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
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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:

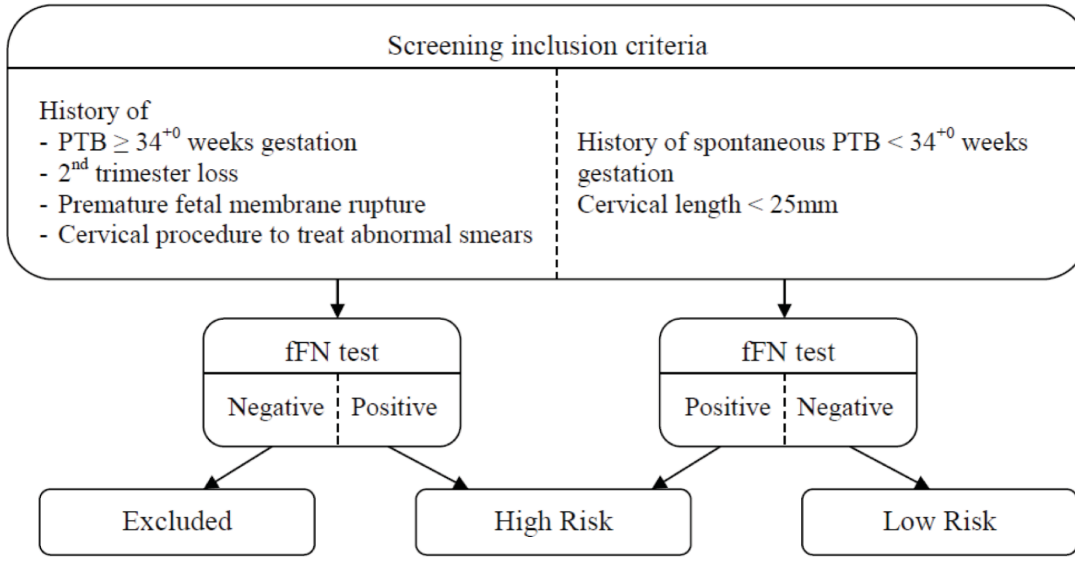

Figure 1 *Screening inclusion criteria, and risk allocation according to fFN status*

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.