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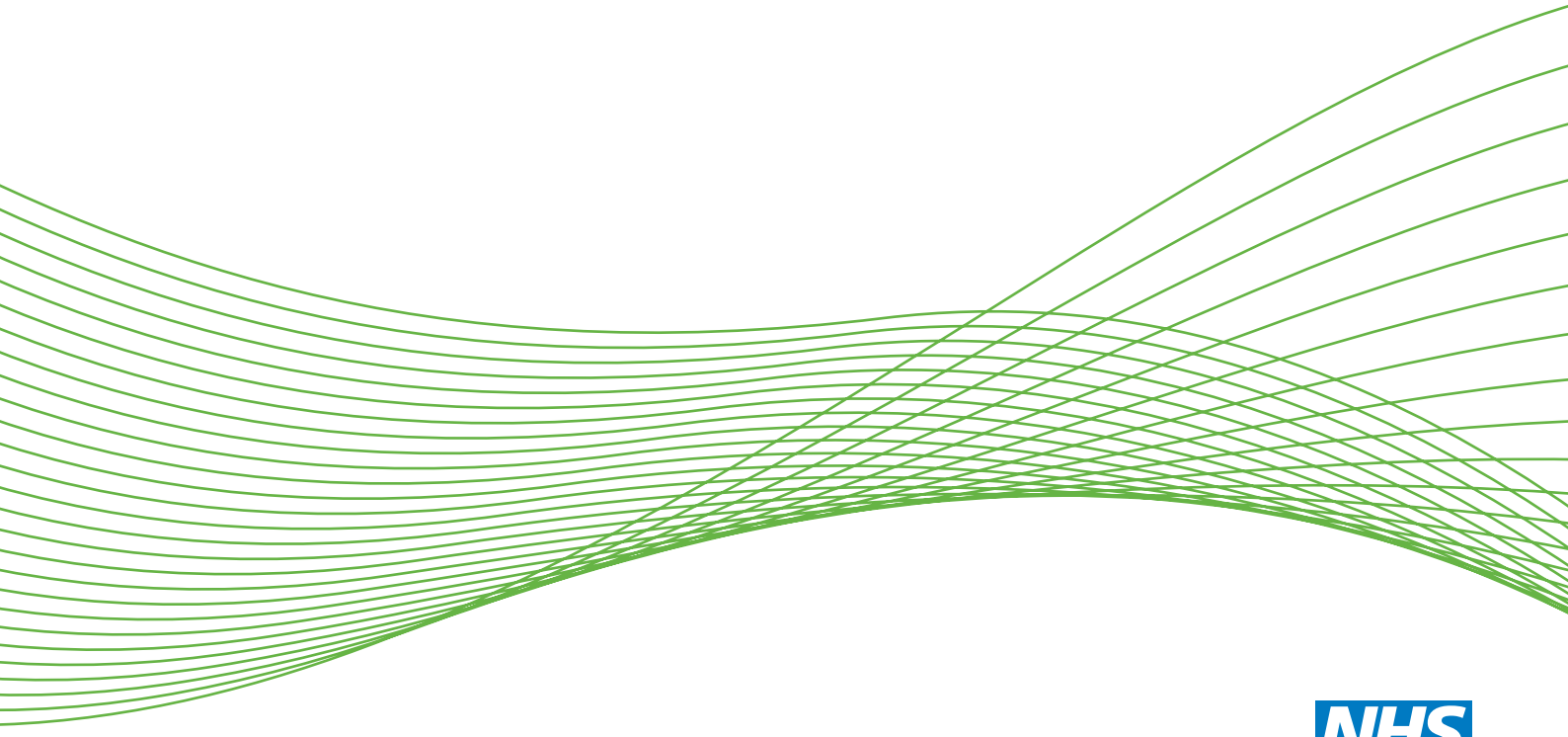
Amnioinfusion in preterm premature rupture of membranes (AMIPROM): a randomised controlled trial of amnioinfusion versus expectant management in very early preterm premature rupture of membranes – a pilot study

Devender Roberts, Sarah Vause, William Martin, Pauline Green, Stephen Walkinshaw, Leanne Bricker, Caroline Beardsmore, Ben NJ Shaw, Andrew McKay, Gaynor Skotny, Paula Williamson and Zarko Alfirevic



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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

Devender Roberts,[1]* Sarah Vause,[2] William Martin,[3] Pauline Green,[4] Stephen Walkinshaw,[1] Leanne Bricker,[1] Caroline Beardsmore,[5] Ben NJ Shaw,[1] Andrew McKay,[6] Gaynor Skotny,[6] Paula Williamson[6] and Zarko Alfirevic[7]

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Abstract

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

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Background: Fetal survival is severely compromised when the amniotic membrane ruptures between 16 and 24 weeks of pregnancy. Reduced amniotic fluid levels are associated with poor lung development, whereas adequate levels lead to better perinatal outcomes. Restoring amniotic fluid by means of ultrasound-guided amnioinfusion (AI) may be of benefit in improving perinatal and long-term outcomes in children of pregnancies with this condition.

Objective: The AI in preterm premature rupture of membranes (AMIPROM) pilot study was conducted to assess the feasibility of recruitment, the methods for conduct and the retention through to long-term follow-up of participants with very early rupture of amniotic membranes (between 16 and 24 weeks of pregnancy). It was also performed to assess outcomes and collect data to inform a larger, more definitive, clinical trial.

Design: A prospective, non-blinded randomised controlled trial. A computer-generated random sequence using a 1 : 1 ratio was used. Randomisation was stratified for pregnancies in which the amniotic membrane ruptured between 16^{+0} and 19^{+6} weeks' gestation and 20^{+0} and 24^{+0} weeks' gestation. The randomisation sequence was generated in blocks of four. Telephone randomisation and intention-to-treat analysis were used.

Setting: Four UK hospital-based fetal medicine units – Liverpool Women's NHS Trust, St. Mary's Hospital, Manchester, Birmingham Women's NHS Foundation Trust and Wirral University Hospitals Trust.

Participants: Women with confirmed preterm prelabour rupture of membranes between 16^{+0} and 24^{+0} weeks' gestation. Women with multiple pregnancies, resultant fetal abnormalities or obstetric indication for immediate delivery were excluded.

Interventions: Participants were randomly allocated to either serial weekly transabdominal AI or expectant management (Exp) until 37 weeks of pregnancy, if the deepest pool of amniotic fluid was < 2 cm.

Main outcome measure: Short-term maternal, pregnancy and neonatal outcomes and long-term outcomes for the child were studied. Long-term respiratory morbidity was assessed using validated respiratory questionnaires at 6, 12 and 18 months of age and infant lung function was assessed at approximately 12 months of age. Neurodevelopment was assessed using Bayley's Scale of Infant Development II at a corrected age of 2 years.

Results: Fifty-eight women were randomised and two were excluded from the analysis owing to termination of pregnancy for lethal anomaly, leaving 56 participants (28 serial AI, 28 Exp) recruited between 2002 and 2009, with annual recruitment rates varying between 2 and 14. Recruitment to the study improved significantly from 2007 with National Institute for Health Research (NIHR) funding. There was no significant difference in perinatal mortality [19/28 vs. 19/28; relative risk (RR) 1.0; 95% confidence interval (CI) 0.70 to 1.43], maternal morbidity or neonatal morbidity. The overall chance of surviving without long-term respiratory or neurodevelopmental disability is 4/56 (7.1%): 4/28 (14.3%) in the AI arm and 0/28 in the expectant arm (0%) (RR 9.0; 95% CI 0.51 to 159.70).

Conclusions: This pilot study found no major differences in maternal, perinatal or pregnancy outcomes. The study was not designed to show a difference between the arms and the number of survivors was too small to draw any conclusions about long-term outcomes. It does signal, however, that a larger, definitive, study to evaluate AI for improvement in healthy survival is indicated. The results suggest that, with appropriate funding, such a study is feasible. A larger, definitive, study with full health economic analysis and patient perspective assessment is required to show whether AI can improve the healthy survivor rate.

Trial registration: Current Controlled Trials ISRCTN 8192589.

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Glossary

Abruption Premature separation of the placenta from the uterine wall.

Amnioinfusion Returning fluid into the amniotic cavity under ultrasound control.

Bradycardia Fetal heart rate below 110 beats per minute.

Oligohydramnios Reduced amniotic fluid around the fetus.

Perinatal mortality Death before, and up to 28 days after, birth.

Pulmonary hypoplasia Small, underdeveloped lungs.

Second trimester Weeks 13–28 of pregnancy.

Very early preterm prelabour rupture of membranes (PPROM) Rupture of amniotic membranes between 16 and 24 weeks of pregnancy.

List of abbreviations

AI	amnioinfusion
AMIPROM	amnioinfusion in preterm premature rupture of membranes pilot study
BSID-II	Bayley's Scale of Infant Development-II
CGA	corrected gestational age
CI	confidence interval
CLRN	comprehensive local research network
CONSORT	Consolidated Standards of Reporting Trials
CPAP	continuous positive airways pressure
CRP	C-reactive protein
DMC	Data Monitoring Committee
Exp	expectant management
FEV_1	forced expired volume in 1 second
FMU	fetal medicine unit
FRC	functional residual capacity
FVC	forced vital capacity
HDU	high-dependency unit
HFOV	high-frequency oscillatory ventilation
HTA	Health Technology Assessment
HVS	high vaginal swab
IPPV	intermittent positive-pressure ventilation
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	intention to treat
ITU	intensive therapy unit
IVH	intraventricular haemorrhage
MDI	Mental Development Index
MREC	Multiresearch Ethics Committee
NEC	necrotising enterocolitis
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PDI	Psychomotor Development Index
PI	principal investigator
PPROM	preterm prelabour rupture of membranes
PVL	periventricular leukomalacia
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	randomised controlled trial
RR	relative risk
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
V_{max}FRC	maximum flow at FRC
WCC	white cell count

Scientific summary

Background

Fetal survival is severely compromised when the amniotic membrane ruptures between 16 and 24 weeks of pregnancy (very early preterm premature rupture of membranes). Reduced amniotic fluid volume is associated with poor lung development, whereas adequate levels lead to better perinatal outcomes. Restoring adequate amniotic fluid by means of ultrasound-guided amnioinfusion (AI) may be of benefit in improving perinatal and long-term outcomes in children of pregnancies with this condition. Current evidence is limited to mostly observational studies; therefore, the National Institute for Health and Care Excellence concluded that more information from randomised controlled trials (RCTs) is required before AI can be considered an effective therapy for very early preterm prelabour rupture of membranes (PPROM). The AI in preterm premature rupture of membranes pilot study (AMIPROM) compares outcomes in pregnancies with rupture of amniotic membranes between 16 and 24 weeks of pregnancy managed with serial weekly transabdominal AI with those managed expectantly.

Objective

The AMIPROM was conducted to assess the feasibility of recruitment, the methods for conduct and the retention through to long-term follow-up of participants with very early rupture of membranes. There was an expectation that the assessment of clinical outcomes would inform the decision about the feasibility of a larger, more definitive, clinical trial.

Methods

Trial design

A prospective RCT stratified for pregnancies in which the amniotic membrane ruptured between 16^{+0} and 19^{+6} weeks' gestation and 20^{+0} and 23^{+6} weeks' gestation was conducted.

Participants

Women with confirmed PPROM between 16^{+0} and 24^{+0} weeks' gestation were considered eligible for the study. Women with multiple pregnancies, resultant fetal abnormalities or obstetric indication for immediate delivery were excluded.

Study settings

Participants were recruited from four UK fetal medicine units – Liverpool Women's NHS Trust, St. Mary's Hospital, Manchester, Birmingham Women's NHS Foundation Trust, Wirral University Hospitals Trust.

Interventions

Participants were randomly allocated to either serial weekly transabdominal AI or expectant management (Exp) until 37 weeks of pregnancy, if the deepest pool of amniotic fluid was < 2 cm.

Outcomes

We collected all maternal, pregnancy and neonatal outcomes using predesigned data sheets. Baseline characteristics such as maternal parity, blood indices, body temperature, length of gestation at rupture of amniotic membranes, and length of gestation at randomisation were recorded. Data on AI, the deepest amniotic fluid pocket (before and after AI, in the AI arm), maternal and neonatal morbidity outcomes such

as antenatal corticosteroid prophylaxis, use of antibiotics, abruption, antepartum haemorrhage, chorioamnionitis, gestational age at delivery, mode of delivery, onset of labour, serious maternal sepsis requiring admission to intensive therapy unit/high-dependency unit and maternal death were obtained. The neonatal outcomes recorded were gestational age at birth, birthweight, Apgar score at 5 minutes, cord blood gases, antepartum death, neonatal death, culture-positive sepsis, days on intermittent positive-pressure ventilation, continuous positive airways pressure and high-frequency oscillatory ventilation (each measured separately), pneumothorax requiring chest drain, discharge on home oxygen, O_2 requirement at day 28, O_2 requirement at week 36, necrotising enterocolitis including those who had surgery or were treated conservatively), treated seizures, treated retinopathy, intraventricular haemorrhage grade (0–3), periventricular leukomalacia, any shunting procedures and fixed orthopaedic deformities. Long-term respiratory morbidity was assessed using validated respiratory questionnaire scores at 6, 12 and 18 months of age and infant lung function test *z*-value at around 12 months of age. Neurodevelopment was assessed using Bayley's Scale of Infant Development II at the corrected age of 2 years.

Randomisation and blinding

The randomisation sequence was generated in blocks of four. Telephone randomisation was used and, owing to the nature of the intervention, neither the participants nor the investigators were blinded to the allocation. Analysis was based on intention to treat (ITT).

Statistical methods

Statistical analysis was performed by the Clinical Trials Research Centre, University of Liverpool. The short-term outcomes statistical analysis plan (SAP) was written prior to completion of recruitment. The Data Monitoring Committee (DMC) agreed to unblinding of the short-term data to the trial team with the caveat that any trial publication should include both short-term and long-term outcome results. This was done once all the short-term outcome data had been analysed using the ITT principle and presented to the DMC. The DMC also requested that a per-protocol analysis be done on the short-term outcome data, defined as mothers who had AI or attended at least one hospital visit (Exp arm). The long-term outcomes SAP incorporated details of the per-protocol analysis the DMC had requested.

Sensitivity analyses were performed to explore the effects of missing data on the long-term outcomes. These considered the neonatal deaths and imputed on a worst-case scenario basis. Where other imputations were considered, these are described alongside the analyses.

Results

Of the 77 eligible women, 58 were randomised to the study (11 declined study, seven miscarried and one decided too late to be included). There was a postrandomisation exclusion in each arm owing to termination of pregnancy for fetal abnormality, leaving 28 women randomised to serial AI and 28 to Exp. Participants were recruited between 2002 and 2009, with annual recruitment rates varying between 2 and 14. Recruitment to the study improved significantly after National Institute for Health Research (NIHR) funding was received in 2007. The median number of AI required was three.

There was no apparent difference in baseline characteristics, maternal morbidity outcomes or pregnancy outcomes. There was no significant difference in neonatal and fetal death combined [19/28 vs. 19/28; relative risk (RR) 1.0; 95% confidence interval (CI) 0.70 to 1.43]. There was no difference in serious neonatal morbidity. Nine children in the AI arm and eight children in the Exp arm survived to be assessed for long-term outcomes. Five children scored < –2.00 in one or more lung function tests (three children from the AI arm and two from the Exp arm) and three children had respiratory questionnaire scores suggestive of asthma.

Three children in each arm had Bayley's scores < 70 in either mental or Psychomotor Development Index (PDI). Of these children, one in each arm also had abnormal lung function tests. The overall chance of surviving without long-term respiratory or neurodevelopmental disability is 7.1%; 4/28 (14%) in the AI arm and 0/28 in the Exp arm (0%) (RR 9.0; 95% CI 0.51 to 159.70).

Conclusions

This study is, to our knowledge, the first to collect data on long-term outcomes in randomised children born after very early PPROM in a randomised trial of serial antenatal AI. The study was not designed to show a difference between the arms and the number of survivors is too small to draw any conclusions about long-term outcomes. It does, however, signal that a larger definitive study to evaluate whether AI has a cost-effective and acceptable role in improving healthy survival in these pregnancies is indicated. The pilot findings do not suggest that clinicians should alter the current practice of expectantly managing rupture of amniotic membranes between 16^{+0} and 24^{+0} weeks of pregnancy.

The research implications centre around determining whether there is a clinically important difference in healthy survival in amnioinfused babies compared with those managed expectantly. We have demonstrated that an adequately funded multicentre randomised trial, with long-term infant follow-up as the primary outcome, is feasible. A larger definitive study with full health economic analysis and patient perspective assessment is required to show whether AI can improve the healthy survivor rate.

Trial registration

The trial is registered as ISRCTN 8192589.

Funding

This project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 18, No. 21. See the NIHR Journals Library website for further project information.

Chapter 1 Background and rationale

What are the risks of very early preterm prelabour rupture of membranes?

Preterm prelabour rupture of membranes (PPROM) is one of the major causes of perinatal mortality and morbidity because it causes preterm delivery in a third of cases in which it occurs.[1,2] Fetal survival is even more compromised when the amniotic membrane ruptures early in the second trimester.

There is a very high risk of delivery after very early PPROM. Moretti and Sibai[3] reported a mean rupture to delivery interval of 13 days in pregnancies with PPROM between 16 and 26 weeks' gestation, suggesting a high risk of delivery of previable fetuses and of infants at the extreme of viability. Forty-eight per cent of the pregnancies in their study delivered within 3 days of amniotic membrane rupture. The overall rate of preterm birth was 54%. Stillbirth after an infection, abruption or cord prolapse, prematurity and pulmonary hypoplasia are the major causes of perinatal mortality and morbidity in this group of babies.

The incidence of pulmonary hypoplasia in very early PPROM is reported to be as high as 62%.[4] Studies have suggested that oligohydramnios is the most important predictor of perinatal mortality in very early PPROM and that adequate residual amniotic fluid plays a critical role in determining the prevalence of pulmonary hypoplasia.[4–7] Oligohydramnios is also said to be associated with a higher risk of chorioamnionitis and neonatal infection.[5] Adequate amniotic fluid volumes, on the other hand, are said to be associated with better outcomes in pregnancies affected by very early PPROM. Locatelli *et al.*[8] found that pregnancies with a median residual amniotic fluid pocket persistently less than 2 cm were at highest risk of poor perinatal and long-term neurological outcome while pregnancies with a pocket greater than 2 cm had significantly better perinatal outcome (73–92% survival) and lower pulmonary hypoplasia rates.[8,9]

What management options are available?

The management of cases with very early PPROM has changed over the years. Traditionally, termination of pregnancy was offered for these women because of the presumed risk of maternal sepsis and very poor fetal outcome. Expectant management (Exp) has, however, been shown to be relatively safe for mothers and results in the survival of a small proportion of infants.

Serial transabdominal amnioinfusion (AI) aiming to restore the amniotic fluid volume in pregnancies complicated by very early PPROM is an invasive procedure which has the potential to improve the perinatal outcome.[6] As discussed above, pregnancies with a median residual amniotic fluid pocket persistently less than 2 cm are at highest risk of poor perinatal and long-term neurological sequela. Those pregnancies that retain a pocket greater than 2 cm, either after AI or spontaneously, have significantly better perinatal outcome (73–92%) and lower pulmonary hypoplasia rates.[8] It has also been shown that women with persistent oligohydramnios after AI have a significantly shorter PPROM to delivery interval, lower neonatal survival (20%), higher rates of pulmonary hypoplasia (62%) and higher abnormal neurological outcomes (60%) than women in whom AI is successful ($p < 0.01$ for all cases).[7] AI is not, however, routinely used in the UK as it is an invasive procedure and its efficacy has not been evaluated fully in a well-conducted randomised controlled trial (RCT).

What is the evidence for management options in very early preterm prelabour rupture of membranes?

Most of the evidence on the management of very early PPROM is based on observational case–control or comparative studies.[3–11] The major risk of expectant is maternal infection leading to sepsis. High rates of postpartum morbidity[10] and chorioamnionitis[11] have been reported: 32% and 28%, respectively. The Royal College of Obstetricians and Gynaecologists (RCOG) guideline on PPROM[12] does not give any specific guidance on the management of these pregnancies. It also does not support the practice of serial AI owing to lack of evidence.

To date, there have, to our knowledge, been no RCTs that have assessed the relative benefit of serial AI over expectant in pregnancies with PPROM between 16 and 26 weeks of pregnancy. Evidence from non-randomised cohorts is likely to be biased owing to selective reporting, and the comparisons are often based on historic cohorts and incomplete outcome data for a sample of pregnancies with PPROM not treated by AI. Long-term outcomes for surviving infants are rarely reported. Moreover, AI is an invasive intervention and, although, anecdotally, these studies suggest that it carries minimal risk to the mother and fetus,[7] the evidence of harm is rarely systematically collected and reported.

Rationale for the trial

There is growing evidence to suggest that AI may have a role to play in improving the perinatal outcome in pregnancies with PPROM. A Cochrane review on AI for PPROM states: 'These results are encouraging but are limited by the sparse data and unclear methodological robustness, therefore further evidence is required before AI for PPROM can be recommended for routine clinical practice'.[13] The National Institute for Health and Care Excellence (NICE) concluded, after review of existing literature, that more information from RCTs is required before AI can be considered routine therapy for very early PPROM.

Preterm birth represents a considerable burden to both patients and the NHS. The risk of neonatal death is high and surviving preterm babies are at risk of developing respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage (IVH), cerebral palsy, blindness and deafness, with huge impact on their families and society. The economic consequences of preterm birth are immense. A multilevel modelling of hospital service utilisation and cost profile of preterm birth using data from 117,212 children showed that the cumulative cost of hospital inpatient admissions averaged £17,819.94 for children born at less than 28 weeks' gestation and £17,751.00 for children born at 28–31 weeks' gestation. Evidence from observational studies suggests that most babies with very early PPROM are delivered before 31 weeks of pregnancy. If there was any chance that AI could improve outcomes for these babies, a well-designed trial would be required to determine that effect.

On the basis of this, we began a single-centre, investigator-led randomised trial in 2001. The trial was sponsored by the Liverpool Women's NHS Foundation Trust and had North West Multiresearch Ethics Committee (MREC) approval. In response to the change in regulations for research trials in 2006, we applied to an open call for trial proposals by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme, which agreed to fund the long-term outcome phase of AI in preterm premature rupture of membranes (AMIPROM) pilot study – a pilot RCT on serial transabdominal AI versus expectant for very early PPROM – provided the trial was analysed as a pilot study and all outcomes were reported.

Specific objectives of the pilot study

- To assess the feasibility of recruitment, the methods for conduct of the study and the retention through to long-term follow-up of participants in the study.
- To perform an outcome assessment and to collect data to inform a larger, more definitive clinical trial if indicated.

Chapter 2 Methods

Trial design

The AMIPROM was a multicentre, two-armed, non-blinded pilot RCT with equal randomisation. Randomisation was stratified for pregnancies with PPROM prior to, and after, 20^{+0} weeks' gestation. Participants were randomised in a 1 : 1 ratio to receive either:

- expectant with weekly ultrasound assessments of the pregnancy, or
- weekly AI if the deepest pool of amniotic fluid measured < 2 cm.

Approvals obtained

North West MREC approved the study in July 2002. Minor amendments to the protocol were made in October 2006. Substantial amendments were made in August 2007 and December 2008. The final protocol is in *Appendix 1*.

Clinical trial authorisations from the Medicines and Healthcare products Regulatory Agency were sought but not required as saline/Hartmann's solution used to perform AI is not a medicinal product. The trial was registered with International Standard RCT number (ISCTRN; ISRCTN no. 8192589).

Trial sites

There were four recruiting sites:

- Liverpool Women's NHS Foundation Trust (~8000 deliveries per annum)
- St. Mary's Hospital, Manchester (~5500 deliveries per annum)
- Birmingham Women's NHS Foundation Trust (~7000 deliveries per annum)
- Wirral University Teaching Hospital (~3700 deliveries per annum).

Participants were recruited from Birmingham Women's NHS Foundation Trust in 2008 following HTA programme funding approval.

Participant eligibility

The participants were women with PPROM between 16^{+0} and 24^{+0} weeks' gestation.

Inclusion criteria

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

Exclusion criteria

- There was an obstetric indication for immediate delivery (i.e. fetal bradycardia, abruption, cord prolapse, advanced labour > 5 cm).
- Multiple pregnancy.
- Fetal abnormality.

Participants were also not recruited if they were unable to give informed consent.

Recruitment to the trial

The principal investigators (PIs) in the pilot received 'good clinical practice' training as well as training in all aspects of the trial, including participant recruitment, eligibility criteria, trial protocol, adverse event reporting procedures and trial documentation. Each study site received a trial pack prior to commencement of recruitment.

Participants were identified by health-care professionals at the study site or one of the hospitals that referred patients to the study site. An appointment for further assessment and confirmation of PPROM at the local fetal medicine unit (FMU) was arranged. Participants were given an information leaflet by the health-care professional who first saw them. Following discussion of the trial at the FMU and confirmation of very early PPROM, consent was obtained.

Women were randomised only if the pregnancy was still ongoing 10 days after rupture because of the high risk of miscarriage in the first week after PPROM. This protocol change was implemented in 2002 following discussion at an international meeting of fetal medicine specialists.[14]

Participants were given a minimum of 24 hours, but more commonly longer, to read the information sheet and consider participation. Consent was obtained only after further discussion of the study with the fetal medicine teams in the study sites.

Randomisation

A computer-generated random sequence using a 1 : 1 ratio was used. Randomisation was stratified for pregnancies in which the amniotic membrane ruptured between 16^{+0} and 19^{+6} weeks' gestation and those in which rupture occurred between 20^{+0} and 23^{+6} weeks' gestation to minimise the risk of random imbalance in gestational age distribution between randomised groups. The randomisation sequence was generated in blocks of four. The sequence was generated by the Division of Statistics and Operational Research, University of Liverpool. Owing to the nature of the intervention (multiple needle insertions during pregnancy), neither clinicians nor participants were blinded to the treatment allocation. Assessors of long-term outcomes were not blinded to the intervention because, although it is a source of bias that the participants were aware of which arm they were allocated to, it would simply not have been possible to prevent them discussing this with the long-term outcome assessors post delivery.

Participants who consented to take part in the study were assigned their trial arm by ringing the telephone randomisation service administered by the Liverpool Women's Hospital Research and Development Office. None of the investigators had access to the randomisation sequence or knew the randomised treatment to be allocated next.

The flow of participants through the trial is presented in a Consolidated Standards of Reporting Trials (CONSORT) diagram (*Figure 1*).

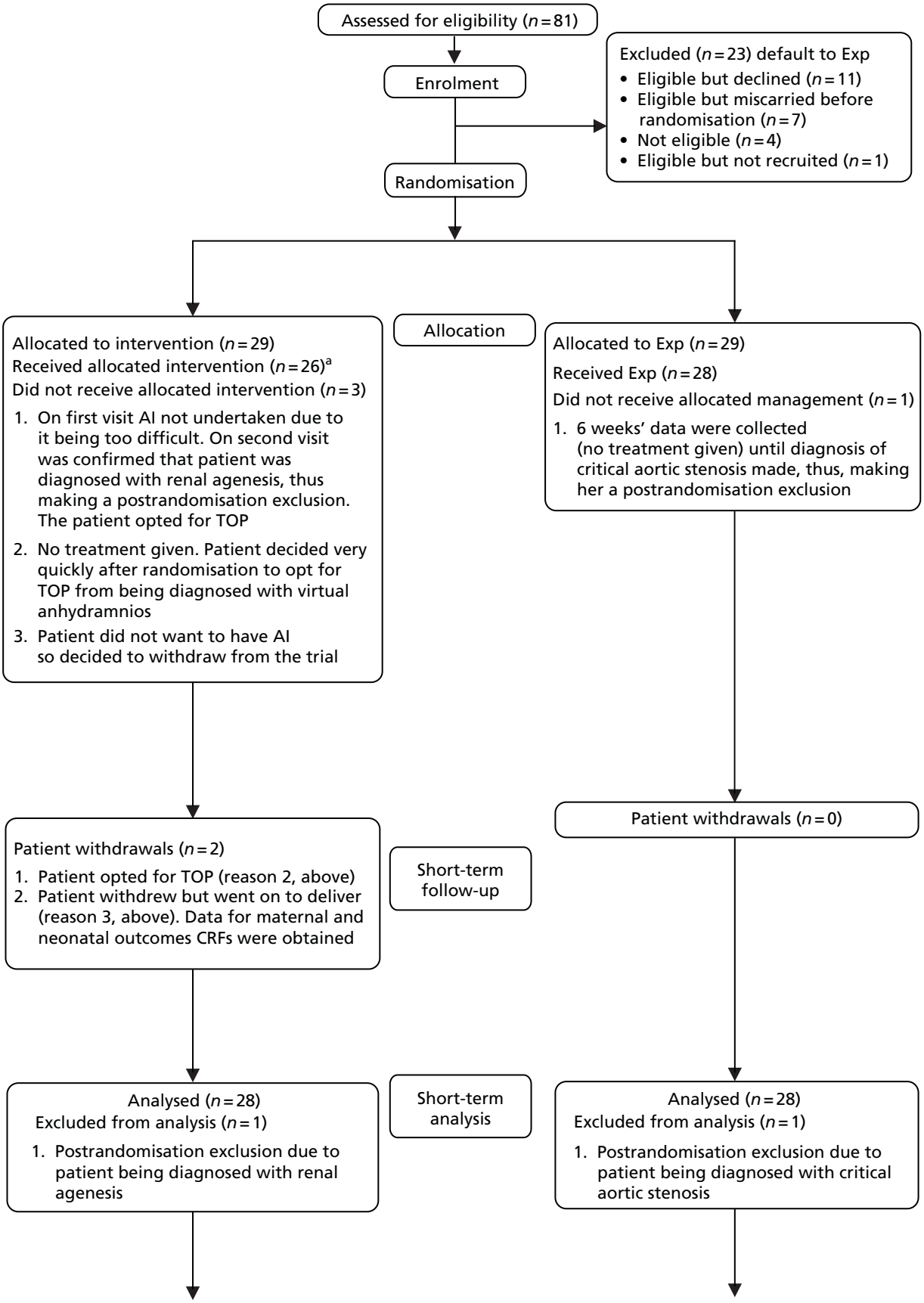
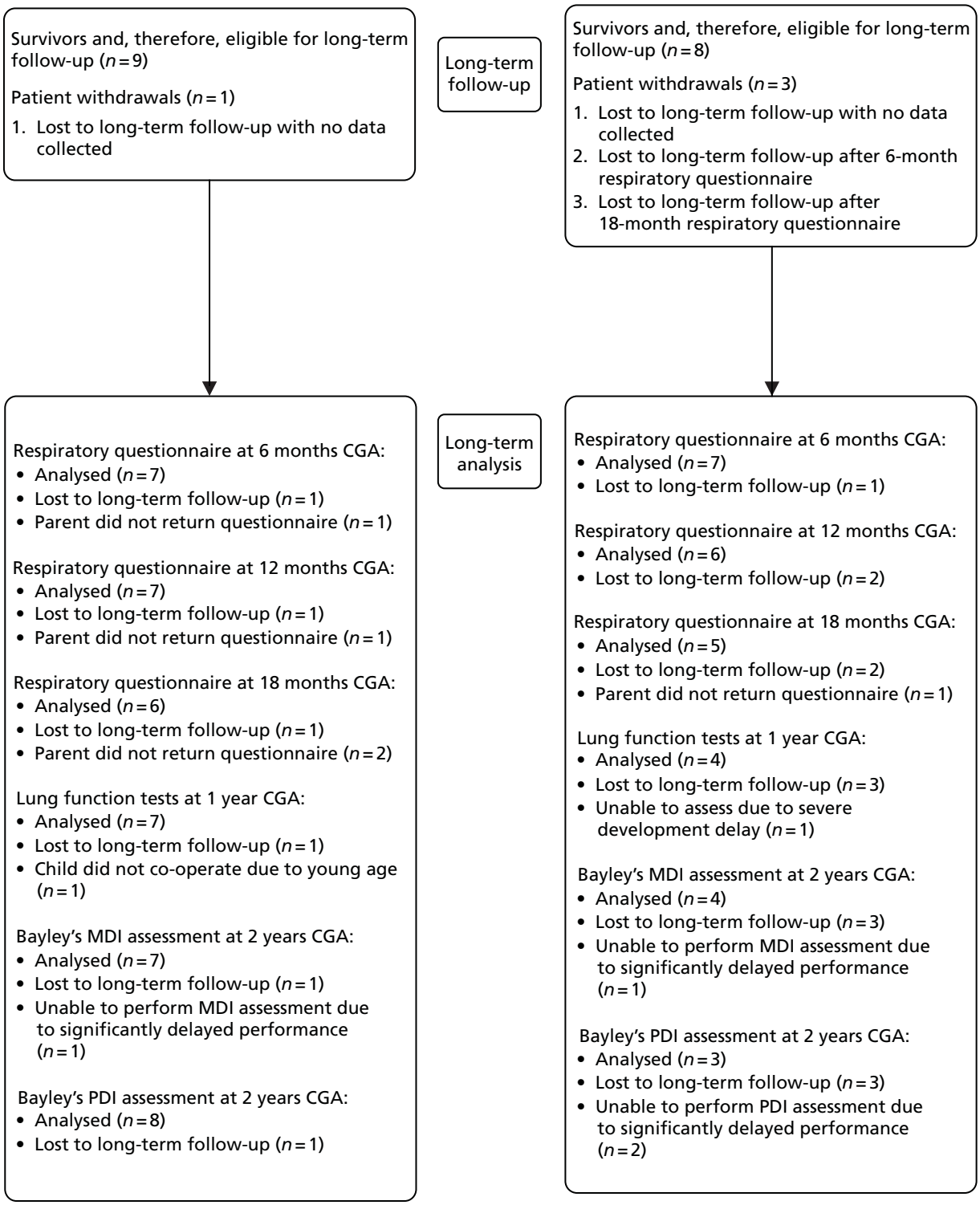


FIGURE 1 The CONSORT flow diagram. a, Four of the 26 women attended the study visits but had maintained a deepest pool of amniotic fluid >2 cm throughout the duration of their participation so did not have any amnioinfusion fluid instilled at any time because they did not require it. They would have received amnioinfusion at a study visit had they required it. CGA, corrected gestational age; CRF, case report form; MDI, Mental Development Index; PDI, Psychomotor Development Index; TOP, termination of pregnancy. (*continued*)



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Eligible women who declined participation

The FMUs were asked to keep a log of patients who were eligible but opted not to participate in the trial, to generate an idea of potentially eligible participants who declined the study or miscarried. This was collected on A4 sheets of plain paper and kept in the trial folder in the FMUs (see *Chapter 3*).

Sample size

An initial presumptive sample size of 62 participants was calculated based on an audit performed at the Liverpool Women's NHS Foundation Trust. The audit revealed a composite adverse outcome of 75% in pregnancies with very early PPROM, in which there was a mortality rate of 65% and approximately 25% respiratory morbidity in the survivors (overall composite outcome approximately 75%). A reduction in composite outcome by 50% was chosen as the target difference 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. To reduce the composite outcome by 50%, at a 5% significance level with 80% power, 31 participants were required in each group. This included an allowance of 10% loss to follow-up. However, review by referees for the HTA programme in 2007 required that the study be treated as a pilot study. The NIHR suggested that smaller differences in substantive outcomes (rather than composite) are of interest and that a much larger 'definitive' study should be considered to determine effectiveness (or lack of it) with much greater precision. The assumptions used for initial sample size calculations are therefore only indicative and were treated as such by the Data Monitoring Committee (DMC). The final sample size in this study was the number of participants recruited at the end of the period defined by the timelines for the grant, i.e. the grant was funded for recruitment until April 2009.

Interventions

Both trial arms

Rupture of amniotic membranes was confirmed by presence of amniotic fluid in the posterior fornix on speculum examination and/or severe oligohydramnios on ultrasound examination. A high vaginal swab (HVS) was taken on admission and oral erythromycin commenced for 10 days.

Once rupture of the amniotic membranes had been confirmed, women were referred to the first available FMU assessment to exclude fetal abnormality, confirm rupture of amniotic membranes using ultrasonography and discuss the study. Women in both groups were assessed weekly by ultrasound and the following measurements recorded: deepest pool of amniotic fluid, thoracic circumference, lung length and abdominal circumference. Maternal haemoglobin level, white cell count (WCC), platelet count, HVS, C-reactive protein (CRP) and temperature were also recorded at each visit if they had been measured.

Antenatal corticosteroids were administered at 26^{+0} weeks' gestation as a matter of routine prophylaxis. Earlier antenatal corticosteroids (between 23^{+0} and 25^{+6} weeks' gestation) were given at the clinician's discretion. Hospital admission for rest was recommended between 26^{+0} and 30^{+0} weeks' gestation, but not mandatory.

Induction of labour at 37 completed weeks' gestation was advised unless there was an obstetric indication for earlier delivery, or delivery by caesarean section (elective or emergency).

Expectant management arm

Women were seen weekly and ultrasonography used to obtain the following measurements: deepest pool of amniotic fluid, thoracic circumference, lung length and abdominal circumference. Maternal haemoglobin level, WCC, platelet count, HVS, CRP and temperature were also recorded at each visit if

they had been measured. Corticosteroid administration and admission was in accordance with the process described for both arms.

Amnioinfusion arm

Women who were randomised to the intervention arm received AI received AI of saline/Hartmann's solution only if the deepest pool of amniotic fluid at the weekly ultrasound assessment was < 2 cm. The protocol did not specify a maximum pool depth of < 2 cm for inclusion to the study as we were keen to capture all women with PPROM at these gestations in case they went on to develop a pool of < 2 cm. Between 2002 and 2006, a small number of randomised women in the AI arm never developed a deepest pool of < 2 cm and, therefore, never required AI. Recruiters were advised that, from then on, they should randomise only at the visit in which the deepest pool measured < 2 cm between 16^{+0} and 24^{+0} weeks' gestation. This was not considered a formal protocol amendment but was recommended.

Amnioinfusion were performed only by fetal medicine specialists who had expertise in invasive procedures. The protocol for the method of AI is given in *Appendix 2*. All AI were performed under ultrasound guidance. All study sites were given a copy of the protocol for AI to ensure consistency of the procedure.

The full calculated volume of Hartmann's solution or normal saline for the pregnancy (10 ml per week of gestation) was always infused. This ensured an adequate amount of fluid replacement to account for immediate leakage through the rupture. AI was ceased if the specialist had concerns about continuing the procedure. Possible reasons for this would have been uncertainty about being in the right space or if uterine contractions began. Antibiotics were not given specifically for the AI procedure. All participants were treated with oral erythromycin for 10 days after diagnosis of PPROM. Tocolysis was not required for AI and the procedures were performed as outpatient procedures. Participants were admitted following the procedure if it was felt necessary to do so by the specialist who performed the procedure. The post AI deepest pool of amniotic fluid was measured after the full calculated volume for gestation was amnioinfused. Participants were seen weekly and the AI repeated if the deepest pool of amniotic fluid remained at < 2 cm.

Participant follow-up

Figure 2 shows a summary of participant follow-up for the AMIPROM trial. Most participants were followed up in the FMUs, with a small proportion (four participants in Exp arm) followed up in their local units. This was mainly at the choice of the participant. Participants were sent paper respiratory questionnaires along with prepaid return envelopes by the trial co-ordinating centre at Liverpool Women's NHS Foundation Trust. No incentives were given to increase the response rates to respiratory questionnaires. The Bayley's assessments were performed in the homes of surviving children to increase response rate. The infant lung function tests were performed either at Leicester University Hospital or at Liverpool Women's NHS Foundation Trust and participants were reimbursed for travel expenses to and from the Hospitals for the childhood follow-up part of the trial alone. Travel expenses were not reimbursed for weekly assessments at hospital or FMU as these were considered part of normal clinical care.

Measurement of outcomes: short-term outcomes

Data were collected on five data sheets (see *Appendix 1*).

First visit post randomisation

Data sheet 1 was filled out by the specialist attending the participant on the day of randomisation. This was called the 'first visit' even though the participant may have attended the FMU previously for confirmation of the diagnosis and discussion about the study. Maternal parity, initial HVS, WCC, CRP and body temperature were recorded on data sheet 1, as well as whether the mother had a tender, irritable uterus or foul-smelling discharge. Other information recorded was the gestation at PPROM in weeks, the

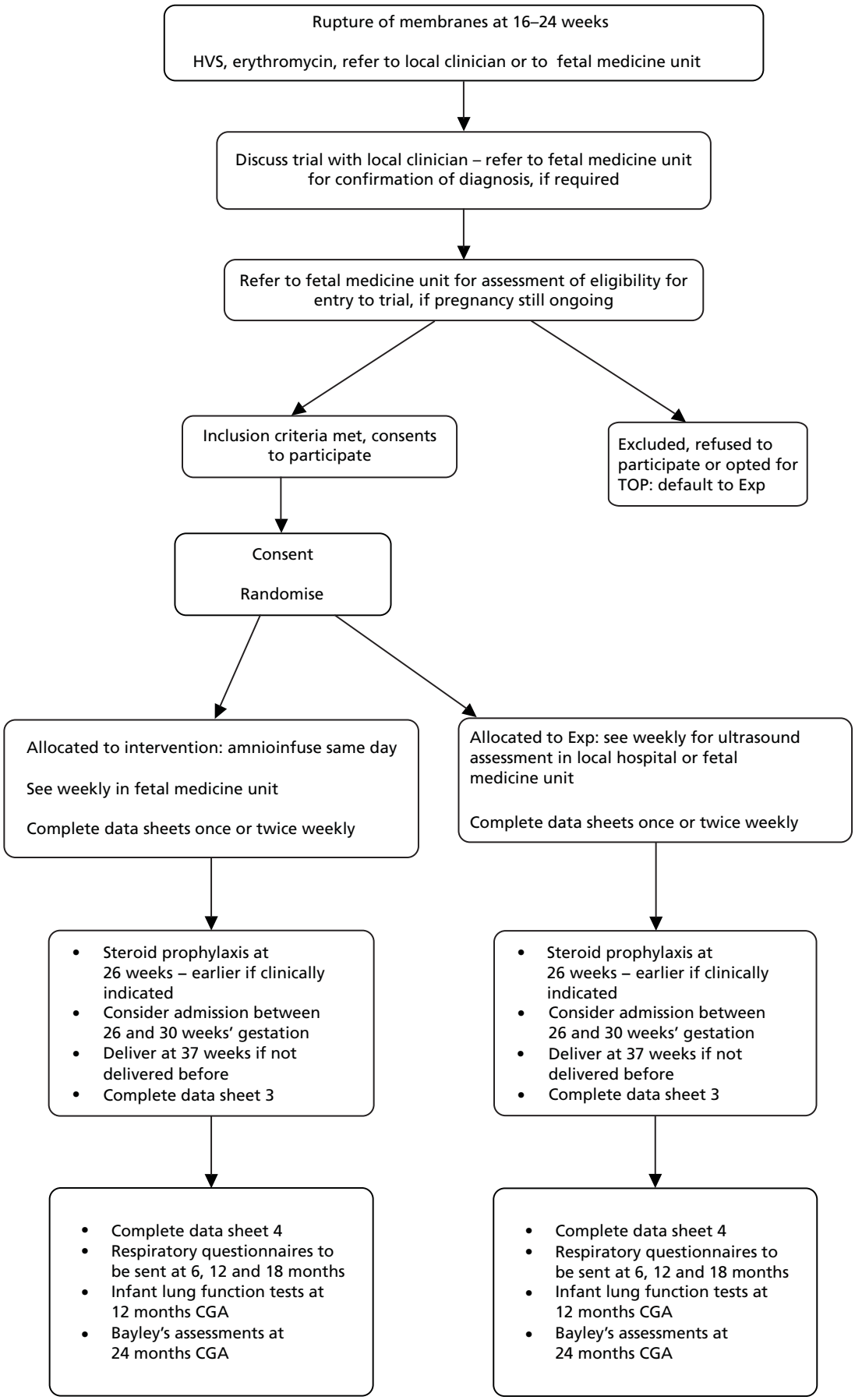

FIGURE 2 Participant follow-up. TOP, termination of pregnancy.

gestation at first AI in weeks, the deepest amniotic fluid pocket (before and after AI in the intervention arm), the thoracic circumference, lung length and abdominal circumference of the baby as measured using ultrasonography.

Subsequent visits

Measurements taken using ultrasonography of the baby's thoracic circumference, the lung length, the abdominal circumference and the deepest amniotic fluid pocket (before and after AI in the AI arm) for subsequent visits were recorded on data sheet 2 by FMU staff.

Maternal outcomes

Maternal outcomes, including the result of maternal investigations, were recorded on data sheet 3. WCC and CRP measurements were performed weekly and HVS was performed at the discretion of the clinician attending the participant. HVS results were recorded whenever they were available and data sheet 3 was completed when the participant had delivered. Any missing data were reconciled by the chief investigator and trial administrator by contact with the PIs and examination of the hospital case notes.

The maternal and pregnancy outcomes recorded were antenatal corticosteroid prophylaxis, if the participant was given antibiotics, placental abruption, antepartum haemorrhage, chorioamnionitis, gestational age at delivery, mode of delivery, onset of labour, serious maternal sepsis requiring intensive therapy unit (ITU)/high-dependency unit (HDU) admission and maternal death.

Neonatal outcomes

Neonatal outcomes were recorded on data sheet 4. The neonatal outcomes recorded were gestational age at birth, birthweight, Apgar score at 5 minutes, cord blood gases, antepartum death, neonatal death, culture-positive sepsis, days on intermittent positive-pressure ventilation (IPPV), continuous positive airways pressure (CPAP) and high-frequency oscillatory ventilation (HFOV) (each analysed separately), pneumothorax requiring chest drain, discharge on home oxygen, O_2 requirement at day 28, O_2 requirement at week 36, necrotising enterocolitis (NEC) (including those who had surgery or were treated conservatively), treated seizures, treated retinopathy, IVH grade (0–3), periventricular leukomalacia (PVL), any shunting procedures and any fixed orthopaedic deformities.

The data sheet was completed when the baby was discharged home or after death. Any missing data were reconciled by the chief investigator and trial administrator by contact with the PIs and examination of the hospital case notes.

The data pack was returned to the trial co-ordination centre after the baby was discharged home or after death.

Measurement of outcomes: long-term outcomes

Respiratory questionnaires

Participants with surviving babies were sent a prepaid postal validated respiratory questionnaire at 6, 12 and 18 months after the birth of their baby.[15] These were sent out by the trial coordination centre at Liverpool Women's NHS Foundation Trust and returned directly to the co-ordinating centre.

The respiratory questionnaire was designed to examine the frequency of mild respiratory symptoms such as wheezing in infants and preschool children. An abnormal score is described as one which falls within the confidence interval (CI) of children with asthma as defined by Powell *et al*.[15] We defined children with long-term mild respiratory symptoms as those at the 18-month questionnaire stage whose scores in any domain fell outside the 95% CI for asthma (*Table 1*).

TABLE 1 Respiratory questionnaire confidence intervals for children with asthma

Score	95% CI for children with a diagnosis of asthma
Daytime symptoms score	21.7 to 43.5
Night-time symptoms score	6.4 to 10.8
Impact on family score	7.0 to 11.0
Impact on child score	5.5 to 9.2

Lung function tests

The protocol specified that surviving children had infant lung function tests performed when they were approaching 12 months' gestational age. Lung function tests can be performed under sedation at this age. From the age of about 3 or 4 years, children can begin to do perform the blowing tests that older children can. Between these ages it is more difficult to perform these tests, for compliance reasons and, where possible, surviving children were invited to have the infant tests performed at Leicester Royal Infirmary. Where this was not possible, the simple blowing tests were performed at Liverpool Women's NHS Foundation Trust.

The tests of lung function were chosen to detect small lung size. The most direct way of doing this is by whole-body plethysmography, which enables us to determine functional residual capacity (FRC). This test requires that the subject is enclosed within a Perspex chamber (that for older children or adults resembles a telephone kiosk) and breathes through an apparatus that measures the amount of air being breathed in or out. As the chest moves in and out, it causes small (but measurable) pressure changes in the Perspex chamber. Then, for a very short period of time, a shutter is transiently closed in the apparatus, so that the subject makes breathing efforts against this obstruction. This does not disturb the subject and, in the case of infant testing, does not last long enough to cause the sleeping infant to rouse. By measuring the pressure generated at the mouth when the shutter is closed, and relating this to the pressure changes in the chamber, it is possible to work out the size of the lungs. An alternative and indirect index of lung size is forced vital capacity (FVC), which is simply a measure of how much air can be breathed out between full inspiration to complete exhalation. The other measurements [forced expired volume in 1 second (FEV_1) and maximum flow at FRC ($V_{max}FRC$)] relate to airway function and give information relating to the dimensions and patency of the airways. Each measure of lung function was repeated at least three times to ensure reproducibility. For each test, predicted scores and *z*-values were calculated. A *z*-value < -2.00 is considered abnormal in any of the lung functions tested.

Neurological assessment

Developmental delay at 2 years corrected gestational age was assessed using the Bayley's Scales of Infant Development-II (BSID-II). BSID-II is a standard series of measurements used primarily to assess the motor and cognitive development of infants and toddlers aged 0–3 years. This measure consists of a series of developmental play tasks. It takes between 45 and 60 minutes to administer, and raw scores of successfully completed items are converted to scale scores and to composite scores between 50 and 150 (mean score 100). These scores are used to determine the child's performance compared with norms taken from typically developing children of their age (in months), e.g. going up the stairs unaided at 24 months.

The two scores reported in this trial are the Mental Development Index (MDI) and the Psychomotor Developmental Index (PDI). Their classifications are as follows:

- A score of 50–69 suggests significantly delayed performance.
- A score of 70–84 suggests mildly delayed performance.

- A score of 85–114 is within normal limits.
- A score of 115–150 suggests accelerated performance.

We defined major neurodevelopmental delay in any child as an MDI < 70 or a PDI < 70 or both MDI/PDI < 70. Mildly delayed performance was defined as a score of between 70 and 84 in any domain.[16]

Neurodevelopmental assessments of the surviving children were performed in their own homes by a trained health professional. The protocol specified that the tests were to be performed at 24 months of age, corrected for prematurity. No monetary or other incentives were used to increase participation in the long-term outcome phase of the pilot. Participants were reimbursed their expenses for travelling to either Leicester or Liverpool for the infant lung function tests.

Trial completion

Recruitment and the final sample size was time limited as the study was funded until April 2009. The last woman was recruited to the study in April 2009. The last baby was assessed for long-term outcomes in July 2011.

Statistical analysis

Statistical analysis was performed by the Clinical Trials Research Centre, University of Liverpool. This pilot trial consists of both short-term outcomes of neonatal morbidity/mortality for the baby and maternal morbidities for the mother at birth and also various long-term developmental outcomes for the children assessed at 2 and 3 years corrected gestational age (CGA). The approach was first to write the short-term outcomes statistical analysis plan (SAP) (see *Appendix 3*) prior to completion of recruitment, then to perform the analyses once all the short-term outcome data had been received and then to present the results to the DMC. All outcomes were analysed using the intention-to-treat (ITT) principle. In the introduction of short-term outcomes SAP it stated that the DMC would give their recommendations to the Trial Steering Committee and they would decide whether to allow publication of the short-term outcome results. The short-term outcome results were presented to the DMC on 15 November 2011. The DMC agreed to unblinding of the short-term data to the trial team at this meeting so they could begin to write up the publication, but the publication should include the short-term and long-term outcome results. The DMC also requested that a per-protocol analysis be carried out on the short-term outcome data defined as mothers that had at least one AI or attended at least one hospital visit (Exp arm). The long-term outcomes SAP (see *Appendix 4*) was then written incorporating details of the per-protocol analysis that the DMC had requested. The statistical team made the decision not to do a per-protocol analysis for the long-term outcomes because so few participants were followed up as a result of all of the antenatal and neonatal deaths. Again, all outcomes were analysed using the ITT principle.

The statistical methods used are shown in *Appendices 3* and *4*. All of the statistical analyses for the trial results were carried out using SAS v.9.2 (SAS Institute Inc., Cary, NC, USA).

Missing data

Sensitivity analyses were performed to explore the effects of missing data on the long-term outcomes. These mostly considered the neonatal deaths and imputed on a worst-case scenario basis. Where other imputations were considered, these are described alongside the analyses.

Adverse events

All neonatal deaths were reported as adverse events on the Liverpool Women's NHS Foundation Trust serious adverse event (SAE) reporting form (see *Appendix 5*). Suspected unexpected serious adverse reactions and all SAEs were reported to the PI or the Research and Development Department of the Liverpool Women's NHS Foundation Trust.

Economic analysis

As this is a pilot study, no economic or cost-effectiveness analysis has been performed. It is envisaged that this will be performed if a larger, definitive trial is funded.

Chapter 3 Results (short-term outcomes)

Trial recruitment

Recruitment began in September 2002 and ceased in April 2009. Centres were chosen for their ability to perform AI if required. There were initially five study sites proposed – Liverpool Women's NHS Foundation Trust (chief investigator site and trial sponsor), St. Mary's Hospital, Wirral University Teaching Hospital, Warrington Hospital and Queen Mother's Glasgow. Owing to local research governance and funding issues, Queen Mother's Glasgow was unable to formalise local ethics and recruit; therefore, it ceased to be a study site in 2006. Warrington Hospital preferred to refer to the tertiary referral unit rather than run the study locally and ceased to be a study site by 2006. Participants were recruited from Birmingham Women's NHS Foundation Trust in 2008 following HTA programme funding approval.

Two sites were recruiting participants and submitting data by 2005 (Liverpool Women's NHS Foundation Trust and St. Mary's Hospital) and the other two were recruiting participants and submitting data by 2008 (Wirral University Teaching Hospital and Birmingham Women's NHS Foundation Trust). The number of patients recruited per annum is shown in *Table 2*. The recruitment rate by each site is shown in *Figure 3*.

In total, 81 women were screened as potential participants and 77 were eligible. The reasons why eligible participants did not enter the study are shown in *Table 3* and *Figure 1*. Eleven women declined to participate in the study, seven miscarried in the 10 days after PPROM while considering the study and one decided too late (after 24 weeks) that she wanted to participate. This woman was not recruited, as she no longer met the criteria for inclusion to the study, i.e. between 16^{+0} and 24^{+0} weeks' gestation.

Baseline participant characteristics

Twenty-nine women were randomised to each group but one from each group was excluded post randomisation due to termination for fetal abnormality (renal agenesis in the AI arm and critical aortic stenosis in the Exp arm), leaving 28 in each arm for ITT analysis (see *Figure 1*).

The baseline characteristics are summarised by treatment arm in *Table 4*.

Both arms are well balanced for possible confounders. There was no apparent difference in the mean WCC, temperature, weeks gestation at rupture of the amniotic membrane, weeks gestation at randomisation or maternal age at randomisation between arms. There was no apparent difference in the median CRP between the arms.

TABLE 2 The number of patients randomised per annum

Number randomised per annum by treatment arm	2002	2003	2004	2005	2006	2007	2008	2009
Exp arm	0	1	4	4	5	9	4	2
AI arm	1	2	4	5	4	5	8	0
Overall	1	3	8	9	9	14	12	2

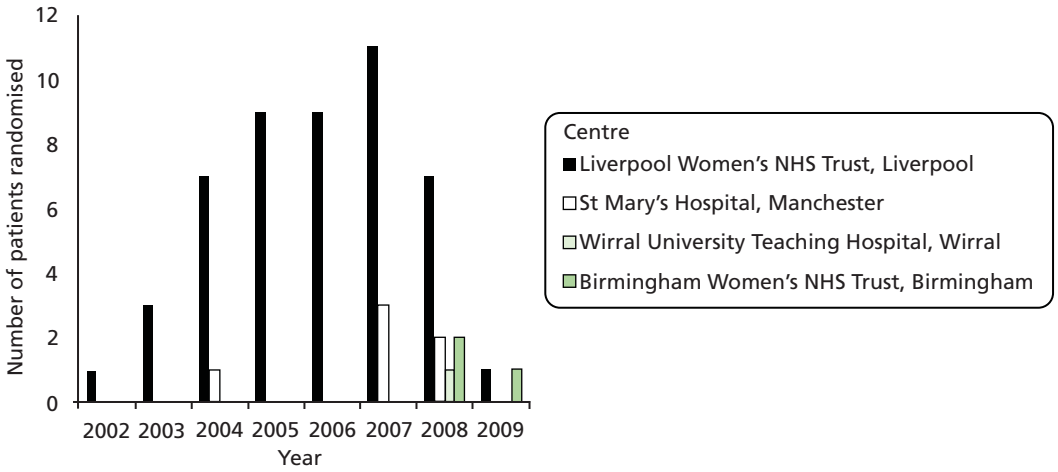

FIGURE 3 The number of patients randomised per centre, per annum.

TABLE 3 Non-participant log

Reason for non-participation	Number of participants	Outcome of pregnancy
Eligible but declined	11	Termination of pregnancy (4)
		Miscarriage (2)
		Live birth with chronic lung disease (1)
		Neonatal death (3)
		No outcome data (1)
Eligible but miscarried before randomisation	7	Miscarriage (7)
Eligible but had exceeded 24 weeks' gestation by the time decided to participate; too late to be randomised	1	Live birth (1)

TABLE 4 Baseline characteristics of participants at randomisation

Baseline characteristics	AI (participants randomised *n* = 28)	Exp (participants randomised *n* = 28)	Total (participants randomised *n* = 56)
Parity, *n*	(*n* = 26)[a]	(*n* = 28)	(*n* = 54)
0	16	11	27
1	4	11	15
2	2	3	5
3	3	2	5
4	1	1	2
HVS, *n* (%)	(*n* = 25)[a] [25 separate types][b]	(*n* = 24)[a] [27 separate types][b]	(*n* = 49)[a] [52 separate types][b]
Bacterial vaginosis	1 (4.0)	2 (7.4)	3 (5.8)
Coliform	0 (0.0)	1 (3.7)	1 (1.9)
Enterococcus	0 (0.0)	1 (3.7)	1 (1.9)
B *Streptococcus*	0 (0.0)	1 (3.7)	1 (1.9)
Mixed anaerobes	1 (4.0)	1 (3.7)	2 (3.8)
None	1 (4.0)	1 (3.7)	2 (3.8)
Normal flora	20 (80.0)	16 (59.3)	36 (69.1)
Staphylococcus aureus	1 (4.0)	0 (0.0)	1 (1.9)
Streptococcus	0 (0.0)	2 (7.4)	2 (3.8)
Yeast	1 (4.0)	2 (7.4)	3 (5.8)
WCC (10^9/l)	(*n* = 26)[a]	(*n* = 26)[a]	(*n* = 52)
Mean (SD)	10.74 (± 2.71)	11.51 (± 2.28)	11.13 (± 2.51)
Range	5.8–18.6	7.1–17.6	5.8–18.6
CRP (mg/l)	(*n* = 25)[a]	(*n* = 25)[a]	(*n* = 50)[a]
Median (IQR)	5 (5–6)	7 (5–16)	6 (5–10)
Range	2–22	3–44	2–44
Temperature (°C)	(*n* = 23)[a]	(*n* = 19)[a]	(*n* = 42)[a]
Mean (SD)	36.80 (± 0.34)	36.93 (± 0.22)	36.86 (± 0.29)
Range	36.0–37.2	36.4–37.3	36.0–37.3
Tender, irritable uterus, *n* (%)	(*n* = 26)[a]	(*n* = 28)[a]	(*n* = 54)[a]
Yes	1 (3.8)	0 (0)	1 (1.9)
Foul-smelling discharge, *n* (%)	(*n* = 26)[a]	(*n* = 28)[a]	(*n* = 54)[a]
Yes	0 (0)	0 (0)	0 (0)
Weeks' gestation at PPROM	(*n* = 24)[c]	(*n* = 28)	(*n* = 52)
Mean (SD)	19.21 (± 2.00)	19.22 (± 2.21)	19.22 (± 2.10)
Range	16.0–22.6	15.1–23.3	15.1–23.3
Weeks' gestation at randomisation	(*n* = 28)	(*n* = 28)	(*n* = 56)
Mean (SD)	21.36 (± 1.75)	21.14 (± 2.00)	21.25 (± 1.87)
Range	17.7–25.4	7.4–24.7	17.4–25.4

continued

TABLE 4 Baseline characteristics of participants at randomisation (*continued*)

Baseline characteristics	AI (participants randomised *n* = 28)	Exp (participants randomised *n* = 28)	Total (participants randomised *n* = 56)
Maternal age at randomisation (years)	(*n* = 28)	(*n* = 28)	(*n* = 56)
Mean (SD)	27.46 (± 5.88)	28.30 (± 6.45)	27.88 (± 6.13)
Range	17.0–39.3	17.7–42.8	17.0–42.8
Vaginal bleeding, *n* (%)	(*n* = 28)	(*n* = 28)	(*n* = 56)
Yes	7 (25.0)	11 (39.3)	18 (32.1)
Thoracic circumference (mm)	(*n* = 23)	(*n* = 22)	(*n* = 45)
Mean (SD)	146.84 (± 26.30)	135.47 (± 25.88)	141.28 (± 26.43)
Range	105.0–238.2	89.5–202.2	89.5–238.2
Abdominal circumference (mm)	(*n* = 24)	(*n* = 26)	(*n* = 50)
Mean (SD)	166.43 (± 28.21)	162.44 (± 24.11)	164.35 (± 25.96)
Range	105.0–218.0	117.8–198.0	105.0–218.0
Lung length (mm)	(*n* = 21)	(*n* = 23)	(*n* = 44)
Mean (SD)	23.34 (± 6.31)	23.86 (± 5.30)	23.61 (± 5.74)
Range	15.0–45.0	12.0–34.6	12.0–45.0

IQR, interquartile range; SD, standard deviation.
a Missing data owing to the baseline test not having been performed or difficulty in retrieving the data.
b Patients can have multiple type of HVS listed (types recorded separately).
c Four cases in which it was impossible to be certain at what gestation the amniotic membrane ruptured.

Antenatal course

The antenatal management of all participants in the trial followed the same pathway from diagnosis until randomisation to the trial. All women had a HVS taken and were given 250 mg oral erythromycin four times a day for 10 days following confirmation of rupture of amniotic membrane. As a result, the most commonly used antibiotic in the antenatal period was erythromycin.

Participants attended for their first fetal medicine assessment at the earliest convenient time, but were randomised to the study at least 10 days after the amniotic membrane ruptured. This criterion was adopted following discussions at an international fetal medicine meeting.[14] The international consensus at the time was that the risk of miscarriage in the first week after rupture was too high. In our cohort, seven of the 81 women (8.6%) miscarried before they could be randomised to the study (see *Table 3*).

Of the 29 women allocated to AI, 22 received the intervention, one had a termination of pregnancy, one declined AI after randomisation and four maintained a deepest pool level of approximately 2 cm throughout. No woman in the Exp arm received AI. One baby in each arm was found to have a fetal abnormality with an impact on neonatal survival (*Figure 1*).

Women were seen weekly for an ultrasonography assessment irrespective of the arm they were randomised to. The median number of antenatal visits prior to delivery was 5 (range 0–15) in the AI arm and 4.5 (range 1–14) in the Exp arm (*Table 5*). The median number of AI performed was 3 (range 0–12; *Table 6*).

TABLE 5 Number of visits per patient (ITT)

Number of visits	AI	Exp
n	(*n* = 28)	(*n* = 28)
Median [Q1, Q3]	5 [2.5, 8.5]	4.5 [2.0, 8.5]
Range	0–15	1–14
0	2	0
1	2	5
2	3	5
3	2	3
4	3	1
5	4	2
6	1	4
7	3	0
8	1	1
9	3	2
10	0	2
11	2	2
12	1	0
13	0	0
14	0	1
15	1	0

Q1, upper quartile; Q3, lower quartile.

Table 7 shows that the volume of Hartmann's solution infused (10 ml per week of gestation) was sufficient to produce an average amniotic fluid pocket difference of 2.66 cm, which is considered adequate to improve the risk of pulmonary hypoplasia. Three women had amniotic fluid pocket sizes of < 2 cm after AI because of amniotic fluid leakage as the procedure was taking place. For two of these women, AI improved the deepest pool from 0 to 1.9 cm and 1.0 cm, respectively. In one woman, there was no change in the deepest pool of amniotic fluid after AI.

Not all participants in the AI arm required AI at every visit as it was performed only if the deepest pool of amniotic fluid was < 2 cm. Sixteen women had no fluid instilled on at least one visit and, for those visits in which no AI was performed, the mean pool depth was 2.73 cm.

The risks to the mother in the antenatal period are mainly of abruption, bleeding or infection. There was no difference in the arms for any of these outcomes (*Tables 8* and *9*).

The protocol required a single course (two doses) of antenatal corticosteroids to be given at 26^{+0} weeks' gestation, or earlier if clinicians felt it was indicated. It is not routine practice to give an additional rescue course of steroids. One woman in the Exp arm was given a first course of corticosteroids before 26^{+0} weeks and a rescue course later in pregnancy (see *Table 9*). Those who did not receive any antenatal corticosteroids were women who delivered prior to achieving 26^{+0} weeks' gestation.

TABLE 6 Number of AI per patient (ITT)

Number of AI	AI	Exp
n	(*n* = 28)	(*n* = 28)
Median [Q1, Q3]	3 [1, 4]	0
Range	0 to 12	
0	6[a]	0
1	2	0
2	5	0
3	4	0
4	5	0
5	3	0
6	1	0
7	0	0
8	0	0
9	0	0
10	1	0
11	0	0
12	1	0

Q1, upper quartile; Q3, lower quartile.
a Four women maintained a deepest pool of amniotic fluid > 2 cm throughout the duration of their participation, one declined AI post randomisation and one opted for termination of pregnancy.

TABLE 7 Summaries of AI variables at visits

Women with at least one AI (*n* = 22)	*n* (%)
Fluid instilled on at least one occasion (*n* = 26[a])	
Yes	22 (84.62%)
Amniotic fluid pocket difference [after minus before (cm)] for those patients that had fluid instilled at visit (*n* = 78[b])	
No. of visits	
Mean (SD)	2.66 (1.33)
Range	0.0–7.0
Amniotic fluid pocket size at visit for patients with no fluid instilled (*n* = 65)	
No. of visits	
Mean (SD)	2.73 (0.73)
Range	1.2[c]–4.6

SD, standard deviation.
a The two patients (one termination of pregnancy) on AI who withdrew did not receive any treatment.
b *n* = those who had both an amniotic fluid pocket before and after measurement.
c Unsuccessful attempt at AI.

TABLE 8 Binary maternal morbidity outcome results (ITT)

Maternal morbidity outcome in the antenatal period	AI (*n* = 28[a])	Exp (*n* = 28)	RR (95% CI) (*n* = 56[a])
Abruption of the placenta	(*n* = 27)	(*n* = 28)	–
n (%)	4 (14.8)	0 (0.0)	–
RR (95% CI)	–	–	9.32 (0.53 to 165.26)
Antepartum haemorrhage	(*n* = 27)	(*n* = 28)	–
n (%)	8 (29.6)	7 (25.0)	–
RR (95% CI)	–	–	1.19 (0.50 to 2.82)
Chorioamnionitis	(*n* = 27)	(*n* = 28)	–
n (%)	4 (14.8)	7 (25.0)	–
RR (95% CI)	–	–	0.59 (0.20 to 1.80)
Required antibiotics antenatally	(*n* = 27)	(*n* = 28)	–
n (%)	22 (81.5)	22 (78.6)	–
RR (95% CI)	–	–	1.04 (0.80 to 1.35)
Number of doses of steroids, *n* (%)	(*n* = 27)	(*n* = 28)	–
0	8 (29.6)	13 (46.4)	–
1	3 (11.1)	3 (10.7)	–
2	15 (55.6)	11 (39.3)	–
3	0 (0.0)	0 (0.0)	–
4	1[b] (3.7)	1[b] (3.6)	–
Chi-squared test for trend *p*-value	–	–	0.25[c]

RR, relative risk.
a No data available for one termination of pregnancy, their onset of labour was recorded as caesarean section and their mode of delivery was recorded as elective lower segment caesarean section.
b Rescue course (a second course at some point in pregnancy) of corticosteroid given.
c Chi-squared test may not be a valid test owing to sparse data cells.

TABLE 9 Binary maternal morbidity outcome results (per protocol)

Maternal morbidity outcome	AI (*n* = 22[a])	Exp (*n* = 25[b])	RR (95% CI) (*n* = 47)
Abruption of the placenta	(*n* = 22)	(*n* = 25)	–
n (%)	3 (13.6)	0 (0.0)	–
RR (95% CI)	–	–	7.91 (0.43 to 145.20)
Antepartum haemorrhage	(*n* = 22)	(*n* = 25)	–
n (%)	7 (31.8)	5 (20.0)	–
RR (95% CI)	–	–	1.59 (0.59 to 4.30)
Chorioamnionitis	(*n* = 22)	(*n* = 25)	–
n (%)	4 (18.2)	6 (24.0)	–
RR (95% CI)	–	–	0.76 (0.25 to 2.34)
Required antibiotics antenatally	(*n* = 22)	(*n* = 25)	–
n (%)	18 (81.8)	20 (80.0)	–
RR (95% CI)	–	–	1.02 (0.77 to 1.35)
Number of doses of steroids, *n* (%)	(*n* = 22)	(*n* = 25)	
0	8 (36.4)	11 (44.0)	–
1	3 (13.6)	2 (8.0)	–
2	11 (50.0)	11 (44.0)	–
3	0 (0.0)	0 (0.0)	–
4	0 (0.0)	1[c] (4.0)	–
Chi-squared test for trend *p*-value	–	–	0.96[d]

RR, relative risk.
a All AI arm participants who had at least one AI – six did not have any, which includes no data available for the one termination of pregnancy.
b All Exp arm participants who attended at least one visit included in the per protocol analysis – three did not attend a visit.
c Rescue course given.
d Chi-squared test may not be a valid test due to sparse data cells.

Labour and delivery

Women in the AI arm went into spontaneous preterm labour at a median gestation of 28.45 weeks ± 4.44 standard deviation (SD) and those in the Exp arm at 29.82 weeks 4.33 SD (*Table 10*). The default mode of delivery was vaginal unless there was a clinical indication to deliver by caesarean section. The pregnancy outcomes are shown in *Tables 11* and *12*. Of 39 pregnancies aiming for vaginal delivery at the onset of labour, 34 delivered vaginally. There were more caesarean sections in the AI arm than in the Exp arm, but this difference was not statistically significant.

Perinatal outcomes

Fourteen out of 81 women who could potentially have been recruited to the study had a miscarriage, giving an overall miscarriage rate of 17% (see *Tables 3*, *11* and *12* and *Figure 1*).

TABLE 10 Neonatal morbidity outcomes at birth results

Neonatal morbidity outcome	AI Fetal deaths omitted (*n* = 23)	Exp Fetal deaths omitted (*n* = 17)	Mean difference Fetal deaths omitted (*n* = 40)
Gestational age at delivery (weeks)	(*n* = 23)	(*n* = 17)	–
Mean (SD)	28.45 (4.44)	29.82 (4.33)	–
Range	19.4–37.6	24.9–38.1	–
Mean difference (SD)	–	–	−1.36 (4.40)
95% CI	–	–	−4.21 to 1.48
Birthweight (kg)	(*n* = 23)	(*n* = 17)	–
Mean (SD)	1.18 (0.62)	1.46 (0.67)	–
Range	0.2–3.0	0.7–3.1	–
Mean difference (SD)	–	–	−0.28 (0.64)
95% CI	–	–	−0.69 to 0.14
Apgar score at 1 minute	(*n* = 21)	(*n* = 16)	–
Mean (SD)	4.38 (2.78)	5.25 (2.74)	–
Range	1–10	0–9	–
Mean difference (SD)	–	–	−0.87 (2.77)
95% CI	–	–	−2.73 to 0.99
Apgar score at 5 minutes	(*n* = 21)	(*n* = 16)	–
Mean (SD)	6.86 (2.78)	7.00 (2.31)	–
Range	1–10	2–10	–
Mean difference (SD)	–	–	−0.14 (2.59)
95% CI	–	–	−1.89 to 1.60
Cord pH	(*n* = 15)	(*n* = 8)	–
Mean (SD)	7.26 (0.15)	7.10 (0.46)	–
Range	6.8–7.4	6.0–7.4	–
Mean difference (SD)	–	–	0.16 (0.29)
95% CI	–	–	−0.10 to 0.43
Base excess	(*n* = 12)	(*n* = 5)	–
Mean (SD)	1.78 (8.42)	−1.18 (6.28)	–
Range	−8.5 to 18.8	−9.3–6.8	–
Mean difference (SD)	–	–	2.96 (7.91)
95% CI	–	–	−6.01 to 11.94
Lactate	(*n* = 0)	(*n* = 1)	–
Mean (SD)	–	4.8	–
Range	–	–	–
Mean difference (SD)	–	–	–
95% CI	–	–	–

continued

TABLE 10 Neonatal morbidity outcomes at birth results (*continued*)

Neonatal morbidity outcome	AI Fetal deaths omitted (*n* = 23)	Exp Fetal deaths omitted (*n* = 17)	Mean difference Fetal deaths omitted (*n* = 40)
Sex, *n* male (%)	(*n* = 26)	(*n* = 25)	–
ITT	17 (65.4)	15 (60.0)	–
Sex, *n* male (%)	(*n* = 21)	(*n* = 24)	–
Per protocol	14 (66.7)	15 (62.5)	–

TABLE 11 Pregnancy outcome (ITT)

Pregnancy outcome	AI (*n* = 28[a])	Exp (*n* = 28)	Chi-squared test *p*-value (*n* = 56[a])
Onset of labour, *n* (%)	(*n* = 28)	(*n* = 28)	–
Induced	4 (14.2)	5 (17.9)	–
Spontaneous	12 (42.9)	18 (64.2)	–
Caesarean section	12 (42.9)	5 (17.9)	–
Chi-squared test *p*-value	–	–	0.12[b]
Mode of delivery, *n* (%)	(*n* = 28)	(*n* = 28)	–
Normal	12 (42.9)	20 (71.4)	–
Instrumental	1 (3.5)	1 (3.6)	–
Emergency LSCS	12 (42.9)	7 (25.0)	–
Elective LSCS	3 (10.7)	0 (0.0)	–
Chi-squared test *p*-value	–	–	0.10[b]
Reason for delivery of fetus	(*n* = 27)	(*n* = 27)	–
APH	2 (7.4)	1 (3.7)	–
APH/abnormal cardiotocography	1 (3.7)	0 (0.0)	–
Placental abruption	3 (11.1)	0 (0.0)	–
Cord prolapse	2 (7.4)	2 (7.4)	–
Elective LSCS	1 (3.7)	1 (3.7)	–
Emergency caesarean section	0 (0.0)	2 (7.4)	–
Fetal death in utero	1 (3.7)	2 (7.4)	–
Fetal distress	1 (3.7)	1 (3.7)	–
Induction of labour	2 (7.4)	1 (3.7)	–
Spontaneous labour	14 (51.9)	11 (40.8)	–
Spontaneous miscarriage	0 (0.0)	6 (22.2)	–

APH, antepartum haemorrhage; LSCS, lower segment caesarean section.
a No data available for one termination of pregnancy, their onset of labour was recorded as caesarean section and their mode of delivery was recorded as elective LSCS.
b Chi-squared may not be a valid test owing to sparse data cells.

TABLE 12 Pregnancy outcome (per protocol)

Pregnancy outcome	AI ($n = 22$[a])	Exp ($n = 25$[b])	Chi-squared test p-value ($n = 47$)
Onset of labour, *n* (%)	($n = 22$)	($n = 25$)	–
Induced	3 (13.6)	4 (16.0)	–
Spontaneous	9 (40.9)	16 (64.0)	–
N/A (caesarean section)	10 (45.5)	5 (20.0)	–
Chi-squared test *p*-value	–	–	0.17[b]
Mode of delivery, *n* (%)	($n = 22$)	($n = 25$)	–
Normal	12 (54.5)	18 (72.0)	–
Instrumental	0 (0.0)	0 (0.0)	–
Emergency LSCS	9 (40.9)	7 (28.0)	–
Elective LSCS	1 (4.6)	0 (0.0)	–
Chi-squared test *p*-value	–	–	0.32[c]
Reason for delivery of fetus, *n* (%)	($n = 22$)	($n = 25$)	–
APH	2 (9.0)	1 (4.0)	–
APH/abnormal cardiotocography	1 (4.6)	0 (0.0)	–
Abruption	3 (13.6)	0 (0.0)	–
Cord prolapse	2 (9.0)	2 (8.0)	–
Elective LSCS	0 (0.0)	1 (4.0)	–
Emergency caesarean section	0 (0.0)	2 (8.0)	–
Fetal death in utero	1 (4.6)	2 (8.0)	–
Fetal distress	1 (4.6)	1 (4.0)	–
Induction of labour	1 (4.6)	1 (4.0)	–
Spontaneous labour	11 (50.0)	10 (40.0)	–
Spontaneous miscarriage	0 (0.0)	5 (20.0)	–

APH, antepartum haemorrhage; LSCS, lower segment caesarean section; N/A, not applicable.

a All AI arm participants who had at least one AI – six did not have any, including one termination of pregnancy for which no data were available.

b All Exp arm participants who attended at least one visit included in the per protocol analysis – three did not attend a visit.

c Chi-squared may not be a valid test owing to sparse data cells.

The overall perinatal survival in both arms was 17 out of 56 (30.4%) and the overall perinatal mortality was 39 out of 56 (69.6%) (*Tables 13* and *14*). Four antepartum deaths were secondary to cord prolapse, two in each arm. Neonatal deaths were attributable to extreme prematurity and/or small lungs and not oxygenating despite maximum ventilation. Further details about the perinatal deaths can be seen in *Serious adverse events*. All SAEs had a severity of 'death'.

There was no significant difference in mean gestational age at delivery between the AI and Exp arms (28.45 weeks vs. 29.82 weeks; mean difference −1.36, 95% CI −4.21 to 1.48) or Apgar score at 5 minutes (6.86 vs. 7.00; mean difference SD −0.14, 95% CI −1.89 to 1.60). Birthweight in the Exp arm was, however, slightly higher (1.18 kg vs. 1.46 kg; mean difference SD −0.28, 95% CI −0.69 to 0.14) and cord pH was noted to be higher in the AI arm (7.26 vs. 7.10; mean difference SD 0.16, 95% CI −0.10 to 0.43) (see *Table 10*).

After removing fetal deaths, there were 23 patients in the AI arm and 17 in the Exp arm. Any neonatal morbidity outcome results with numbers lower than this are a result of missing patient data.

There was no difference between the arms in the overall risk of any serious neonatal morbidity by ITT [23/28 vs. 25/28; relative risk (RR) 0.92, 95% CI 0.74 to 1.14] (*Tables 15* and *16*), or in any morbidity at birth or some time after birth (*Tables 17* and *18*).

The data presented in *Tables 15* and *16* are indicative of the overall morbidity and death in the cohort. Although outcomes such as culture-positive sepsis, pneumothorax, O_2 requirement at day 28, NEC, seizures, retinopathy, PVL, shunt and IVH 3 or 4 have been described in the analysis of the short-term outcomes, the sequelae of these morbidities are assessed in terms of their impact on long-term outcomes, i.e. blindness, long-term respiratory morbidity as assessed by infant lung function tests and neurodevelopmental delay as assessed by BSID-II (see *Chapter 4*).

There was no difference between arms in O_2 requirement at day 28 (*Tables 17* and *18*).

The incidence of IVH grades 2 and 3 (two from the AI arm vs. four from the Exp arm) and postural orthopaedic deformities (one from the AI arm vs. two from the Exp arm) were similar in both arms. The numbers are too small to conclude any significant differences. This would require a larger study. There were no incidences of fixed orthopaedic deformities (*Tables 19* and *20*). The number of days a patient spent on ventilation and the number of days that a patient required O_2 are shown in *Tables 21* and *22*, respectively.

TABLE 13 Perinatal mortality (ITT)

Outcome	AI (*n* = 28[a])	Exp (*n* = 28)	RR (95% CI) (*n* = 56[a])
Fetal death, *n*	5	11	0.4545 (0.1815 to 1.1386)
Neonatal and fetal death, *n*	19	19	1.0000 (0.6973 to 1.4341)
Infant, neonatal and fetal death, *n*	19	20	0.9500 (0.6720 to 1.3430)

RR, relative risk.
a Withdrawn: patient 24 (termination of pregnancy), classed as a fetal death for ITT purposes.

TABLE 14 Perinatal mortality (per protocol)

Outcome	AI ($n = 22$[a])	Exp ($n = 25$[b])	RR (95% CI) ($n = 47$)
Fetal death, *n*	4	9	0.5051 (0.1805 to 1.4133)
Neonatal and fetal death, *n*	17	16	1.2074 (0.8330 to 1.7501)
Infant, neonatal and fetal death, *n*	17	17	1.1364 (0.7995 to 1.6153)

RR, relative risk.
a All AI arm participants who had at least one AI – six did not have, including one termination of pregnancy for which no data were available.
b All Exp arm participants who attended at least one visit included in the per protocol analysis – three did not attend a visit.

TABLE 15 Death or serious neonatal morbidity[a] (ITT)

Outcome	AI ($n = 28$)	Exp ($n = 28$)	RR ($n = 56$[b])
Death or serious neonatal morbidity, *n* (%)	($n = 28$)	($n = 28$)	–
Yes	23 (82.1)	25 (89.3)	–
RR (95% CI)	–	–	0.9200 (0.7419 to 1.1408)

a Serious neonatal morbidity is defined as culture-positive sepsis, pneumothorax, O_2 requirement day 28, NEC (operated), NEC (treated conservatively), treated seizures, treated retinopathy, PVL, shunt or IVH 3 or 4.
b Withdrawn patient 24 (termination of pregnancy) classed as a fetal death for ITT purposes.

TABLE 16 Death or serious neonatal morbidity[a] (per protocol)

Outcome	AI ($n = 22$[b])	Exp ($n = 25$[c])	RR ($n = 47$)
Death or serious neonatal morbidity, *n* (%)	($n = 22$)	($n = 25$)	–
Yes	20 (90.9)	22 (88.0)	–
RR (95% CI)	–	–	1.0331 (0.8492 to 1.2567)

a Serious neonatal morbidity is defined as culture-positive sepsis, pneumothorax, O_2 requirement day 28, NEC (operated), NEC (treated conservatively), treated seizures, treated retinopathy, PVL, shunt or IVH 3 or 4.
b All AI arm participants who had at least one AI – six did not have any, including one termination of pregnancy for which no data were available.
c All Exp arm participants who attended at least one visit included in the per protocol analysis – three did not attend a visit.

TABLE 17 Binary neonatal morbidity outcomes at birth and some time after birth (ITT)

Neonatal morbidity outcome	AI		Exp		RR	
	All patients with data ($n = 28$[a,b])	Fetal deaths omitted ($n = 24$[a])	All patients with data ($n = 28$[c])	Fetal deaths omitted ($n = 17$)	All patients with data ($n = 56$[a])	Fetal deaths omitted ($n = 41$[a])
Culture-positive sepsis, *n* (%)	(*n* = 27)	(*n* = 23)	(*n* = 28)	(*n* = 17)	–	–
Yes	5 (18.5)	5 (21.7)	7 (25.0)	7 (41.2)	–	–
RR (95% CI)	–	–	–	–	0.74 (0.27 to 2.05)	0.53 (0.20 to 1.38)
Pneumothorax, *n* (%)	(*n* = 27)	(*n* = 23)	(*n* = 28)	(*n* = 17)	–	–
Yes	3 (11.1)	3 (13.0)	3 (10.7)	3 (17.7)	–	–
RR (95% CI)	–	–	–	–	1.04 (0.23 to 4.70)	0.74 (0.17 to 3.22)
NEC (operated), *n* (%)	(*n* = 27)	(*n* = 23)	(*n* = 28)	(*n* = 17)	–	–
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–	–
RR (95% CI)	–	–	–	–	N/A as no events in either arm	N/A as no events in either arm
NEC (treated conservatively), *n* (%)	(*n* = 27)	(*n* = 23)	(*n* = 28)	(*n* = 17)	–	–
Yes	2 (7.4)	2 (8.7)	1 (3.6)	1 (5.9)	–	–
RR (95% CI)	–	–	–	–	2.07 (0.20 to 21.56)	1.48 (0.15 to 15.00)
Treated seizures, *n* (%)	(*n* = 27)	(*n* = 23)	(*n* = 28)	(*n* = 17)	–	–
Yes	1 (3.7)	1 (4.4)	1 (3.6)	1 (5.9)	–	–
RR (95% CI)	–	–	–	–	1.04 (0.07 to 15.76)	0.74 (0.05 to 11.00)
Treated retinopathy, *n* (%)	(*n* = 27)	(*n* = 23)	(*n* = 28)	(*n* = 17)	–	–
Yes	1 (3.7)	1 (4.4)	0 (0.0)	0 (0.0)	–	–
RR (95% CI)	–	–	–	–	3.11 (0.13 to 73.11)	2.25 (0.10 to 52.07)
PVL, *n* (%)	(*n* = 27)	(*n* = 23)	(*n* = 28)	(*n* = 17)	–	–
Yes	0 (0.0)	0 (0.0)	1 (3.6)	1 (5.9)	–	–
RR (95% CI)	–	–	–	–	0.35 (0.01 to 8.12)	0.25 (0.01 to 5.79)

Neonatal morbidity outcome	AI		Exp		RR	
	All patients with data ($n = 28$[a,b])	Fetal deaths omitted ($n = 24$[a])	All patients with data ($n = 28$[c])	Fetal deaths omitted ($n = 17$)	All patients with data ($n = 56$[a])	Fetal deaths omitted ($n = 41$[a])
Shunt, *n* (%)	($n = 27$)	($n = 23$)	($n = 28$)	($n = 17$)	–	–
Yes	1 (3.7)	1 (4.4)	0 (0.0)	0 (0.0)	–	–
RR (95% CI)	–	–	–	–	3.11 (0.13 to 73.11)	2.25 (0.10 to 52.07)
Home O_2,[d] *n* (%)	($n = 27$)	($n = 9$)	($n = 28$)	($n = 9$)	–	–
Yes	2 (7.4)	2 (22.2)	3 (10.7)	3 (33.3)	–	–
RR (95% CI)	–	–	–	–	0.69 (0.13 to 3.82)	0.67 (0.14 to 3.09)
O_2 requirement at day 28,[d] *n* (%)	($n = 27$)	($n = 9$)	($n = 28$)	($n = 9$)	–	–
Yes	3 (11.1)	3 (33.3)	4 (14.3)	3 (33.3)	–	–
RR (95% CI)	–	–	–	–	0.78 (0.19 to 3.16)	1.00 (0.27 to 3.69)

N/A, not applicable.
a One termination of pregnancy was randomised to the AI arm so does not have any neonatal morbidity outcome data.
b All AI arm participants who had at least one AI – six did not have, including one termination of pregnancy for which no data were available.
c All Exp arm participants who attended at least one visit included in the per protocol analysis – three did not attend a visit.
d The sensitivity analysis summarised in the three 'fetal deaths omitted' columns had the neonatal deaths omitted in addition as this outcome was measured a while after birth.

TABLE 18 Binary neonatal morbidity outcomes at birth and sometime after birth (per protocol)

Neonatal morbidity outcome	AI		Exp		RR	
	All patients with data ($n = 22$[a])	Fetal deaths omitted ($n = 18$)	All patients with data ($n = 25$[b])	Fetal deaths omitted ($n = 16$)	All patients with data ($n = 47$)	Fetal deaths omitted ($n = 34$)
Culture-positive sepsis, *n* (%)	($n = 22$)	($n = 18$)	($n = 25$)	($n = 16$)	–	–
Yes	4 (18.2)	4 (22.2)	7 (28.0)	7 (43.8)	–	–
RR (95% CI)	–	–	–	–	0.65 (0.22 to 1.92)	0.51 (0.18 to 1.42)
Pneumothorax, *n* (%)	($n = 22$)	($n = 18$)	($n = 25$)	($n = 16$)	–	–
Yes	3 (13.6)	3 (16.7)	2 (8.0)	2 (12.5)	–	–
RR (95% CI)	–	–	–	–	1.70 (0.31 to 9.28)	1.33 (0.25 to 7.00)
NEC (operated), *n* (%)	($n = 22$)	($n = 18$)	($n = 25$)	($n = 16$)	–	–
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–	–
RR (95% CI)	–	–	–	–	N/A as no events in either arm	N/A as no events in either arm
NEC (treated conservatively), *n* (%)	($n = 22$)	($n = 18$)	($n = 25$)	($n = 16$)	–	–
Yes	2 (9.1)	2 (11.1)	1 (4.0)	1 (6.3)	–	–
RR (95% CI)	–	–	–	–	2.27 (0.22 to 23.38)	1.78 (0.18 to 17.80)
Treated seizures, *n* (%)	($n = 22$)	($n = 18$)	($n = 25$)	($n = 16$)	–	–
Yes	0 (0.0)	0 (0.0)	1 (4.0)	1 (6.3)	–	–
RR (95% CI)	–	–	–	–	0.38 (0.02 to 8.80)	0.30 (0.01 to 6.84)
Treated retinopathy, *n* (%)	($n = 22$)	($n = 18$)	($n = 25$)	($n = 16$)	–	–
Yes	1 (4.6)	1 (5.6)	0 (0.0)	0 (0.0)	–	–
RR (95% CI)	–	–	–	–	3.39 (0.15 to 79.22)	2.68 (0.12 to 61.58)
PVL, *n* (%)	($n = 22$)	($n = 18$)	($n = 25$)	($n = 16$)	–	–
Yes	0 (0.0)	0 (0.0)	1 (4.0)	1 (6.3)	–	–
RR (95% CI)	–	–	–	–	0.38 (0.02 to 8.80)	0.30 (0.01 to 6.84)

Neonatal morbidity outcome	AI		Exp		RR	
	All patients with data ($n = 22$[a])	Fetal deaths omitted ($n = 18$)	All patients with data ($n = 25$[b])	Fetal deaths omitted ($n = 16$)	All patients with data ($n = 47$)	Fetal deaths omitted ($n = 34$)
Shunt, *n* (%)	($n = 22$)	($n = 18$)	($n = 25$)	($n = 16$)	–	–
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–	–
RR (95% CI)	–	–	–	–	N/A as no events in either arm	N/A as no events in either arm
Home O_2,[c] *n* (%)	($n = 22$)	($n = 5$)	($n = 25$)	($n = 9$)	–	–
Yes	2 (9.1)	2 (40.0)	3 (12.0)	3 (33.3)	–	–
RR (95% CI)	–	–	–	–	0.76 (0.14 to 4.13)	1.20 (0.29 to 4.95)
O_2 requirement at day 28,[c] *n* (%)	($n = 22$)	($n = 5$)	($n = 25$)	($n = 9$)	–	–
Yes	3 (13.6)	3 (60.0)	4 (16.0)	3 (33.3)	–	–
RR (95% CI)	–	–	–	–	0.85 (0.21 to 3.40)	1.80 (0.19 to 1.93)

N/A, not applicable.
a All AI arm participants who had at least one AI – six did not have, including one termination of pregnancy for which no data were available.
b All Exp arm participants who attended at least one visit included in the per protocol analysis – three did not attend a visit.
c The sensitivity analysis summarised in the three 'fetal deaths omitted' columns had the neonatal deaths omitted in addition as this outcome was measured a while after birth.

TABLE 19 Categorical neonatal morbidity outcomes at birth results (ITT)

Neonatal morbidity outcome	AI (*n* = 28)	Exp (*n* = 28)	Chi-squared test *p*-value (*n* = 56)
IVH grade, *n* (%)	(*n* = 27)	(*n* = 28)	–
No IVH	25 (92.6)	24 (85.7)	–
Grade 1	0 (0.0)	0 (0.0)	–
Grade 2	1 (3.7)	1 (3.6)	–
Grade 3	1 (3.7)	3 (10.7)	–
Chi-squared test for trend *p*-value	–	–	0.34[a]
Orthopaedic deformities, *n* (%)	(*n* = 27)	(*n* = 28)	–
None	26 (96.3)	26 (92.9)	–
Fixed	0 (0.0)	0 (0.0)	–
Postural	1[b] (3.7)	2[c] (7.1)	–
Chi-squared test *p*-value	–	–	0.57[a]

a Chi-squared may not be a valid test owing to sparse data cells.
b Deform site: both knees and hips; deform type: hyperextension and subluxation; not referred to orthopaedic surgeon.
c Patient 1: deform site – foot; deform type: intoeing gait; not referred to orthopaedic surgeon. Patient 2: deform site – knee, elbow, right foot; deform type: bilateral knee and elbow contracture; referred to orthopaedic surgeon but did not require surgery.

TABLE 20 Categorical neonatal morbidity outcomes at birth results (per protocol)

Neonatal morbidity outcome	AI (*n* = 22[a])	Exp (*n* = 25[b])	Chi-squared test *p*-value (*n* = 47)
IVH grade, *n* (%)	(*n* = 22)	(*n* = 25)	–
No IVH	21 (95.5)	21 (84.0)	–
Grade 1	0 (0.0)	0 (0.0)	–
Grade 2	0 (0.0)	1 (4.0)	–
Grade 3	1 (4.5)	3 (12.0)	–
Chi-squared test for trend *p*-value	–	–	0.12[a]
Orthopaedic deformities, *n* (%)	(*n* = 22)	(*n* = 25)	–
None	21 (95.5)	23 (92.0)	–
Fixed	0 (0.0)	0 (0.0)	–
Postural	1 (4.5)	2 (8.0)	–
Chi-squared test *p*-value	–	–	0.63[c]

a All AI arm participants who had at least one AI – six did not have any, including one termination of pregnancy for which no data were available.
b All Exp arm participants who attended at least one visit included in the per protocol analysis – three did not attend a visit.
c Chi-squared may not be a valid test owing to sparse data cells.

TABLE 21 Number of days a patient was on IPPV, CPAP and HFOV

Analysis	AI Fetal deaths excluded, neonatal deaths with maximum observed value in trial imputed (*n* = 23)	Exp Fetal deaths excluded, neonatal deaths with maximum observed value in trial imputed (*n* = 17)
Number of neonatal deaths	14	8
Days IPPV, *n* (%)	(*n* = 23)	(*n* = 17)
Yes	10 (43.5)	10 (58.8)
Median (IQR)	69 (3–69)	5 (2–69)
Range	0–69	0–69
Days CPAP, *n* (%)	(*n* = 23)	(*n* = 17)
Yes	7 (30.4)	5 (29.4)
Median (IQR)	35 (2–35)	23 (1–35)
Range	0–35	0–35
Days HFOV, *n* (%)	(*n* = 23)	(*n* = 17)
Yes	3 (13.0)	2 (11.8)
Median (IQR)	4 (0–4)	2 (0–4)
Range	0–4	0–4

IQR, interquartile range.

TABLE 22 Number of days that a patient required O_2

Outcome	AI Fetal deaths excluded, neonatal deaths with maximum observed value in trial imputed (*n* = 23)	Exp Fetal deaths excluded, neonatal deaths with maximum observed value in trial imputed (*n* = 17)
Number of neonatal deaths	14	8
Days on O_2, *n* (%)	(*n* = 23)	(*n* = 15[a])
Median (IQR)	28 (24–28)	28 (5–28)
Range	0–28	0–28

IQR, interquartile range.
a One patient with no data and one with unusable data.

Postnatal maternal outcomes

Coamoxiclav, cephalosporins and metronidazole were most commonly used postnatally. One woman in the Exp arm had serious maternal sepsis requiring admission to ITU/HDU (*Tables 23* and *24*). There were no maternal deaths.

TABLE 23 Maternal outcomes (ITT)

Maternal morbidity outcome	AI ($n = 28$[a])	Exp ($n = 28$)	RR ($n = 56$[a])
Required antibiotics postnatally	***(n = 27)***	***(n = 28)***	**–**
n (%), yes	6 (22.2)	8 (28.6)	–
RR (95% CI)	–	–	0.78 (0.31 to 1.95)
Serious maternal sepsis requiring ITU/HDU admission			
ITT	($n = 27$)	($n = 28$)	–
n (%), yes	0 (0.0)	1 (3.6)	–
RR (95% CI)	–	–	0.35 (0.01 to 8.12)
Maternal death	0/28	0/28	N/A

N/A, not applicable.
a No data for one termination of pregnancy.

TABLE 24 Maternal outcomes (per protocol)

Maternal morbidity outcome	AI ($n = 22$[a])	Exp ($n = 25$[b])	RR ($n = 47$)
Required antibiotics postnatally, *n* (%)	($n = 22$)	($n = 25$)	–
Yes	5 (22.7)	6 (24.0)	–
RR (95% CI)	–	–	0.95 (0.33 to 2.68)
Serious maternal sepsis requiring ITU/HDU admission, *n* (%)	($n = 22$)	($n = 25$)	–
Yes	0 (0.0)	1 (4.0)	–
RR (95% CI)	–	–	0.38 (0.02 to 8.80)
Maternal death	0/22	0/25	N/A

N/A, not applicable.
a All AI arm participants who had at least one AI – six did not have any which includes no data available for the one termination of pregnancy.
b All Exp arm participants who attended at least one visit included in the per protocol analysis – three did not attend a visit.

Serious adverse events

All SAEs had a severity of 'death' (*Tables 25* and *26*).

TABLE 25 Serious adverse events (ITT)

Event	Description	AI (*n*)	Exp (*n*)
Antepartum death	Antepartum death – no additional information	1	1
	Cord prolapse	2	1
	Cord prolapse, stillbirth	0	1
	Miscarriage	0	5
	Spontaneous miscarriage	0	2
	Stillbirth	1	1
	Termination of pregnancy	1	0
	Total	5	11
Neonatal death	Cord prolapse, emergency caesarean section	0	1
	Extreme prematurity, pulmonary hypoplasia, placental abruption	1	0
	Fetal abnormalities undiagnosed prior to birth	1	0
	Neonatal death – no additional information	5	1
	Preterm birth and extreme prematurity	3	4
	Preterm birth and extreme prematurity, pulmonary hypoplasia	2	1
	Pulmonary hypoplasia	1	0
	Pulmonary hypoplasia, pulmonary stenosis and small right ventricle	0	1
	Pulmonary hypoplasia, renal agenesis	1	0
	Total	14	8
Infant death	Chronic lung disease	0	1
	Total	0	1
Total SAEs		19	20

TABLE 26 Serious adverse events (per protocol)

Event	Description	AI (*n*)	Exp (*n*)
Antepartum death	Antepartum death – no additional information	1	1
	Cord prolapse	2	1
	Cord prolapse, stillbirth	0	0
	Miscarriage	0	4
	Spontaneous miscarriage	0	2
	Stillbirth	1	1
	Termination of pregnancy	0	0
	Total	4	9
Neonatal death	Cord prolapse, emergency caesarean section	0	1
	Extreme prematurity, pulmonary hypoplasia, placental abruption	1	0
	Fetal abnormalities undiagnosed prior to birth	1	0
	Neonatal death – no additional information	4	1
	Preterm birth and extreme prematurity	3	3
	Preterm birth and extreme prematurity, pulmonary hypoplasia	2	1
	Pulmonary hypoplasia	1	0
	Pulmonary hypoplasia, pulmonary stenosis and small right ventricle	0	1
	Pulmonary hypoplasia, renal agenesis	1	0
	Total	13	7
Infant death	Chronic lung disease	0	1
	Total	0	1
Total SAEs		17	17

Chapter 4 Results (long-term outcomes)

There were nine survivors in the AI arm and eight in the Exp arm. The numbers are too small to make meaningful comparisons. This is, however, the first time that long-term follow-up of respiratory and neurodevelopmental outcomes has been performed in survivors of very early prelabour rupture of the amniotic membranes.

Respiratory questionnaires

Respiratory questionnaires were sent out three times in the period of long-term outcome analysis: at 6 months, 12 months and 18 months. *Table 27* shows the questionnaire status at each of the time points.

The respiratory questionnaire scores at each time point are summarised in *Table 28* and the outcomes of the latest returned questionnaires are shown in *Table 29*. At 18 months, two children in the Exp arm and two children in the AI arm had scores within the CIs for asthma defined by Powell *et al.*[15] Additionally, three children in the Exp arm (patient numbers 22, 28, 31) and three patients in the AI arm (patient numbers 8, 11, 16) did not have outcome data available at 18 months.

Complete-case analysis is defined as analysis of only those domain scores and overall scores that have no missing data owing to there being no validated methods available to handle missing data in this respiratory questionnaire.

- Best case is sensitivity analysis assigning missing questions a score of 0.
- Worst case is sensitivity analysis assigning missing questions a score of 4.

There was only one patient with missing answers to the questions in one of the sections in the 'daytime symptoms' domain so the best- and worst-case sensitivity analyses are only needed for 'daytime symptoms' and 'overall total' scores (*Table 30*).

The mean profile plots for overall total score of the respiratory questionnaires is shown in *Figure 4*.

Table 31 shows descriptive statistics regarding asthma diagnosis, medications for asthma, and hospital and general practitioner visits for chest symptoms. Numbers were too small to perform meaningful statistical analyses.

TABLE 27 Questionnaire status

Questionnaire status	Questionnaire time point					
	6 months		12 months		18 months	
	AI survivors ($n = 9$)	Exp survivors ($n = 8$)	AI survivors ($n = 9$)	Exp survivors ($n = 8$)	AI survivors ($n = 9$)	Exp survivors ($n = 8$)
Questionnaires returned (and analysed)	7	7	7	6	6	5
Lost to follow-up	1	1	1	2	1	2
Parent did not return questionnaire	1	0	1	0	2	1

TABLE 28 Respiratory questionnaire score analyses

Domain	Questionnaire time point								
	6 months			12 months			18 months		
	AI	Exp	Difference in medians (95% CI)	AI	Exp	Difference in medians (95% CI)	AI	Exp	Difference in medians (95% CI)
Overall total									
Complete case									
	n = 7	*n* = 7		*n* = 7	*n* = 6		*n* = 6	*n* = 5	
Median (IQR)	16 (14–32)	13.5 (7–35)	2 (–31 to 24)	18 (3–28)	15.5 (6–29)	1.5 (–26 to 23)	10.5 (4–40)	13 (4–42)	0 (–44 to 40)
Range	4–59			0–63	0–50		0–62	0–60	
Sensitivity analysis, neonatal									
	n = 21	*n* = 15		*n* = 21	*n* = 14		*n* = 20	*n* = 13	
Median (IQR)	84 (32–84)		0 (0 to 6)	84 (28–84)	84 (16–84)	0 (0 to 34)	84 (51–84)	84 (42–84)	0 (0 to 20)
Range	4–84			0–84	0–84		0–84	0–84	
Daytime symptoms									
Complete case									
	n = 7[c]	*n* = 6[a]		*n* = 7	*n* = 6		*n* = 6	*n* = 5	
	10 (9–20)	10 (5–18)	1 (–17 to 15)	14 (1–20)	6 (3–22)	–0.5 (–17 to 17)	6.5 (2–17)	6 (4–21)	–3 (–29 to 17)
	3–37	5–54		0–35	0–31		0–35	0–40	
Sensitivity analysis, neonatal									
	n = 21	*n* = 14		*n* = 21	*n* = 14		*n* = 20	*n* = 13	
Median (IQR)	54 (20–54)	54 (11–54)	0 (0 to 4)	54 (20–54)	54 (8–54)	0 (0–20)	54 (26–54)	54 (21–54)	0 (0–11)
Range[a]	3–54	5–54		0–54	0–54		0–54	0–54	
Night-time symptoms									
Complete case									
	n = 7	*n* = 7		*n* = 7	*n* = 6[a]		*n* = 6	*n* = 5	
Median (IQR)	2 (0–6)	4 (1–10)	–2 (–10 to 1)	2 (1–4)	3 (0–5)	0 (–4 to 4)	4 (2–5)	6 (0–7)	–0.5 (–6 to 5)
Range	0–7	1–13		0–12	0–7		0–11	0–9	

Domain	Questionnaire time point: 6 months AI	6 months Exp	6 months Difference in medians (95% CI)	12 months AI	12 months Exp	12 months Difference in medians (95% CI)	18 months AI	18 months Exp	18 months Difference in medians (95% CI)
Sensitivity analysis neonatal									
	n = 21	*n* = 15		*n* = 21	*n* = 14		*n* = 20	*n* = 13	
Median (IQR)	13 (6–13)	13 (4–13)	0 (0 to 1)	13 (4–13)	13 (5–13)	0 (0 to 6)	13 (8–13)	13 (7–13)	
Range	0–13	1–13		0–13	0–13		0–13	0–13	0 (0 to 4)
Effect on the child									
Complete case									
	n = 7	*n* = 7		*n* = 7	*n* = 6		*n* = 6	*n* = 5	
Median (IQR)	2 (0–3)	0 (0–6)	0 (–4 to 3)	1 (0–3)	2 (0–3)	0 (–3 to 3)	0 (0–8)[b]	1 (0–5)	0 (–5 to 8)
Range	0–8	0–6		0–8	0–5		0–8	0–5	
Sensitivity analysis, neonatal									
	n = 21	*n* = 15		*n* = 21	*n* = 14		*n* = 20	*n* = 13	
	8 (3–8)	8 (0–8)	0 (0 to 2)	8 (3–8)	8 (3–8)	0 (0 to 3)	8 (8–8)	8 (5–8)	0 (0 to 3)
	0–8	0–8		0–8	0–8		0–8	0–8	
Effect on the family									
Complete case									
	n = 7	*n* = 7		*n* = 7	*n* = 6		*n* = 6	*n* = 5	
Median (IQR)	2 (0–8)	2 (0–6)	0 (–5 to 5)	1 (0–8)	2.5 (1–3)	–0.5 (–3 to 7)	0 (0–8)[b]	0 (0–6)	0 (–9 to 8)
Range	0–10	0–11		0–11	0–9		0–10	0–9	
Sensitivity analysis, neonatal									
	n = 21	*n* = 15		*n* = 21	*n* = 14		*n* = 20	*n* = 13	
Median (IQR)	11 (8–11)	11 (2–11)	0 (0 to 2)	11 (8–11)	11 (3–11)	0 (0 to 2)	11 (9–11)	11 (6–11)	0 (0 to 2)
Range	0–11	0–11		0–11	0–11		0–11	0–11	

IQR, interquartile range.

a One patient had incomplete daytime symptoms domain so was excluded from the daytime symptoms and overall total summaries.

b The complete-case analysis is analysis of only those domain scores and overall scores for which no data are missing as a result of there being no validated methods available to handle missing data in this respiratory questionnaire.

Sensitivity analysis, neonatal: sensitivity analysis in which the deaths are assigned the largest value observed in the trial for that particular domain/overall score.

TABLE 29 Respiratory questionnaire scores

Study arm	Patient number	Latest questionnaire available	Outcome
AI	8	12 months	No indication of asthma
	10	18 months	Asthma
	11	No questionnaires returned	Missing data
	16	Lost to follow-up	Missing data
	20	18 months	No indication of asthma
	30	18 months	No indication of asthma
	35	18 months	No indication of asthma
	45	18 months	No indication of asthma
	55	18 months	Asthma
Exp	5	18 months	No indication of asthma
	22	12 months	Asthma
	25	18 months	Asthma
	28	6 months	Asthma
	31	Lost to follow-up	Missing data
	33	18 months	No indication of asthma
	44	18 months	No indication of asthma
	58	18 months	Asthma

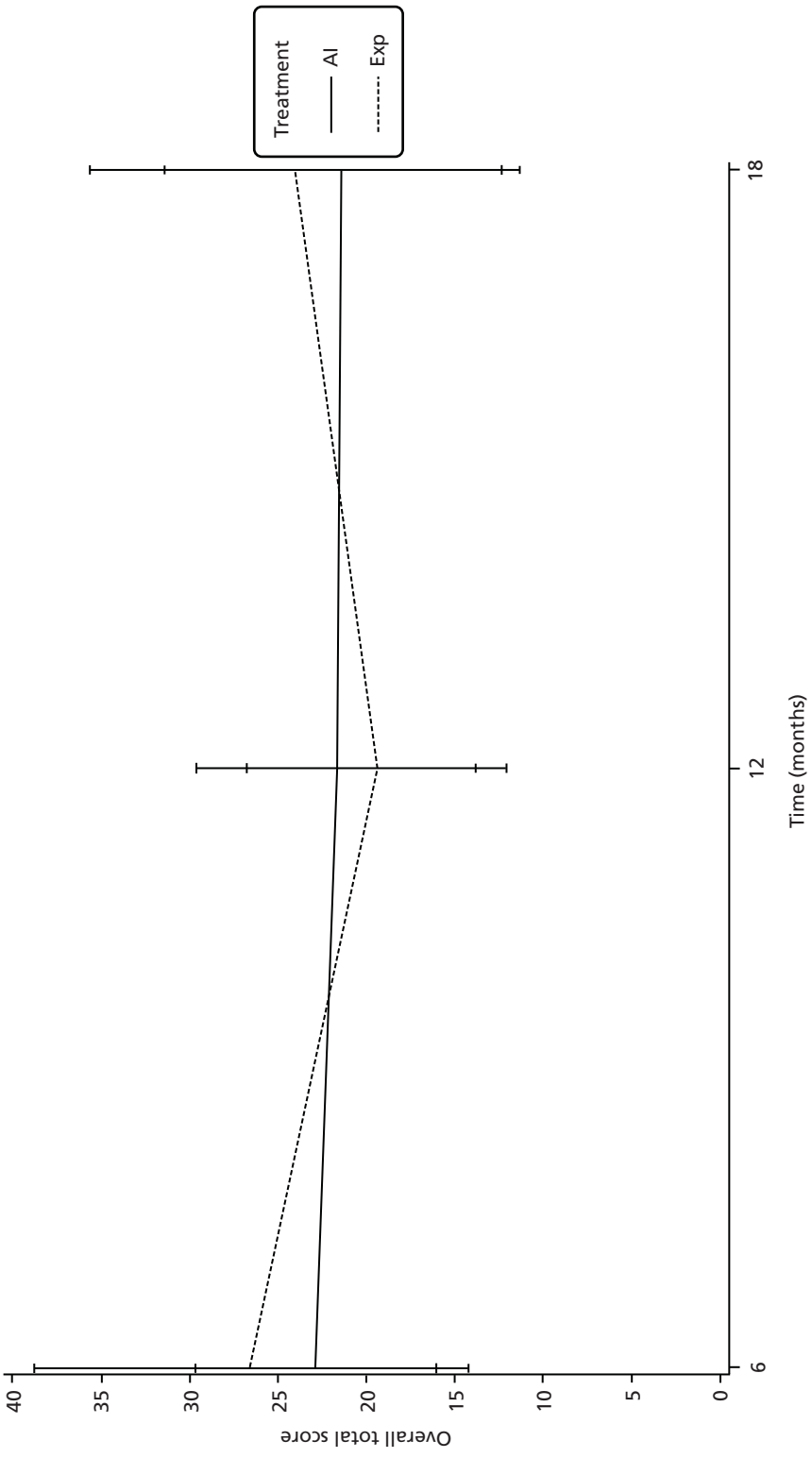

FIGURE 4 Mean profile plots for overall total score of the respiratory questionnaire.

TABLE 30 Sensitivity analysis for respiratory questionnaire scores

Domain	6 months		
	AI	Exp	Difference in medians (95% CI)
Overall total			
Complete case			
	n = 7	*n* = 6[a]	
Median (IQR)	16 (14–32)	13.5 (7–35)	2 (−31 to 24)
Range	4–59	6–84	
Best case (missing answers = 0)			
		n = 7	
Median (IQR)		14 (7–41)	1 (−27 to 18)
Range		6–84	
Worst case (missing answers = 4)			
		n = 7	
Median (IQR)		14 (7–65)	0 (−50 to 18)
Range		6–84	
Daytime symptoms			
Complete case			
	n = 7	*n* = 6[a]	
Median (IQR)	10 (9–20)	10 (5–18)	1 (−17 to 15)
Range	3–37	5–54	
Best case (missing answers = 0)			
		n = 7	
Median (IQR)		11 (5–19)	0 (−15 to 11)
Range		5–54	
Worst case (missing answers = 4)			
		n = 7	
Median (IQR)		11 (5–43)	−1 (−33 to 10)
Range		5–54	

IQR, interquartile range.
a One patient had incomplete daytime symptoms domain so was excluded from the daytime symptoms and overall total summaries.

TABLE 31 Respiratory questionnaire scores for chest symptoms (number responding positively)

Domain	Questionnaire time point					
	6 months		12 months		18 months	
	AI (*n* = 7)	Exp (*n* = 7)	AI (*n* = 7)	Exp (*n* = 6)	AI (*n* = 6)	Exp (*n* = 5)
Inhalers taken as treatment for chest symptoms,[a] *n* (%)	2/7 (28.6)	3/7 (42.9)	3/7 (42.9)	3/6 (50.0)	2/6 (33.3)	2/5 (40.0)
Medicines taken as treatment for chest symptoms,[b] *n* (%)	4/7 (57.1)	3/7 (42.9)	2/7 (28.6)	1/6 (16.7)	2/6 (33.3)	2/5 (40.0)
Child had visited or had a visit from a general practitioner for chest problems, *n* (%)	5/7 (71.4)	3/7 (50.0)	5/7 (71.4)	2/6 (33.3)	3/6 (50.0)	2/5 (40.0)
Child had attended hospital clinics for chest problems, *n* (%)	2/7 (28.6)	0/7 (0.0)	1/7 (13.3)	3/6 (50.0)	2/6 (33.3)	1/5 (20.0)
Has child been diagnosed with asthma by a doctor, *n* (%)	1/7 (14.3)	1/7 (14.3)	1/7 (14.3)	0/6 (0.0)	1/6 (16.7)	0/5 (0.0)

a All inhalers taken as treatment for chest symptoms were inhalers for asthma.
b All medicines given as treatment for chest symptoms were taken for up to 1 week at any one time.

Lung function tests

The purpose of the lung function tests was primarily to determine whether there was evidence of small lungs in either patient arm. The individual lung function test results are shown in *Table 32*. Data presented in *Table 32* are for means of at least three recorded values, unless otherwise indicated.

Age categories:

- Age < 2 years CGA: infant-style testing, studied supine while sleeping.
- Age ≥ 2 years CGA: preschool testing, requiring the child to breathe or blow through a mouthpiece; getting good results is dependent on child co-operation.

One child in each arm had a *z*-value below −2.00 for FVC and the two values were −2.01 (number 5) and −2.58 (number 11). Two children in each arm had evidence of reduced maximum expiratory flow, whether shown by V_{max}FRC or FEV_1 (study numbers 30, 35, 22, 5). The child in study number 5 had initial tests that indicated a reduced FEV_1 and an FVC just below the lower limit of prediction. His tests were repeated following bronchodilator and both indices improved to well within normal values. The finding of reduction in maximum expiratory flow in some children in this study is consistent with other reports of lung function in children born preterm.[17]

There was one child in the AI arm and four children in the Exp arm that were lost to follow-up or were not able to provide test results. These children may have experienced reduced lung capacity; hence, for sensitivity will be included with those children showing a *z*-value below −2.0.

The difference in medians in *z*-values for infant lung function tests could not be performed, as there was too little data to do so. However, when sensitivity analyses were performed for missing data, there was no difference between arms for any of the functions (*Table 33*).

Analysis of lung function *z*-values was performed using complete-case analysis, i.e. only surviving patients who had lung function assessments were analysed. Sensitivity analysis neonatal (maximum) is defined as the sensitivity analysis that assigned the neonatal deaths the largest observed positive *z*-value for each test.

TABLE 32 Individual infant lung function test results

Study number	Treatment	Reason tests not performed	Age at tests (years)	Age category	FRC_P (l)	FRC_P predicted (l)	FRC_P *z*-value	FVC (l)	FVC predicted (l)
8	AI	–	3.50	Preschool	0.88	–	–	0.98	0.83
10	AI	–	3.08	Preschool	1.07	–	–	0.85	0.73
11	AI	–	2.89	Preschool	0.83[a]	–	–	0.34	0.61
16	AI	Lost to long-term follow-up	–	–		–	–	–	–
20	AI	–	4.18	Preschool		–	–	0.89	1.00
30	AI	–	1.42	Infant	0.25	0.26	−0.18	–	–
35	AI	–	1.06	Infant	0.18	0.27	−1.16	–	–
45	AI	–	2.26	Preschool		–	–	0.68	0.62
55	AI	–	2.44	Preschool		–	–	–	–
5	Exp	–	3.95	Preschool	1.37[a]	–	–	0.61	0.90

FVC *z*-value	FEV_1 (l)	FEV_1 predicted (l)	FEV_1 *z*-value	V_{max} FRC (ml/s)	V_{max}FRC predicted (ml/s)	V_{max} FRC *z*-value	Comment on test	Comment on result
1.08	0.83	0.81	0.16	–	–	–	Plethysmography done with child sitting on mother's knee. All measurements somewhat variable, as expected in a young child, but child did very well	Spirometry indicates normal forced expiratory volumes and the shape of the flow-volume curve was normal
0.95	0.76	0.71	0.41	–	–	–	Child did very well	Flow-volume loop showed no evidence of gross abnormality
–2.58	–	–	–	–	–	–	Child did well for his age. FRC_p is based on a single value so should be viewed with extreme caution	Predicted values are scarce for small preschool children so measured values should be interpreted with caution
–	–	–	–	–	–	–	–	–
–0.69	0.84	0.96	–0.80				Excellent co-operation	Normal spirometry
–	–	–	–	117.00	315.00	–2.31	Very good. Settled well. No problems	Resting lung volume is normal but maximum expiratory flow is somewhat reduced
–	–	–	–	64.00	253.00	–2.63	Straightforward, no problems. Child noted to be a little snuffly, either was just starting a cold or was teething	
0.61	0.67	0.60	0.68				Did well for his age	Normal spirometry
–	–	–	–	–	–	–	Not really old enough to have the co-operation for spirometry	Co-operation not good enough for results to be reliable. Cautious report sent to medical staff caring for him
–2.01	0.44	0.87	–3.20	–	–	–	Data shown are baseline. Child responded to bronchodilator, so that FEV_1 increased to 0.64 l (*z*-value –1.70) and FVC increased to 0.87 (*z*-value –0.22)	

continued

TABLE 32 Individual infant lung function test results (*continued*)

Study number	Treatment	Reason tests not performed	Age at tests (years)	Age category	FRC_P (l)	FRC_P predicted (l)	FRC_P *z*-value	FVC (l)	FVC predicted (l)
22	Exp	–	1.67	Infant	0.18	0.21	–0.49	–	–
25	Exp	–	1.02	Infant	0.18	0.22	–0.60	–	–
28	Exp	Lost to long-term follow-up	–	–	–	–	–	–	–
31	Exp	Lost to long-term follow-up	–	–	–	–	–	–	–
33	Exp	Lost to long-term follow-up	–	–	–	–	–	–	–
44	Exp		2.45	Preschool	–	–	–	0.71	0.65
58	Exp	Unable to assess owing to severe developmental delay	–	–	–	–	–	–	–

a Score based on a single recording as opposed to three recordings but single estimate not reliable. These are shown in the line listings but not included in the summary tables.

Reasons are given for those patients that did not have a lung function test visit in the 'Reason Tests Not Performed' column.

FVC *z*-value	FEV_1 (l)	FEV_1 predicted (l)	FEV_1 *z*-value	V_{max} FRC (ml/s)	V_{max}FRC predicted (ml/s)	V_{max} FRC *z*-value	Comment on test	Comment on result
–	–	–	–	74.00	158.00	–1.31	Uneventful. Child slept well. No problems, no alarms	All normal for body size
–	–	–	–	74.00	269.00	–2.86	Child had only a short sleep after sedation. Child woke up so was given a second dose of chloral hydrate, after which child slept well and measurements were completed without any problems. No desaturations or alarms	Resting lung volume is normal but maximum expiratory flow is somewhat reduced
–	–	–	–	–	–	–	–	–
–	–	–	–	–	–	–	–	–
–	–	–	–	–	–	–	–	–
0.54	–	–	–	–	–	–	Not really old enough to have the co-operation for spirometry	–
–	–	–	–	–	–	–	–	–

TABLE 33 Analysis of lung function *z*-values

	AI	Exp	Difference in medians (95% CI)
FRC_P			
Complete case (n_{AI} = 2, n_{exp} = 2)			
	n = 2	*n* = 2	N/A[a]
Median (IQR)	−0.67 (−1.16 to −0.18)	−0.54 (−0.60 to −0.49)	
Range	−1.16 to −0.18	−0.60 to −0.49	
Sensitivity analysis neonatal (maximum[b]) (n_{AI} = 16, n_{exp} = 11[c])			
	n = 16	*n* = 11[c]	
Median (IQR)	−0.18 (−0.18 to −0.18)	−0.18 (−0.18 to −0.18)	0 (0 to 0)
Range	−1.16 to −0.18	−0.60 to −0.18	
Sensitivity analysis neonatal (minimum) (n_{AI} = 16, n_{exp} = 11[c])			
	n = 16	*n* = 11[c]	
Median (IQR)	−1.16 (−1.16 to −1.16)	−1.16 (−1.16 to −1.16)	0 (0 to 0)
Range	−1.16 to −0.18	−1.16 to −0.49	
FVC			
Complete case (n_{AI} = 5, n_{exp} = 2)			
Median (IQR)	*n* = 5	*n* = 2	N/A[a]
Range	0.61 (−0.69 to 0.95)	−0.74 (−2.01 to 0.54)	0 (0 to 0)
	−2.58 to 1.08	−2.01 to 0.54	
Sensitivity analysis neonatal (maximum) (n_{AI} = 19, n_{exp} = 10)			
	n = 19	*n* = 10	
Median (IQR)	1.08 (1.08 to 1.08)	1.08 (1.08 to 1.08)	0 (0 to 0)
Range	−2.58 to 1.08	−2.01 to 1.08	
Sensitivity analysis neonatal (minimum) (n_{AI} = 19, n_{exp} = 10)			
	n = 19	*n* = 10	
Median (IQR)	−2.58 (−2.58 to −2.58)	−2.58 (−2.58 to −2.58)	
Range	−2.58 to 1.08	−2.58 to 0.54	
FEV_1			
Complete case (n_{AI} = 4, n_{exp} = 1)			
	n = 4	*n* = 1	N/A[a]
Median (IQR)	0.29 (−0.32 to 0.55)	−3.20	
Range	−0.80 to 0.68		
Sensitivity analysis neonatal (maximum) (n_{AI} = 18, n_{exp} = 9)			
Median (IQR)	*n* = 18	*n* = 9	
Range	0.68 (0.68 to 0.68)	0.68 (0.68 to 0.68)	0 (0 to 0)
	−0.80 to 0.68	−3.20 to 0.68	

TABLE 33 Analysis of lung function *z*-values (*continued*)

	AI	Exp	Difference in medians (95% CI)
Sensitivity analysis neonatal (minimum) ($n_{AI} = 18$, $n_{exp} = 9$)			
Median (IQR)	$n = 18$	$n = 9$	
Range	−3.20 (−3.20 to −3.20)	−3.20 (−3.20 to −3.20)	0 (0 to 0)
	−3.20 to 0.68	−3.20 to −3.20	
V*$_{max}$*FRC			
Complete case ($n_{AI} = 2$, $n_{exp} = 2$)			
	$n = 2$	$n = 2$	N/A[a]
Median (IQR)	−2.47 (−2.63 to −2.31)	−2.09 (−2.86 to −1.31)	
Range	−2.63 to −2.31	−2.86 to −1.31	
Sensitivity analysis neonatal (maximum[b]) ($n_{AI} = 16$, $n_{exp} = 11$[c])			
	$n = 16$	$n = 11$[c]	
	−1.31 (−1.31 to −1.31)	−1.31 (−1.31 to −1.31)	0 (0 to 0)
	−2.63 to −1.31	−2.86 to −1.31	
Sensitivity analysis neonatal (minimum) ($n_{AI} = 16$, $n_{exp} = 11$[c])			
	$n = 16$	$n = 11$[c]	
Median (IQR)	−2.86 (−2.86 to −2.86)	−2.86 (−2.86 to −2.86)	0 (0 to 0)
Range	−2.86 to −2.31	−2.86 to −1.31	

IQR, interquartile range.
a Too few data to be able to calculate difference in medians.
b There were no positive *z*-values for any of these patients so largest value available was imputed instead.
c Includes one patient in whom lung function tests were unable to be performed and assessed due to severe developmental delay as per SAP.

In addition, any patients in whom lung function tests could not be performed and assessed because of severe developmental delay were included in the infant analyses (FRC_P and $V_{max}FRC$) and handled the same way as the neonatal deaths, as per the SAP. Sensitivity analysis neonatal (minimum) is defined as the sensitivity analysis that assigned the neonatal deaths the smallest observed negative *z*-value for each test.

Neurodevelopment

The Bayley assessments were carried out between the ages of 2 years 3 months and 3 years 3 months. The assessments were performed at the home of the child by a trained nurse. At the protocol stage, a trained nurse was not identified, so this explains why Bayley assessment was delayed in some of the earlier children. Other delays were due to parents and trained nurse finding it difficult to agreee a convenient time to meet.

A sensitivity analysis was performed to account for the children in whom a Bayley assessment for either MDI, PDI or both was not possible owing to a significantly delayed performance. These are assigned a score of 50 (i.e. the worst possible score) for the score analysis and classified as 'significantly delayed performance' for the classification summary. The results are shown in *Table 34* (Sens. 1 is the sensitivity analysis including the imputations described).

Overall, both Bayley's scores were within the normal range in only 31% of surviving children (4 out of 13) (*Figure 5*). Three out of eight children (37.5%) in the AI arm had normal scores for both PDI and MDI,

TABLE 34 Bayley's assessment (plus sensitivity analysis)

	AI	Exp
MDI classification		
Complete case,[a] n *(%)*		
	n = 7	*n* = 4
Significantly delayed performance	1 (14.3)	1 (25.0)
Mildly delayed performance	1 (14.3)	2 (50.0)
Within normal limits	5 (71.4)	1 (25.0)
Accelerated performance	0 (0.0)	0 (0.0)
Sensitivity analysis including the imputations described, n *(%)*		
	n = 8	*n* = 5
Significantly delayed performance	2 (25.0)	2 (40.0)
Mildly delayed performance	1 (12.5)	2 (40.0)
Within normal limits	5 (62.5)	1 (20.0)
Accelerated performance	0 (0.0)	0 (0.0)
PDI classification		
Complete case, n *(%)*		
	n = 8	*n* = 3
Significantly delayed performance	1 (12.5)	0 (0.0)
Mildly delayed performance	4 (50.0)	1 (33.3)
Within normal limits	3 (37.5)	2 (66.7)
Accelerated performance	0 (0.0)	0 (0.0)
Sensitivity analysis including the imputations described, n *(%)*		
	n = 8	*n* = 5
Significantly delayed performance	1 (12.5)	2 (40.0)
Mildly delayed performance	4 (50.0)	1 (20.0)
Within normal limits	3 (37.5)	2 (40.0)
Accelerated performance	0 (0.0)	0 (0.0)

a Complete-case analysis: only surviving patients that have Bayley's data are analysed.

compared with 1 out of 5 in the Exp arm (20%). Only one child, overall, had both MDI and PDI assessed as severely delayed. This child was in the Exp arm and did not have a test result for either domain as the assessor was unable to perform the tests owing to significantly delayed performance; these results were assumed to be in the severely delayed category. The average deepest pool of amniotic fluid in this pregnancy was 1.4 cm. The amniotic membrane ruptured at 23 weeks and delivery was at 31 weeks' gestation. Three children in the AI arm (37.5%) and three in the Exp arm (60%) had significant delay in either PDI or MDI scores, including one child in the AI arm and two children in the Exp arm who did not have a test result as the assessor was unable to perform the tests owing to significantly delayed performance.

Complete-case analysis: only surviving patients who have Bayley's data are analysed

Sens. 1 is defined as sensitivity analysis that includes three additional patients in whom a Bayley's assessment for either MDI, PDI or both was unable to be carried out due to the children having a

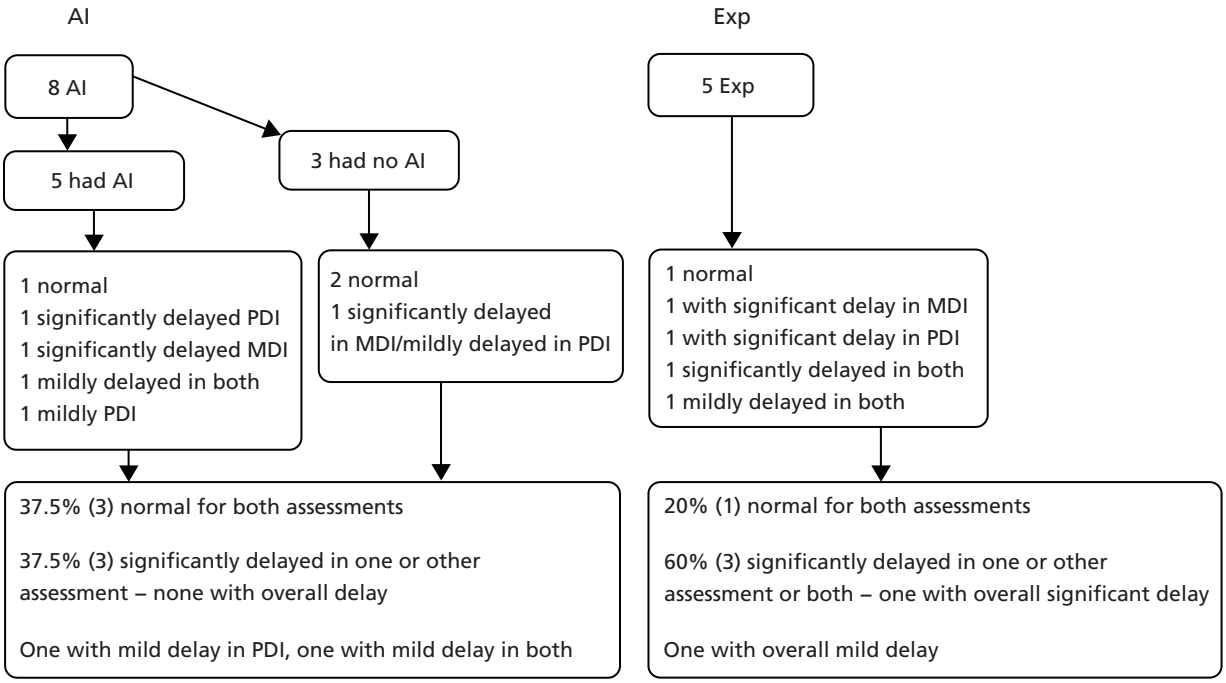

FIGURE 5 Neurodevelopmental outcome of followed-up survivors by study arm (includes children who were too delayed to be scored).

significantly delayed performance. These are assigned a score of 50 (i.e. the worst possible score) for the score analysis and classified as 'significantly delayed performance' for the classification summary.

The number of surviving children in each arm with normal MDI and PDI and cross-tabulation of all other Bayley's assessments is shown in *Table 35*.

TABLE 35 Cross-tabulation of MDI versus PDI by study arm

		PDI			
		Significantly delayed performance	Mildly delayed performance	Within normal limits	Unable to do due to significantly delayed performance
AI					
MDI	Significantly delayed performance	–	1	–	–
	Mildly delayed performance	–	1	–	–
	Within normal limits	1	1	3	–
	Unable to do due to significantly delayed performance	–	1	–	–
Exp					
MDI	Significantly delayed performance	–	–	1	–
	Mildly delayed performance	–	1	–	1
	Within normal limits	–		1	–
	Unable to do due to significantly delayed performance	–	–	–	1

Orthopaedic follow-up

Three babies had postural orthopaedic problems identified in the neonatal period; in two the problems resolved spontaneously and one surviving child required only referral for orthopaedic follow-up. This child was in the Exp arm. The child had bilateral contractures in the right knee and elbow but surgery was not required as all resolved by 9.5 months. This is patient number 2 in the third footnote of the neonatal morbidity outcomes (see *Table 19*). The numbers of survivors are too small to draw any conclusions, but the rate of orthopaedic deformity appears low.

Chapter 5 Exploratory summary analysis of the long-term outcome data

All pre-specified outcomes analysed as per the SAP (*Appendices 3* and *4*) have been presented in *Chapters 3* and *4*. The initial focus of this study was on short-term outcomes and, while these are clearly of interest, particularly because of their impact on the utilisation of health-care resources (e.g. neonatal intensive care unit), in this chapter we present additional, post-hoc analysis that focuses on a clinically most important outcome in this cohort – *a healthy survivor*. We have opted to do this to summarise the long-term outcome results from this pilot study in a clinically meaningful way. In the context of this study, being healthy is defined as being alive with the absence of serious respiratory and neurological problems at the end of a follow-up period (27–39 months). For the purpose of this post-hoc analysis we needed to define clinically meaningful definitions of respiratory and neurological disability.

1. Respiratory disability. Abnormal respiratory function has been defined as a *z*-value < –2.00 on any of the whole body plethysmography parameters (FRC, FVC), FEV_1 and V_{max}FRC. Although the respiratory questionnaires are validated, the authors acknowledge that more work, in terms of sensitivity/specificity analyses to define cut off points, is required. The results from the questionnaire are, therefore, not currently decisive enough to be used in the definition of respiratory disability in the long term.
2. Neurological disability. We defined major neurodevelopmental delay in any child with an MDI < 70 or a PDI < 70 or both MDI/PDI < 70. Mildly delayed performance was defined as a score of between 70 and 84 in any domain. Adopting this post-hoc definition of healthy survivors, and assuming that all babies lost to follow-up were unhealthy, there were 4 out of 56 (7.1%) healthy survivors in the whole cohort, 4 out of 28 (14.3%) in the AI arm and 0 out of 28 (0.0%) in the Exp arm (RR 9.0; 95% CI 0.51 to 159.70) (*Figure 6*).

One of the babies with an abnormal *z*-value also had a PDI score < 70. This baby is, therefore, included in the babies with significant disability.

The long-term outcomes by arm are shown in *Figure 7*. There were 4 out of 28 healthy survivors in the AI arm, compared with 0 out of 28 in the Exp arm (*Table 36*). The frequency of respiratory and neurological morbidity in each arm is shown in *Table 37*.

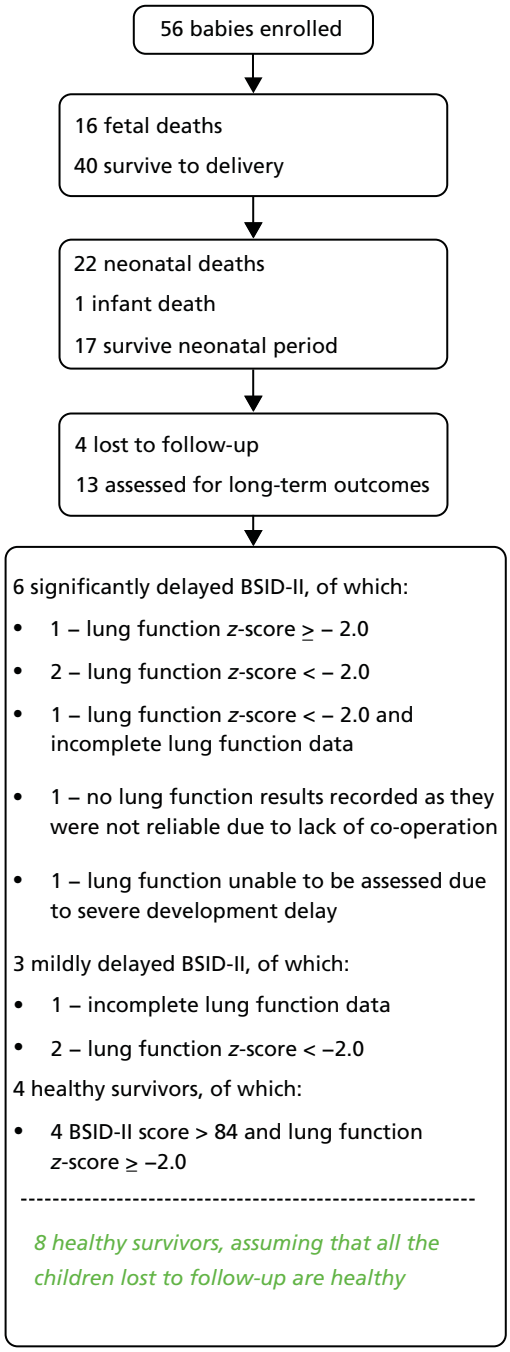

FIGURE 6 Long-term healthy survivors by cohort.

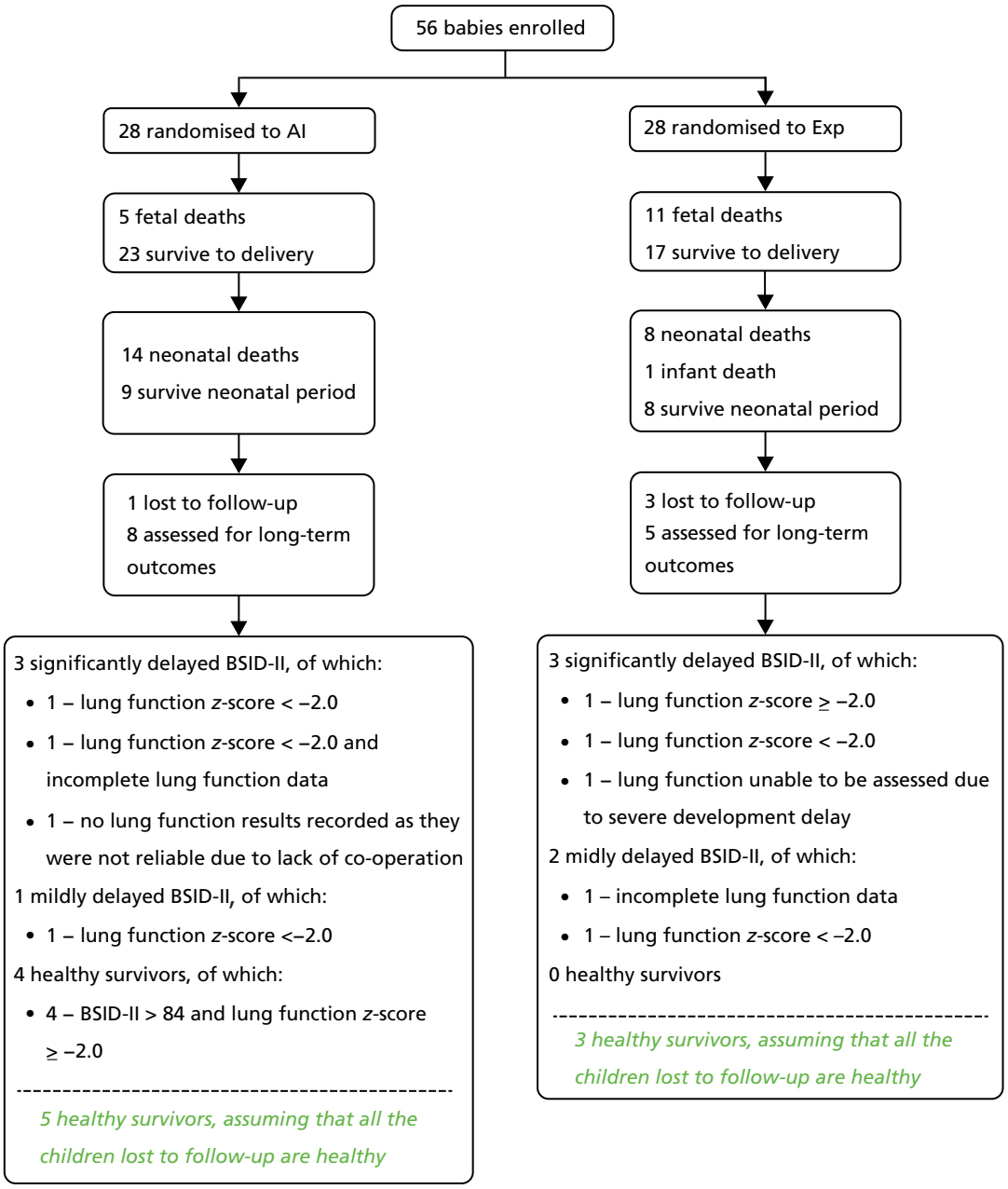

FIGURE 7 Long-term healthy survivors by arm.

TABLE 36 The frequency of healthy survivors in each arm

Analysis	AI	Exp	Relative risk (95% CI)
Observed (ITT)	4/28 (14.3%)	0/28 (0.0%)	9.0 (0.51 to 159.70)
If all lost to follow-up were healthy	5/28 (17.9%)	3/28 (10.7%)	1.27 (0.44 to 6.31)

TABLE 37 The frequency of severe morbidity in each arm

Analysis	AI	Exp	RR (95% CI)
Severe respiratory morbidity[a]			
Observed (ITT)	3[b]	2[b]	RR1:[c] 4.00 (0.48 to 33.58)
			RR2:[d] 1.71 (0.31 to 9.61)
If all lost to follow-up and those that did not have a test done had respiratory morbidity	5	7	
Severe neurological morbidity[e]			
Observed (ITT)	3	3	RR2:[d] 2.50 (0.53 to 11.82)
			RR2:[d] 2.14 (0.40 to 11.35)
If all lost to follow-up had severe neuromorbidity	4	6	

a Defined as abnormal infant lung function test *z*-value < –2.00 in any of the tests performed.
b Two children in the AI arm and one child in the Exp arm also had abnormal BSID-II.
c All deaths. Survivors with severe respiratory/neurological morbidity and survivors with missing data were included in the numerator with the denominator as all patients for each arm.
d All survivors with severe respiratory/neurological morbidity were included in the numerator with number of survivors with non-missing data as the denominator; however, this is not based on equally randomised groups.
e Defined as abnormal BSID-II (< 70 on MDI or PDI score).

Chapter 6 Discussion

Here we report the results of a pilot RCT designed to assess the effect on the pregnancy, maternal and perinatal outcomes of women with very early PPROM (16^{+0} to 24^{+0} weeks' gestation) treated with serial AI when compared with expectant and whether such a trial is feasible. The study was conducted because of increasing reports of this intervention, which had not been evaluated in an RCT. The intervention is very invasive and has the potential to increase maternal morbidity, although there were no reports of this in the observational studies in the literature. We were motivated to conduct this study to determine whether such a study was feasible, to inform and help design a definitive trial on the subject and also because NICE[18] concluded that more information from RCTs is required before AI can be considered routine therapy for very early PPROM.

This discussion summarises the key findings, compares the findings with the results of published studies, considers the strengths and limitations of the present study and the lessons learnt and summarises the clinical and research implications of the work.

Key findings

This pilot study demonstrates that, with appropriate funding, it is possible to recruit to such a study. During the study period, very early PPROM was a rare event, and, with no external funding, most of the recruitment relied on the main recruiting centre. NIHR funding had a significant impact on the enthusiasm of other large tertiary FMUs to recruit to the study. The key factor was the adoption on the NIHR portfolio, which allowed access to comprehensive local research network (CLRN) research staff that facilitated identification of potential participants and recruitment/consenting. They were also instrumental in improving completeness of follow-up. The HTA programme funding gave the pilot study more weight, attracted a large tertiary centre to the trial and allowed the other centres to maintain involvement in the study.

Seventy-five per cent of eligible women participated in the study; therefore, acceptance rate for the study was high. There were very few postrandomisation exclusions, and these were mainly due to fetal abnormalities that are difficult to detect on ultrasound when there is no residual amniotic fluid in the amniotic sac. Retention of participants throughout the study period was high. Long-term follow-up of the surviving infants was feasible, although the loss rate was around 38%, and this is an area that will require more input in a larger study.

The overall perinatal mortality rate was higher than expected, at 67.9%, and the proportion of healthy survivors was much lower than anticipated, 7%. We found no statistically significant difference in any of the outcomes between the two arms, although it must be noted that patient numbers were small and it is, therefore, not appropriate to draw too many conclusions from the statistical testing.

The assessment of long-term respiratory morbidity was performed using two modalities: respiratory questionnaires and infant lung function tests. The respiratory questionnaires, although validated, had cut-off points that were not defined enough to be used in the identification of long-term respiratory morbidity. Lung function tests had clearer defined cut-offs and were, therefore, found to be the most useful tests for long-term respiratory morbidity.

Overall, only 7.1% of babies [4/28 (14.3%) in the AI arm and 0/28 (0.0%) in the Exp arm] were known to be alive without respiratory or neurological disability at 2 years of age. The findings from this pilot study suggest that the clinically meaningful outcome of a healthy survivor (alive without defined respiratory or neurological disability at 2 years of age) should be the outcome on which to base a larger, and more definitive, study.

Comparison with other studies

The AMIPROM pilot included a very strict definition for very early PPROM i.e. rupture of amniotic membranes between 16^{+0} and 24^{+0} weeks of pregnancy. This is the first randomised study to use these inclusion criteria. Only one other randomised trial[19] which included pregnancies with rupture of amniotic membranes at < 27 weeks' gestation has been performed. In order to put our results in the wider context of other available evidence, we have performed a systematic review of published studies with data on singleton pregnancies with PPROM at $< 28^{+0}$ weeks' gestation, treated with serial non-continuous transabdominal AI. The full results will be published in a separate publication. In brief, we have searched MEDLINE from 1985 to date, using the medical subject heading terms AI, preterm premature rupture of amniotic membranes, rupture of amniotic membranes, preterm premature rupture of fetal amniotic membranes, rupture of fetal amniotic membranes, PROM. No language restrictions were employed. The results were pooled using StatsDirect Version 2.7.8 (StatsDirect Ltd, Cheshire, UK) and previously described methodology.[20] In the presence of significant heterogeneity we have used random effects to pool the results.

Data from seven eligible studies (including AMIPROM pilot) were analysed.[4,9,19,21–23] Our pilot suggests that perinatal mortality in infants treated with AI is likely to be higher than previously reported (*Figure 8*). This is most likely due to the inclusion of the clinically relevant group of pregnancies between 16^{+0} and 24^{+0} weeks' gestation in the AMIPROM study. Pregnancies with PPROM after 24 weeks' gestation would be expected to do better as the critical time for lung development and the need for adequate volumes of amniotic fluid is between 16^{+0} and 24^{+0} weeks' gestation.

The pooled respiratory morbidity in AMIPROM, when compared with the other studies, is not significantly different (*Figure 9*). Pooled neurodisability at any time as defined by authors is shown in *Figure 10*.

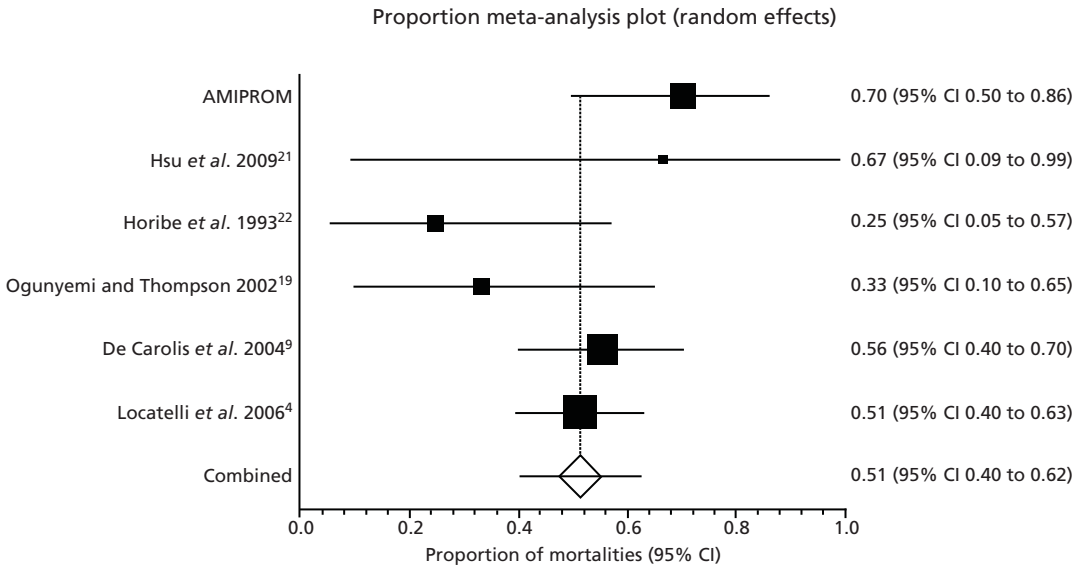

FIGURE 8 Pooled perinatal mortality in pregnancies treated with AI (AMIPROM compared with other studies), heterogeneity $I^2 = 46.2\%$.

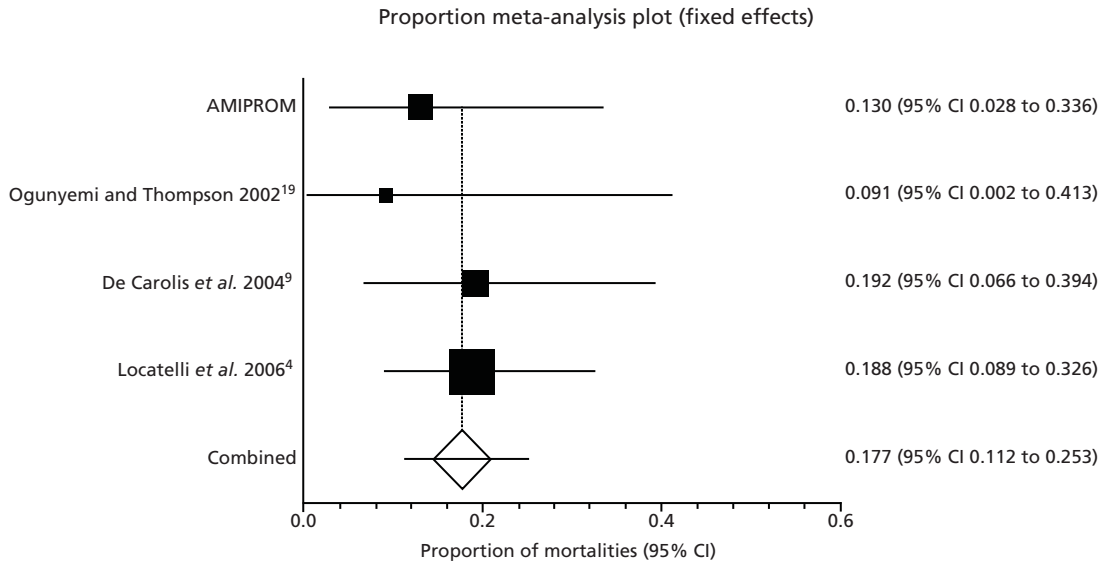

FIGURE 9 Pooled respiratory morbidity in pregnancies treated with AI (AMIPROM compared with other studies), heterogeneity $I^2 = 0\%$.

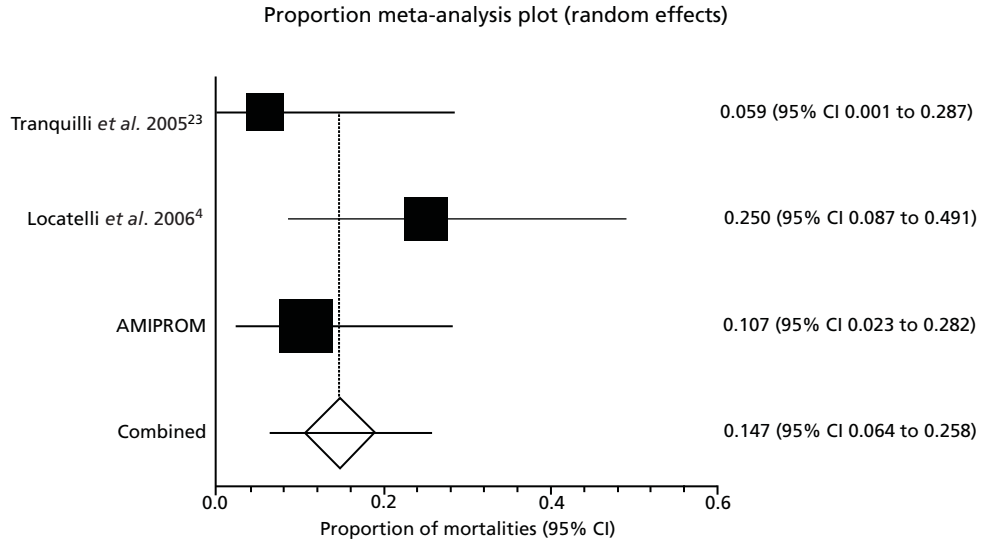

FIGURE 10 Pooled neurodisability at any age (as defined by authors) in pregnancies treated with AI (AMIPROM compared with other studies), heterogeneity $I^2 = 25.8\%$.

Strengths and limitations of current study

This is the first study to evaluate outcomes in PPROM pregnancies between 16^{+0} and 24^{+0} weeks' gestation. It is also the first study to evaluate long-term respiratory and neurodevelopmental outcomes in this group of babies at high risk of neonatal mortality and morbidity.

Data on post-mortems were not specifically collected and were not pre-specified in the SAP. This is a potential source of bias. A postmortem was carried out on only one of the neonatal deaths; in addition, a limited postmortem was carried out on one neoonatal death and one antenatal death. All these babies were normal. All fetal abnormalities detected antenatally and postnatally are accounted for either as postrandomisation exclusions or SAE (see *Tables 25* and *26*). The authors are sure, therefore, that any potential confounders to outcomes from undetected fetal abnormalities have been accounted for. Collecting data from post-mortem exminations is something to consider in a future study.

The limitations of this study are that, as a pilot, it does not have adequate power to evaluate the effectiveness and safety of serial AI. The lack of clear methods for assessment of asthma using respiratory questionnaires was identified. More work needs to be done in this area to reach a consensus on what constitute clinically significant respiratory morbidity in very young children. Even with this caveat, the study indicates that the overall chance of healthy survival at age two is small in this group of infants.

Lessons learnt about conduct of the study

- Traditionally, women with very early PPROM are not referred to tertiary FMUs for assessment. To maximise recruitment, we realised that all clinicians in local referring units had to be informed about the study. We found that this was best done by presenting at their local obstetrics and gynaecology study/audit days to get the largest audience of clinicians. This allowed for question and answer sessions and more detail around the study to be explored. We also found that the junior doctors rotating to different units were particularly useful in informing local clinicians about the study. NIHR funding contributed significantly towards the recruitment of one large FMU to the study and facilitated the recruitment of five additional participants to the study. In a future study, CLRN nurses and research staff would be crucial in improving recruitment. Their impact in this study came late (as the study was mainly funded for the long-term outcome phase) but we have survey evidence to suggest that more units would be interested in participating, if assured the support of the CLRN.
- Women were informed about the study as soon as the diagnosis of very early PPROM was made. They were then seen at the next FMU to discuss the study in detail. Clinical staff in all emergency attendance areas were informed about the study. The use of posters in the emergency areas was particularly useful as reminders.
- Randomisation occurred only if participants were still pregnant 10 days after rupture of amniotic membranes. This is crucial to avoid attrition from the high likelihood of miscarriage within the first week after rupture has occurred.
- Registration of the study on the ISRCTN and the NIHR website meant that clinicians out of the area and, in some instances, patients were aware of the study and approached the PI directly.
- Retention of participants from randomisation to delivery was excellent. The losses to follow-up tended to be those participants with social issues or those in the experimental arm who were managed in local units. As NIHR funding was granted towards the end of the recruitment phase of the study, it was not possible to assess the impact of funding on retention in long-term follow-up. In a larger study, funding for a research programme manager would be imperative to improve this area. NIHR funding would be required for this.
- Parts of the protocol, such as admission from 26 to 30 weeks' gestation and steroid administration at 26^{+0} weeks' gestation as routine, will need to be discussed in a larger study. This is not currently routine care, but was done to standardise care in both arms and to reduce bias in the analysis of outcomes.
- As this was a pilot study, all outcomes and results were collected. Longitudinal data on blood tests and ultrasound measurements were collected but no differences between arms were found. In a future study, it may be necessary only to compare the differences in these data at inclusion to the study.
- Data were also collected on respiratory questionnaires for long-term respiratory outcomes. In analysis, it became clear that this method although validated, requires more work in terms of sensitivity/specificity analyses to define cut off points. The results from the questionnaire are therefore not currently decisive enough to be used in the definition of respiratory disability in the long term. They will therefore not be used in a larger study.
- Bayley's scores were obtained in all surviving children. Since AMIPROM, other fetal medicine studies, such as the Trial of Umbilical and Foetal Flow in Europe,[24] have used questionnaire-based screening tools, reserving Bayley's assessment for those children for whom the questionnaire suggests it is required. The use of this methodology will significantly reduce the reliance on assessors and improve long-term follow-up in a future study.

Generalisability of the findings

The AMIPROM study recruited participants across four large tertiary referral units offering fetal medicine expertise. AI were performed in FMUs with specialists trained in invasive procedures. Expectant, which is the mainstay of management of this condition currently, was shown to be feasible in all hospital settings with some recourse to specialist outpatient care.

The findings from this study should generate enough reasons for equipoise to allow clinicians in all hospital settings to refer eligible women for participation in a larger, more definitive, study.

Chapter 7 Conclusion

Implications for health care

The findings from this pilot study do not suggest that clinicians should alter the current practice of expectant management rupture of amniotic membranes between 16^{+0} and 24^{+0} weeks' gestation.

Implications for research

A larger, definitive, study with full health economic analysis and patient perspective assessment is required to show whether AI can improve the healthy survivor rate (*Table 38*).

The pilot study allowed the assessment of factors critical for the success of future trials, namely:

- Timely identification of eligible women across the whole footprint (District General Hospitals and Tertiary FMUs) and clinical staff involvement. It is important that a network is set up to identify eligible women in local areas.
- NIHR support is critical to improving recruitment and retention and to allowing units to access the infrastructure of the CLRN.
- Publication of the study protocol on the ISRCTN allows access to lay personnel as well as health professionals.
- Counselling by specialists is the key to prevent interventions that are not evidence-based, to avoid misinformation and to allow time to consider the full impact of the condition and the study.
- The timing and eligibility criteria for randomisation are important to avoid high loss rate from the study.
- The study population and the comparisons were feasible and adequate.
- Long-term respiratory outcomes need to be based on infant lung function tests alone.

To explore a definitive study, indicative samples size calculations were performed based on the assumption that healthy survival rate in the definitive study would range between 0.1% and 15.0%, in keeping with our pilot data and other similar cohorts.

The feasibility of the definitive study of this magnitude has been discussed at the RCOG British Maternal Fetal Medicine Society Fetal Medicine Clinical Scientific Group in which considerable interest has been expressed by 12 FMU centres nationally. Our pilot suggests that even with full NIHR support, the definitive study would have to include international centres in other to be achieve even the minimum sample size in a reasonable time frame (2–3 years).

TABLE 38 Sample size of the definitive trial designed to have adequate power to detect 15% absolute difference in the primary outcome (alpha 0.05; power 80%)

Anticipated incidence of healthy outcome in Exp arm	Sample size per arm	Total sample size allowing for 10% loss to follow-up
0.01	58	128
0.02	65	144
0.03	71	158
0.04	76	168
0.05	82	182
0.06	88	194
0.07	94	208
0.08	99	218
0.09	105	232
0.10	110	242

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Trial Steering Committee chairperson Professor Jim Thornton.

ISDMC chairpersons Professor Kate Costeloe, until 2009, and Professor Andrew Shennan, from 2009.

Liverpool Women's NHS Foundation Trust Research and Development Department for sponsoring the study and support throughout the trial.

Contributions of authors

Devender Roberts formulated the research idea, designed the study, randomised to the study, performed the intervention, trial management, conducted the study, analysed the data and prepared the HTA report.

Sarah Vause, **William Martin** and **Pauline Green** were PIs in their centres, randomised participants to the study, performed the intervention and contributed to the final version of the HTA report.

Stephen Walkinshaw and **Leanne Bricker** assisted with initial study design, randomised participants to the study, performed the intervention and contributed to the final version of the HTA report.

Caroline Beardsmore advised on, performed and analysed infant lung function tests and contributed to the final version of the HTA report.

Ben NJ Shaw advised on neonatal outcome data and contributed to the final version of the HTA report.

Andrew McKay, **Gaynor Skotny** and **Paula Williamson** advised on statistical performance of the study, collated and analysed the data and contributed to the final version of the HTA report.

Zarko Alfirevic conducted trial management, assisted with initial study design, they randomised participants to the study, performed the intervention and is main co-author of the final version of the HTA report.

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Appendix 1 AMIPROM trial protocol

AMIPROM: Version 5 December 2008

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

ISRCTN – 8192589

CTA exempt
MREC ref – 01/8/075

HTA Project 07/39/01

AMIPROM: A pilot study

AMNIOINFUSION IN PRETERM PREMATURE RUPTURE OF MEMBRANES

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HTA Project 07/39/01

BACKGROUND

Premature rupture of membranes (PROM) is one of the major causes of perinatal mortality and morbidity because it is the cause of preterm delivery in 30% of cases.[1,2] Fetal survival is even more compromised when the membranes rupture early in the second trimester (very early PROM).

The management of cases with very early PROM has changed over the years. Traditionally, termination of pregnancy was offered for these women because of the presumed risk of maternal sepsis and very poor fetal outcome. Expectant management has, however, been shown to be relatively safe for mothers over the past few years and results in the survival of a small proportion of infants. It is the current mainstay of management in very early PROM.

Underdevelopment of fetal lungs (pulmonary hypoplasia), a complication of prolonged PROM is a major cause of death in these babies. The other major cause of death or damage is premature birth. The perinatal mortality rate in very early PROM can be as high as 54% [3] and the incidence incidence of pulmonary hypoplasia ranges from 5% to 13%.[3] Recent papers have suggested that oligohydramnios is the most important predictor of perinatal mortality in very early PROM and that adequate residual amniotic fluid plays a critical role in determining the prevalence of pulmonary hypoplasia.[4,5] As a result of this, amnioinfusion is being used to restore the amniotic fluid volume in pregnancies complicated by very early PROM and this has been shown to significantly improve the perinatal outcome.[6] Locatelli et al found, that women with persistent oligohydramnios after amnioinfusion had a significantly shorter interval to delivery, lower neonatal survival(20%),higher rates of pulmonary hypoplasia (62%),and abnormal neurological outcomes(60%) than women in whom amnioinfusion was successful (all $p<0.01$).[7] There is, however, not enough evidence available from randomised controlled trials comparing expectant management of very early PROM with amnioinfusion. These studies are limited by the absence of data for outcomes in pregnancies with very early PROM not treated by amnioinfusion. Moreover, amnioinfusion is an invasive intervention, and although anecdotally these studies suggest that it carries minimal risk to the mother and fetus[7], this needs to be assessed by prospective studies. More information is required from randomised controlled trials before amnioinfusion can be considered routine therapy for such pregnancies.

STUDY DESIGN

A randomised controlled trial

AIM

- To compare the neonatal, maternal and pregnancy outcomes in very early PROM managed expectantly with those managed with serial amnioinfusions.

PRIMARY OUTCOME

This is a pilot study, therefore all outcomes will be reported including:

-fetal and neonatal death,

-neonatal morbidity,

-long term respiratory morbidity (assessed by questionnaire on respiratory symptoms at 6, 12 and 18 months corrected age and lung function tests)

-long term developmental outcomes (assessed by cerebral palsy, developmental delay at 2 years age, corrected for prematurity, using Bayley's score)

-maternal morbidity

-maternal death

-pregnancy outcomes

DEFINITIONS

- **Very early PROM:** Spontaneous rupture of membranes after 16 weeks gestation and prior to 24 weeks gestation
- **Respiratory morbidity:** requiring supplemental oxygen at day 28 post delivery.
- **Pulmonary hypoplasia:** In survivors, this will be assessed by means of formal infant lung function tests at 12 months age, corrected for prematurity (*ref: Beardsmore et al, 1994, 1996)*
- **Chorioamnionitis:** temperature $\geq 37.5^{O}C$ and/or foul smelling amniotic fluid/ tender irritable uterus/ WCC $\geq$20,000/ CRP$\geq$35 or histological evidence of chorioamnionitis. UTI needs to be excluded.
- **Maternal death:** any maternal death
- **Neonatal sepsis:** culture positive infection
- **Long term respiratory morbidity:** questionnaire assessed respiratory symptoms (*ref: Shaw et al, 2001*) at 6, 12 and 18 months age, corrected for prematurity.
- **Long term neurological problems:** cerebral palsy, developmental delay at 2 years age, corrected for prematurity. (Griffith's/Bayley's score)
- **Oligohydramnios on ultrasound scan:** Amniotic fluid index

≤ 5cms or single deepest pocket < 2cms (*ref Magann et al, AmJOG 182(6):1581-8,2000)*

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.

Multicentre Research Ethics Committee approval was obtained in February 2002.

The trial is now an HTA funded pilot study. The sample size will therefore be the number recruited at the end of the specified recruitment period. The funders suggested that smaller differences in substantive outcomes (rather than composite) are of interest and that a much larger 'definitive' study should be considered to determine effectiveness (or lack of it) with much greater precision. The sample size calculations are therefore only indicative and will be treated as such by the Data Monitoring Committee

ELIGIBILITY CRITERIA

- All women with very early PROM who are booked at recruiting centre.
- 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

- 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

EXCLUSION CRITERIA

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

SCIENTIFIC RATIONALE FOR STUDY

Rationale for amnioinfusion:

Oligohydramnios is associated with a shorter interval from preterm premature rupture of membranes to delivery and this therefore has a significant effect on perinatal mortality.[8] Oligohydramnios is also the single most important independent predictor of pulmonary hypoplasia.[4] Pulmonary hypoplasia carries a significant risk of perinatal mortality and therefore oligohydramnios appears to be a causative factor in both outcomes. It is also said to be associated with a higher risk of chorioamnionitis and neonatal infection. [5]

Adequate amniotic fluid volume on the other hand, is associated with better outcomes in pregnancies affected by very early PROM. Locatelli et al, found that pregnancies with a median residual amniotic fluid pocket persistently less than 2cms were at highest risk of poor perinatal and long term neurological. Pregnancies with a pocket greater than 2cms, after amnioinfusion or spontaneously, had significantly better perinatal outcome (73-92%) and lower pulmonary hypoplasia rates.[7] Other authors corroborate this finding. [9,10] Amnioinfusion has also been found to be a useful tool for prophylactic therapy of pulmonary hypoplasia and neonatal respiratory distress syndrome in selected cases of oligohydramnios associated with intrauterine growth retardation.[11]

To date, there have only been observational comparative studies into amnioinfusion in very early preterm premature rupture of membranes. One randomised controlled trial has been performed, but this trial only included women who ruptured their membranes after 24 weeks of pregnancy and the numbers included in the study were small (17 in each arm). This is not the group that the proposed research will be examining as the risks for adverse perinatal outcome are much higher when the membranes rupture between 16-24 weeks of pregnancy.

A comparative study, by Vergani et al, 2004, compared women with successful amnioinfusion and those with persistent oligihydramnios after amnioinfusion at less than 26 weeks. They found a 50% improvement in pulmonary hypoplasia, neonatal survival and abnormal neurological outcome in survivors. This study suffers from lack of data in women who did not have amnioinfusion, which is the default management in most units. This group first published results of their observational data in 2001. Our methodology is based on theirs.

The results from these studies would suggest that the restoration of amniotic fluid after amnioinfusion results in a much better outcome than if oligohydramnios persists. Serial amnioinfusion is recommended, even in those pregnancies where fluid is not retained at first amnioinfusion, because it can be retained at subsequent procedures.

Two other comparative studies (De Carolis 2004, Ogunyemi 2002) in women with premature rupture of membranes before 27 weeks of pregnancy, failed to show any significant difference in pulmonary hypoplasia rates or neonatal mortality when amnioinfusion was compared to expectant management. The case selection in these trials is not random and therefore it is difficult to use the information from these trials in routine practice. A further, very small UK trial of 19 women by Tan et al, 2003, suffers from a large attrition rate secondary to termination of pregnancy.
NICE guidance after review of existing literature suggests that 'current evidence on the safety and efficacy of therapeutic amnioinfusion does not appear adequate for it to be used without special arrangements for consent and for audit and research. Clinicians are encouraged to enter patients into well designed randomised controlled trials comparing therapeutic amnioinfusion with no intervention'. NICE may review the procedure upon publication of further evidence. This trial will aim to provide that evidence.

Rationale for infant lung function tests:

Pulmonary hypoplasia is extremely difficult to diagnose antenatally or for that matter, postnatally. Ultrasound indicators of pulmonary hypoplasia such as, thoracic circumference, thoracic/abdominal circumference ratio and fetal lung length have been described, but the correlation with outcome is not consistently good. This information will however, be collected for this study. Pathological criteria such as lung/body ratio less than 0.08 or abnormally low alveolar counts adjusted for gestational age are used.[7] In this study, pathological criteria will not be used because death before discharge is a primary outcome. We are interested in the prevalence of pulmonary hypoplasia in the survivors and some formal test for assessing this is necessary. Although radiological criteria such as small, well-aerated lung fields with elevated diaphragms and a bell-shaped chest can be used, these are subjective assessments. Beardsmore et al, have studied respiratory function in infants following repair of oesophageal atresia and in children with cystic fibrosis from infancy to school age.[12,13] They use infant respiratory function tests, which can be adjusted for the clinical condition being studied.[14] These tests provide an objective measurement of infant lung function and are therefore currently the best method of assessing long term respiratory function. Less serious respiratory morbidity will be assessed by means of a validated questionnaire described in the methods.

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RANDOMISATION

Liverpool Clinical Trials Unit, Royal Liverpool and Broadgreen University Hospitals drew up the telephone randomisation list. Telephone randomisation will be used. Randomisation is stratified by gestational age.

DATA MONITORING

In view of the small number of cases to be studied in order to half the primary outcome, an interim analysis will not be performed.

A Trial Steering Committee (TSC) based on MRC recommendation for conduct of clinical trials has been set up. A Data Monitoring Committee (DMC) has been set up. The DMC will be independent of the applicants and of the TSC, while reporting to the TSC and, via the TSC, to the HTA programme. No overseas members are proposed.

RESEARCH GOVERNANCE

The trial is sponsored by The Liverpool Women's Hospital NHS Foundation Trust R&D Dept. The trial protocol is published on the North West Clinical Trials network website. www.rwctognetwork.org.uk

The trial has been adopted by the UKCRN.

Each trial centre will report the following serious untoward adverse events to the Steering Committee and the sponsor:

- Fetal injury caused by the procedure
- Fetal death caused by the procedure
- Maternal sepsis requiring HDU/ITU admission
- Maternal death

SAEs will be reported using the standard SAE/AE report form.

STATISTICAL ANALYSIS

Dichotomous data will be analysed as relative risks with 95% confidence intervals. Logistic regression will be used to correct for confounding factors such as gestational age at rupture of membranes and at delivery. Continuous data will be analysed as weighted mean difference with 95% confidence intervals. Statistical analysis and trial support had been requested from MCRN Clinical Trials Unit, Institute of Child Health, Royal Liverpool Children's Hospital, Liverpool, L12 2AP.

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TRIAL PROCEDURES

On admission: Speculum examination and HVS
Check temperature
FBC and CRP
Inform AMIPROM team
Good documentation of clinical findings (tender uterus, any foul smelling discharge)

First fetal-medicine consultation:

- Ultrasound confirmation of clinical findings
- Discussion re: prognosis of very early PROM
- Discussion regarding study and routine management
- Detailed information leaflet is given
- Treat with oral Erythromycin for 10 days
- Review 5-10 days later

Second fetal medicine consultation:

If woman decides against taking part in the study, default management will be conservative management. An initial amnioinfusion may need to be performed to confirm normal fetal anatomy

If patient agrees to take part in the study

- Obtain informed consent
- Fill maternal demographics form
- Fill randomisation form
- Telephone randomisation to either amnioinfusion arm or conservative management using separate randomisation sheet.
- In-patient or out-patient management following procedure according to discretion of attending physician
- Weekly FBC and CRP checks
- Watch for any signs of chorioamnionitis

INTERVENTIONS

Expectant management group

FIRST VISIT

- Following randomisation to expectant management, check HVS results and antibiotics have been given if culture positive
- Ultrasound examination to exclude fetal anomaly
- Measure amniotic fluid (deepest pocket)
- Fill data sheet 1: expectant management arm

SUBSEQUENT VISITS

- Weekly follow up visits at recruiting/referring hospital
- Fill data sheet 2.

Amnioinfusion group

FIRST VISIT

- Following randomisation to amnioinfusion, check HVS results and antibiotics have been given if culture positive
- Ultrasound examination to exclude fetal anomaly
- Measure amniotic fluid (deepest pocket)
- If deepest pocket ≥ 2cms, no amnioinfusion
- If deepest pocket < 2cms, perform amnioinfusion (10mls/week of gestation age, Hartmanns/Saline, see method for amnioinfusion – Appendix 1.)
- Ultrasound assessment of fetus following amnioinfusion to assess fetal heart, further anatomy and amniotic fluid
- Fill data sheet 1.

SUBSEQUENT VISITS

- 1st subsequent visit for all cases should be 3-4 days later
- No amnioinfusion if pocket is ≥2 cm
- Repeat amnioinfusion if pocket < 2 cm
- Serial weekly amnioinfusions are carried on if amniotic fluid pocket is < 2 cm until 34 weeks gestation
- Fill data sheet 2.

STEROID ADMINISTRATION

- Single course of betamethasone 12mg, 12 hours apart (24 hours apart if given as outpatient) at 25-26 weeks gestation
- Further doses of steroids can be given at the discretion of the attending physician

DELIVERY

- Induction of labour at 37 weeks gestation unless there is an obstetric indication for earlier delivery or delivery by Caesarean section (elective or emergency).
- Fill data sheet no. 3. Complete and return data sheet no. 3 to principal investigator when woman discharged from hospital or in the event of transfer to ITU/another hospital.
- See appendix 2 for neonatal data sheets.

Appendix 1.

METHOD FOR AMNIOINFUSION

Equipment required

Sterile abdominal tap pack as usually used in each recruiting unit for sterile invasive procedures

5ml syringe	1
20 gauge needle for injection	1
1% Lignocaine	5mls
20 gauge needle with trocar (outer sleeve 20 gauge)	1
Three way tap	1
50 ml syringe with screw top	1
Connection tubing for infusion	1
Hartmann's solution	500mls

Procedure

The procedure will be performed under lignocaine local anaesthesia, according to the protocol for sterile invasive procedure in each recruiting unit.

Prior to commencing the procedure, attach the three-way tap to the tubing of infusion and attach the tubing to the bag of 500mls Hartmann's solution. Run the Hartmann's through avoiding air bubbles. The 50 ml syringe can be attached to the side port of the three-way tap leaving one port free to be attached to the needle once it is inserted.

Use a size 18Ch needle with trocar for the procedure. Once the needle has been introduced and is found to be clear of fetal parts and umbilical cord, attach the third port of the three-way tap to the needle. A test dose of 10 mls Hartmann's can be introduced under ultrasound visualisation.

Once sure that satisfactory amnioinfusion can be performed, draw up 50mls of Hartmann's at a time and introduce into uterine cavity under ultrasound control to a maximum of 10mls/week gestational age[7]. The Hartmann's solution should be at room temperature.

Withdraw the needle under ultrasound control once the correct amount of fluid has been inserted. Complete ultrasound examination and measurements required for the study.

Appendix 2.

NEONATAL FOLLOW UP

- Fill immediate delivery data in data sheet 4 at delivery and attach form to the baby's case sheet.
- If admitted to neonatal intensive care unit, fill remaining parts of data sheet 4.
- Complete and return data sheet 4 to principal investigator when the baby is discharged or in the event of neonatal death.
- The investigators will fill in data sheet 5 once long term follow up has been undertaken.
- Long term assessment of neurological outcome: An appointment will be sent to all surviving children at postnatal age 2 to attend for a Griffith's/Bayley's assessment of development
- Long term follow up for respiratory problems:
    - Questionnaires will be sent out to parents of surviving babies at 6, 12 and 18 months postnatal age.
    - Formal respiratory function tests on surviving infants will be performed. Parents will be provided with information sheets about the infant lung function tests when their child approaches one year of age. As some time will have elapsed and the tests necessitate a visit to Leicester, separate information sheets and consent forms have been provided for this part of the study.
- Long term follow up for those babies with postural deformities: Orthopaedic surgeons will be contacted for information on surviving babies referred for surgery.

AMIPROM: Version 5 December 2008

DATA SHEET 1: amnioinfusion arm

Maternal demographics : Name

Age

Unit No

Addressograph label

Parity .....

HVS .....

WCC .....

CRP .....

Temperature .....

Tender irritable uterus .....

Foul smelling discharge .....

Gestation at PPROM ..... weeks

Gestation at 1st amnioinfusion ..... weeks

Fluid instilled	Pocket before amnioinfusion	Pocket after amnioinfusion

Thoracic circumference .....

Abdominal circumference .....

Lung length .....

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AMIPROM: Version 5 December 2008

DATA SHEET 1: expectant management arm

Maternal demographics : Name

Age

Addressograph label

Unit No

Mother's GP

Parity .....

HVS .....

WCC .....

CRP .....

Temperature .....

Tender irritable uterus .....

Foul smelling discharge .....

Gestation at PPROM ..... weeks

Gestation at 1st visit ..... weeks

Amniotic fluid pocket at 1st visit .....

Thoracic circumference at 1st visit .....

Abdominal circumference at 1st visit .....

Lung length at 1st visit .....

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DATA SHEET 2.

Addressograph label

Subsequent Visits (scan examinations)

Visit No.	Gestation	Amnioinfusion (Y/N)	Fluid instilled	Pocket before	Pocket after	Thoracic circumference	Lung length	Abdominal circumference

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DOI: 10.3310/hta18210

AMIPROM: Version 5 December 2008

DATA SHEET 3: maternal outcome

Mother's addressograph label

Maternal

Gestational age at delivery	…… weeks
Onset of labour	spontaneous/ induced
Mode of Delivery	Normal/ Instrumental/ Emergency LSCS/Elective LSCS
No. of doses of steroids	.....
Dates of steroid administration	.....
Abruptio placenta	yes/no
Antepartum haemorrhage	yes/no
Chorioamnionitis	yes/no
Required antibioitics antenatally?	yes/no
If yes, name antibiotic and duration of treatment	.....
Required antibiotics postnatally?	yes/no
If yes, name antibiotic and duration of treatment	.....
Serious maternal sepsis requiring ITU/HDU admission	yes/no
If yes, state number of days in ITU/HDU	.....
Maternal death	yes/no
If yes, state cause of death	.....

(see reverse of sheet for results of maternal investigations)

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Maternal investigations

Date	Gestation	Haemoglobin g/dl	White cell count x10^9/ml	Platelet count	HVS	Tender uterus	CRP	Temperature

DOI: 10.3310/hta18210

AMIPROM: Version 5 December 2008

DATA SHEET 4: neonatal outcomes

Mother's addressograph label

Baby's name .....

Baby's date of birth .....

Gender Male Female

Address .....

.....

.....

Gestational age at delivery ..... weeks

Birth weight ..... kgs

Apgar at 1 minute…….. Apgar at 5 minutes……

Cord Ph …….. Base excess ……..

Lactate ……..

Booking hospital .....

Delivery hospital .....

Reason for delivery .....

Antenatal steroids (date) .....

Antepartum death .....

Neonatal death .....

Date of death .....

Culture positive sepsis .....

Date and site 1 .....

Date and site 2 .....

Date and site 3 .....

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Date and site 4 .....

Date and site 5 .....

Date and site 6 .....

Days IPPV .....

Days CPAP .....

Days HFOV .....

Pneumothorax (chest drain) .....

Home 0_2 .....

0_2 at day 28 .....

0_2 at week 36 .....

NEC (operated) .....

NEC (treated as such) .....

Treated seizures .....

Treated retinopathy .....

IVH grade (0 – 3) .....

PVL .....

Shunt .....

Orthopaedic deformities (fixed) Fixed Postural

Describe site and type of deformity

.....

.....

Referred to orthopaedic surgeons? Y N

If yes, surgery required? Y N

Describe site and type of surgery

.....

.....

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Discharge date .....

Discharge destination .....

Discharge address .....

.....

.....

.....

.....

.....

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AMIPROM: Version 5 December 2008

Data Sheet 4: Oxygen requirement

(maximum daily FiO_2 required for > 1 hour)

Day 1	.....	**Day 15**	.....
Day 2	.....	**Day 16**	.....
Day 3	.....	**Day 17**	.....
Day 4	.....	**Day 18**	.....
Day 5	.....	**Day 19**	.....
Day 6	.....	**Day 20**	.....
Day 7	.....	**Day 21**	.....
Day 8	.....	**Day 22**	.....
Day 9	.....	**Day 23**	.....
Day 10	.....	**Day 24**	.....
Day 11	.....	**Day 25**	.....
Day 12	.....	**Day 26**	.....
Day 13	.....	**Day 27**	.....
Day 14	.....	**Day 28**	.....

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AMIPROM: Version 5 December 2008

DATA SHEET 5: long term neonatal outcomes

Respiratory questionnaire @ 6 months age, corrected for prematurity
Performed Y N If no, reason why……

……..

Respiratory questionnaire @ 12 months age, corrected for prematurity
Performed Y N If no, reason why……

……..

Respiratory questionnaire @ 18 months age, corrected for prematurity
Performed Y N If no, reason why……

……..

Infant lung function tests
Performed Y N If no, reason why……

……..

Griffiths/Bayley's assessment
Performed Y N If no, reason why……

……..

Orthopaedic follow up results
Performed Y N If no, reason why……

……..

TO INVESTIGATORS:
Please **staple** completed results of the tests above to this sheet

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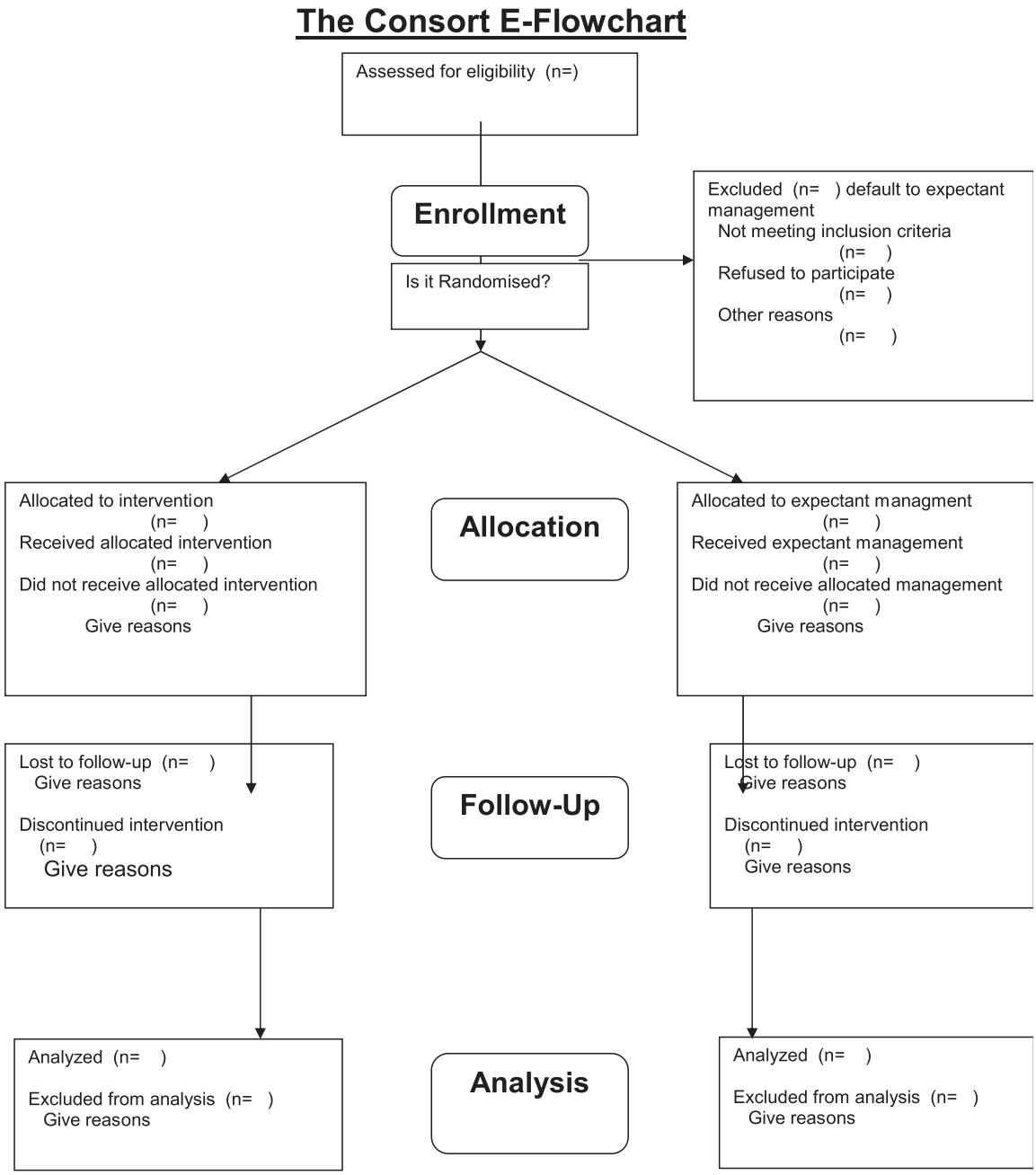
AMIPROM: Version 5 December 2008



HTA Project 07/39/01

Appendix 2 Method for amnioinfusion

Equipment required

Sterile abdominal tap pack as usually used in each recruiting unit for sterile invasive procedures

5ml syringe	1
20 gauge needle for injection	1
1% Lignocaine	5mls
20 gauge needle with trocar (outer sleeve 20 gauge)	1
Three way tap	1
50 ml syringe with screw top	1
Connection tubing for infusion	1
Hartmann's solution	500mls

Procedure

The procedure will be performed under lignocaine local anaesthesia, according to the protocol for sterile invasive procedure in each recruiting unit.

Prior to commencing the procedure, attach the three-way tap to the tubing of infusion and attach the tubing to the bag of 500mls Hartmann's solution. Run the Hartmann's through avoiding air bubbles. The 50 ml syringe can be attached to the side port of the three-way tap leaving one port free to be attached to the needle once it is inserted.

Use a size 18Ch needle with trocar for the procedure. Once the needle has been introduced and is found to be clear of fetal parts and umbilical cord, attach the third

port of the three-way tap to the needle. A test dose of 10 mls Hartmann's can be introduced under ultrasound visualisation.

Once sure that satisfactory amnioinfusion can be performed, draw up 50mls of Hartmann's at a time and introduce into uterine cavity under ultrasound control to a maximum of 10mls/week gestational age.[7] The Hartmann's solution should be at room temperature.

Withdraw the needle under ultrasound control once the correct amount of fluid has been inserted. Complete ultrasound examination and measurements required for the study.

Appendix 3 Statistical analysis plan for short-term outcomes

AMIPROM Short-Term Outcome Data SAP V1 04/01/2010

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

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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	Any of the specified entry criteria violated	Major	Violations of these criteria would result in a different prognosis
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			
Exclusion criteria			
Obstetric indication for immediate delivery (i.e. fetal bradycardia, abruption, cord prolapse, advanced labour > 5cm)	Any of the specified exclusion criteria violated	Major	Patient may not have time to receive any treatment
Multiple pregnancy		Major	Violation of this criterion would result in a different prognosis
Fetal abnormality		Major	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: _____

Appendix 4 Statistical analysis plan for long-term outcomes

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

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1. Introduction

This Statistical Analysis Plan (SAP) provides a detailed and comprehensive description of the main, pre-planned analyses of the long-term outcome data for 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, as outlined in the introduction section of the short-term outcome data SAP, is to analyse the long-term outcomes after the short-term data results were presented to the DMC on 15th November 2011. The DMC have agreed to unblinding of the short-term data and this has been documented. It has been agreed that the publication will include results of both the short-term and long-term outcomes.

This statistical analysis plan details the intended analyses and should be clear and detailed enough to be followed by any statistician. This will prevent the introduction of bias or data dredging.

These planned analyses will be performed by the trial statistician under the supervision of the lead 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 (SAS). The final analysis datasets, programs and outputs will be archived following good clinical practice guidelines (ICH E9). The testing and validation of the statistical analysis programs will be performed following the relevant Standard Operation Procedure.

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 planned to recruit 62 patients, 31 into each of the study arms. 58 participants had been recruited at the close of recruitment. Mothers randomised to receive the study treatment were treated with amnioinfusion and mothers randomised to the control treatment were treated with expectant management. Patients were randomised from a central randomisation list, held in the R&D office at Liverpool Women's Hospital, to one of the two treatment arms in a 1:1 ratio.

It was impossible to blind the treatments that the patients received due to the nature of the interventions so therefore AMIPROM was an open trial. However, due to the nature of the randomisation process allocation concealment prevented foreknowledge of the intervention they were due to receive and therefore preventing bias here. Analyses will be performed on unblinded data.

2.2 Study objectives

The aim of this analysis is to compare the long-term respiratory morbidity, orthopaedic and developmental outcomes in babies with 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. Long-term respiratory morbidity:

- Respiratory questionnaire taken at 6 months, 12 months and 18 months corrected gestational age.
- Lung function tests taken after 1 year corrected gestational age.

2. Long-term developmental outcomes:
   - Developmental delay at 2 years corrected gestational age using Bayley's score.
   - Cerebral palsy.
   - Orthopaedic follow-up.

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 with last follow-up on 26/07/2011.

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

Baseline characteristics of all randomised patients were presented with the short-term outcome results. For the long-term outcomes the same baseline characteristics of the survivors will be presented split by treatment group and overall. Again, these will be the 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 Definition of outcomes and losses to follow-up

The number (and percentage) of patients with scheduled follow-up for amnioinfusions and maternal investigations were presented with the short-term outcome results 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.

3.3.1 Long-term respiratory morbidity

1. Respiratory questionnaire taken at 6 months, 12 months and 18 months corrected gestational age. The questionnaire consists of two questions. The first of which asks if the child has ever had wheezing in the past (yes/no) and the second is split up into 9 separate domains. The first 8 domains (A-H) each contain 3-5 questions and ask about the child's wheeze, cough, rattly chest, shortness of breath and other symptoms in different situations and at different times of the day over the previous 3 months.

   A) During the day (when awake) – 4 questions.
   B) During the night (when asleep) – 5 questions.
   C) Number of colds and if the child had at least one there are questions that apply when the child has had a cold – 4 questions.
   D) When the child does not have a cold – 4 questions.
   E) When the child has been more active – 4 questions.
   F) Other problems the child may have had – 3 questions
   G) Child's chest symptoms affecting the child – 4 questions.
   H) Child's chest symptoms affecting the parent – 4 questions.

   The 9th domain 'I' consists of 6 questions asking about any treatment received during the previous 3 months. Domains A-H count towards the overall score and domain I is standalone. Details on how the questionnaire is scored are described in section 5.1.1.

2. Lung function tests taken after 1 year corrected gestational age. The three respiratory measurements that were specified in the protocol were lung volume FRC_P, resistance R_{eff} and airway function V_{maxFRC}. There is no standardised way of making resistance R_{eff} measurements equations to calculate predicted values so it was agreed that this data will not be collected.

   Only a small handful of babies were able to have lung function tests at around 1 year corrected gestational age. There are many reasons why such as difficulties getting the babies to Leicester to be tested, work pattern of the part-time research nurse, delay getting R&D approval, losing the lab when funding expired so having to arrange to take portable spirometer to Liverpool to do the remaining unseen patients.

   For infant testing they require sedation which is a big difficulty. Parents don't like it, it necessitates finding a doctor who is willing to write up a dose of chloral hydrate that exceeds what is usually used clinically, and provide the medical cover for several hours. The upper age limit at which these tests can be done is around 15-18 months. After that they are too big and stroppy to take the sedation and settle to sleep well enough to do the tests. Beyond 18 months there isn't anything much that can be done until they can start blowing down tubes in a reasonably consistent manner around the age of 3 (pre-school age).

   The measurements that were taken were:

   - FRC_P – predicted values are well-established in infants but there are none in place for pre-school children. Therefore, infants have the FRC_P results, predicted values and Z-scores were taken/calculated but the pre-school children only have the FRC_P results.
   - V_{maxFRC} –used to measure airway function in infants. V_{maxFRC} results, predicted values and Z-scores were taken/calculated.
   - FEV_1 – used to measure airway function in pre-school children. FEV_1 results, predicted values and Z-scores were taken/calculated.
   - FVC – used to measure forced vital capacity in pre-school children. FVC results, predicted values and Z-scores were taken/calculated.

3.3.2 Long-term developmental outcomes

1. Developmental delay at 2 years corrected gestational age using Bayley's score. The Bayley Scales of Infant Development (BSID-II) is a standard series of measurements originally developed by psychologist Nancy Bayley used primarily to assess the motor and cognitive development of infants and toddlers, ages 0-3. This measure consists of a series of developmental play tasks and takes between 45 - 60 minutes to administer. Raw scores of successfully completed items are converted to scale scores and to composite scores between 50-150. These scores are used to determine the child's performance compared with norms taken from typically developing children of their age (in months). The two scores reported in this trial are the Mental Developmental Index (MDI) score and the Psychomotor Developmental Index (PDI) score. Their classifications are as follows:
   - 50- 69 – Significantly delayed performance.
   - 70-84 – Mildly delayed performance.
   - 85-114 – Within normal limits.
   - 115-150 – Accelerated performance.

   The Bayley's assessments were carried out between the ages of 2 years and 3 months to 3 years and 3 months. The assessments were performed at the home of the child by a trained nurse. At the protocol stage a trained nurse was not identified so this explains why

some of the earlier children had their Bayley's assessment delayed. Other delays were due to the parents/trained nurse finding a convenient time to meet.

2. Orthopaedic follow-up. This is an opportunistic outcome. If any babies develop orthopaedic problems then they will be assessed accordingly.

3.4 Description of intervention received

Deviations from intended treatment (e.g. withdrawals from randomised treatment) were summarised for each treatment group and the distribution of the number of amnioinfusions received were described for women in the amnioinfusion group with the short-term outcome results.

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.

4.2 Per protocol analysis

Patients randomised to amnioinfusion that received at least one amnioinfusion and all patients randomised to expectant management that attended at least one visit will be included in the per protocol analysis set. Patients that withdrew from treatment or had a major protocol deviation will be excluded. This is a sensitivity analysis and will be used to demonstrate the robustness of the results. They will be performed for short term assessments of mortality and binary maternal and neonatal morbidty.

4.3 Safety analysis

Data for serious adverse events (SAEs) were only recorded for the short-term outcomes and were presented with the short-term outcome results.

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.

5.1 Long-term respiratory morbidity

5.1.1 Respiratory questionnaire

The data for the respiratory questionnaires taken at 6 months, 12 months and 18 months corrected gestational age will be summarised separately by treatment group.

The first question that asks if the child has ever had wheezing in the past (binary yes/no) will be presented as a relative risk with 95% confidence interval. Fetal deaths and neonatal deaths will be excluded from this analysis. A sensitivity analysis will be performed to include the neonatal deaths using the 'worst-case' approach by assigning them to be 'yes' to have wheezed.

Each question in sections A-H are answered on a 5-point scale starting at 'not at all' and increasing in descriptive frequency to 'every day/night/cold' depending on the question. They are scored from 0-4 with 'not at all' being 0 and 'every day/night/cold' being 4. For each patient, the total score for each section is the sum of the within-section question scores. The overall questionnaire score is calculated as the sum of all question scores for sections A-H. Higher scores indicate more severe respiratory symptoms.

A) During the day (when awake) – 4 questions, score between 0-16.
B) During the night (when asleep) – 5 questions, score between 0-20.
C) Number of colds and if the child had at least one there are questions that apply when the child has had a cold – 4 questions, score between 0-16.
D) When the child does not have a cold – 4 questions, score between 0-16.
E) When the child has been more active – 4 questions, score between 0-16.
F) Other problems the child may have had – 3 questions, score between 0-12.
G) Child's chest symptoms affecting the child – 4 questions, score between 0-16.
H) Child's chest symptoms affecting the parent – 4 questions, score between 0-16.
Overall score: between 0-128.

The questions from domain 'I' will be summarised descriptively by treatment group with n (%).

Sections A-H are grouped into four domains:

1. Daytime symptoms (sections A, C, D, E, F).
2. Night-time symptoms (section B).
3. Effect on the child (section G).
4. Effect on the family (section H).

Each domain score and overall score will be summarised and presented for each treatment group separately at 6 months, 12 months and 18 months. There are no validated methods available to handle missing data in this respiratory questionnaire so only those domain scores and overall scores that have no missing data (complete-case) will be summarised. The number of incomplete domains will be reported for each of the 3 time points.

If the data appear to be normal the summary measures of mean and standard deviation will be presented for each treatment group. The difference in means with 95% confidence intervals will be presented.

If the data appear to be skewed (i.e. non-normal) the summary measures of median and inter-quartile range (IQR) will be presented for each treatment The difference in medians with 95% confidence intervals will be presented. The difference in medians will be calculated using the Hodges-Lehman estimate with the corresponding Moses distribution-free 95% confidence intervals.

Fetal deaths and neonatal deaths will be excluded from these analyses. Any missing questionnaires due to loss to follow-up or parents not returning them will be excluded. Sensitivity analyses will be performed for each domain score and overall score by assigning the neonatal deaths the largest value observed in the trial for that particular domain/overall score. Further sensitivity analyses for each domain score and overall score will be conducted to include just the surviving patients that have questionnaires returned with missing answers to any of the questions:

(i) Best-case: assigning the missing question a score of 0.
(ii) Worst-case: assigning the missing question a score of 4.

In addition, the overall score will be analysed longitudinally using mixed models. Mean profile plots and individual plots by treatment groups will be presented. A table of summary measures at each time point will be also presented.

5.1.2 Infant lung function tests

Line listings of each patient's lung function test results will be presented in a table showing age at test, treatment group, test results, predicted values (where applicable) and Z-scores (where applicable).

For the infants, the Z-scores for FRC_P and V_{maxFRC} will be summarised and presented for each treatment group. For the pre-school children, the Z-scores for FEV_1 and FVC will be summarised and presented for each treatment group.

If the data appear to be normal the summary measures of mean and standard deviation will be presented for each treatment group. The difference in means with 95% confidence intervals will be presented.

If the data appear to be skewed (i.e. non-normal) the summary measures of median and inter-quartile range (IQR) will be presented for each treatment The difference in medians with 95% confidence intervals will be presented. The difference in medians will be calculated using the Hodges-Lehman estimate with the corresponding Moses distribution-free 95% confidence intervals.

Fetal deaths, neonatal deaths and patients that had no lung function tests performed will be excluded from this analysis. Sensitivity analyses will be performed:

(a) Firstly, assume that the neonatal deaths reached 1 year corrected gestational age to have FRC_P and V_{maxFRC} measured:
  (i) Assign the neonatal deaths the largest observed positive Z-score for each test.
  (ii) Assign the neonatal deaths the smallest observed negative Z-score for each test.

(b) Secondly, assume that the neonatal deaths reached pre-school age of around 3 years corrected gestational age to have FEV_1 and FVC measured:
  (i) Assign the neonatal deaths the largest observed positive Z-score for each test.
  (ii) Assign the neonatal deaths the smallest observed negative Z-score for each test.

If lung function tests are unable to be performed and assessed due to severe developmental delay they will be included in a sensitivity analysis. It will be assumed that they would have had their lung function tests at the correct time of 1 year corrected gestational age so they will be included in sensitivity analysis (a). These cases can be identified through supporting data and comments on the lung function test form and will be confirmed by the Chief Investigator and documented accordingly.

5.2 Long-term developmental outcomes

5.2.1 Developmental delay at 2 years corrected gestational age using Bayley's score

The MDI and PDI scores will be summarised and presented for each treatment group. If the data appear to be normal the summary measures of mean and standard deviation will be presented for each treatment group. The difference in means with 95% confidence intervals will be presented.

If the data appear to be skewed (i.e. non-normal) the summary measures of median and inter-quartile range (IQR) will be presented for each treatment The difference in medians with 95% confidence intervals will be presented. The difference in medians will be calculated using the Hodges-Lehman estimate with the corresponding Moses distribution-free 95% confidence intervals.

A summary table of classifications (shown below) by treatment group will also be presented.

- 50- 69 – Significantly delayed performance.
- 70-84 – Mildly delayed performance.
- 85-114 – Within normal limits.
- 115-150 – Accelerated performance.

Age is taken account for when assessing the child's developmental performance so this is not an issue for the analysis. Fetal deaths, neonatal deaths and patients that had no Bayley's assessment carried out will be excluded from this analysis. This will be a complete-case analysis so any missing data from the survivors will be ignored. Two sensitivity analyses will be performed for both the difference in means/medians and the classification summary:

(1) If a Bayley's assessment for either MDI, PDI or both was unable to be carried out due to the child having a significantly delayed performance then they will be included in a sensitivity analysis for the corresponding score analysis and classification summary. They will be assigned a score of 50 (i.e. the worst possible score) for the score analysis and classified as 'Significantly delayed performance' for the classification summary. These cases can be identified through supporting data and comments on the Bayley's form and will be confirmed by the Chief Investigator and documented accordingly.

(2) Those survivors with missing MDI/PDI data for reasons highlighted above will be handled as per sensitivity analysis (1) and the neonatal deaths will also be included by assigning them the lowest (i.e. worst scores) MDI and PDI scores and corresponding worst classification observed in the trial.

5.2.2 Orthopaedic follow-up

Any babies that have developed orthopaedic problems that required surgery for the two groups will be presented in terms of relative risks with 95% confidence intervals. However, if there are no babies that have developed orthopaedic problems then this will be reported. More specific details of these orthopaedic problems will be given if the Chief Investigator feels necessary.

5.3 Missing data

The amount 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 is large (>10%).

6. Reporting Protocol Deviations

Decisions to be made by an "Endpoint Adjudication Committee" (on masked data).
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

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Outcome data			
Respiratory questionnaire	Missing data in survivors	Major	May influence interpretation of results
	Timing of questionnaire: completed less than 3 month prior to or more than 3 months after completion due date	Major	May influence interpretation of results
Infant lung function tests	Missing data in survivors	Major	May influence interpretation of results
	Timing of lung function tests: completed less than 3 month prior to or more than 3 months after 1 year corrected gestational age	Major	May influence interpretation of results
Neurodevelopmental assessment	Missing data in survivors	Major	May influence interpretation of results
	Timing of neurodevelopmental assessment: completed less than 3 month prior to or more than 3 months after 2 years corrected gestational age	Major	May influence interpretation of results

8. 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.

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Measurement conditions in *'Infant Respiratory Function Testing'* Eds Stocks J, Sly P, Tepper R & Morgan W. Wiley (New York) 1996 (Jan) 558 pages, hardback. ISBN 0-471-07682-1. Gaultier C, Fletcher ME, Beardsmore CS, et al. P29-44.

Powell CVE, McNamara P, Solis A, Shaw NJ. A parent completed questionnaire to describe the patterns of wheezing and other respiratory symptoms in infants and preschool children. *Arch Dis Child* 2002; 87: 376-379.

Appendix 1: Approval of AMIPROM Long-Term Outcome Data Protocol Deviations table

This AMIPROM Long-Term Outcome Data Protocol Deviations table (Version 1, 08/03/2012) has been completed and approved by the following personnel:

Trial statistician

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

Signature: _____

Supervising statistician

Print Name: Mrs. Gaynor Skotny **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. Andrew Shennan **Date:** _____

Signature: _____

Appendix 2: Approval of AMIPROM Long-Term Outcome Data Statistical Analysis Plan

This AMIPROM Long-Term Outcome Data Statistical Analysis Plan (Version 1, 08/03/2012) has been completed and approved by the following personnel:

Trial statistician

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

Signature: _____

Supervising statistician

Print Name: Mrs. Gaynor Skotny **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. Andrew Shennan **Date:** _____

Signature: _____

Appendix 3: Respiratory questionnaire

Study No : .....

Date .....

Name : .....

Sex : male female (please circle)

Date of birth : .....

Place of birth : .....

Age (weeks) : .....

Address : .....

.....

.....

Telephone no : .....

The following questionnaire asks questions about your child and what has been happening to him/her over the last three months.

Please could you fill in the questionnaire by putting a circle around your response to each question.

It is important that every question is answered, even if your child has been perfectly well, with no problems at all.

Thank you.

Name of Child **Study Number**

1. This first question refers to at any time in your child's life:

Has your child ever had wheezing (whistling noise coming from the chest) at <u>any time in the past</u>?	*Yes*	*No*

2. The next questions are specifically aimed at the <u>last three months</u>:

A) During the day (when awake) in the <u>last three months</u>:

i) My child has had wheezing (whistling noise coming from the chest):

Every day *most days* *some days* *a few days* *not at all*

ii) My child has had a cough:

Every day *most days* *some days* *a few days* *not at all*

iii) My child has had a rattly chest:

Every day *most days* *some days* *a few days* *not at all*

iv) My child has been short of breath:

Every day *most days* *some days* *a few days* *not at all*

B) During the night (when asleep) in the <u>last three months</u> :

i) My child has had wheezing (whistling noise coming from the chest):

Every night *most nights* *some nights* *a few nights* *not at all*

ii) My child has had a cough:

Every night *most nights* *some nights* *a few nights* *not at all*

iii) My child has had a rattly chest:

Every night *most nights* *some nights* *a few nights* *not at all*

iv) My child has been short of breath:

Every night *most nights* *some nights* *a few nights* *not at all*

v) My child has snored :

Every night *most nights* *some nights* *a few nights* *not at all*

Name of Child **Study Number**

C) How many colds has your child had in the last three months:

None	*one*	*two*	*three*	*more than three*	*always has a cold*

If the answer to the above question is *'none'* continue to questions in section D:

When my child has had a COLD in the last three months:

i) My child has had wheezing (whistling noise coming from the chest):

Every cold *most colds* *some colds* *a few colds* *not at all with colds*

ii) My child has had a cough:

Every cold *most colds* *some colds* *a few colds* *not at all with colds*

iii) My child has had a rattly chest:

Every cold *most colds* *some colds* *a few colds* *not at all with colds*

iv) My child has been short of breath:

Every cold *most colds* *some colds* *a few colds* *not at all with colds*

D) When my child does NOT have a COLD, in the last three months:

i) My child has had wheezing (whistling noise coming from the chest):

Every day *most days* *some days* *a few days* *not at all*

ii) My child has had a cough:

Every day *most days* *some days* *a few days* *not at all*

iii) My child has had a rattly chest:

Every day *most days* *some days* *a few days* *not at all*

iv) My child has been short of breath:

Every day *most days* *some days* *a few days* *not at all*

Name of Child **Study Number**

E) When my child has been MORE ACTIVE (e.g. crawling, walking or when excited) in the last three months:

i) My child has had wheezing (whistling noise coming from the chest):

Every day *most days* *some days* *a few days* *not at all*

ii) My child has coughed:

Every day *most days* *some days* *a few days* *not at all*

iii) My child has had a rattly chest:

Every day *most days* *some days* *a few days* *not at all*

iv) My child has been short of breath:

Every day *most days* *some days* *a few days* *not at all*

F) These next three questions are about other problems your child may have had. Over the last three months:

i) My child has had noisy breathing that does not seem to come from the chest :

Every day *most days* *some days* *a few days* *not at all*

ii) My child has had fast breathing:

Every day *most days* *some days* *a few days* *not at all*

iii) My child has had noisy breathing that appears to come from the throat or back of the throat:

Every day *most days* *some days* *a few days* *not at all*

Name of Child **Study Number**

G) The next four questions are on how your child's chest symptoms actually affect HIM or HER over the last three months:

i) My child's chest symptoms have affected my child's feeding or eating:

Every day *most days* *some days* *a few days* *not at all*

ii) My child's chest symptoms have woken up my child:

Every night *most nights* *some nights* *a few nights* *not at all*

iii) My child's chest symptoms have reduced my child's activity:

Every day *most days* *some days* *a few days* *not at all*

iv) My child's chest symptoms have made my child unusually tired:

Every day *most days* *some days* *a few days* *not at all*

H) The next four questions are on how your child's chest symptoms actually affect YOU and YOUR family's life the last three months:

i) My child's chest symptoms have limited my activities:

Every day *most days* *some days* *a few days* *not at all*

ii) My child's chest symptoms have resulted in adjustments being made to our family life:

Every day *most days* *some days* *a few days* *not at all*

iii) My child's chest symptoms have disturbed our sleep:

Every night *most nights* *some nights* *a few nights* *not at all*

iv) I have been worried about my child's chest symptoms:

Every day *most days* *some days* *a few days* *not at all*

Name of Child **Study Number**

I) This last section is asking about treatment. In the last three months:
(Please circle answers)

i) My child has taken treatment for chest symptoms (medicines, tablets or inhalers):

a. Inhaler **Yes** **No**

Name or describe .....

b. Medicine / tablets **Yes** **No**

Name or describe .....

For more than a week at any one time? **Yes** **No**

ii) My child has visited or has had a visit from the General Practitioner for chest problems: **Yes** **No**

Number of times .....

iii) In the last 3 months my child has attended hospital clinics for chest problems: **Yes** **No**

Number of times .....

iv) Has a doctor ever diagnosed asthma in your child? **Yes** **No**

v) My child has been admitted to hospital because of chest symptoms:

not at all once twice three times greater than three times

vi) If your child has problems with their chest or breathing, what diagnosis or label has been given or made?

Person completing the questionnaire :

mother father guardian other (specify)

Appendix 5 Serious adverse event form

Liverpool Women's NHS
NHS Foundation Trust

SAE / AE Report Form

Complete sections 1-5

Section 1: Research participant (complete all sections)	
Participant study number	
Participant initials	
Weight:	Height (not required for neonates):

Section 2: Research study (complete all sections)			
Title of the Study:			
		Medication/intervention	Mode of administration:
EudraCT number of trial		Dose	Frequency

Section 3: Adverse event

Description of event (please provide sufficient detail for independent review of causality where the event is deemed to be serious)

Check all appropriate to adverse event

Resulted in death* ☐

Life threatening at time of event* ☐

Requires inpatient hospitalisation* or extension of existing hospitalisation* ☐

Resulted in persistent or significant disability/incapacity* ☐

Is a congenital anomaly/defect* ☐

May lead to one of the above outcomes or require treatment to prevent one of the above outcomes ☐

** event is a **SUSAR‡** if it is serious, not expected and if it is possible, probable or highly probable to be in relation to the study intervention*

Relation with study intervention

Highly probable* ☐

Probable* ☐

Possible* ☐

Unlikely (remote) ☐

None (inter-current event) ☐

See Managing and reporting adverse events SOP for definitions of causality

Onset of event (date - dd/mm/yy and time - 24 hour clock):

Event stopped (date - dd/mm/yy and time - 24 hour clock):

Ongoing at time of report?
Yes ☐ No ☐

Date event cleared completely:

Severity
Mild ☐
Moderate ☐
Severe ☐
Life-threatening ☐
Death ☐

Was the event expected on the basis of what is known about the study intervention?

Yes ☐ No* ☐

Frequency
Event occurred only once and cleared in 24 hours ☐
Event occurred episodically between onset and clearance dates ☐
Event was present for the entire time between onset and clearance dates ☐

Outcome
Resolved ☐
Resolved with sequelae ☐
Not resolved/ongoing ☐
Ongoing at death ☐
Fatal ☐

Action taken
None ☐
Dose reduced ☐
Dose increased ☐
Temporarily interrupted ☐
Permanently discontinued ☐

‡ If the event is a SUSAR it requires expedited reporting as detailed in LWFT SAE procedure guideline – contact Liverpool Women's R&D office (tel: 0151 702 4346 / 4241)

Section 4: Other medication (at the time of onset and for duration of event)			
Name	Dose	Route	IMP/NIMP/Concomitant medication

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Section 5: Reporter of adverse event (complete all sections)		
Name:	Position:	Report Date:
Tel No:	Email:	Report type (please tick): Initial ☐ Follow up to telephone.☐
Verification of assessment by study Principal Investigator*	**Name:**	**Signature:** **Date:**

* Causality and severity assessed and agreed

Reporting Procedure

All SAEs must be reported **within 24 hours** of the investigator becoming aware of them to the Sponsor (this should be via the R&D office). SAEs from Commercial Clinical Trials should be reported to the Sponsor and a copy sent to R&D. **Phone 0151 702 4346 / 4241 to report, leaving a message if unanswered or fax this form to 0151 702 4299.**

Please submit a copy of this report to the Trust R&D office situated on the second floor of the hospital.

R&D should acknowledge receipt of your report via e-mail within 24 hours – if you have not been notified of receipt, you must follow this up with R&D to ensure the department has received notification and that appropriate reporting has been undertaken.

For use by R&D Office

Section 6: Informing Sponsor		
Is LWFT Sponsor / Co-sponsor with responsibility for pharmacovigilance	Yes / No	If no: date Sponsor informed: If yes: complete sections 7 & 8.

Section 7: Sponsor assessment (complete all sections if LWFT has responsibility for pharmacovigilance)		
Name:	Position*:	Date report received:
Date of sponsor's assessment		
People involved in sponsor's assessment		
Sponsor's assessment of causality, with summary of justification:		
Sponsor's assessment of seriousness, with summary of justification		

*Please note independent assessment can be conducted on behalf of the Sponsor by an independent clinician at the site the participant was recruited. Confirmation of independent assessment can be documented via email correspondence with the Sponsor R&D office (to be kept on file with this completed form).

Section 8: Actions to be taken by Sponsor (delete those that do not apply):			
Requires un-blinding	Yes / No	**Un-blinding indicates need for expedited reporting**	Yes / No
Expedited report to MHRA within 7 days	Date initial report made: Date detailed report made:	**Expedited report to MHRA within 15 days**	Date initial report made: Date detailed report made:
Report to LREC	Date initial report made: Date detailed report made:	**Inform investigators**	Date investigators informed
Inform marketing authorisation holders	Date M.A. holders informed	**Review of trial risk management plan**	Date of review: Date of actions:
Inform co-sponsors:	Name of co-sponsor and date informed:	Name of co-sponsor and date informed:	

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EME
HS&DR
HTA
PGfAR
PHR

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