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The Preterm Prelabour Rupture of Membranes close to Term (PPROMT) Trial

Statistical Analysis Plan

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List of Abbreviations

Abbreviation	Definition
AR-DRG	Australian Refined Diagnosis Related Groups
CI	Confidence intervals
CONSORT	Consolidated Standards of Reporting Trials
CPAP	Continuous positive airway pressure
CRP	C-Reactive protein
CSF	Cerebrospinal fluid
CTG	Cardiotocography
EPDS	Edinburgh Postnatal Depression Scale
FBC	Full blood count
GA	Gestational age
GBS	Group B streptococcus
HFOV	High frequency oscillatory ventilation
ICU	Intensive care unit
IPPV	Intermittent positive pressure ventilation
NICU	Neonatal Intensive care unit
PROM	Prelabour rupture of membranes
PPROM	Preterm prelabour rupture of membranes
PPROMT	Preterm Prelabour Rupture of Membranes Close to Term Trial
RDS	Respiratory distress syndrome
ROM	Rupture of membranes
RR	Relative risks
SCN	Special care nursery
SGA	Small for gestational age
WCC	White cell count

1. BRIEF BACKGROUND

1.1 Trial overview

The optimal management for women with preterm prelabour rupture of membranes (PPROM) is not known. Delivery may be planned for soon after the woman presents with PPROM, or alternatively delivery may be delayed (expectant management) in order for the fetus to gain additional maturity and reduce the risk of neonatal morbidity. However, expectant management may also increase the risk of ascending infection in the mother and thus of neonatal sepsis in the infant. In the face of insufficient evidence both forms of treatment are currently utilised. In Australia and New Zealand the two treatments (immediate delivery and expectant management) are equally employed amongst obstetricians. (reference #1)

PPROMT is a prospective, multicentre randomised controlled trial comparing early planned birth versus expectant management for PPROM. The protocol for the trial was published in 2006 (reference #2). The trial is registered with the International Standard Randomised Controlled Trial Register (ISRCTN44485060]. Funding is from the Australian National Health and Medical Research (Grant Numbers 358387 and 1009898) and the University of Sydney. Eligible women were centrally randomised by the coordinating centre to either immediate planned delivery or expectant management, stratified by participating centre. Endpoint assessment is blinded, although blinding for participants was not possible.

1.2 Timeline for the trial

28 May 2004	First participant recruited to the trial
26 February 2010	Interim analysis performed by Data Monitoring Committee, determination made that trial should continue
30 June 2013	Final participant recruited
July 2013	Expert adjudication of primary outcome commences
23 August 2013	Final participant gives birth,
December 2013	Final peripartum trial forms received (collection of 4 month postpartum data will continue into 2014)
January 2014	Trial baseline and peripartum data entry expected to be finalised and birth outcomes dataset locked, treatment assignment to be unblinded to data analysts and other trial researchers.
2014	Final 4 month follow-up data to be received

1.3 Aims

The primary aim of the study was to conduct a randomised controlled trial to answer the clinical question: *In women with preterm prelabour ruptured membranes (PPROM) between 34^0 weeks and 36^6 weeks gestation is planned early delivery compared with expectant management associated with less neonatal and maternal morbidity?*

A secondary aim, to be carried out for centres in Australia, New Zealand and the UK, was to perform a costing of the outcomes to establish the economic impact of planned early delivery compared with expectant management. The costing will determine the net impact of each intervention on hospital resources.

1.4 Study Design

This was an international multi-centre randomised controlled clinical trial. Once women consented to be involved in the trial, they were randomised via a central telephone randomisation service to one of two treatment groups, early planned birth or expectant management. Randomisation was 1:1, in balanced variable blocks and stratified by centre. Although treatment group allocation was concealed prior to randomisation, this was necessarily an unblinded trial. Both participants and obstetric care providers were aware of the treatment allocation. However, adjudication of the primary outcome (neonatal sepsis) was blinded to treatment allocation.

Importantly, some women allocated to expectant management went into spontaneous labour and birth quickly. On the other hand, some women allocated to immediate delivery (by labour induction or prelabour caesarean section) had the birth delayed due to insufficient availability of delivery room resources. In the latter case, immediate delivery proceeded as soon as it was deemed safe.

1.5 Eligibility criteria

Pregnant women between 34^0 weeks and 36^6 weeks gestation with PPROM and a singleton pregnancy were eligible for inclusion in the trial. Women with PPROM before 34 weeks gestation were approached about entering the trial, but could not be consented and randomised before 34^0 weeks.

Exclusion criteria included established labour and indications for immediate delivery (clinical evidence of chorioamnionitis, meconium staining, haemorrhage or other contraindication to

expectant management). The presence of Group B streptococcus (GBS) was specifically not to be considered as a contraindication to expectant management.

After randomisation, participants were to be managed in other respects according to local practice and protocols. Participating hospitals were encouraged to collect vaginal swabs and other pathology results (i.e. white cell count, C-Reactive protein [CRP]) after ROM but this was not a requirement.

1.6 Intervention

Early planned delivery group: Those women randomised to early planned birth were to have delivery scheduled as close to randomisation as possible and preferably within 24 hours of randomisation. The mode of birth was determined by usual obstetric indications. Antibiotics were to be continued in the intrapartum period.

Expectant management group: In women randomised to expectant management birth was to occur after spontaneous labour, at term or when the attending clinician felt that birth was indicated according to usual care.

Care of the women was otherwise managed according to usual practice by the obstetric team with care of the infant by the attending neonatologist.

1.7 Data collection and follow up

Trial data was collected using separate forms at each of the following time points:

Trial Entry Form: recorded at randomisation, with maternal and pregnancy characteristics including date of PPROM and management
Antenatal Form (randomisation until birth): investigations and services use
Labour and Delivery Form: delivery management
Postnatal Form: delivery outcomes (ie birthweight, Apgar score), maternal complications, breastfeeding, maternal discharge from hospital
Neonatal Form: completed at delivery hospital and includes neonatal investigations, management, adverse events and separation from hospital.

Additionally, any neonatal death following discharge was requested to be separately notified to the trial manager.

Four month questionnaires were posted out to participants in English speaking countries (Australia, New Zealand, United Kingdom) to assess maternal wellbeing, satisfaction with care, breast feeding duration and early infant development.

1.8 Trial endpoints

1.8.1 Primary outcome: neonatal sepsis

The primary outcome is neonatal sepsis at any time prior to discharge home of the neonate. Neonatal sepsis can be based on either definite indications such as a positive culture (definite sepsis) or on clinical signs and laboratory evidence of infection resulting in treatment with antibiotics (probable sepsis). Both definite and probable sepsis will count as an occurrence of the primary outcome. The outcome is being adjudicated by two neonatologists from the coordinating centre (see Appendix 1 for list of information used in the adjudication). The null hypothesis assumes that there will be no difference in the rate of neonatal sepsis between the two randomised arms of the trial.

Definite systemic neonatal infection (definite sepsis) is defined as the presence of clinical signs of infection and a positive culture of a known pathogen from blood or cerebrospinal fluid (CSF), where the baby was treated with antibiotics for 5 or more days (or died before 5 days). For organisms of low virulence and/or high likelihood of skin contamination of the blood culture, such as coagulase negative staphylococcus, both a positive blood culture and an abnormal full blood count or abnormal C-Reactive Protein (CRP) were required.

Clinical signs of infection include respiratory distress (requiring ventilation, continuous positive airway pressure or supplemental oxygen for more than one hour), apnea, lethargy, abnormal level of consciousness, circulatory compromise (including hypotension, poor perfusion, need for inotropic support or volume expansion) and/or temperature instability (temperature $<36^{o}$C or $\geq 38^{o}$C)

An abnormal full blood count (FBC) count includes abnormal white cell count[1] (white cell count [WCC]$<5 \times 10^{9}$/L or WCC$>30 \times 10^{9}$/L), low platelet count[2] (platelets <100,000), low neutrophil count[1] (neutrophils $<1.5 \times 10^{9}$/L) or raised immature to total neutrophil ratio[1] (I:T ratio >0.2). A CRP > 10mg/L was considered abnormal[3,4].

Probable neonatal infection (probable sepsis) is defined as the presence of clinical signs where the baby was treated with antibiotics for 5 or more days together with one or more of: an abnormal FBC; abnormal CRP; positive Group B Streptococcal (GBS) antigen on bladder

tap urine, blood or CSF; elevated CSF white cell count [5] (CSF WCC>100 $x10^6$/L); growth of a known virulent pathogen (eg GBS, E.coli, Listeria) from surface swab; or a histologic diagnosis of pneumonia in an early neonatal death.

1.8.2 Secondary infant outcomes

1. *Composite neonatal morbidity (sepsis, mechanical ventilation or death)* will be analysed as a dichotomous outcome and includes infants with one or more of:

   Sepsis (the primary outcome), mechanical ventilation ≥24 hours (#6 below), or perinatal death (#2 below).

   The purpose of the composite outcome is to represent the competing risks (neonatal sepsis versus need for respiratory support) posed by expectant management versus immediate delivery.

2. *Perinatal death* (stillbirth or neonatal death) will be analysed as a dichotomous outcome as obtained from:

   Yes in response to Question 9 of the trial Postnatal Form ['yes' or 'no' tick box for Perinatal death] or,

   "Died" as the response to Question 46.2 of the trial Neonatal Form [This question relates to the discharge status of live born infants has 3 options – discharged home, transferred hospital, or died] or,

   A neonatal death (death within the first 28 days of life) directly notified by the site coordinator.

3. *Respiratory distress syndrome* will be analysed as a dichotomous outcome, as obtained from:

   Respiratory distress syndrome (RDS) in response to Question 6 of the trial Neonatal Form [nine tick box options, 6.2 is RDS].

4. *Pneumonia* will be analysed as a dichotomous outcome, as obtained from:

   Pneumonia in response to Question 6 of the trial Neonatal Form [nine tick box options, 6.4 is Pneumonia]

5. *Any mechanical ventilation* will be analysed as a dichotomous variable as obtained from:

Yes in response to Question 7 of the trial Neonatal Form ['yes' or 'no' tick box for Mechanical ventilation including intermittent positive pressure ventilation (IPPV), continuous positive airway pressure (CPAP) and/or high frequency oscillatory ventilation (HFOV)].

6. *Mechanical ventilation for twenty four hours or more* will be analysed as a dichotomous variable obtained from:

   Duration of the mechanical ventilation in days in response to Question 7.1 of the trial Neonatal Form [free text fields for duration of ventilation collected in days, or if less than 1 day, in hours].

7. *Birthweight* will be analysed as a continuous variable, as obtained from:

   Birthweight in the response to Question 6 in the "Infant Details" section of the trial Postnatal Form [free text field for birthweight in grams].

8. *Small for gestational age* (SGA) defined as <10th percentile birthweight for week of gestation, by gender, will be analysed as a dichotomous variable using an Australian standard for singletons (10^{th} percentiles shown in Appendix 2), with the data obtained from:

   Birthweight in the response to Question 6 in the "Infant Details" section of the trial Postnatal Form [free text field for birthweight in grams], and

   Gestational age (GA) in completed weeks in the response to Question 1 in the "Infant Details" section of the trial Postnatal Form [free text field in weeks and days], and

   Baby sex in the response to Question 2 in the "Infant Details" section of the trial Postnatal Form.

9. *Apgar score <7 at 5 minutes* will be analysed as a dichotomous variable, as obtained from:

   Apgar Scores at 5 minutes in response to Question 3 in the "Infant Details" section of the trial Postnatal Form [free text field for Apgar scores range from 0 to 10].

10. *Antibiotics in first 48 hours* will be analysed as a dichotomous variable, as obtained from:

    Yes in response to Question 20 of the trial Neonatal Form ['yes' or 'no' tick box for Antibiotics administered in 1st 48 hours]

11. *Lumbar puncture* will be analysed as a dichotomous variable, as obtained from:

    Yes in response to Question 15 of the trial Neonatal Form ['yes' or 'no' tick box for Lumbar puncture in 1st 48 hours after birth] and/or

    Yes in response to Question 28 of the trial Neonatal Form ['yes' or 'no' tick box for Lumbar puncture in >48 hours after birth] and/or

    Recording one or more investigations for Lumbar puncture in Question 45.9 of the trial Neonatal Form

12. *Circulatory compromise* requiring arterial line, fluid bolus or inotropic support will be analysed as a dichotomous variable, as obtained from:

    Yes in response to Question 21 of the trial Neonatal Form ['yes' or 'no' tick box for Circulatory compromise in 1st 48 hours. Question 21.1 contains five tick box indications 'a' being Arterial line inserted, 'c' being Fluid bolus/volume expansion, and 'd' being Ionotropic support, more than one indication can be ticked] and/or

    Yes in response to Question 32 of the trial Neonatal Form ['yes' or 'no' tick box for Circulatory compromise at time of 1st systemic infection >48 hours. Question 32.1 contains five tick box indications 'a' being Arterial line inserted, 'c' being Fluid bolus/volume expansion, and 'd' being Ionotropic support, more than one indication can be ticked]

13. *Total duration of stay in special care nursery (SCN) or intensive care unit (ICU)* will be analysed as a continuous variable as obtained from:

    Total time in days spent in a SCN and/or ICU in response to Question 4.2 of the trial Neonatal Form [free text fields for duration of admission collected in days, or if less than 1 day, in hours].

14. *Duration of infant hospitalisation at the birth hospital* for infants discharged alive will be analysed as a continuous variable, as obtained from:

    The difference between the date of birth [delivery date (day/month/year) from Question 3 of the labour and Delivery form] and date of transfer or discharge home [(day/month/year) in response to Question 46 of the trial Neonatal Form].

15. *Infant receiving breast milk* at discharge will be analysed as a dichotomous variable, as obtained from:

    Yes if infant receiving any breast milk based upon the response to Question 2 in the "Feeding" section of the trial Postnatal Form [tick box options for exclusive breast milk, partial breast milk, formula only or unknown at the time of maternal discharge].

1.8.3 Secondary maternal and pregnancy outcomes

1. *Antepartum haemorrhage* will be analysed as a dichotomous variable, as obtained from:

    Yes in response to Question 9 of the trial Antenatal Form ["yes' or 'no' tick box for Antepartum Haemorrhage], and/or

    Yes in response to Question 12 of the trial Labour and Delivery Form ["yes' or 'no' tick box for Intrapartum bleeding].

2. *Cord prolapse* will be analysed analysed as a dichotomous variable, as obtained from:

    Yes in response to Question 10 of the trial Antenatal Form ['yes' or 'no' tick box for Cord Prolapse]

3. *Cephalic presentation* at birth will be analysed as a dichotomous variable, as obtained from:

    Cephalic presentation in response to Question 5 of the trial Labour and Delivery Form [tick box options of 'cephalic', breech' or 'other'].

4. *Chorioamnionitis as delivery indication* will be analysed as a dichotomous variable, as obtained from:

Yes if indicated on any of Question 7.2.e of the Labour and Delivery Form [among women who have labour induced, Question 7.2 contains six tick box indications for induction ‘e’ being Chorioamnionitis, more than one indication can be ticked], or

Yes if indicated on any of Question 8.2.e of the Labour and Delivery Form [among women who have a caesarean section, Question 8.2 contains six tick box indications for induction ‘i’ being Chorioamnionitis, more than one indication can be ticked]

Chorioamnionitis as a finding from placental histology will be not be used. Placental histology was not uniformly requested. Obstetric teams were not blinded to treatment assignment and may have differentially requested placental histology based upon awareness of allocation to expectant management or not.

5. *Intrapartum fever* will be analysed as a dichotomous variable, as obtained from:

   Yes in response to Question 13 of the trial Labour and Delivery Form [‘yes’ or ‘no’ tick box for Pyrexia above or equal to 38.5 degrees Celsius].

6. *Postpartum antibiotics* will be analysed as a dichotomous variable, as obtained from:

   Yes response to Question 5 in the “Postnatal Maternal Complications” section of the trial Postnatal Form [‘yes’ or ‘no’ tick box for Antibiotics postpartum].

7. *Postpartum haemorrhage* will be analysed as a dichotomous variable, as obtained from:

   Defined as blood loss ≥1000 ml in response to Question 17 of the trial Labour and Delivery Form [blood loss records in millilitre].

8. *Thromboembolism* (which can include superficial thrombophlebitis) will be analysed as a dichotomous variable, as obtained from:

   Yes response to Question 11 of the trial Antenatal Form [‘yes’ or ‘no’ tick box for Thrombosis/Thromboembolism requiring treatment], and/or

   Yes in response to Question 4 in the “Postnatal Maternal Complications” section of the trial Postnatal Form [‘yes’ or ‘no’ tick box for Deep Vein Thrombosis (DVT)/Thromboembolism].

9. *Maternal length of hospitalisation* at the birth hospital will be analysed as a continuous variable, as obtained from:

Days in hospital from randomisation to delivery response to Question 24 of the trial Antenatal Form [free text fields for duration of hospitalisation(s) collected in days], plus

The difference between the date of birth [delivery date (day/month/year) from Question 3 of the labour and Delivery form] and date of transfer or discharge home [(day/month/year) in response to Question 6 in the "Mother's Separation from Delivery Hospital" section of the trial Postnatal Form].

Time until delivery, onset of labour and mode of delivery

Time from randomisation until delivery should be directly related to treatment allocation. The onset of labour and mode of delivery will also be directly related, as planned immediate delivery would require either induction or a prelabour caesarean, unless labour commences spontaneously prior to a planned birth. Time until delivery, labour onset and mode of delivery are not trial endpoints, but are important results. Time until delivery, by treatment allocation and week of randomisation, will be reported as shown in dummy Table 2. Onset of labour and subsequent mode of delivery by treatment allocation will be reported as shown in dummy Table 3. The percentage of "expectant management" women who delivered within 48 hours of randomisation, and the number of women in "immediate delivery" who delivered at or more than 48 hours after randomisation will be reported in the trial text, as an indication of how well treatment allocation and actual treatment were aligned.

2. STATISTICAL ANALYSIS

2.1 Study size

The study sample size, as described in the trial protocol, was set at 1812 women so as to have 80% power to detect a statistically significant difference if the population sepsis rate was 5.0% in one arm and 2.5% in the other arm. The significance level was set at a two-tailed $P<0.05$, even though a reduced sepsis rate in the expectant management group was considered improbable.

2.2 Participant flow diagram

A CONSORT (Consolidated Standards of Reporting Trials) type diagram will be used to show the flow of participants into the final analysis. This is expected to be Figure 1. Only participants for whom the primary outcome is available will be included in the final analyses.

2.3 Analysis Principles

All analyses will be by intention-to-treat. The number of participants lost to follow-up will be reported. No participants will be excluded from the primary intention to treat analysis due to protocol violations. There will be no per-protocol analyses. Analyses will conform with guidelines promulgated by Consolidated Standards of Reporting Trials (CONSORT) (reference # 3)

Preliminary descriptive analyses of the frequency of randomisation and pre-randomisation characteristics using blinded trial data (does not include a treatment assignment field) will be performed. Analyses of trial outcomes will not be performed until the statistics plan is finalised.

2.3.1 Distribution of baseline variables

Maternal and pregnancy characteristics at or before randomisation, by trial arm, will be shown in Table 1 (see dummy table, page 17). Additional information, such as participants by country/region will be included in the Results text of the trial report.

2.3.2 Missing baseline variables

There will be no imputation for missing values, with one exception: women who are missing either time of randomisation (24 hour clock) or time of PPROM, but not missing day of randomisation or day of PPROM. For these women, the hours from PPROM to randomisation will be calculated as the difference in days between randomisation and PPROM (multiplied by 24) plus an imputed nine hours (four, five and six hours were the mode values for non-missing participants randomised within 24 hours, nine hours was the median).

2.3.3 Missing primary outcome

Only participants for whom the primary outcome is available will be included in the final analyses. Thus there will be no imputation for missing values of the primary outcome.

2.3.4 Unadjusted analysis of primary outcome

Event numbers and percentages will be reported, by treatment arm as in dummy Table 4. Statistical significance will be two-sided at the $P<0.05$ level. Effect measures (relative risk) will be reported with a 95% confidence interval.

2.3.5 Adjusted analysis of primary outcome

A decision as to whether to perform adjusted analyses will NOT be determined by statistical testing of baseline differences between treatment arms, consistent with CONSORT recommendations (CONSORT Additional analyses, Item 12b). The randomisation process will be assessed by comparing the trial arms for clinically meaningful differences in the two important factors (at time of randomisation) in relation to potential neonatal sepsis and morbidity: 1) duration from PROM to randomisation 2) gestational age at randomisation. Criterion 1 will be triggered if there is a relative difference (the difference in median duration, divided by the larger of the two duration times) of >15% between trial arms in the median hours from PPROM to randomisation. As an example, a median of 22 hours in one arm and 26 hours in the other would meet this criterion. Criterion 2 is if the median gestational age at randomisation differs by > 3 days between arms. If either of these two conditions is met, then adjusted analyses will be required.

If adjusted analyses is required per the above, a logistic regression model will be used. The covariates initially included as potential confounders will be: maternal age category (<20, 20-24, 25-29, 30-34, ≥35), parity category (0, 1, ≥2), gestational week at PPROM, hours from PPROM to randomisation (<4, 4 to <24, 24 to <48, ≥48), any pregnancy hypertension (yes/no), gestational diabetes, antenatal urinary tract infection, positive culture for GBS at or before randomisation (yes/no), any other positive culture for abnormal vaginal flora at PPROM (yes/no), and treatment with antibiotics at randomisation or preceding 24 hours (yes/no). Backwards elimination will be used for factors which do not meet a statistical significance level of P=0.50, or alternatively to maintain a minimum events:covariates ratio of 10:1n the model. Results will be reported as RR and 95% CI, as estimated from the model odds ratio and 95% CI.

2.3.6 Missing secondary outcomes

There will be no imputation for missing values.

2.3.7 Analysis of secondary outcomes

Event numbers and percentages will be reported, by treatment arm. Dichotomous primary and secondary outcomes will be compared between treatment arms by calculating relative risks and 95% confidence intervals (RR, 95% CI), using expectant management as the comparison group. No adjustment to the level of statistical significance will be made for multiple comparisons. Comparison of mean birthweight will be performed using a t-test. Comparisons of maternal and infant length of stay (days) will be performed using non-parametric Mann-Wilcoxon tests.

If an adjusted analysis of the primary outcomes is required (per the “adjusted analysis of primary outcome” section above), there will also be similar adjusted analyses for secondary outcomes.

2.3.8 A priori subgroup analyses

The only pre-specified subgroup analyses will be for the primary outcome of neonatal sepsis and are shown in dummy Table 5: baseline subgroups by time from PPROM until randomisation, gestational week of PPROM, vaginal swab culture result and antibiotic administration at randomisation.

2.3.9 Post-hoc hypotheses generating subgroup analyses

Any post-hoc analyses (analyses not pre-specified in this SAP) which are completed to support the planned analyses will be clearly identified as such in any reporting of the trial.

3. DUMMY TABLES

Table 1 Maternal and pregnancy factors at or before time of randomisation

	Early planned birth n (%)	**Expectant management n (%)**
Rupture of membranes		
<28^0 weeks		
28^0 to 29^6 weeks		
30^0 to 31^6 weeks		
32^0 to 33^6 weeks		
34^0 to 34^6 weeks		
35^0 to 35^6 weeks		
36^0 to 36^6 weeks		
Randomised		
34^0 to 34^6 weeks		
35^0 to 35^6 weeks		
36^0 to 36^6 weeks		
PPROM ≥ 48 hours before randomisation		
Maternal age (years) (mean, std.dev.)		
Previous pregnancies		
0		
1		
≥ 2		
Cephalic presentation		
Previous caesarean section		
Previous PPROM or preterm delivery		
Previous stillbirth or neonatal death		
Pregnancy hypertension (onset ≥ 20 weeks)		
Gestational diabetes		
Antenatal urinary tract infection		
Antibiotics given†		
intravenous (+/- oral)		
oral only		
Steroids given		
Positive culture from a vaginal swab††		
any positive culture		
Group B streptococcus positive		

† antibiotics at randomisation or in preceding 48 hours

†† culture resulting from vaginal swab after PPROM and at or before randomisation

Table 2 Time from randomisation until birth, by treatment assignment

Week randomised	Immediate delivery days until birth median (10^{th}- 90^{th} centiles)	Expectant management days until birth median (10^{th}-90^{th} centiles)
34		
35		
36		

Table 3 Onset of labour and delivery mode, by treatment assignment

Onset of labour and delivery mode	Immediate delivery n (%)	Expectant management n (%)
Spontaneous labour		
Vaginal birth		
Caesarean section		
Labour induction		
Vaginal birth		
Caesarean section		
Pre-labour caesarean section		
Total caesarean sections		

Table 4 Infant and maternal outcomes by treatment assignment

Infant outcome	**Immediate delivery n (%)**	**Expectant management n (%)**	**Relative risk RR (95% CI)**
Neonatal sepsis			
Secondary infant outcomes			
Composite of neonatal morbidity (sepsis, ventilation ≥24 hours or death)			
Perinatal death			
Respiratory distress syndrome			
Pneumonia			
Any mechanical ventilation			
mechanical ventilation for ≥ 24 hours			
Birthweight (grams; mean and std. dev.)			
SGA <10th percentile size			
Apgar score <7 at 5 minutes			
Antibiotics in first 48 hours			
Lumbar puncture			
Circulatory compromise			
Infant days in hospital*			
Days in SCN/NICU†*			
Receiving breast milk at discharge			
Secondary maternal and pregnancy outcomes			
Antepartum haemorrhage			
Cord prolapse			
Chorioamnionitis as delivery indication			
Intrapartum fever			
Postpartum antibiotics			
Postpartum haemorrhage			
Maternal duration of hospitalisation*			

* median and interquartile range reported for duration of admission, Wilcoxon P value for test of null hypothesis of no difference in distribution between treatment arms

† days in a Special Care Nursery and/or Neonatal Intensive Care Unit

Table 5: Pre-specified subgroup analyses for neonatal sepsis

Infant outcome	**Immediate delivery Sepsis n/N (%)**	**Expectant management Sepsis n/N (%)**	**Neonatal sepsis RR (95% CI)**
Duration from PPROM to randomisation			
< 48 hours			
≥ 48 hours			
Gestation of PPROM			
before 34 weeks			
≥ 34 weeks			
Positive vaginal culture after PPROM†			
GBS			
other organism			
normal flora or no culture collected			
Maternal antibiotics at randomisation††			
Yes			
No			
Cephalic presentation at randomisation			
Yes			
No			

† culture resulting from vaginal swab after PPROM and at or before randomisation
†† antibiotics at randomisation or in preceding 48 hours

4. ADDITIONAL ANALYSES

4.1 Costing Analysis

The costing analysis will be limited to participants from hospitals in Australia, New Zealand and the UK depending upon availability of cost information.

The costing component will be conducted in accordance with the methods outlined in Drummond et al 1997 and will adopt a health system approach (reference #4). Costs will be based on direct health care costs for mothers and babies and the cost of additional resources associated with interventions of the study; and determined for women and their infants in each treatment group. Maternal health service utilisation will be estimated from the time of recruitment and all subsequent maternal and infant hospitalisations, length of stay and resource use applied up to discharge home from the birth admission. A further analysis will include costs up to four months postpartum for subgroup of women for whom this information is available.

Costing for each maternal and infant hospitalisation will be determined using the Australian Refined Diagnosis Related Groups (AR-DRG) classification code assigned for each episode of care (hospitalisation). This code is developed by the Commonwealth Department of Health and Ageing and is based on clinical diagnosis and procedures and their associated costs of treatment and resource consumption for each episode of acute inpatient care. Maternal AR-DRG are calculated and based on maternal medical conditions, mode of delivery and obstetric complications, while neonatal AR-DRG are categorised by birth weight, with or without significant operating procedures or major problems. Average *per diem* costs will be applied to each AR-DRG. Cumulative number of hospital in-patient days will be calculated by aggregating the length of stay of each relevant admission.

Additional micro-costing of health care resource use will be conducted as these may be related to treatment allocation in the trial and prescribed in addition to routine clinical care. Further, many tests and procedures may not require hospitalisation or only outpatient care and thus, would not be recorded as an episode of care or assigned an AR-DRG. For mothers, diagnostic procedures and testing that may be carried out include blood tests, vaginal swabs and cultures, CTG monitoring, ultrasound and use of medications and antibiotics. For babies, additional procedures such as oxygen therapy, resuscitation, blood tests, blood and urine cultures, lumbar puncture, chest x-rays, ultrasounds and use of medications may be required for investigation and treatment. These will then be costed by

aggregating the corresponding scheduled unit cost assigned by the Medicare Benefits Schedule or Pharmaceutical Benefits Schedule.

All of the results will be analysed according to the intention to treat approach. The number of episodes of care and resource utilisation and associated costs over the trial period will be quantified and aggregated for mothers and infants in each arm of the trial. Average cost analysis will be conducted whereby the mean rate of hospitalisations and use of resources will be calculated and compared between groups using t-tests or the distribution-free equivalent, as required. The distribution of costs data is commonly skewed so bootstrap re-sampling will be used to estimate standard error and 95% confidence intervals. (reference #5) Sensitivity analyses will be explore any uncertainty of costs.

4.2 Four month postpartum follow-up

Trial data collected also includes an SF36 Health Survey questionnaire sent out at four months postpartum, on maternal satisfaction with care and wellbeing. Data collection for this part of the study was ongoing as of the end of 2013. The results of the questionnaire will be analysed and reported separately from the main trial analysis. Participants in the trial were necessarily aware of their treatment assignment, so their self-reported outcomes on the SF36 were not blinded. **A separate analysis plan will be prepared for the 4 month follow-up, prior to commencing that analysis.**

APPENDIX 1

PPROMT SEPSIS ADJUDICATION

Sepsis definitions: modified from trial protocol published in BMC Pregnancy and Childbirth with additions (*noted in italics*) and some minor alterations/exclusions due to lack of data alterations (see comments).
prepared by Dr. Jennifer Bowen, Department of Neonatology, Royal North Shore Hospital

Definite systemic neonatal infection was defined as the presence of clinical signs of infection and a positive culture of a known pathogen from blood or cerebrospinal fluid, *where the baby was treated with antibiotics for 5 or more days (or died before 5 days)*. For organisms of low virulence and/or high likelihood of skin contamination of the blood culture, such as coagulase negative staphylococcus, both a positive blood culture and an abnormal full blood count *or abnormal C-Reactive Protein (CRP)* were required.
Clinical signs of infection include respiratory distress *(requiring ventilation, continuous positive airway pressure or supplemental oxygen for more than one hour)*, apnoea, lethargy, abnormal level of consciousness, circulatory compromise (including hypotension, poor perfusion, need for inotropic support or volume expansion) and/or temperature instability *(temperature <36^{o}C or ≥38 ^{o}C)*. Poor feeding was not included as a clinical sign of infection, as IG tubes may be required due to prematurity alone.
An abnormal FBC count includes abnormal white cell count[1] *(wcc <5 x 10^{9} /L or wcc >30 x 10^{9} /L)*, low platelet count[2] (platelets <100,000), low neutrophil count[1] *(neutrophils <1.5 x 10^{9} /L)* or raised immature to total neutrophil ratio[1] *(I:T ratio >0.2). A CRP > 10mg/L was considered abnormal*[3,4].
Raised immature neutrophil count was not included as a sign of clinical infection, as it is not useful alone. Information on degenerative morphological changes to neutrophils (toxic granulation or vacuolization) was not available from the trial data.
Probable neonatal infection was defined as the presence of clinical signs where the baby was treated with antibiotics for 5 or more days together with one or more of: an abnormal FBC; abnormal CRP; positive Group B Streptococcal (GBS) antigen on bladder tap urine, blood or CSF; *elevated CSF white cell count* [5] *(CSF wcc >100 x10^{6}/L)*; growth of a known virulent pathogen (eg GBS, E.coli, Listeria) from surface swab; or a histologic diagnosis of pneumonia in an early neonatal death.

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APPENDIX 2 – 10th birthweight percentile cut-points by gestational age and gender (from Dobbins et al. Australian national birthweight percentiles by sex and gestational age, 1998-2007. MJA. 2012 Sep 3;197(5):291–4**)**

Gestation (weeks)	Males	Females
34	1860	1764
35	2080	1980
36	2295	2198
37	2540	2430
38	2800	2690
39	2950	2830
40	3090	2975
41	3220	3090
42	3250	3110
43	3085	3010
44	3110	3070

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