AMIPROM: Amnioinfusion in preterm premature rupture of membranes

A randomised controlled trial of amnioinfusion versus expectant management in very early preterm premature rupture of membranes – a pilot study

Statistical Analysis Plan for Short-Term Outcome Data

Contents

1. Introduction

This Statistical Analysis Plan (SAP) provides a detailed and comprehensive description of the main, pre-planned analyses for the short-term data from the study "Amnioinfusion in preterm premature rupture of membranes (AMIPROM) – A randomised controlled trial of amnioinfusion versus expectant management in very early preterm premature rupture of membranes – a pilot study".

The approach will be to analyse the short-term data first to present to the DMC with the long-term outcomes to be analysed later. The DMC will give their recommendations to the TSC and they will decide whether to allow early publication of the short-term results.

These planned analyses will be performed by the trial statistician. The results will be described in a statistical analysis report, to be used as the basis of the primary research publication.

All analyses are performed with standard statistical software (R or SAS). The final analysis datasets, programs and outputs are archived following good clinical practice guidelines (ICH E9). The testing and validation of the statistical analysis programs will be performed following the 'Statistical Quality Assurance' Standard Operation Procedure (SOP ST-003).

2. Study design and objectives

2.1 Study design

This is a multi-centre, randomised controlled pilot trial involving 4 sites in the United Kingdom that plans to recruit 62 patients, 31 into each of the study arms. Mothers randomised to receive the study treatment will be treated with amnioinfusion and mothers randomised to the control treatment will be treated with expectant management. Patients are randomised from a central randomisation list, held in the R&D office at Liverpool Women's Hospital, to one of two treatment arms in a 1:1 ratio.

2.2 Study objectives

The aim of this analysis is to compare the neonatal, maternal and pregnancy outcomes in very early PROM managed expectantly with those managed with serial amnioinfusions. As this is a pilot study all outcome measurements will be reported. These outcomes are:

1. Fetal death

2. Neonatal death

3. Neonatal morbidity:
   - Gestational age at delivery, birth weight, apgar at 1 minute, apgar at 5 minutes, cord pH, base excess, lactate, culture positive sepsis, pneumothorax (chest drain), home O_2, O_2 measured daily for the first 28 days, O_2 at day 28, O_2 at week 36, NEC (operated), NEC (treated as such), treated seizures, treated retinopathy, IVH (grade 0-3), PVL, shunt, orthopaedic deformities
   - Days: IPPV, CPAP, HFOV

4. Maternal death

5. Maternal morbidity:

- Onset of labour, mode of delivery, abruption placenta, antepartum haemorrhage, chorioamnionitis, maternal sepsis requiring ITU/HDU

2.3 Inclusion/exclusion criteria

Eligibility criteria

a) All women with very early PROM who are booked at recruiting centre.
b) All women with very early PROM booked at other hospitals in the region but who are referred for assessment or delivery to the recruiting centre.

Entry criteria

a) Singleton pregnancy
b) Rupture of membranes between 16 weeks gestation and 24 weeks gestation
c) Rupture of membranes confirmed by presence of amniotic fluid in the posterior fornix on speculum examination and/or severe oligohydramnios on ultrasound examination

Exclusion criteria

a) Obstetric indication for immediate delivery (i.e. fetal bradycardia, abruption, cord prolapse, advanced labour > 5cm)
b) Multiple pregnancy
c) Fetal abnormality

2.4 Sample size

An initial sample size was calculated for this study based on an audit performed at The Liverpool Women's Hospital. The audit revealed a composite adverse outcome of 75% in pregnancies with very early PROM: deaths 65% and 10% respiratory morbidity in the survivors (25% of survivors).

To reduce the composite outcome by half, the trial would need 31 cases and 31 controls. (80% power). A reduction in composite outcome by 50% has been chosen because the nature of the intervention is such (i.e. invasive and repeated) that only a large difference would justify its introduction into routine practice.

In the above-mentioned audit, 48 patients were studied over a 3.5-year period (~14 per annum). If we assume that 75% of women whose pregnancies are affected by very early PROM agree to take part in the study, it would take 6 years to recruit the necessary cases to complete the study. To reduce the time for recruitment, it is proposed that a multicentre trial be undertaken.

It is proposed that there will be five hospitals taking part in the study. If each hospital recruits five patients a year, recruitment will take less than three years.

2.5 Recruitment

The date first patient recruited was 03/09/2002. The last patient recruited before trial closure was 01/04/2009 and the expected date of end of follow-up will be April 2011.

3. Description of study population

3.1 Representativeness of study sample and patient throughput

Details of patients assessed for eligibility, those who meet the study inclusion criteria, those who are eligible and randomised, those who are eligible but not randomised, those who withdraw from the study after randomisation and those who are lost to follow-up will be summarised in a CONSORT flow diagram.

The number of ineligible patients randomised will be reported.

3.2 Baseline comparability of randomised groups

Eligible patients who are randomised will be described, both split by treatment group and overall, with respect to demographic details and history (parity, HVS, WCC, CRP, temperature, tender irritable uterus, foul smelling discharge, gestation at PPROM, gestation at randomisation, maternal age at randomisation, vaginal bleeding, thoracic circumference, abdominal circumference, lung length) at baseline. Details of measurements for the first amnioinfusion in amnioinfusion group at baseline will be summarised (fluid instilled, pocket before amnioinfusion, pocket after amnioinfusion, pocket difference (before-after)). Tests of statistical significance will not be undertaken for baseline characteristics; rather the clinical importance of any imbalance will be noted.

3.3 Follow-up data and losses to follow-up

The number (and percentage) of patients with scheduled follow-up for amnioinfusions and maternal investigations will be reported by treatment group (where applicable). The number lost to follow-up within each treatment group will be reported and reasons where known will be documented in the CONSORT flow diagram. Any deaths and their causes will be reported.

3.4 Description of intervention received

In this study, treatment should be directly observed. Deviations from intended treatment (e.g. withdrawals from randomised treatment) will be summarised for each treatment group. The distribution of the number of amnioinfusions received will be described for women in the amnioinfusion group.

4. Patients groups for analysis

4.1 Intention to treat (ITT) analysis

To provide a pragmatic comparison of the policies of the different drug treatments, the principle of invention to treat, as far as is practically possible, will be the main strategy of analysis adopted for the primary efficacy outcomes. These analyses will be conducted on all patients assigned to the two treatment groups Amnioinfusion or Expectant Management as randomised, regardless of the study treatment or non-study treatment received.

5. Description for analysis of outcome data

Analysis will focus on estimation of treatment effects including 95% confidence intervals and will follow the intention to treat (ITT) approach. No significance testing will be undertaken. The list of outcomes covers all aspects of safety and efficacy.

If TMG decides there is an imbalance in the baseline characteristics between the two treatment groups (through eyeballing of distribution rather than formal significance testing) or if there are any factors that are deemed to be confounders (such as gestational age) then logistic regression will be used for all outcomes including baseline characteristics as covariates. We would be concerned if there was an imbalance of gestational age at rupture across the two treatment groups and we would adjust for this accordingly. However, this is unlikely to occur as the randomisation is stratified by this variable.

1. Fetal death data for the two groups will be presented in terms of relative risks with 95% confidence intervals.

2. Neonatal death data for the two groups will be presented in terms of relative risks with 95% confidence intervals.

3. The analysis of neonatal binary morbidity data will be two-fold: firstly, including all patients randomised by analysing the 'any pathology' outcome, thus preserving the balance achieved from randomisation, and secondly a subsidiary analysis of specific morbidities will be conducted, with fetal deaths omitted from the denominator for outcomes measured at birth and with both fetal and neonatal deaths omitted from the denominator for outcomes measured sometime after birth. They will be presented in terms of relative risks with 95% confidence intervals.

   The days on IPPV, CPAP and HFOV for the two groups will be presented as proportions/means/medians with ranges/standard deviations. Fetal deaths will be excluded from this analysis. Neonatal deaths will be assigned the largest value observed in the trial.

   The O_2 measured daily for the first 28 days for the two groups will be presented as medians and ranges for the time spent on O_2. Fetal deaths will be excluded from this analysis. Neonatal deaths will be assigned the largest value observed in the trial.

   A table will be provided summarising all neonatal outcomes per group.

4. Maternal death data for the two groups will be presented in terms of relative risks with 95% confidence intervals. However, if there are no maternal deaths then this will be reported.

5. Maternal morbidity will be presented as relative risks with 95% confidence intervals for the binary outcomes, number and percentage for categorical data and mean difference with 95% confidence intervals for the continuous outcomes. Maternal death data for the two groups will be presented in terms of relative risks with 95% confidence intervals.

Although the maternal measurements (haemoglobin, white cell count, platelet count, HVS, tender uterus, CRP and temperature) and the amnioinfusion measurements (fluid instilled, pocket before, pocket after, thoracic circumference, lung length and abdominal circumference) taken during the weekly study visits are not considered as outcomes, they

will be included as explanatory variables (along with number of doses of steroids) for investigational logistic regression models for predicting neonatal morbidity.

5.1 Missing data

The amount of and reasons for missing data will be reported for all outcomes listed above.

Consideration will be given to a sensitivity analysis, in which assumptions regarding missing data are made, if the amount of missing data for a particular outcome is large (>10%). Decisions regarding the approach to the sensitivity analysis will be documented prior to the comparison of treatment groups.

6. Reporting and analysing protocol deviations

Protocol violations will be classified according to the following table and summarised for each treatment group.

Protocol specification	Potential deviation(s)	Impact	Justification
Entry criteria Singleton pregnancy Rupture of membranes between 16 weeks gestation and 24 weeks gestation Rupture of membranes confirmed by presence of amniotic fluid in the posterior fornix on speculum examination and/or severe oligohydramnios on ultrasound examination	Any of the specified entry criteria violated	Major	Violations of these criteria would result in a different prognosis
Exclusion criteria Obstetric indication for immediate delivery (i.e. fetal bradycardia, abruption, cord prolapse, advanced labour > 5cm) Multiple pregnancy Fetal abnormality	Any of the specified exclusion criteria violated	Major Major Major	Patient may not have time to receive any treatment Violation of this criterion would result in a different prognosis Violation of this criterion could result in a different prognosis

Treatment regime Allocated to amnioinfusion	Patient missing either 2 consecutive infusions or 3 infusions in total	Major	May influence effectiveness
Outcome data Fetal death Neonatal death Neonatal morbidity (gestational age at delivery, birth weight, apgar at 1 minute, apgar at 5 minutes, cord pH, base excess, lactate, culture positive sepsis, pneumothorax (chest drain), home O_2, O_2 measured daily for the first 28 days, O_2 at day 28, O_2 at week 36, NEC (operated), NEC (treated as such), treated seizures, treated retinopathy, IVH (grade 0-3), PVL, shunt, orthopaedic deformities, days: IPPV, CPAP, HFOV) Maternal morbidity: (maternal death, onset of labour, mode of delivery, abruption placenta, antepartum haemorrhage, chorioamnionitis, serious maternal sepsis requiring ITU/HDU)	Missing data	Major	Violation of this criterion would result in a different outcome

In a secondary analysis of the group randomised to receive amnioinfusions, outcomes will be compared between the women who missed either 2 consecutive infusions or 3 infusions in total, and those who did not.

7. Setting results in context of previous research

We will integrate the results of this trial within the context of up-to-date systematic review of relevant evidence from other trials (Clarke et al 2007).

References

Clarke M, Hopewell S, Chalmers I. Reports of clinical trials should begin and end with up-to-date systematic reviews of other relevant evidence: a status report. *JRSM* 2007; 100: 187-190

Appendix 1: Approval of AMIPROM Protocol Deviations Table

This AMIPROM Protocol Deviations table (Version 1, 04/01/2010) has been completed and approved by the following personnel:

Trial statistician

Print Name: Mr. Andrew McKay **Date:** _____

Signature: _____

Supervising statistician

Print Name: Prof. Paula Williamson **Date:** _____

Signature: _____

Chief Investigator

Print Name: Dr. Devender Roberts **Date:** _____

Signature: _____

Chair of Trial Steering Committee

Print Name: Prof. Jim Thornton **Date:** _____

Signature: _____

Chair of Independent Data Safety Monitoring Committee

Print Name: Prof. Kate Costelloe **Date:** _____

Signature: _____

Appendix 2: Approval of AMIPROM Statistical Analysis Plan

This AMIPROM Statistical Analysis Plan (Version 1, 04/01/2010) has been completed and approved by the following personnel:

Trial statistician

Print Name: Mr. Andrew McKay **Date:** _____

Signature: _____

Supervising statistician

Print Name: Prof. Paula Williamson **Date:** _____

Signature: _____

Chief Investigator

Print Name: Dr. Devender Roberts **Date:** _____

Signature: _____

Chair of Trial Steering Committee

Print Name: Prof. Jim Thornton **Date:** _____

Signature: _____

Chair of Independent Data Safety Monitoring Committee

Print Name: Prof. Kate Costelloe **Date:** _____

Signature: _____