		Placebo	Progesterone
Enough information about treatment			
N_{obs} (N_{miss})	640 (586)	331 (279)	309 (307)
Yes, *n* (%)	626 (97.8)	324 (97.9)	302 (97.7)
No, *n* (%)	14 (2.2)	7 (2.1)	7 (2.3)
Satisfaction with treatment			
N_{obs} (N_{miss})	634 (592)	327 (283)	307 (309)
Extremely satisfied, *n* (%)	445 (70.2)	244 (74.6)	201 (65.5)
Fairly satisfied, *n* (%)	163 (25.7)	70 (21.4)	93 (30.3)
Somewhat dissatisfied, *n* (%)	22 (3.5)	10 (3.1)	12 (3.9)
Extremely dissatisfied, *n* (%)	4 (0.6)	3 (0.9)	1 (0.3)

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:04 2015.

TABLE 64 Summaries of secondary outcome measures for all patients and according to treatment groups: women's views at 1 month post delivery (part 2)

	All	Trial group	
		Placebo	Progesterone
The treatment was messy			
N_{obs} (N_{miss})	628 (598)	325 (285)	303 (313)
Strongly agree and would not repeat treatment, *n* (%)	35 (5.6)	14 (4.3)	21 (6.9)
Agree but would still repeat treatment, *n* (%)	223 (35.5)	110 (33.8)	113 (37.3)
Neither agree nor disagree, *n* (%)	94 (15.0)	48 (14.8)	46 (15.2)
Disagree, *n* (%)	276 (43.9)	153 (47.1)	123 (40.6)
The treatment smelt unpleasant			
N_{obs} (N_{miss})	620 (606)	322 (288)	298 (318)
Strongly agree and would not repeat treatment, *n* (%)	19 (3.1)	9 (2.8)	10 (3.4)
Agree but would still repeat treatment, *n* (%)	40 (6.5)	18 (5.6)	22 (7.4)
Neither agree nor disagree, *n* (%)	75 (12.1)	43 (13.4)	32 (10.7)
Disagree, *n* (%)	486 (78.4)	252 (78.3)	234 (78.5)
The application of treatment was uncomfortable			
N_{obs} (N_{miss})	624 (602)	323 (287)	301 (315)
Strongly agree and would not repeat treatment, *n* (%)	37 (5.9)	19 (5.9)	18 (6.0)
Agree but would still repeat treatment, *n* (%)	125 (20.0)	64 (19.8)	61 (20.3)
Neither agree nor disagree, *n* (%)	121 (19.4)	62 (19.2)	59 (19.6)
Disagree, *n* (%)	341 (54.6)	178 (55.1)	163 (54.2)

continued

TABLE 64 Summaries of secondary outcome measures for all patients and according to treatment groups: women's views at 1 month post delivery (part 2) (*continued*)

	All	Trial group	
		Placebo	Progesterone
The treatment interfered with sexual activity			
N_{obs} (N_{miss})	619 (607)	320 (290)	299 (317)
Strongly agree and would not repeat treatment, *n* (%)	33 (5.3)	16 (5.0)	17 (5.7)
Agree but would still repeat treatment, *n* (%)	154 (24.9)	68 (21.2)	86 (28.8)
Neither agree nor disagree, *n* (%)	145 (23.4)	90 (28.1)	55 (18.4)
Disagree, *n* (%)	287 (46.4)	146 (45.6)	141 (47.2)
The treatment stopped me working			
N_{obs} (N_{miss})	625 (601)	324 (286)	301 (315)
Strongly agree and would not repeat treatment, *n* (%)	17 (2.7)	12 (3.7)	5 (1.7)
Agree but would still repeat treatment, *n* (%)	11 (1.8)	8 (2.5)	3 (1.0)
Neither agree nor disagree, *n* (%)	28 (4.5)	16 (4.9)	12 (4.0)
Disagree, *n* (%)	569 (91.0)	288 (88.9)	281 (93.4)
The treatment made me feel dirty			
N_{obs} (N_{miss})	624 (602)	324 (286)	300 (316)
Strongly agree and would not repeat treatment, *n* (%)	22 (3.5)	11 (3.4)	11 (3.7)
Agree but would still repeat treatment, *n* (%)	70 (11.2)	32 (9.9)	38 (12.7)
Neither agree nor disagree, *n* (%)	65 (10.4)	34 (10.5)	31 (10.3)
Disagree, *n* (%)	467 (74.8)	247 (76.2)	220 (73.3)
The treatment caused irritation			
N_{obs} (N_{miss})	625 (601)	322 (288)	303 (313)
Strongly agree and would not repeat treatment, *n* (%)	27 (4.3)	14 (4.3)	13 (4.3)
Agree but would still repeat treatment, *n* (%)	69 (11.0)	32 (9.9)	37 (12.2)
Neither agree nor disagree, *n* (%)	67 (10.7)	33 (10.2)	34 (11.2)
Disagree, *n* (%)	462 (73.9)	243 (75.5)	219 (72.3)
The treatment made me feel constipated			
N_{obs} (N_{miss})	625 (601)	323 (287)	302 (314)
Strongly agree and would not repeat treatment, *n* (%)	16 (2.6)	10 (3.1)	6 (2.0)
Agree but would still repeat treatment, *n* (%)	26 (4.2)	13 (4.0)	13 (4.3)
Neither agree nor disagree, *n* (%)	47 (7.5)	21 (6.5)	26 (8.6)
Disagree, *n* (%)	536 (85.8)	279 (86.4)	257 (85.1)

N_{miss}, number of women with missing data; N_{obs}, number of observations.

Note

OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:04 2015.

TABLE 65 Summaries of secondary outcome measures for all patients and according to treatment groups: women's views at 1 month post delivery (part 3)

		Trial group	
	All	Placebo	Progesterone
The treatment gave me backache			
N_{obs} (N_{miss})	624 (602)	324 (286)	300 (316)
Strongly agree and would not repeat treatment, *n* (%)	15 (2.4)	9 (2.8)	6 (2.0)
Agree but would still repeat treatment, *n* (%)	11 (1.8)	6 (1.9)	5 (1.7)
Neither agree nor disagree, *n* (%)	42 (6.7)	22 (6.8)	20 (6.7)
Disagree, *n* (%)	556 (89.1)	287 (88.6)	269 (89.7)
Panty liners or sanitary towels used?			
N_{obs} (N_{miss})	630 (596)	327 (283)	303 (313)
Yes, *n* (%)	412 (65.4)	212 (64.8)	200 (66.0)
No, *n* (%)	218 (34.6)	115 (35.2)	103 (34.0)
Number of towels used per day			
N_{obs} (N_{miss})	391 (835)	197 (413)	194 (422)
Mean (SD)	2.3 (1.4)	2.3 (1.4)	2.3 (1.3)
Median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)
Range	0.0–10.0	0.0–10.0	0.0–7.0
Did treatment interfere with daily activities?			
N_{obs} (N_{miss})	629 (597)	324 (286)	305 (311)
Yes, *n* (%)	11 (1.7)	8 (2.5)	3 (1.0)
No, *n* (%)	618 (98.3)	316 (97.5)	302 (99.0)
Was the frequency of appointment with health professional . . .			
N_{obs} (N_{miss})	608 (618)	311 (299)	297 (319)
Too often, *n* (%)	3 (0.5)	1 (0.3)	2 (0.7)
Enough, *n* (%)	583 (95.9)	302 (97.1)	281 (94.6)
Not enough, *n* (%)	22 (3.6)	8 (2.6)	14 (4.7)
How would you feel if treatment became normal practice?			
N_{obs} (N_{miss})	623 (603)	320 (290)	303 (313)
Disappointed, *n* (%)	6 (1.0)	3 (0.9)	3 (1.0)
Not sure, *n* (%)	168 (27.0)	89 (27.8)	79 (26.1)
Pleased, *n* (%)	449 (72.1)	228 (71.2)	221 (72.9)
If time went backwards would you take part again?			
N_{obs} (N_{miss})	635 (591)	327 (283)	308 (308)
Definitely not, *n* (%)	6 (0.9)	4 (1.2)	2 (0.6)
Probably not, *n* (%)	21 (3.3)	9 (2.8)	12 (3.9)
Not sure, *n* (%)	37 (5.8)	19 (5.8)	18 (5.8)
Probably yes, *n* (%)	159 (25.0)	85 (26.0)	74 (24.0)
Definitely yes, *n* (%)	412 (64.9)	210 (64.2)	202 (65.6)

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:04 2015.

TABLE 66 Summaries of secondary outcome measures for all patients and according to treatment groups: women's views at 1 month post delivery (part 4)

	All	Trial group	
		Placebo	Progesterone
Did you have access to health professional for medical support?			
N_{obs} (N_{miss})	632 (594)	325 (285)	307 (309)
Yes, *n* (%)	618 (97.8)	319 (98.2)	299 (97.4)
No, *n* (%)	14 (2.2)	6 (1.8)	8 (2.6)
Did you have access to a health professional for emotional support?			
N_{obs} (N_{miss})	623 (603)	321 (289)	302 (314)
Yes, *n* (%)	566 (90.9)	294 (91.6)	272 (90.1)
No, *n* (%)	57 (9.1)	27 (8.4)	30 (9.9)
Did partner have adequate support from care providers?			
N_{obs} (N_{miss})	611 (615)	315 (295)	296 (320)
Yes, *n* (%)	543 (88.9)	281 (89.2)	262 (88.5)
No, *n* (%)	68 (11.1)	34 (10.8)	34 (11.5)
Willing to complete 6-month questionnaire?			
N_{obs} (N_{miss})	222 (1004)	119 (491)	103 (513)
Yes, *n* (%)	205 (92.3)	112 (94.1)	93 (90.3)
No, *n* (%)	17 (7.7)	7 (5.9)	10 (9.7)

N_{miss}, number of women with missing data; N_{obs}, number of observations.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:04 2015.

TABLE 67 Summaries of secondary outcome measures for all patients and according to treatment groups: women's views at 6 months post delivery

	All	Trial group	
		Placebo	Progesterone
Enough information about treatment			
N_{obs} (N_{miss})	79 (1147)	45 (565)	34 (582)
Yes, *n* (%)	77 (97.5)	44 (97.8)	33 (97.1)
No, *n* (%)	2 (2.5)	1 (2.2)	1 (2.9)
Satisfaction with treatment			
N_{obs} (N_{miss})	78 (1148)	44 (566)	34 (582)
Extremely satisfied, *n* (%)	60 (76.9)	33 (75.0)	27 (79.4)
Fairly satisfied, *n* (%)	18 (23.1)	11 (25.0)	7 (20.6)
Somewhat dissatisfied, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Extremely dissatisfied, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)

TABLE 67 Summaries of secondary outcome measures for all patients and according to treatment groups: women's views at 6 months post delivery (*continued*)

	All	Trial group	
		Placebo	Progesterone
How would you feel if treatment became normal practice?			
N_{obs} (N_{miss})	78 (1148)	44 (566)	34 (582)
Disappointed, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Not sure, *n* (%)	10 (12.8)	7 (15.9)	3 (8.8)
Pleased, *n* (%)	68 (87.2)	37 (84.1)	31 (91.2)
If time went backwards would you take part again?			
N_{obs} (N_{miss})	79 (1147)	45 (565)	34 (582)
Definitely not, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Probably not, *n* (%)	1 (1.3)	1 (2.2)	0 (0.0)
Not sure, *n* (%)	4 (5.1)	1 (2.2)	3 (8.8)
Probably yes, *n* (%)	11 (13.9)	5 (11.1)	6 (17.6)
Definitely yes, *n* (%)	63 (79.7)	38 (84.4)	25 (73.5)
Did you have access to a health professional for medical support?			
N_{obs} (N_{miss})	79 (1147)	45 (565)	34 (582)
Yes, *n* (%)	76 (96.2)	44 (97.8)	32 (94.1)
No, *n* (%)	3 (3.8)	1 (2.2)	2 (5.9)
Did you have access to a health professional for emotional support?			
N_{obs} (N_{miss})	76 (1150)	43 (567)	33 (583)
Yes, *n* (%)	70 (92.1)	41 (95.3)	29 (87.9)
No, *n* (%)	6 (7.9)	2 (4.7)	4 (12.1)
Did partner have adequate support from care providers?			
N_{obs} (N_{miss})	77 (1149)	44 (566)	33 (583)
Yes, *n* (%)	67 (87.0)	41 (93.2)	26 (78.8)
No, *n* (%)	10 (13.0)	3 (6.8)	7 (21.2)
Willing participate in interview			
N_{obs} (N_{miss})	377 (849)	200 (410)	177 (439)
Yes, *n* (%)	301 (79.8)	164 (82.0)	137 (77.4)
No, *n* (%)	76 (20.2)	36 (18.0)	40 (22.6)

N_{miss}, number of women with missing data; N_{obs}, number of observations.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:04 2015.

TABLE 68 Summaries of EQ-5D health utility scores

	All	Trial group	
		Placebo	Progesterone
Randomisation			
N_{obs} (N_{miss})	1056 (170)	524 (86)	532 (84)
Mean (SD)	0.876 (0.190)	0.874 (0.190)	0.879 (0.190)
Median (IQR)	1.000 (0.796–1.000)	1.000 (0.796–1.000)	1.000 (0.796–1.000)
Range	–0.349 to 1.000	–0.349 to 1.000	–0.074 to 1.000
Birth			
N_{obs} (N_{miss})	394 (832)	202 (408)	192 (424)
Mean (SD)	0.867 (0.198)	0.866 (0.203)	0.868 (0.194)
Median (IQR)	1.000 (0.796–1.000)	1.000 (0.796–1.000)	1.000 (0.796–1.000)
Range	–0.184 to 1.000	–0.184 to 1.000	–0.016 to 1.000
12-month follow-up			
N_{obs} (N_{miss})	616 (610)	307 (303)	309 (307)
Mean (SD)	0.875 (0.194)	0.872 (0.202)	0.878 (0.186)
Median (IQR)	0.883 (0.848–1.000)	0.883 (0.848–1.000)	0.883 (0.848–1.000)
Range	–0.135 to 1.000	–0.135 to 1.000	–0.135 to 1.000
24-month follow-up			
N_{obs} (N_{miss})	5 (1221)	2 (608)	3 (613)
Mean (SD)	0.940 (0.083)	0.925 (0.106)	0.949 (0.088)
Median (IQR)	1.000 (0.850–1.000)	0.925 (0.888–0.962)	1.000 (0.924–1.000)
Range	0.848–1.000	0.850–1.000	0.848–1.000
Change from baseline			
Birth			
N_{obs} (N_{miss})	390 (836)	199 (411)	191 (425)
Mean (SD)	–0.022 (0.214)	–0.023 (0.220)	–0.021 (0.207)
Median (IQR)	0.000 (–0.152 to 0.036)	0.000 (–0.152 to 0.061)	0.000 (–0.114 to 0.000)
Range	–1.032 to 0.970	–1.032 to 0.807	–0.787 to 0.970
12-month follow-up			
N_{obs} (N_{miss})	553 (673)	274 (336)	279 (337)
Mean (SD)	–0.012 (0.217)	–0.015 (0.221)	–0.009 (0.213)
Median (IQR)	0.000 (–0.117 to 0.035)	0.000 (–0.117 to 0.064)	0.000 (–0.117 to 0.000)
Range	–1.135 to 1.128	–1.135 to 1.128	–0.841 to 0.829
24-month follow-up			
N_{obs} (N_{miss})	4 (1222)	1 (609)	3 (613)
Mean (SD)	0.068 (0.136)	0.000 (–)	0.091 (0.158)
Median (IQR)	0.000 (0.000–0.068)	0.000 (0.000–0.000)	0.000 (0.000–0.136)
Range	0.000–0.273	0.000–0.000	0.000–0.273

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:05 2015.

Part 4: regression models for primary and secondary outcomes

Does progesterone prophylaxis to prevent preterm labour improve outcome?	
OPPTIMUM	
Final report tables	
Part 4: regression models for primary and secondary outcomes	
v1.0	
2 October 2015	
Martina Messow	
Robertson Centre for Biostatistics	
EudraCT number	2007-007950-77
CTA number	22931/0009/001-0001 revised by MHRA to 01384/0208/001
MREC number	08/MRE00/6
ISRCTN	ISRCTN14568373
Co-sponsors	University of Edinburgh/NHS Lothian
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Funding reference number	G0700452, Grant No: 84982 – 09/800/27
Protocol version	15.1 (1 April 2015)
SAP version	1.1 (8 September 2015)

CTA, Clinical Trial Authorisation; EudraCT, European Union Drug Regulating Authorities Clinical Trials; MREC, Multicentre Research Ethics Committee; SAP, statistical analysis plan.

TABLE 69 Mixed effects logistic regression model for the effect of treatment on the primary obstetric outcome death or delivery before 34 weeks' gestation adjusted for previous pregnancy of ≥ 14 weeks' gestation and study centre as a random effect

Parameter	OR	95% CI	*p*-value
Treatment (progesterone vs. placebo)	0.86	0.64 to 1.17	0.336
Previous pregnancy of ≥ 14 weeks' gestation	1.05	0.55 to 1.99	0.879
$n = 1197$			

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:06 2015.

TABLE 70 Mixed effects logistic regression model for the effect of treatment on the primary neonatal outcome death, brain injury or severe chronic lung disease adjusted for previous pregnancy of ≥ 14 weeks' gestation and study centre as a random effect

Parameter	OR	95% CI	*p*-value
Treatment (progesterone vs. placebo)	0.62	0.41 to 0.94	0.024
Previous pregnancy of ≥ 14 weeks' gestation	1.05	0.45 to 2.44	0.913
$n = 1176$			

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:06 2015.

TABLE 71 Mixed effects logistic regression model for the effect of treatment on the primary neonatal outcome death, brain injury or severe chronic lung disease adjusted for previous pregnancy of ≥ 14 weeks' gestation and study centre as a random effect

Parameter	OR	95% CI	*p*-value
Treatment (progesterone vs. placebo)	0.72	0.48 to 1.07	0.104
Previous pregnancy ≥ 14 weeks' gestation	1.50	0.48 to 2.74	0.757
$n = 869$			

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:07 2015.

TABLE 72 Mixed effects logistic regression model for the effect of treatment on the primary childhood outcome survival adjusted for previous pregnancy of ≥ 14 weeks' gestation and study centre as a random effect

Parameter	OR	95% CI	*p*-value
Treatment (progesterone vs. placebo)	0.78	0.40 to 1.52	0.465
Previous pregnancy of ≥ 14 weeks' gestation	0.38	0.05 to 2.81	0.344
$n = 1009$			

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:07 2015.

TABLE 73 Mixed effects proportional hazards regression model for the effect of treatment on the primary childhood outcome survival adjusted for previous pregnancy of ≥ 14 weeks' gestation and study centre as a random effect

Parameter	Hazard ratio	95% CI	*p*-value
Treatment (progesterone vs. placebo)	1.26	0.65 to 2.42	0.497
Previous pregnancy of ≥ 14 weeks' gestation	2.38	0.33 to 17.36	0.393
$n = 1198$			

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:07 2015.

TABLE 74 Mixed effects proportional hazards regression model for the effect of treatment on the secondary birth outcome gestational age at delivery adjusted for previous pregnancy of ≥ 14 weeks' gestation and study centre as a random effect

Parameter	Hazard ratio	95% CI	*p*-value
Treatment (progesterone vs. placebo)	1.03	0.92 to 1.15	0.616
Previous pregnancy of ≥ 14 weeks' gestation	1.13	0.89 to 1.43	0.330
$n = 1197$			

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:08 2015.

TABLE 75 Mixed effects logistic regression model for the effect of treatment on the secondary birth outcome fetal death after trial entry adjusted for previous pregnancy of ≥ 14 weeks' gestation and study centre as a random effect

Parameter	OR	95% CI	*p*-value
Treatment (progesterone vs. placebo)	1.14	0.41 to 3.17	0.802
Previous pregnancy of ≥ 14 weeks' gestation	0.91	0.12 to 7.00	0.924
$n = 1197$			

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:08 2015.

TABLE 76 Logistic regression models for the effect of treatment on secondary neonatal outcomes adjusted for previous pregnancies of ≥ 14 weeks' gestation

Outcome	*n*	OR	95% CI	*p*-value
Brain injury	1158	0.50	0.31 to 0.84	0.008
Severe chronic lung disease	1154	0.94	0.49 to 1.78	0.843
Need for surfactant administration	1156	1.03	0.68 to 1.55	0.903
Infection	1154	1.22	0.79 to 1.88	0.364
Mother or child suffering a SAE during pregnancy and birth	1224	0.83	0.58 to 1.16	0.274

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:12 2015.

TABLE 77 Poisson or binomial regression models for the effect of treatment on secondary neonatal outcomes adjusted for previous pregnancies of ≥ 14 weeks' gestation

Outcome	*n*	Expected mean ratio	95% CI	*p*-value
Number of discrete episodes of bloodstream infection	73	0.73	0.42 to 1.27	0.269
Outcome	***n***	**OR**	**95% CI**	***p*-value**
Number of days of level 1 care > 0	1149	0.75	0.53 to 1.06	0.104
Number of days of level 1 care > 5	1149	0.90	0.56 to 1.43	0.643
Number of days of level 1 or 2 care > 0	1149	0.84	0.61 to 1.16	0.299
Number of days of level 1 or 2 care > 5	1149	0.77	0.52 to 1.13	0.185
Number of days of special or higher level of care > 0	1149	0.86	0.66 to 1.12	0.268
Number of days of special or higher level of care > 5	1149	0.80	0.60 to 1.08	0.145
Number of days of special or higher level of care > 14	1149	0.74	0.53 to 1.05	0.092
Number of days of normal or higher level of care > 3	1148	0.81	0.64 to 1.04	0.101
Number of days of normal or higher level of care > 7	1148	0.80	0.60 to 1.08	0.142
Number of days of normal or higher level of care > 14	1148	0.70	0.50 to 0.99	0.044

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:17 2015.

TABLE 78 Logistic regression models for the effect of treatment on secondary childhood outcomes adjusted for previous pregnancies of ≥ 14 weeks' gestation and centre as a random effect

Outcome	*n*	OR	95% CI	*p*-value
Death or moderate/severe neurodevelopmental impairment	818	1.45	0.98 to 2.15	0.064
Moderate/severe neurodevelopmental impairment	782	1.48	0.95 to 2.33	0.087
Any hospitalisation	850	0.98	0.65 to 1.47	0.919
Any hospitalisation for respiratory reason	127	0.97	0.47 to 2.02	0.944
Any hospitalisation for surgery	118	2.48	1.01 to 6.09	0.049
Any hospitalisation for other reason	119	0.99	0.42 to 2.30	0.977

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:19 2015.

TABLE 79 Regression models for the effect of treatment on secondary childhood outcomes adjusted for previous pregnancies of ≥ 14 weeks' gestation and centre as a random effect. Scores analysed as binary variable (raised vs. normal score). Scores analysed as continuous variables where approximately normally distributed

Outcome	*n*	OR	95% CI	*p*-value
SDQ emotional problems score above normal	669	1.01	0.61 to 1.67	0.958
SDQ conduct problems score above normal	668	0.92	0.65 to 1.31	0.656
SDQ hyperactivity score above normal	649	1.10	0.79 to 1.55	0.570
SDQ peer problems score above normal	663	1.22	0.88 to 1.69	0.223
SDQ total difficulties score above normal	597	1.23	0.85 to 1.78	0.282
SDQ prosocial score below normal	659	1.20	0.88 to 1.63	0.254
SDQ impact score above normal	828	1.31	0.73 to 2.35	0.368
Outcome	***n***	**Parameter estimate**	**95% CI**	***p*-value**
SDQ hyperactivity score (continuous)	649	0.32	–0.03 to 0.68	0.074
SDQ total difficulties score (continuous)	597	0.41	–0.36 to 1.18	0.301
SDQ prosocial score (continuous)	659	–0.38	–0.72 to –0.03	0.032

SDQ, Strengths and Difficulties Questionnaire.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:21 2015.

Part 5: other trial information

Does progesterone prophylaxis to prevent preterm labour improve outcome?	
OPPTIMUM	
Final report tables	
Part 5: other trial information	
v1.0	
2 October 2015	
Martina Messow	
Robertson Centre for Biostatistics	
EudraCT number	2007-007950-77
CTA number	22931/0009/001-0001 revised by MHRA to 01384/0208/001
MREC number	08/MRE00/6
ISRCTN	ISRCTN14568373
Co-sponsors	University of Edinburgh/NHS Lothian
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Funding reference number	G0700452, Grant No: 84982 – 09/800/27
Protocol version	15.1 (1 April 2015)
SAP version	1.1 (8 September 2015)

CTA, Clinical Trial Authorisation; EudraCT, European Union Drug Regulating Authorities Clinical Trials; MREC, Multicentre Research Ethics Committee; SAP, statistical analysis plan.

TABLE 80 Treatment compliance (ITT population)

		Trial group	
Compliance	**All**	**Placebo**	**Progesterone**
Percentage of medication taken			
N_{obs} (N_{miss})	1011 (215)	509 (101)	502 (114)
Mean (SD)	78.6 (72.0)	77.9 (32.8)	79.3 (96.7)
Median (IQR)	92.7 (65.0–98.7)	92.3 (71.6–98.7)	92.9 (59.0–98.6)
Range	0.0–2100.0	0.0–138.5	0.0–2100.0
Expected number of doses			
N_{obs} (N_{miss})	1197 (29)	597 (13)	600 (16)
Mean (SD)	71.0 (17.4)	70.6 (17.3)	71.4 (17.6)
Median (IQR)	76.0 (72.0–81.0)	76.0 (72.0–80.0)	76.0 (72.0–81.0)
Range	1.0–86.0	1.0–85.0	2.0–86.0
Compliant			
N_{obs} (N_{miss})	1011 (215)	509 (101)	502 (114)
No, *n* (%)	317 (31.4)	148 (29.1)	169 (33.7)
Yes, *n* (%)	694 (68.6)	361 (70.9)	333 (66.3)

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:22 2015.

TABLE 81 Trial termination (ITT population)

Outcome	All	Trial group	
		Placebo	Progesterone
Trial completed			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
No, *n* (%)	374 (30.5)	176 (28.9)	198 (32.1)
Yes, *n* (%)	852 (69.5)	434 (71.1)	418 (67.9)
Reason for trial termination			
N_{obs} (N_{miss})	374 (852)	176 (434)	198 (418)
Woman unwilling to continue, *n* (%)	56 (15.0)	25 (14.2)	31 (15.7)
Adverse event, *n* (%)	1 (0.3)	1 (0.6)	0 (0.0)
SAE, *n* (%)	1 (0.3)	1 (0.6)	0 (0.0)
Detection of significant structural chromosomal anomalies after randomisation, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Other, *n* (%)	207 (55.3)	101 (57.4)	106 (53.5)
Physician recommended withdrawal, *n* (%)	1 (0.3)	1 (0.6)	0 (0.0)
Lost to follow-up, *n* (%)	72 (19.3)	31 (17.6)	41 (20.7)
Death, *n* (%)	36 (9.6)	16 (9.1)	20 (10.1)

N_{miss}, number of women with missing data; N_{obs}, number of observations.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:22 2015.

TABLE 82 Consent withdrawal (ITT population)

Outcome	All	Trial group	
		Placebo	Progesterone
Withdrawn consent from any part of the study			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
No, *n* (%)	1113 (90.8)	558 (91.5)	555 (90.1)
Yes, *n* (%)	113 (9.2)	52 (8.5)	61 (9.9)
Withdrawn consent for future evaluation of mother and child			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
No, *n* (%)	1124 (91.7)	561 (92.0)	563 (91.4)
Yes, *n* (%)	102 (8.3)	49 (8.0)	53 (8.6)
Withdrawn consent for future evaluation of health records			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
No, *n* (%)	1170 (95.4)	587 (96.2)	583 (94.6)
Yes, *n* (%)	56 (4.6)	23 (3.8)	33 (5.4)

TABLE 82 Consent withdrawal (ITT population) (*continued*)

Outcome	All	Trial group	
		Placebo	Progesterone
Withdrawn consent for neonatal head scan			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
No, *n* (%)	1217 (99.3)	607 (99.5)	610 (99.0)
Yes, *n* (%)	9 (0.7)	3 (0.5)	6 (1.0)
Withdrawn consent for use of placental tissue			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
No, *n* (%)	1224 (99.8)	610 (100.0)	614 (99.7)
Yes, *n* (%)	2 (0.2)	0 (0.0)	2 (0.3)
Withdrawn consent for completing the 2-year follow-up questionnaire			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
No, *n* (%)	1223 (99.8)	609 (99.8)	614 (99.7)
Yes, *n* (%)	3 (0.2)	1 (0.2)	2 (0.3)
Withdrawn consent for completing the 2-year follow-up visit			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
No, *n* (%)	1223 (99.8)	609 (99.8)	614 (99.7)
Yes, *n* (%)	3 (0.2)	1 (0.2)	2 (0.3)
Withdrawn consent for health economics questionnaire			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
No, *n* (%)	1223 (99.8)	609 (99.8)	614 (99.7)
Yes, *n* (%)	3 (0.2)	1 (0.2)	2 (0.3)
Withdrawn consent for women's views questionnaire			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
No, *n* (%)	1223 (99.8)	609 (99.8)	614 (99.7)
Yes, *n* (%)	3 (0.2)	1 (0.2)	2 (0.3)

N_{miss}, number of women with missing data; N_{obs}, number of observations.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:22 2015.

TABLE 83 Availability of information at different stages (ITT population)

Outcome	All	Trial group	
		Placebo	Progesterone
Information available from end of treatment visit			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
No, *n* (%)	20 (1.6)	10 (1.6)	10 (1.6)
Yes, *n* (%)	1206 (98.4)	600 (98.4)	606 (98.4)
Information on labour			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
Available, *n* (%)	1197 (97.6)	597 (97.9)	600 (97.4)
Missing, *n* (%)	1 (0.1)	1 (0.2)	0 (0.0)
Lost, *n* (%)	28 (2.3)	12 (2.0)	16 (2.6)
Information on birth in those not lost			
N_{obs} (N_{miss})	1198 (0)	598 (0)	600 (0)
Available, *n* (%)	1197 (99.9)	597 (99.8)	600 (100.0)
Missing, *n* (%)	1 (0.1)	1 (0.2)	0 (0.0)
Lost, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Information on neonatal outcomes in those not lost			
N_{obs} (N_{miss})	1198 (0)	598 (0)	600 (0)
Available, *n* (%)	1158 (96.7)	574 (96.0)	584 (97.3)
Died, *n* (%)	23 (1.9)	13 (2.2)	10 (1.7)
Missing, *n* (%)	5 (0.4)	2 (0.3)	3 (0.5)
Lost, *n* (%)	12 (1.0)	9 (1.5)	3 (0.5)
Paediatric assessment available in those not lost at neonatal stage			
N_{obs} (N_{miss})	1186 (0)	589 (0)	597 (0)
No, *n* (%)	292 (24.6)	136 (23.1)	156 (26.1)
Yes, *n* (%)	858 (72.3)	437 (74.2)	421 (70.5)
Died, *n* (%)	36 (3.0)	16 (2.7)	20 (3.4)
Parent questionnaire available in those not lost at neonatal stage			
N_{obs} (N_{miss})	1186 (0)	589 (0)	597 (0)
No, *n* (%)	300 (25.3)	141 (23.9)	159 (26.6)
Yes, *n* (%)	850 (71.7)	432 (73.3)	418 (70.0)
Died, *n* (%)	36 (3.0)	16 (2.7)	20 (3.4)
Womens' views questionnaire available in those not lost at neonatal stage			
N_{obs} (N_{miss})	1186 (0)	589 (0)	597 (0)
No, *n* (%)	515 (43.4)	245 (41.6)	270 (45.2)
Yes, *n* (%)	642 (54.1)	331 (56.2)	311 (52.1)
Died, *n* (%)	29 (2.4)	13 (2.2)	16 (2.7)

N_{miss}, number of women with missing data; N_{obs}, number of observations.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:22 2015.

Part 6: serious adverse events

Does progesterone prophylaxis to prevent preterm labour improve outcome?	
OPPTIMUM	
Final report tables	
Part 6: SAEs	
v1.0	
2 October 2015	
Martina Messow	
Robertson Centre for Biostatistics	
EudraCT number	2007-007950-77
CTA number	22931/0009/001-0001 revised by MHRA to 01384/0208/001
MREC number	08/MRE00/6
ISRCTN	ISRCTN14568373
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Protocol version	15.1 (1 April 2015)
SAP version	1.1 (8 September 2015)

CTA, Clinical Trial Authorisation; EudraCT, European Union Drug Regulating Authorities Clinical Trials; MREC, Multicentre Research Ethics Committee; SAP, statistical analysis plan.

TABLE 84 Patients with at least one SAE by System Organ Class and Preferred Term for all SAEs in reporting window (maximum of end of treatment date + 28 days and date of delivery + 30 days) or where it is unclear whether or not they are in the reporting window

		Trial group, *n* (%)	
Outcome	All patients, *n* (%)	Placebo	Progesterone
Number of patients, *n*	1183	590	593
Blood and lymphatic system disorders	1 (0.1)	1 (0.2)	0 (0.0)
Thrombocytopenia	1 (0.1)	1 (0.2)	0 (0.0)
Congenital, familial and genetic disorders	19 (1.6)	8 (1.4)	11 (1.9)
Cardiac septal defect	1 (0.1)	1 (0.2)	0 (0.0)
Cleft lip and palate	1 (0.1)	0 (0.0)	1 (0.2)
Congenital central nervous system anomaly	1 (0.1)	0 (0.0)	1 (0.2)
Congenital oesophageal anomaly	1 (0.1)	0 (0.0)	1 (0.2)
Cryptorchism	1 (0.1)	0 (0.0)	1 (0.2)
Cystic fibrosis	1 (0.1)	1 (0.2)	0 (0.0)
Congenital dacryostenosis	1 (0.1)	0 (0.0)	1 (0.2)
Hip dysplasia	1 (0.1)	1 (0.2)	0 (0.0)
Holoprosencephaly	1 (0.1)	0 (0.0)	1 (0.2)
Hydrocele	1 (0.1)	1 (0.2)	0 (0.0)

continued

TABLE 84 Patients with at least one SAE by System Organ Class and Preferred Term for all SAEs in reporting window (maximum of end of treatment date + 28 days and date of delivery + 30 days) or where it is unclear whether or not they are in the reporting window (*continued*)

Outcome	All patients, *n* (%)	Trial group, *n* (%)	
		Placebo	Progesterone
Hypospadias	2 (0.2)	0 (0.0)	2 (0.3)
Kidney malformation	1 (0.1)	0 (0.0)	1 (0.2)
Oculoauriculovertebral dysplasia	1 (0.1)	1 (0.2)	0 (0.0)
Patent ductus arteriosus	2 (0.2)	2 (0.3)	0 (0.0)
Polydactyly	2 (0.2)	0 (0.0)	2 (0.3)
Congenital pulmonary artery stenosis	1 (0.1)	1 (0.2)	0 (0.0)
Gastrointestinal disorders	8 (0.7)	8 (1.4)	0 (0.0)
Abdominal pain	2 (0.2)	2 (0.3)	0 (0.0)
Ileus paralytic	1 (0.1)	1 (0.2)	0 (0.0)
Inguinal hernia	1 (0.1)	1 (0.2)	0 (0.0)
Necrotising colitis	2 (0.2)	2 (0.3)	0 (0.0)
Neonatal necrotising enterocolitis	3 (0.3)	3 (0.5)	0 (0.0)
General disorders and administration site conditions	4 (0.3)	2 (0.3)	2 (0.3)
Adverse drug reaction	1 (0.1)	1 (0.2)	0 (0.0)
Death neonatal	17 (1.4)	8 (1.3)	9 (1.5)
Infections and infestations	17 (1.4)	8 (1.4)	9 (1.5)
Appendicitis	1 (0.1)	1 (0.2)	0 (0.0)
Bacterial sepsis	2 (0.2)	0 (0.0)	2 (0.3)
Bronchiolitis	1 (0.1)	0 (0.0)	1 (0.2)
Bronchopneumonia	1 (0.1)	0 (0.0)	1 (0.2)
Infection	1 (0.1)	1 (0.2)	0 (0.0)
Lower respiratory tract infection	1 (0.1)	1 (0.2)	0 (0.0)
Meningitis	1 (0.1)	1 (0.2)	0 (0.0)
Meningitis bacterial	1 (0.1)	1 (0.2)	0 (0.0)
Rash pustular	2 (0.2)	1 (0.2)	1 (0.2)
Sepsis	4 (0.3)	2 (0.3)	2 (0.3)
Urinary tract infection	3 (0.3)	1 (0.2)	2 (0.3)
Wound infection	1 (0.1)	0 (0.0)	1 (0.2)
Injury, poisoning and procedural complications	4 (0.3)	1 (0.2)	3 (0.5)
Post-lumbar puncture	2 (0.2)	0 (0.0)	2 (0.3)
Syndrome post-procedural complication	1 (0.1)	1 (0.2)	0 (0.0)
Uterine rupture	1 (0.1)	0 (0.0)	1 (0.2)

TABLE 84 Patients with at least one SAE by System Organ Class and Preferred Term for all SAEs in reporting window (maximum of end of treatment date + 28 days and date of delivery + 30 days) or where it is unclear whether or not they are in the reporting window (*continued*)

Outcome	All patients, *n* (%)	Trial group, *n* (%)	
		Placebo	Progesterone
Investigations	5 (0.4)	2 (0.3)	3 (0.5)
Echocardiogram abnormal	1 (0.1)	0 (0.0)	1 (0.2)
Echography abnormal	1 (0.1)	1 (0.2)	0 (0.0)
Fetal heart rate abnormal	1 (0.1)	0 (0.0)	1 (0.2)
Weight decreased	2 (0.2)	1 (0.2)	1 (0.2)
Metabolism and nutrition disorders	4 (0.3)	3 (0.5)	1 (0.2)
Gestational diabetes	1 (0.1)	1 (0.2)	0 (0.0)
Hypoglycaemia	3 (0.3)	2 (0.3)	1 (0.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	3 (0.3)	1 (0.2)	2 (0.3)
Breast cancer	1 (0.1)	1 (0.2)	0 (0.0)
Haemangioma of skin	1 (0.1)	0 (0.0)	1 (0.2)
Teratoma	1 (0.1)	0 (0.0)	1 (0.2)
Nervous system disorders	4 (0.3)	4 (0.7)	0 (0.0)
Cerebral ventricle dilatation	2 (0.2)	2 (0.3)	0 (0.0)
Hydrocephalus	1 (0.1)	1 (0.2)	0 (0.0)
Migraine	1 (0.1)	1 (0.2)	0 (0.0)
Pregnancy, puerperium and perinatal conditions	83 (7.0)	44 (7.5)	39 (6.6)
Amniorrhexis	3 (0.3)	3 (0.5)	0 (0.0)
Antepartum haemorrhage	9 (0.8)	5 (0.8)	4 (0.7)
Complication of pregnancy	1 (0.1)	1 (0.2)	0 (0.0)
Eclampsia	1 (0.1)	1 (0.2)	0 (0.0)
Fetal growth restriction	1 (0.1)	1 (0.2)	0 (0.0)
Fetal hypokinesia	2 (0.2)	1 (0.2)	1 (0.2)
Intrauterine death	9 (0.8)	4 (0.7)	5 (0.8)
Jaundice neonatal	1 (0.1)	1 (0.2)	0 (0.0)
Oligohydramnios	1 (0.1)	0 (0.0)	1 (0.2)
Placenta praevia haemorrhage	1 (0.1)	0 (0.0)	1 (0.2)
Post-partum haemorrhage	33 (2.8)	17 (2.9)	16 (2.7)
Pre-eclampsia	1 (0.1)	1 (0.2)	0 (0.0)
Premature baby	13 (1.1)	7 (1.2)	6 (1.0)
Premature labour	4 (0.3)	3 (0.5)	1 (0.2)
Premature rupture of membranes	3 (0.3)	1 (0.2)	2 (0.3)
Premature separation of placenta	4 (0.3)	3 (0.5)	1 (0.2)

continued

TABLE 84 Patients with at least one SAE by System Organ Class and Preferred Term for all SAEs in reporting window (maximum of end of treatment date + 28 days and date of delivery + 30 days) or where it is unclear whether or not they are in the reporting window (*continued*)

Outcome	All patients, *n* (%)	Trial group, *n* (%)	
		Placebo	Progesterone
Retained placenta or membranes	1 (0.1)	0 (0.0)	1 (0.2)
Stillbirth	2 (0.2)	0 (0.0)	2 (0.3)
Threatened labour	4 (0.3)	1 (0.2)	3 (0.5)
Uterine contractions during pregnancy	2 (0.2)	1 (0.2)	1 (0.2)
Renal and urinary disorders	1 (0.1)	1 (0.2)	0 (0.0)
Pyelocaliectasis	1 (0.1)	1 (0.2)	0 (0.0)
Reproductive system and breast disorders	10 (0.8)	6 (1.0)	4 (0.7)
Chordee	1 (0.1)	0 (0.0)	1 (0.2)
Coital bleeding	1 (0.1)	1 (0.2)	0 (0.0)
Cterine atony	1 (0.1)	0 (0.0)	1 (0.2)
Vaginal haemorrhage	7 (0.6)	5 (0.8)	2 (0.3)
Respiratory, thoracic and mediastinal disorders	6 (0.5)	2 (0.3)	4 (0.7)
Bronchopulmonary dysplasia	1 (0.1)	0 (0.0)	1 (0.2)
Cyanosis neonatal	1 (0.1)	1 (0.2)	0 (0.0)
Grunting	1 (0.1)	0 (0.0)	1 (0.2)
Neonatal asphyxia	1 (0.1)	0 (0.0)	1 (0.2)
Pneumothorax	1 (0.1)	0 (0.0)	1 (0.2)
Transient tachypnoea of the newborn	1 (0.1)	1 (0.2)	0 (0.0)
Skin and subcutaneous tissue disorders	1 (0.1)	1 (0.2)	0 (0.0)
Rash	1 (0.1)	1 (0.2)	0 (0.0)
Surgical and medical procedures	6 (0.5)	5 (0.8)	1 (0.2)
Caesarean section	1 (0.1)	1 (0.2)	0 (0.0)
Mechanical ventilation	1 (0.1)	1 (0.2)	0 (0.0)
Patent ductus arteriosus repair	1 (0.1)	0 (0.0)	1 (0.2)
Spinal decompression	1 (0.1)	1 (0.2)	0 (0.0)
Steroid therapy	1 (0.1)	1 (0.2)	0 (0.0)
Surgery	1 (0.1)	1 (0.2)	0 (0.0)
Vascular disorders	2 (0.2)	1 (0.2)	1 (0.2)
Deep-vein thrombosis	1 (0.1)	1 (0.2)	0 (0.0)
Essential hypertension	1 (0.1)	0 (0.0)	1 (0.2)

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:23 2015.

TABLE 85 Patients with at least one SAE by System Organ Class and Preferred Term for all SAEs definitely outside reporting window (maximum of end of treatment date + 28 days and date of delivery + 30 days)

Outcome	All patients, *n* (%)	Trial group, *n* (%)	
		Placebo	Progesterone
Number of patients, *n*	1183	590	593
Congenital, familial and genetic disorders	2 (0.2)	1 (0.2)	1 (0.2)
Multiple congenital abnormalities	1 (0.1)	0 (0.0)	1 (0.2)
Pyloric stenosis	1 (0.1)	1 (0.2)	0 (0.0)
Eye disorders	1 (0.1)	0 (0.0)	1 (0.2)
Retinopathy of prematurity	1 (0.1)	0 (0.0)	1 (0.2)
Gastrointestinal disorders	1 (0.1)	0 (0.0)	1 (0.2)
Neonatal necrotising enterocolitis	1 (0.1)	0 (0.0)	1 (0.2)
General disorders and administration site conditions	1 (0.1)	1 (0.2)	0 (0.0)
Drowning	1 (0.1)	1 (0.2)	0 (0.0)
Nervous system disorders	1 (0.1)	0 (0.0)	1 (0.2)
Convulsion	1 (0.1)	0 (0.0)	1 (0.2)
Pregnancy, puerperium and perinatal conditions	1 (0.1)	0 (0.0)	1 (0.2)
Premature baby	1 (0.1)	0 (0.0)	1 (0.2)
Surgical and medical procedures	1 (0.1)	1 (0.2)	0 (0.0)
Inguinal hernia repair	1 (0.1)	1 (0.2)	0 (0.0)

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:23 2015.

TABLE 86 Patients with at least one SAE of at least moderate severity or missing severity by System Organ Class and Preferred Term for all SAEs in reporting window (maximum of end of treatment date + 28 days and date of delivery + 30 days) or where it is unclear whether or not they are in the reporting window

Outcome	All patients, *n* (%)	Trial group, *n* (%)	
		Placebo	Progesterone
Number of patients, *n*	1183	590	593
Congenital, familial and genetic disorders	10 (0.8)	4 (0.7)	6 (1.0)
Cleft lip and palate	1 (0.1)	0 (0.0)	1 (0.2)
Congenital central nervous system anomaly	1 (0.1)	0 (0.0)	1 (0.2)
Congenital oesophageal anomaly	1 (0.1)	0 (0.0)	1 (0.2)
Cystic fibrosis	1 (0.1)	1 (0.2)	0 (0.0)
Congenital dacryostenosis	1 (0.1)	0 (0.0)	1 (0.2)
Holoprosencephaly	1 (0.1)	0 (0.0)	1 (0.2)
Kidney malformation	1 (0.1)	0 (0.0)	1 (0.2)
Patent ductus arteriosus	2 (0.2)	2 (0.3)	0 (0.0)
Congenital pulmonary artery stenosis	1 (0.1)	1 (0.2)	0 (0.0)

continued

TABLE 86 Patients with at least one SAE of at least moderate severity or missing severity by System Organ Class and Preferred Term for all SAEs in reporting window (maximum of end of treatment date + 28 days and date of delivery + 30 days) or where it is unclear whether or not they are in the reporting window (*continued*)

Outcome	All patients, *n* (%)	Trial group, *n* (%)	
		Placebo	Progesterone
Gastrointestinal disorders	5 (0.4)	5 (0.8)	0 (0.0)
Inguinal hernia	1 (0.1)	1 (0.2)	0 (0.0)
Necrotising colitis	2 (0.2)	2 (0.3)	0 (0.0)
Neonatal necrotising enterocolitis	3 (0.3)	3 (0.5)	0 (0.0)
General disorders and administration site conditions	4 (0.3)	2 (0.3)	2 (0.3)
Adverse drug reaction	1 (0.1)	1 (0.2)	0 (0.0)
Death neonatal	17 (1.4)	8 (1.3)	9 (1.5)
Infections and infestations	11 (0.9)	6 (1.0)	5 (0.8)
Appendicitis	1 (0.1)	1 (0.2)	0 (0.0)
Bronchopneumonia	1 (0.1)	0 (0.0)	1 (0.2)
Infection	1 (0.1)	1 (0.2)	0 (0.0)
Lower respiratory tract infection	1 (0.1)	1 (0.2)	0 (0.0)
Meningitis	1 (0.1)	1 (0.2)	0 (0.0)
Meningitis bacterial	1 (0.1)	1 (0.2)	0 (0.0)
Rash pustular	1 (0.1)	1 (0.2)	0 (0.0)
Sepsis	3 (0.3)	1 (0.2)	2 (0.3)
Urinary tract infection	1 (0.1)	0 (0.0)	1 (0.2)
Wound infection	1 (0.1)	0 (0.0)	1 (0.2)
Injury, poisoning and procedural complications	2 (0.2)	0 (0.0)	2 (0.3)
Post-lumbar puncture syndrome	1 (0.1)	0 (0.0)	1 (0.2)
Uterine rupture	1 (0.1)	0 (0.0)	1 (0.2)
Investigations	2 (0.2)	1 (0.2)	1 (0.2)
Fetal heart rate abnormal	1 (0.1)	0 (0.0)	1 (0.2)
Weight decreased	1 (0.1)	1 (0.2)	0 (0.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (0.2)	1 (0.2)	1 (0.2)
Breast cancer	1 (0.1)	1 (0.2)	0 (0.0)
Teratoma	1 (0.1)	0 (0.0)	1 (0.2)
Nervous system disorders	3 (0.3)	3 (0.5)	0 (0.0)
Cerebral ventricle dilatation	2 (0.2)	2 (0.3)	0 (0.0)
Hydrocephalus	1 (0.1)	1 (0.2)	0 (0.0)

TABLE 86 Patients with at least one SAE of at least moderate severity or missing severity by System Organ Class and Preferred Term for all SAEs in reporting window (maximum of end of treatment date + 28 days and date of delivery + 30 days) or where it is unclear whether or not they are in the reporting window (*continued*)

Outcome	All patients, *n* (%)	Trial group, *n* (%)	
		Placebo	Progesterone
Pregnancy, puerperium and perinatal conditions	56 (4.7)	27 (4.6)	29 (4.9)
Amniorrhexis	1 (0.1)	1 (0.2)	0 (0.0)
Antepartum haemorrhage	6 (0.5)	3 (0.5)	3 (0.5)
Eclampsia	1 (0.1)	1 (0.2)	0 (0.0)
Fetal hypokinesia	1 (0.1)	0 (0.0)	1 (0.2)
Intrauterine death	8 (0.7)	4 (0.7)	4 (0.7)
Jaundice neonatal	1 (0.1)	1 (0.2)	0 (0.0)
Oligohydramnios	1 (0.1)	0 (0.0)	1 (0.2)
Placenta praevia haemorrhage	1 (0.1)	0 (0.0)	1 (0.2)
Post-partum haemorrhage	20 (1.7)	9 (1.5)	11 (1.9)
Premature baby	13 (1.1)	7 (1.2)	6 (1.0)
Premature labour	3 (0.3)	2 (0.3)	1 (0.2)
Premature rupture of membranes	3 (0.3)	1 (0.2)	2 (0.3)
Premature separation of placenta	4 (0.3)	3 (0.5)	1 (0.2)
Retained placenta or membranes	1 (0.1)	0 (0.0)	1 (0.2)
Stillbirth	2 (0.2)	0 (0.0)	2 (0.3)
Threatened labour	1 (0.1)	0 (0.0)	1 (0.2)
Reproductive system and breast disorders	2 (0.2)	0 (0.0)	2 (0.3)
Uterine atony	1 (0.1)	0 (0.0)	1 (0.2)
Vaginal haemorrhage	1 (0.1)	0 (0.0)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	4 (0.3)	1 (0.2)	3 (0.5)
Bronchopulmonary dysplasia	1 (0.1)	0 (0.0)	1 (0.2)
Neonatal asphyxia	1 (0.1)	0 (0.0)	1 (0.2)
Pneumothorax	1 (0.1)	0 (0.0)	1 (0.2)
Transient tachypnoea of the newborn	1 (0.1)	1 (0.2)	0 (0.0)
Surgical and medical procedures	5 (0.4)	4 (0.7)	1 (0.2)
Caesarean section	1 (0.1)	1 (0.2)	0 (0.0)
Mechanical ventilation	1 (0.1)	1 (0.2)	0 (0.0)
Patent ductus arteriosus repair	1 (0.1)	0 (0.0)	1 (0.2)
Spinal decompression	1 (0.1)	1 (0.2)	0 (0.0)
Surgery	1 (0.1)	1 (0.2)	0 (0.0)
Vascular disorders	2 (0.2)	1 (0.2)	1 (0.2)
Deep-vein thrombosis	1 (0.1)	1 (0.2)	0 (0.0)
Essential hypertension	1 (0.1)	0 (0.0)	1 (0.2)

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:24 2015.

TABLE 87 Patients with at least one severe SAE or an SAE with missing severity by System Organ Class and Preferred Term for all SAEs in reporting window (maximum of end of treatment date + 28 days and date of delivery + 30 days) or where it is unclear whether or not they are in the reporting window

Outcome	All patients, *n* (%)	Trial group, *n* (%)	
		Placebo	Progesterone
Number of patients, *n*	1183	590	593
Congenital, familial and genetic disorders	5 (0.4)	0 (0.0)	5 (0.8)
Cleft lip and palate	1 (0.1)	0 (0.0)	1 (0.2)
Congenital central nervous system anomaly	1 (0.1)	0 (0.0)	1 (0.2)
Congenital oesophageal anomaly	1 (0.1)	0 (0.0)	1 (0.2)
Holoprosencephaly	1 (0.1)	0 (0.0)	1 (0.2)
Kidney malformation	1 (0.1)	0 (0.0)	1 (0.2)
Gastrointestinal disorders	3 (0.3)	3 (0.5)	0 (0.0)
Necrotising colitis	2 (0.2)	2 (0.3)	0 (0.0)
Neonatal necrotising enterocolitis	2 (0.2)	2 (0.3)	0 (0.0)
General disorders and administration site conditions	3 (0.3)	1 (0.2)	2 (0.3)
Death neonatal	17 (1.4)	8 (1.3)	9 (1.5)
Infections and infestations	3 (0.3)	2 (0.3)	1 (0.2)
Appendicitis	1 (0.1)	1 (0.2)	0 (0.0)
Meningitis	1 (0.1)	1 (0.2)	0 (0.0)
Sepsis	1 (0.1)	0 (0.0)	1 (0.2)
Injury, poisoning and procedural complications	1 (0.1)	0 (0.0)	1 (0.2)
Uterine rupture	1 (0.1)	0 (0.0)	1 (0.2)
Investigations	1 (0.1)	0 (0.0)	1 (0.2)
Fetal heart rate abnormal	1 (0.1)	0 (0.0)	1 (0.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (0.2)	1 (0.2)	1 (0.2)
Breast cancer	1 (0.1)	1 (0.2)	0 (0.0)
Teratoma	1 (0.1)	0 (0.0)	1 (0.2)
Nervous system disorders	1 (0.1)	1 (0.2)	0 (0.0)
Hydrocephalus	1 (0.1)	1 (0.2)	0 (0.0)
Pregnancy, puerperium and perinatal conditions	30 (2.5)	15 (2.5)	15 (2.5)
Amniorrhexis	1 (0.1)	1 (0.2)	0 (0.0)
Antepartum haemorrhage	3 (0.3)	2 (0.3)	1 (0.2)
Eclampsia	1 (0.1)	1 (0.2)	0 (0.0)
Intrauterine death	8 (0.7)	4 (0.7)	4 (0.7)
Oligohydramnios	1 (0.1)	0 (0.0)	1 (0.2)
Post-partum haemorrhage	5 (0.4)	2 (0.3)	3 (0.5)
Premature baby	12 (1.0)	6 (1.0)	6 (1.0)
Premature labour	1 (0.1)	0 (0.0)	1 (0.2)
Premature separation of placenta	2 (0.2)	1 (0.2)	1 (0.2)
Retained placenta or membranes	1 (0.1)	0 (0.0)	1 (0.2)

TABLE 87 Patients with at least one severe SAE or an SAE with missing severity by System Organ Class and Preferred Term for all SAEs in reporting window (maximum of end of treatment date + 28 days and date of delivery + 30 days) or where it is unclear whether or not they are in the reporting window (*continued*)

Outcome	All patients, *n* (%)	Trial group, *n* (%)	
		Placebo	Progesterone
Stillbirth	2 (0.2)	0 (0.0)	2 (0.3)
Reproductive system and breast disorders	1 (0.1)	0 (0.0)	1 (0.2)
Uterine atony	1 (0.1)	0 (0.0)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	2 (0.2)	0 (0.0)	2 (0.3)
Bronchopulmonary dysplasia	1 (0.1)	0 (0.0)	1 (0.2)
Pneumothorax	1 (0.1)	0 (0.0)	1 (0.2)
Surgical and medical procedures	1 (0.1)	1 (0.2)	0 (0.0)
Spinal decompression	1 (0.1)	1 (0.2)	0 (0.0)
Vascular disorders	1 (0.1)	0 (0.0)	1 (0.2)
Essential hypertension	1 (0.1)	0 (0.0)	1 (0.2)

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:24 2015.

TABLE 88 Patients with at least one SAE that is at least possibly related to treatment or SAE with missing relationship by System Organ Class and Preferred Term for all SAEs in reporting window (maximum of end of treatment date + 28 days and date of delivery + 30 days) or where it is unclear whether or not they are in the reporting window

Outcome	All patients, *n* (%)	Trial group, *n* (%)	
		Placebo	Progesterone
Number of patients, *n*	1183	590	593
Blood and lymphatic system disorders	1 (0.1)	1 (0.2)	0 (0.0)
Thrombocytopenia	1 (0.1)	1 (0.2)	0 (0.0)
Congenital, familial and genetic disorders	1 (0.1)	1 (0.2)	0 (0.0)
Hydrocele	1 (0.1)	1 (0.2)	0 (0.0)
General disorders and administration site conditions	1 (0.1)	1 (0.2)	0 (0.0)
Adverse drug reaction	1 (0.1)	1 (0.2)	0 (0.0)
Infections and infestations	1 (0.1)	1 (0.2)	0 (0.0)
Infection	1 (0.1)	1 (0.2)	0 (0.0)
Rash pustular	1 (0.1)	1 (0.2)	0 (0.0)
Investigations	1 (0.1)	0 (0.0)	1 (0.2)
Fetal heart rate abnormal	1 (0.1)	0 (0.0)	1 (0.2)
Metabolism and nutrition disorders	1 (0.1)	1 (0.2)	0 (0.0)
Gestational diabetes	1 (0.1)	1 (0.2)	0 (0.0)
Nervous system disorders	3 (0.3)	3 (0.5)	0 (0.0)
Cerebral ventricle dilatation	2 (0.2)	2 (0.3)	0 (0.0)
Migraine	1 (0.1)	1 (0.2)	0 (0.0)

continued

TABLE 88 Patients with at least one SAE that is at least possibly related to treatment or SAE with missing relationship by System Organ Class and Preferred Term for all SAEs in reporting window (maximum of end of treatment date + 28 days and date of delivery + 30 days) or where it is unclear whether or not they are in the reporting window (*continued*)

Outcome	All patients, *n* (%)	Trial group, *n* (%)	
		Placebo	Progesterone
Pregnancy, puerperium and perinatal conditions	6 (0.5)	5 (0.8)	1 (0.2)
Antepartum haemorrhage	2 (0.2)	2 (0.3)	0 (0.0)
Fetal growth restriction	1 (0.1)	1 (0.2)	0 (0.0)
Post-partum haemorrhage	3 (0.3)	2 (0.3)	1 (0.2)
Premature labour	1 (0.1)	1 (0.2)	0 (0.0)
Premature separation of placenta	1 (0.1)	1 (0.2)	0 (0.0)
Reproductive system and breast disorders	2 (0.2)	2 (0.3)	0 (0.0)
Vaginal haemorrhage	2 (0.2)	2 (0.3)	0 (0.0)
Surgical and medical procedures	1 (0.1)	1 (0.2)	0 (0.0)
Steroid therapy	1 (0.1)	1 (0.2)	0 (0.0)

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 14:34:25 2015.

Part 7: subgroup regressions

Does progesterone prophylaxis to prevent preterm labour improve outcome?	
OPPTIMUM	
Final report tables	
Part 7: subgroup regressions	
v1.0	
9 October 2015	
Martina Messow	
Robertson Centre for Biostatistics	
EudraCT number	2007-007950-77
CTA number	22931/0009/001-0001 revised by MHRA to 01384/0208/001
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Protocol version	15.1 (1 April 2015)
SAP version	1.1 (8 September 2015)

CTA, Clinical Trial Authorisation; EudraCT, European Union Drug Regulating Authorities Clinical Trials; MREC, Multicentre Research Ethics Committee; SAP, statistical analysis plan.

TABLE 89 Logistic regression model for the effect of treatment on the primary obstetric outcome death or delivery before 34 weeks' gestation adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to risk group

Separate models in each subgroup				
Risk group	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
Low	0.88	0.58 to 1.32	0.535	859
High	0.91	0.57 to 1.47	0.708	338
Interaction model ($n = 1197$)				
Risk group	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
Low	0.88	0.58 to 1.33	0.542	0.907
High	0.91	0.57 to 1.46	0.707	

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 09 14:55:02 2015.

TABLE 90 Logistic regression model for the effect of treatment on the primary neonatal outcome death, brain injury or severe chronic lung disease adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to risk group

Separate models in each subgroup				
Risk group	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
Low	0.78	0.46 to 1.33	0.361	847
High	0.70	0.37 to 1.31	0.262	329
Interaction model ($n = 1176$)				
Risk group	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
Low	0.78	0.46 to 1.33	0.357	0.786
High	0.69	0.37 to 1.30	0.254	

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 09 14:55:04 2015.

TABLE 91 Linear regression model for the effect of treatment on the primary childhood outcome Bayley-III cognitive scale adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to risk group

Separate models in each subgroup				
Risk group	**Expected mean difference (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
Low	–0.62	–3.14 to 1.90	0.629	628
High	–1.12	–5.99 to 3.76	0.654	241
Interaction model ($n = 869$)				
Risk group	**Expected mean difference (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
Low	–0.63	–3.28 to 2.03	0.644	0.858
High	–1.09	–5.41 to 3.23	0.621	

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 09 14:55:05 2015.

TABLE 92 Logistic regression model for the effect of treatment on the primary childhood outcome survival at 2 years adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to risk group

Separate models in each subgroup				
Risk group	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
Low	Regression failed			
High	0.87	0.36 to 2.08	0.749	284
Interaction model (*n* = 1009)				
Risk group	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
Low	0.56	0.19 to 1.68	0.305	0.546
High	0.87	0.36 to 2.06	0.744	
Model in low risk subgroup not adjusting for previous pregnancy of ≥ 14 weeks				
Risk group	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
Low	0.56	0.19 to 1.70	0.309	725

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 09 14:55:07 2015.

TABLE 93 Proportional hazards regression model for the effect of treatment on the primary childhood outcome survival adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to risk group

Separate models in each subgroup				
Risk group	**Hazard ratio (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
Low	1.74	0.58 to 5.18	0.323	860
High	1.19	0.51 to 2.79	0.692	338
Interaction model (*n* = 1198)				
Risk group	**Hazard ratio (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
Low	1.73	0.58 to 5.17	0.325	0.540
High	1.13	0.49 to 2.60	0.778	

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 09 14:55:09 2015.

TABLE 94 Logistic regression model for the effect of treatment on the primary obstetric outcome death or delivery before 34 weeks' gestation adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to cervical length at baseline

Separate models in each subgroup				
Cervical length at baseline (mm)	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
> 25	Regression failed			
≤ 25	0.69	0.39 to 1.20	0.192	251
Interaction model (*n* = 696)				
Cervical length at baseline (mm)	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
> 25	0.88	0.50 to 1.57	0.672	0.542
≤ 25	0.69	0.39 to 1.20	0.191	
Model in subgroup with a cervical length of > 25 mm at baseline, not adjusting for previous pregnancy of ≥ 14 weeks' gestation				
Cervical length at baseline (mm)	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
> 25	0.88	0.51 to 1.54	0.658	445

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 09 14:55:12 2015.

TABLE 95 Logistic regression model for the effect of treatment on the primary neonatal outcome death, brain injury or severe chronic lung disease adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to cervical length at baseline

Separate models in each subgroup				
Cervical length at baseline (mm)	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
> 25	Regression failed			
≤ 25	0.56	0.26 to 1.19	0.133	246
Interaction model (*n* = 682)				
Cervical length at baseline (mm)	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
> 25	0.86	0.42 to 1.77	0.690	0.380
≤ 25	0.54	0.26 to 1.15	0.112	
Model in subgroup with a cervical length of > 25 mm at baseline, not adjusting for previous pregnancy of ≥ 14 weeks' gestation				
Cervical length at baseline (mm)	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
> 25	0.87	0.43 to 1.78	0.706	436

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 09 14:55:16 2015.

TABLE 96 Linear regression model for the effect of treatment on the primary childhood outcome Bayley-III cognitive scale adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to cervical length at baseline

Separate models in each subgroup				
Cervical length at baseline (mm)	**Expected mean difference (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
> 25	–2.13	–5.79 to 1.54	0.256	317
≤ 25	–2.25	–7.70 to 3.20	0.419	179
Interaction model ($n = 496$)				
Cervical length at baseline (mm)	**Expected mean difference (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
> 25	–2.27	–6.10 to 1.56	0.247	0.971
≤ 25	–2.15	–7.23 to 2.93	0.408	

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 09 14:55:17 2015.

TABLE 97 Logistic regression model for the effect of treatment on the primary childhood outcome survival adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to cervical length at baseline

Separate models in each subgroup				
Cervical length at baseline (mm)	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
> 25	Regression failed			
≤ 25	1.10	0.46 to 2.67	0.825	214
Interaction model ($n = 583$)				
Cervical length at baseline (mm)	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
> 25	1.24	0.27 to 5.62	0.782	0.807
≤ 25	0.97	0.29 to 3.30	0.963	
Model in subgroup with a cervical length of > 25 mm at baseline, not adjusting for previous pregnancy of ≥ 14 weeks' gestation				
Cervical length at baseline (mm)	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
> 25	1.31	0.57 to 3.01	0.520	369

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 09 14:55:19 2015.

TABLE 98 Proportional hazards regression model for the effect of treatment on the primary childhood outcome survival adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to cervical length at baseline

Separate models in each subgroup				
Cervical length at baseline (mm)	Hazard ratio (progesterone vs. placebo)	95% CI	*p*-value	*n*
> 25	0.78	0.17 to 3.49	0.747	445
≤ 25	0.97	0.29 to 3.20	0.957	252
Interaction model (*n* = 697)				
Cervical length at baseline (mm)	Hazard ratio (progesterone vs. placebo)	95% CI	*p*-value	*p*-value for interaction
> 25	0.79	0.18 to 3.51	0.752	0.766
≤ 25	1.05	0.32 to 3.44	0.937	

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 09 14:55:21 2015.

TABLE 99 Logistic regression model for the effect of treatment on the primary obstetric outcome death or delivery before 34 weeks' gestation adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to cervical length at baseline

Separate models in each subgroup				
Cervical length at baseline (mm)	OR (progesterone vs. placebo)	95% CI	*p*-value	*n*
> 15	0.77	0.48 to 1.22	0.262	599
≤ 15	0.91	0.40 to 2.06	0.815	97
Interaction model (*n* = 696)				
Cervical length at baseline (mm)	OR (progesterone vs. placebo)	95% CI	*p*-value	*p*-value for interaction
> 15	0.77	0.48 to 1.23	0.274	0.727
≤ 15	0.91	0.41 to 2.04	0.819	

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 09 14:55:23 2015.

TABLE 100 Logistic regression model for the effect of treatment on the primary neonatal outcome death, brain injury or severe chronic lung disease adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to cervical length at baseline

Separate models in each subgroup				
Cervical length at baseline (mm)	OR (progesterone vs. placebo)	95% CI	*p*-value	*n*
> 15	0.81	0.44 to 1.51	0.514	588
≤ 15	0.49	0.18 to 1.35	0.168	94
Interaction model (*n* = 682)				
Cervical length at baseline (mm)	OR (progesterone vs. placebo)	95% CI	*p*-value	*p*-value for interaction
> 15	0.82	0.44 to 1.52	0.526	0.389
≤ 15	0.49	0.18 to 1.32	0.158	

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 09 14:55:24 2015.

TABLE 101 Linear regression model for the effect of treatment on the primary childhood outcome Bayley-III cognitive composite score adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to cervical length at baseline

Separate models in each subgroup				
Cervical length at baseline (mm)	**Expected mean difference (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
> 15	–2.55	–5.73 to 0.63	0.116	423
≤ 15	–0.34	–9.75 to 9.08	0.944	73
Interaction model (*n* = 496)				
Cervical length at baseline (mm)	**Expected mean difference (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
> 15	–2.49	–5.77 to 0.78	0.137	0.680
≤ 15	–0.69	–8.60 to 7.22	0.865	

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 09 14:55:24 2015.

TABLE 102 Logistic regression model for the effect of treatment on the primary childhood outcome survival adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to cervical length at baseline

Separate models in each subgroup				
Cervical length at baseline (mm)	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
> 1	Regression failed			
≤ 15	1.88	0.40 to 8.74	0.424	85
Interaction model (*n* = 583)				
Cervical length at baseline (mm)	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
> 15	0.66	0.19 to 2.33	0.515	0.304
≤ 15	1.83	0.41 to 8.12	0.426	
Model in subgroup with a cervical length of > 15 mm at baseline, not adjusting for previous pregnancy of ≥ 14 weeks' gestation				
Cervical length at baseline (mm)	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
> 15	0.66	0.18 to 2.36	0.519	498

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 09 14:55:27 2015.

TABLE 103 Proportional hazards regression model for the effect of treatment on the primary childhood outcome survival adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to cervical length at baseline

Separate models in each subgroup				
Cervical length at baseline (mm)	**Hazard ratio (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
> 15	1.49	0.42 to 5.28	0.536	600
≤ 15	0.53	0.13 to 2.25	0.391	97
Interaction model (*n* = 697)				
Cervical length at baseline (mm)	**Hazard ratio (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
> 15	1.50	0.42 to 5.32	0.530	0.292
≤ 15	0.55	0.13 to 2.28	0.406	

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 09 14:55:28 2015.

TABLE 104 Logistic regression model for the effect of treatment on the primary obstetric outcome death or delivery before 34 weeks' gestation adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to history of spontaneous preterm birth

Separate models in each subgroup				
History of spontaneous preterm birth	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
No	0.99	0.51 to 1.92	0.972	273
Yes	Regression failed			
Interaction model (*n* = 1176)				
History of spontaneous preterm birth	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
No	0.99	0.51 to 1.92	0.972	0.618
Yes	0.82	0.58 to 1.16	0.254	
Model in subgroup with a history of spontaneous preterm birth, not adjusting for previous pregnancy of ≥ 14 weeks' gestation				
History of spontaneous preterm birth	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
Yes	0.82	0.58 to 1.15	0.253	903

Note
OPPTIMUM Output created by OPPTIMUM_additional03_v1_0.R.R Last run on Tue Feb 16 15:08:44 2016.

TABLE 105 Logistic regression model for the effect of treatment on the primary neonatal outcome death, brain injury or severe chronic lung disease adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to history of spontaneous preterm birth

Separate models in each subgroup				
Cervical length at baseline (mm)	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
No	1.24	0.55 to 2.82	0.601	270
Yes	Regression failed			
Interaction model ($n = 1156$)				
History of spontaneous preterm birth	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
No	1.23	0.54 to 2.77	0.623	0.0135
Yes	0.60	0.37 to 0.96	0.033	
Model in subgroup with a history of spontaneous preterm birth, not adjusting for previous pregnancy of ≥ 14 weeks' gestation				
History of spontaneous preterm birth	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
Yes	0.68	0.37 to 0.96	0.034	887

Note
OPPTIMUM Output created by OPPTIMUM_additional03_v1_0.R.R Last run on Tue Feb 16 15:08:47 2016.

TABLE 106 Linear regression model for the effect of treatment on the primary childhood outcome Bayley-III cognitive composite score adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to history of spontaneous preterm birth

Separate models in each subgroup				
History of spontaneous preterm birth	**Expected mean difference (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
No	–1.05	–5.89 to 3.79	0.672	201
Yes	Regression failed			
Interaction model ($n = 857$)				
History of spontaneous preterm birth	**Expected mean difference (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
No	–1.11	–5.96 to 3.73	0.653	0.730
Yes	–0.14	–2.79 to 2.52	0.919	
Model in subgroup with a history of spontaneous preterm birth, not adjusting for previous pregnancy of ≥ 14 weeks' gestation				
History of spontaneous preterm birth	**Parameter estimate**	**95% CI**	***p*-value**	***n***
Yes	–0.22	–2.89 to 2.44	0.870	656

Note
OPPTIMUM Output created by OPPTIMUM_additional03_v1_0.R.R Last run on Tue Feb 16 15:08:50 2016.

TABLE 107 Logistic regression model for the effect of treatment on the primary childhood outcome survival adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to history of spontaneous preterm birth

Separate models in each subgroup				
History of spontaneous preterm birth	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
No	0.64	0.17 to 2.40	0.506	243
Yes	Regression failed			
Interaction model ($n = 993$)				
History of spontaneous preterm birth	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
No	0.64	0.17 to 2.44	0.510	0.754
Yes	0.82	0.38 to 1.76	0.605	
Model in subgroup with a history of spontaneous preterm birth, not adjusting for previous pregnancy of ≥ 14 weeks' gestation				
History of spontaneous preterm birth	**OR**	**95% CI**	***p*-value**	***n***
Yes	0.82	0.38 to 1.77	0.606	750

Note
OPPTIMUM Output created by OPPTIMUM_additional03_v1_0.R.R Last run on Tue Feb 16 15:08:52 2016.

TABLE 108 Proportional hazards regression model for the effect of treatment on the primary childhood outcome survival adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to history of spontaneous preterm birth

Separate models in each subgroup				
History of spontaneous preterm birth	**Hazard ratio (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
No	1.55	0.42 to 5.78	0.513	273
Yes	Regression failed			
Interaction model ($n = 1177$)				
History of spontaneous preterm birth	**Hazard ratio (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
No	1.55	0.42 to 5.78	0.513	0.734
Yes	1.19	0.56 to 2.55	0.650	
Model in subgroup with a history of spontaneous preterm birth, not adjusting for previous pregnancy of ≥ 14 weeks' gestation				
History of spontaneous preterm birth	**Hazard ratio**	**95% CI**	***p*-value**	***n***
Yes	1.20	0.56 to 2.55	0.645	904

Note
OPPTIMUM Output created by OPPTIMUM_additional03_v1_0.R.R Last run on Tue Feb 16 15:08:53 2016.

TABLE 109 Logistic regression model for the effect of treatment on the primary obstetric outcome death or delivery before 34 weeks' gestation adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to history of preterm birth

Separate models in each subgroup				
History of preterm birth	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
No	1.06	0.53 to 2.13	0.862	250
Yes	Regression failed			
Interaction model ($n = 1196$)				
History of preterm birth	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
No	1.06	0.53 to 2.12	0.868	0.497
Yes	0.81	0.58 to 1.14	0.225	
Model in subgroup with a history of preterm birth, not adjusting for previous pregnancy of ≥ 14 weeks' gestation				
History of spontaneous preterm birth	**OR**	**95% CI**	***p*-value**	***n***
Yes	0.81	0.58 to 1.14	0.226	946

Note
OPPTIMUM Output created by OPPTIMUM_additional03_v1_0.R.R Last run on Tue Feb 16 15:08:56 2016.

TABLE 110 Logistic regression model for the effect of treatment on the primary neonatal outcome death, brain injury or severe chronic lung disease adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to history of preterm birth

Separate models in each subgroup				
History of preterm birth	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
No	1.11	0.48 to 2.57	0.802	248
Yes	Regression failed			
Interaction model ($n = 1175$)				
History of preterm birth	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
No	1.09	0.47 to 2.52	0.836	0.263
Yes	0.63	0.40 to 1.00	0.052	
Model in subgroup with a history of preterm birth, not adjusting for previous pregnancy of ≥ 14 weeks' gestation				
History of spontaneous preterm birth	**OR**	**95% CI**	***p*-value**	***n***
Yes	0.64	0.40 to 1.01	0.054	928

Note
OPPTIMUM Output created by OPPTIMUM_additional03_v1_0.R.R Last run on Tue Feb 16 15:08:59 2016.

TABLE 111 Linear regression model for the effect of treatment on the primary childhood outcome Bayley-III cognitive composite score adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to history of preterm birth

Separate models in each subgroup				
History of preterm birth	**Expected mean difference (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
No	–0.83	–5.96 to 4.29	0.750	187
Yes	Regression failed			
Interaction model ($n = 868$)				
History of preterm birth	**Expected mean difference (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
No	–0.91	–5.92 to 4.11	0.724	0.852
Yes	–0.37	–2.96 to 2.23	0.782	
Model in subgroup with a history of preterm birth, not adjusting for previous pregnancy of ≥ 14 weeks' gestation				
History of spontaneous preterm birth	**Parameter estimate**	**95% CI**	***p*-value**	***n***
Yes	–0.44	–3.02 to 2.14	0.739	681

Note
OPPTIMUM Output created by OPPTIMUM_additional03_v1_0.R.R Last run on Tue Feb 16 15:09:01 2016.

TABLE 112 Logistic regression model for the effect of treatment on the primary childhood outcome survival adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to history of preterm birth

Separate models in each subgroup				
History of preterm birth	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
No	0.63	0.17 to 2.39	0.500	223
Yes	Regression failed			
Interaction model ($n = 1008$)				
History of preterm birth	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
No	0.63	0.16 to 2.43	0.505	0.747
Yes	0.82	0.38 to 1.77	0.607	
Model in subgroup with a history of preterm birth, not adjusting for previous pregnancy of ≥ 14 weeks' gestation				
History of spontaneous preterm birth	**OR**	**95% CI**	***p*-value**	***n***
Yes	0.82	0.38 to 1.77	0.609	785

Note
OPPTIMUM Output created by OPPTIMUM_additional03_v1_0.R.R Last run on Tue Feb 16 15:09:03 2016.

TABLE 113 Proportional hazards regression model for the effect of treatment on the primary childhood outcome survival adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to history of preterm birth

Separate models in each subgroup				
History of preterm birth	**Hazard ratio (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
No	1.52	0.41 to 5.68	0.530	250
Yes	Regression failed			
Interaction model (*n* = 1197)				
History of preterm birth	**Hazard ratio (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
No	1.52	0.41 to 5.66	0.533	0.762
Yes	1.20	0.56 to 2.57	0.633	
Model in subgroup with a history of preterm birth, not adjusting for previous pregnancy of ≥ 14 weeks' gestation				
History of spontaneous preterm birth	**Hazard ratio**	**95% CI**	***p*-value**	***n***
Yes	1.21	0.56 to 2.58	0.629	947

Note
OPPTIMUM Output created by OPPTIMUM_additional03_v1_0.R.R Last run on Tue Feb 16 15:09:04 2016.

TABLE 114 Logistic regression model for the effect of treatment on the primary obstetric outcome death or delivery before 34 weeks' gestation adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to chorioamnionitis diagnosed on pathology

Separate models in each subgroup				
Chorioamnionitis diagnosed on pathology	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
No	Regression failed			
Yes	2.16	0.69 to 6.83	0.194	57
Interaction model (*n* = 172)				
Chorioamnionitis diagnosed on pathology	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
No	1.38	0.55 to 3.45	0.497	0.547
Yes	2.17	0.68 to 6.85	0.190	
Model in subgroup without chorioamnionitis, not adjusting for previous pregnancy of ≥ 14 weeks' gestation				
Chorioamnionitis diagnosed on pathology	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
No	1.36	0.55 to 3.41	0.509	115

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 09 14:55:53 2015.

TABLE 115 Logistic regression model for the effect of treatment on the primary neonatal outcome death, brain injury or severe chronic lung disease adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to chorioamnionitis diagnosed on pathology

Separate models in each subgroup				
Chorioamnionitis diagnosed on pathology	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
No	Regression failed			
Yes	2.53	0.75 to 8.59	0.141	56
Interaction model (*n* = 171)				
Chorioamnionitis diagnosed on pathology	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
No	1.81	0.30 to 4.68	0.810	0.429
Yes	2.53	0.71 to 9.06	0.156	
Model in subgroup without chorioamnionitis, not adjusting for previous pregnancy of ≥ 14 weeks' gestation				
Chorioamnionitis diagnosed on pathology	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
No	1.16	0.28 to 4.80	0.841	115

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 09 14:55:56 2015.

TABLE 116 Linear regression model for the effect of treatment on the primary childhood outcome Bayley-III cognitive composite score adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to chorioamnionitis diagnosed on pathology

Separate models in each subgroup				
Chorioamnionitis diagnosed on pathology	**Expected mean difference (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
No	–2.15	–9.80 to 5.49	0.582	81
Yes	–2.57	–14.76 to 9.62	0.682	43
Interaction model (*n* = 124)				
Chorioamnionitis diagnosed on pathology	**Expected mean difference (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
No	–2.30	–10.30 to 5.70	0.575	0.859
Yes	–1.08	–11.91 to 9.76	0.846	

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 09 14:55:57 2015.

TABLE 117 Logistic regression model for the effect of treatment on the primary childhood outcome survival adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to chorioamnionitis diagnosed on pathology

Separate models in each subgroup				
Chorioamnionitis diagnosed on pathology	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
No	Regression failed			
Yes	Regression failed			
Interaction model failed				

Fisher's exact test in subgroups according to history of spontaneous preterm birth			
	Treatment		
History of spontaneous preterm birth	**Placebo**	**Progesterone**	***p*-value**
No, N_{obs} (N_{miss})	52 (6)	49 (8)	0.353
Alive at 2 years			
No, *n* (%)	1 (1.9)	3 (6.1)	
Yes, *n* (%)	51 (98.1)	46 (93.9)	
Yes, N_{obs} (N_{miss})	26 (3)	25 (3)	0.099
Alive at 2 years			
No, *n* (%)	1 (3.8)	5 (20.0)	
Yes, *n* (%)	25 (96.2)	20 (80.0)	

N_{miss}, number of women with missing data; N_{obs}, number of observations.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 09 14:56:02 2015.

TABLE 118 Proportional hazards regression model for the effect of treatment on the primary childhood outcome survival adjusted for previous pregnancy of ≥ 14 weeks' gestation and site as a random effect in subgroups according to chorioamnionitis diagnosed on pathology

Separate models in each subgroup				
Chorioamnionitis diagnosed on pathology	**Hazard ratio (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
No	3.48	0.36 to 33.47	0.280	115
Yes	5.74	0.67 to 49.18	0.111	57
Interaction model failed				

Interaction model not adjusting for previous pregnancy of at least 14 weeks' gestation (*n* = 172)				
Chorioamnionitis diagnosed on pathology	**Hazard ratio (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
No	3.55	0.37 to 34.38	0.274	0.538
Yes	5.40	0.62 to 46.81	0.126	

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 09 14:56:04 2015.

TABLE 119 Logistic regression model for the effect of treatment on the primary obstetric outcome death or delivery before 34 weeks' gestation in subgroups according to previous pregnancy of ≥ 14 weeks' gestation

Separate models in each subgroup				
Previous pregnancy of ≥ 14 weeks' gestation	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
No	1.65	0.47 to 5.85	0.440	73
Yes	0.83	0.61 to 1.13	0.235	1124
Interaction model (*n* = 1197)				
Previous pregnancy of ≥ 14 weeks' gestation	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
No	1.65	0.47 to 5.79	0.434	0.296
Yes	0.83	0.61 to 1.13	0.235	

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 09 14:56:07 2015.

TABLE 120 Logistic regression model for the effect of treatment on the primary neonatal outcome death, brain injury or severe chronic lung disease in subgroups according to previous pregnancy of ≥ 14 weeks' gestation

Separate models in each subgroup				
Previous pregnancy of ≥ 14 weeks' gestation	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
No	6.64	0.70 to 62.89	0.103	73
Yes	0.64	0.42 to 0.97	0.035	1104
Interaction model (*n* = 1176)				
Previous pregnancy of ≥ 14 weeks' gestation	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
No	6.19	0.68 to 56.24	0.106	0.048
Yes	0.64	0.42 to 0.97	0.035	

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 09 14:56:09 2015.

TABLE 121 Linear regression model for the effect of treatment on the primary childhood outcome Bayley-III cognitive composite score in subgroups according to previous pregnancy of ≥ 14 weeks' gestation

Separate models in each subgroup				
Previous pregnancy of ≥ 14 weeks' gestation	**Expected mean difference (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
No	–3.03	–11.54 to 5.47	0.488	57
Yes	–0.40	–2.78 to 1.99	0.745	812
Interaction model (*n* = 869)				
Previous pregnancy of ≥ 14 weeks' gestation	**Expected mean difference (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
No	–1.72	–10.70 to 7.26	0.707	0.780
Yes	–0.40	–2.77 to 1.98	0.744	

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 09 14:56:10 2015.

TABLE 122 Logistic regression model for the effect of treatment on the primary childhood outcome survival in subgroups according to previous pregnancy of ≥ 14 weeks' gestation

Separate models in each subgroup				
Previous pregnancy of ≥ 14 weeks' gestation	**OR (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
No	Regression failed			
Yes	0.82	0.42 to 1.62	0.571	940
Interaction model failed				

Fisher's exact test in subgroups according to previous pregnancy of ≥ 14 weeks' gestation			
	Treatment		
Previous pregnancy of ≥ 14 weeks' gestation	**Placebo**	**Progesterone**	***p*-value**
No, N_{obs} (N_{miss})	35 (3)	34 (3)	0.493
Alive at 2 years			
No, *n* (%)	0 (0.0)	1 (2.9)	
Yes, *n* (%)	35 (100.0)	33 (97.1)	

N_{miss}, number of women with missing data; N_{obs}, number of observations.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 09 14:56:14 2015.

TABLE 123 Proportional hazards regression model for the effect of treatment on the primary childhood outcome survival in subgroups according to previous pregnancy of ≥ 14 weeks' gestation

Separate models in each subgroup				
Previous pregnancy of ≥ 14 weeks' gestation	**Hazard ratio (progesterone vs. placebo)**	**95% CI**	***p*-value**	***n***
No	4781116004.75	0.00 to Infinity	1.000	73
Yes	1.19	0.61 to 2.32	0.605	1125

Interaction model (*n* = 1198)				
Previous pregnancy of ≥ 14 weeks' gestation	**Hazard ratio (progesterone vs. placebo)**	**95% CI**	***p*-value**	***p*-value for interaction**
No	60718556.85	0.00 to Infinity	0.998	0.262
Yes	1.19	0.61 to 2.32	0.606	
Log-rank test for the effect of treatment (unadjusted) in the group with no previous pregnancy of ≥ 14 weeks' gestation				0.297

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 09 14:56:16 2015.

Part 8: summaries of safety outcomes

Does progesterone prophylaxis to prevent preterm labour improve outcome?	
OPPTIMUM	
Final report tables	
Part 8: summaries of safety outcomes	
v1.0	
2 October 2015	
Martina Messow	
Robertson Centre for Biostatistics	
EudraCT number	2007-007950-77
CTA number	22931/0009/001-0001 revised by MHRA to 01384/0208/001
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ISRCTN	ISRCTN14568373
Co-sponsors	University of Edinburgh/NHS Lothian
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Protocol version	15.1 (1 April 2015)
SAP version	1.1 (8 September 2015)

CTA, Clinical Trial Authorisation; EudraCT, European Union Drug Regulating Authorities Clinical Trials; MREC, Multicentre Research Ethics Committee; SAP, statistical analysis plan.

TABLE 124 Pregnancy complications

		Trial group	
Outcome	All	Placebo	Progesterone
Obstetric cholestasis			
N_{obs} (N_{miss})	1182 (1)	589 (1)	593 (0)
No, *n* (%)	1172 (99.2)	583 (99.0)	589 (99.3)
Yes, *n* (%)	10 (0.8)	6 (1.0)	4 (0.7)
Hypertension			
N_{obs} (N_{miss})	1183 (0)	590 (0)	593 (0)
No, *n* (%)	1136 (96.0)	566 (95.9)	570 (96.1)
Yes, *n* (%)	47 (4.0)	24 (4.1)	23 (3.9)
Pre-eclampsia			
N_{obs} (N_{miss})	1183 (0)	590 (0)	593 (0)
No, *n* (%)	1162 (98.2)	579 (98.1)	583 (98.3)
Yes, *n* (%)	21 (1.8)	11 (1.9)	10 (1.7)
Eclampsia			
N_{obs} (N_{miss})	1183 (0)	590 (0)	593 (0)
No, *n* (%)	1182 (99.9)	589 (99.8)	593 (100.0)
Yes, *n* (%)	1 (0.1)	1 (0.2)	0 (0.0)

continued

TABLE 124 Pregnancy complications (*continued*)

Outcome	All	Trial group	
		Placebo	Progesterone
Preterm membrane rupture			
N_{obs} (N_{miss})	1183 (0)	590 (0)	593 (0)
No, *n* (%)	1046 (88.4)	518 (87.8)	528 (89.0)
Yes, *n* (%)	137 (11.6)	72 (12.2)	65 (11.0)
Antepartum haemorrhage			
N_{obs} (N_{miss})	1183 (0)	590 (0)	593 (0)
No, *n* (%)	1110 (93.8)	554 (93.9)	556 (93.8)
Yes, *n* (%)	73 (6.2)	36 (6.1)	37 (6.2)
Confirmed deep-vein thrombosis			
N_{obs} (N_{miss})	1183 (0)	590 (0)	593 (0)
No, *n* (%)	1181 (99.8)	588 (99.7)	593 (100.0)
Yes, *n* (%)	2 (0.2)	2 (0.3)	0 (0.0)
Gestational diabetes			
N_{obs} (N_{miss})	1183 (0)	590 (0)	593 (0)
No, *n* (%)	1119 (94.6)	553 (93.7)	566 (95.4)
Yes, *n* (%)	64 (5.4)	37 (6.3)	27 (4.6)
Cerclage			
N_{obs} (N_{miss})	728 (455)	360 (230)	368 (225)
No, *n* (%)	648 (89.0)	321 (89.2)	327 (88.9)
Yes, *n* (%)	80 (11.0)	39 (10.8)	41 (11.1)
Other maternal complication			
N_{obs} (N_{miss})	1183 (0)	590 (0)	593 (0)
No, *n* (%)	853 (72.1)	426 (72.2)	427 (72.0)
Yes, *n* (%)	330 (27.9)	164 (27.8)	166 (28.0)

N_{miss}, number of women with missing data; N_{obs}, number of observations.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 13:41:37 2015.

TABLE 125 Pregnancy complications: other fetal

Outcome	All	Trial group	
		Placebo	Progesterone
Other fetal complication			
N_{obs} (N_{miss})	1183 (0)	590 (0)	593 (0)
No, *n* (%)	1146 (96.9)	572 (96.9)	574 (96.8)
Yes, *n* (%)	37 (3.1)	18 (3.1)	19 (3.2)
Abdominal circumference < 5th centile			
N_{obs} (N_{miss})	37 (0)	18 (0)	19 (0)
No, *n* (%)	27 (73.0)	14 (77.8)	13 (68.4)
Yes, *n* (%)	10 (27.0)	4 (22.2)	6 (31.6)

TABLE 125 Pregnancy complications: other fetal (*continued*)

Outcome	All	Trial group	
		Placebo	Progesterone
Liquor volume reduced			
N_{obs} (N_{miss})	37 (0)	18 (0)	19 (0)
No, *n* (%)	25 (67.6)	12 (66.7)	13 (68.4)
Yes, *n* (%)	12 (32.4)	6 (33.3)	6 (31.6)
Doppler > 95th centile (umbilical artery)			
N_{obs} (N_{miss})	37 (0)	18 (0)	19 (0)
No, *n* (%)	35 (94.6)	17 (94.4)	18 (94.7)
Yes, *n* (%)	2 (5.4)	1 (5.6)	1 (5.3)
Absent end-diastolic flow (umbilical artery)			
N_{obs} (N_{miss})	37 (0)	18 (0)	19 (0)
No, *n* (%)	36 (97.3)	18 (100.0)	18 (94.7)
Yes, *n* (%)	1 (2.7)	0 (0.0)	1 (5.3)
Reversed end-diastolic flow (umbilical artery)			
N_{obs} (N_{miss})	37 (0)	18 (0)	19 (0)
No, *n* (%)	35 (94.6)	17 (94.4)	18 (94.7)
Yes, *n* (%)	2 (5.4)	1 (5.6)	1 (5.3)
Abnormal cardiotocogram			
N_{obs} (N_{miss})	37 (0)	18 (0)	19 (0)
No, *n* (%)	27 (73.0)	11 (61.1)	16 (84.2)
Yes, *n* (%)	10 (27.0)	7 (38.9)	3 (15.8)

N_{miss}, number of women with missing data; N_{obs}, number of observations.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 13:41:39 2015.

TABLE 126 Antenatal hospital admissions: number of admissions and number of days in hospital per woman

Outcome	All	Trial group	
		Placebo	Progesterone
Number of antenatal hospital admissions (per woman)			
N_{obs} (N_{miss})	1160 (23)	581 (9)	579 (14)
Mean (SD)	0.7 (1.2)	0.7 (1.3)	0.6 (1.1)
Median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)
Range	0.0–10.0	0.0–10.0	0.0–8.0
Number of antenatal hospital admissions for threatened preterm labour			
N_{obs} (N_{miss})	1160 (23)	581 (9)	579 (14)
Mean (SD)	0.3 (0.8)	0.4 (0.9)	0.3 (0.7)
Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Range	0.0–9.0	0.0–9.0	0.0–5.0

continued

TABLE 126 Antenatal hospital admissions: number of admissions and number of days in hospital per woman (*continued*)

Outcome	All	Trial group	
		Placebo	Progesterone
Number of antenatal hospital admissions for other reasons			
N_{obs} (N_{miss})	1160 (23)	581 (9)	579 (14)
Mean (SD)	0.3 (0.8)	0.4 (0.8)	0.3 (0.8)
Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Range	0.0–7.0	0.0–7.0	0.0–6.0
Total number of days in hospital antenatally (per woman)			
N_{obs} (N_{miss})	1153 (30)	576 (14)	577 (16)
Mean (SD)	2.9 (7.6)	3.0 (7.6)	2.7 (7.7)
Median (IQR)	0.0 (0.0–2.0)	0.0 (0.0–3.0)	0.0 (0.0–2.0)
Range	0.0–97.0	0.0–97.0	0.0–84.0
Total number of days in hospital for threatened preterm labour			
N_{obs} (N_{miss})	1156 (27)	579 (11)	577 (16)
Mean (SD)	1.7 (5.8)	1.8 (6.2)	1.6 (5.3)
Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Range	0.0–97.0	0.0–97.0	0.0–56.0
Total number of days in hospital for other reasons			
N_{obs} (N_{miss})	1157 (26)	578 (12)	579 (14)
Mean (SD)	1.2 (5.0)	1.2 (4.3)	1.1 (5.6)
Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Range	0.0–84.0	0.0–39.0	0.0–84.0

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 13:41:48 2015.

TABLE 127 Antenatal hospital admissions: number of admissions per indication on admission and discharge diagnosis

Outcome	All, *n* (%)	Trial group, *n* (%)	
		Placebo	Progesterone
Number of hospital admissions per indication for admission (multiple indications possible)			
Total number of admissions, *n*	381	206	175
Hypertension	18 (4.7)	11 (5.3)	7 (4.0)
Pre-eclampsia	8 (2.1)	4 (1.9)	4 (2.3)
Eclampsia	0 (0.0)	0 (0.0)	0 (0.0)
Membranes ruptured	18 (4.7)	7 (3.4)	11 (6.3)
Antepartum haemorrhage	39 (10.2)	20 (9.7)	19 (10.9)
Suspected deep-vein thrombosis	1 (0.3)	1 (0.5)	0 (0.0)

TABLE 127 Antenatal hospital admissions: number of admissions per indication on admission and discharge diagnosis (*continued*)

Outcome	All, *n* (%)	Trial group, *n* (%)	
		Placebo	Progesterone
Diabetes	10 (2.6)	4 (1.9)	6 (3.4)
Abdominal pain	91 (23.9)	44 (21.4)	47 (26.9)
Symphyseal pain	7 (1.8)	3 (1.5)	4 (2.3)
Other maternal	204 (53.5)	113 (54.9)	91 (52.0)
Other fetal	11 (2.9)	8 (3.9)	3 (1.7)
Abdominal circumference	2 (0.5)	1 (0.5)	1 (0.6)
Reduced liquor volume	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal Doppler	0 (0.0)	0 (0.0)	0 (0.0)
Absent end-diastolic flow	0 (0.0)	0 (0.0)	0 (0.0)
Reverse end-diastolic flow	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal cardiotocogram	1 (0.3)	1 (0.5)	0 (0.0)
None	12 (3.1)	7 (3.4)	5 (2.9)
Number of hospital admissions per discharge diagnosis (multiple indications possible)			
Hypertension	12 (3.1)	8 (3.9)	4 (2.3)
Pre-eclampsia	6 (1.6)	3 (1.5)	3 (1.7)
Eclampsia	0 (0.0)	0 (0.0)	0 (0.0)
Membranes ruptured	9 (2.4)	3 (1.5)	6 (3.4)
Antepartum haemorrhage	37 (9.7)	17 (8.3)	20 (11.4)
Suspected deep-vein thrombosis	1 (0.3)	1 (0.5)	0 (0.0)
Diabetes	8 (2.1)	3 (1.5)	5 (2.9)
Abdominal pain	63 (16.5)	33 (16.0)	30 (17.1)
Symphyseal pain	8 (2.1)	3 (1.5)	5 (2.9)
Other maternal	214 (56.2)	123 (59.7)	91 (52.0)
Other fetal	9 (2.4)	7 (3.4)	2 (1.1)
Abdominal circumference	0 (0.0)	0 (0.0)	0 (0.0)
Reduced liquor volume	1 (0.3)	1 (0.5)	0 (0.0)
Doppler	0 (0.0)	0 (0.0)	0 (0.0)
Absent end-diastolic flow	0 (0.0)	0 (0.0)	0 (0.0)
Reverse end-diastolic flow	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal cardiotocogram	1 (0.3)	0 (0.0)	1 (0.6)
None	38 (10.0)	18 (8.7)	20 (11.4)

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 13:41:51 2015.

TABLE 128 Antenatal hospital admissions: number of women with at least one admission for each indication on admission and discharge diagnosis

Outcome	All	All, *n* (%)	Placebo, *n* (%)
Indication for hospitalisation, *n*	242	135	107
Hypertension	12 (5.0)	7 (5.2)	5 (4.7)
Pre-eclampsia	8 (3.3)	4 (3.0)	4 (3.7)
Eclampsia,	0 (0.0)	0 (0.0)	0 (0.0)
Membranes ruptured	16 (6.6)	7 (5.2)	9 (8.4)
Antepartum haemorrhage	28 (11.6)	16 (11.9)	12 (11.2)
Suspected deep-vein thrombosis	1 (0.4)	1 (0.7)	0 (0.0)
Diabetes	5 (2.1)	3 (2.2)	2 (1.9)
Abdominal pain	73 (30.2)	37 (27.4)	36 (33.6)
Symphyseal pain	7 (2.9)	3 (2.2)	4 (3.7)
Other maternal	142 (58.7)	79 (58.5)	63 (58.9)
Other fetal	9 (3.7)	6 (4.4)	3 (2.8)
Abdominal circumference	2 (0.8)	1 (0.7)	1 (0.9)
Reduced liquor volume	0 (0.0)	0 (0.0)	0 (0.0)
Doppler	0 (0.0)	0 (0.0)	0 (0.0)
Absent end-diastolic flow	0 (0.0)	0 (0.0)	0 (0.0)
Reverse end-diastolic flow	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal cardiotocogram	1 (0.4)	1 (0.7)	0 (0.0)
None	10 (4.1)	7 (5.2)	3 (2.8)
Number of women discharged from hospital at least once per discharge diagnosis (multiple indications possible)			
Hypertension	7 (2.9)	5 (3.7)	2 (1.9)
Pre-eclampsia	6 (2.5)	3 (2.2)	3 (2.8)
Eclampsia	0 (0.0)	0 (0.0)	0 (0.0)
Membranes ruptured	9 (3.7)	3 (2.2)	6 (5.6)
Antepartum haemorrhage	23 (9.5)	12 (8.9)	11 (10.3)
Suspected deep-vein thrombosis	1 (0.4)	1 (0.7)	0 (0.0)
Diabetes	4 (1.7)	2 (1.5)	2 (1.9)
Abdominal pain	51 (21.1)	27 (20.0)	24 (22.4)
Symphyseal pain	8 (3.3)	3 (2.2)	5 (4.7)
Other maternal	153 (63.2)	90 (66.7)	63 (58.9)
Other fetal	9 (3.7)	7 (5.2)	2 (1.9)
Abdominal circumference	0 (0.0)	0 (0.0)	0 (0.0)
Reduced liquor volume	1 (0.4)	1 (0.7)	0 (0.0)
Doppler	0 (0.0)	0 (0.0)	0 (0.0)
Absent end-diastolic flow	0 (0.0)	0 (0.0)	0 (0.0)
Reverse end-diastolic flow	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal cardiotocogram	1 (0.4)	0 (0.0)	1 (0.9)
None	31 (12.8)	16 (11.9)	15 (14.0)

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 13:41:53 2015.

TABLE 129 Antenatal hospital admissions: other details of hospital admissions

Outcome	All	Trial group	
		Placebo	Progesterone
Number of hospital admissions with tocolysis, *n* (%)	33 (8.5)	18 (8.1)	15 (8.9)
Type of tocolysis			
N_{obs} (N_{miss})	33 (0)	18 (0)	15 (0)
Nifedipine, *n* (%)	17 (51.5)	8 (44.4)	9 (60.0)
Indomethacine, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Atosiban, *n* (%)	15 (45.5)	9 (50.0)	6 (40.0)
Other, *n* (%)	1 (3.0)	1 (5.6)	0 (0.0)
Number of hospital admissions with steroid, *n* (%)	160 (41.0)	77 (34.8)	83 (49.1)
Number of hospital admissions with antibiotic, *n* (%)	94 (24.1)	54 (24.4)	40 (23.7)
Number of hospital admissions with suture, *n* (%)	18 (4.6)	10 (4.5)	8 (4.7)
Number of hospital admissions with magnesium, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)

N_{miss}, number of women with missing data; N_{obs}, number of observations.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 13:41:55 2015

TABLE 130 Labour

Outcome	All	Trial group	
		Placebo	Progesterone
Duration of first stage (hours)			
N_{obs} (N_{miss})	933 (250)	463 (127)	470 (123)
Mean (SD)	4.2 (5.2)	4.1 (5.1)	4.3 (5.3)
Median (IQR)	3.0 (1.2–5.4)	2.8 (1.2–5.3)	3.2 (1.3–5.5)
Range	0.0–70.0	0.0–56.0	0.0–70.0
Duration of second stage (minutes)			
N_{obs} (N_{miss})	933 (250)	462 (128)	471 (122)
Mean (SD)	44.1 (113.9)	47.0 (132.8)	41.2 (91.6)
Median (IQR)	16.0 (6.0–40.0)	16.0 (6.0–42.8)	16.0 (5.0–39.0)
Range	0.0–1800.0	0.0–1800.0	0.0–1383.0
Duration of third stage (minutes)			
N_{obs} (N_{miss})	942 (241)	465 (125)	477 (116)
Mean (SD)	16.6 (49.0)	17.0 (46.2)	16.1 (51.6)
Median (IQR)	7.0 (4.0–11.0)	6.0 (4.0–11.0)	7.0 (5.0–10.0)
Range	0.0–900.0	0.0–600.0	0.0–900.0
Membranes ruptured			
N_{obs} (N_{miss})	1149 (34)	575 (15)	574 (19)
No, *n* (%)	235 (20.5)	109 (19.0)	126 (22.0)
Yes, *n* (%)	914 (79.5)	466 (81.0)	448 (78.0)

continued

TABLE 130 Labour (*continued*)

Outcome	All	Trial group	
		Placebo	Progesterone
Type of membrane rupture			
N_{obs} (N_{miss})	916 (267)	468 (122)	448 (145)
Artificial, *n* (%)	253 (27.6)	131 (28.0)	122 (27.2)
Spontaneous, *n* (%)	663 (72.4)	337 (72.0)	326 (72.8)
Analgesic			
N_{obs} (N_{miss})	1150 (33)	576 (14)	574 (19)
No, *n* (%)	217 (18.9)	121 (21.0)	96 (16.7)
Yes, *n* (%)	933 (81.1)	455 (79.0)	478 (83.3)
Analgesics used			
General anaesthetic, *n* (%)	28 (2.4)	16 (2.7)	12 (2.0)
Epidural, *n* (%)	388 (32.8)	191 (32.4)	197 (33.2)
Opiates, *n* (%)	176 (14.9)	88 (14.9)	88 (14.8)
Entonox, *n* (%)	572 (48.4)	269 (45.6)	303 (51.1)
Other, *n* (%)	65 (5.5)	34 (5.8)	31 (5.2)

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 13:41:59 2015.

TABLE 131 Delivery

Outcome	All	Trial group	
		Placebo	Progesterone
Delivery method			
N_{obs} (N_{miss})	1154 (29)	578 (12)	576 (17)
Spontaneous vaginal delivery, *n* (%)	755 (65.4)	380 (65.7)	375 (65.1)
Lower segment caesarean section in labour, *n* (%)	115 (10.0)	58 (10.0)	57 (9.9)
Lower segment caesarean section pre labour, *n* (%)	176 (15.3)	92 (15.9)	84 (14.6)
Forceps, *n* (%)	48 (4.2)	21 (3.6)	27 (4.7)
Ventouse, *n* (%)	38 (3.3)	18 (3.1)	20 (3.5)
Vaginal breech (spontaneous or assisted), *n* (%)	22 (1.9)	9 (1.6)	13 (2.3)
Reason for assisted delivery, *n* (%)			
Abnormal cardiotocogram	89 (7.5)	45 (7.6)	44 (7.4)
Abnormal pH	1 (0.1)	0 (0.0)	1 (0.2)
Slow stage 1	14 (1.2)	4 (0.7)	10 (1.7)
Slow stage 2	64 (5.4)	29 (4.9)	35 (5.9)
Malpresentation	54 (4.6)	30 (5.1)	24 (4.0)
Suspected maternal compromise	29 (2.5)	18 (3.1)	11 (1.9)

TABLE 131 Delivery (*continued*)

Outcome	All	Trial group	
		Placebo	Progesterone
Suspected fetal compromise	60 (5.1)	33 (5.6)	27 (4.6)
Obstetric history	85 (7.2)	39 (6.6)	46 (7.8)
Other	76 (6.4)	37 (6.3)	39 (6.6)
Blood loss, ml			
N_{obs} (N_{miss})	1144 (39)	572 (18)	572 (21)
Mean (SD)	405.5 (375.8)	387.4 (356.4)	423.7 (393.8)
Median (IQR)	300.0 (200.0–500.0)	300.0 (200.0–450.0)	300.0 (200.0–500.0)
Range	0.0–4000.0	0.0–4000.0	0.0–4000.0
Suture			
N_{obs} (N_{miss})	1151 (32)	578 (12)	573 (20)
No, *n* (%)	793 (68.9)	413 (71.5)	380 (66.3)
Yes, *n* (%)	358 (31.1)	165 (28.5)	193 (33.7)
Reason for suture			
Episiotomy, *n* (%)	98 (8.3)	48 (8.1)	50 (8.4)
Degree 1 tear, *n* (%)	46 (3.9)	21 (3.6)	25 (4.2)
Degree 2 tear, *n* (%)	201 (17.0)	91 (15.4)	110 (18.5)
Degree 3 tear, *n* (%)	23 (1.9)	11 (1.9)	12 (2.0)
Blood transfusion			
N_{obs} (N_{miss})	1152 (31)	578 (12)	574 (19)
No, *n* (%)	1124 (97.6)	568 (98.3)	556 (96.9)
Yes, *n* (%)	28 (2.4)	10 (1.7)	18 (3.1)
Antibiotics during labour and delivery			
N_{obs} (N_{miss})	1151 (32)	578 (12)	573 (20)
No, *n* (%)	963 (83.7)	482 (83.4)	481 (83.9)
Yes, *n* (%)	188 (16.3)	96 (16.6)	92 (16.1)
Surgical procedure required			
N_{obs} (N_{miss})	1153 (30)	578 (12)	575 (18)
No, *n* (%)	1120 (97.1)	563 (97.4)	557 (96.9)
Yes, *n* (%)	33 (2.9)	15 (2.6)	18 (3.1)
Duration of hospital stay (days)			
N_{obs} (N_{miss})	1144 (39)	577 (13)	567 (26)
Mean (SD)	3.3 (3.3)	3.2 (2.2)	3.3 (4.1)
Median (IQR)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)
Range	1.0–86.0	1.0–19.0	1.0–86.0

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 13:42:02 2015.

TABLE 132 Placental examination

Result of placental examination	All	Trial group	
		Placebo	Progesterone
N_{obs} (N_{miss})	167 (1016)	84 (506)	83 (510)
None, *n* (%)	113 (67.7)	57 (67.9)	56 (67.5)
Chorioamnionitis, *n* (%)	19 (11.4)	10 (11.9)	9 (10.8)
Chorioamnionitis and funisitis, *n* (%)	35 (21.0)	17 (20.2)	18 (21.7)

N_{miss}, number of women with missing data; N_{obs}, number of observations.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 13:42:03 2015.

TABLE 133 Post-partum complications

Outcome	All	Trial group	
		Placebo	Progesterone
Thrombophlebitis			
N_{obs} (N_{miss})	1157 (26)	580 (10)	577 (16)
No, *n* (%)	1155 (99.8)	579 (99.8)	576 (99.8)
Yes, *n* (%)	2 (0.2)	1 (0.2)	1 (0.2)
Deep-vein thrombosis			
N_{obs} (N_{miss})	1157 (26)	580 (10)	577 (16)
No, *n* (%)	1157 (100.0)	580 (100.0)	577 (100.0)
Wound infection			
N_{obs} (N_{miss})	1157 (26)	580 (10)	577 (16)
No, *n* (%)	1144 (98.9)	574 (99.0)	570 (98.8)
Yes, *n* (%)	13 (1.1)	6 (1.0)	7 (1.2)
Urine infection			
N_{obs} (N_{miss})	1157 (26)	580 (10)	577 (16)
No, *n* (%)	1150 (99.4)	574 (99.0)	576 (99.8)
Yes, *n* (%)	7 (0.6)	6 (1.0)	1 (0.2)
Wound breakdown			
N_{obs} (N_{miss})	1157 (26)	580 (10)	577 (16)
No, *n* (%)	1154 (99.7)	579 (99.8)	575 (99.7)
Yes, *n* (%)	3 (0.3)	1 (0.2)	2 (0.3)
Mastitis			
N_{obs} (N_{miss})	1157 (26)	580 (10)	577 (16)
No, *n* (%)	1155 (99.8)	579 (99.8)	576 (99.8)
Yes, *n* (%)	2 (0.2)	1 (0.2)	1 (0.2)
Unknown infection			
N_{obs} (N_{miss})	1157 (26)	580 (10)	577 (16)
No, *n* (%)	1145 (99.0)	574 (99.0)	571 (99.0)
Yes, *n* (%)	12 (1.0)	6 (1.0)	6 (1.0)

TABLE 133 Post-partum complications (*continued*)

Outcome	All	Trial group	
		Placebo	Progesterone
Post-partum haemorrhage			
N_{obs} (N_{miss})	1157 (26)	580 (10)	577 (16)
No, *n* (%)	1070 (92.5)	539 (92.9)	531 (92.0)
Yes, *n* (%)	87 (7.5)	41 (7.1)	46 (8.0)
Depression			
N_{obs} (N_{miss})	1157 (26)	580 (10)	577 (16)
No, *n* (%)	1155 (99.8)	579 (99.8)	576 (99.8)
Yes, *n* (%)	2 (0.2)	1 (0.2)	1 (0.2)
Other complication			
N_{obs} (N_{miss})	1157 (26)	580 (10)	577 (16)
No, *n* (%)	1099 (95.0)	553 (95.3)	546 (94.6)
Yes, *n* (%)	58 (5.0)	27 (4.7)	31 (5.4)
No complication			
N_{obs} (N_{miss})	1157 (26)	580 (10)	577 (16)
No, *n* (%)	173 (15.0)	83 (14.3)	90 (15.6)
Yes, *n* (%)	984 (85.0)	497 (85.7)	487 (84.4)

N_{miss}, number of women with missing data; N_{obs}, number of observations.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 13:42:05 2015.

TABLE 134 Child assessment at birth

Outcome	All	Trial group	
		Placebo	Progesterone
Sex			
N_{obs} (N_{miss})	1156 (27)	578 (12)	578 (15)
Male, *n* (%)	582 (50.3)	289 (50.0)	293 (50.7)
Female, *n* (%)	573 (49.6)	289 (50.0)	284 (49.1)
Indeterminate, *n* (%)	1 (0.1)	0 (0.0)	1 (0.2)
Birthweight (g)			
N_{obs} (N_{miss})	1154 (29)	577 (13)	577 (16)
Mean (SD)	2849 (866)	2822 (884)	2875 (847)
Median (IQR)	3000 (2470–3448)	2960 (2350–3420)	3040 (2550–3450)
Range	380–6400	455–6400	380–5025
Apgar score at 1 minute			
N_{obs} (N_{miss})	1110 (73)	553 (37)	557 (36)
Mean (SD)	8.1 (1.9)	8.1 (1.8)	8.1 (1.9)
Median (IQR)	9.0 (8.0–9.0)	9.0 (8.0–9.0)	9.0 (8.0–9.0)
Range	0.0–10.0	0.0–10.0	0.0–10.0

continued

TABLE 134 Child assessment at birth (*continued*)

Outcome	All	Trial group	
		Placebo	Progesterone
Apgar score at 5 minutes			
N_{obs} (N_{miss})	1115 (68)	555 (35)	560 (33)
Mean (SD)	9.1 (1.4)	9.1 (1.3)	9.0 (1.4)
Median (IQR)	9.0 (9.0–10.0)	9.0 (9.0–10.0)	9.0 (9.0–10.0)
Range	0.0–10.0	0.0–10.0	0.0–10.0
Length of hospital stay (days)			
N_{obs} (N_{miss})	1118 (65)	556 (34)	562 (31)
Mean (SD)	9.1 (20.6)	9.8 (20.9)	8.4 (20.2)
Median (IQR)	2.0 (1.0–5.0)	2.0 (1.0–6.0)	2.0 (1.0–4.0)
Range	0.0–220.0	0.0–152.0	0.0–220.0

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 13:42:08 2015.

TABLE 135 Child assessment at 2 years

Outcome	All	Trial group	
		Placebo	Progesterone
Weight (kg)			
N_{obs} (N_{miss})	687 (496)	355 (235)	332 (261)
Mean (SD)	13.3 (2.7)	13.2 (2.6)	13.4 (2.7)
Median (IQR)	13.0 (12.0–14.2)	13.0 (11.9–14.2)	13.1 (12.0–14.2)
Range	7.0–45.4	7.0–39.3	9.0–45.4
Height (cm)			
N_{obs} (N_{miss})	716 (467)	369 (221)	347 (246)
Mean (SD)	87.3 (9.5)	87.2 (10.7)	87.4 (7.9)
Median (IQR)	88.0 (85.0–91.0)	88.0 (84.1–91.4)	87.6 (85.0–91.0)
Range	0.9–111.0	0.9–111.0	0.9–109.0
Head circumference (cm)			
N_{obs} (N_{miss})	686 (497)	354 (236)	332 (261)
Mean (SD)	49.2 (5.7)	48.9 (4.6)	49.6 (6.7)
Median (IQR)	49.0 (48.0–50.4)	49.0 (48.0–50.3)	49.1 (48.0–50.5)
Range	0.5–98.0	0.5–84.9	0.5–98.0
Respiration rate (breaths per minute)			
N_{obs} (N_{miss})	76 (1107)	38 (552)	38 (555)
Mean (SD)	23.6 (11.3)	25.2 (14.1)	21.9 (7.3)
Median (IQR)	23.0 (16.0–28.0)	24.0 (20.0–28.0)	22.0 (16.0–27.5)
Range	12.0–98.0	12.0–98.0	12.0–38.0

TABLE 135 Child assessment at 2 years (*continued*)

Outcome	All	Trial group	
		Placebo	Progesterone
Heart rate (beats per minute)			
N_{obs} (N_{miss})	73 (1110)	36 (554)	37 (556)
Mean (SD)	109.7 (18.3)	111.4 (17.3)	108.1 (19.3)
Median (IQR)	110.0 (100.0–119.0)	111.0 (102.2–118.0)	110.0 (100.0–120.0)
Range	40.0–170.0	68.0–170.0	40.0–160.0
Systolic blood pressure (mmHg)			
N_{obs} (N_{miss})	46 (1137)	24 (566)	22 (571)
Mean (SD)	98.7 (14.0)	96.6 (13.2)	100.9 (14.7)
Median (IQR)	98.5 (90.2–107.8)	97.0 (89.2–103.5)	103.5 (91.8–108.0)
Range	59.0–128.0	64.0–123.0	59.0–128.0
Diastolic blood pressure (mmHg)			
N_{obs} (N_{miss})	37 (1146)	20 (570)	17 (576)
Mean (SD)	64.2 (12.3)	66.0 (12.9)	62.1 (11.7)
Median (IQR)	64.0 (54.0–70.0)	65.5 (58.5–72.5)	63.0 (54.0–68.0)
Range	42.0–90.0	42.0–90.0	44.0–85.0

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 02 13:42:09 2015.

Part 9: additional analyses of primary outcomes (primary protocol analysis, multiple imputation and adjusted analysis)

Does progesterone prophylaxis to prevent preterm labour improve outcome?

OPPTIMUM

Final report tables

Part 9: additional analyses of primary outcomes (PP analysis, multiple imputation, adjusted analysis)

v1.1

20 November 2015

Martina Messow

Robertson Centre for Biostatistics

EudraCT number	2007-007950-77
CTA number	22931/0009/001-0001 revised by MHRA to 01384/0208/001
MREC number	08/MRE00/6
ISRCTN	ISRCTN14568373
Co-sponsors	University of Edinburgh/NHS Lothian
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Protocol version	15.1 (1 April 2015)
SAP version	1.1 (8 September 2015)

CTA, Clinical Trial Authorisation; EudraCT, European Union Drug Regulating Authorities Clinical Trials; MREC, Multicentre Research Ethics Committee; SAP, statistical analysis plan.

TABLE 136 Mixed effects logistic regression model for the effect of treatment on the primary obstetric outcome death or delivery before 34 weeks' gestation adjusted for previous pregnancy of ≥ 14 weeks' gestation and study centre as a random effect (PP population)

Parameter	OR	95% CI	*p*-value
Treatment (progesterone vs. placebo)	0.86	0.55 to 1.35	0.512
Previous pregnancy of ≥ 14 weeks' gestation	1.21	0.50 to 2.92	0.675
$n = 687$			

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Nov 20 11:27:20 2015.

TABLE 137 Mixed effects logistic regression model for the effect of treatment on the primary neonatal outcome death, brain injury or severe chronic lung disease adjusted for previous pregnancy of ≥ 14 weeks' gestation and study centre as a random effect (PP population)

Parameter	OR	95% CI	*p*-value
Treatment (progesterone vs. placebo)	0.63	0.35 to 1.15	0.113
Previous pregnancy of ≥ 14 weeks' gestation	1.41	0.42 to 4.76	0.583
$n = 682$			

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Nov 20 11:27:20 2015

TABLE 138 Mixed effects linear regression model for the effect of treatment on the primary childhood outcome Bayley-III cognitive composite score adjusted for previous pregnancy of ≥ 14 weeks' gestation and study centre as a random effect (PP population)

Parameter	Parameter estimate	95% CI	*p*-value
Treatment (progesterone vs. placebo)	0.49	–2.22 to 3.20	0.725
Previous pregnancy of ≥ 14 weeks' gestation	–7.13	–12.29 to –1.97	0.007
$n = 575$			

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Nov 20 11:27:20 2015.

TABLE 139 Mixed effects logistic regression model for the effect of treatment on the primary childhood outcome survival adjusted for previous pregnancy of ≥ 14 weeks' gestation and study centre as a random effect (PP population)

Parameter	OR	95% CI	*p*-value
Treatment (progesterone vs. placebo)	0.92	0.43 to 1.97	0.831
Previous pregnancy of ≥ 14 weeks' gestation	0.00	0.00 to infinity	1.000
$n = 638$			

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Nov 20 11:27:22 2015.

TABLE 140 Mixed effects proportional hazards regression model for the effect of treatment on the primary childhood outcome survival adjusted for previous pregnancy of ≥ 14 weeks' gestation and study centre as a random effect (PP population)

Parameter	Hazard ratio	95% CI	*p*-value
Treatment (progesterone vs. placebo)	1.08	0.40 to 2.87	0.884
Previous pregnancy of ≥ 14 weeks' gestation	NA	NA to NA	NA
$n = 687$			

NA, not appropriate.
Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Nov 20 11:27:22 2015.

TABLE 141 Sensitivity analysis: multiple imputation of primary outcomes

Outcome	Parameter estimate or hazard ratio	95% CI	*p*-value
Variables used for predicting outcome: previous pregnancy of ≥ 14 weeks' gestation, high/low risk, maternal age and sex			
Obstetric outcome	0.866	0.640 to 1.170	0.348
Neonatal outcome	0.728	0.487 to 1.088	0.112
Variables used for predicting outcome: gestational age, birth weight, chronic lung disease, brain injury, previous pregnancy of ≥ 14 weeks' gestation, high/low risk, maternal age and sex			
Alive at 2 years	0.760	0.392 to 1.476	0.418
Bayley-III cognitive composite score	–0.019	–0.372 to 0.334	0.908
Variables used for predicting outcome: birth weight, chronic lung disease, brain injury, previous pregnancy of ≥ 14 weeks' gestation, high/low risk, maternal age and sex			
Alive at 2 years	0.744	0.384 to 1.441	0.380
Bayley-III cognitive composite score	–0.051	–0.371 to 0.269	0.737

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Nov 20 11:27:38 2015.

TABLE 142 Analysis of the obstetric outcome adjusted for previous pregnancy of ≥ 14 weeks' gestation, cervical length at baseline and risk group

Variable	OR	95% CI	*p*-value
Treatment (progesterone vs. placebo)	0.86	0.57 to 1.31	0.495
Previous pregnancy of ≥ 14 weeks' gestation	2.01	0.92 to 4.39	0.082
Cervical length at baseline	0.96	0.94 to 0.98	< 0.001
High risk vs. low risk	3.06	1.96 to 4.78	< 0.001
$n = 696$			

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Nov 20 11:27:38 2015.

TABLE 143 Analysis of Bayley-III cognitive composite score adjusted for previous pregnancy of ≥ 14 weeks' gestation, age, time in education, ethnicity (black vs. other ethnicities), height, number of previous live births, number of previous pregnancies and risk group

Variable	Parameter estimate	95% CI	*p*-value
Treatment (progesterone vs. placebo)	–0.52	–2.74 to 1.69	0.645
Previous pregnancy of ≥ 14 weeks' gestation	–2.94	–7.94 to 2.05	0.248
Age	0.40	0.18 to 0.62	< 0.001
Time in education	0.52	0.13 to 0.90	0.008
Ethnicity (black vs. all other)	–4.31	–7.98 to –0.65	0.021
Height	0.34	0.17 to 0.51	< 0.001
Number of previous live births	–1.85	–3.03 to –0.68	0.002
Number of previous pregnancies	–0.64	–1.43 to 0.15	0.114
High risk vs. low risk	–6.46	–9.07 to –3.86	< 0.001
$n = 811$			

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Nov 20 11:27:39 2015.

Additional analyses for paper

Does progesterone prophylaxis to prevent preterm labour improve outcome?	
OPPTIMUM	
Additional analyses for paper	
v1.0	
23 October 2015	
Martina Messow	
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EudraCT number	2007-007950-77
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CTA, Clinical Trial Authorisation; EudraCT, European Union Drug Regulating Authorities Clinical Trials; MREC, Multicentre Research Ethics Committee; SAP, statistical analysis plan.

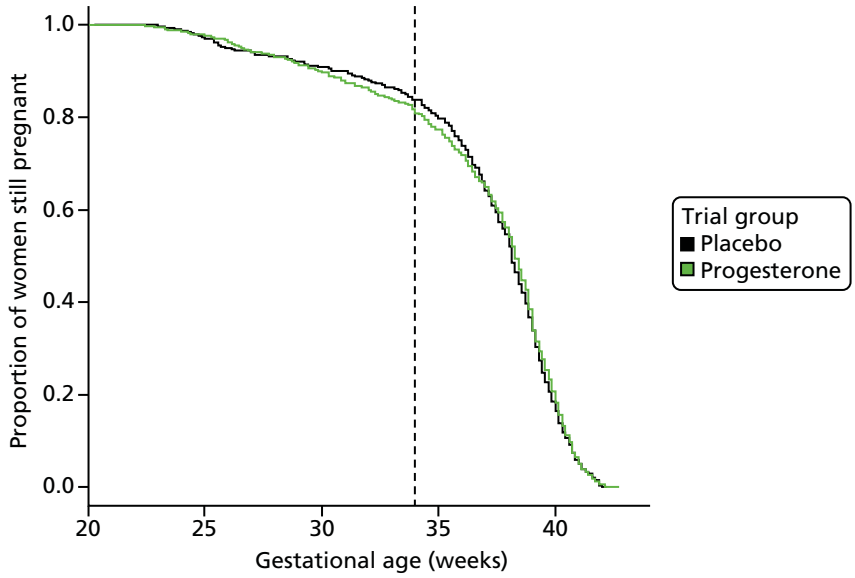

FIGURE 4 Survival curve for gestational age at delivery. These results have not been independently checked. Every effort has been made to ensure their accuracy, but the possibility of error remains. OPPTIMUM Output created by OPPTIMUM_main_v2_0.R. Last run on Friday 23 October 2015 at 13:07:12.

TABLE 144 Age at Bayley-III cognitive composite score assessment (ITT population)

		Trial group	
Parameter or outcome	**All**	**Placebo**	**Progesterone**
Age (weeks) at Bayley-III cognitive composite score assessment in those with cognitive composite score available			
N_{obs} (N_{miss})	830 (3)	422 (1)	408 (2)
Mean (SD)	115.7 (17.1)	116.1 (18.3)	115.3 (15.8)
Median (IQR)	111.1 (104.3–122.0)	111.6 (104.6–122.2)	110.4 (104.0–121.5)
Range	2.6–184.4	2.6–180.0	94.0–184.4
Age (weeks) at Bayley-III cognitive composite score assessment in those with cognitive composite score available and in the 22- to 26-month window			
N_{obs} (N_{miss})	446 (0)	221 (0)	225 (0)
Mean (SD)	104.6 (4.5)	104.8 (4.6)	104.5 (4.4)
Median (IQR)	104.7 (101.0–108.3)	104.7 (101.3–108.4)	104.6 (101.0–107.7)
Range	95.6–113.1	95.6–113.1	95.6–113.1
Bayley-III cognitive composite score available for those in the 22- to 26-month window or those who died before			
N_{obs} (N_{miss})	482 (6)	237 (4)	245 (2)
Mean (SD)	95.5 (19.9)	95.1 (19.3)	95.9 (20.4)
Median (IQR)	100.0 (90.0–105.0)	95.0 (85.0–105.0)	100.0 (90.0–110.0)
Range	49.0–149.0	49.0–149.0	49.0–145.0
	n	**Effect estimate**	**95% CI**	***p*-value**
Regression analysis for subgroup with age in 22- to 26-month window or those who died before				
Treatment	482	0.76	–2.74 to 4.27	0.670

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Notes
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 23 13:07:14 2015.
These results have not been independently checked. Every effort has been made to ensure their accuracy, but the possibility of error remains.

TABLE 145 Number of cases using information from general practitioner letters

In the first step the components of disability have been defined from the paediatric assessment. Only for patients where there was no, or not enough, information in the paediatric assessment data the GP letters have been used to try to impute missing values. This has been done for each variable at a time, i.e. there could be slight differences in the number of imputed items from one variable to the next. Expressed differently, for patients with both records it is possible that some of the variables come from the paediatric assessment and others from the GP letters	
Number of cases with a record in the disability section of the paediatric assessment questionnaire	857
Number of cases with a GP letter	92
Number with both (included in both rows above)	6

GP, general practitioner.
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 23 13:07:16 2015.
Note
These results have not been independently checked. Every effort has been made to ensure their accuracy, but the possibility of error remains.

TABLE 146 Neonatal outcome in the subgroup without previous pregnancy of ≥ 14 weeks' gestation. Summary and Fisher's exact test

		Trial group	
Neonatal outcome	**All**	**Placebo**	**Progesterone**
N_{obs} (N_{miss})	38 (0)	35 (2)	$p = 0.098$
No, *n* (%)	37 (97.4)	30 (85.7)	
Yes, *n* (%)	1 (2.6)	5 (14.3)	

N_{miss}, number of women with missing data; N_{obs}, number of observations.
Notes
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 23 13:07:18 2015.
These results have not been independently checked. Every effort has been made to ensure their accuracy, but the possibility of error remains.

TABLE 147 Additional sensitivity analyses for brain injury

		Trial group	
Parameter or outcome	**All**	**Placebo**	**Progesterone**
Any information on neonatal outcomes			
N_{obs} (N_{miss})	1226 (0)	610 (0)	616 (0)
Available, *n* (%)	1158 (94.5)	574 (94.1)	584 (94.8)
Died, *n* (%)	23 (1.9)	13 (2.1)	10 (1.6)
Missing, *n* (%)	5 (0.4)	2 (0.3)	3 (0.5)
Lost, *n* (%)	40 (3.3)	21 (3.4)	19 (3.1)
Ultrasonography done			
N_{obs} (N_{miss})	1152 (74)	572 (38)	580 (36)
No, *n* (%)	376 (32.6)	172 (30.1)	204 (35.2)
Yes, *n* (%)	776 (67.4)	400 (69.9)	376 (64.8)
Intraventricular haemorrhage			
N_{obs} (N_{miss})	740 (486)	383 (227)	357 (259)
No, *n* (%)	720 (97.3)	370 (96.6)	350 (98.0)
Yes, *n* (%)	20 (2.7)	13 (3.4)	7 (2.0)

TABLE 147 Additional sensitivity analyses for brain injury (*continued*)

Parameter or outcome	All	Trial group	
		Placebo	Progesterone
Parenchymal cystic or haemorrhagic lesion			
N_{obs} (N_{miss})	739 (487)	382 (228)	357 (259)
No, *n* (%)	708 (95.8)	359 (94.0)	349 (97.8)
Yes, *n* (%)	31 (4.2)	23 (6.0)	8 (2.2)
Persistent ventriculomegaly (VI > 97th percentile)			
N_{obs} (N_{miss})	721 (505)	372 (238)	349 (267)
No, *n* (%)	710 (98.5)	364 (97.8)	346 (99.1)
Yes, *n* (%)	11 (1.5)	8 (2.2)	3 (0.9)
	n	**OR**	**95% CI**	***p*-value**
Regression analysis only including those with information on whether or not scan has been done				
Treatment	1152	0.51	0.31 to 0.84	0.009
Regression analysis only including those where scan has been done				
Treatment	776	0.54	0.32 to 0.88	0.015

N_{miss}, number of women with missing data; N_{obs}, number of observations.
Notes
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 23 13:07:24 2015.
These results have not been independently checked. Every effort has been made to ensure their accuracy, but the possibility of error remains.

TABLE 148 Follow-up information summarised separately for those with and those without brain injury

Brain injury		All	Trial group	
			Placebo	Progesterone
No	Bayley-III cognitive composite score			
	N_{obs} (N_{miss})	805 (301)	400 (140)	405 (161)
	Mean (SD)	99.2 (15.9)	99.9 (15.4)	98.6 (16.3)
	Median (IQR)	100.0 (90.0–110.0)	100.0 (90.0–110.0)	100.0 (90.0–110.0)
	Range	49.0–149.0	49.0–149.0	49.0–149.0
Yes	Bayley-III cognitive composite score			
	N_{obs} (N_{miss})	38 (14)	24 (10)	14 (4)
	Mean (SD)	89.5 (17.1)	87.3 (14.4)	93.2 (21.0)
	Median (IQR)	90.0 (85.0–100.0)	90.0 (85.0–95.0)	95.0 (82.5–100.0)
	Range	55.0–145.0	55.0–105.0	55.0–145.0
No	Survival status			
	N_{obs} (N_{miss})	1106 (0)	540 (0)	566 (0)
	0, *n* (%)	1093 (98.8)	537 (99.4)	556 (98.2)
	1, *n* (%)	13 (1.2)	3 (0.6)	10 (1.8)
Yes	Survival status			
	N_{obs} (N_{miss})	52 (0)	34 (0)	18 (0)
	0, *n* (%)	52 (100.0)	34 (100.0)	18 (100.0)

continued

TABLE 148 Follow-up information summarised separately for those with and those without brain injury (*continued*)

Brain injury		All	Trial group: Placebo	Trial group: Progesterone
No	Moderate/severe neurodevelopmental impairment			
	N_{obs} (N_{miss})	743 (363)	379 (161)	364 (202)
	No, *n* (%)	672 (90.4)	350 (92.3)	322 (88.5)
	Yes, *n* (%)	71 (9.6)	29 (7.7)	42 (11.5)
Yes	Moderate/severe neurodevelopmental impairment			
	N_{obs} (N_{miss})	36 (16)	22 (12)	14 (4)
	No, *n* (%)	25 (69.4)	16 (72.7)	9 (64.3)
	Yes, *n* (%)	11 (30.6)	6 (27.3)	5 (35.7)

N_{miss}, number of women with missing data; N_{obs}, number of observations.
Notes
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 23 13:07:27 2015.
These results have not been independently checked. Every effort has been made to ensure their accuracy, but the possibility of error remains.

TABLE 149 Days of care summaries

Parameter or outcome	All	Trial group: Placebo	Trial group: Progesterone
Number of days of level 1 care > 0			
N_{obs} (N_{miss})	1149 (77)	569 (41)	580 (36)
No, *n* (%)	1002 (87.2)	487 (85.6)	515 (88.8)
Yes, *n* (%)	147 (12.8)	82 (14.4)	65 (11.2)
Number of days of level 1 care > 5			
N_{obs} (N_{miss})	1149 (77)	569 (41)	580 (36)
No, *n* (%)	1078 (93.8)	532 (93.5)	546 (94.1)
Yes, *n* (%)	71 (6.2)	37 (6.5)	34 (5.9)
Number of days of level 1 or 2 care > 0			
N_{obs} (N_{miss})	1149 (77)	569 (41)	580 (36)
No, *n* (%)	970 (84.4)	474 (83.3)	496 (85.5)
Yes, *n* (%)	179 (15.6)	95 (16.7)	84 (14.5)
Number of days of level 1 or 2 care > 5			
N_{obs} (N_{miss})	1149 (77)	569 (41)	580 (36)
No, *n* (%)	1037 (90.3)	507 (89.1)	530 (91.4)
Yes, *n* (%)	112 (9.7)	62 (10.9)	50 (8.6)
Number of days of special or higher level of care > 0			
N_{obs} (N_{miss})	1149 (77)	569 (41)	580 (36)
No, *n* (%)	844 (73.5)	410 (72.1)	434 (74.8)
Yes, *n* (%)	305 (26.5)	159 (27.9)	146 (25.2)

TABLE 149 Days of care summaries (*continued*)

Parameter or outcome	All	Trial group	
		Placebo	Progesterone
Number of days of special or higher level of care > 5			
N_{obs} (N_{miss})	1149 (77)	569 (41)	580 (36)
No, *n* (%)	930 (80.9)	451 (79.3)	479 (82.6)
Yes, *n* (%)	219 (19.1)	118 (20.7)	101 (17.4)
Number of days of special or higher level of care > 14			
N_{obs} (N_{miss})	1149 (77)	569 (41)	580 (36)
No, *n* (%)	999 (86.9)	485 (85.2)	514 (88.6)
Yes, *n* (%)	150 (13.1)	84 (14.8)	66 (11.4)
Number of days of normal or higher level of care > 3			
N_{obs} (N_{miss})	1148 (78)	569 (41)	579 (37)
No, *n* (%)	771 (67.2)	369 (64.9)	402 (69.4)
Yes, *n* (%)	377 (32.8)	200 (35.1)	177 (30.6)
Number of days of normal or higher level of care > 7			
N_{obs} (N_{miss})	1148 (78)	569 (41)	579 (37)
No, *n* (%)	922 (80.3)	447 (78.6)	475 (82.0)
Yes, *n* (%)	226 (19.7)	122 (21.4)	104 (18.0)
Number of days of normal or higher level of care > 14			
N_{obs} (N_{miss})	1148 (78)	569 (41)	579 (37)
No, *n* (%)	996 (86.8)	482 (84.7)	514 (88.8)
Yes, *n* (%)	152 (13.2)	87 (15.3)	65 (11.2)

N_{miss}, number of women with missing data; N_{obs}, number of observations.
Notes
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 23 13:07:32 2015.
These results have not been independently checked. Every effort has been made to ensure their accuracy, but the possibility of error remains.

TABLE 150 Linear mixed effects regression analyses predicting EQ-5D from treatment adjusting for EQ-5D at baseline, previous pregnancy of ≥ 14 weeks' gestation and centre as a random effect

Time	*n*	Effect estimate	95% CI	*p*-value
Birth	390	0.001	–0.034 to 0.036	0.966
12 months	553	0.003	–0.026 to 0.032	0.833

N_{miss}, number of women with missing data; N_{obs}, number of observations.
Notes
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 23 13:07:36 2015
These results have not been independently checked. Every effort has been made to ensure their accuracy, but the possibility of error remains.

TABLE 151 Cervical length summaries

Parameter or outcome	All	Trial group	
		Placebo	Progesterone
Cervical length at baseline (mm)			
N_{obs} (N_{miss})	712 (514)	351 (259)	361 (255)
> 25, *n* (%)	456 (64.0)	232 (66.1)	224 (62.0)
≤ 25, *n* (%)	256 (36.0)	119 (33.9)	137 (38.0)
Cervical length at baseline (mm)			
N_{obs} (N_{miss})	712 (514)	351 (259)	361 (255)
> 15, *n* (%)	614 (86.2)	304 (86.6)	310 (85.9)
≤ 15, *n* (%)	98 (13.8)	47 (13.4)	51 (14.1)

N_{miss}, number of women with missing data; N_{obs}, number of observations.
Notes
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 23 13:07:38 2015.
These results have not been independently checked. Every effort has been made to ensure their accuracy, but the possibility of error remains.

TABLE 152 Logistic regression models for the effect of treatment on secondary outcomes adjusted for previous pregnancies of ≥ 14 weeks' gestation

Outcome	*n*	OR	95% CI	*p*-value
Fetal death	1197	1.14	0.41 to 3.17	0.802
Fetal death before 34 weeks' gestation	1197	1.16	0.39 to 3.49	0.786
Delivery before 34 weeks' gestation (excluding deaths before 34 weeks' gestation)	1184	0.85	0.62 to 1.15	0.292
Neonatal deaths (excluding fetal deaths)[a]	1182	1.14	0.44 to 2.98	0.79
Neonatal or fetal death	1197	1.13	0.56 to 2.29	0.728
Necrotising enterocolitis (suspected or treated)	1155	1.37	0.76 to 2.45	0.291
Any episode of infection with positive blood culture vs. no infection or infection without positive blood culture	1147	0.87	0.49 to 1.56	0.642
Any episode of infection with positive blood or cerebrospinal fluid culture vs. no infection or infection without positive blood or cerebrospinal fluid culture	1147	0.92	0.52 to 1.65	0.789

a Not adjusted for previous pregnancy of ≥ 14 weeks' gestation.
Notes
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 23 13:07:46 2015.
These results have not been independently checked. Every effort has been made to ensure their accuracy, but the possibility of error remains.

TABLE 153 Logistic regression models for the effect of treatment on components of disability adjusted for previous pregnancies of ≥ 14 weeks' gestation and centre as a random effect

Component	*n*	OR	95% CI	*p*-value
Components of disability				
Motor	Regression failed			
Cognitive	913	1.03	0.58 to 1.84	0.918
Hearing	Regression failed			
Speech and language	891	1.32	0.72 to 2.43	0.364
Vision	Regression failed			
Respiratory	Regression failed			
Gastrointestinal	Regression failed			
Renal	848	3.65	1.96 to 6.82	< 0.001
Not adjusted for previous pregnancy of ≥ 14 weeks				
Components of disability				
Motor	917	0.99	0.25 to 3.98	0.988
Hearing	931	0.56	0.33 to 0.94	0.028
Vision	Regression failed			
Respiratory	847	3.03	1.56 to 5.88	0.001
Gastrointestinal	844	2.67	1.37 to 5.20	0.004

	Treatment		
Fisher's exact test	Placebo	Progesterone	*p*-value
Components of disability: vision			
N_{obs} (N_{miss})	466 (144)	447 (169)	0.125
No, *n* (%)	462 (99.1)	447 (100.0)	
Yes, *n* (%)	4 (0.9)	0 (0.0)	

N_{miss}, number of women with missing data; N_{obs}, number of observations.

Notes

OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 23 13:08:05 2015.
These results have not been independently checked. Every effort has been made to ensure their accuracy, but the possibility of error remains.

TABLE 154 Logistic regression models for the effect of treatment on treatment satisfaction adjusted for previous pregnancies of ≥ 14 weeks' gestation and centre as a random effect

Parameter or outcome	*n*	OR	95% CI	*p*-value
Extremely or fairly satisfied	634	0.93	0.42 to 2.04	0.854
Extremely satisfied	634	0.64	0.45 to 0.90	0.011
Extremely satisfied (6 months)	78	1.34	0.46 to 3.88	0.591

Notes

OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 23 13:08:08 2015.
These results have not been independently checked. Every effort has been made to ensure their accuracy, but the possibility of error remains.

TABLE 155 Summaries of categorical Strengths and Difficulties Questionnaire scores

Parameter or outcome	All	Trial group	
		Placebo	Progesterone
SDQ emotional problems score normal (≤ 2)			
N_{obs} (N_{miss})	669 (557)	341 (269)	328 (288)
No, *n* (%)	69 (10.3)	35 (10.3)	34 (10.4)
Yes, *n* (%)	600 (89.7)	306 (89.7)	294 (89.6)
SDQ conduct problems score normal (≤ 3)			
N_{obs} (N_{miss})	668 (558)	342 (268)	326 (290)
No, *n* (%)	174 (26.0)	92 (26.9)	82 (25.2)
Yes, *n* (%)	494 (74.0)	250 (73.1)	244 (74.8)
SDQ hyperactivity score normal (≤ 5)			
N_{obs} (N_{miss})	649 (577)	334 (276)	315 (301)
No, *n* (%)	191 (29.4)	95 (28.4)	96 (30.5)
Yes, *n* (%)	458 (70.6)	239 (71.6)	219 (69.5)
SDQ peer problems score normal (≤ 2)			
N_{obs} (N_{miss})	663 (563)	345 (265)	318 (298)
No, *n* (%)	225 (33.9)	110 (31.9)	115 (36.2)
Yes, *n* (%)	438 (66.1)	235 (68.1)	203 (63.8)
SDQ total score normal (≤ 12)			
N_{obs} (N_{miss})	597 (629)	302 (308)	295 (321)
No, *n* (%)	149 (25.0)	70 (23.2)	79 (26.8)
Yes, *n* (%)	448 (75.0)	232 (76.8)	216 (73.2)
SDQ prosocial score normal (≥ 7)			
N_{obs} (N_{miss})	659 (567)	339 (271)	320 (296)
No, *n* (%)	364 (55.2)	180 (53.1)	184 (57.5)
Yes, *n* (%)	295 (44.8)	159 (46.9)	136 (42.5)
SDQ impact score normal (0)			
N_{obs} (N_{miss})	828 (398)	424 (186)	404 (212)
No, *n* (%)	49 (5.9)	22 (5.2)	27 (6.7)
Yes, *n* (%)	779 (94.1)	402 (94.8)	377 (93.3)

N_{miss}, number of women with missing data; N_{obs}, number of observations; SDQ, Strengths and Difficulties Questionnaire.

Notes

OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Oct 23 13:08:12 2015.

These results have not been independently checked. Every effort has been made to ensure their accuracy, but the possibility of error remains.

Additional analyses for paper: part 2

Does progesterone prophylaxis to prevent preterm labour improve outcome?	
OPPTIMUM	
Additional analyses for paper – part 2	
v1.1	
27 November 2015	
Martina Messow	
Robertson Centre for Biostatistics	
EudraCT number	2007-007950-77
CTA number	22931/0009/001-0001 revised by MHRA to 01384/0208/001
MREC number	08/MRE00/6
ISRCTN	ISRCTN14568373
Co-sponsors	University of Edinburgh/NHS Lothian
Funder	Medical Research Council/ NIHR EME
Funding reference number	G0700452, Grant No: 84982 – 09/800/27
Protocol Version	15.1 (1 April 2015)
SAP Version	1.1 (8 September 2015)

CTA, Clinical Trial Authorisation; EudraCT, European Union Drug Regulating Authorities Clinical Trials; MREC, Multicentre Research Ethics Committee; SAP, statistical analysis plan.

TABLE 156 Adjusted CI using Bonferroni–Holm adjustment

Outcome	95% CI
Obstetric	0.61 to 1.22
Neonatal	0.44 to 1.17

Note
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Nov 27 13:41:38 2015.

TABLE 157 Number randomised before change in inclusion criteria (1 September 2010)

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Notes
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Nov 27 13:41:39 2015.
These results have not been independently checked. Every effort has been made to ensure their accuracy, but the possibility of error remains.

TABLE 158 Rates of primary outcome in subgroups

Risk group	Trial group, *n*/*N* (%)	
	Placebo	Progesterone
Low/high risk group		
Low	54/418 (12.9)	51/442 (11.5)
High	54/179 (30.2)	45/159 (28.3)
Cervical length at baseline (mm)		
> 25	29/228 (12.7)	25/217 (11.5)
≤ 25	38/118 (32.2)	33/133 (24.8)
Cervical length at baseline (mm)		
> 15	46/299 (15.4)	37/300 (12.3)
≤ 15	21/47 (44.7)	21/50 (42.0)
History of spontaneous preterm birth		
No	26/154 (16.9)	22/130 (16.9)
Yes	82/443 (18.5)	74/470 (15.7)
History of any preterm birth		
No	23/152 (15.1)	19/131 (14.5)
Yes	84/442 (19.0)	77/469 (16.4)

Notes
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Nov 27 13:41:45 2015.
These results have not been independently checked. Every effort has been made to ensure their accuracy, but the possibility of error remains.

TABLE 159 Baseline characteristics (part 1). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of Bayley-III cognitive composite score at 2 years

Characteristic	All	Bayley-III cognitive composite score at 2 years available	
		No	Yes
Age (years)			
N_{obs} (N_{miss})	1225 (1)	356 (1)	869 (0)
Mean (SD)	31.4 (5.7)	29.6 (5.7)	32.2 (5.5)
Median (IQR)	31.5 (27.4–35.7)	29.3 (25.7–33.3)	32.3 (28.2–36.2)
Range	16.8–49.2	16.8–45.3	17.5–49.2
Height (cm)			
N_{obs} (N_{miss})	1221 (5)	354 (3)	867 (2)
Mean (SD)	163.5 (6.6)	163.6 (6.6)	163.5 (6.6)
Median (IQR)	163.0 (159.0–168.0)	163.0 (159.0–168.0)	164.0 (159.0–168.0)
Range	144.0–183.0	147.0–183.0	144.0–183.0
Weight (kg)			
N_{obs} (N_{miss})	1221 (5)	354 (3)	867 (2)
Mean (SD)	71.6 (17.1)	70.3 (15.7)	72.2 (17.6)
Median (IQR)	68.0 (60.0–81.0)	67.0 (59.0–80.0)	68.0 (60.0–81.0)
Range	41.0–186.0	43.0–130.0	41.0–186.0

TABLE 159 Baseline characteristics (part 1). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of Bayley-III cognitive composite score at 2 years (*continued*)

		Bayley-III cognitive composite score at 2 years available	
Characteristic	All	No	Yes
BMI (kg/m^2)			
N_{obs} (N_{miss})	1221 (5)	354 (3)	867 (2)
Mean (SD)	26.8 (6.3)	26.3 (5.5)	27.0 (6.5)
Median (IQR)	25.5 (22.3–29.8)	25.0 (22.2–29.4)	25.6 (22.4–30.1)
Range	15.2–80.5	16.3–49.5	[5.2–80.5
Systolic blood pressure (mmHg)			
N_{obs} (N_{miss})	1219 (7)	356 (1)	863 (6)
Mean (SD)	111.9 (12.4)	111.1 (12.0)	112.2 (12.5)
Median (IQR)	110.0 (102.0–120.0)	110.0 (102.0–120.0)	110.0 (103.0–120.0)
Range	78.0–189.0	78.0–159.0	80.0–189.0
Diastolic blood pressure (mmHg)			
N_{obs} (N_{miss})	1219 (7)	356 (1)	863 (6)
Mean (SD)	66.0 (8.6)	65.4 (8.8)	66.2 (8.5)
Median (IQR)	65.0 (60.0–71.0)	64.0 (60.0–70.0)	65.0 (60.0–71.0)
Range	40.0–104.0	44.0–98.0	40.0–104.0

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Notes
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Nov 27 13:41:47 2015.
These results have not been independently checked. Every effort has been made to ensure their accuracy, but the possibility of error remains.

TABLE 160 Baseline characteristics (part 2). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of Bayley-III cognitive composite score at 2 years

		Bayley-III cognitive composite score at 2 years available	
Characteristic	All	No	Yes
Smoking			
N_{obs} (N_{miss})	1220 (6)	355 (2)	865 (4)
No, *n* (%)	984 (80.7)	245 (69.0)	739 (85.4)
Yes, *n* (%)	236 (19.3)	110 (31.0)	126 (14.6)
Alcohol consumption			
N_{obs} (N_{miss})	1223 (3)	356 (1)	867 (2)
No, *n* (%)	1160 (94.8)	335 (94.1)	825 (95.2)
Yes, *n* (%)	63 (5.2)	21 (5.9)	42 (4.8)

continued

TABLE 160 Baseline characteristics (part 2). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of Bayley-III cognitive composite score at 2 years (*continued*)

Characteristic	All	Bayley-III cognitive composite score at 2 years available	
		No	Yes
Drug use			
N_{obs} (N_{miss})	1223 (3)	356 (1)	867 (2)
No, *n* (%)	1206 (98.6)	348 (97.8)	858 (99.0)
Yes, *n* (%)	17 (1.4)	8 (2.2)	9 (1.0)

N_{miss}, number of women with missing data; N_{obs}, number of observations.
Notes
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Nov 27 13:41:49 2015.
These results have not been independently checked. Every effort has been made to ensure their accuracy, but the possibility of error remains.

TABLE 161 Baseline characteristics (part 3). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of Bayley-III cognitive composite score at 2 years

Characteristic	All	Bayley-III cognitive composite score at 2 years available	
		No	Yes
In full-time education			
N_{obs} (N_{miss})	1216 (10)	353 (4)	863 (6)
No, *n* (%)	1175 (96.6)	339 (96.0)	836 (96.9)
Yes, *n* (%)	41 (3.4)	14 (4.0)	27 (3.1)
Years in full-time education			
N_{obs} (N_{miss})	1122 (53)	315 (24)	807 (29)
Mean (SD)	13.5 (3.1)	12.7 (2.8)	13.8 (3.1)
Median (IQR)	13.0 (11.0–16.0)	12.0 (11.0–14.0)	13.0 (11.0–16.0)
Range	1.0–31.0	1.0–26.0	3.0–31.0
Educated in the UK			
N_{obs} (N_{miss})	1206 (20)	347 (10)	859 (10)
No, *n* (%)	211 (17.5)	61 (17.6)	150 (17.5)
Yes, *n* (%)	995 (82.5)	286 (82.4)	709 (82.5)

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Notes
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Nov 27 13:41:49 2015.
These results have not been independently checked. Every effort has been made to ensure their accuracy, but the possibility of error remains.

TABLE 162 Baseline characteristics (part 4): this pregnancy. Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of Bayley-III cognitive composite score at 2 years

		Bayley-III cognitive composite score at 2 years available	
Characteristic	All	No	Yes
Gestation (weeks) at fFN test			
N_{obs} (N_{miss})	1226 (0)	357 (0)	869 (0)
Mean (SD)	22.9 (0.6)	22.9 (0.6)	22.9 (0.6)
Median (IQR)	22.9 (22.4–23.4)	22.9 (22.4–23.4)	22.9 (22.4–23.3)
Range	21.7–27.1	22.0–24.1	21.7–27.1
Fetal anomaly scan done			
N_{obs} (N_{miss})	1226 (0)	357 (0)	869 (0)
No, *n* (%)	63 (5.1)	22 (6.2)	41 (4.7)
Yes, *n* (%)	1163 (94.9)	335 (93.8)	828 (95.3)
Fetal anomaly scan result			
N_{obs} (N_{miss})	1163 (0)	335 (0)	828 (0)
Normal, *n* (%)	1150 (98.9)	333 (99.4)	817 (98.7)
Defined abnormality, *n* (%)	7 (0.6)	0 (0.0)	7 (0.8)
Uncertain abnormality, *n* (%)	6 (0.5)	2 (0.6)	4 (0.5)
Amniocentesis done			
N_{obs} (N_{miss})	1226 (0)	357 (0)	869 (0)
No, *n* (%)	1218 (99.3)	356 (99.7)	862 (99.2)
Yes, *n* (%)	8 (0.7)	1 (0.3)	7 (0.8)
Results of amniocentesis			
N_{obs} (N_{miss})	8 (0)	1 (0)	7 (0)
Normal, *n* (%)	8 (100.0)	1 (100.0)	7 (100.0)
Other, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Chorionic villus sampling done			
N_{obs} (N_{miss})	1225 (1)	357 (0)	868 (1)
No, *n* (%)	1216 (99.3)	354 (99.2)	862 (99.3)
Yes, *n* (%)	9 (0.7)	3 (0.8)	6 (0.7)
Results of chorionic villus sampling			
N_{obs} (N_{miss})	9 (0)	3 (0)	6 (0)
Normal, *n* (%)	9 (100.0)	3 (100.0)	6 (100.0)
Other, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Cervical length (mm)			
N_{obs} (N_{miss})	712 (514)	216 (141)	496 (373)
Mean (SD)	28.5 (10.8)	29.0 (10.1)	28.3 (11.1)
Median (IQR)	30.0 (22.0–36.0)	30.0 (23.0–36.0)	30.0 (22.0–36.0)
Range	0.0–84.0	0.0–50.0	0.0–84.0

continued

TABLE 162 Baseline characteristics (part 4): this pregnancy. Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of Bayley-III cognitive composite score at 2 years (*continued*)

Characteristic	All	Bayley-III cognitive composite score at 2 years available	
		No	Yes
Risk			
N_{obs} (N_{miss})	1226 (0)	357 (0)	869 (0)
Low, *n* (%)	882 (71.9)	254 (71.1)	628 (72.3)
High, *n* (%)	344 (28.1)	103 (28.9)	241 (27.7)

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Notes
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Nov 27 13:41:53 2015.
These results have not been independently checked. Every effort has been made to ensure their accuracy, but the possibility of error remains.

TABLE 163 Baseline characteristics (part 5). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of Bayley-III cognitive composite score at 2 years

Characteristic	All	Bayley-III cognitive composite score at 2 years available	
		No	Yes
Any previous pregnancy			
N_{obs} (N_{miss})	1224 (2)	355 (2)	869 (0)
No, *n* (%)	52 (4.2)	10 (2.8)	42 (4.8)
Yes, *n* (%)	1172 (95.8)	345 (97.2)	827 (95.2)
Number of previous pregnancies			
N_{obs} (N_{miss})	1224 (2)	355 (2)	869 (0)
Mean (SD)	2.6 (2.0)	2.9 (2.1)	2.5 (1.9)
Median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–4.0)	2.0 (1.0–3.0)
Range	0.0–14.0	0.0–12.0	0.0–14.0
Any previous pregnancy of ≥ 14 weeks' gestation			
N_{obs} (N_{miss})	1224 (2)	355 (2)	869 (0)
No, *n* (%)	75 (6.1)	18 (5.1)	57 (6.6)
Yes, *n* (%)	1149 (93.9)	337 (94.9)	812 (93.4)
Number of previous pregnancies of ≥ 14 weeks' gestation			
N_{obs} (N_{miss})	1224 (2)	355 (2)	869 (0)
Mean (SD)	1.9 (1.4)	2.1 (1.5)	1.8 (1.3)
Median (IQR)	2.0 (1.0–2.0)	2.0 (1.0–3.0)	1.0 (1.0–2.0)
Range	0.0–13.0	0.0–8.0	0.0–13.0
Any previous live birth			
N_{obs} (N_{miss})	1224 (2)	355 (2)	869 (0)
No, *n* (%)	197 (16.1)	56 (15.8)	141 (16.2)
Yes, *n* (%)	1027 (83.9)	299 (84.2)	728 (83.8)

TABLE 163 Baseline characteristics (part 5). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of Bayley-III cognitive composite score at 2 years (*continued*)

		Bayley-III cognitive composite score at 2 years available	
Characteristic	All	No	Yes
Number of previous live births			
N_{obs} (N_{miss})	1224 (2)	355 (2)	869 (0)
Mean (SD)	1.5 (1.3)	1.7 (1.3)	1.5 (1.3)
Median (IQR)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)
Range	0.0–13.0	0.0–8.0	0.0–13.0
Any previous pregnancy that ended with baby alive and well			
N_{obs} (N_{miss})	1224 (2)	355 (2)	869 (0)
No, *n* (%)	646 (52.8)	194 (54.6)	452 (52.0)
Yes, *n* (%)	578 (47.2)	161 (45.4)	417 (48.0)
Number of previous pregnancies that ended with baby alive and well			
N_{obs} (N_{miss})	1224 (2)	355 (2)	869 (0)
Mean (SD)	0.8 (1.2)	0.9 (1.2)	0.8 (1.2)
Median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)
Range	0.0–13.0	0.0–6.0	0.0–13.0

IQR, interquartile range; N_{miss}, number of women with missing data; N_{obs}, number of observations; SD, standard deviation.
Notes
OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Nov 27 13:41:55 2015.
These results have not been independently checked. Every effort has been made to ensure their accuracy, but the possibility of error remains.

TABLE 164 Baseline characteristics (part 6). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of Bayley-III cognitive composite score at 2 years

		Bayley-III cognitive composite score at 2 years available	
Characteristic	All	No	Yes
History of induced labour or elective caesarean section			
N_{obs} (N_{miss})	1224 (2)	355 (2)	869 (0)
No, *n* (%)	1065 (87.0)	304 (85.6)	761 (87.6)
Yes, *n* (%)	159 (13.0)	51 (14.4)	108 (12.4)
History of miscarriage			
N_{obs} (N_{miss})	1224 (2)	355 (2)	869 (0)
No, *n* (%)	701 (57.3)	193 (54.4)	508 (58.5)
Yes, *n* (%)	523 (42.7)	162 (45.6)	361 (41.5)
History of ectopic pregnancy			
N_{obs} (N_{miss})	1224 (2)	355 (2)	869 (0)
No, *n* (%)	1193 (97.5)	345 (97.2)	848 (97.6)
Yes, *n* (%)	31 (2.5)	10 (2.8)	21 (2.4)

continued

TABLE 164 Baseline characteristics (part 6). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of Bayley-III cognitive composite score at 2 years (*continued*)

Characteristic	All	Bayley-III cognitive composite score at 2 years available	
		No	Yes
History of termination of pregnancy			
N_{obs} (N_{miss})	1224 (2)	355 (2)	869 (0)
No, *n* (%)	1085 (88.6)	308 (86.8)	777 (89.4)
Yes, *n* (%)	139 (11.4)	47 (13.2)	92 (10.6)
History of termination of pregnancy before 14 weeks' gestation			
N_{obs} (N_{miss})	1226 (0)	357 (0)	869 (0)
No, *n* (%)	1106 (90.2)	317 (88.8)	789 (90.8)
Yes, *n* (%)	120 (9.8)	40 (11.2)	80 (9.2)
History of termination of pregnancy at ≥ 14 weeks' gestation			
N_{obs} (N_{miss})	1226 (0)	357 (0)	869 (0)
No, *n* (%)	1201 (98.0)	347 (97.2)	854 (98.3)
Yes, *n* (%)	25 (2.0)	10 (2.8)	15 (1.7)
History of live birth followed by neonatal death			
N_{obs} (N_{miss})	1224 (2)	355 (2)	869 (0)
No, *n* (%)	1059 (86.5)	311 (87.6)	748 (86.1)
Yes, *n* (%)	165 (13.5)	44 (12.4)	121 (13.9)
History of live birth followed by death other than neonatal			
N_{obs} (N_{miss})	1224 (2)	355 (2)	869 (0)
No, *n* (%)	1208 (98.7)	347 (97.7)	861 (99.1)
Yes, *n* (%)	16 (1.3)	8 (2.3)	8 (0.9)
History of stillbirth			
N_{obs} (N_{miss})	1224 (2)	355 (2)	869 (0)
No, *n* (%)	1129 (92.2)	326 (91.8)	803 (92.4)
Yes, *n* (%)	95 (7.8)	29 (8.2)	66 (7.6)

N_{miss}, number of women with missing data; N_{obs}, number of observations.

Notes

OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Nov 27 13:41:57 2015.

These results have not been independently checked. Every effort has been made to ensure their accuracy, but the possibility of error remains.

TABLE 165 Baseline characteristics (part 7). Number of observed values, number of missing values, number and percentage per category or mean, standard deviation, median and quartiles, minimum and maximum for all patients and by availability of Bayley-III cognitive composite score at 2 years

		Bayley-III cognitive composite score at 2 years available	
Characteristic	All	No	Yes
Ethnic group			
N_{obs} (N_{miss})	1224 (2)	356 (1)	868 (1)
White, *n* (%)	895 (73.1)	254 (71.3)	641 (73.8)
Black, *n* (%)	180 (14.7)	62 (17.4)	118 (13.6)
Asian, *n* (%)	104 (8.5)	27 (7.6)	77 (8.9)
Mixed, *n* (%)	28 (2.3)	8 (2.2)	20 (2.3)
Other, *n* (%)	17 (1.4)	5 (1.4)	12 (1.4)

N_{miss}, number of women with missing data; N_{obs}, number of observations.

Notes

OPPTIMUM Output created by OPPTIMUM_main_v2_0.R Last run on Fri Nov 27 13:47:03 2015.

These results have not been independently checked. Every effort has been made to ensure their accuracy, but the possibility of error remains.

Appendix 4 Patient information sheet

A patient information sheet for each of the main and screening phases of the study is attached.

a)

PARTICIPANT INFORMATION LEAFLET ***FIBRONECTIN TESTING***

Helping you decide whether or not to join our study

1. Study Title

Does progesterone prophylaxis to prevent preterm labour improve outcome? – A randomised double blind placebo controlled trial. "OPPTIMUM".

Short title: Does progesterone to prevent preterm labour improve outcome?

2. Invitation Paragraph

You are being invited to take part in a research study, as you have been identified by your doctor or midwife as someone who may be suitable. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

3. What is the purpose of the study?

The purpose of the study is to see if progesterone given to women at high risk of preterm delivery is good for mother's and baby's health. However in order

to know if you are suitable to enter the study we need to do a fibronectin test. This information leaflet is to tell you about fibronectin testing.

Fibronectin is a substance made naturally by the body in pregnancy, and binds the fetal membranes (around the amniotic fluid) to the lining of the womb. If it is found in high quantities in your vagina in pregnancy, you are more likely to deliver preterm. The fibronectin test measures the amount of fibronectin in the vagina.

If you are fibronectin positive you will be eligible for the main study to see if giving progesterone to women at high risk of preterm delivery is good for both the mother's and baby's health. Regardless of the fFN result, you will also be eligible if you had a previous spontaneous labour resulting in a preterm birth ≤ 34 weeks gestation or short cervix in index pregnancy, defined as cervical length ≤ 25mm, but we would like to find out whether the fibronectin test is positive, as this will help us determine the group of women that progesterone works best in.

Information on the main study is available in a separate sheet and will be given to you if you are eligible, or would like further information before deciding whether or not to participate in the screening.

4. Why have I been chosen?

You have been chosen because we believe you might be at higher than average risk of preterm delivery. This may be because of what happened in a previous pregnancy, or because you have been found to have a short cervix on ultrasound. We would like now to do a fibronectin test to check whether you really are at high risk of preterm delivery. If the fibronectin test is positive, then we believe your risk of having a preterm delivery is around 4 in 10. We will then ask if you would like to participate in the main study.

If your fibronectin test is negative, this means that you are at lower risk of preterm delivery, and you will not be eligible for participation in the main study unless you have a spontaneous labour resulting in a preterm birth ≤ 34 weeks

gestation in a previous pregnancy or a short cervix in index pregnancy, defined as cervical length ≤ 25mm in this pregnancy.

.

5. Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and 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 the standard of care you receive.

6. What will happen to me if I take part?

If you agree to take part we will take a swab from your vagina. The swab will then be tested for "fibronectin". You will be informed of the results and, if appropriate, you will be invited to participate in the main study looking at a treatment that we hope will reduce the risk of having your baby early. Whatever the result of your fibronectin test, we will follow you up to see how many weeks pregnant you are when you have the baby, how your baby is delivered, and your own and your baby's health details at delivery.

7. What do I have to do?

We ask that you agree to a vaginal swab for the fibronectin test to be performed. Once the fibronectin test is completed, you will be informed of the results and, if appropriate, you will be invited to participate in the main study and given further information.

Women who are not randomised to progesterone or placebo will be provided with a (pre paid) postcard to let us know when they have delivered their baby. The local care team will then collect information from your hospital notes about you and your baby's, delivery; such as the date and type of delivery. Information collected will help us to evaluate the outcomes for all women who were considered at risk of preterm delivery and will contribute towards the understanding we have about preterm labour.

8. What is the drug, device or procedure that is being tested?

The drug that is being tested in the main study is called progesterone. There is some evidence to suggest that it might be helpful in preventing preterm delivery but further research is needed to understand its long term effects. This information form is for the fibronectin testing part of the study only.

9. What are the alternatives for diagnosis or treatment?

At present, there are no licensed or recommended treatments for the prevention of preterm delivery in women at high risk in the UK.

10. What are the side effects of any treatment received when taking part?

At this stage you will not be given any treatment with medication but information is available in the leaflet about the main study. You can request the leaflet from your doctor or view it on our website, www.opptimum.org.uk

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

A vaginal swab can be a little uncomfortable.

12. What are the possible benefits of taking part?

We will be able to give you a clearer idea of how likely you are to have a preterm delivery. In the event that you are at high risk of preterm birth, you would be eligible for participation in the main study.

13. What happens when the research study stops?

At the end of the study in 2015, the results will be published on the study website and in medical journals.

14. What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. Please direct complaints to the local research doctor in the first instance.

15. What will happen if I don't want to carry on with the study?

You can withdraw from treatment at any time. The information collected up

until the point you decide not to continue will be used.

16. What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation against (the local Hospital or the Study Sponsors: University of Edinburgh/NHS Lothian) but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

17. Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential.

With your consent we will notify your own GP of your participation in the study. We may also ask your GP how you and your baby are getting on in the future. This may happen, approximately every five years from the time that your baby reaches the age of 5 years.

The data will be stored for following NHS guidelines: at least 25 years and possibly longer.

18. What will happen to any samples I give?

The fibronectin test will be done using the vaginal swab. The swab will be destroyed thereafter.

19. Will any genetic tests be done?

No.

20. What will happen to the results of the research study?

The results of the study will be published in a medical journal, and on the study website in due course (www.opptimum.org.uk). You will not be identified in any report/publication.

21. Who is organising and funding the research?

The study is being funded by the UK Medical Research Council: NIHR Efficacy and Mechanism Evaluation (EME). It is organised and sponsored by the University of Edinburgh/NHS Lothian. The sponsors of this study will contribute to the expenses of the hospital for including you in this study.

22. Who has reviewed the study?

This study was given a favourable ethical opinion for conduct in the NHS by the Scotland A Research Ethics Committee.

23. Who should I contact?

If you are interested in participating in Opptimum or would like further information, please contact:

Name of local Doctor _____

Hospital: _____

Address: _____

_____

_____

Telephone: _____

Email: _____

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

Thank you for or taking time to read this sheet and for considering taking part

Version 7, January 2012

b)

Opptimum
Progesterone prophylaxis to prevent pre-term labour

LOCAL LOGO TO BE INSERTED

PARTICIPANT INFORMATION LEAFLET (MAIN)

Additional Information to help you decide whether or not to join the treatment part of our study

1. Study Title

Does progesterone prophylaxis to prevent preterm labour improve outcome? – A randomised double blind placebo controlled trial "OPPTIMUM".

Short title: Does progesterone to prevent preterm labour improve outcome?

2. Invitation Paragraph

You are being invited to join the treatment part of the Opptimum study;, before you decide to participate it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask your doctor if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

3. What is the purpose of the study?

The purpose of the study is to see if giving progesterone to women at high risk of preterm delivery is good for mother's and baby's health. We plan to look at your health during your pregnancy and the baby's health until the baby is two years of age. We will also ask you to complete questionnaires about your experience of using the treatment. These questionnaires will also ask

about you, and your baby's, health following the pregnancy, in order to assess the effects of giving progesterone. It is possible these questionnaires may also indicate if this treatment is costly or money-saving for the NHS.

4. Why have I been chosen?

You have been invited because the fetal fibronectin test was positive or because you had a spontaneous preterm labour resulting in a birth ≤ 34 weeks gestation or a short cervix in this pregnancy, (defined as cervical length ≤ 25mm) and we therefore believe that you might be at higher than average risk of preterm delivery. Fibronectin is a substance made naturally by the body in pregnancy. It binds the fetal membranes (around the amniotic fluid) to the lining of the womb. If it is found in high quantities in your vagina in pregnancy, you are more likely to deliver preterm.

We hope that 1250 women in your situation will agree to participate in the study, of whom 625 will be treated with progesterone and 625 will be treated with a placebo (dummy) treatment.

5. Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and will be asked to sign another consent form. You are free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the care you receive.

6. What will happen to me if I take part?

Sometimes we don't know which way of treating patients is best. To find out, we need to make comparisons between different treatments. We do this by putting people into groups and give each group a different treatment; the results are then compared to see if one is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly). The results are then compared.

If you agree to take part we will give you a pack of study medication. The

study medication is in the form of a capsule. The capsule will either contain progesterone or a “placebo”. A placebo is a “dummy treatment”, which looks like the genuine medicine but contains no active ingredient. One capsule should be inserted into the vagina every evening before going to bed, using your finger.

The study doctor / midwife will write down the date you should start medication and also when to stop taking the medication; this will be recorded in the patient diary we will ask you to keep. Most women will start taking the treatment between 22 and 24 weeks of pregnancy. All women will be asked to stop taking the treatment when they are 34 weeks pregnant.

You will not know which treatment group you are in. The trial is a double blind trial, and so neither you nor your doctor will know which treatment group you are (although, if your doctor needs to find out he/she can do so).

We hope that you will agree to stay in this study until after you have had your baby. Participation in this study may require around three extra visits to hospital during your pregnancy, each of which will last 30 minutes. During this time you will have a check up and will be asked some questions about your health. We will also ask you to fill in questionnaires to tell us how you are getting on, after you have had your baby. We may also ask you to take part in an interview telling us what you think about your experience of using the treatment. We will collect some information from your medical notes about your health.

We would also like to collect information about the baby’s health. We can (with your permission) get most of this from the baby’s notes. We will ask your permission to do an ultrasound scan of the baby’s head when he / she is born and ask you to fill in further questionnaires when your baby is approximately one year old, to tell us about their health and experience. Additionally, we would like to see your baby again when he / she is two years old to see how he / she is getting on.

Lastly, we would like your permission to contact you in the future to see how your baby gets on as he / she grows up; and to access information in health records about you and your baby. We cannot be certain when this would happen, but it may be approximately every five years from the time that your baby reaches the age of 5 years.

7. **What do I have to do?**

We ask you to take the study medication as directed, and attend the extra clinic visits we invite you to. We also ask that you complete the study related diary and questionnaires.

8. **What is the drug, device or procedure that is being tested?**

The drug that is being tested is called progesterone. There is some evidence to suggest that it might be helpful in preventing preterm delivery but further research is needed to understand its long term effects. The treatment dose being tested is 200mg (one capsule) per day inserted in to the vagina every evening.

9. **What are the alternatives for diagnosis or treatment?**

At present, there are no licensed or recommended treatments for the prevention of preterm delivery in women at high risk.

10. **What are the side effects of any treatment received when taking part?**

These are unlikely but possible side effects of this treatment are: acne, flushing, rashes, fluid retention, weight changes, tummy upset, changes in libido, breast discomfort, migraine, tiredness and premenstrual symptoms. If you agree to participate in the main study and have side effects that concern you, please contact the local study team.

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

The other disadvantage is the inconvenience for you in making extra hospital visits during your pregnancy, completing questionnaires and bringing your child in for follow up studies in the future.

12. What are the possible benefits of taking part?

We cannot promise the study will help you but the information we obtain might help improve the treatment of women with a high risk of preterm delivery in the future.

13. What happens when the research study stops?

At the end of the study in 2015, we will be able to inform you of the study results if you wish. If you wish us to do so, please inform your study doctor. The results will also be published on the study website and in medical journals. We will keep the information about you for as long as possible: at least 25 years.

14. What will happen if I don't want to carry on with the study?

You can withdraw from treatment but you may wish to keep in contact with us to let us know your progress. If you do withdraw from treatment, the information already collected about you will still be used. We are required to follow up each case, to collect information about your pregnancy up until the time your baby is born. We will collect this information from your notes, unless you tell us otherwise.

15. What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the local researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation against (your local hospital or the Study Sponsors: University of Edinburgh/NHS Lothian) but you may have to pay your legal costs. The normal National Health Service complaints mechanisms

will still be available to you (if appropriate).

16. Will my taking part in this study be kept confidential?

Yes, all information that is collected about you during the course of the research will be kept strictly confidential. The Medical Research Council: NIHR Efficacy and Mechanism Evaluation (EME) who fund this study may ask us to share the information with other approved researchers; however, your identity (eg name, date of birth) will not be passed on.

We plan to send the details of you and your baby to the National Health Service Care Register (NHSCR) so that we can be informed of any major illnesses that you or your baby have in future. In order to be able to contact you about your own and your baby's health in future, your name and contact details, those of a relative or friend, and your GP details will be requested. These contacts will be kept securely, with access restricted on a secure database managed by the University of Glasgow. This information will be used only to contact you about the study by the study doctor or researchers running this trial. You will not be named or otherwise identified in any study publication.

In addition, with your consent we will notify your own GP of your participation in the study. We may also ask your GP how you and your baby are getting on in the future.

17. Will any genetic tests be done?

Yes. Once you have had the baby we would like your permission to store a sample of the placenta (afterbirth) and placental DNA. We may keep some of these samples in a tissue bank for future research. Ethical permission will be sought for any future research projects. Although the placenta may need to be examined as part of your care, it is optional whether you agree to the use of the surplus tissue and DNA for future research.

18. What will happen to the results of the research study?

The results of the study will be published in a medical journal, and on the

study website in due course (www.opptimum.org.uk). You will not be identified in any report/publication.

19. Who is organising and funding the research?

The study is being funded by the NIHR Efficacy and Mechanism Evaluation (EME). It is organised and sponsored by the University of Edinburgh/NHS Lothian. The sponsors of this study will contribute towards the expenses of the hospital for including you in this study

20. Who has reviewed the study?

This study was given a favourable ethical opinion for conduct in the NHS by the Scotland A Research Ethics Committee. Each hospital participating in the study also reviews the study and must agree to your Doctor taking part

21. Who should I contact?

If you are interested in participating in Opptimum main study or would like further information, please contact:

Name of local Doctor _____

Hospital: _____

Address: _____

_____

_____

Telephone: _____

Email: _____

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

Thank you for or taking time to read this sheet and for considering taking part.

Version 7, January 2012

Appendix 5 Informed consent form

A consent form for each of the main and screening phases of the study is attached.

a)

Centre Number: [_][_]

Trial (Screening) Number:
[_][_][_][_][_][_]

Title of study: Does progesterone prophylaxis to prevent preterm labour improve outcome?
CONSENT FORM (FIBRONECTIN TESTING)

Insert name of local researcher (PI):
_____

TO BE COMPLETED BY THE PARTICIPANT: If you agree to the following statements, please confirm by initialling boxes below:

1. I confirm that I have read and understand the OPPTIMUM Study Patient Information entitled "Participation Information Leaflet (Fibronectin testing)" dated January 2012 (Version 7.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my, and my baby's, medical notes and data collected during the study may be looked at by individuals from the University of Edinburgh, the University of Glasgow, from regulatory authorities or from the NHS Organisation, where it is relevant to my taking part in this research study. I give permission for these individuals to have access to my records. ☐
4. I agree to take part in the above study. ☐
5. I would like my GP to be informed of my participation in the study. ☐

Signature of Person taking Consent: _____ Date: _____
PRINT NAME: _____
Participant's signature: _____ Date: _____
PRINT NAME: _____

Version 7, January 2012

Centre Number: [_][_]
Trial (Screening) Number: [_][_][_][_][_][_]

Trial Subject (Randomisation) identification:
[_][_][_][_][_][_]

b) **Title of study: Does progesterone prophylaxis to prevent preterm labour improve outcome?**

CONSENT FORM (MAIN)

Insert name of local researcher (PI) _____

TO BE COMPLETED BY THE PARTICIPANT : If you agree to the following statements, please confirm by **initialling boxes below:**

1. I confirm that I have read and understand the OPPTIMUM Study Patient Information entitled "Participation Information Leaflet (Main)" dated January 2012 (Version 7.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I confirm that I agree to sections of placental tissue being examined. ☐
3. I confirm that I agree to placental DNA stored for use in subsequent research. ☐
4. I confirm that I agree to to my baby having a neonatal head scan. ☐
5. I understand that my, and my baby's, participation is voluntary, that the study will last until my baby is two years of age; and that I and my baby are free to withdraw at any time without giving any reason, without our medical care or legal rights being affected. ☐
6. I understand that relevant sections of my, and my baby's, medical notes and data collected during the study may be looked at by individuals from the University of Edinburgh, the University of Glasgow, from regulatory authorities or from the NHS Organisation, where it is relevant to my taking part in this research study. I give permission for these individuals to have access to my records ☐
7. I agree to take part in the above study. ☐
8. I would like my GP to be informed of my participation in the study. ☐

Participant's signature:	_____	Date:	_____
PRINT NAME:	_____		_____
Signature of Person taking Consent:	_____	Date:	_____
PRINT NAME:	_____		_____

Version 7, January 2012

Appendix 6 Case report forms

Parts of this appendix have been reproduced with permission from Sharon Kean, Robertson Centre for Biostatistics, 2018, personal communication.

OPPTIMUM

Annotated CRF

Version 2.0

Does progesterone prophylaxis to prevent preterm labour improve outcome?

Isobel Docherty, Robertson Centre for Biostatistics

09 March 2013

Based on: eCRF (SDP Ref 146)

Contents

e-CRF Screen	Table Name (OPPTIMUM)	New/ Potential Participant	Screening	Randomisation visit	34 Weeks Gestation (End of Treatment)	Hospital Admissions	Outcome only
Participant Identification	webSubjects – if eligible webScreenExcl – if not eli ible						
Consent	webConsent OPPTIMUM_priv.dbo.webIdent						
Inclusion Criteria	webIncl						
Exclusion Criteria	webExcl						
Schedule fFN Test	webFibTestSch						
fFN Test Results	webFibTestRes						
Pregnancy Complications	webCompPreg						
Demographics	webDemog OPPTIMUM_priv.dbo.webPcode						
Medical History	webMedHistPreg webOthAbTest						
Prev Pregnancies	webPrevPreg						
Other Med History	webMedHistOth						
Contact Details	OPPTIMUM_priv.webContactDetails						
Randomisation	webRand						
Trial Treatment	webTrialTreatment						
Labour Hospital	webLabourHosp						
Labour	webLabour webAnalgesics						
Delivery	webDelivery webTransfer						
Postnatal Complications	webCompPostnatal						
Baby	webBaby2 OPPTIMUM_priv.dbo.webIdent						
Threatened Preterm Labour or PPROM	webHospAdmTPL webTransfer						
Antenatal Hospital Admission	webHospAdmOth webTransfer						

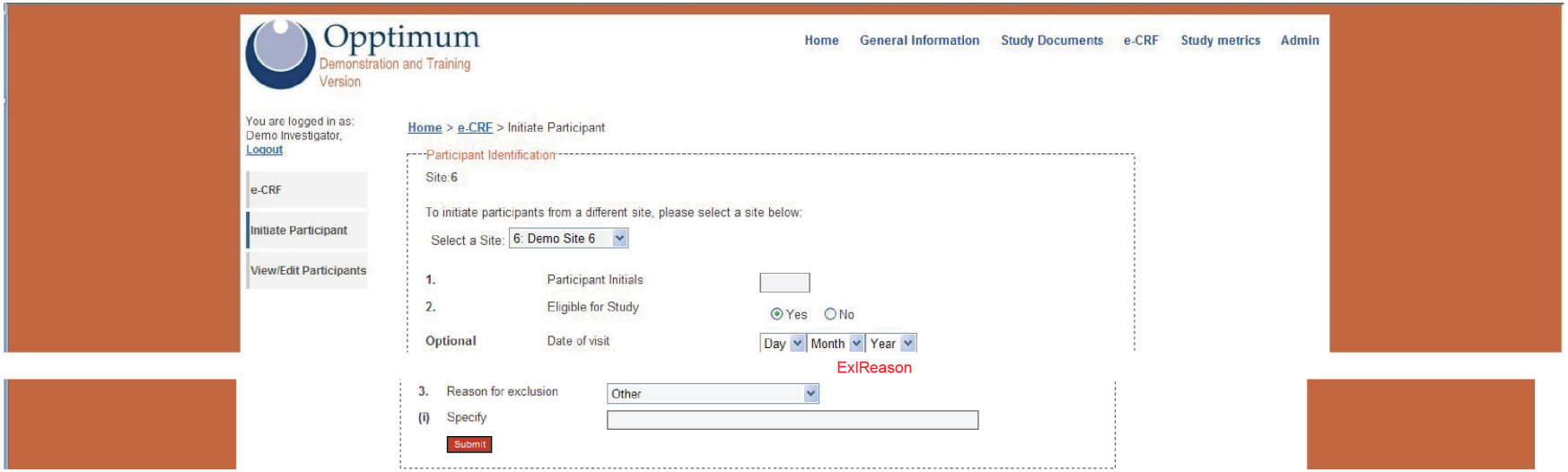
e-CRF Screen	Table Name (OPPTIMUM)	New/ Potential Participant	Screening	Randomisation visit	34 Weeks Gestation (End of Treatment)	Hospital Admissions	Outcome only
Neonatal Outcome	webNeoNatal2 webSurfactant webNeoDiag webTransfer						
Consent Withdrawal	webConsentWithdrawal						
End of Study	webTermination						
Protocol Violations	webProtViol						
Outcome only: Labour	webOoLabour						
Outcome only: Delivery	webOoDelivery						
Outcome only: Baby	webOoBaby						
Outcome only: Withdrawal	webOoWithdrawal						

Document history

Version	Date	Created by	Description
Version 1.0	27/04/2012	I. Docherty	Initial Creation
Version 2.0	09/04/2013		Incorporating changes to eCRF

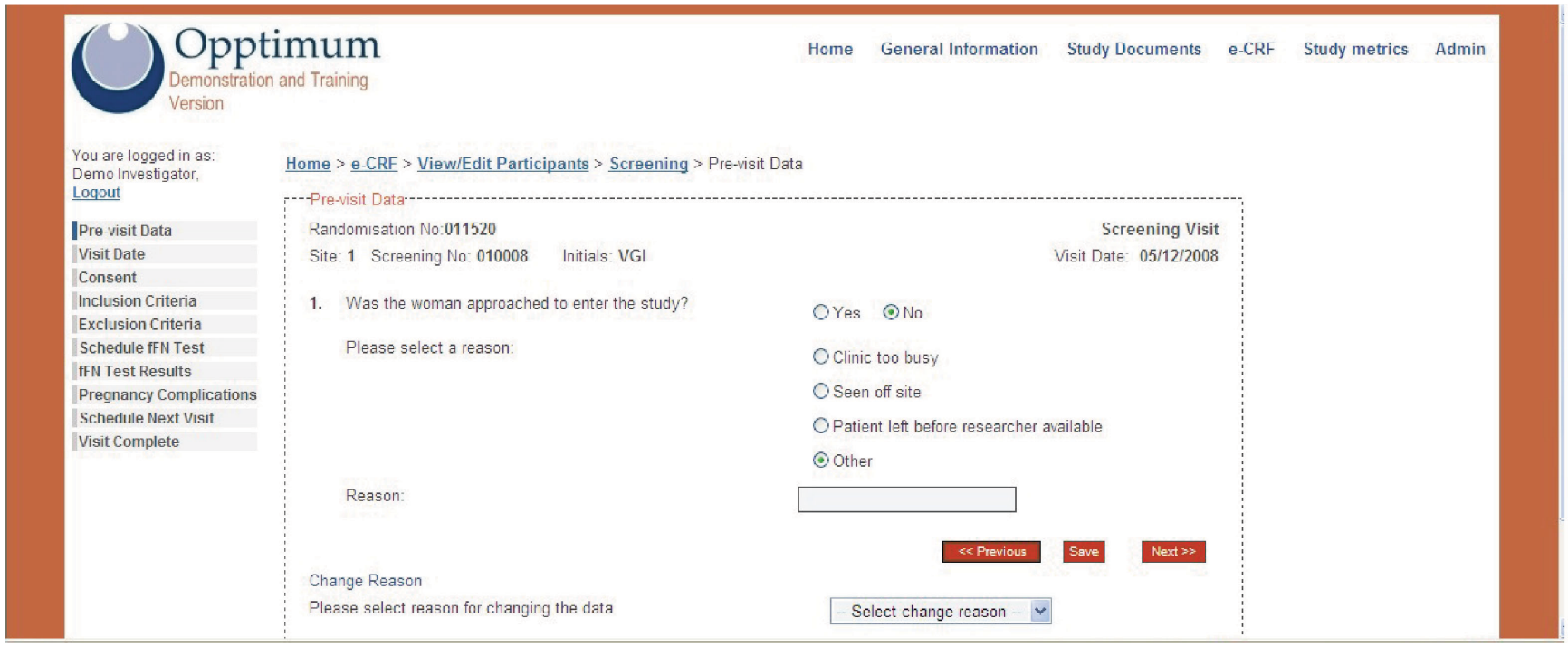
1. New/potential Participant –

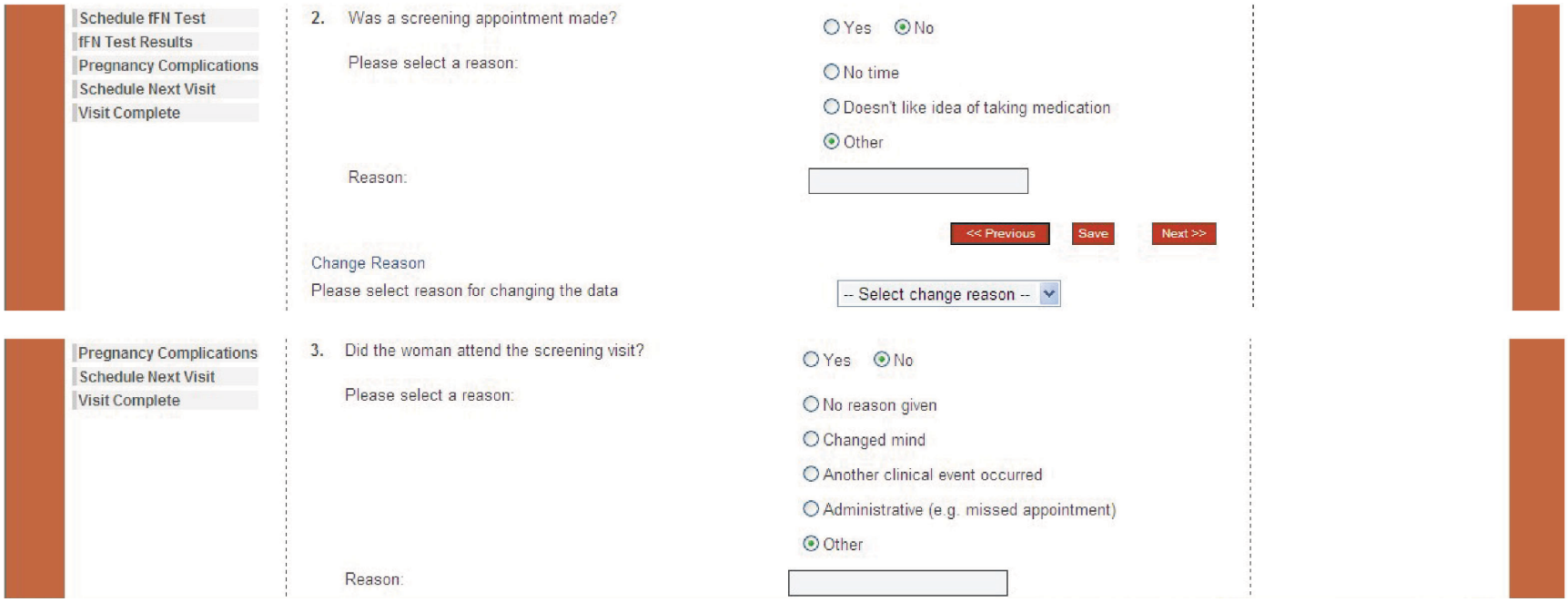
a. Initiate Participant



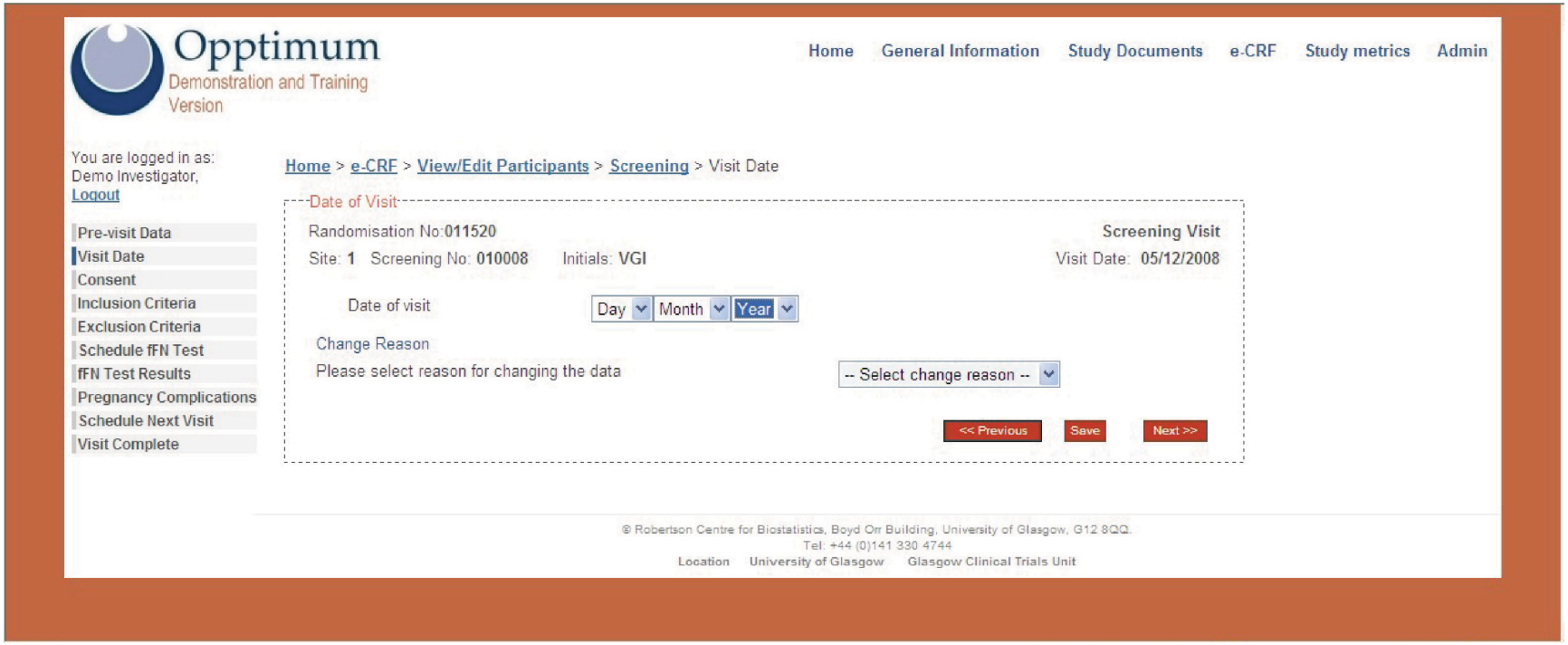
2. Screening Visit –

a. Pre-visit Data

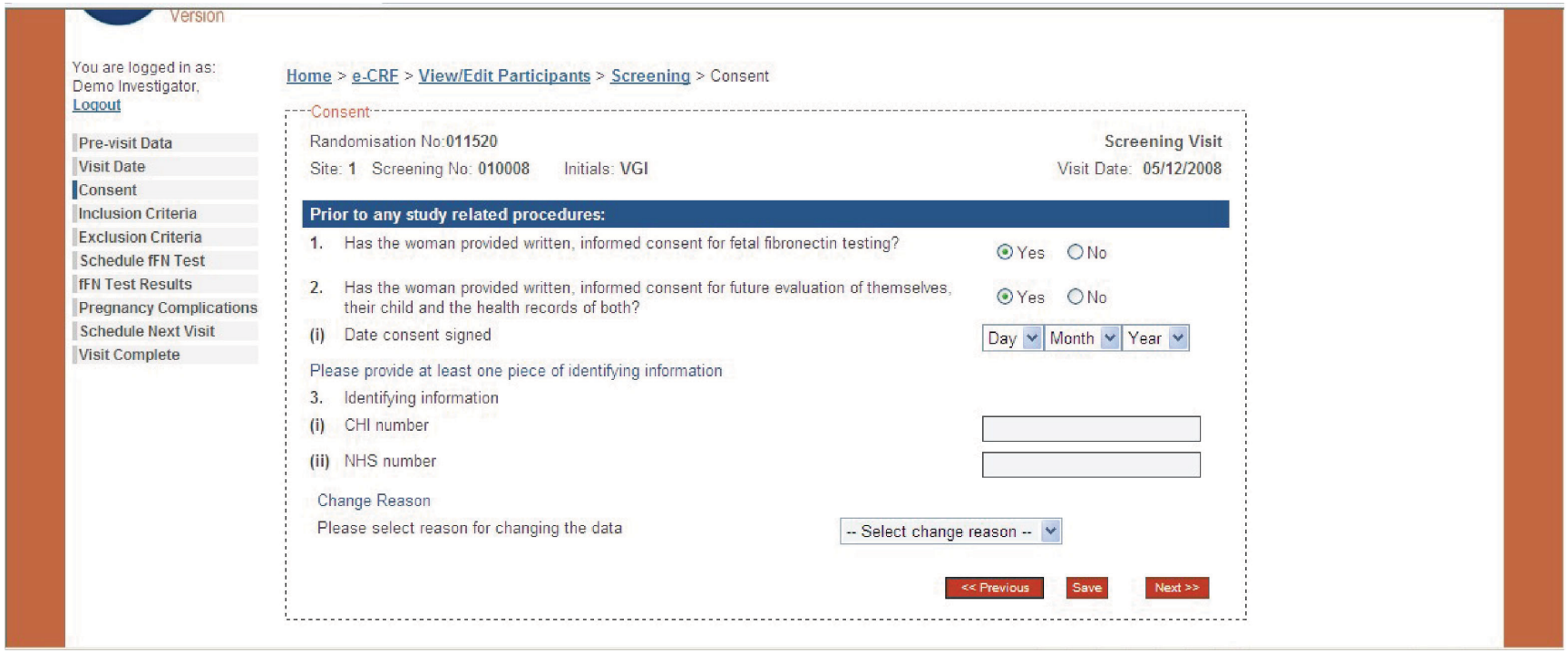




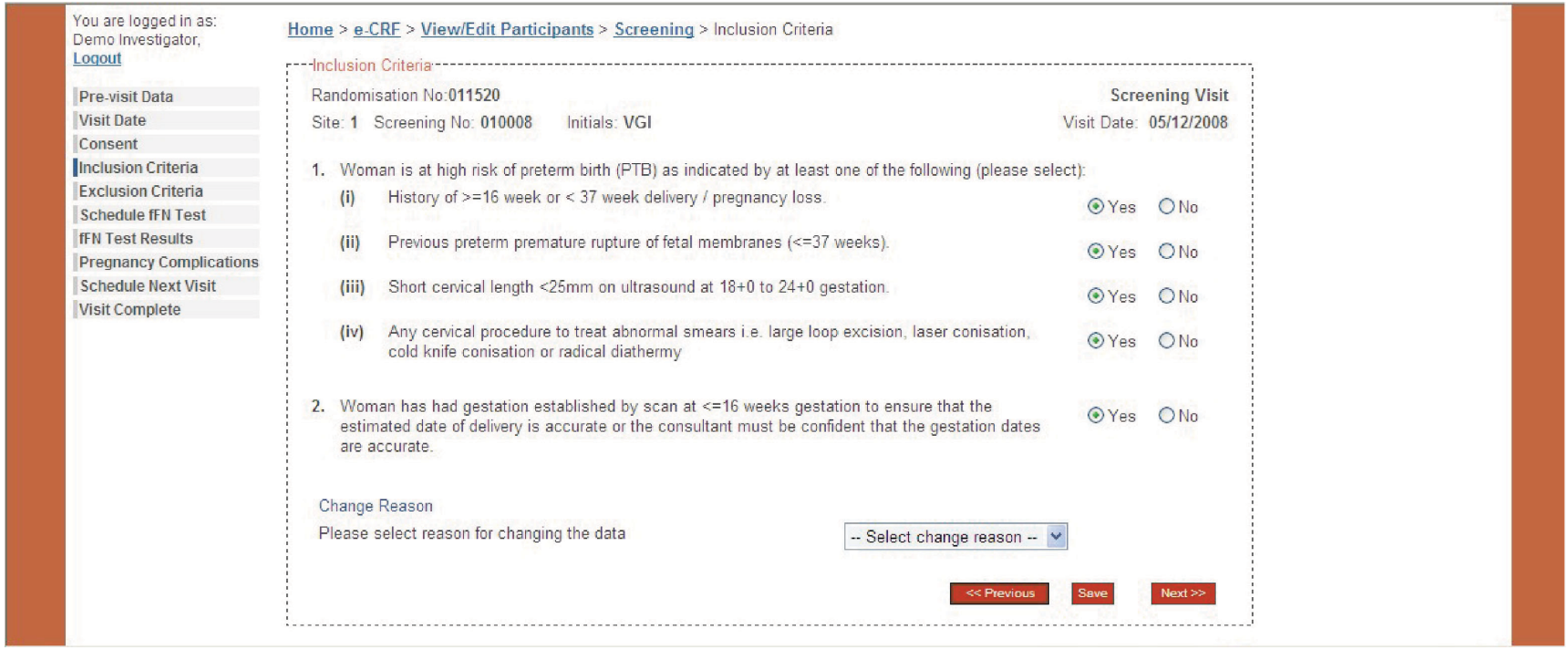
b. Visit Date



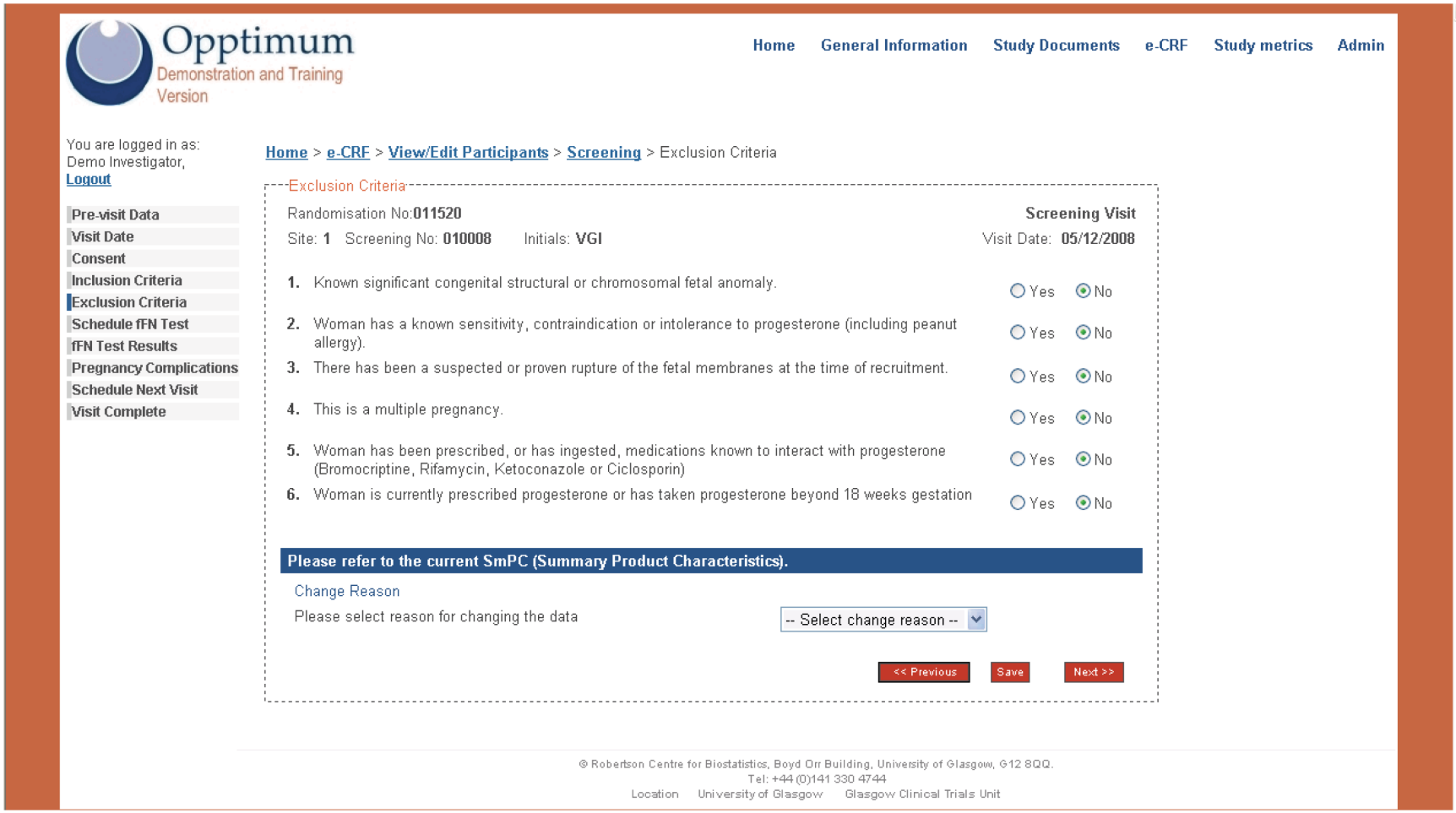
c. Consent



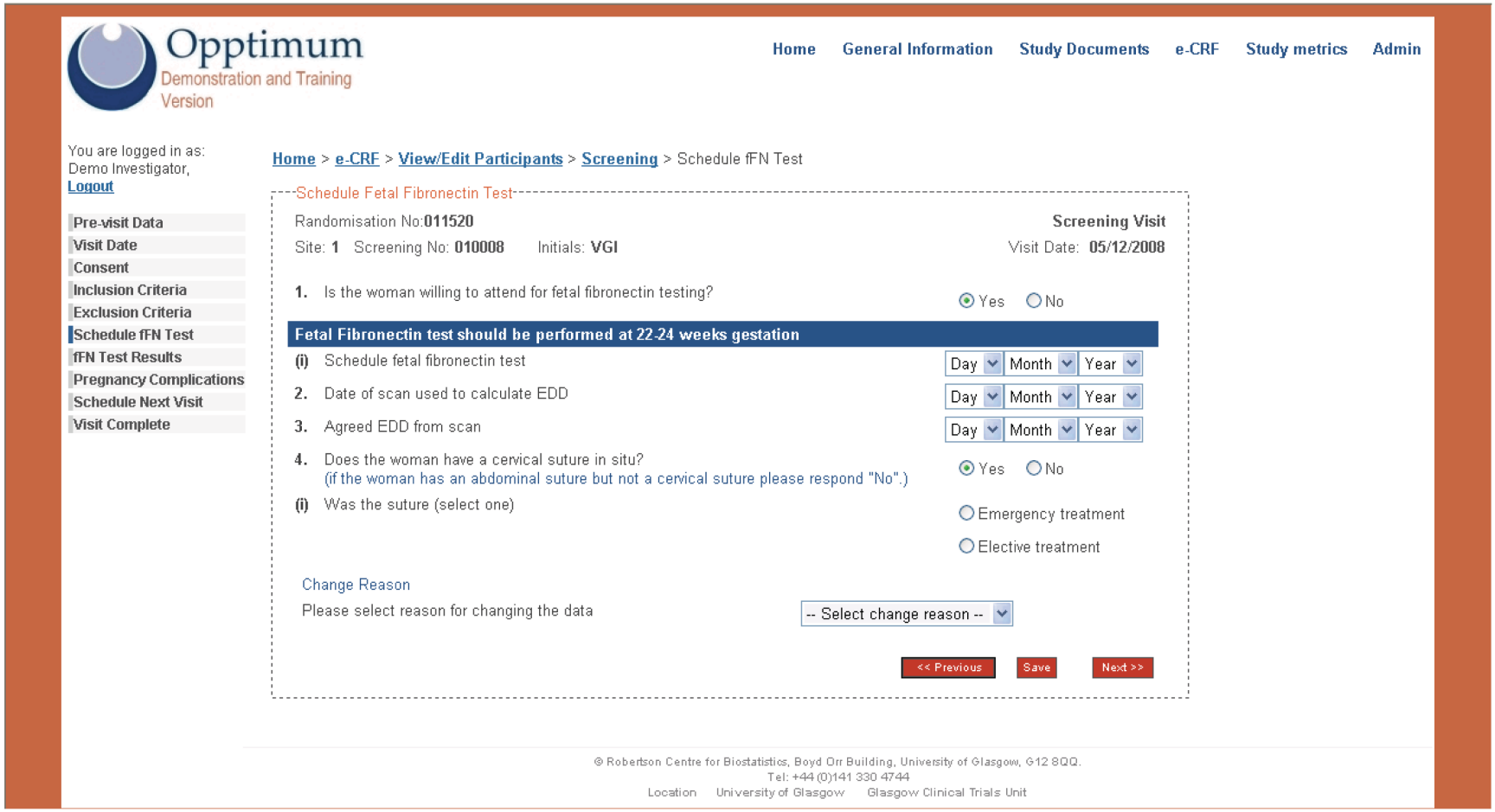
d. Inclusion Criteria



e. Exclusion Criteria

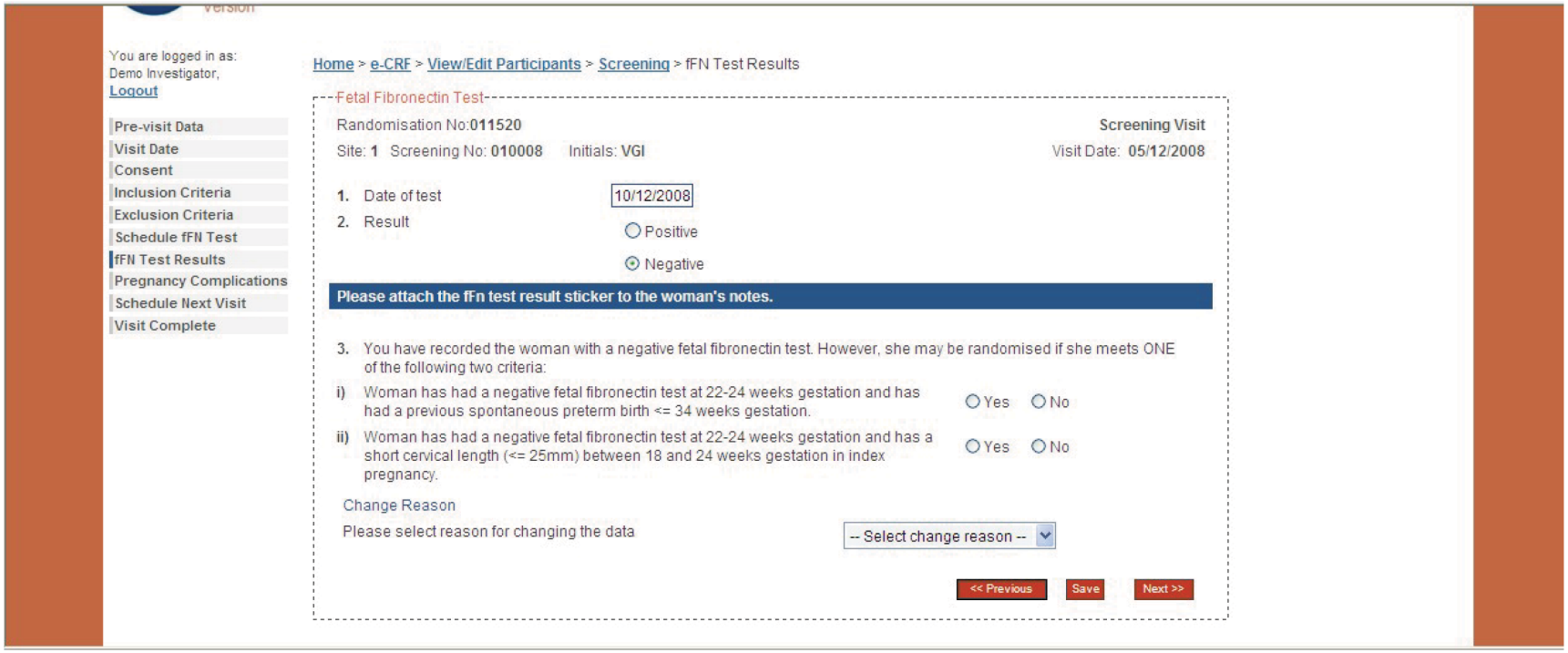


f. Schedule fFn Test

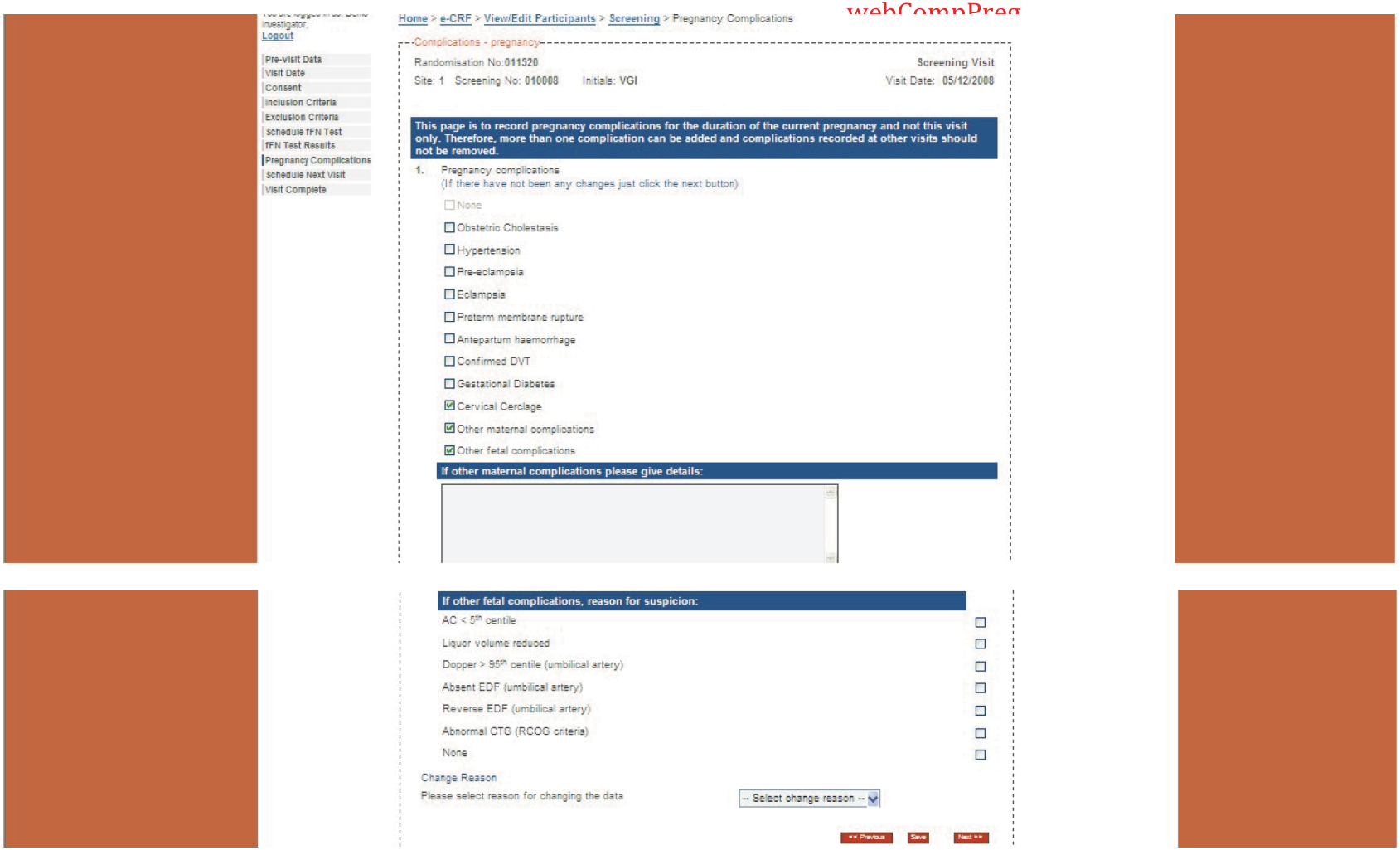


DOI: 10.3310/hta22350

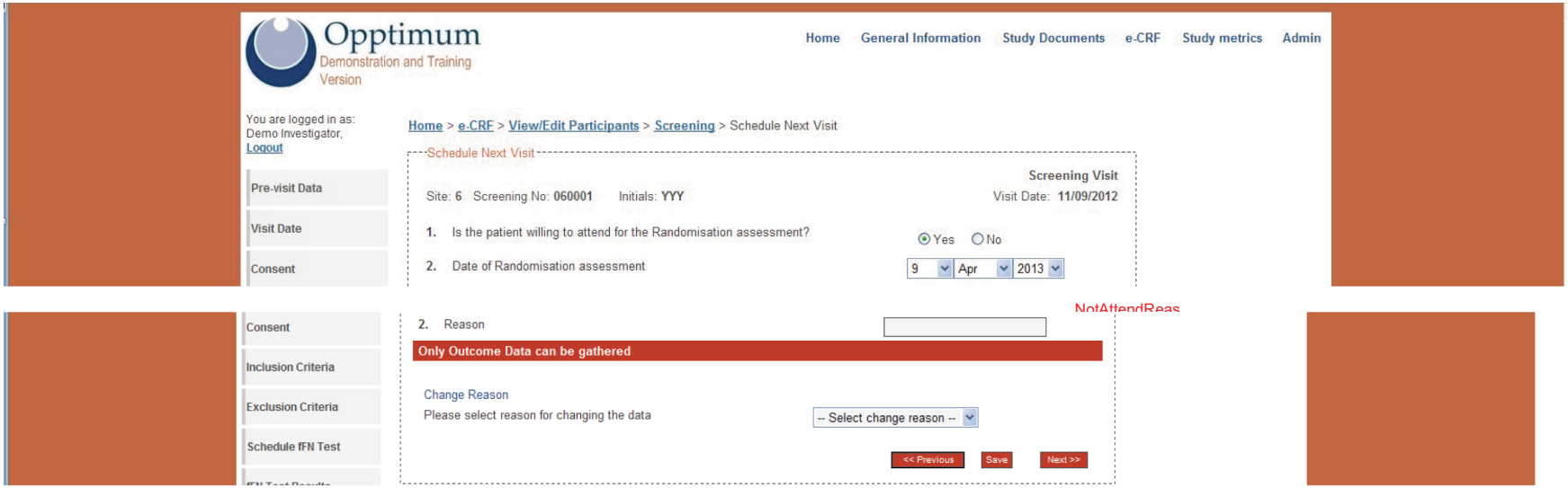
g. fFN Test Results



h. Pregnancy Complications



i. Schedule Next Visit

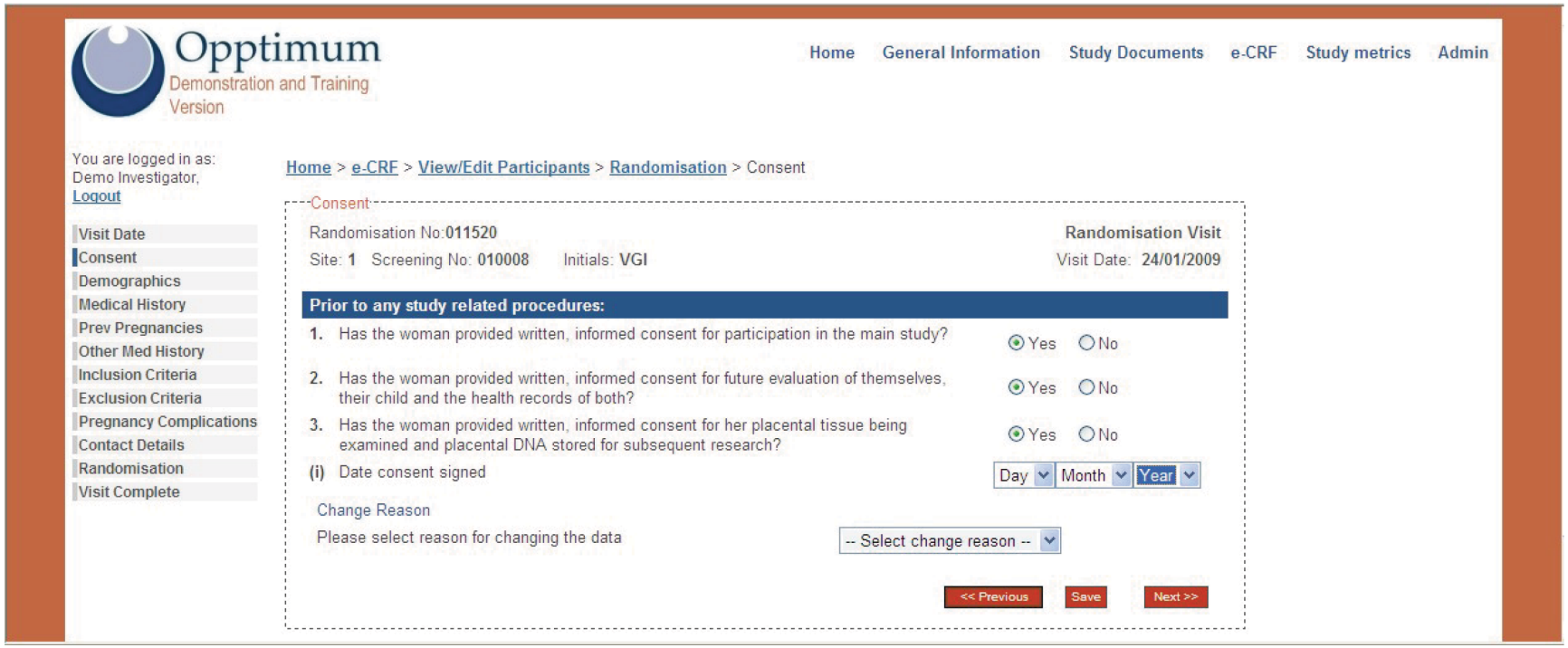


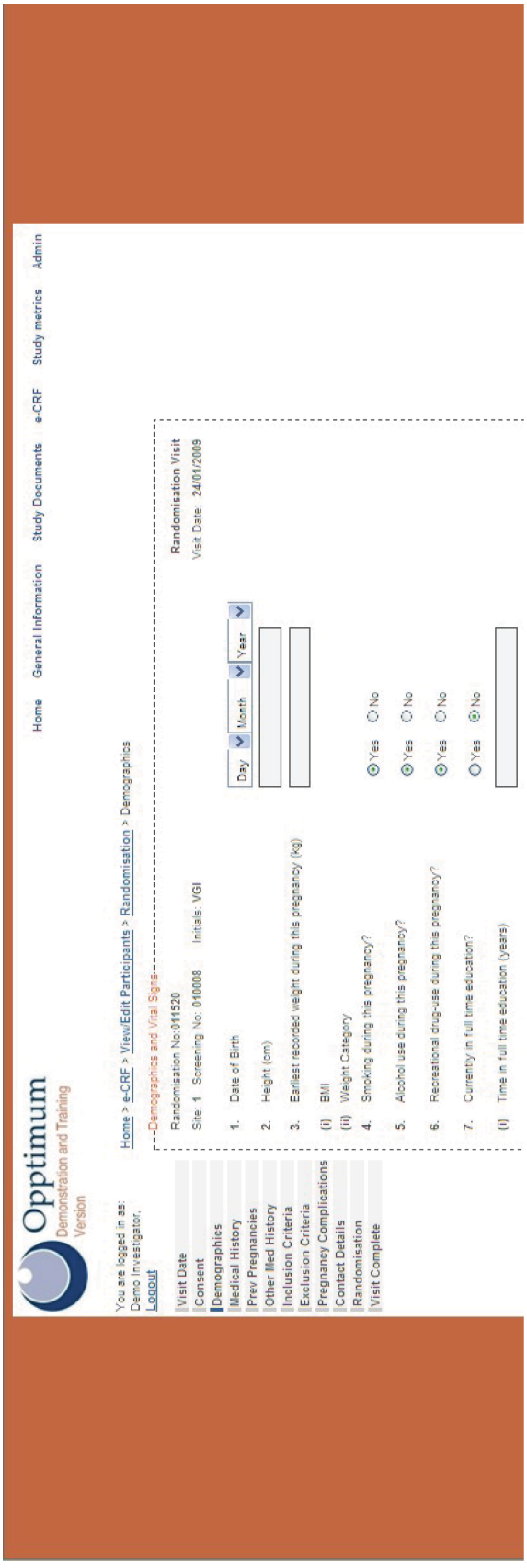
3. Randomisation Visit –

a. **Visit Date – See Section 2 (b)**

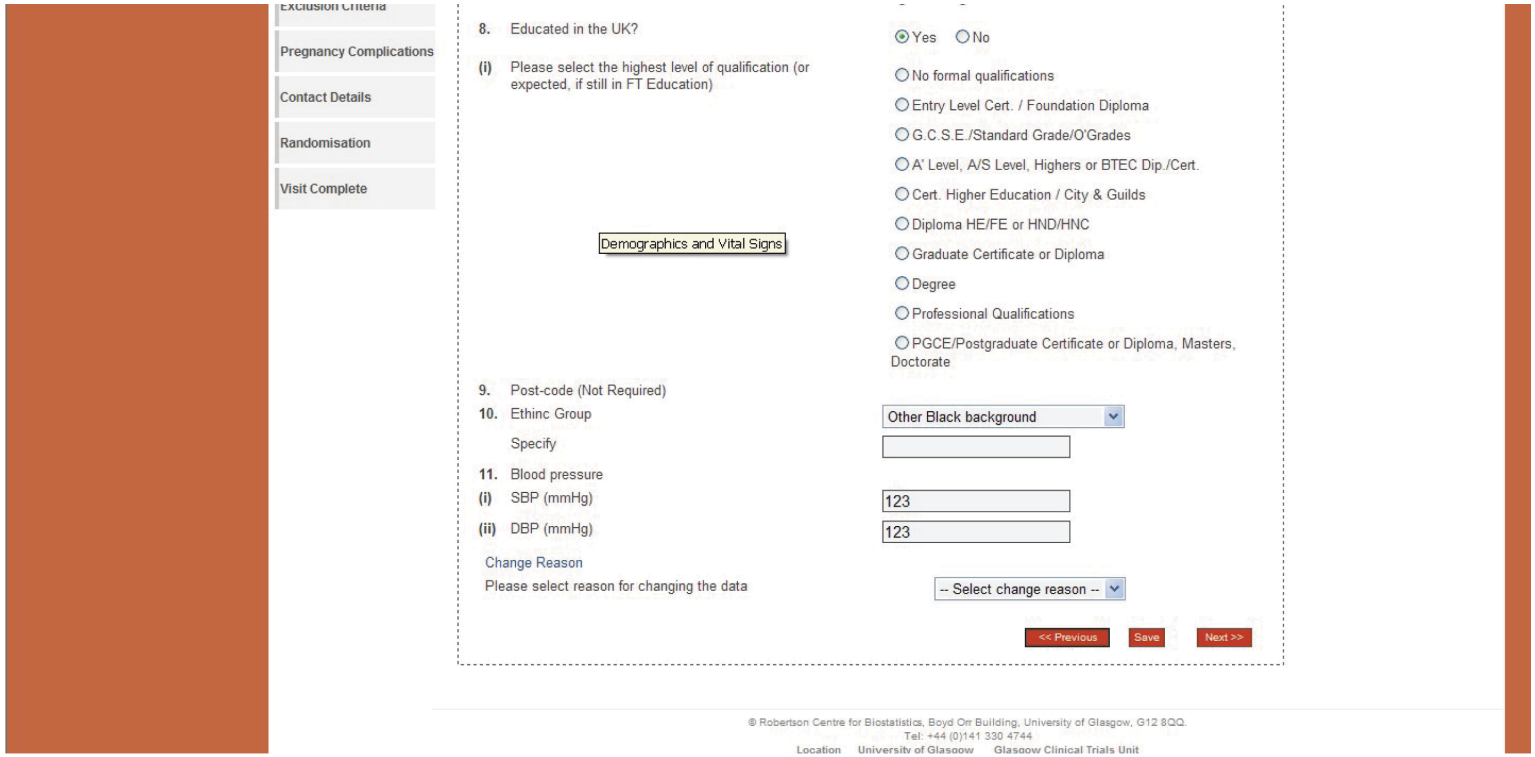
b. **Pregnancy Complications – See Section 2 (h)**

c. Consent

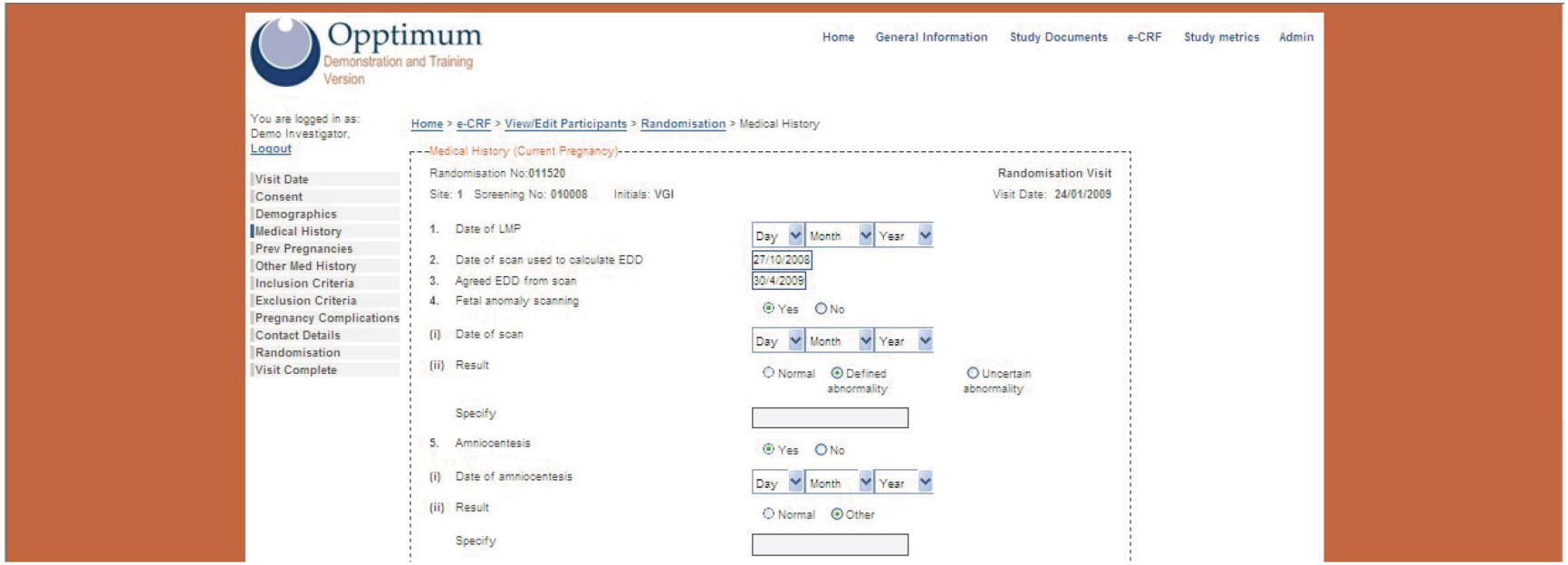


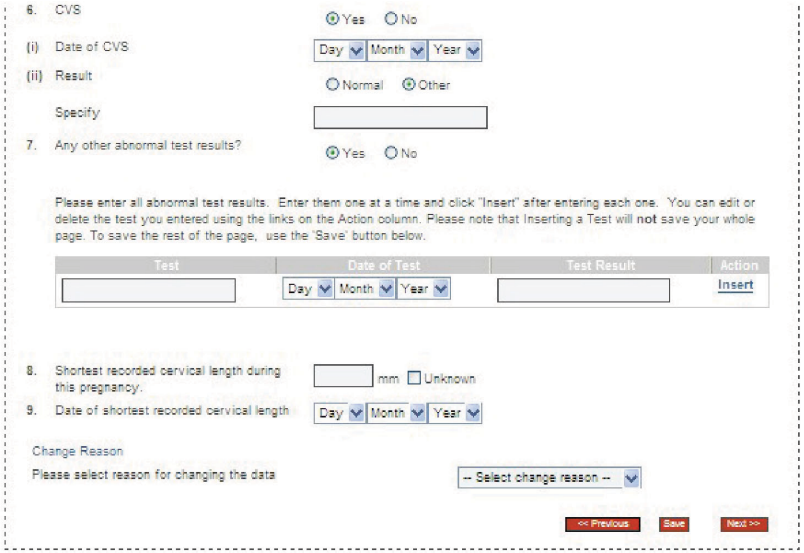


d. Demographics



e. Medical History – Current pregnancy





6. CVS ○ Yes ○ No

(i) Date of CVS Day Month Year

(ii) Result ○ Normal ○ Other

Specify

7. Any other abnormal test results? ○ Yes ○ No

Please enter all abnormal test results. Enter them one at a time and click "Insert" after entering each one. You can edit or delete the test you entered using the links on the Action column. Please note that Inserting a Test will **not** save your whole page. To save the rest of the page, use the 'Save' button below.

Test	Date of Test	Test Result	Action
	Day Month Year		Insert

8. Shortest recorded cervical length during this pregnancy. mm ☐ Unknown

9. Date of shortest recorded cervical length Day Month Year

Change Reason

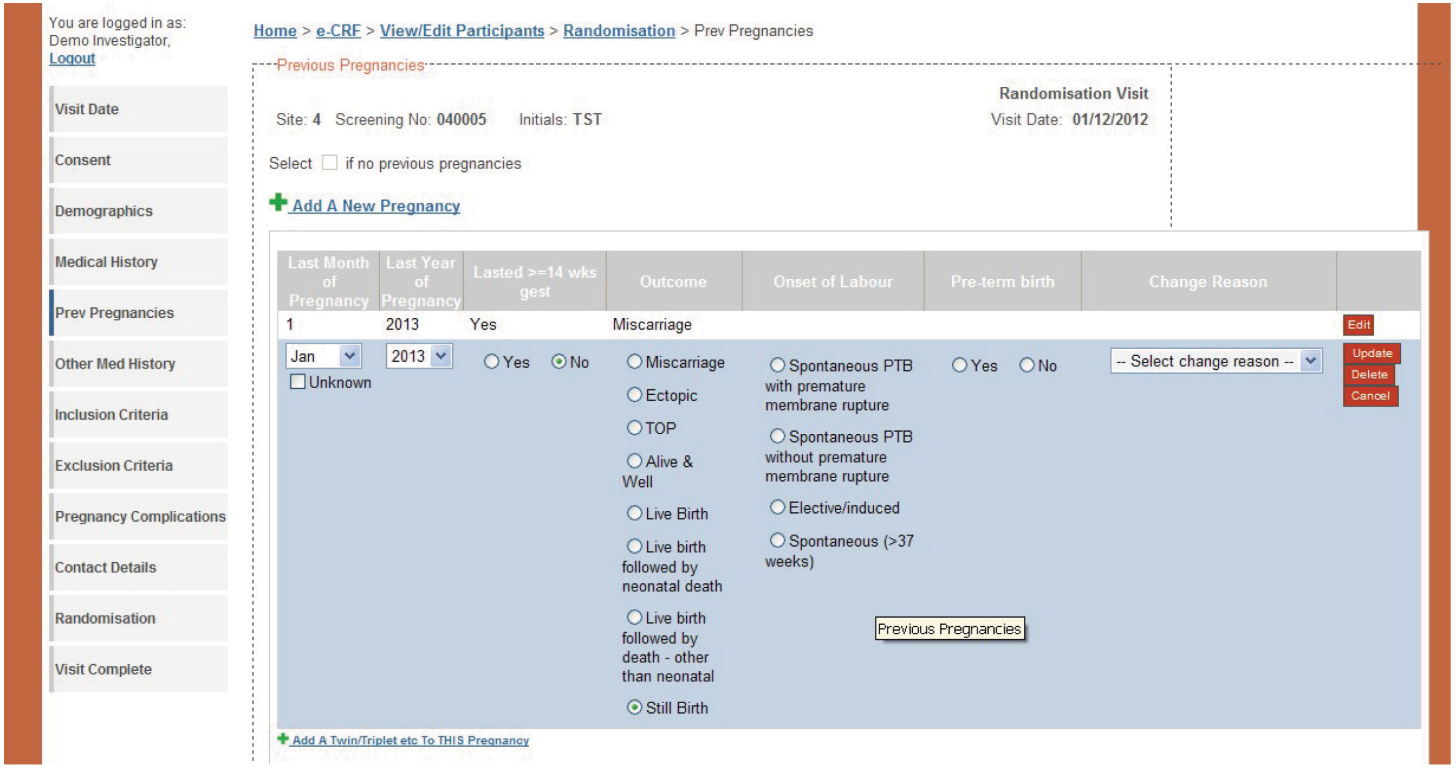
Please select reason for changing the data -- Select change reason --

<< Previous Save Next >>

DOI: 10.3310/hta22350

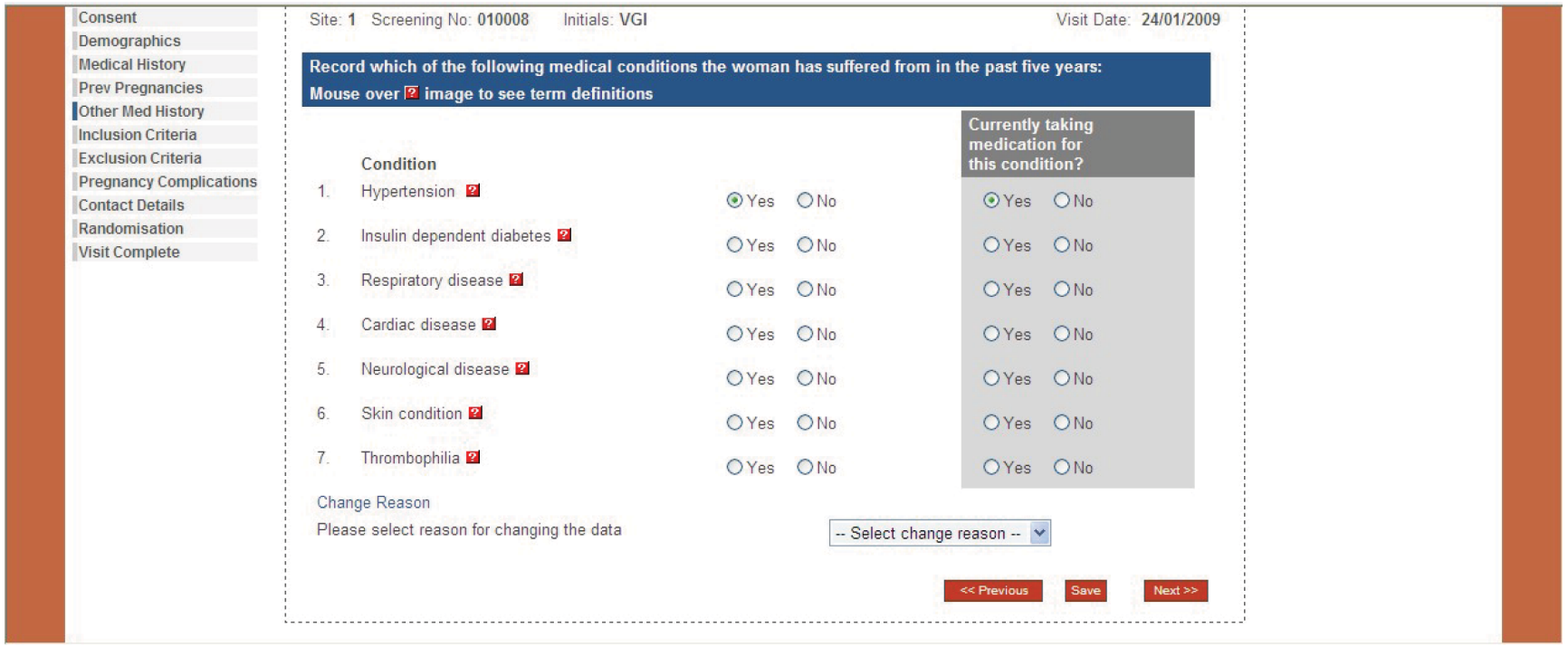
f. Previous Pregnancies

webPrevPreg

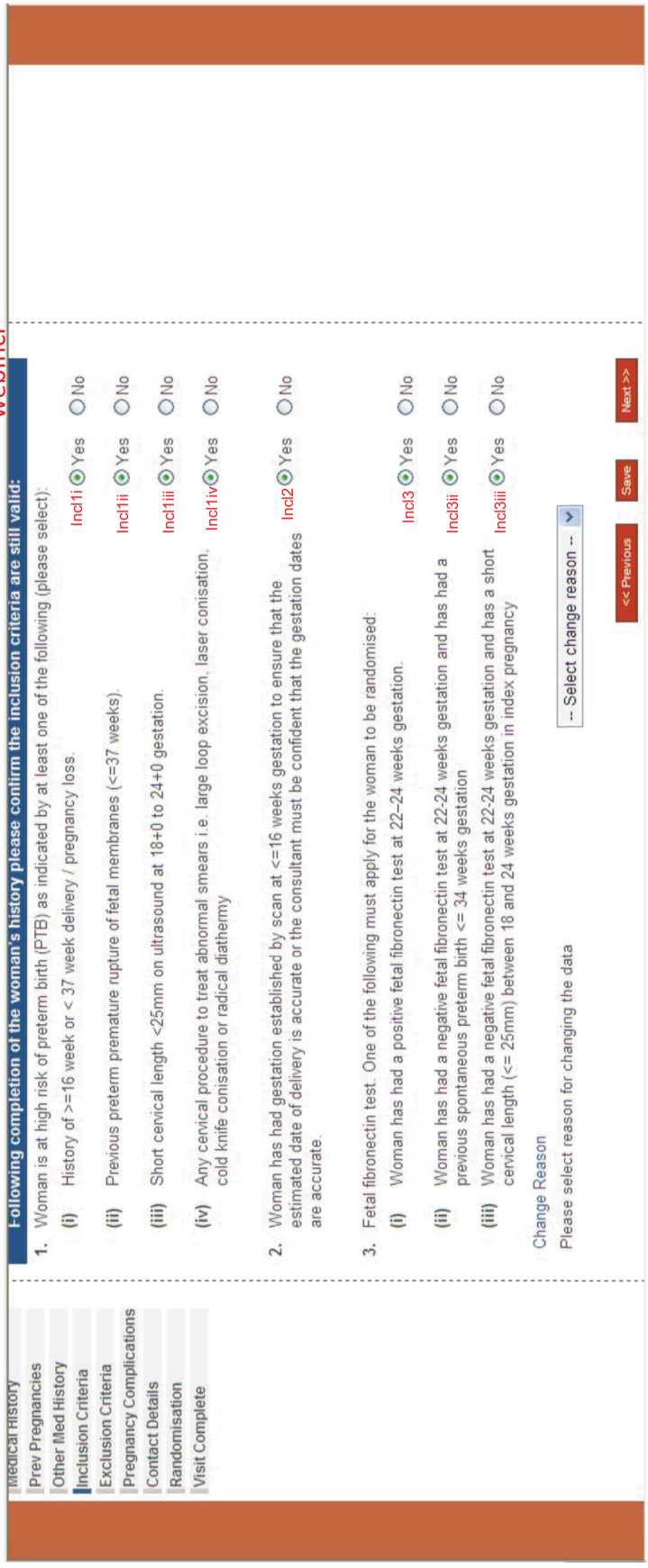


g. Other Med History

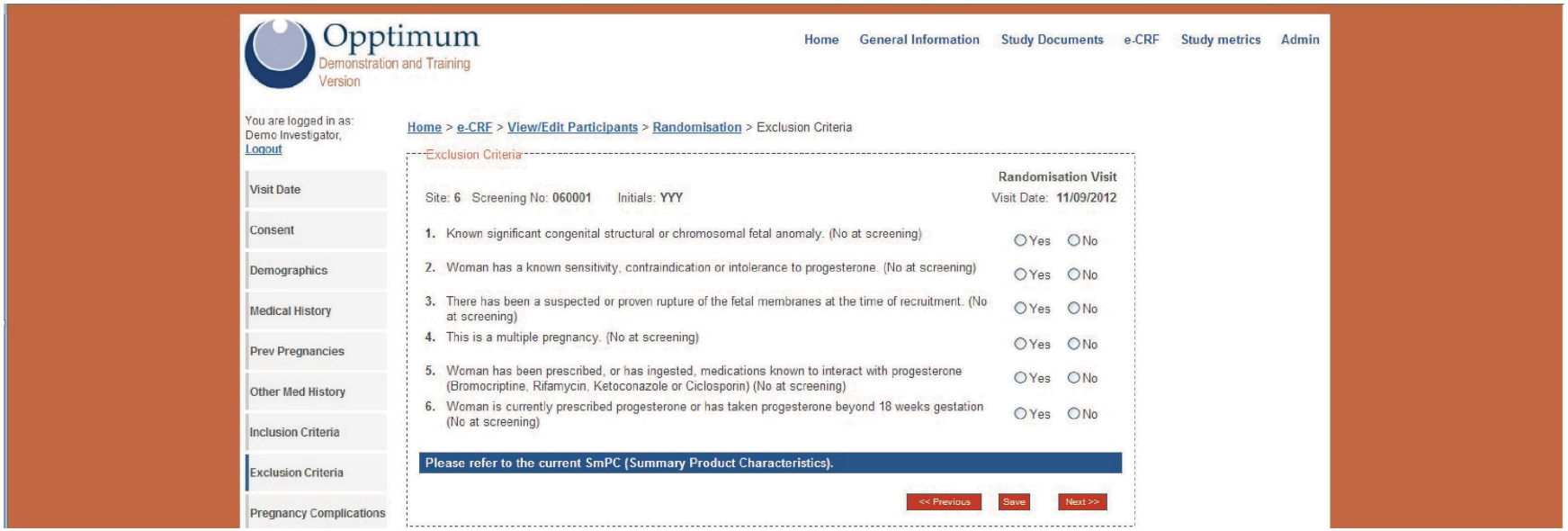
webMedHistOth



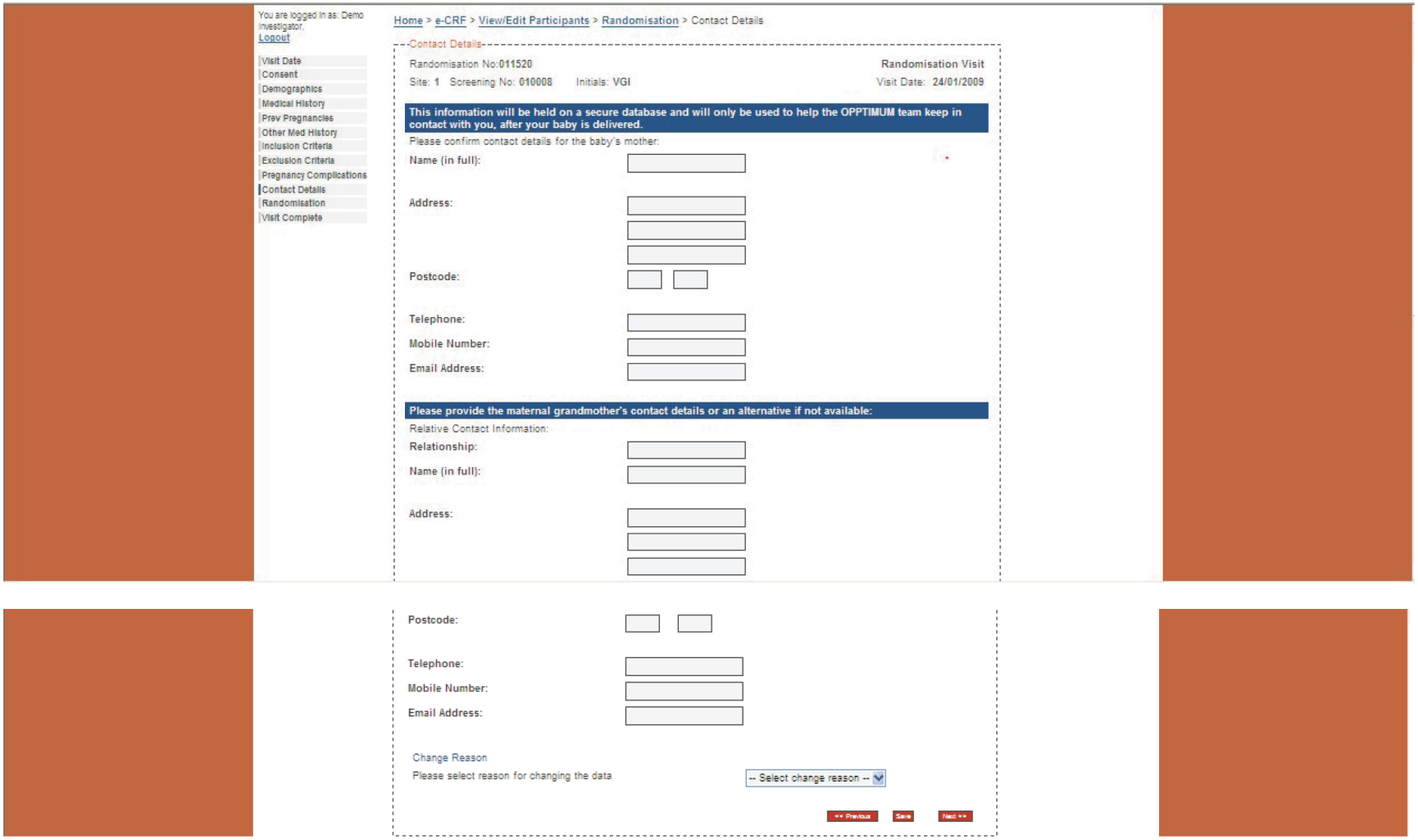
h. Inclusion Criteria

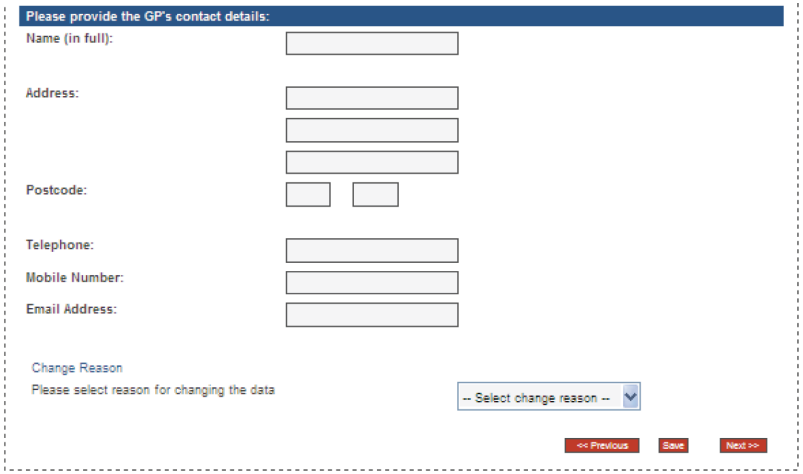


i. Exclusion Criteria

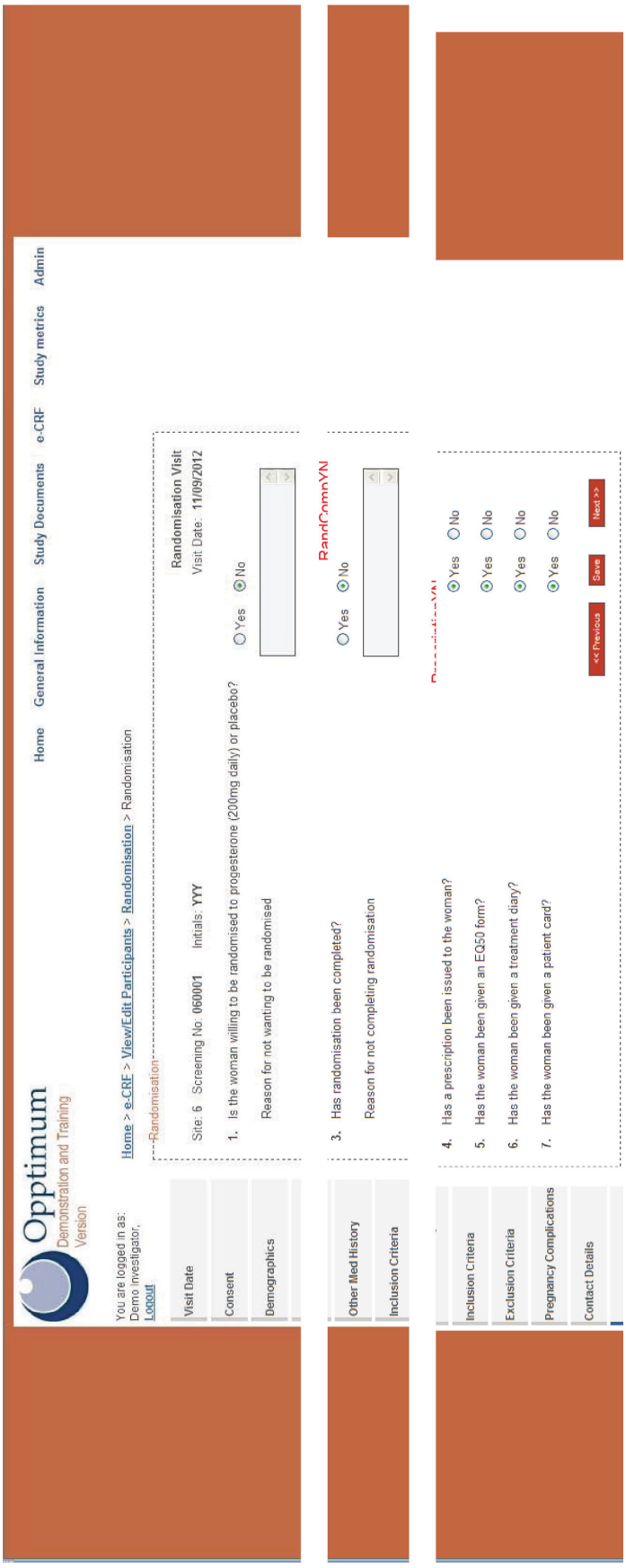


j. Contact Details




Please provide the GP's contact details:
Name (in full):
Address:
Postcode:
Telephone:
Mobile Number:
Email Address:
Change Reason
Please select reason for changing the data
-- Select change reason --
<< Previous
Save
Next >>

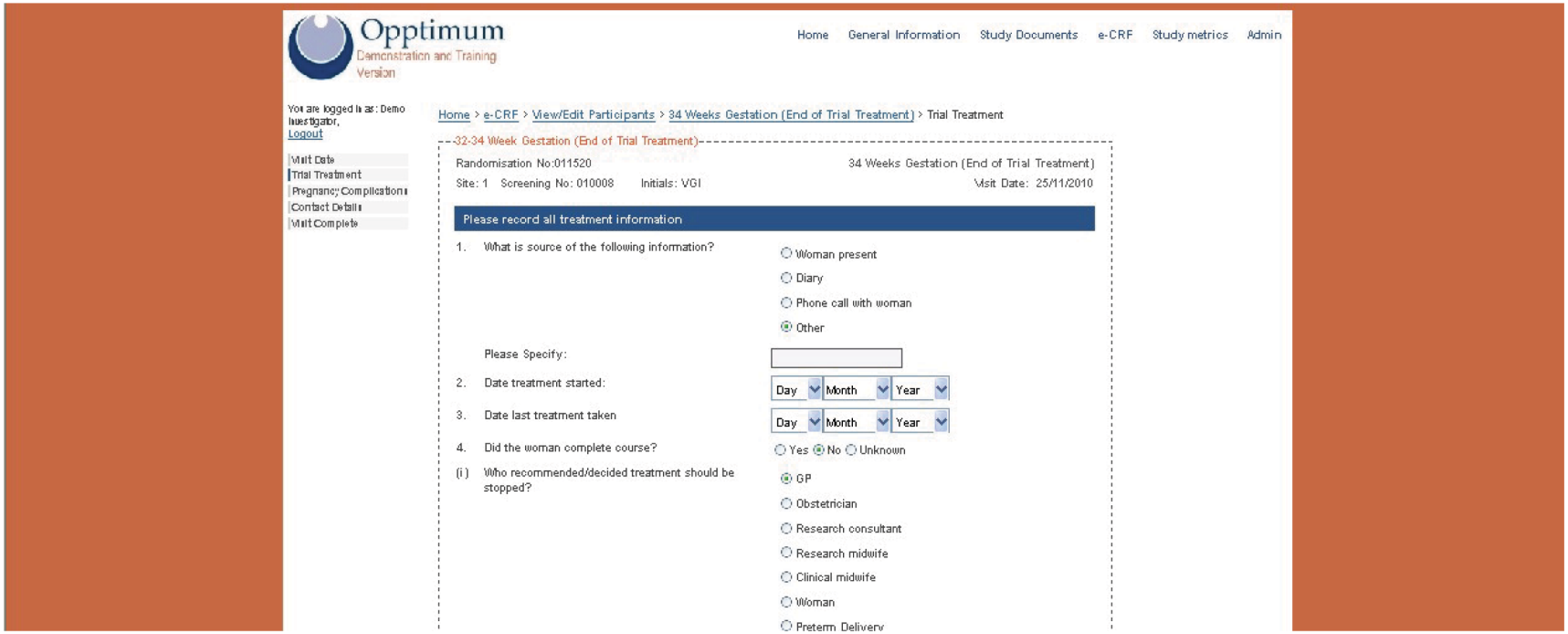
k. Randomisation

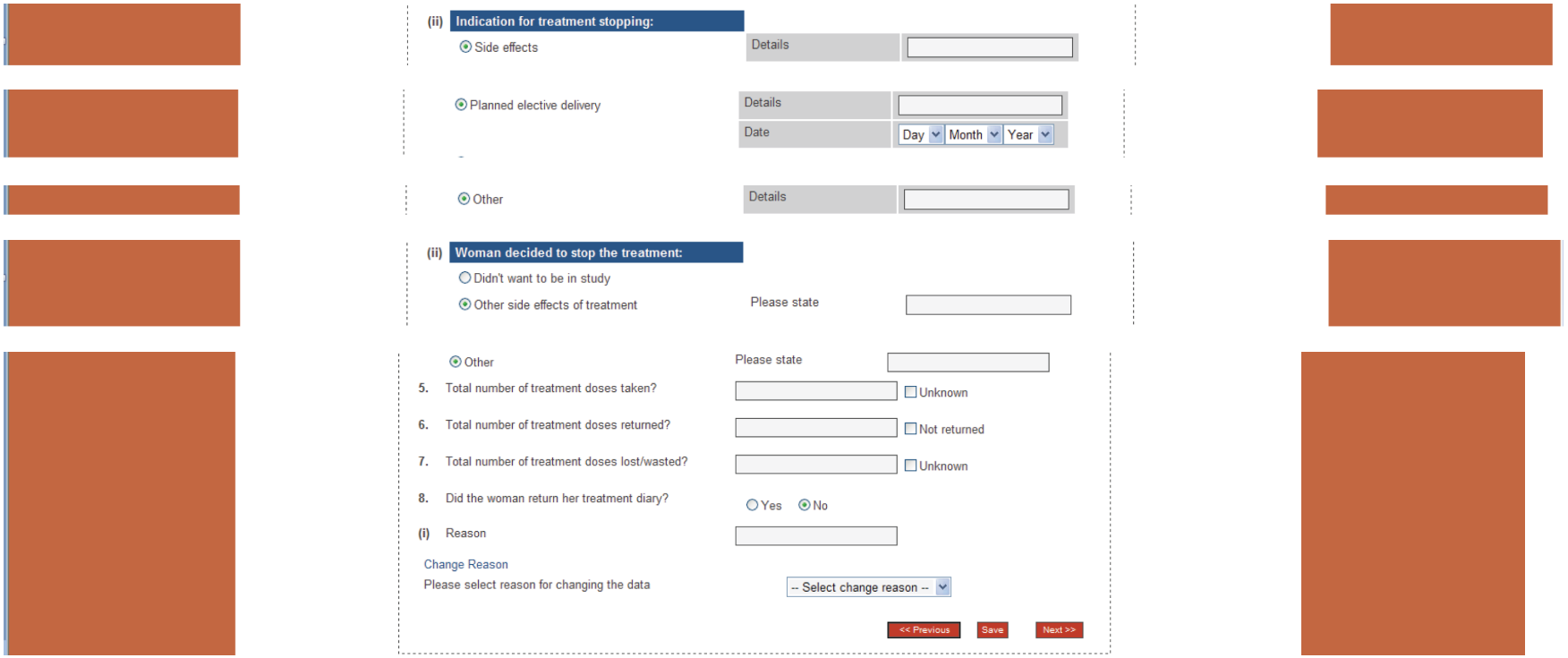


4. 34 Weeks Gestation (End of Trial Treatment) –

- **a.** Visit Date – See Section 2 (b)
- **b.** Pregnancy Complications – See Section 2 (h)
- **c.** Contact Details – See Section 3 (j)

d. Trial Treatment

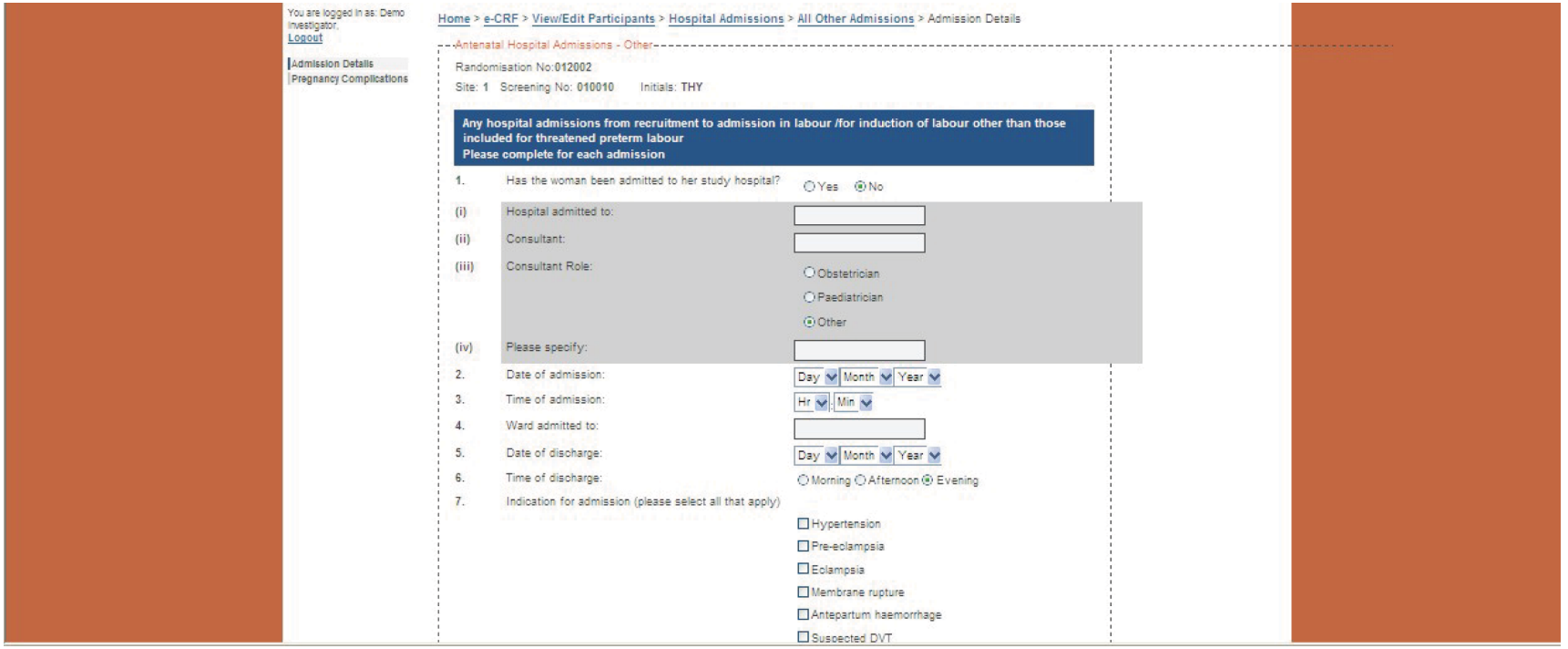



(ii) Indication for treatment stopping:
Side effects
Details
Planned elective delivery
Details
Date
Day Month Year
Other
Details
(ii) Woman decided to stop the treatment:
Didn't want to be in study
Other side effects of treatment
Please state
Other
Please state
5. Total number of treatment doses taken?
Unknown
6. Total number of treatment doses returned?
Not returned
7. Total number of treatment doses lost/wasted?
Unknown
8. Did the woman return her treatment diary?
Yes
No
(i) Reason
Change Reason
Please select reason for changing the data
-- Select change reason --
<< Previous
Save
Next >>

5. Hospital Admissions –

a. Pregnancy Complications – See Section 2 (h)

b. Admission Details – Antenatal Hospital Admissions



You are logged in as: Demo Investigator.
Logout

Admission Details
Pregnancy Complications

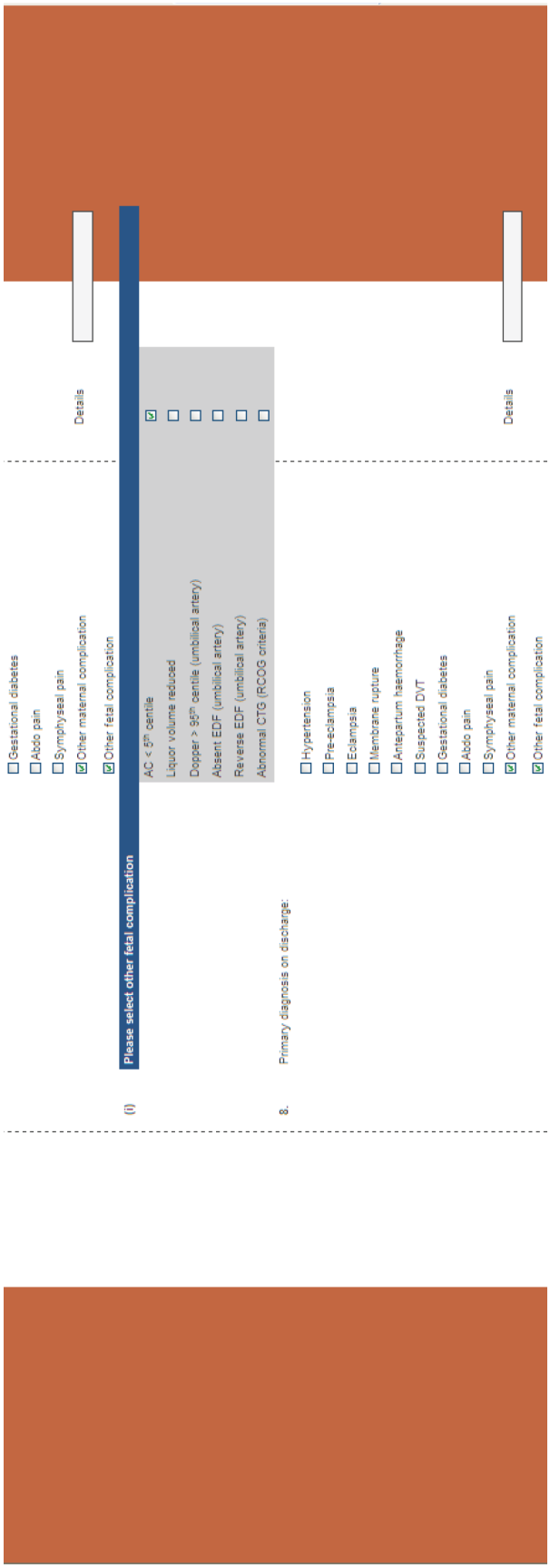
Home > e-CRF > View/Edit Participants > Hospital Admissions > All Other Admissions > Admission Details

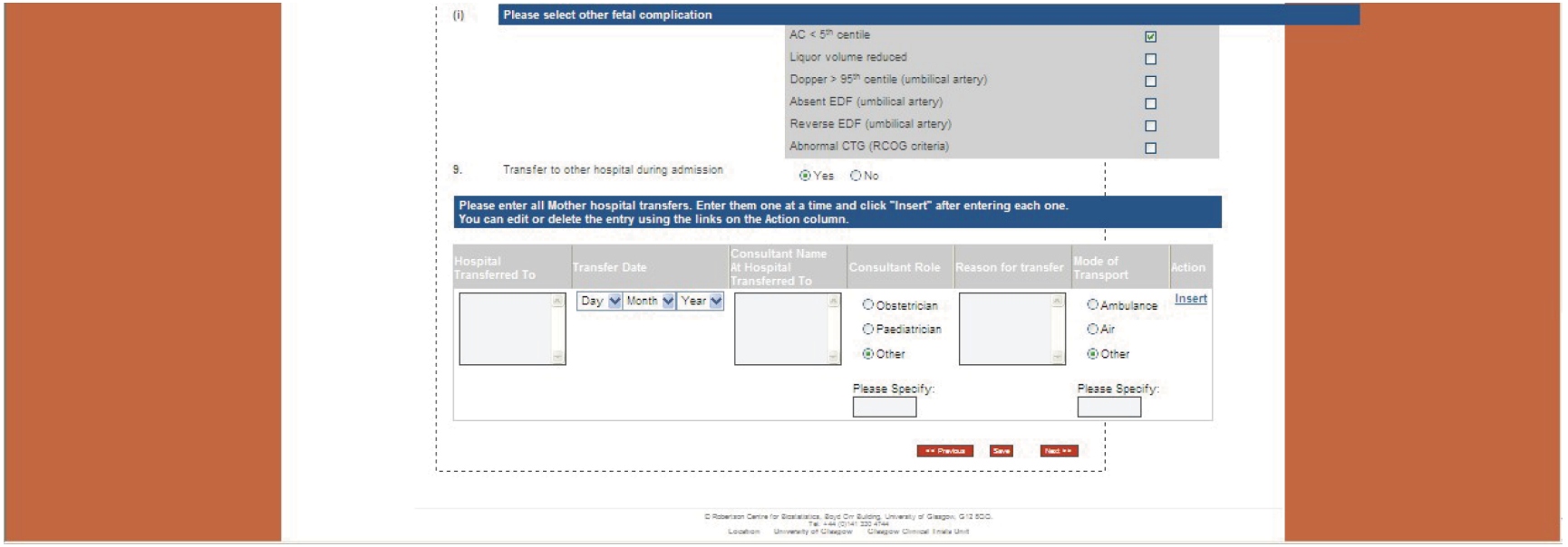
Antenatal Hospital Admissions - Other

Randomisation No:012002
Site: 1 Screening No: 010010 Initials: THY

Any hospital admissions from recruitment to admission in labour /for induction of labour other than those included for threatened preterm labour
Please complete for each admission

1. Has the woman been admitted to her study hospital? ○ Yes ◉ No
(i) Hospital admitted to:
(ii) Consultant:
(iii) Consultant Role: ○ Obstetrician ○ Paediatrician ◉ Other
(iv) Please specify:
2. Date of admission: Day Month Year
3. Time of admission: Hr Min
4. Ward admitted to:
5. Date of discharge: Day Month Year
6. Time of discharge: ○ Morning ○ Afternoon ◉ Evening
7. Indication for admission (please select all that apply)
☐ Hypertension
☐ Pre-eclampsia
☐ Eclampsia
☐ Membrane rupture
☐ Antepartum haemorrhage
☐ Suspected DVT





(i) **Please select other fetal complication**

AC < 5th centile	☑
Liquor volume reduced	☐
Dopper > 95th centile (umbilical artery)	☐
Absent EDF (umbilical artery)	☐
Reverse EDF (umbilical artery)	☐
Abnormal CTG (RCOG criteria)	☐

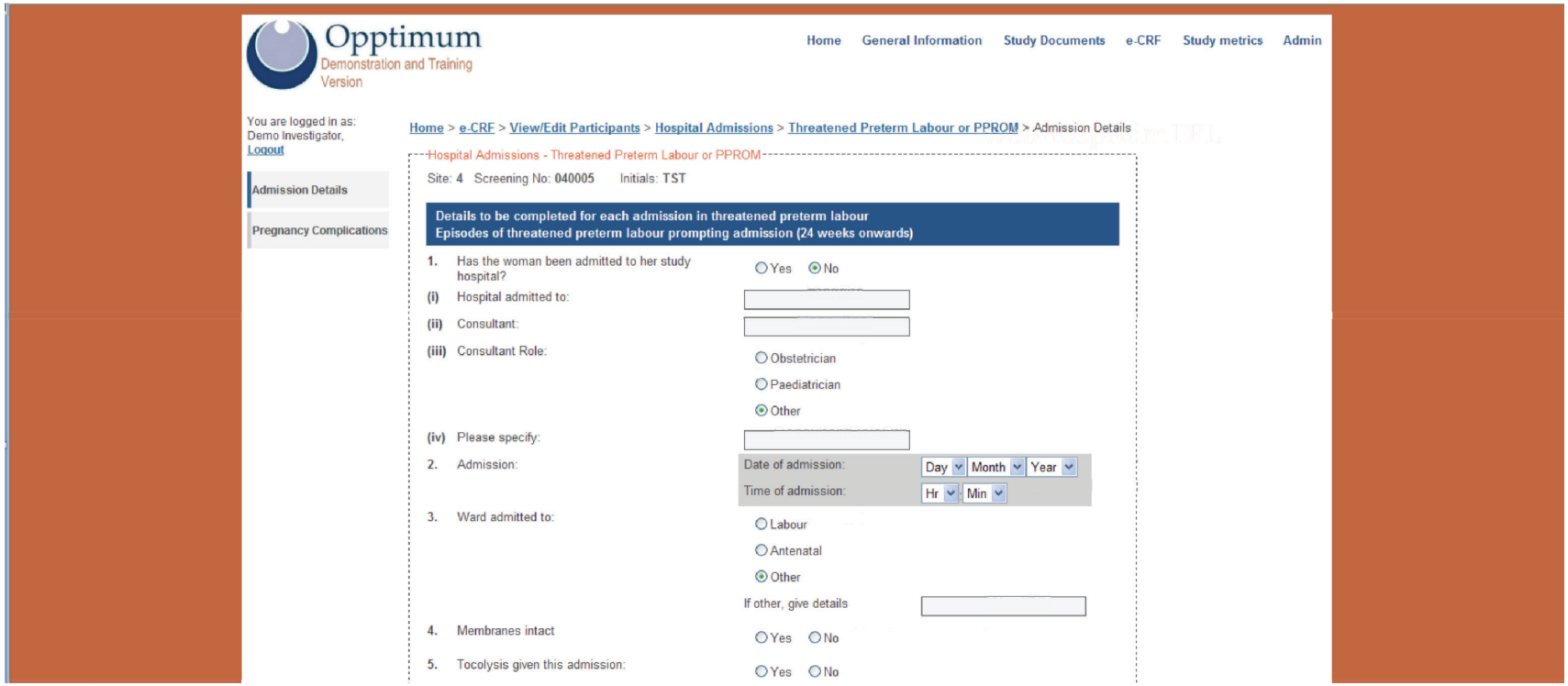
9. Transfer to other hospital during admission ◉ Yes ○ No

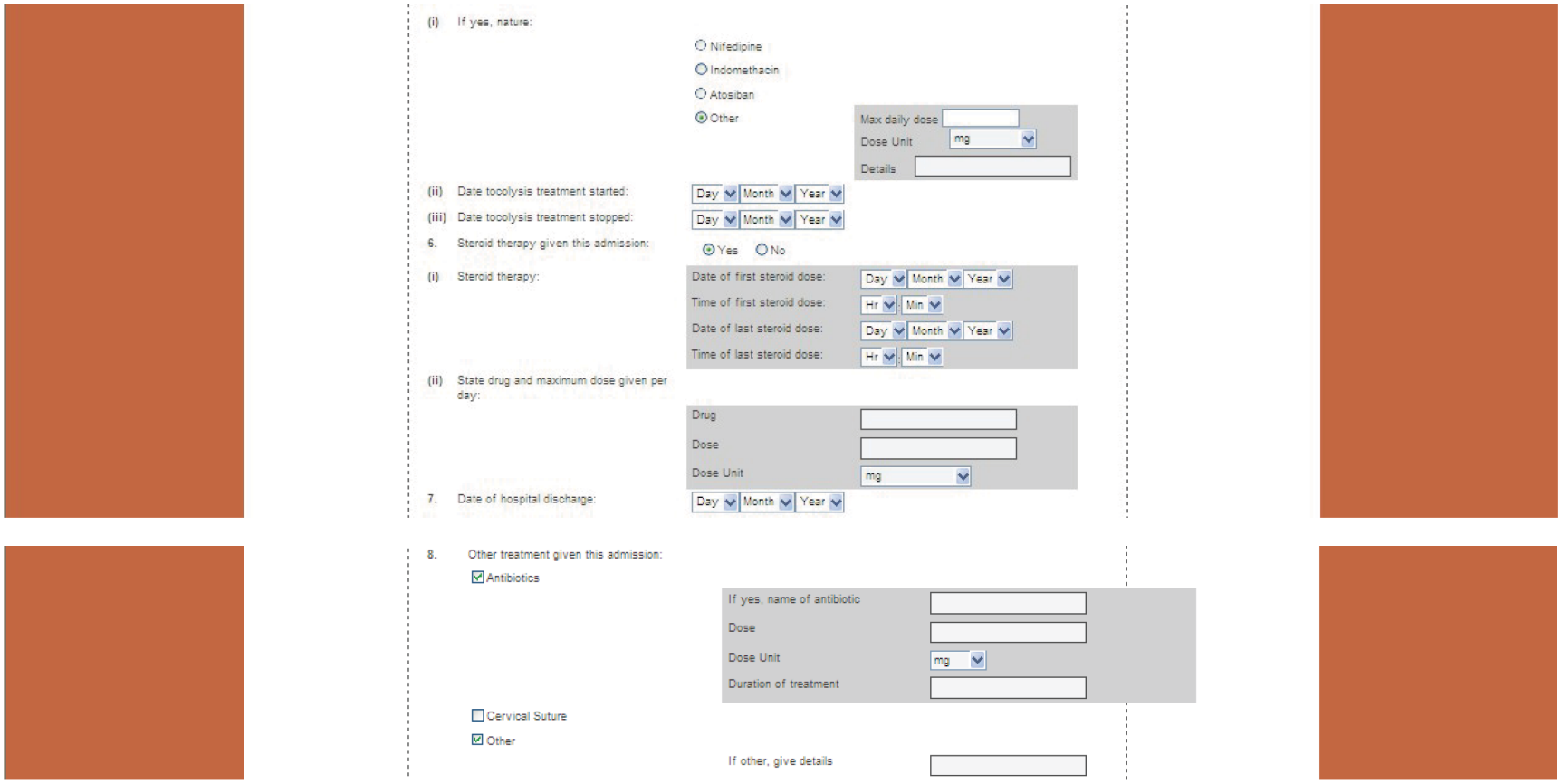
Please enter all Mother hospital transfers. Enter them one at a time and click "Insert" after entering each one. You can edit or delete the entry using the links on the Action column.

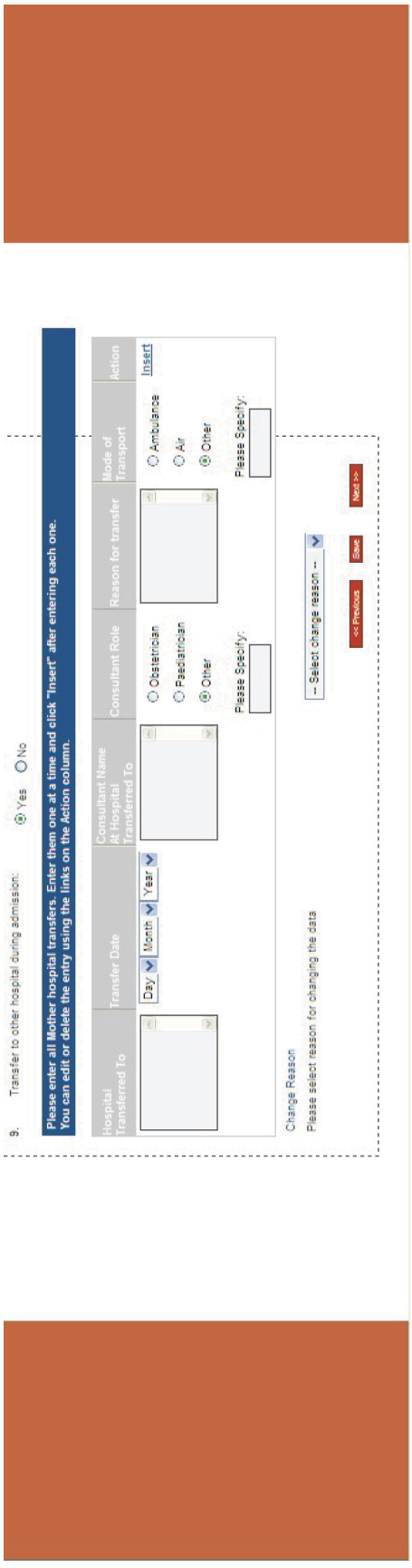
Hospital Transferred To	Transfer Date	Consultant Name At Hospital Transferred To	Consultant Role	Reason for transfer	Mode of Transport	Action
	Day Month Year		○ Obstetrician ○ Paediatrician ◉ Other Please Specify:		○ Ambulance ○ Air ◉ Other Please Specify:	Insert

<< Previous Save Next >>

C. Hospital Admissions – Threatened Preterm Labour or PPROM



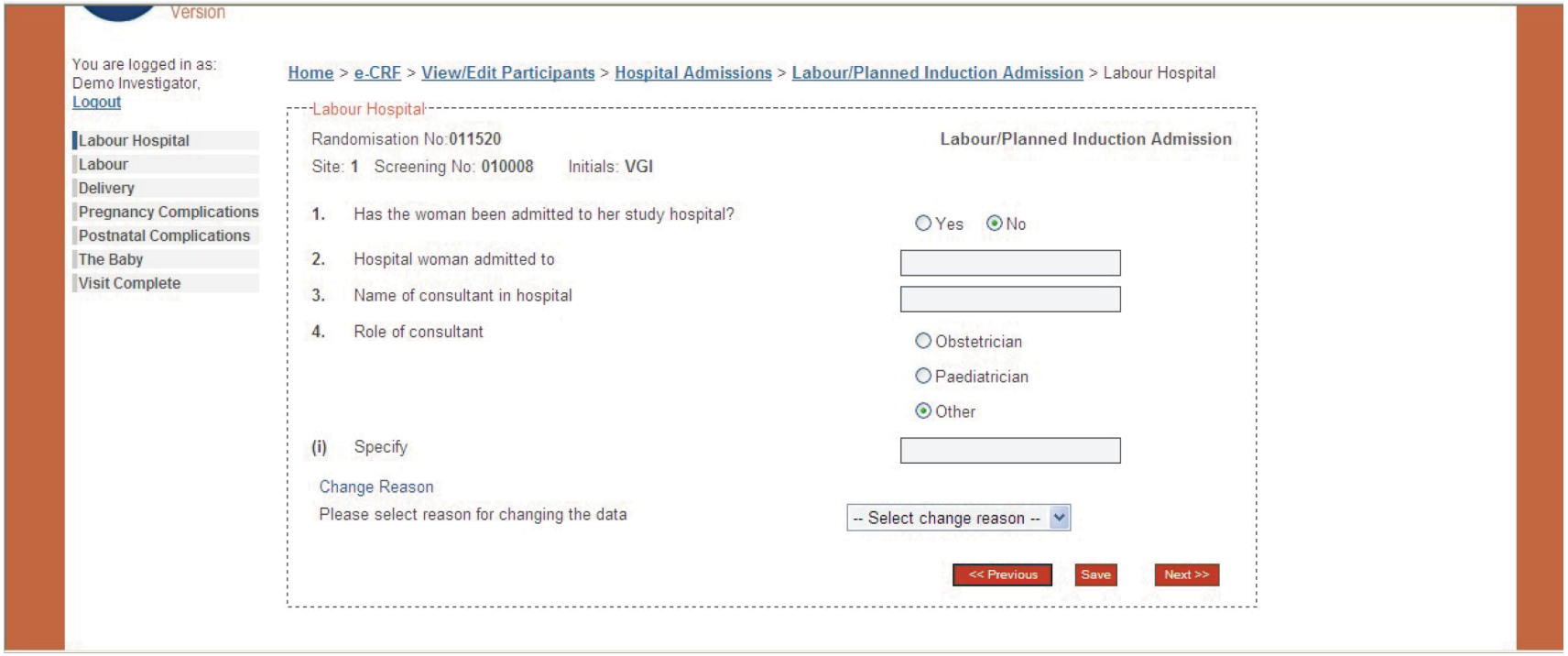

(i) If yes, nature:
Nifedipine
Indomethacin
Atosiban
Other
Max daily dose
Dose Unit
mg
Details
(ii) Date tocolysis treatment started:
Day Month Year
(iii) Date tocolysis treatment stopped:
Day Month Year
6. Steroid therapy given this admission:
Yes No
(i) Steroid therapy:
Date of first steroid dose:
Day Month Year
Time of first steroid dose:
Hr Min
Date of last steroid dose:
Day Month Year
Time of last steroid dose:
Hr Min
(ii) State drug and maximum dose given per day:
Drug
Dose
Dose Unit
mg
7. Date of hospital discharge:
Day Month Year
8. Other treatment given this admission:
Antibiotics
If yes, name of antibiotic
Dose
Dose Unit
mg
Duration of treatment
Cervical Suture
Other
If other, give details



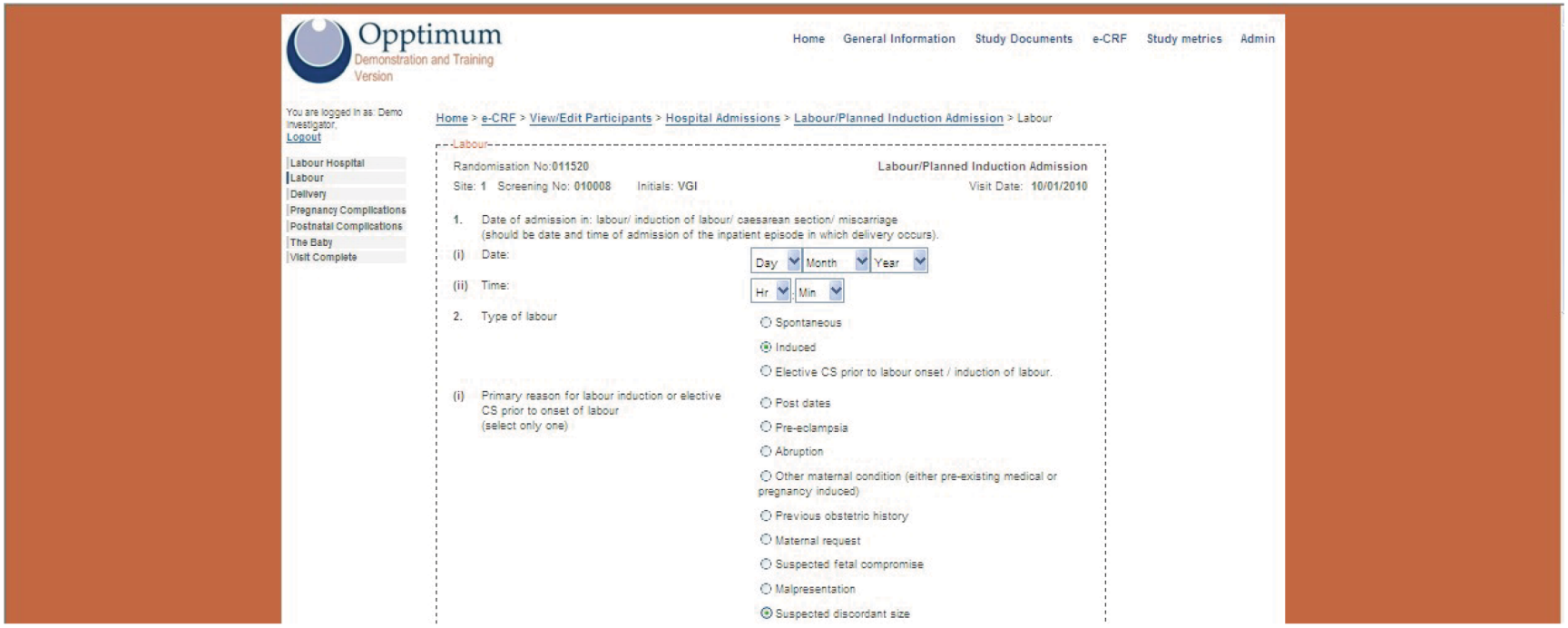
6. Labour/Planned Induction Admission

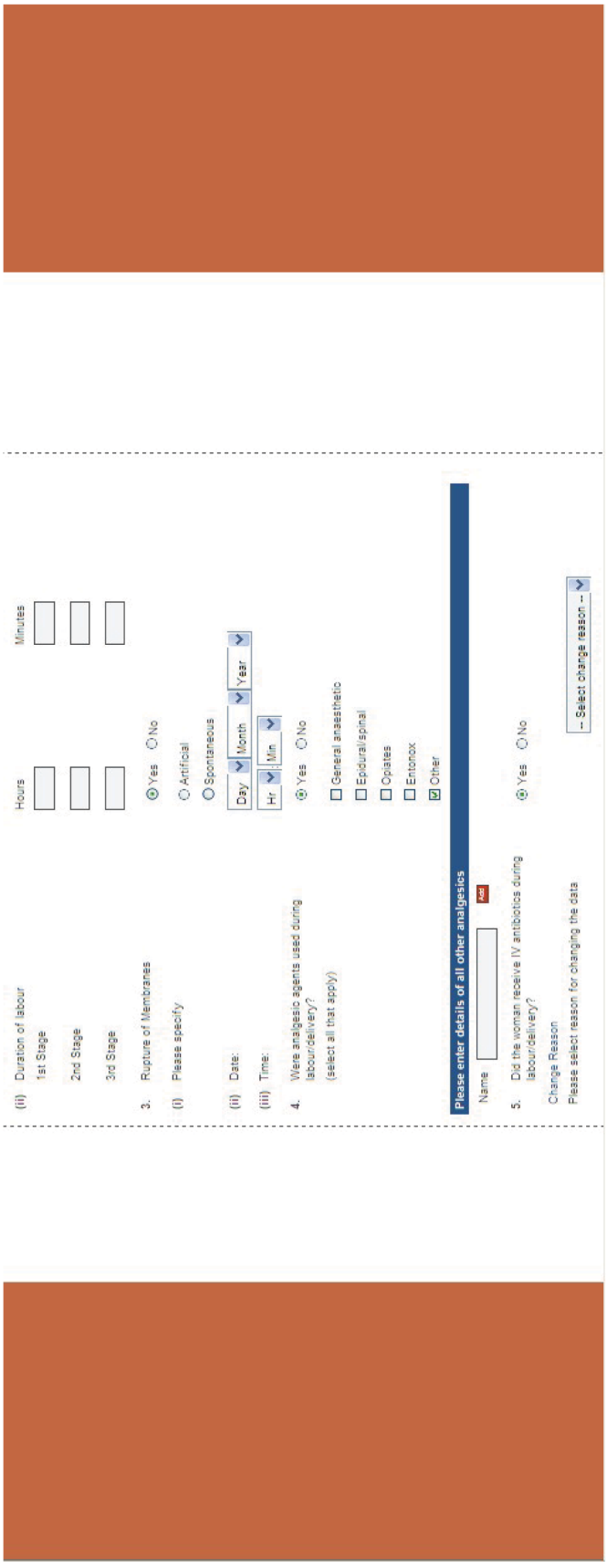
a. Pregnancy Complications – See Section 2 (h)

b. Labour Hospital

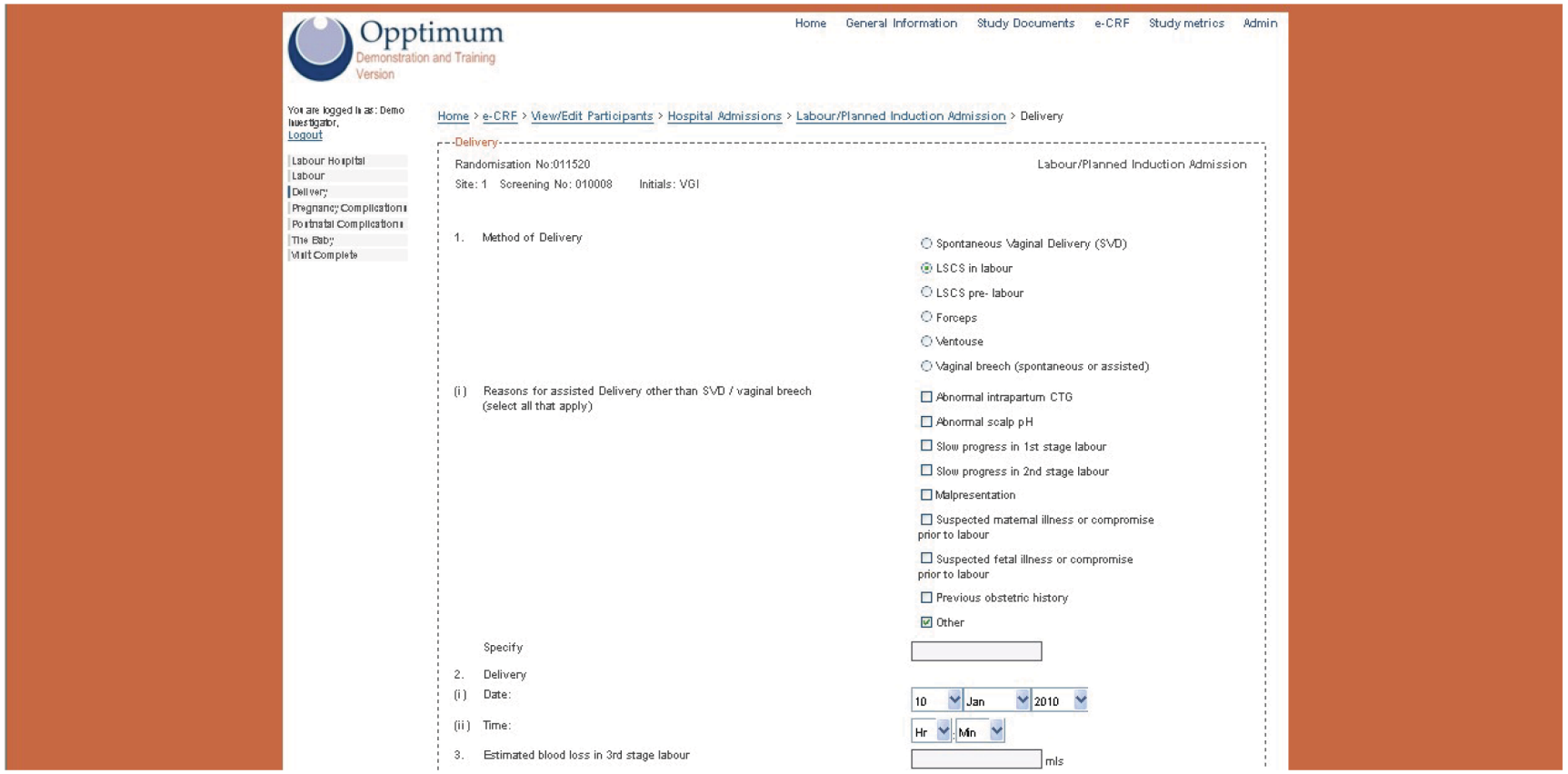


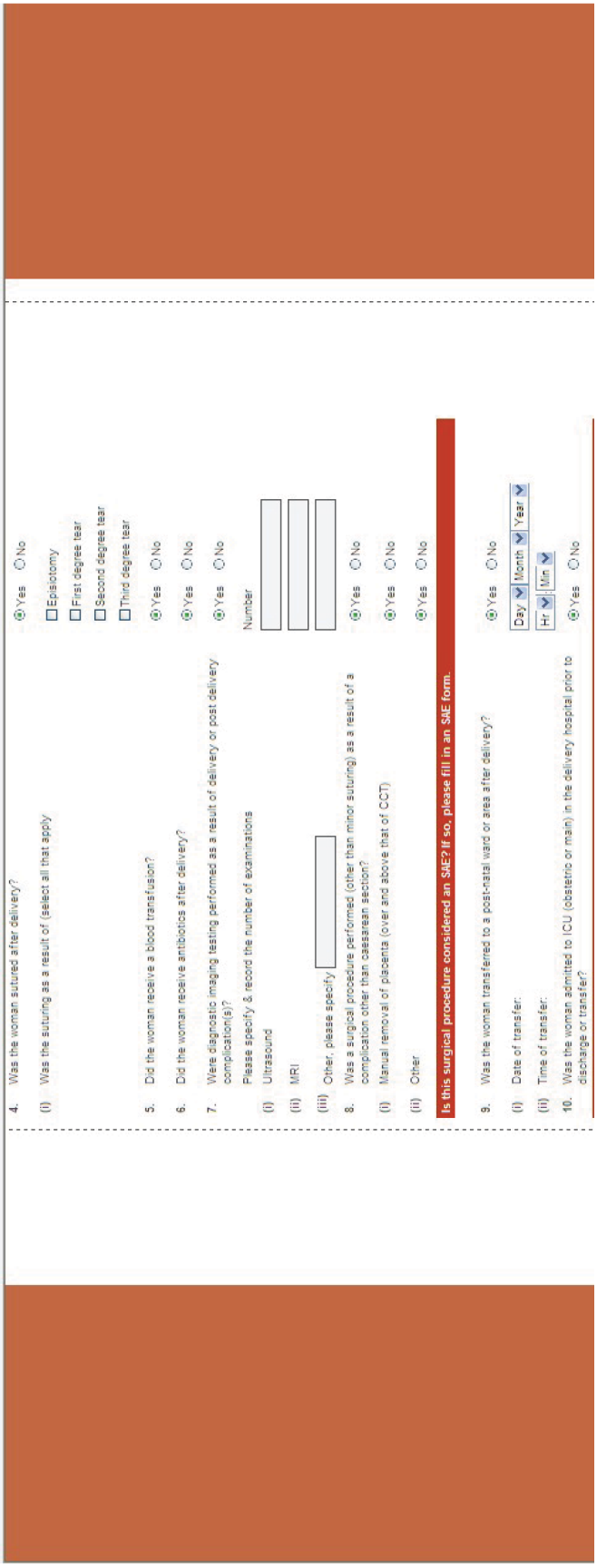
c. Labour

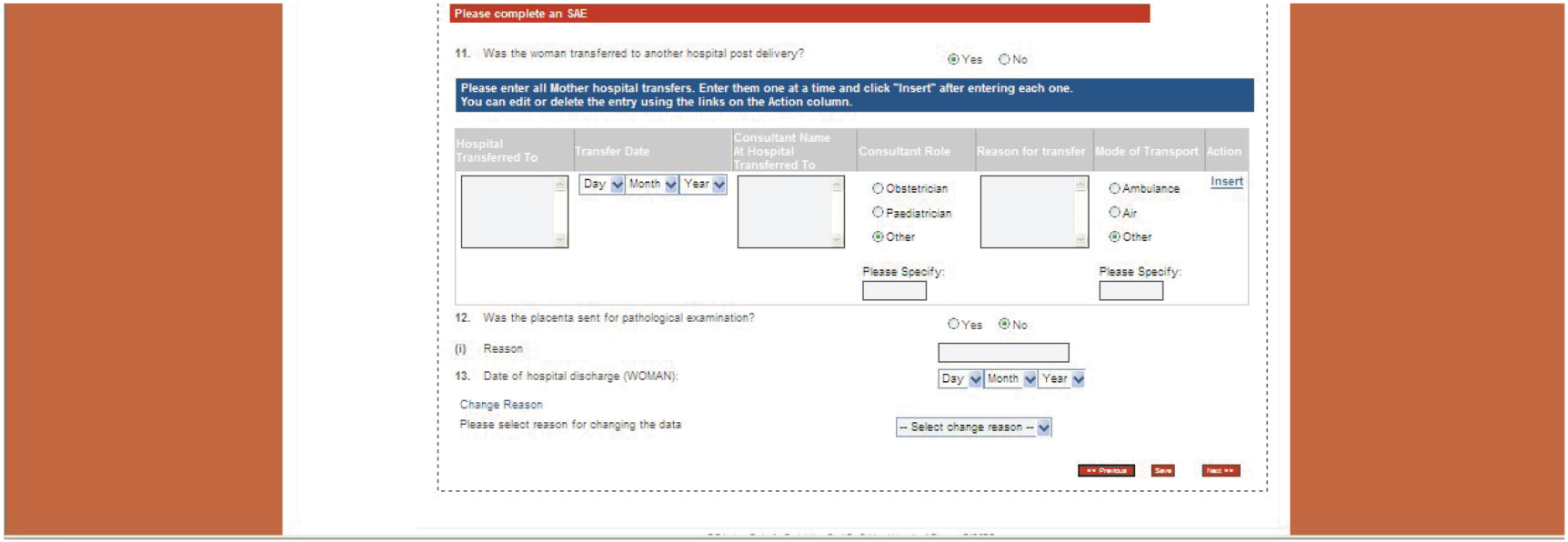




d. Delivery







Please complete an SAE

11. Was the woman transferred to another hospital post delivery? ◉ Yes ○ No

Please enter all Mother hospital transfers. Enter them one at a time and click "Insert" after entering each one.
You can edit or delete the entry using the links on the Action column.

Hospital Transferred To	Transfer Date	Consultant Name At Hospital Transferred To	Consultant Role	Reason for transfer	Mode of Transport	Action
	Day Month Year		○ Obstetrician ○ Paediatrician ◉ Other Please Specify:		○ Ambulance ○ Air ◉ Other Please Specify:	Insert

12. Was the placenta sent for pathological examination? ○ Yes ◉ No

(i) Reason

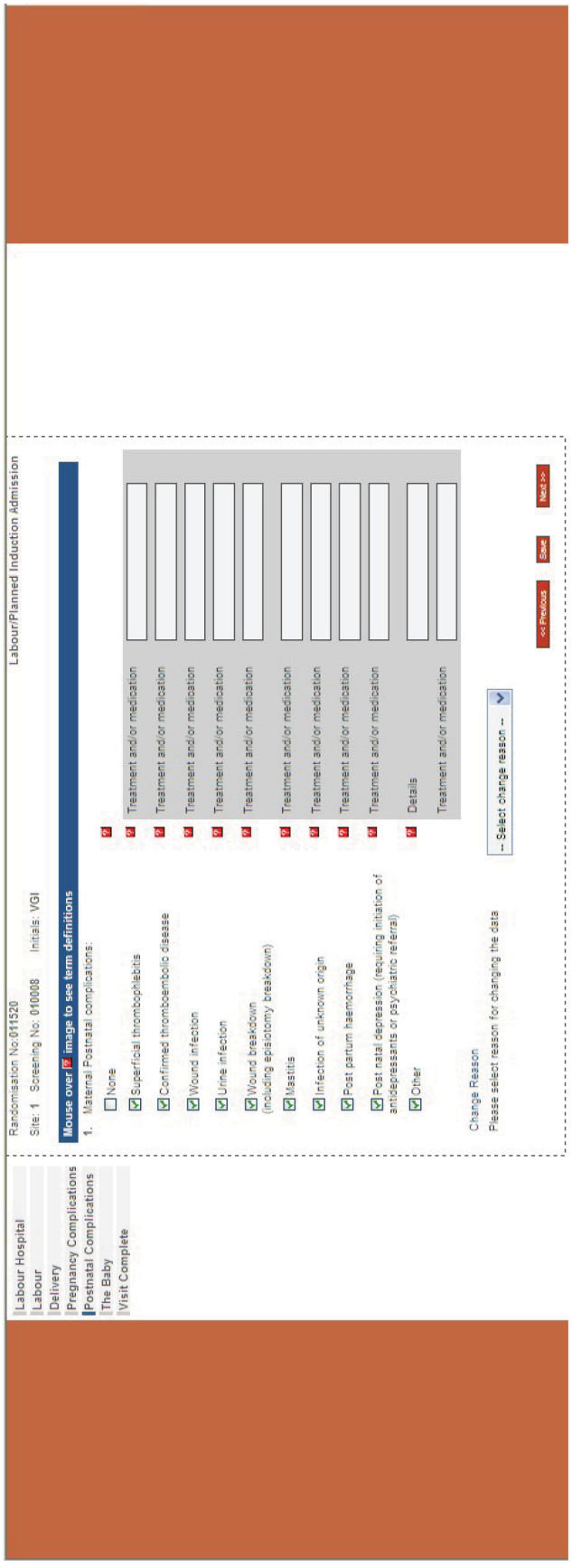
13. Date of hospital discharge (WOMAN): Day Month Year

Change Reason

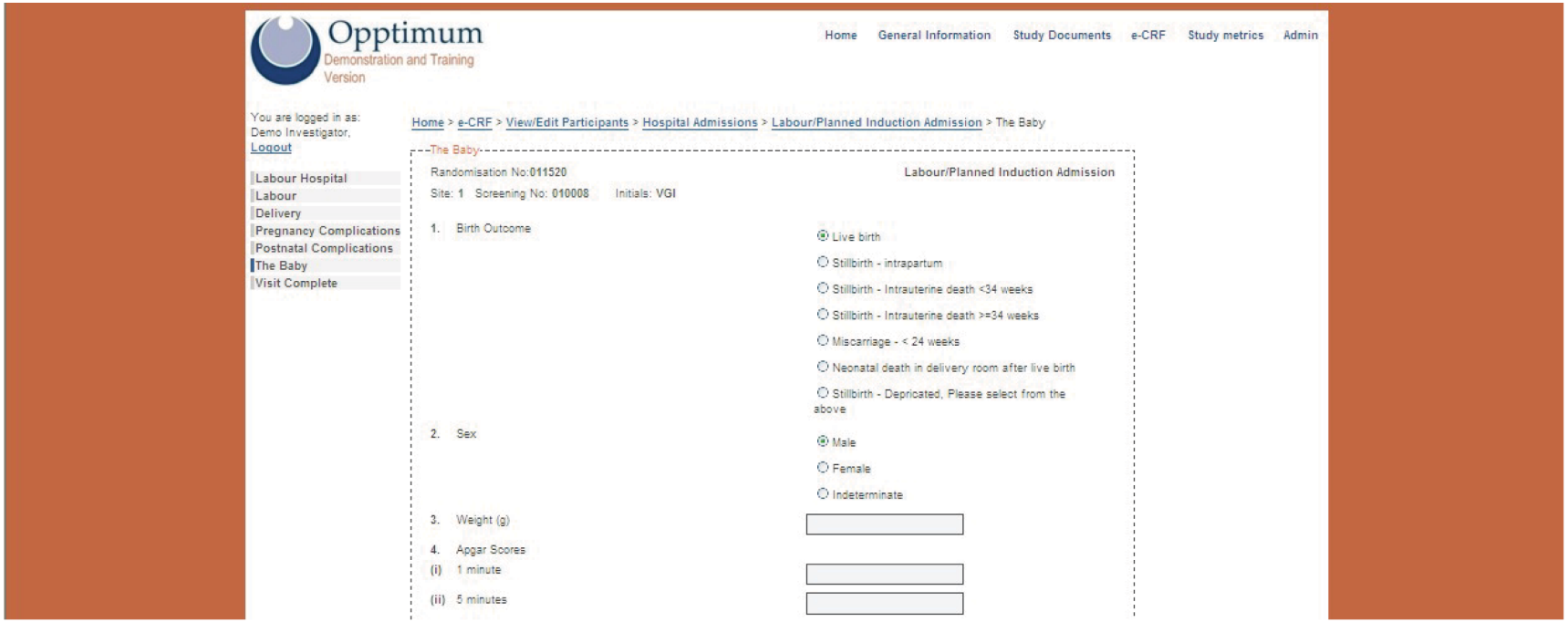
Please select reason for changing the data -- Select change reason --

<< Previous Save Next >>

e. Maternal Postnatal Complications



f. The Baby


Opptimum
Demonstration and Training Version
Home
General Information
Study Documents
e-CRF
Study metrics
Admin
You are logged in as: Demo Investigator, Logout
Labour Hospital
Labour
Delivery
Pregnancy Complications
Postnatal Complications
The Baby
Visit Complete
Home > e-CRF > View/Edit Participants > Hospital Admissions > Labour/Planned Induction Admission > The Baby
The Baby
Randomisation No:011520
Labour/Planned Induction Admission
Site: 1 Screening No: 010008 Initials: VGI
1. Birth Outcome
Live birth
Stillbirth - intrapartum
Stillbirth - Intrauterine death <34 weeks
Stillbirth - Intrauterine death >=34 weeks
Miscarriage - < 24 weeks
Neonatal death in delivery room after live birth
Stillbirth - Depricated, Please select from the above
2. Sex
Male
Female
Indeterminate
3. Weight (g)
4. Apgar Scores
(i) 1 minute
(ii) 5 minutes

5. Highest level of care given in the delivery room

- (•) Minimal (none required or tactile stimulation)
- ( ) Suction
- ( ) Suction and facial 02 only
- ( ) Mask ventilation only
- ( ) Intubation
- ( ) Intubation plus chest compressions
- ( ) Intubation plus chest compressions and/or adrenaline

7. Care after delivery:

- ( ) Transferred to ward with mother
- (•) Transferred to neonatal unit

8. Did the baby have a neonatal screening examination prior to discharge: ( ) Yes (•) No

(i) Reason

(i) Were any abnormal findings recorded (•) Yes ( ) No

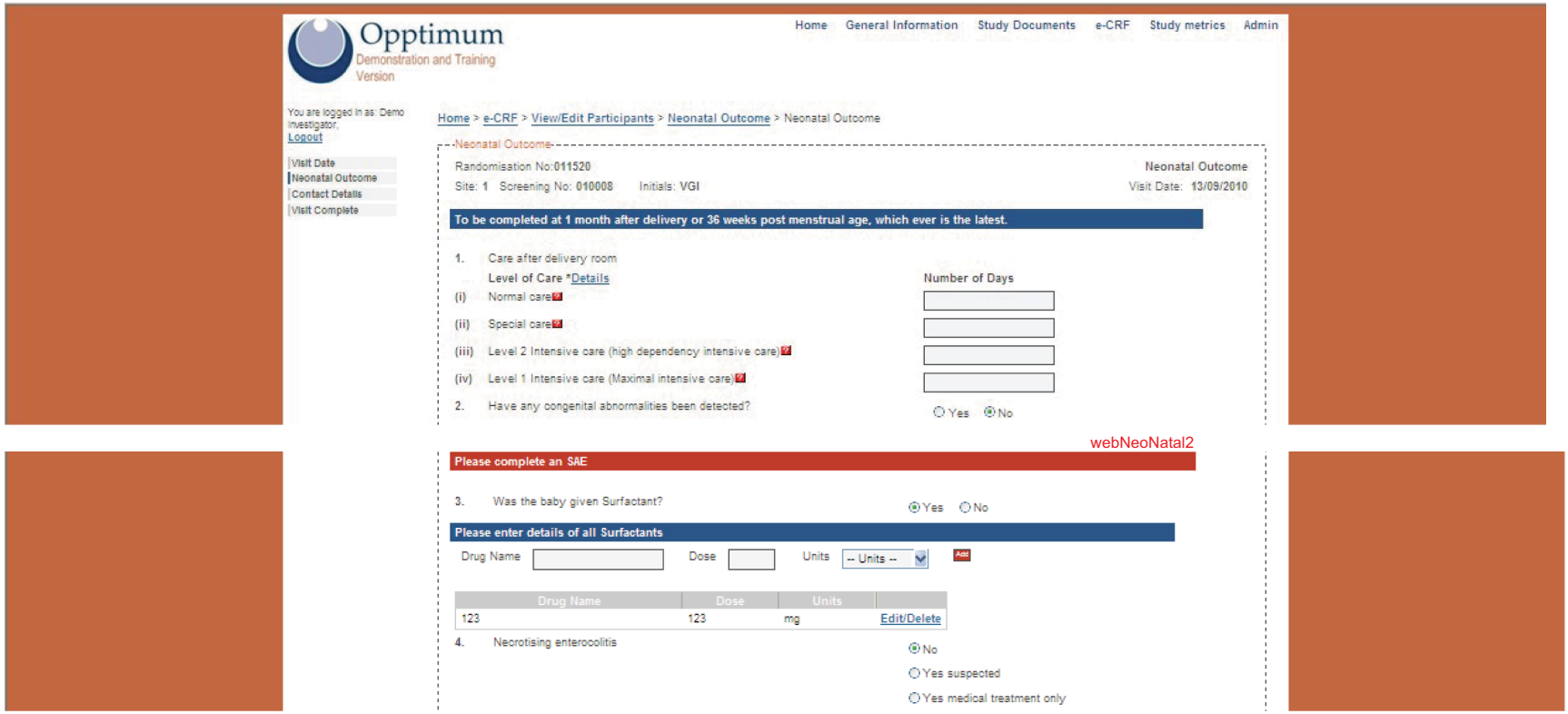
(ii) Specify

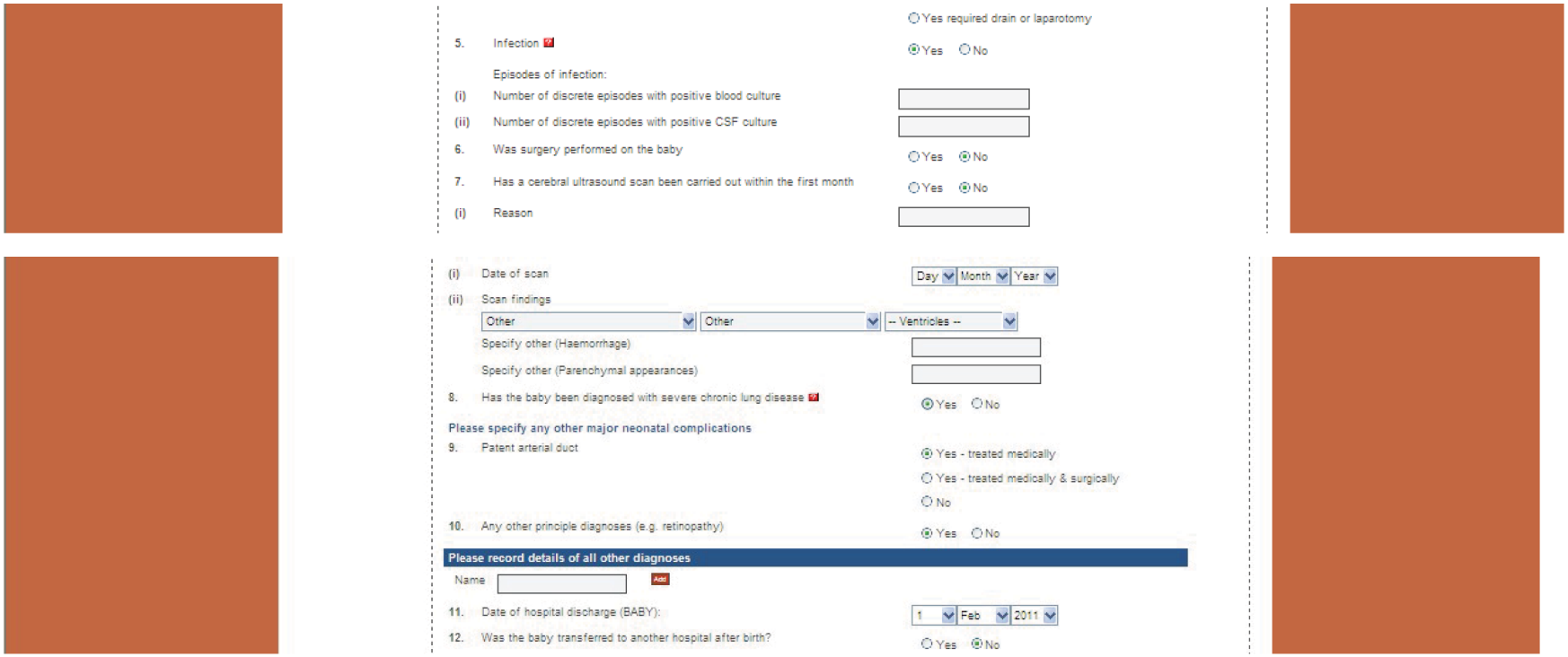
<< Previous Save Next >>

7. Neonatal Outcome

a. Contact Details – See Section 3 (j)

b. Neonatal Outcome





Yes required drain or laparotomy

5. Infection — Yes / No

Episodes of infection:

(i) Number of discrete episodes with positive blood culture

(ii) Number of discrete episodes with positive CSF culture

6. Was surgery performed on the baby — Yes / No

7. Has a cerebral ultrasound scan been carried out within the first month — Yes / No

(i) Reason

(i) Date of scan — Day / Month / Year

(ii) Scan findings

Other / Other / -- Ventricles --

Specify other (Haemorrhage)

Specify other (Parenchymal appearances)

8. Has the baby been diagnosed with severe chronic lung disease — Yes / No

Please specify any other major neonatal complications

9. Patent arterial duct — Yes - treated medically / Yes - treated medically & surgically / No

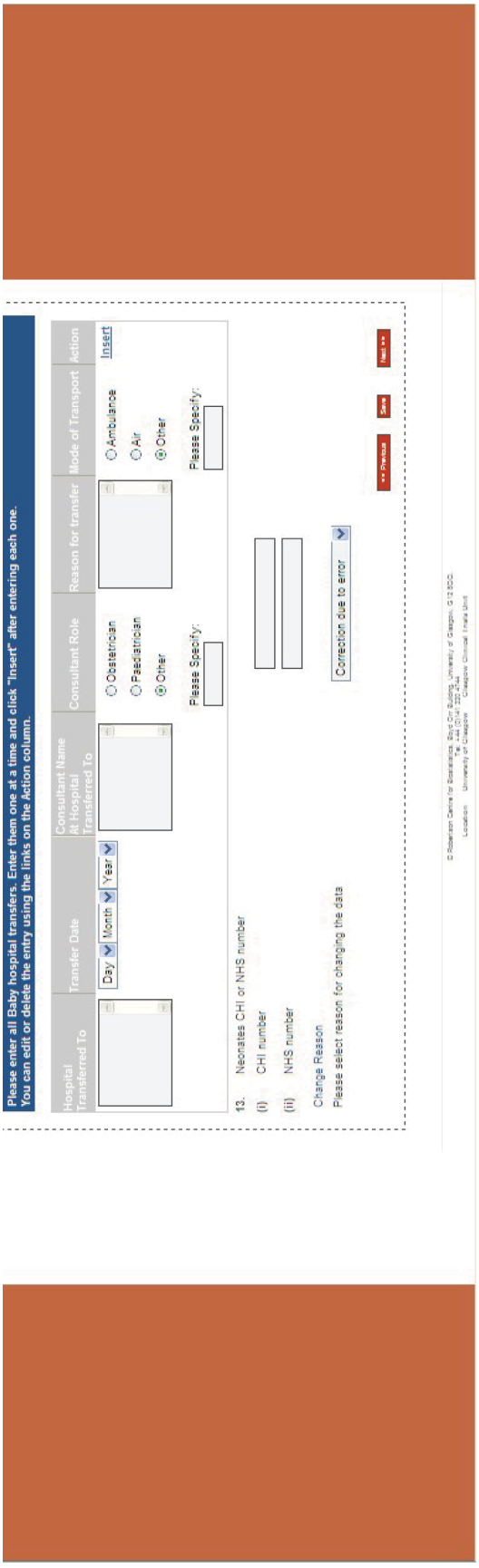
10. Any other principle diagnoses (e.g. retinopathy) — Yes / No

Please record details of all other diagnoses

Name Add

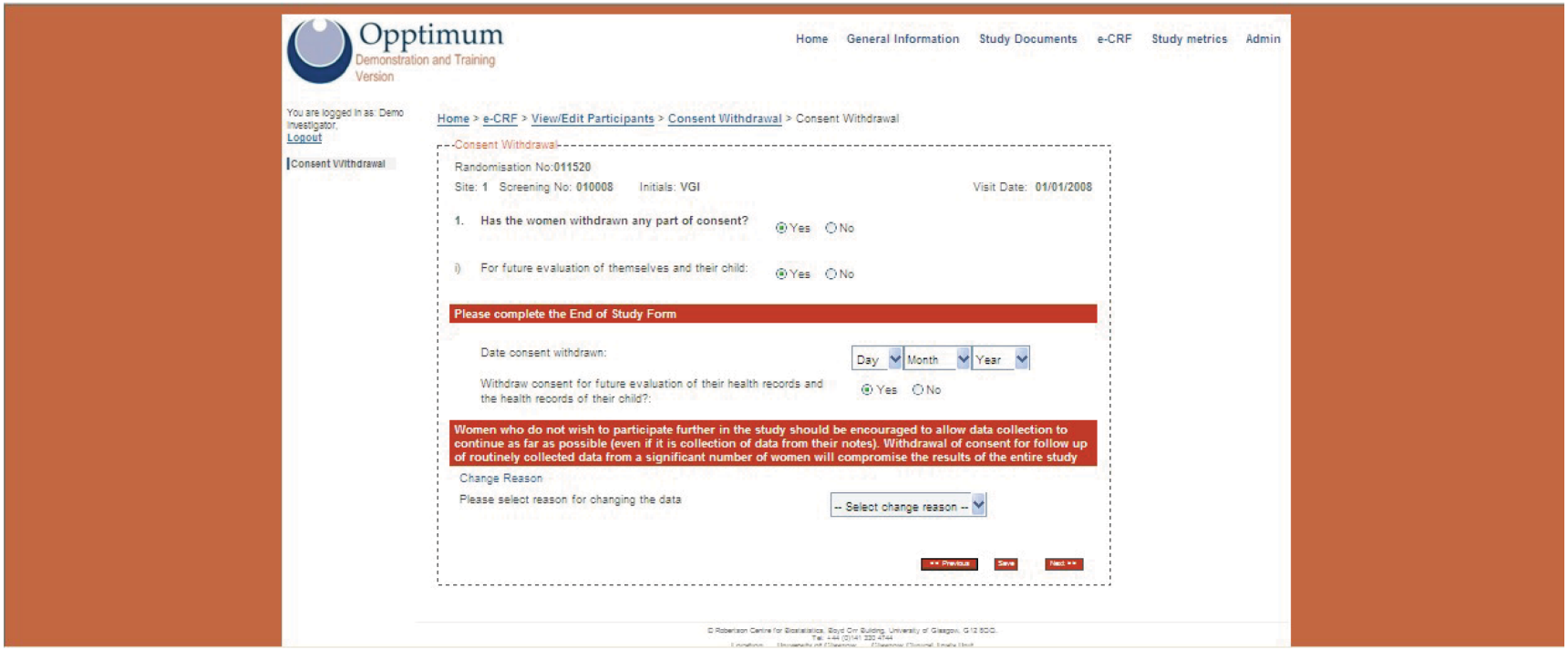
11. Date of hospital discharge (BABY): 1 Feb 2011

12. Was the baby transferred to another hospital after birth? — Yes / No



8. Consent Withdrawal

a. Consent Withdrawal



You are logged in as:
Demo Investigator,
Logout

Consent Withdrawal

Home > e-CRF > View/Edit Participants > Consent Withdrawal > Consent Withdrawal

Consent Withdrawal

Site: 4 Screening No: 040001 Initials: AB

1. **Has the women withdrawn any part of consent?** ◉ Yes ○ No

i) For future evaluation of themselves **and** their child: ○ Yes ◉ No

ii) For a child having a neonatal head scan ◉ Yes ○ No

Date Consent withdrawn: Day Month Year

iii) For use of placental tissue in subsequent research ◉ Yes ○ No

Date Consent withdrawn: Day Month Year

iv) For completing the 2 year follow-up questionnaire ◉ Yes ○ No

Date Consent withdrawn: Day Month Year

v) For completing the 2 year follow-up visit ◉ Yes ○ No

Date Consent withdrawn: Day Month Year

vi) For completing the Health Economics questionnaire (EQ-5D) ◉ Yes ○ No

Date Consent withdrawn: Day Month Year

vii) For completing the Women's Views questionnaire ◉ Yes ○ No

Date Consent withdrawn: Day Month Year

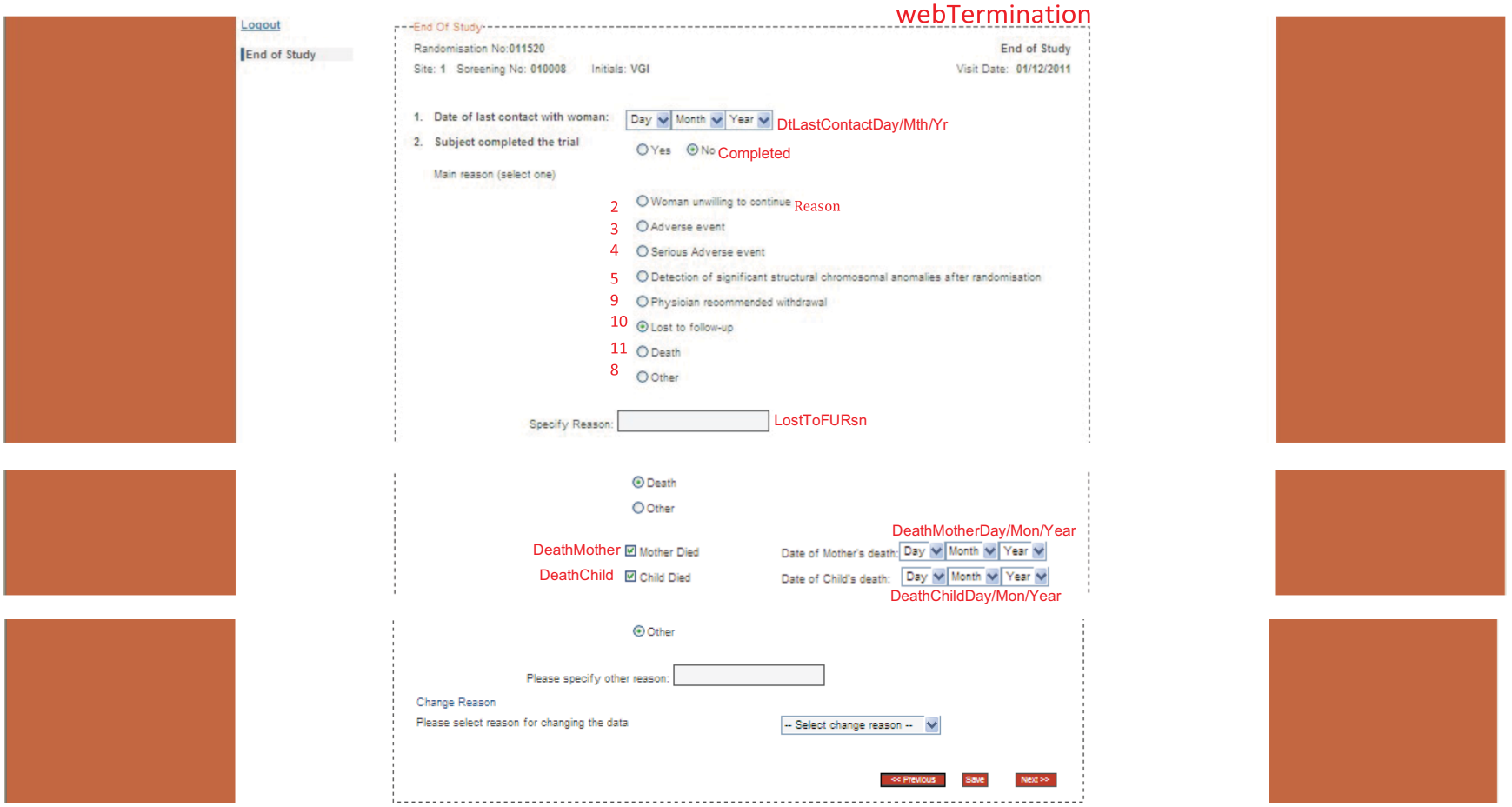
Change Reason

Please select reason for changing the data -- Select change reason --

<< Previous Save Save

9. End of Study

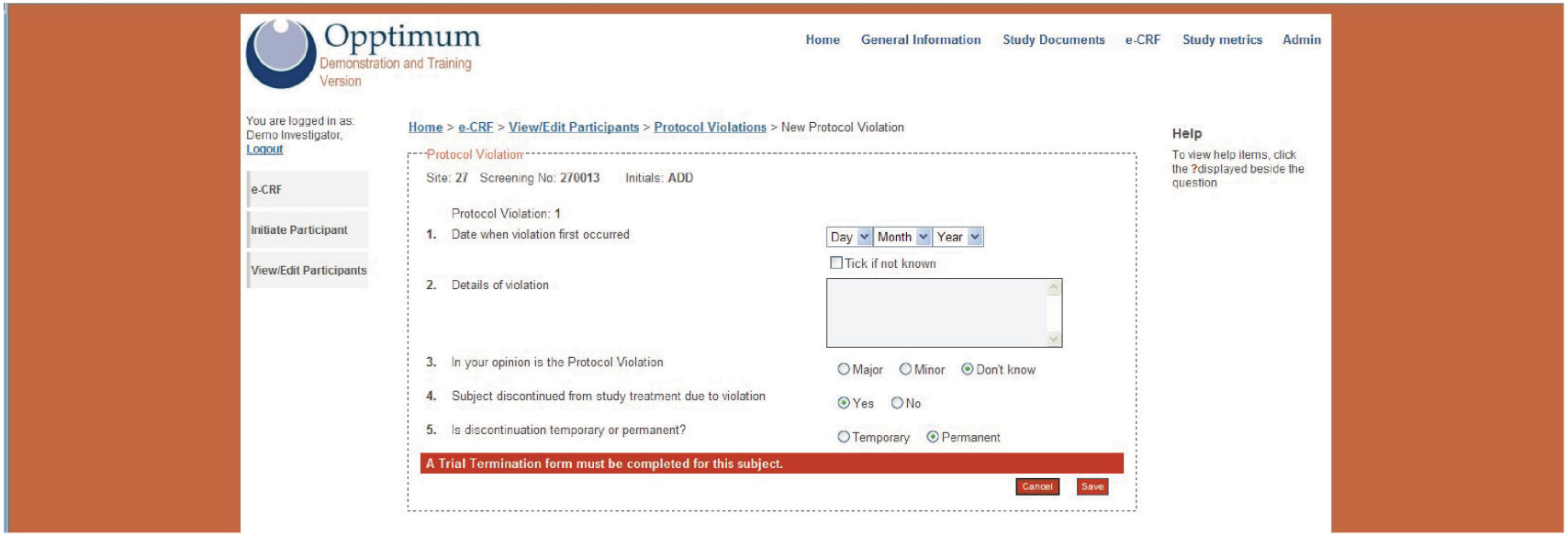
a. End of Study



DOI: 10.3310/hta22350

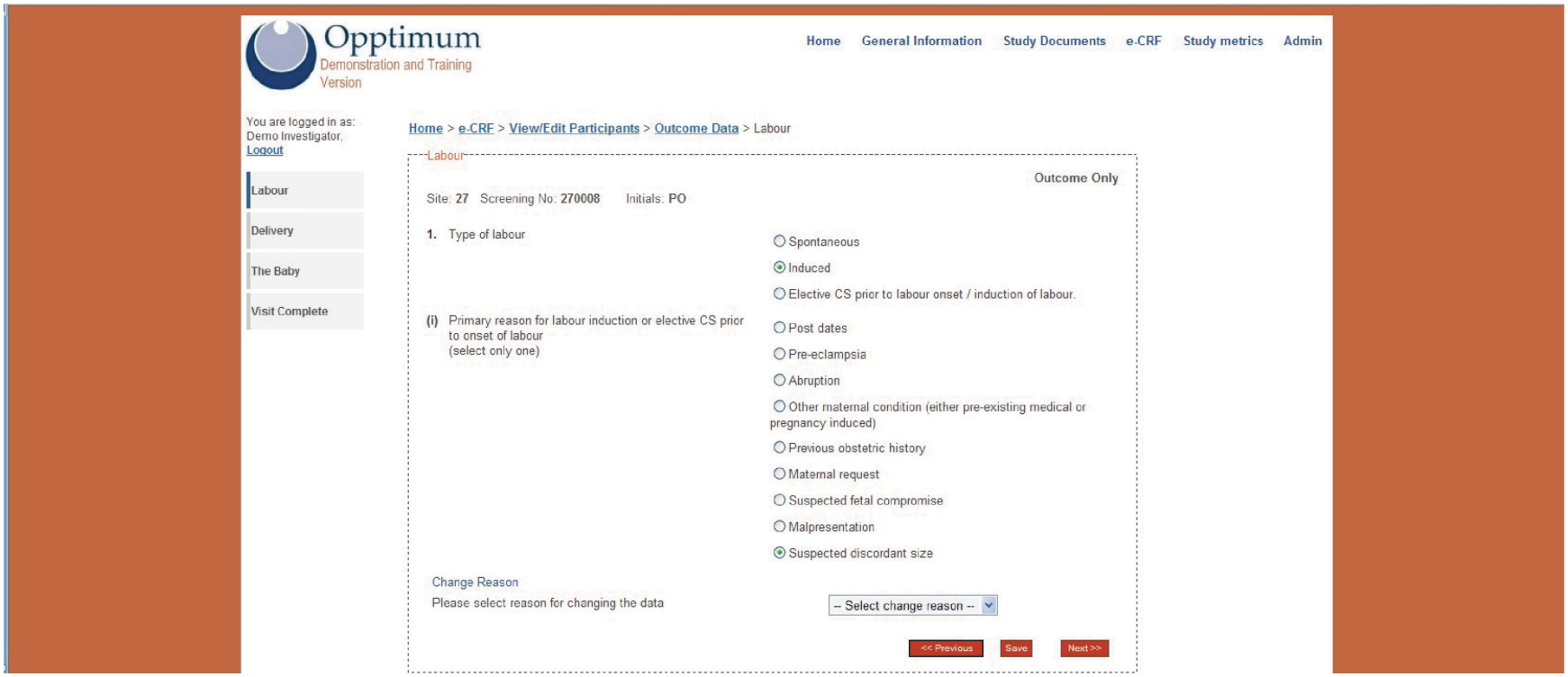
10. Protocol Violation

a. Protocol Violation

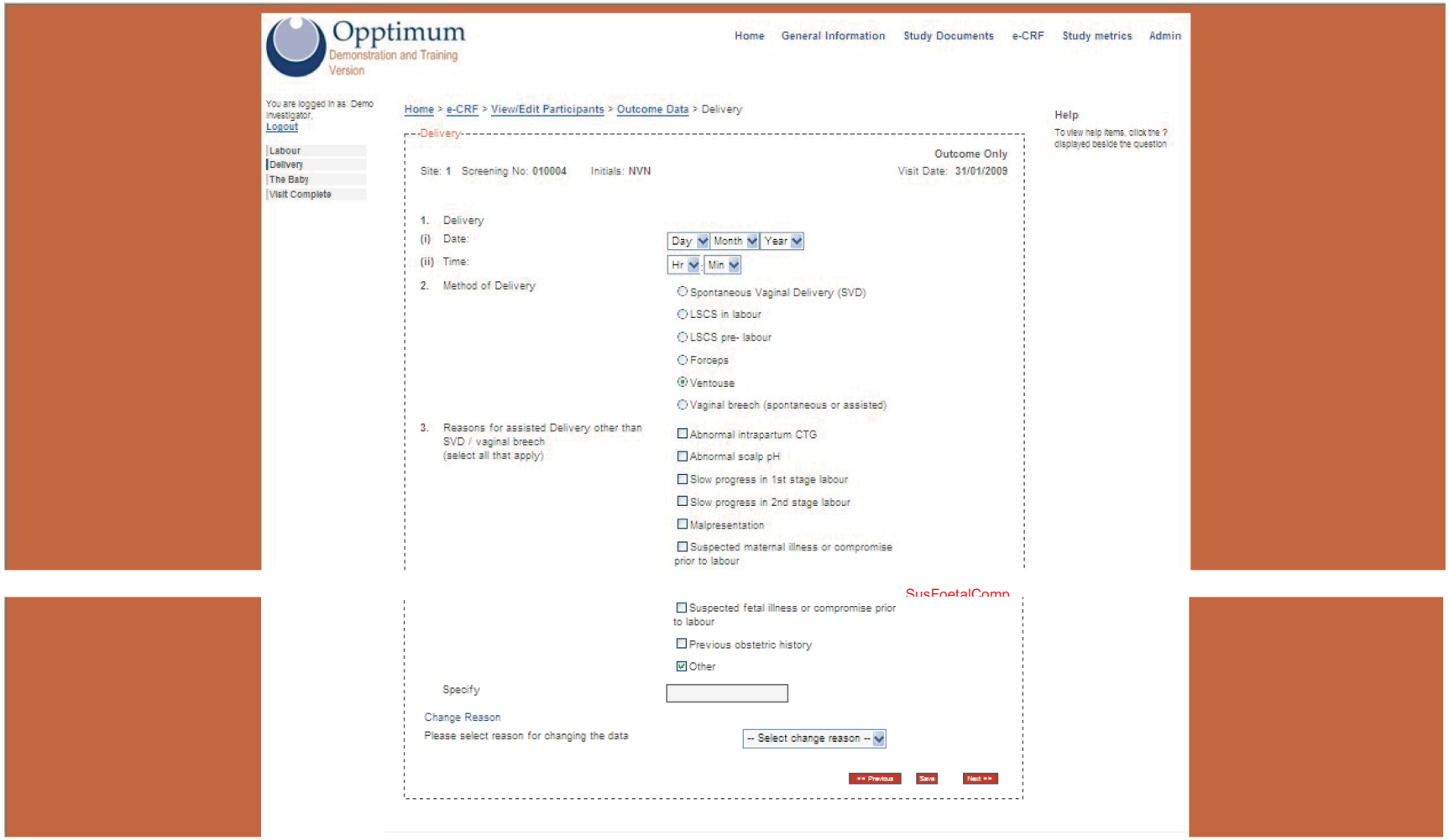


11. Outcome Data

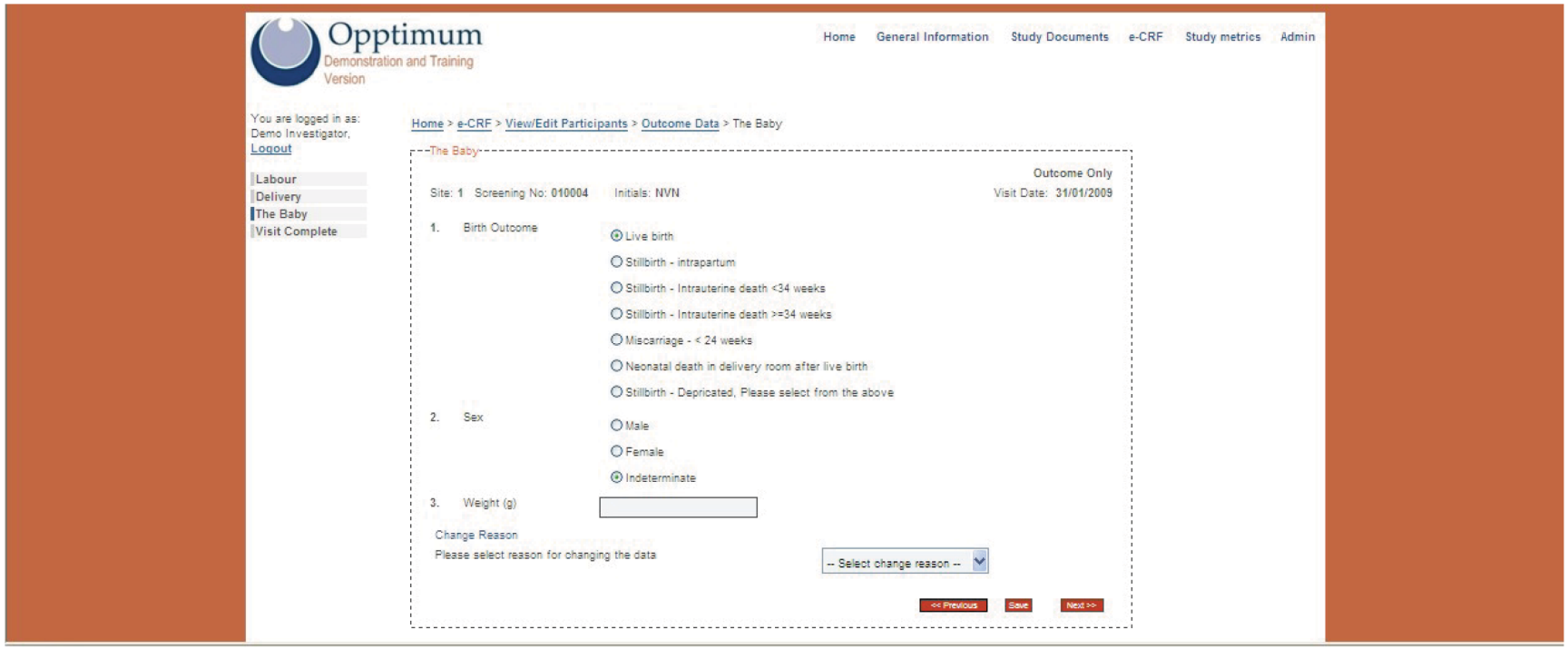
a. Labour



b. Delivery

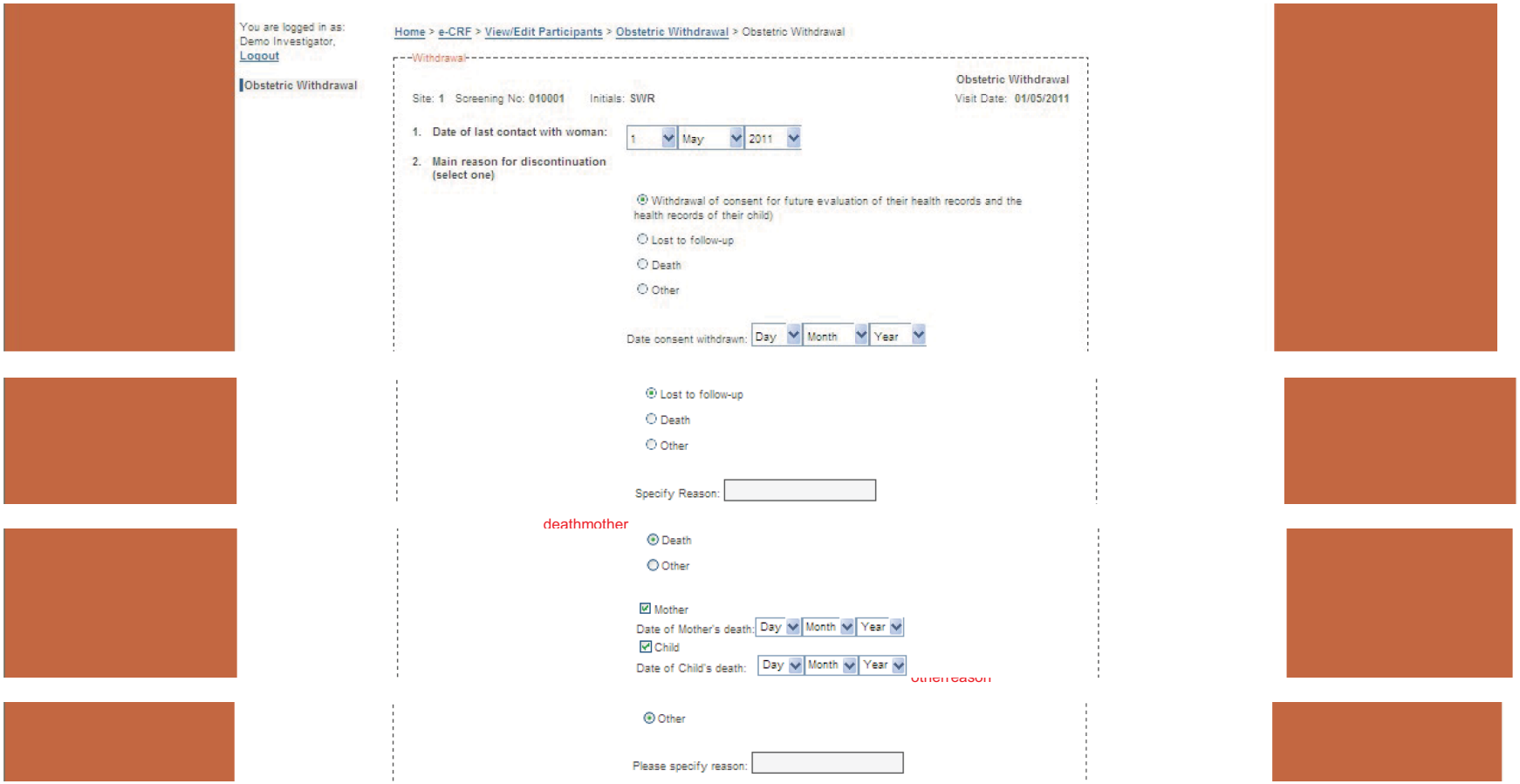


c. The Baby



12. Obstetric Withdrawal

a. Withdrawal



Appendix 7 Approval letters

The ethics committee approval (initial approval letter and approval for final amendment), MHRA approval letter and regulatory approvals are attached.

a)

Scotland A Research Ethics Committee

Secretariat
Deaconess House
[redacted]

NHS SCOTLAND

Professor J E Norman
Regius Professor of Obstetrics and Gynaecology
University of Glasgow
Section of Reproductive and Maternal Medicine
Queen Elizabeth Building
Glasgow Royal Infirmary
10 Alexandra Parade
Glasgow G31 2ER

Date: 19 February 2008
Your Ref.:
Our Ref.: 08/MRE00/6

Enquiries to: Walter Hunter
Extension: 89026
Direct Line:
Email: [redacted]

[redacted]

Dear Professor Norman

Study title: **Does progesterone prophylaxis to prevent preterm labour improve outcome? - A randomised double blind placebo controlled trial**

REC reference: **08/MRE00/6**

EudraCT number: **2007-007950-77**

Thank you for your letter of 1 February 2008, responding to the Committee's request for further information on the above research. The further information has been considered on behalf of the Committee by their Scientific Officer including the revised participant information sheet and consent form.

Ethical opinion

The Scientific Officer is satisfied that you have satisfactorily responded to the issue raised by the Committee.

Approved documents

The updated documents reviewed and approved are:

Document	Version	Date
Application Form Parts A and B		04 January 2008
Investigator CV		03 January 2008

Chairman Professor Kennedy Lees
Vice-Chairman Dr Malcolm Booth

NHS SCOTLAND

Protocol	1	01 January 2008
Covering Letter		03 January 2008
Summary/Synopsis	1	01 January 2008
Letter from Sponsor		26 January 2007
GP/Consultant Information Sheets	1	01 January 2008
Participant Information Sheet: Fibronectin Testing	2.0	01 February 2008
Participant Information Sheet: Main	2.0	01 February 2008
Participant Consent Form: Fibronectin Testing	2	01 February 2008
Participant Consent Form: Main	2.	01 February 2008
Letter from Funding Body		10 December 2007

Research governance approval

The study should not commence at any NHS site until the local Principal Investigator has obtained final research governance approval from the R&D Department for the relevant NHS care organisation.

All researchers and research collaborators who will be participating in the research must obtain research governance approval from the relevant care organisation before commencing any research procedures. Where a substantive contract is not held with the care organisation, it may be necessary for an honorary contract to be issued before approval for the research can be given.

Statement of compliance

The Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

NHS SCOTLAND

REC reference number: 08/MRE00/6-Please quote this number on all correspondence

Yours sincerely

[redacted]

WALTER HUNTER
Committee Co-ordinator

cc: Dr Fiona Graham *Clinical Trials Unit, MHRA*

[redacted]

b)

Scotland A Research Ethics Committee

Research Ethics Service
[redacted]

NHS SCOTLAND

21 October 2013

Professor Jane Norman
[redacted]

Dear Prof Norman

Study title:	**Does progesterone prophylaxis to preventpreterm labour improve outcome? - a randomised double blind placebo controlled trial**
REC reference:	**08/MRE00/6**
EudraCT number:	**2007-007950-77**
Amendment number:	**No 21 (REC REF AM33)**
Amendment date:	**04 October 2013**

The above amendment was reviewed held in correspondence by the Sub-Committee.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Chairman Dr Ian Zealley
Vice-Chairman Dr Colin Selby

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Covering Letter		04 October 2013
European Commission Notification of Substantial Amendment Form		04 October 2013
Letter to woman from sites	V1	30 September 2013
Expenses Letter at 2 years	V1	26 September 2013
Protocol with and without tracked changes	V15	04 October 2013

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

08/MRE00/6:	***Please quote this number on all correspondence***

Yours sincerely

Dr Colin Selby
Committee Vice Chair

Copy to: *Lorraine Adamson*
Marise Bucukoglu, University of Edinburgh

Scotland A REC

Attendance at Sub-Committee
of the REC meeting

Name	Profession	Capacity
Dr Anthony Pottage	Retired Physician/Clinical Pharmacologist	Expert
Dr Colin Selby	Consultant Physician	Expert
Mrs Margaret Thomson	Retired	Lay Plus

Also in attendance:

Name	Position (or reason for attending)
Dr Alex Bailey	Scientific Officer
Mrs Dorothy Garrow	Sub-Committee Coordinator

c)

Safeguarding public health

MHRA

DR J NORMAN
[redacted]

18/03/2008

Dear DR J NORMAN

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031

Our Reference:	22931/0009/001-0001
Eudract Number:	2007-007950-77
Product:	UTROGESTAN CAPSULES 200MG
Protocol number:	OPPTIMUM

NOTICE OF ACCEPTANCE OF AMENDED REQUEST

I am writing to inform you that the Licensing Authority accepts your amended request for a clinical trial authorisation (CTA), received on 13/03/2008.

Authorisation of your clinical trial is subject to the following condition(s):
* The labelling will remain legible at the size intended for use.
If these conditions are met, the trial is authorised and you do not need to respond to this letter. If your trial does not meet these conditions, your trial does not have authorisation and therefore you can not proceed with the trial. You must inform the MHRA immediately if the trial does not meet the above conditions. All changes to the terms and conditions of this trial must be made as a request for a substantial amendment to this clinical trial authorisation.

The authorisation is effective from the date of this letter although your trial may be suspended or terminated at any time by the Licensing Authority in accordance with regulation 31. You must notify the Licensing Authority within 90 days of the trial ending.

Finally, you are reminded that a favourable opinion from the Ethics Committee is also required before this trial can proceed; changes made as part of your amended request may need to be notified to the Ethics Committee.

Yours sincerely,

Clinical Trials Unit
MHRA

[redacted]

An executive agency of the Department of Health

Appendix 8 Results letters

Letters provided to participants to share results of study and drug allocation are attached.

a)

Participant study number (Screening no/randomisation no)

Dear Ms (Surname)

I am writing to thank you for your participation in the OPPTIMUM study and to share the findings with you.

As you may remember, the study was designed to find out whether giving Progesterone to women between 22-24 weeks and up to 34 weeks of gestation improves outcome in women at high risk of preterm delivery. The outcomes we were interested in were the number of weeks of pregnancy at delivery and the wellbeing of the baby from birth to the age of two. We spoke to 15,132 women and 6,408 women agreed to be tested and randomised 1,228 women into the study treatment of whom you were one. We are grateful for your participation.

Following analysis of the data, we found that progesterone had no significant effect on the timing of delivery or on the health of the child at birth; nor on the results of the "Bayley" developmental assessment that was done at around 2 years of age of the child. In this large study, vaginal progesterone did not reduce the risk of preterm birth or improve the risk of complex neonatal outcomes. There was no long term benefit or harm on outcomes in children at two years of age.

These findings are very useful. The study helps us to plan how best to care for pregnant women at high risk of preterm birth and we will be able to give future women at risk much more information about the effects of progesterone.

If you would like a full copy of the study report, or if you would like to know which treatment you were allocated, please contact the clinical trials team using the slip enclosed OR please call the Clinical Trials Office on 0131-242-2696. Alternatively you can email Opptimum.study@ed.ac.uk.

We are extremely grateful to you for participating in this important research. Please do not hesitate to contact me at Opptimum.study@ed.ac.uk, or your local study team, if you have any questions about the results of the study.

We hope to be able to keep in contact with you to invite you, or your baby, to participate in future research. If you do not wish to be contacted again, please let us know at Opptimum.study@ed.ac.uk or telephone 131-242-2696.

With best wishes

[redacted]

Professor Jane Norman, on behalf of the OPPTIMUM study team

The OPPTIMUM study was funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership (Reference number: 84982 - 09/800/27). The EME Programme is funded by the MRC and NIHR, with contributions from the CSO in Scotland and NISCHR in Wales.

Opptimum
Progesterone prophylaxis to prevent pre-term labour

REPLY SLIP

NAME: Name

STUDY NUMBER: (Screening no/randomisation no)

I WOULD LIKE TO KNOW MY TREATMENT ALLOCATION – YES / NO

I WOULD LIKE TO HAVE A COPY OF THE FULL STUDY RESULTS - YES/NO

I AM HAPPY FOR YOU TO CONTACT ME AGAIN - YES/ NO

MY CURRENT ADDRESS IS:

……
……

……
……

……
……

……
……

MY CURRENT PHONE NUMBER IS:

Landline
……

Mobile
……

MY CURRENT EMAIL ADDRESS IS:
……..

b)

Participant study number:Screening/randomisation Dear Ms (Name)

I am writing to thank you for your valued participation in the OPPTIMUM study, to share the findings with you and to offer my sincere condolences on the loss of your baby.

As you may remember, the study was designed to find out whether giving Progesterone to women between 22-24 weeks and up to 34 weeks of gestation improves outcome in women at high risk of preterm delivery. The outcomes we were interested in were the number of weeks of pregnancy at delivery and the wellbeing of the baby from birth to the age of two. We spoke to 15,132 women and 6,408 women agreed to be tested. We randomised 1,228 women into the study treatment of whom you were one. We are grateful for your participation.

Following analysis of the data, we found that progesterone had no significant effect on the timing of delivery or on the health of the child at birth; nor on the results of the "Bayley" developmental assessment that was done at around 2 years of age of the child. In this large study, vaginal progesterone did not reduce the risk of preterm birth or improve the risk of complex neonatal outcomes. There was no long term benefit or harm on outcomes in children at two years of age.

These findings are very useful. The study helps us to plan how best to care for pregnant women at high risk of preterm birth and we will be able to give future women at risk much more information about the effects of progesterone.

If you would like a full copy of the study report, or if you would like to know which treatment you were allocated, please contact the clinical trials team using the slip enclosed OR please call the Clinical Trials Office on 0131-242-2696. Alternatively you can email Opptimum.study@ed.ac.uk.

We are extremely grateful to you for participating in this important research. Please do not hesitate to contact me at Opptimum.study@ed.ac.uk, or your local study team if you have any questions about the results of the study.

With best wishes

Professor Jane Norman, on behalf of the OPPTIMUM study team.

The OPPTIMUM study was funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership (Reference number: 84982 - 09/800/27). The EME Programme is funded by the MRC and NIHR, with contributions from the CSO in Scotland and NISCHR in Wales.

Opptimum
Progesterone prophylaxis to prevent pre-term labour

REPLY SLIP

NAME: (Name)

STUDY NUMBER: Screening/randomisation

I WOULD LIKE TO KNOW MY TREATMENT ALLOCATION – YES / NO

I WOULD LIKE TO HAVE A COPY OF THE FULL STUDY RESULTS - YES/NO

MY CURRENT ADDRESS IS:

……

……

……

……

c)

THE UNIVERSITY of EDINBURGH

MRC Centre for Reproductive Health

Opptimum
Progesterone prophylaxis to prevent pre-term labour

NHS
National Institute for Health Research

Participant number:

Dear (Participant name),

Thank you for supporting the OPPTIMUM trial and for your enquiry about your treatment allocation.

You were allocated to treatment with PROGESTERONE/PLACEBO.

If you have any questions about the treatment you received, please contact your local study team (Site name and contact details) who will be happy to help you.

With best wishes

Prof Jane Norman on behalf of the OPPTIMUM study team

[redacted]

cc. Local investigator name and contact details

The OPPTIMUM study was funded by the (reference number 08/246/09). The views expressed in this letter are those of the authors and not necessarily those of the MRC, NHS, NIHR or the Department of Health.

Appendix 9 Literature search

A literature search was performed in PubMed on 11 July 2016 using the search terms progesterone OR progestogens AND preterm birth, with filters clinical trial and date restriction of 1 January 2013. Of the 27 publications, the only study referring to asymptomatic women with singleton pregnancy was OPPTIMUM,[8] which is the study described in this publication. An output file is attached below.

1. Nicolaides KH, Syngelaki A, Poon LC, Picciarelli G, Tul N, Zamprakou A, *et al.* A randomized trial of a cervical pessary to prevent preterm singleton birth. *N Engl J Med* 2016;**374**:1044–52. https://doi.org/10.1056/NEJMoa1511014

2. Norman JE, Marlow N, Messow CM, Shennan A, Bennett PR, Thornton S, *et al.* Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial. *Lancet* 2016;**387**:2106–16.

3. Kiefer DG, Peltier MR, Keeler SM, Rust O, Ananth CV, Vintzileos AM, Hanna N. Efficacy of midtrimester short cervix interventions is conditional on intraamniotic inflammation. *Am J Obstet Gynecol* 2016;**214**:276.e1–6. https://doi.org/10.1016/j.ajog.2015.09.006

4. Gordon MC, McKenna DS, Stewart TL, Howard BC, Foster KF, Higby K, *et al.* Transvaginal cervical length scans to prevent prematurity in twins: a randomized controlled trial. *Am J Obstet Gynecol* 2016;**214**:277.e1–7.

5. Nicolaides KH, Syngelaki A, Poon LC, de Paco Matallana C, Plasencia W, Molina FS, *et al.* Cervical pessary placement for prevention of preterm birth in unselected twin pregnancies: a randomized controlled trial. *Am J Obstet Gynecol* 2016;**214**:3.e1–9. https://doi.org/10.1016/j.ajog.2015.08.051

6. Heyborne KD, Allshouse AA, Carey JC. Does 17-alpha hydroxyprogesterone caproate prevent recurrent preterm birth in obese women? *Am J Obstet Gynecol* 2015;**213**:844.e1–6.

7. El-refaie W, Abdelhafez MS, Badawy A. Vaginal progesterone for prevention of preterm labor in asymptomatic twin pregnancies with sonographic short cervix: a randomized clinical trial of efficacy and safety. *Arch Gynecol Obstet* 2016;**293**:61–7.

8. Ragab A, Mesbah Y. To do or not to do emergency cervical cerclage (a rescue stitch) at 24–28 weeks gestation in addition to progesterone for patients coming early in labor? A prospective randomized trial for efficacy and safety. *Arch Gynecol Obstet* 2015;**292**:1255–60.

9. Combs CA, Garite TJ, Maurel K, Abril D, Das A, Clewell W, *et al.* 17-hydroxyprogesterone caproate for preterm rupture of the membranes: a multicenter, randomized, double-blind, placebo-controlled trial. *Am J Obstet Gynecol* 2015;**213**:364.e1–12.

10. Kuang Y, Chen Q, Fu Y, Wang Y, Hong Q, Lyu Q, *et al.* Medroxyprogesterone acetate is an effective oral alternative for preventing premature luteinizing hormone surges in women undergoing controlled ovarian hyperstimulation for in vitro fertilization. *Fertil Steril* 2015;**104**:62–70.e3.

11. van Os MA, van der Ven AJ, Kleinrouweler CE, Schuit E, Kazemier BM, Verhoeven CJ, *et al.* Preventing preterm birth with progesterone in women with a short cervical length from a low-risk population: a multicenter double-blind placebo-controlled randomized trial. *Am J Perinatol* 2015;**32**:993–1000.

12. Brizot ML, Hernandez W, Liao AW, Bittar RE, Francisco RP, Krebs VL, Zugaib M. Vaginal progesterone for the prevention of preterm birth in twin gestations: a randomized placebo-controlled double-blind study. *Am J Obstet Gynecol* 2015;**213**:82.e1–9.

13. Winer N, Bretelle F, Senat MV, Bohec C, Deruelle P, Perrotin F, *et al.* 17 alpha-hydroxyprogesterone caproate does not prolong pregnancy or reduce the rate of preterm birth in women at high risk for preterm delivery and a short cervix: a randomized controlled trial. *Am J Obstet Gynecol* 2015;**212**:485.e1–485.e10.

14. Martinez de Tejada B, Karolinski A, Ocampo MC, Laterra C, Hösli I, Fernández D, *et al.* Prevention of preterm delivery with vaginal progesterone in women with preterm labour (4P): randomised double-blind placebo-controlled trial. *BJOG* 2015;**122**:80–91.

15. Awwad J, Usta IM, Ghazeeri G, Yacoub N, Succar J, Hayek S, *et al.* A randomised controlled double-blind clinical trial of 17-hydroxyprogesterone caproate for the prevention of preterm birth in twin gestation (PROGESTWIN): evidence for reduced neonatal morbidity. *BJOG* 2015;**122**:71–9.

16. Okabe H, Makino S, Kato K, Matsuoka K, Seki H, Takeda S. The effect of progesterone on genes involved in preterm labor. *J Reprod Immunol* 2014;**104–105**:80–91. https://doi.org/10.1016/j.jri.2014.03.008

17. Choudhary M, Suneja A, Vaid NB, Guleria K, Faridi MM. Maintenance tocolysis with oral micronized progesterone for prevention of preterm birth after arrested preterm labor. *Int J Gynaecol Obstet* 2014;**126**:60–3. https://doi.org/10.1016/j.ijgo.2014.01.019

18. Combs CA, Garite TJ, Maurel K, Das A, Obstetrix Collaborative Research Network. Fetal fibronectin versus cervical length as predictors of preterm birth in twin pregnancy with or without 17-hydroxyprogesterone caproate. *Am J Perinatol* 2014;**31**:1023–30.

19. Briery CM, Klauser CK, Martin RW, Magann EF, Chauhan SP, Morrison JC. The use of 17-hydroxy progesterone in women with arrested preterm labor: a randomized clinical trial. *J Matern Fetal Neonatal Med* 2014;**27**:1892–6.

20. Kamat S, Veena P, Rani R. Comparison of nifedipine and progesterone for maintenance tocolysis after arrested preterm labour. *J Obstet Gynaecol* 2014;**34**:322–5. https://doi.org/10.3109/01443615.2013.874407

21. Caritis SN, Venkataramanan R, Thom E, Harper M, Klebanoff MA, Sorokin Y, *et al.* Relationship between 17-alpha hydroxyprogesterone caproate concentration and spontaneous preterm birth. *Am J Obstet Gynecol* 2014;**210**:128.e1–6.

22. Senat MV, Porcher R, Winer N, Vayssière C, Deruelle P, Capelle M, *et al.* Prevention of preterm delivery by 17 alpha-hydroxyprogesterone caproate in asymptomatic twin pregnancies with a short cervix: a randomized controlled trial. *Am J Obstet Gynecol* 2013;**208**:194.e1–8.

23. El-Gharib MN, El-Hawary TM. Matched sample comparison of intramuscular versus vaginal micronized progesterone for prevention of preterm birth. *J Matern Fetal Neonatal Med* 2013;**26**:716–19.

24. Maher MA, Abdelaziz A, Ellaithy M, Bazeed MF. Prevention of preterm birth: a randomized trial of vaginal compared with intramuscular progesterone. *Acta Obstet Gynecol Scand* 2013;**92**:215–22. https://doi.org/10.1111/aogs.12017

25. Gaggini TS, Perin J, Arend LS, Bernardi ML, Wentz I, Bortolozzo FP. Altrenogest treatment associated with a farrowing induction protocol to avoid early parturition in sows. *Reprod Domest Anim* 2013;**48**:390–5.

26. Alfirevic Z, Owen J, Carreras Moratonas E, Sharp AN, Szychowski JM, Goya M. Vaginal progesterone, cerclage or cervical pessary for preventing preterm birth in asymptomatic singleton pregnant women with a history of preterm birth and a sonographic short cervix. *Ultrasound Obstet Gynecol* 2013;**41**:146–51.

27. Serra V, Perales A, Meseguer J, Parrilla JJ, Lara C, Bellver J, *et al.* Increased doses of vaginal progesterone for the prevention of preterm birth in twin pregnancies: a randomised controlled double-blind multicentre trial. *BJOG* 2013;**120**:50–7.

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PHR

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