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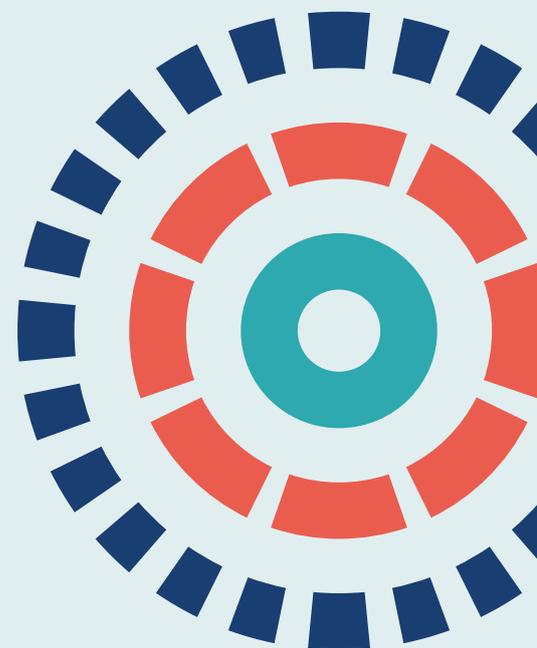
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Improving quality of care and outcome at very preterm birth: the Preterm Birth research programme, including the Cord pilot RCT

*Lelia Duley, Jon Dorling, Susan Ayers, Sandy Oliver, Charles William Yoxall,
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on behalf of the Preterm Birth Programme Collaborative Group*



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Abstract

Improving quality of care and outcome at very preterm birth: the Preterm Birth research programme, including the Cord pilot RCT

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Background: Being born very premature (i.e. before 32 weeks' gestation) has an impact on survival and quality of life. Improving care at birth may improve outcomes and parents' experiences.

Objectives: To improve the quality of care and outcomes following very preterm birth.

Design: We used mixed methods, including a James Lind Alliance prioritisation, a systematic review, a framework synthesis, a comparative review, qualitative studies, development of a questionnaire tool and a medical device (a neonatal resuscitation trolley), a survey of practice, a randomised trial and a protocol for a prospective meta-analysis using individual participant data.

Setting: For the prioritisation, this included people affected by preterm birth and health-care practitioners in the UK relevant to preterm birth. The qualitative work on preterm birth and the development of the questionnaire involved parents of infants born at three maternity hospitals in southern England. The medical device was developed at Liverpool Women's Hospital. The survey of practice involved UK neonatal units. The randomised trial was conducted at eight UK tertiary maternity hospitals.

Participants: For prioritisation, 26 organisations and 386 individuals; for the interviews and questionnaire tool, 32 mothers and seven fathers who had a baby born before 32 weeks' gestation for interviews evaluating the trolley, 30 people who had experienced it being used at the birth of their baby (19 mothers, 10 partners and 1 grandmother) and 20 clinicians who were present when it was being used; for the trial, 261 women expected to have a live birth before 32 weeks' gestation, and their 276 babies.

Interventions: Providing neonatal care at very preterm birth beside the mother, and with the umbilical cord intact; timing of cord clamping at very preterm birth.

Main outcome measures: Research priorities for preterm birth; feasibility and acceptability of the trolley; feasibility of a randomised trial, death and intraventricular haemorrhage.

Review methods: Systematic review of Cochrane reviews (umbrella review); framework synthesis of ethics aspects of consent, with conceptual framework to inform selection criteria for empirical and analytical studies. The comparative review included studies using a questionnaire to assess satisfaction with care during childbirth, and provided psychometric information.

Results: Our prioritisation identified 104 research topics for preterm birth, with the top 30 ranked. An ethnographic analysis of decision-making during this process suggested ways that it might be improved. Qualitative interviews with parents about their experiences of very preterm birth identified two differences with term births: the importance of the staff appearing calm and of staff taking control. Following a comparative review, this led to the development of a questionnaire to assess parents' views of care during very preterm birth. A systematic overview summarised evidence for delivery room neonatal care and revealed significant evidence gaps. The framework synthesis explored ethics issues in consent for trials involving sick or preterm infants, concluding that no existing process is ideal and identifying three important gaps. This led to the development of a two-stage consent pathway (oral assent followed by written consent), subsequently evaluated in our randomised trial. Our survey of practice for care at the time of birth showed variation in approaches to cord clamping, and that no hospitals were providing neonatal care with the cord intact. We showed that neonatal care could be provided beside the mother using either the mobile neonatal resuscitation trolley we developed or existing equipment. Qualitative interviews suggested that neonatal care beside the mother is valued by parents and acceptable to clinicians. Our pilot randomised trial compared cord clamping after 2 minutes and initial neonatal care, if needed, with the cord intact, with clamping within 20 seconds and initial neonatal care after clamping. This study demonstrated feasibility of a large UK randomised trial. Of 135 infants allocated to cord clamping ≥ 2 minutes, 7 (5.2%) died and, of 135 allocated to cord clamping ≤ 20 seconds, 15 (11.1%) died (risk difference -5.9% , 95% confidence interval -12.4% to 0.6%). Of live births, 43 out of 134 (32%) allocated to cord clamping ≥ 2 minutes had intraventricular haemorrhage compared with 47 out of 132 (36%) allocated to cord clamping ≤ 20 seconds (risk difference -3.5% , 95% CI -14.9% to 7.8%).

Limitations: Small sample for the qualitative interviews about preterm birth, single-centre evaluation of neonatal care beside the mother, and a pilot trial.

Conclusions: Our programme of research has improved understanding of parent experiences of very preterm birth, and informed clinical guidelines and the research agenda. Our two-stage consent pathway is recommended for intrapartum clinical research trials. Our pilot trial will contribute to the individual participant data meta-analysis, results of which will guide design of future trials.

Future work: Research in preterm birth should take account of the top priorities. Further evaluation of neonatal care beside the mother is merited, and future trial of alternative policies for management of cord clamping should take account of the meta-analysis.

Study registration: This study is registered as PROSPERO CRD42012003038 and CRD42013004405. In addition, Current Controlled Trials ISRCTN21456601.

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Glossary

Bliss The special care baby charity.

List of abbreviations

ASQ	Ages and Stages Questionnaire	JLA	James Lind Alliance
BASICS	Bedside Assessment, Stabilisation and Initial Circulatory Support	NCT	National Childbirth Trust
Bayley-III	Bayley Scales of Infant Development III	NICE	National Institute for Health and Care Excellence
CCPTP	Cord Clamping and Placental Transfusion at Preterm birth	NICU	neonatal intensive care unit
CE	Conformité Européenne	NIHR	National Institute for Health Research
CI	confidence interval	P-BESS	Preterm Birth experience and Satisfaction Scale
COREQ	Consolidated Criteria for Reporting Qualitative Research	PhD	doctor of philosophy
CPAP	continuous positive airways pressure	PSP	Priority Setting Partnership
IPD	individual participant data	RCT	randomised controlled trial
IVH	intraventricular haemorrhage	RR	relative risk
		SD	standard deviation
		TSC	Trial Steering Committee

Plain English summary

Babies born before 32 weeks' gestation (very preterm) may have poor health or they may not survive. Our research focused on care at the birth, with close co-operation between parent representatives, clinicians and researchers.

We interviewed parents who described their experience of very preterm birth as a 'rollercoaster of emotions', and said that touching their baby helped bonding. About one-third of parents see and touch their baby for the first time on the neonatal unit. Parents were mostly positive about care during the birth, but some women felt that they had not been listened to or had not been believed; in addition, some fathers felt excluded. Parents found it helpful when staff were calm and took control. We developed a questionnaire to measure parents' satisfaction with care during preterm birth.

We designed a small trolley so that immediate care for the baby could be beside their mother, and also showed that this care could be done using existing equipment. Parents and clinicians were largely positive about this care.

We do not know when is best to clamp the umbilical cord at birth. Our randomised trial at very preterm birth found that cord clamping after ≥ 2 minutes and initial care for the baby with the cord intact may be beneficial, compared with immediate clamping and care after clamping. A brief process for offering participation in the trial (consent) when birth was imminent, with a detail explanation later, was acceptable to women and clinicians. We will pool our data with other trials to help find out the best way of managing cord clamping at preterm birth.

Through involving parents, the public and health-care professionals, we identified 104 unanswered research questions around care for preterm birth, and ranked the top 30.

Our work has improved understanding of parents' experiences, provided research ideas and developed a consent process and ways of caring for babies at birth beside their mother.

Scientific summary

Background

Preterm birth has major impact on survival and quality of life, psychosocial and emotional stress for the family, and costs for health services and society. Mortality and morbidity are highest for infants born very preterm, before 32 weeks' gestation, and impairment may persist into early adulthood. This programme focused on care in the delivery room at very preterm birth.

Aims

Our aims were to improve the quality of immediate care at preterm birth, enhance family-centred care, and improve outcome for babies born very preterm and their families.

Methods

Our range of methods were delivered through five interconnected work packages.

- Work package 1: James Lind Alliance Priority Setting Partnership between service users and health-care professionals to identify and prioritise the top research questions in preterm birth –
 - with an ethnographic analysis of partnership working.
- Work package 2: two systematic reviews –
 - umbrella review to identify effective interventions in the delivery room for babies born very preterm
 - framework synthesis addressing ethics issues in recruiting preterm or sick babies to clinical trials.
- Work package 3: strategies for providing initial neonatal care beside the mother at preterm birth, with umbilical cord intact –
 - survey of neonatal care
 - qualitative interviews with parents: (1) comparative review of tools to assess experiences of care at birth; and (2) developing a new questionnaire for use after very preterm birth
 - measuring umbilical cord flow before cord clamping
 - developing and evaluating a mobile trolley to support neonatal care at birth beside the mother, with cord intact: (1) service evaluation; and (2) qualitative interviews with parents and clinicians
- Work package 4: pilot randomised controlled trial evaluating timing of cord clamping, including –
 - qualitative interviews with women and clinicians about consent
 - 1-year follow-up of women
 - 2-year follow-up of children (corrected for gestation).
- Work package 5: protocol for an individual participant data meta-analysis.

Results

Work package 1

We identified and distributed for public voting 104 unanswered research questions. The 30 most popular were ranked at a workshop. The top 15 were:

1. Which interventions are most effective to predict or prevent preterm birth?
2. How can infection in preterm babies be better prevented?
3. How best to prevent necrotising enterocolitis in premature babies?
4. What is the best treatment for lung damage in premature babies?
5. What should be included in packages of care to support families when a premature baby is discharged from hospital?
6. What is the optimum milk-feeding guidance for premature babies?
7. What is the best way to judge whether a premature baby is feeling pain?
8. Which treatments are best to prevent early-onset pre-eclampsia?
9. What emotional and practical support improves outcomes for premature babies and their families?
10. Which treatments are most effective for preterm premature rupture of membranes?
11. When is the best time to clamp the umbilical cord in preterm birth?
12. What support is most effective at improving breastfeeding for premature babies?
13. How best to treat necrotising enterocolitis in premature babies?
14. Does specialist antenatal care for women at risk of preterm birth improve outcomes?
15. What are the best ways to optimise the environment (such as light and noise) to improve outcomes?

Future prioritisations should endeavour to anticipate potentially differing perspectives, mitigate any imbalance where possible, and report voting by 'service users' and health-care professionals separately.

Work package 2

Our systematic review (umbrella review) identified 18 Cochrane reviews covering four topics:

1. *Delivery room interventions for airway management, respiratory or circulatory support (four reviews)*. Two reviews found no eligible trials and one included one small trial. The fourth concluded that there is no evidence that routine endotracheal intubation reduces mortality or morbidity in vigorous term babies with meconium staining, compared with standard resuscitation.
2. *Surfactant replacement therapy for preterm infants with or at risk of respiratory distress syndrome (eight reviews)*. The strongest evidence supported type and timing of surfactant administration: for very preterm infants surfactant reduced the risk of death by about 40%, and natural surfactant was more effective than synthetic. Early surfactant administration with brief ventilation reduced mechanical ventilation, but delivery room administration was no better than delayed selective administration. Uncertainty remains about the comparative effects of newer synthetic surfactants, and novel non-invasive administrations.
3. *Supplemental oxygen or other drugs for infants compromised at birth (five reviews)*. There was insufficient evidence for reliable recommendations about using air or 100% oxygen for newborn resuscitation, about using adrenaline or sodium bicarbonate, and about using naloxone for infants exposed in utero to opiates. Various measures for keeping newborn very preterm infants warm reduced the risk of hypothermia, but effects on morbidity and mortality remain unclear.
4. *Strategies for influencing placental transfusion (one review)*. Deferring cord clamping for between 30 and 120 seconds, rather than clamping before 30 seconds, possibly reduced blood transfusions and intraventricular haemorrhage. Effects on death and long-term neurodevelopment remained unclear.

Our framework synthesis addressing ethics issues in recruitment identified two types of study:

1. *Empirical (49 studies)*. Revealed themes about parents' attitudes, clinicians' attitudes, validity of consent, different consent processes and miscellaneous topics. Empirical research confirmed that there are difficulties for some parents giving valid consent.

2. *Analytical (30 studies)*. Revealed themes about the ethical basis of parental informed consent for neonatal research, parental consent validity, other options for seeking consent, risk and the double standard between consent for treatment versus research.

There was agreement that it is important for parents give or decline consent for neonatal trial participation. However, none of the existing consent processes reviewed was satisfactory. Clinicians have concerns that research participation is dropping because of problems with consent, and they may face ethical difficulties in discharging conflicting duties to research, neonates and parents.

We identified three important gaps:

1. evaluation of a process for obtaining emergency consent in perinatal research
2. studies on trials where both the mother and the fetus or neonate are participants
3. studies that report the views of bereaved parents on the consent process.

We developed a two-stage oral assent consent pathway and included this in our pilot trial (work package 4), which addressed the first two research gaps. The third research gap has been addressed elsewhere.

Work package 3

Our survey showed variation in delivery room practice for infants born very preterm. In tertiary units, the care provided was more consistent with current international guidance than in non-tertiary units. There was variation in how policies for cord clamping at very preterm birth were implemented, both between and within units. No unit provided neonatal care with cord intact, and staff were anxious about this practice. Implementation of deferred cord clamping seemed more successful if there was strong local interdisciplinary support, with agreement on a single technique and the eligibility criteria. Clinical leadership and training in the practical techniques also appeared helpful.

Parents' views and experiences of very preterm birth

Almost half of the parents interviewed described difficulty remembering aspects of the birth. The anticipation before seeing and touching their baby for the first time was characterised by contrasting and rapidly changing emotions. Parents who talked about touching and holding their baby described immediate bonding. Visiting the neonatal unit was initially overpowering, especially for those who had not been before or were seeing their baby for the first time. Parents referred to the awkwardness and exclusion felt by fathers.

Overall parents' experiences of care were positive. We identified four determinants of parents' experience: staff professionalism, staff empathy, involvement of the father, and the birth environment. These are consistent with research on term births. Two factors unique to very preterm birth were the importance of staff appearing calm and staff taking control during the birth. Two areas where parents felt that care could have been improved were staff not believing the women, or appearing not to listen to them, and fathers not being involved.

Our comparative review of measures of parents' satisfaction with care during childbirth identified nine questionnaires, none of which evaluated care at very preterm birth. Therefore, we developed a questionnaire to measure this. There were 17 items, with subscales on 'staff professionalism and empathy', 'information and explanations', 'confidence in staff' and 'involvement of the partner'. The total scores may be useful to compare satisfaction across hospitals, whereas individual aspects of care can be evaluated using the subscales. We used this questionnaire in our pilot trial. Further research should explore whether or not there is variation in experiences for parents from different backgrounds and in different settings.

Neonatal care at birth beside the mother

We developed a small trolley to support newborn resuscitation at birth beside the mother, marketed as LifeStart™ (Inditherm Medical, Rotherham, UK), and conducted a service evaluation within a busy tertiary hospital. Common delivery room resuscitation procedures were performed successfully on the trolley,

including with cord intact. Compared with conventional resuscitation equipment, for most aspects of care clinicians rated the trolley as 'the same', 'better' or 'much better'. Reported problems included difficulty in getting close to the operating table at caesareans and trip hazard from gas hoses.

When interviewed, parents said that they liked having their baby close and they felt reassured knowing what was going on. Some felt that their watching helped staff communicate with them. Others said that they would have liked more explanation. No parent whose baby received intensive intervention, such as intubation and cardiac massage, expressed regrets about watching.

Clinicians interviewed were also largely positive about care beside the mother, and felt that allowing parents to see and touch their baby at birth was especially important if the baby was subsequently admitted to the neonatal unit. They reported positive comments from parents about being close to their baby, and none mentioned negative comments. Most clinicians had no reservations about parents watching them, but some thought that staff with less experience might feel insecure. Practical challenges at caesarean sections were that parents were sometimes unable to see their baby, scrubbing for the sterile field took time and the trolley controls were under sterile drapes.

We also showed that neonatal care can be provided beside the mother using standard resuscitation equipment. This has advantages of being already available and staff being familiar with its use. Further research should assess experiences in other hospitals, using a trolley or standard equipment, and including parents from more diverse backgrounds and babies requiring advanced resuscitation.

Work package 4

This pilot trial assessed the feasibility of conducting a large UK multicentre randomised controlled trial comparing deferred cord clamping (after at least 2 minutes) and immediate neonatal care with the cord intact, with immediate clamping (within 20 seconds) and immediate neonatal care after cord clamping for very preterm births. Initially, recruitment was for 1 year but, as feasibility was demonstrated, the study continued while funding for the main trial was sought, but it closed when the application was unsuccessful.

Recruitment was above target, largely because of the two-stage consent pathway that allowed women to be offered participation when birth was imminent. Overall, 261 women were randomised and gave birth to 276 babies. Randomisation was across the range of gestation. Compliance with the allocated interventions was good. Fewer babies allocated to cord clamping after at least 2 minutes died than those allocated to cord clamping within 20 seconds, but the difference was not statistically significant. Three-quarters of deaths were in infants born before 28 weeks' gestation. For live births, there was no clear difference in intraventricular haemorrhage, or other outcomes at discharge for baby or mother.

Women's experiences of the two consent pathways were similar. Those recruited following oral assent reported having less information about the trial, but felt that it was sufficient to make their decision. Irrespective of the consent pathway, there were gaps in women's understanding. Clinicians were supportive of the two-stage consent pathway in time-critical situations and thought that providing information on a 'need-to-know' basis was an advantage over the usual process. They emphasised the importance of a team approach to inviting participation, regardless of the consent pathway. In the questionnaires at 1 year, women were largely positive about the trial. Suggestions about what could have been improved included being approached earlier in labour and better communication about the study from staff.

At the age of 2 years (corrected for gestation at birth), we found no clear difference in the composite of death or adverse neurodevelopment between the allocated groups after adjusting for missing data using multiple imputation.

Work package 5

A key challenge here was unpredictability of the time scale for analysis. The number of new trials has increased (29 registered in the past 2 years) but many are small and had begun data analysis before being

contacted. Therefore, we expanded the protocol to include a retrospective individual participant data meta-analysis. Currently, we know of 53 trials involving 11,811 infants (3020 for long-term outcomes). This meta-analysis will inform future trial design.

Conclusions

Central to the success of the programme was service user representatives being equal partners throughout. Parent experiences were heard and explored throughout. This allowed us to tackle emotive issues at very preterm birth, such as neonatal care in the delivery room and seeking consent for participation in an intrapartum trial.

Our work on neonatal care beside the mother brings family-centred care to the delivery room and has major implications for maternity services. Although this is a relatively simple change in practice, it requires a change in culture to multidisciplinary teamworking. Both parents and clinicians felt that this improved communication. The trolley was important in providing 'proof of concept' for care beside the mother, but existing equipment can be used. Hospitals can use the questionnaire we developed on parents' experiences.

Limitations of our work include participants in the prioritisation process not being representative of those most affected by preterm birth, the small sample for the qualitative interviews about preterm birth, evaluation of neonatal care beside the mother being conducted at a single hospital, and the randomised trial being a pilot.

Key implications for future research for funders and researchers:

- Consider the top 30 research priorities, ranked by those affected by preterm birth and by health-care professionals.
- Improve understanding of parent experiences at preterm birth through further research involving parents (including fathers) from a wider range of backgrounds and settings.
- Evaluate neonatal care beside the mother in a wider range of settings, using standard equipment or the mobile trolley (e.g. in a multicentre randomised controlled trial).
- Evaluation of interventions around the time of preterm birth in large multicentre NHS trials is feasible and should be considered.
- The two-stage consent pathway should be included in future intrapartum clinical research trials, and merits evaluation in other emergency or time-critical trials.
- Design of future clinical research trials comparing alternative policies for cord clamping should take account of results from our trial and the planned individual participant data meta-analysis.

Study registration

The study is registered as PROSPERO CRD42012003038 and CRD42013004405. The Cord pilot trial is registered as ISRCTN21456601.

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SYNOPSIS

Background

Being born too early (preterm birth) has a major impact on survival and quality of life for the child, on psychosocial and emotional stress on the family, and on costs for health services and society.¹⁻³ Mortality is highest for infants born very preterm, before 32 weeks' gestation. In the UK, infant mortality (deaths in the first year of life) for babies born very preterm is 144 deaths per 1000 live births, compared with 1.8 deaths per 1000 live births at term.⁴ Although only 1.4% of live births in the UK are very preterm, these babies account for 51% of infant deaths.⁴

The costs of neonatal care for infants born very preterm are high. For those born before 28 weeks' gestation, duration of hospital stay is 85 times that for term births and hospital inpatient costs are £15,000 higher. For those born at 28 to 31 weeks, duration of hospital stay is 16 times that for term births and hospital inpatient costs are £12,000 higher.⁵ Morbidity among children born very preterm who survive is also higher than those born at term.³ Of very preterm infants who survive, around 5% develop cerebral palsy and those without severe disability have a twofold or greater increased risk for developmental, cognitive and behavioural difficulties.^{1,2} These impairments may persist into adolescence and early adulthood.^{6,7} Even modest improvements in outcome would be of substantial benefit to the children, their families and the health services.

Aims and objectives

The aims of this programme were to improve the quality of immediate care at very preterm birth, enhance family-centred care, and improve outcome for infants born very premature and their families.

Specific objectives were to:

- Develop a James Lind Alliance (JLA) Priority Setting Partnership (PSP) between service users and clinicians to identify and prioritise treatment uncertainties relevant to preterm birth (work package 1; *Figure 1*) and to:
 - identify and prioritise research gaps for preterm birth, using the methods developed by the JLA
 - describe how service users and clinicians interact when making collective decisions about research priorities, and how they communicate when deciding research priorities together.
- Develop strategies for providing initial neonatal care at birth beside the mother, rather than away from the mother, for preterm or sick babies by:
 - conducting a survey of current practice for initial neonatal care with the cord intact at NHS hospitals (work package 3.1)
 - describing parents' experiences and views of care at very preterm birth, and developing a questionnaire tool to assess their views of care at very preterm birth (work package 3.2)
 - improving understanding of the physiology of transition from fetal to neonatal circulation by measuring umbilical flow at preterm birth and assessing how it varies with gestation (work package 3.3)
 - conducting systematic reviews and overviews (umbrella review) to assess the evidence for delivery room transitional assessment and support, and to identify research gaps (work package 2.1)
 - developing a mobile Bedside Assessment, Stabilisation and Initial Circulatory Support (BASICS) trolley to support providing newborn life support beside the mother, and with the cord intact (work package 3.4)
 - describing parents' and clinicians' experiences and views of neonatal care at birth beside the mother, and of the BASICS trolley (work package 3.5).

- Generate information that will inform the design of a high-quality large multicentre UK trial comparing a policy for very preterm births of deferred cord clamping and initial neonatal care with umbilical cord intact, against immediate clamping and initial neonatal care after cord clamping, by:
 - conducting a narrative systematic review (framework synthesis) to identify the ethical challenges and their potential solutions in consent to recruitment of preterm or sick infants to clinical trials (work package 2.2)
 - conducting a pilot randomised trial comparing deferred cord clamping and initial neonatal care with the cord intact, against immediate clamping and initial neonatal care after cord clamping for very preterm births, including follow-up of the women for 1 year and until 2 years of age (corrected for gestation at birth) for the children (work package 4)
 - establishing a collaborative group to conduct a prospective meta-analysis of trials evaluating alternative strategies to influence placental transfusion at preterm birth, and developing the protocol for this analysis (work package 5).

The prioritisation process ran in parallel to other work packages. It was added to the programme in response to feedback from the funding board at stage 1 of the grant application process. Hence, other work packages were not dependent on its outcomes. Although cord clamping did emerge as a top priority, we had already identified this as a priority via an informal process.

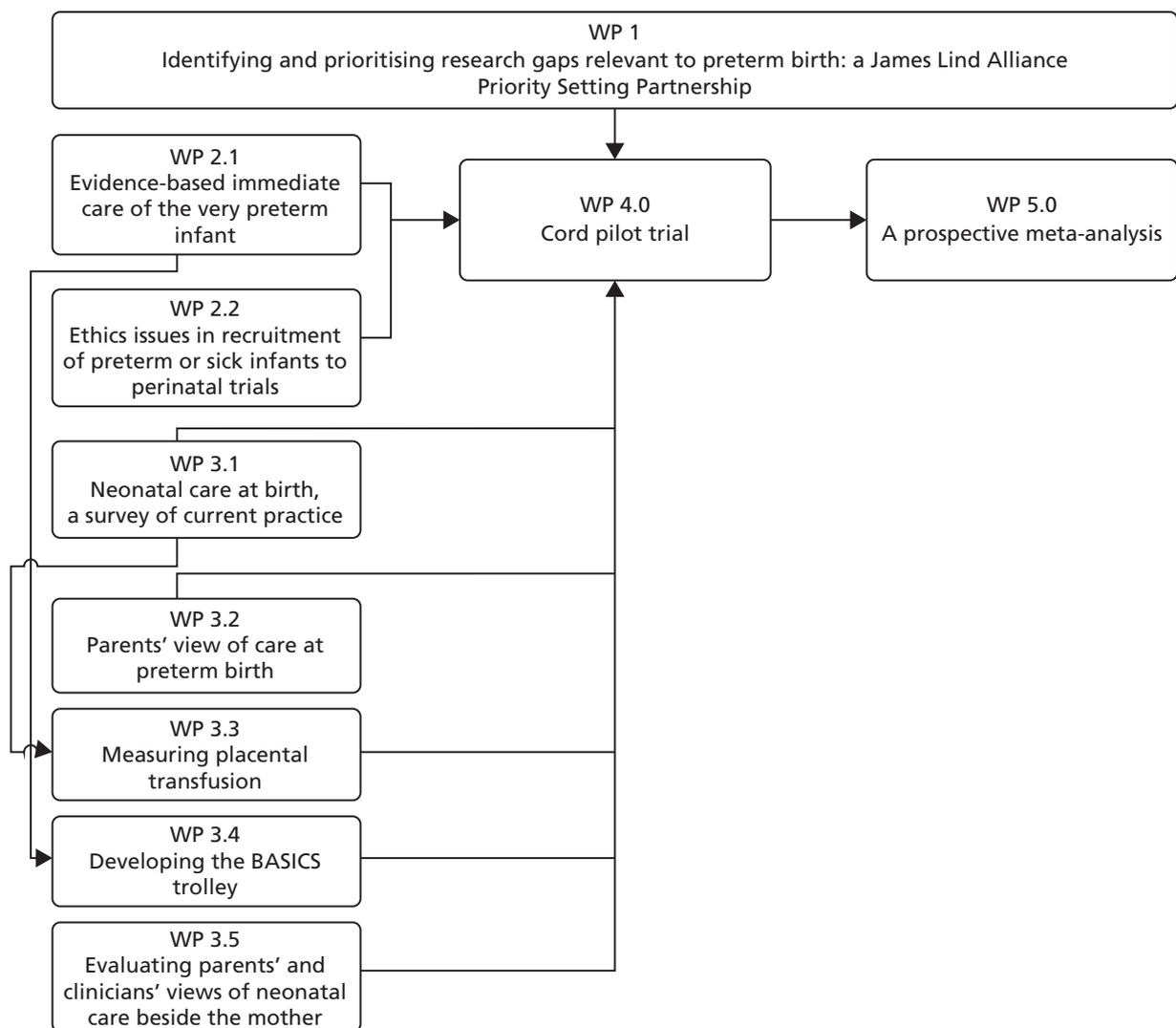


FIGURE 1 Overview of work packages. WP, work package.

Priority setting for future preterm birth research

In the past, the health-care research agenda was determined primarily by researchers, and the processes for priority setting in research lacked transparency.⁸ Often, research does not address the questions about treatments that are of greatest importance to patients, their carers and practising clinicians.^{9,10} Many research questions have not been investigated and for many more the existing evidence is incomplete. The JLA (www.lindalliance.org/; accessed 24 January 2019) has developed methods for bringing patients and clinicians together to establish PSPs that then identify and prioritise ‘treatment uncertainties’ to inform publicly funded research.¹¹ This approach has been used successfully for a wide range of topics including asthma,¹² urinary incontinence,¹³ vitiligo,¹⁴ prostate cancer^{15,16} and schizophrenia.¹⁷ For urinary incontinence, of the top 10 priorities, five came from clinicians, four from patients and one from researchers.¹³

When uncertainty about the effects of treatments relates to preterm birth, it seems particularly pertinent that research should address the most important priorities, and the most pressing needs, of these vulnerable children and their families and clinicians. Failure to identify and prioritise these uncertainties may result in suffering and death.¹⁸ Examples in perinatal care where this failure to identify and prioritise important uncertainties has happened include the use of caffeine, which was shown to reduce the risk of cerebral palsy and developmental delay, and so was widely taken up in clinical practice, but only 30 years after being suggested for prevention of apnoea in premature babies.^{19,20} In addition, the use of magnesium sulphate, which, after 60 years of controversy, was finally shown to be better for women with eclampsia than either diazepam or phenytoin.^{21–23} Although the importance of women and their clinicians contributing to the perinatal research agenda is well established,⁸ we proposed the first PSP in the perinatal field.

To establish a PSP required bringing together representatives of women and their families and of clinicians and other health-care workers. Understanding of how people interact and make collective decisions in groups or committees with members from diverse organisations comes from health research, and from social psychology and business administration.²⁴ Larger groups may increase membership diversity,²⁵ although this may be offset by a reduction in reliability of decision-making. The chairperson is crucial for establishing inclusiveness, openness and trust in the discussion.^{25–28} If time is short, less knowledge is shared and evaluated and then decisions result more from judgement based on prior preferences than problem-solving,²⁹ which may mean that they are more influenced by an individual’s status within the group.²⁵

When we planned the Preterm Birth PSP, evidence about how service users and clinicians make joint decisions on research priorities was lacking.²⁴ Improved understanding of how such partnerships work (e.g. if expertise based on qualifications, experience or problem-solving skills influences decisions³⁰ or if the way arguments are framed changes as consensus develops) may offer insight into how the process could be improved.

The Preterm Birth PSP published a list of the top 15 research priorities,³¹ which is being used by the National Institute for Health Research (NIHR) and by researchers in planning new research. Study of the groups’ working processes has also led to recommendations about how decision-making might be improved.

Parents’ views and experiences of very preterm birth

Very preterm birth and subsequent hospitalisation of the baby can be an extremely distressing time for parents.^{1,32} There has been little research into parents’ experiences at the time of very preterm birth, or their satisfaction with their care during the birth. In addition, previous work has often failed to include fathers. Women’s views and experiences during labour and childbirth are increasingly important to health-care providers and policy-makers,³³ and may have an impact on subsequent health and well-being for the woman and her baby.^{34,35}

To ensure a strong parent focus throughout our programme, we planned qualitative interviews to explore parents' experiences of very preterm birth and their first moments with their baby.^{36–38} Regular multidisciplinary project meetings to plan these interviews, and to discuss the emerging themes and verbatim transcripts, were immensely valuable for subsequent work packages. These were particularly valuable for developing strategies for neonatal care beside the mother, and for planning the pilot trial. Our experience in conducting these interviews also contributed to further qualitative work exploring the views of both parents and clinicians of neonatal care at birth beside the mother,^{39,40} and of the new two-stage consent pathway in our pilot trial.^{41,42}

A number of instruments have been developed to assess women's satisfaction with care during childbirth. When planning our programme we were not aware that any of these were designed to be used following very preterm birth, which is usually a different experience from giving birth to a healthy term baby. To confirm this we conducted a systematic review of available measures to assess parents' satisfaction with care during labour and birth.⁴³ Having demonstrated there was not a suitable tool for very preterm birth, we developed a 20-item questionnaire called Preterm Birth experience and Satisfaction Scale (P-BESS) for use in this situation.⁴⁴ We used this questionnaire for the follow-up of women recruited to our pilot trial. It has been translated into Spanish and Portuguese.

Placental transfusion and neonatal transition

At birth, if the umbilical cord is not clamped then blood flow between the baby and the placenta may continue for several minutes.^{45–48} This umbilical flow is part of the physiological transition from fetal to neonatal circulation, which, for very preterm infants, may improve resilience during this transition.^{49–51} 'Placental transfusion' refers to the net transfer of blood to the baby between birth and cord clamping.

Cord clamping before umbilical flow ceases may restrict neonatal blood volume and red cell mass, and/or disrupt transition from fetal to neonatal circulation. For term births, umbilical flow usually continues for 2 minutes, but may continue for over 5 minutes.^{46,48} The mean volume of placental transfusion at term is 100 ml, which is 29 ml/kg birthweight and 36% of neonatal blood volume at birth.⁴⁸ For preterm births, umbilical flow may continue for longer than for term births⁵² and is incomplete if the cord is clamped in 30–90 seconds.⁵³ This corresponds with development during gestation; at term, two-thirds of the fetoplacental circulation is in the infant, whereas for those born below 30 weeks' gestation, a greater proportion of the fetoplacental circulation is in the placenta.⁴⁵ In addition, the preterm umbilical vein is smaller than at term, and uterine contraction less efficient; therefore, transition from the fetal to the neonatal circulation may be slower. Cord milking or 'stripping' seems to be an attractive option for preterm births, as potentially it increases neonatal blood volume without the need to defer cord clamping.⁵⁴ However, cord milking over-rides the infant's physiological control of its own blood volume and blood pressure, and it interrupts transition to the neonatal circulation.⁵⁵

To improve understanding of the physiology of placental transfusion and assess when might be the best time to clamp the cord for preterm births, we measured umbilical flow at preterm birth. Although this proved to be more challenging than we had anticipated, the resulting data helped to inform the decision to wait at least 2 minutes before clamping the cord in the pilot trial.

Neonatal stabilisation and resuscitation at birth beside the mother

In the UK, about one-third of all newborn babies are attended at birth by neonatal resuscitation staff. For most, all that happens is an assessment, stimulation, thermal care and simple airway management. However, around 15% of these babies receive active stabilisation and/or resuscitation at birth, such as mask ventilation, intubation, cardiac massage or drug administration.

Transition to the neonatal circulation begins at birth when pulmonary vascular resistance falls as the lungs expand and fill with air, pulmonary blood flow increases and ductal blood flow declines as peripheral resistance falls.⁵⁶ Stabilisation at very preterm birth aims to assist this transition, and recommendations for newborn life support for very preterm infants are to prioritise establishment of respiration and a resting lung volume.⁵⁷ Traditionally, this was facilitated by immediate cord clamping, allowing the baby to be transferred quickly away from the mother for interventions such as airway opening manoeuvres, continuous positive airways pressure (CPAP) and tracheal intubation with or without prophylactic surfactant administration.

Providing initial neonatal stabilisation and resuscitation for very preterm or sick infants beside the mother would potentially allow newborn life support to be provided with the cord intact, facilitating a longer period before cord clamping than was possible at the time when we were planning this programme. It would also allow the woman and her partner to share the first moments of their child's life, a more family-centred approach to care at birth.^{58,59} Family-centred care in neonatal units, with improved communication and involvement of parents in their baby's care, appears to benefit babies, is welcomed by parents⁶⁰ and has been prioritised by the NHS.⁶¹ Providing initial neonatal care beside the mother also has parallels with family presence during resuscitation of adults and children, an approach that is preferred by families and clinicians, and that appears to be beneficial.^{62–65} Should the baby subsequently die, this time spent with the parents may prove to be an important factor in their experience of the life of their baby, and could potentially be of benefit in bereavement.

At the start of our programme, information about neonatal care beside the mother within the UK was anecdotal.^{53,66} Therefore, we began by describing current practice at that time for care at birth^{67,68} and by assessing the evidence from randomised trials for delivery room neonatal interventions. We then developed and piloted strategies for providing initial neonatal care beside the mother, and assessed whether or not this was acceptable to parents and clinicians. This included both developing a new mobile trolley designed specifically for this purpose⁶⁹ and adapting the existing equipment.⁷⁰ Our work demonstrating that providing newborn life support beside the mother is valued by parents and clinicians,^{39,40} and that care with the cord intact is feasible, contributed to the success of the Cord pilot trial.⁷¹ Providing neonatal care beside the mother, with the cord intact, compared with after clamping and cutting the cord, has growing interest nationally and internationally.^{72,73}

Ethics issues in recruitment of preterm or sick infants to perinatal trials

Recruitment of preterm or sick infants to clinical trials requires approaching parents at a particularly difficult time, often with a tight time scale for making a decision. This raises challenges for obtaining informed consent to such research, especially issues regarding competence for consent, understanding of complex issues, insufficient time for parents to consider participation, and voluntariness if parents have a sense of obligation or feeling of debt to the clinician-researcher who is caring for their child.⁷⁴ On the other hand, if the problem of consent is not successfully addressed, this risks becoming an 'orphan' area of research. That is, if ethically permissible research cannot be designed, then this area of medical research will be abandoned.

Earlier work has explored these difficulties, specifically in the neonatal context.⁷⁴ Discussion of both the nature and the importance of consent, as well as empirical work on methods of obtaining consent and parental experience of those methods, has continued.^{75–77} Hence, when we planned our programme it seemed timely to review understanding of these ethics issues in the light of this expanding literature, and of both the changing regulation for clinical trials and the increased public expectations of the conduct of research. Our overall aim was to identify a way of conducting ethical neonatal research in those circumstances where obtaining valid consent from parents has proved to be a significant challenge. The goal was to identify both the challenges to an ethically defensible consent process and their potential solutions.^{78,79} This led to the development of a two-stage pathway for consent used and evaluated in the Cord pilot trial.

This pathway accounted for almost one-third of recruitment to the trial, and was viewed positively by both parents and clinicians.^{41,42} It was rapidly included in updated guidance for intrapartum research from the Royal College of Obstetricians and Gynaecologists.^{80,81} The same two-stage approach has also been adapted for use in an acute stroke trial, for which randomisation is within 8 hours of the stroke.⁸²

Systematic review of timing of cord clamping at very preterm birth

Thirty years ago, it was first suggested that immediate cord clamping for preterm babies might increase the risk of intraventricular haemorrhage (IVH).⁸³ Postulated mechanisms for this increase were hypovolaemia or increased fluctuation in blood pressure during the abrupt transition from fetal to neonatal circulation.

At the time that we planned this programme, the Cochrane review of timing of cord clamping and other strategies for influencing placental transfusion at preterm birth included 10 trials, with 454 mother–infant pairs largely recruited before 33 weeks' gestation.^{84,85} In these trials, deferred cord clamping ranged from 31 to 120 seconds and immediate cord clamping ranged from 5 to 20 seconds. Many outcomes were reported by only a few studies, with potential for reporting bias. Immediate clamping was associated with an increased risk of transfusion for anaemia [relative risk (RR) 1.57, 95% confidence interval (CI) 1.14 to 2.16; four trials, 183 infants] or hypotension (RR 1.94, 95% CI 1.06 to 3.54; 3 trials, 90 infants) compared with deferred clamping. The risk of IVH on ultrasound scan was also higher for babies allocated immediate clamping (RR 1.90, 95% CI 1.27 to 2.84; seven trials, 329 infants), but for severe IVH (grade 3 or 4), a more reliable predictor of long-term outcome, there was no clear difference (RR 1.17, 95% CI 0.27 to 5.02; five trials, 269 infants). There was no clear difference between the groups in temperature on admission to a neonatal unit, but only three trials (143 infants) reported this outcome. One study had reported follow-up at a median age of 7 months for 58 out of 67 surviving infants, with no clear differences between the groups.⁸⁶

Alternative policies for timing of cord clamping at very preterm birth

In previous trials for deferred clamping, the decision about when to clamp the cord was usually a balance between allowing some umbilical flow and what was perceived as an acceptable delay in transferring the baby to the neonatal team. As standard practice was for the neonatal team to be located either at the side of the room or in a room nearby, this necessitated early clamping and cutting of the cord, particularly for infants requiring stabilisation or resuscitation at birth. Therefore, providing initial neonatal care at birth with the cord intact would make it feasible to defer cord clamping for longer than had previously been possible, including for high-risk infants who have the most potential for benefit.

Our programme to improve the quality of care and outcome at very preterm birth focused on care at the time of birth. We reviewed evidence from systematic reviews^{36–38,67,68,70,78,79,87} relevant to delivery room neonatal care, surveyed current practice, described parent experiences, measured umbilical blood flow, developed strategies for providing newborn life support beside the mother, and reviewed ethics issues in recruitment of preterm and sick babies to clinical trials. These work packages all contributed to the design and conduct of the Cord pilot trial, a pilot randomised trial to assess the feasibility of conducting a large UK trial comparing alternative strategies for cord clamping. To provide adequate power for long-term follow-up of the children and inform the design of a large definitive trial, we planned a prospective meta-analysis of similar studies.

This focus on the time of birth and cord clamping was identified as a priority by informal discussion with parent representatives,⁸⁸ and parent representatives worked in partnership with clinicians and researchers to develop the application and conduct the research. The topic had also been identified as a research priority by researchers,^{58,84,85,89} obstetricians,⁹⁰ midwives,⁹⁰ neonatologists (Duley L, Farrar D, McGuire W, Oddie S. *Survey of the Extended Neonatal Network to Assess Views on Timing of Cord Clamping and Placental Transfusion: Report Prepared for the Extended Neonatal Network*. 2009. Unpublished), the National Institute for Care Excellence (NICE),^{91,92} and the Royal College of Obstetricians and Gynaecologists.⁵⁹ Therefore, it was unsurprising that this uncertainty was included in the list of top priorities from our JLA Preterm Birth PSP.³¹

Changes from the original programme plan

The phrase 'preterm birth' is broad. Our programme had a specific focus on care around the time of birth, and our intention was that this would be reflected in the scope of our JLA PSP (work package 1). However, from the initial scoping meeting, it was clear that both service users and clinicians had a different view and the discussion ranged from risk factors to prognosis and the grandparent perspective. This continued at the first meeting of the partnership steering group. As the partnership was between service users and clinicians, the researchers agreed that their views should determine scope. The challenge of too wide a scope led to delays in progressing the priority setting, and the process progressed only once it was agreed that this should be narrowed. This delay and the resource demands of the priority setting process meant that it was not possible to conduct the planned work on outcomes.

Although our sampling frame for the qualitative interviews with parents (work package 3.2) included one hospital where deferred cord clamping was in routine practice for very preterm birth, no parents interviewed had experienced neonatal care beside the mother. It was, therefore, not possible at that time to assess their experiences of this type of care. Instead, we did this by assessing parent and clinician experiences of neonatal care beside the mother using semistructured interviews, rather than the planned focus groups (work package 3.5). This was in order to gain more detailed accounts of the events and experiences than would be available in a focus group. In addition, because in focus groups individuals might be reluctant to disagree with the dominant view, you get a socially constructed view rather than people's individual views and experiences.

Measuring placental transfusion at preterm birth proved to be far more challenging than our earlier work at term birth.⁴⁸ This was primarily because of the unpredictability of preterm birth, which made it difficult for the research team to be present and with the equipment set up in time for the birth. As we secured funding to assess feasibility of a similar trial in low and middle income countries, this study was replicated successfully in India.⁴⁷

The Cord pilot trial was conducted as planned. Added value of this multidisciplinary programme led to several additional elements. First, innovative methods for consent to participate in emergency perinatal trials was identified as a research gap by the ethics framework review. This led to the development of a two-stage oral assent pathway used in the trial when birth was imminent, which boosted recruitment. Second, to evaluate this pathway we used our experience of semistructured interviews with parents and clinicians (work packages 3.2 and 3.5) and of the framework analysis of ethics issues (work package 2.2) to design and conduct qualitative interviews with women and clinicians who had experience of consent in the Cord pilot trial. Finally, excellent recruitment contributed to the Trial Steering Committee (TSC) assessment that feasibility had been demonstrated and that we should seek funding to progress to the definitive trial. The TSC also recommended that recruitment continue while funding was sought, to avoid 'stop/start'. Hence, recruitment was extended and only closed when the funding application was rejected. To maximise the value of this additional recruitment, follow-up of both women and children was also extended and data for all those randomised are presented here.

For the prospective meta-analysis, the first cycle of analysis had been planned within the programme. However, as data from the two largest studies (Cord pilot trial⁹³ and the Australian Placental Transfusion Study⁹⁴) were not available within the time scale of the programme, this analysis has been postponed. In addition, the collaborative group of triallists has agreed to expand the protocol to a retrospective individual participant meta-analysis with nested prospective meta-analysis.

Programme management

The co-applicants formed a programme steering group to oversee implementation of the research programme as well as integration and timely delivery of the work packages. This group met every 4 months for the first 3 years, and every 6 months thereafter. A project management group of coinvestigators supported each work package. In addition, the JLA Preterm Birth Priority Setting Partnership (PSP) formed a steering group from

membership organisations and stakeholders, and independent oversight of the Cord pilot trial was by an independent TSC and Data Monitoring Committee.

Patient and public involvement

Throughout this report, we use the term ‘service users’ to describe patient and public involvement. Because having a baby is a physiological event, pregnant women and parents are not ‘patients’. The topic of when to clamp the umbilical cord at very preterm birth was identified through discussion with parent representatives, including Gill Gyte, offering perspectives from the National Childbirth Trust (NCT). Consultation with parents, through Bliss, quickly made clear that parents viewed change in practice at this difficult time with considerable caution. A strong parent perspective throughout the planning and conduct of our research was clearly essential to ensure relevance, quality and a timely delivery. This was achieved through partnership with representatives of the NCT (<https://www.nct.org.uk/>) (GG) and Bliss (<https://www.bliss.org.uk/>) (Jane Abbott and Zoe Chivers). Their input included being co-applicants in the grant application, membership of the programme steering group, membership of most project management groups, co-authorship of many programme publications, and active dissemination of outputs through their organisations. Success of this collaboration was reflected in a Bliss ‘Advancing care through research’ award for the programme.

Additional patient and public involvement contributed to the JLA Preterm Birth PSP, which involved both service user organisations and service users (parents and adults born premature). A personal reflection from one service user member of the steering group demonstrates both the value and the challenges of such involvement (*Box 1*). In addition, the TSC for the Cord pilot trial included two independent parent representatives, and parents commented on information for participants.

BOX 1 Personal reflections from a parent member of the steering group for the JLA Preterm Birth PSP

In the early part of 2012, I received an e-mail in my work capacity at the charity KIDS. Attached to the introductory e-mail was a survey about preterm birth research, which I circulated to my caseload of parents in the London borough of Camden. I then completed the survey myself, as I also happen to be a parent of a daughter who was born 11 weeks prematurely.

I was at the time just completing a Master’s degree and my research dissertation regarded an aspect of preterm birth and the development of Cerebral Palsy. With this added interest, I contacted the researcher who had sent out the survey in order to discuss the research further. During our meeting, she mentioned that a fundamental part of this project was for service users and health-care professionals to come together to set priorities and that my involvement, as a parent, within the steering group would be most welcome.

The journey that followed was both fascinating and rewarding. There was a steep learning curve about a process like this – which saw the identification of unanswered questions about causes, care and treatment of preterm birth through to the prioritisation by service users, clinicians and researchers of the Top 15 issues for future research. There was also great validation in being a respected and involved participant of the steering group throughout the process, culminating in my presentation of the parent perspective on this piece of work at the European Congress of Perinatal Medicine in Florence (where our work won a prize in the top 6)!

Having felt incredibly held and supported during steering group meetings where my contribution was encouraged and valued, there were times, particularly during group conference calls or in the e-mail rounds, when I wondered whether my input was necessary or appropriate and I often felt quite overwhelmed by the scientific complexity of the overall process and project. This seems pertinent to acknowledge in a field that has patients at its centre, but often has to go beyond their sphere of understanding or comfort.

BOX 1 Personal reflections from a parent member of the steering group for the JLA Preterm Birth PSP (*continued*)

Initially it felt that my value was to bring in my personal experience, and I was often called on to reflect my perspective as someone who had been impacted by preterm birth. However, at times it was hard to know how to pitch this within the high level of theoretical rhetoric, both from a medical and a research position. I did often wonder at how the personal voice can be lost in the higher level of complexities and detail.

All of that said, the overarching feeling has been one of being embraced and encouraged, with the reminder that this sort of collaborative work brings together individuals with very different skills and experience for a reason. The process as a whole felt empowering and the knowledge that my personal experience was playing a vital part in bringing fresh understanding was validating.

Bev Chambers

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Work package 1: identifying and prioritising research gaps relevant to preterm birth – a James Lind Alliance Priority Setting Partnership

See *Appendices 2–4* for the published and unpublished reports of this work.

Research aims

Our aims were to:

- identify and prioritise research gaps relevant to preterm birth that are most important to people affected by preterm birth and health-care practitioners in the UK
- describe how service users and clinicians interact when making collective decisions about research priorities, and how they communicate when deciding research priorities together.

Identifying and prioritising research gaps relevant to preterm birth

Prioritisation process

Using methods established by the JLA,⁹⁵ we first identified unanswered questions about the prevention and treatment of preterm birth from people affected by preterm birth, clinicians and researchers. Then we prioritised those questions that people affected by preterm birth and clinicians agreed are the most important (*Figure 2*).

Initiation of the partnership

The Preterm Birth PSP was initiated in November 2011, following an earlier introductory meeting of potential stakeholders. The 29 participating organisations were asked to complete a declaration of interests, and a steering group was convened that included members from nine of these organisations. At the introductory workshop it was clear that many participants felt that the scope of the partnership should be wider than was initially envisaged, for example including uncertainties about the causes of preterm birth, the prognosis following being born preterm, and interventions long before birth.

Consultation

As widening the scope too far risked making the prioritisation unachievable, the steering group restricted the scope to uncertainties about treatments and to interventions during pregnancy and around the time of birth or shortly afterwards (taken up to the time of hospital discharge for the baby after birth).

Research questions were gathered from people affected by preterm birth, clinicians and researchers using methods developed by the JLA.⁹⁵ This included a survey completed online by 349 people, and in paper format by 37 women attending specialist preterm birth antenatal clinics at two tertiary level hospitals and parents visiting two neonatal intensive care units. These 386 responses contained 593 potential research questions. In addition, 540 potentially relevant research questions were identified from systematic reviews of existing research and from national UK clinical guidelines.^{96–107}

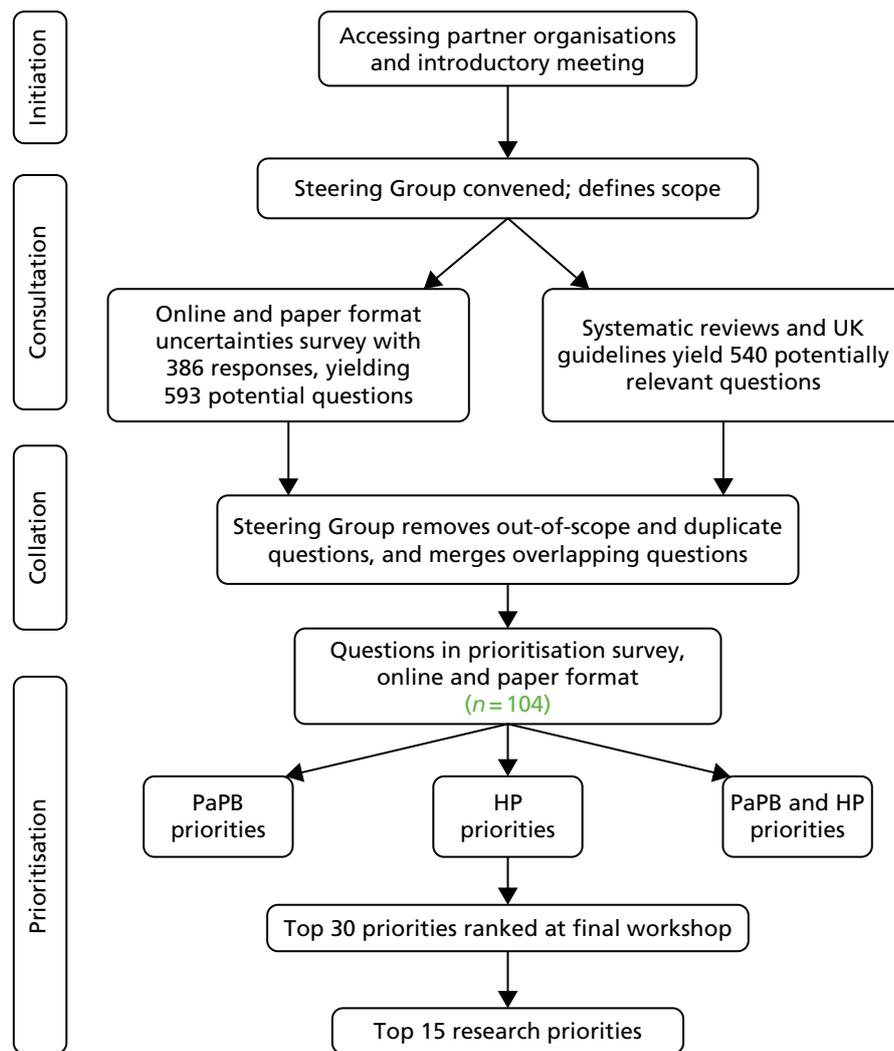


FIGURE 2 Flow chart of the JLA Preterm Birth PSP. HP, health professional; PaPB, people affected by preterm birth.

Collation

All questions were screened to identify those sufficiently similar to either merge or group into broader questions and to remove any that were out of scope, unclear or being answered by a subsequent or in-progress randomised trial. This left 70 unanswered questions from the survey, 28 from systematic reviews and 24 from clinical guidelines remaining in the process. Of these 122 questions, 18 overlapped with other questions and were merged to give a final 'long list' of 104 unanswered research questions.

Prioritisation

This was a two-stage process. First, the long list of 104 questions was sent out for voting on the top 10 questions, online and in paper format, using a modified Delphi survey. The steering group reviewed ranking by the 507 people who voted, overall and by stakeholder group. They removed remaining overlap or repetition between questions, before agreeing the shortlist of 30 questions to go forward to the second stage: a prioritisation workshop. This workshop had 34 participants, including representatives from people affected by preterm birth and clinician organisations as well as parents of babies born preterm and adults who were born preterm. At the workshop, nominal group technique⁹⁵ was used to achieve consensus on ranking the 30 questions.

Key findings

We identified 104 unanswered research questions (Oliver S, Duley L, Uhm S, Crowe S, David A, James CP, et al. *Top Research Priorities for Preterm Birth: Results of a Prioritisation Partnership Between People Affected by Preterm Birth and Healthcare Professionals*. Unpublished). Consensus was not achieved on a top 10, and so a top 15 research priorities was agreed (Box 2).³¹ This top 15 had significant differences to the ranking following public voting. The most noticeable were two questions ranked 18 (*How do stress, trauma and physical workload contribute to the risk of preterm birth, are there effective ways to reduce those risks and does modifying those risks alter outcome?*) and 26 (*What treatments can predict reliably the likelihood of subsequent infants being preterm?*) at the workshop. These were outside the top 15 but had been ranked 3 and 4, respectively, in the public vote.

Describing how service users and health-care professionals interact when making collective decisions about research priorities

Methods for data collection

The study sample comprised attendees at 13 meetings of the Preterm Birth PSP: 12 steering group meetings (three conference calls, nine face to face) and the final prioritisation workshop. These were all recorded and transcribed. An ethnographical approach¹⁰⁸ was adopted with participant observation¹⁰⁹ and discourse analysis¹¹⁰ of the recordings, field notes and analysis of documentary records of meetings and steering group activities.

Analysis

Transcribed data were coded using an analytical framework based on the Elaboration Likelihood Model^{111–113} using NVivo 10 (QSR International, Warrington, UK) software. We coded discussion as using either a central route (rational argument with evidence) for persuasion or a peripheral route (relying on emotional responses

BOX 2 Top 15 UK research priorities for preterm birth.

1. Which interventions are most effective to predict or prevent preterm birth?
2. How can infection in preterm babies be better prevented?
3. Which interventions are most effective to prevent necrotising enterocolitis in premature babies?
4. What is the best treatment for lung damage in premature babies?
5. What should be included in packages of care to support parents and families/carers when a premature baby is discharged from hospital?
6. What is the optimum milk-feeding strategy and guidance (including quantity and speed of feeding and use of donor and formula milk) for the best long-term outcomes of premature babies?
7. What is the best way to judge whether or not a premature baby is feeling pain (for example, by their face, behaviours or brain activities)?
8. Which treatments are most effective to prevent early-onset pre-eclampsia?
9. What emotional and practical support improves attachment and bonding, and does the provision of such support improve outcomes for premature babies and their families?
10. Which treatments are most effective for preterm premature rupture of membranes?
11. When is the best time to clamp the umbilical cord in preterm birth?
12. What type of support is most effective at improving breast feeding for premature babies?
13. Which interventions are most effective to treat necrotising enterocolitis in premature babies?
14. Does specialist antenatal care for women at risk of preterm birth improve outcomes for mother and baby?
15. What are the best ways to optimise the environment (such as light and noise) in order to improve outcomes for premature babies?

Reprinted from *The Lancet*, Vol. 383, Duley et al.,³¹ Top 15 UK research priorities for preterm birth, pp. 2041–2, © 2014, with permission from Elsevier.

to cues such as authority, commitment, consistency, liking, reciprocation, social proof or scarcity). For example, prioritising a treatment because the speaker 'wanted to know if there would be better outcomes' was coded as 'central' because of its rational approach. Asserting 'I think this topic has to be number one because that is sort of nice' was coded as 'peripheral' with a 'liking' cue.

To investigate decision-making based on values, transcripts were coded into three types of discussion:¹¹⁴ informational (facilitator encourages participants to speak, defers controversy and lets participants know their ideas will not be evaluated), problematical (participants consider the information and/or values needed to address the issue intelligently) and reflexive (participants discuss their own discussion to learn from the process).

To understand the process of consensus development, the JLA approach was compared with the 'Group Development Model'¹¹⁵ (Figure 3), which argues that every group experiences these five stages before becoming a self-reliant unit. At each stage, the dynamics of the group change from periods of inefficiency and uneasiness through to a period of high performance.

Key findings

Throughout their meetings, steering group members used a central route pathway (281/502, 56%) more often than a peripheral route (221/502, 44%), and the peripheral cues they used most were 'commitment' and 'consistency'. During the final workshop, 'social proof' (i.e. peer pressure, 'we do this in our group') was used most frequently. Health-care professionals used the central route ($n = 33$) more than service users ($n = 15$), and service users used the peripheral route ($n = 23$) more often than health-care professionals ($n = 17$).

The main types of discussion were 'informational' and 'problematical', with 'problematical' increasing over time. For the first 18 months (up to compiling the long list of uncertainties) there were no 'reflexive' discussions, and these remained less frequent ($n = 9$) than 'informational' ($n = 104$) and 'problematical' ($n = 169$). For both 'informational' and 'problematical' discussion, speakers used central routes more often than peripheral ones. When they used peripheral routes, for 'informational' discussion they used all the peripheral cues. For 'problematical' discussion, cues used the most were 'consistency' during steering group meetings, and 'social proof' during the final workshop. 'Scarcity' was more common later in the process when there was more time pressure. Participants were less likely to accept peripheral route messages, although when supported by a central route message from another speaker it became more persuasive.

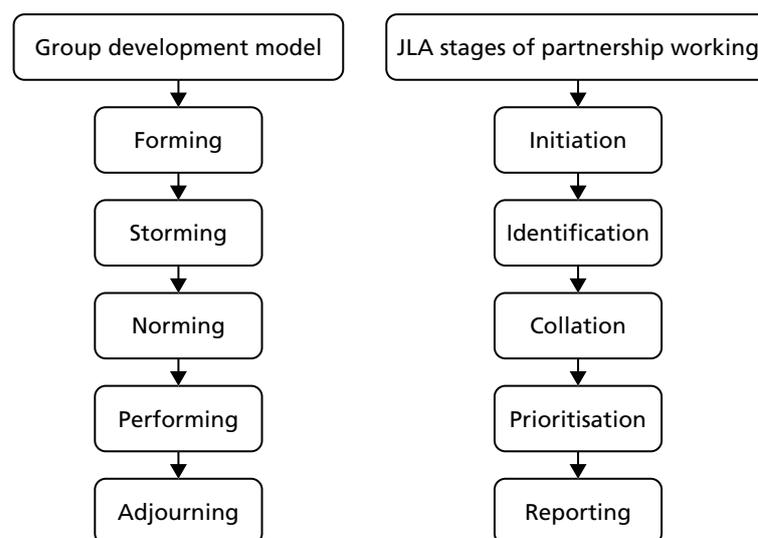


FIGURE 3 Group Development Model versus JLA stages of partnership working.

Four questions ranked in the top 10 after public voting were outside the final top 15. These were stress and physical workload, preventing subsequent preterm birth, screening in the first trimester and multiple birth. The last three moved down the ranking based on the argument that they were included in the overarching top ranked question 'Which interventions are most effective to predict or prevent preterm birth?'. Arguments against 'stress and physical workload' were that it was similar to another question and that it is not a conventional treatment and would be difficult to define or change.

There were similarities between the Group Development Model stages and the JLA PSP process, in particular that 'forming' (or team building) was comparable with 'initiation', and 'adjourning'¹¹⁶ was comparable with 'reporting'. At 'storming', team members were comfortable expressing discontent and challenging other opinions, and at 'norming' they had a common goal and shared responsibility for achieving it. In the PSP, these two stages were difficult to distinguish because the group repeated 'storming' after 'norming'. At 'performing', team members were competent, autonomous and able to handle the decision-making process, which was similar to 'prioritisation' in the PSP. However, when new members joined for the final workshop, this returned the group to an early development stage ('forming'), as they needed to get to know each other and define their roles and tasks. Only then could the group begin to 'perform' and prioritise the research questions. This discrepancy in terms of group development between steering group members and the new participants may have influenced the quality of the final consensus.

Strengths

Strengths of this Preterm Birth PSP include the large numbers of participants in the process and the range of stakeholders involved. Although several of the top priorities are already well recognised as important, such as what is the optimum milk-feeding regimen for preterm infants, others are indicative of areas previously under-represented in research (e.g. packages of care to support families after discharge and the role of stress, trauma and physical workload in the risk of preterm birth). This is in keeping with findings from previous JLA partnerships and highlights the value of shared decision-making.¹¹⁷

Challenges

Preterm birth is associated with factors such as lower socioeconomic status, ethnicity and maternal age.¹¹⁸ Despite implementing strategies to reach a representative population, our respondents remained primarily white and with a relatively high proportion of homeowners and so were not representative of those most affected by preterm birth. This may limit the relevance of these priorities to other populations.

The JLA PSP process uses a modified Delphi with individual voting, followed by a face-to-face workshop using Nominal Group Technique. Combining these two methods aims to maximise the advantages of both while minimising their disadvantages. The 'lost priorities' demonstrate that merging the two methods may, in some instances, weaken the benefits of each method. Large changes in ranking between individual voting and the final workshop appeared to be related to difficulty in the perspective of people affected by preterm birth being heard in the large group session, and a difference in the priorities of two key groups of health professionals (neonatologists and obstetricians).

Maintaining balanced representation between people affected by preterm birth and the different groups of health professionals for the final prioritisation workshop was challenging, and may have influenced the final ranking. The difficulty in achieving consensus underlines the complexity of priority setting for research, particularly for preterm birth. Pregnancy is not an illness or disease, and it involves at least two people (mother and child); preterm birth can have lifelong consequences for them and their families, as well as for the health services and society. This complexity and the differing priorities of different stakeholders make it important to consider the top 30 list, and the long list of 104 questions (Oliver *et al.*, unpublished), as well as the top 15 priorities, when planning and funding new research.³¹

Implications for future research

These 15 top priorities provide guidance for researchers and funding bodies to ensure that future preterm birth research addresses questions that are important both to service users and to clinicians. Although people affected by preterm birth and health-care professionals had many shared priorities, they had different perspectives on some questions. Priorities may also change over time and in different settings. Therefore, when planning and funding research it is important to consider not only the top 15 priorities but also the top 30 ranked by those affected by preterm birth and the top 30 ranked by health-care professionals.

Future prioritisation processes, particularly those with a similar wide range of health-care professionals, should endeavour to anticipate potential different perspectives and mitigate any imbalance where possible, and should report voting separately by 'service users' and health-care professionals. Health-care professionals who are also researchers should declare this potential conflict before participating in the prioritisation workshop, so that it can be taken into account.

Work package 2.1: evidence-based immediate care of the very preterm infant

Newborn infants who have delay in establishing independent respiratory effort after birth may require transition support in the delivery room. To support development of guidance for providing initial neonatal care beside the mother, and also to provide a context for determining how deferred cord clamping might be integrated with evidence-based transitional assessment and support practices in the Cord pilot trial, we conducted an overview or 'umbrella review' of relevant Cochrane reviews.

See *Appendix 5* for the unpublished report of this work.

Research aims

Our aims were to identify Cochrane reviews of delivery room transition support interventions, appraise review quality and identify important gaps in the evidence.

Methods for data collection

We undertook a systematic overview (umbrella review) using the standard methods of the Cochrane Collaboration and the Centre for Reviews and Dissemination.^{119,120} We registered the overview on PROSPERO (registration number CRD42012003038). We searched the Cochrane Database of Systematic Reviews¹²¹ (Issue 6, 2015) for reviews evaluating any intervention for delivery room support of newborn infants. We excluded reviews of interventions that are more usually or feasibly delivered following admission to the neonatal unit, and those administered to all infants as part of routine practice.

Analysis

For each review, two reviewers independently extracted information on review quality characteristics, and on the participants, treatment and control interventions, and outcomes. Review quality was assessed using the 11-item AMSTAR (A Measurement Tool to Assess systematic reviews) tool.^{122,123}

Key findings

Eighteen Cochrane reviews were identified. Broadly, these reviews assessed delivery room interventions for airway management, respiratory or circulatory support (four reviews); surfactant replacement therapy for preterm infants with or at risk of respiratory distress syndrome (eight reviews); supplemental oxygen or other drugs for infants compromised at birth (five reviews); and strategies for influencing placental transfusion (one review). The overall quality of reviews was good, but methodological quality of the included trials varied greatly. Four reviews had no included trials. The most commonly prespecified primary outcomes were death, incidence of chronic lung disease and neurodisability. Two reviews prespecified surrogate outcomes, such as physiological measures, rather than clinically important primary outcomes. There are few data on long-term neurodevelopmental outcomes.

Of the four reviews that assessed interventions to support the infant airway and breathing, two did not find any eligible trials and one included only a single small trial.^{124–126} The fourth review assessed delivery room airway support for infants at risk of meconium aspiration (four trials, 2884 participants) and concluded that there is no evidence that routine endotracheal intubation reduces mortality or morbidity in vigorous term babies with meconium staining compared with standard resuscitation.¹²⁷

The strongest evidence supported type and timing of surfactant administration for preterm infants. Two reviews, originally published in 1997, provided strong evidence that for very preterm infants, surfactant replacement reduced the risk of death by about 40%.^{128,129} A related review concludes that natural surfactant is more effective than synthetic surfactant for reducing the risk of death.¹³⁰ These reviews are now regarded as 'complete', as further trials would be unlikely to change their conclusions. Subsequent reviews found evidence that early surfactant administration with brief ventilation reduces the need for mechanical ventilation and associated morbidity, but that prophylactic (delivery room) administration is not more effective than delayed selective administration when infants have prophylactic nasal continuous positive airway pressure support.^{131,132} Uncertainty remains about the comparative effects of newer synthetic surfactants that contain surfactant protein mimics, and of novel non-invasive routes for administering these.^{133,134}

Five reviews assessed supplemental oxygen or other drugs for infants compromised at birth. One compared using air rather than 100% oxygen for newborn resuscitation at birth.¹³⁵ Five trials were identified (three were quasi-randomised), but the review concluded that there was insufficient evidence to support a recommendation for using either intervention. Three reviews assessed other drug interventions.^{136–138} Of these, two assessed adrenaline or sodium bicarbonate during resuscitation and found insufficient evidence for reliable conclusions.^{136,137} The third review assessed naloxone for infants exposed in utero to opiates and identified nine trials, but none assessed clinically important outcomes.¹³⁸ The fifth review examined interventions to prevent hypothermia in newborn very preterm infants,¹³⁹ and it concluded that various measures, including plastic wraps or bags and warming mattresses, reduce the risk of delivery room hypothermia, but found insufficient data to assess effects on infant morbidity and mortality.

One review assessed timing of cord clamping and other strategies for influencing placental transfusion at preterm birth.¹⁴⁰ This review found evidence that deferring cord clamping for 30–120 seconds, rather than clamping before 30 seconds, probably reduced the need for blood transfusion and possibly reduced the risk of IVH. Data from 13 out of the 15 included trials did not identify a statistically significant effect on risk of death. Long-term neurodevelopmental outcomes were not reported.

Implications for research

Some reviews identified key evidence gaps. These were mainly related to pharmacological intervention for transition support or resuscitation of newborn infants, and the effectiveness of new, less invasive forms of airway management (and related issues regarding surfactant delivery).

Work package 2.2: ethics issues in recruitment of preterm or sick infants to perinatal trials

The recruitment of very preterm or sick infants to clinical trials requires approaching parents at a difficult time, often with a tight time scale for making a decision. This raises challenges for obtaining valid informed consent to such research.

See *Appendices 6* and *7* for the published reports of this work.

Research aims

We aimed to synthesise:

- Observational and qualitative studies that explored the process of recruitment and consent, and reported parents' and clinicians' views and experiences.
- Analytical (or philosophical) studies that have examined the pertinent ethical questions. These concern the validity of consent, the proper understanding of the parental role in giving or withholding consent, varied possible methods of seeking consent, the best interests of those involved, issues of risk, and the parallels between consent processes in relevant research and clinical contexts.

The goal was to identify both the challenges to an ethically defensible consent process and their potential solutions. Ideally, these solutions would include strategies that we could implement to improve the consent process in the Cord pilot trial.

Methods for data collection

The methods used for this review conformed to those set out for a framework synthesis.¹⁴¹ The first stage was the development of a tentative initial conceptual framework based on prior knowledge of the existing philosophical literature on informed consent, including in neonatal research.^{142,143} This initial framework informed the criteria for including studies and it suggested terms for the literature searches. After refining the framework in the light of the literature from the first searches, the second searches were developed. All searches were updated (for examples of search strategies, see *Appendices 6* and *7*).

Analysis

Empirical studies

For the empirical studies, the conceptual framework was modified to focus on specific questions prioritised by the authors, and further searches devised, guided by bioethics review methods studies.^{144,145} We screened abstracts of the papers from identified citations for inclusion, using the five criteria from the modified framework:

1. parents' views of neonatal trials
2. clinicians' views of neonatal trials
3. parents' and clinicians' views of parental consent/decision-making in clinical practice *if* the articles concerned the validity of the consent in an emergency situation, or during or soon after labour
4. validity of consent
5. other options for gaining consent.

Analytical studies

For the analytical studies, discussion of the initial themes that were identified confirmed the conceptual framework. Further searches were informed by this framework and by bioethics review methods studies.¹⁴⁴⁻¹⁴⁶ We screened abstracts of papers from identified citations for inclusion, using the five criteria from the confirmed framework:

1. consent, participation or recruitment for neonatal research (relevant to clinical trials)
2. parental decision-making for treatment of, or research with, sick or preterm neonates
3. parental decision-making for birth and/or labour
4. methodology in emergency/urgent neonatal research
5. alternative ways of gaining consent for neonatal research.

Overall, we ‘included’ 49 empirical papers and 30 analytical papers (Figure 4). All studies met the quality assessment criteria. For the empirical papers, we identified five themes: (1) attitudes of parents, (2) attitudes of clinicians, (3) validity of consent, (4) different consent processes and (5) miscellaneous topics. For the analytical papers we identified four themes: (1) ethical basis of parental informed consent for neonatal research, (2) validity of parental consent, (3) other options for gaining consent, and (4) risk and the double

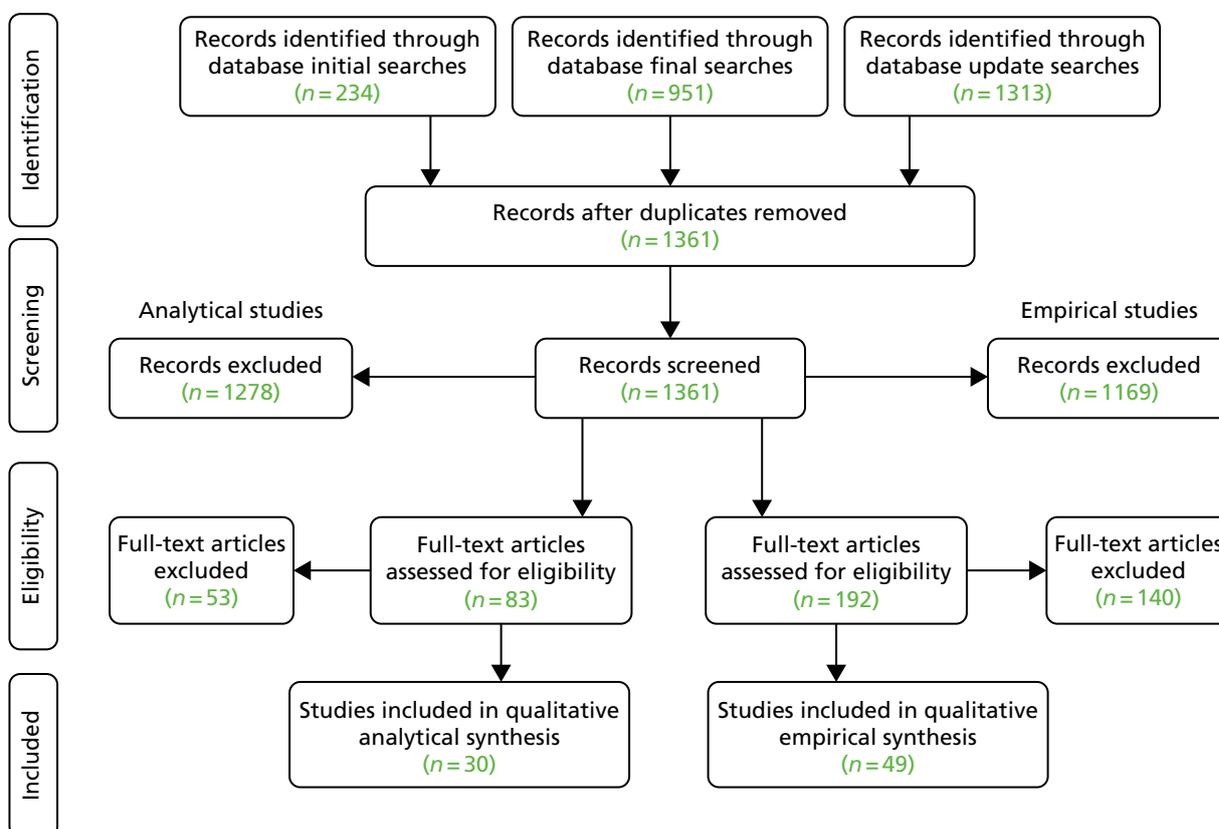


FIGURE 4 The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for the framework synthesis. Derived from Wilman *et al.*⁷⁹ [© Wilman *et al.*, 2015. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated] and Megone *et al.*⁷⁸ [© The Authors, 2016. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated].

standard between consent for treatment and consent for research. We coded articles and tabulated them against these themes.

Key findings

Empirical research

Our review found that the stated motivations for parents to consent were altruistic: the benefit entering the trial might bring to others; the possibility of some benefit for their baby, or themselves; or the trial bringing some hope in a hopeless situation.⁷⁹ Motivations to decline participation in research were inconvenience to parents, burden to their child, or worries about risks, particularly for the baby. Some parents felt that they did not have enough time to decide. Severity of illness of the infant did not appear to affect trial participation.

Parents felt that formal consent for research was necessary and protected their child. Most parents felt that they ought to make the decision about whether or not their child participated in research. They wanted to feel informed and involved, and considered it their responsibility to make this sort of decision. However, many parents also wanted input from others before making the decision, including family and their doctor. Some parents did not want to make the decision. Others felt that being approached about a trial added to their stress and anxiety, particularly if they were approached at an inappropriate time.

Clinicians respected parental authority and largely felt that parental consent was necessary for trials. Reasons for this were that it respects 'parental rights', parents are best placed to act in the best interests of their child, and parents must live with the long-term outcomes of their decision. On the other hand, some clinicians felt that clinicians are the best decision-makers for sick babies, and some wanted to spare parents the burden of making this decision.

Clinicians felt that consent forms protected researchers (by providing confirmation that information was given), and aided communication with parents. However, clinicians also worried that too much information added to parents' burden, and noted barriers to effective communication (e.g. intimidation of parents, and lack of care and support for them). Clinicians raised concerns about balancing their responsibility to the trial with their responsibilities to the parents. Some considered these 'equal responsibilities' and felt that it was possible to discharge both. Others saw the possibility of 'divided responsibilities' causing anxiety to clinicians, or saw the need for 'prioritised responsibility' in which clinicians put parents' interests before the interests of the trial.

Interviews with parents who had given consent for neonatal trials suggested that this consent was valid for only 59% in terms of voluntariness, competence and informedness. Some parents reported feeling pressure to participate, whereas others felt no pressure. Competence, or capacity, to give valid consent may be affected by factors such as emotional state, understanding and time available to decide. Parents reported being calm when they made the decision, but some felt that they had been anxious or stressed. Some parents reported not making a proper decision because of the pain or anxiety, others reported making considered decisions despite pain, time pressure or anxiety. Some parents had clear understanding of a trial, but others reported problems with understanding a trial about which they were asked for consent. Some parents felt that they could make a genuine decision even with suboptimal understanding. Communication skills of the clinician affected understanding. Although parents largely felt that they had adequate time, in the circumstances, to make the decision, a significant minority did not. Parents made rapid decisions regardless of how much time was available, and they needed more time if there was a greater risk. Parents largely received satisfactory information; however, some parents reported problems with the information that they were given. The information sheet was often unread, although in some studies parents remembered being given the sheet and used it when making their decision.

In general, mothers acknowledged the difficulties for researchers in finding the 'right time' to approach them for consent for perinatal research. Some parents would prefer antenatal consent rather than consent during, or after, labour, and would like information earlier in pregnancy even if not recruited then. However, parents were not completely comfortable with antenatal consent as they reported not seeing the relevance of the trial at that time, and felt greater anxiety if told about the trial earlier in pregnancy. Some parents were comfortable with consent in labour, but some were not. Parents were not comfortable with waived consent.

Opting out is when consent is presumed unless the parent explicitly opts out of the trial. Although some parents were comfortable with opting out, others were not. For continuous consent, there is initial agreement to participate with further discussion and information after recruitment. Validity of the later 'continued' consent improves when discussion continues after recruitment. Some parents approve of continuous consent, but some have concerns about receiving further information at a later stage when that might have affected their original decision. One study reported a staged consent process in which consent (oral or written) is sought antenatally and the consent is sought again at the point of intervention. However, at present this is only reported, not discussed.

The main conclusions are that:

- there is widely held agreement that it is important that parents do give or decline consent for neonatal participation in trials, but that
- there is evidence that existing consent procedures are unsatisfactory, and that
- none of the proposed alternative consent processes reviewed by the research is satisfactory
- there are some significant gaps in the empirical research in this area.

Analytical research

The analytical research addressed the justification for seeking consent from a parent (or parents) to neonatal or perinatal trials.⁷⁸ This issue arises because it may be thought that it is not sensible to seek consent when the most affected party is unable to give consent, in which case the focus should simply be on that individual's best interests. Hence, it is relevant to query the basis for consent being given, or declined, by the parent. Justification for parental consent includes the importance of autonomy, such as parental autonomy, or the parents' own rights to make decisions about their child. A similar claim holds that parenting decisions are part of deciding how to conduct one's own life, while another defence suggests that fetal rights are part of maternal autonomy. However, others have rejected any defence of parental consent that appeals to autonomy, arguing that a parent's interest in autonomous parenting may not outweigh the child's interests, or that parents do not 'own' their children.

A second claim in defence of parental consent is that parents should be seen as surrogate or proxy decision-makers, where 'proxy' means not simply someone who acts on behalf of another but one who represents another's views. Some suggest that there might be reason for a parent to give consent even if an appeal to autonomy or rights is rejected. Thus, it is held that it is not appropriate to think of the 'autonomy' of a neonate and, therefore, it is not appropriate to think of 'informed consent' for a child. Another line of argument is that consent in the neonatal context is a case of 'family decision-making', because it is not appropriate to consider the child's decision in isolation. In addition, it is suggested that parents should give consent because they will bear the consequences of the decision. However, some claim that the requirement for parental consent rests on the value of beneficence; as the purpose of informed consent is protection of the best interests of the child, it is the responsibility of parents to make decisions as a way of promoting their child's best interests, so they should give consent. Some have argued that parents should be allowed to make the decision only when it is in the best interests of their child. In reply to this, it is argued that the protection of the child's best interests should not rest entirely or even mainly on informed consent. It is the responsibility of the researcher or the ethics review process to protect

the participant's best interests (therefore, it is inappropriate to defend parental consent by an appeal to the protection of those interests). In addition, the concept of parental consent is a misnomer; for neonates, what should be discussed is parental permission (or authorisation).

An important theme was whether or not, in the neonatal and perinatal context, parental consent is valid, and to what extent validity matters. Potential barriers to obtaining valid consent in these circumstances include time limitations, which adversely affect the amount and quality of the information given; stress, anxiety or pain of the parents; and the mother's sedation. However, some writers have claimed that these features can also contribute (positively) to an autonomous decision process. Parental desperation or fear may affect the voluntariness of any consent given. Parents may also see the researcher as a figure of authority, which may affect the voluntariness of their decision. A more indirect problem for gaining valid consent is that the consent process itself increases parental anxiety.

Barriers to informed consent in this context have implications for respect for the principle of autonomy, if that is the basis for seeking parental consent. Some argue that parental autonomy will be violated if there is a defect in the consent process, whereas others suggest that parents are being used as a means to an end in a consent process that may be flawed. A further argument is that the principle of beneficence (acting for the benefit of the child and/or mother) becomes a more important ethical principle in research with neonates because informed consent is not possible. Another response to the difficulties with and barriers to consent is that we must strive for improvements in what we do to seek consent, and attempt to get the best possible consent even when perfect informed consent is not possible.

The analytical research has examined a cluster of issues around risk in medical research and clinical treatment. There are disagreements about the nature of the risks involved in research. One claim is that if the context for the clinical trial is a potentially life-threatening condition, and the outcome of the intervention is unknown, then the trial intervention should itself be viewed as a significant risk for the participant. An opposing claim in this situation is that this is a risk of the disease and/or the situation, and not of the trial, so it should not be viewed as a risk of the trial intervention. Another view is that fully informed consent is not possible for clinical trials because the very information needed for fully informed consent is that which is uncertain and under investigation.

Other ways of addressing the consent requirement include a claim that defends the idea of a waiver of consent in emergencies. The suggestion is that consent can be waived, but that provisional assent must be given at the time of being invited to participate, and there should be community involvement at the design stage. The aim is to make research possible for the benefit of patients, so this waiver should not be used to make research easier for researchers. Another approach defends a method by which consent is achieved through giving women antenatal notification of the intended clinical trial, and then seeking consent if they meet the criteria for trial entry. A third option discussed is that of deferred or continuing consent. This is a process in which, if the parents are absent or affected by situational incapacity, they are assumed to give initial consent and then provide consent when they are capable of taking in the information and making the decision. However, this leaves open the possibility that consent is not given, in which case the trial intervention would have constituted assault. Retrospective consent is argued to be 'logically incongruent' and, if consent is retrospectively withheld, the researcher is left in the position of never having had consent. Another option is the Zelen method, in which parents are not informed if the novel 'intervention' will not be offered to the child. This final suggestion is the opt-out method for giving consent. This may lessen the burden on parents, increase recruitment and increase understanding, but autonomy may be overridden, for example if a participant fails to exercise their opt-out right by default rather than opting out autonomously. All of these approaches involve a parent giving (or waiving) consent, but a final alternative is to have a consent process in which an independent proxy gives consent for the child.

These results reveal five key points about the consent process and highlight one important gap in the research. The key points are as follows:

1. There is a variety of possible defences for seeking parental 'consent' to neonatal and/or perinatal trials, and these are consistent with the strongly and widely held view that it is important that parents do give (or decline) consent for such research, as found in the empirical literature.
2. In giving parental 'consent' in a perinatal context, parents are authorising infant participation, not giving 'proxy consent'.
3. There are philosophical reasons for supposing that at least some parents will fail to give valid consent in a neonatal context. These support concerns about the consent process raised in the empirical literature.
4. None of the existing consent processes reviewed by the research is satisfactory. This matches the findings of the empirical research.
5. There are reasons for giving weight to both parental 'consent' and the infant's best interests in both research and clinical treatment, but also reasons to treat these factors differently in the two contexts, and this may be partly attributable to the differing relevance of risk in each case.

The significant gap in the philosophical literature is the lack of any detailed discussion of a process of emergency and/or urgent assent followed by later full consent. This matches a gap found in the empirical literature.

Successes

This is the first review focusing on the ethics issues around consent to neonatal or perinatal research. Other reviews have focused on methods for increasing recruitment or improving how information is conveyed, but none has focused directly on the ethics issues.^{61,147–151}

Challenges

The key challenge lay in this project being a relatively novel departure for systematic review methods, as it involved reviewing systematically across the disciplinary boundaries between philosophy, social science and medicine. To address this, the multidisciplinary team included expertise in philosophy, clinical practice, social science, information science and advocacy for parents. For the philosophers, the systematic review methods were somewhat different from those that are conventionally adopted in work on ethics. The notion of a systematic review is uncommon, indeed almost unknown, as a method for conducting research in philosophy, both in philosophy as a whole and in philosophical medical ethics in particular.^{144,152} On the other hand, for the social scientists and clinicians the standard philosophical means for resolving ethics problems were unconventional. As a result, the whole process of developing a systematic review in ethics through interdisciplinary collaboration has given rise to considerable reflection in its own right.

Implications for future research

We identified three important gaps relevant to consent for perinatal trials:

1. Studies on a new process for obtaining urgent or emergency consent in perinatal research where there is little time in which to seek consent to participation. This process involves seeking 'assent' to participation in the trial from parents, accepting that there is insufficient information for fully informed consent at that point, but then providing further information over time which allows the parents to give full consent (or an informed withdrawal).
2. Studies on fetal–maternal research, that is, trials in which both the mother and the fetus or neonate are participants and thus in which both fetal/neonatal interests and maternal interests are in question.
3. Empirical studies that report the views of bereaved parents on the consent process.

This review provided part of the rationale and justification for including a two-stage consent pathway in our Cord pilot trial (see *Work Package 4*), as part of the feasibility assessment for a large trial. Participation by parent representatives (members of NCT and Bliss) in the ethics review, in the development of the pilot trial protocol and in the programme steering group contributed to robust discussion about development of this pathway. They focused on how it should be presented to women and their partners and how it should be evaluated. Endorsement of the trial protocol from these organisations was important in securing ethics committee approval and in communication with parents. Hence, this programme has contributed to filling the first two research gaps identified in our review.

At the time of our research, empirical studies had almost completely excluded views of parents whose sick child participated in research and died. Since then, however, the Bereavement and RAndomised ControlLEd Trials (BRACELET) study addressing this gap has been published.¹⁵³

Work package 3.1: neonatal care at birth, a survey of current practice

There are guidelines for initial resuscitation and stabilisation of preterm or sick babies at birth. To assess compliance with these guidelines and determine if any units were providing initial neonatal care beside the mother, we conducted a survey and interviewed selected sites.

See *Appendices 8 and 9* for published reports of this work.

Research aims

This study aimed to describe current practice for providing neonatal care in the delivery room, and for providing neonatal care at birth beside the mother.

Methods for data collection

We surveyed all neonatal units in the UK using a short online questionnaire to ask about neonatal care in the delivery room at very preterm births. Units reporting they were using deferred cord clamping or cord milking were selected, using purposive sampling, to participate in semistructured interviews. Two researchers interviewed experienced practitioners either in person or by telephone. Interviews were recorded and transcribed.

Analysis

Overall, 197 survey responses were received from 199 hospitals, of which 186 (94%) were fully completed. Seven units participated in the semistructured interviews: five tertiary hospitals, and one large and one small district hospital. Overall, 33 staff members were interviewed: seven midwives, seven neonatologists, two paediatricians, six neonatal nurses, seven obstetricians and four managers. Constant comparative analysis identified five core themes: (1) variability in guidelines and practice, (2) assessing eligibility, (3) competing priorities, (4) anxiety about timing and (5) persisting uncertainty.

Key findings

There was variation in delivery room stabilisation practice for infants born very premature, and in tertiary units the care provided was more consistent with current international guidance than in non-tertiary units.⁶⁸ For example, tertiary units administered more surfactant in the delivery room (93% vs. 78%), were more likely to provide CPAP (77% vs. 50%) or positive end-expiratory pressure in the delivery room (91% vs. 69%), and were more likely to start resuscitation in air or blended oxygen (91% vs. 78%) than non-tertiary units. Routine out of hours consultant attendance at very preterm birth was also more common in tertiary units (82% vs. 55%).

Our interviews suggested that variation in how deferred cord clamping and other strategies to influence placental transfusion at very preterm birth were being implemented, both between units and within the same unit.⁶⁷ For example, there was variation in when the cord was clamped, position of the baby with the cord intact, timing of the prophylactic uterotonic drug, and which babies were seen as eligible for this intervention. Deferring cord clamping was felt to require multidisciplinary agreement because of the perceived conflict between waiting to allow placental transfusion and a wish to 'get on' with keeping the baby warm and

providing newborn life support interventions. In some units, whether or not this happened depended on which staff members were present. No unit was providing neonatal care with the cord intact, and there was staff anxiety associated with this practice.

Implementation of deferred cord clamping, or cord milking, appeared most likely to be successful if there was strong local multidisciplinary support, with agreement on a single technique and the eligibility criteria. Clinical leadership and training in the practical techniques, combined with audit, also appeared to be helpful.

Successes

Use of telephone reminders for the online survey helped us achieve a high response rate. A strength of our interviews was the inclusion of all the relevant professional groups, and that the prior survey allowed us to identify units with relevant experience.

Challenges

Both the survey and the interviews relied on reported practice rather than direct observation. The interviews were based on a small sample and, as at that time deferred cord clamping was not widely practised, may not be representative of all UK units.

One of the reasons this study was included in the programme was to identify UK units where neonatal care was being provided with the cord intact, so that we could learn from their experience. No such unit was identified, although introducing neonatal care with the cord intact was being discussed at one unit.

Implications for future research

Since this work was completed,¹⁵⁴ both the timing of cord clamping for very preterm births and providing neonatal care with the cord intact have become increasingly topical. This has been fuelled by new research, including the work conducted within this programme. A change in culture is leading to a shift away from the previous practice of immediate cord clamping at very preterm birth. In the UK, waiting at least 30 seconds, but no longer than 3 minutes, before clamping the cord of preterm babies is now recommended if the mother and baby are stable.¹⁵⁵ Hence it would be timely to repeat a survey of practice for timing of cord clamping and immediate neonatal care.

Work package 3.2: parents' views of care at preterm birth

There has been little research looking at parents' initial experiences and reactions to very preterm birth, or into their experiences and satisfaction with care during very preterm birth.

See *Appendices 10–12* for the published reports of this work.

Research aims

The aims of this work package were to:

- Explore parents' experiences of very preterm birth, and their first moments with their baby, through three separate analyses to explore:
 1. mothers' and fathers' initial experiences of the birth of their very preterm baby
 2. parents' experiences and satisfaction with their care during very preterm birth, and to identify the domains associated with positive and negative experiences of care
 3. parents' views and experiences of the care for their very premature baby on a neonatal intensive care unit (NICU).
- Systematically review available measures of parents' satisfaction with care during labour and giving birth.
- Develop a questionnaire to measure parents' satisfaction with care during very preterm birth (P-BESS).

Methods for data collection

Parents whose baby was born before 32 weeks' gestation during a 6-month period at three NHS hospitals in the south of England were sent letters of invitation to participate in the qualitative interviews (see *Appendices 10 and 11* for full details). Of 123 eligible parents, 39 (32%) agreed to be interviewed (32 mothers and 7 fathers).³⁶ Two babies died shortly after birth. Interviews contained 13 open-ended questions and lasted about 45 minutes. They were conducted by one psychologist and took place at the participants' home, or in a private hospital room. Interviews were recorded and transcribed. Reporting complied with COREQ (Consolidated criteria for reporting qualitative research).¹⁵⁴

For the comparative review, studies were included if they reported use of a questionnaire that was a multi-item scale of satisfaction with care during labour and birth, and provided psychometric information (about questionnaire construction, reliability or validity) for the satisfaction measure.⁴³ To identify potentially eligible studies we used the search terms (Birth or Childbirth or Lab*r or Intrapart*) AND (Satisfaction or Perception or Evaluation) AND (Questionnaire or Measure* or Scale or Instrument). We searched Scopus, PsycArticles, PsycINFO, PubMed and Web of Science from inception to 30 July 2011, and checked reference lists in reports of included studies for additional studies. Duplicate citations were removed. Finally, Web of Knowledge and Scopus were searched for all reports that cited the final questionnaire measures; no new citations were identified. Data extraction was by two reviewers.

Initially we developed the questionnaire using data from the interviews and studies identified in the comparative review. We identified seven areas of satisfaction with care during preterm birth: (1) information and explanations, (2) emotional support, (3) encouragement and reassurance, (4) staff being confident

and in control, (5) staff being calm in a crisis, (6) involvement of the partner and (7) birth environment. Thirty questions were included, both positively and negatively phrased, and responses scored on a Likert scale; we made minor changes following feedback from nine parent representatives. The questionnaire was then posted to parents of babies born very preterm during the previous 12 months at five tertiary care centres in England.

Analysis

We used inductive systematic thematic analysis to identify themes across interviews. Data were managed using NVivo software. For the systematic review, we assessed psychometric quality of each questionnaire using questionnaire construction (item generation, pilot study), reliability (internal consistency, test retest reliability) and validity (content, face, criterion and construct).

For the questionnaire, a factor analysis was conducted to explore whether questions could be combined into subscales that represent different aspects of satisfaction with care during very preterm birth. Three questions asked about partner's involvement so, as they were not relevant for all women, they were excluded from the initial analysis. Hence, 27 questions entered into the factor analysis. The number of factors to be retained was determined using the scree plot and eigenvalues > 1 . Questions that loaded on a factor at > 0.4 were considered significant and were retained. Questions that loaded on more than one factor ≥ 0.3 were removed and the analysis was rerun. To check whether questions and subscales for the women were applicable to partners, we conducted a confirmatory factor analysis.

Content validity is evident through the systematic series of steps taken when designing the questionnaire. Convergent validity was explored by examining the relationship between the total score (and associated subscales) with two questions assessing overall satisfaction with care during the birth, and reliability by looking at indicators of internal consistency.

Key findings

Parents' experiences of very preterm birth and their first moments with their baby

Following very preterm birth, almost half of parents had difficulty remembering aspects of the birth.³⁶ Two-thirds saw their baby at birth and one-third saw their baby for the first time in the neonatal unit. The anticipation before seeing their baby for the first time was characterised by contrasting emotions, with some parents eager and excited, whereas others, while wanting to see their baby, nevertheless felt scared and even dreaded the experience. For example, one father (2, caesarean section, delayed card clamping) said 'They rang down and said "do you want to come up and see little one?" We went "yeah course we do, you know, brilliant"', one mother (27, caesarean section, delayed card clamping) said 'I was very scared of seeing him', and another mother (24, vaginal birth, delayed cord clamping) said 'I thought I'll go onto the ward and, thoughts running through my mind of what I was, what I was gonna find, how many tubes was he gonna have, was he gonna be OK, what colour was he gonna be, did he have everything, 10 fingers 10 toes, and I found myself sitting by the incubator counting and making sure he had 10 fingers and had 10 toes'.

Similar contrasting emotions were described about touching their baby, for example one mother saying 'You don't want to hurt them. You're so on edge, and you want to care for them and touch them if you can, or whatever, but also you just feel terrible if you think you've done something wrong'.

First contact with their baby was characterised by turbulent emotions, described as a 'rollercoaster of emotions'. Parents spoke about the confusion of feeling both elated and devastated, and others felt guilt about the preterm birth. One mother said '. . . I was all prepared, arms out and they give her to me, and it was wonderful, absolutely wonderful', and another commented 'you just feel guilt, the guilt is overwhelming, you know you do kind of go through aah, not feeling sorry for yourself, it's just the guilt, it's not "oh why's this happened to me?" it's "why's it happened to her?"'. Half of parents who talked about touching and holding their babies described immediate bonding with the first touch.³⁷ Visiting NICU was initially overpowering, especially for

those who had not been before or who were seeing their baby for the first time. This was described as 'a little hidden world, full of poorly babies'.³⁸ Parents described awkwardness and exclusion felt by fathers, particularly during emergency caesarean section, one comment being 'It's different being a man . . .'. Nevertheless, fathers often saw their baby first, and typically experienced this alone.

Overall, the parents' experiences of care during the birth were positive.³⁶ Our study identified four determinants of parents' experiences of care during very preterm birth: (1) staff professionalism, (2) staff empathy, (3) involvement of the father and (4) the birth environment. These are consistent with previous research on term births. However, two factors unique to very preterm birth were the importance of the staff appearing calm during the birth, and staff taking control during the birth. Parents felt that care could have been improved in two areas: staff could listen more to what women said, and believe them; and the father could be more involved in the birth.

Comparative review of measures of parents' satisfaction with care during labour and birth

Nine questionnaires measuring satisfaction with care during labour and birth were identified (Figure 5). For seven of these questionnaires, how the items were selected was described. Eight of these questionnaires

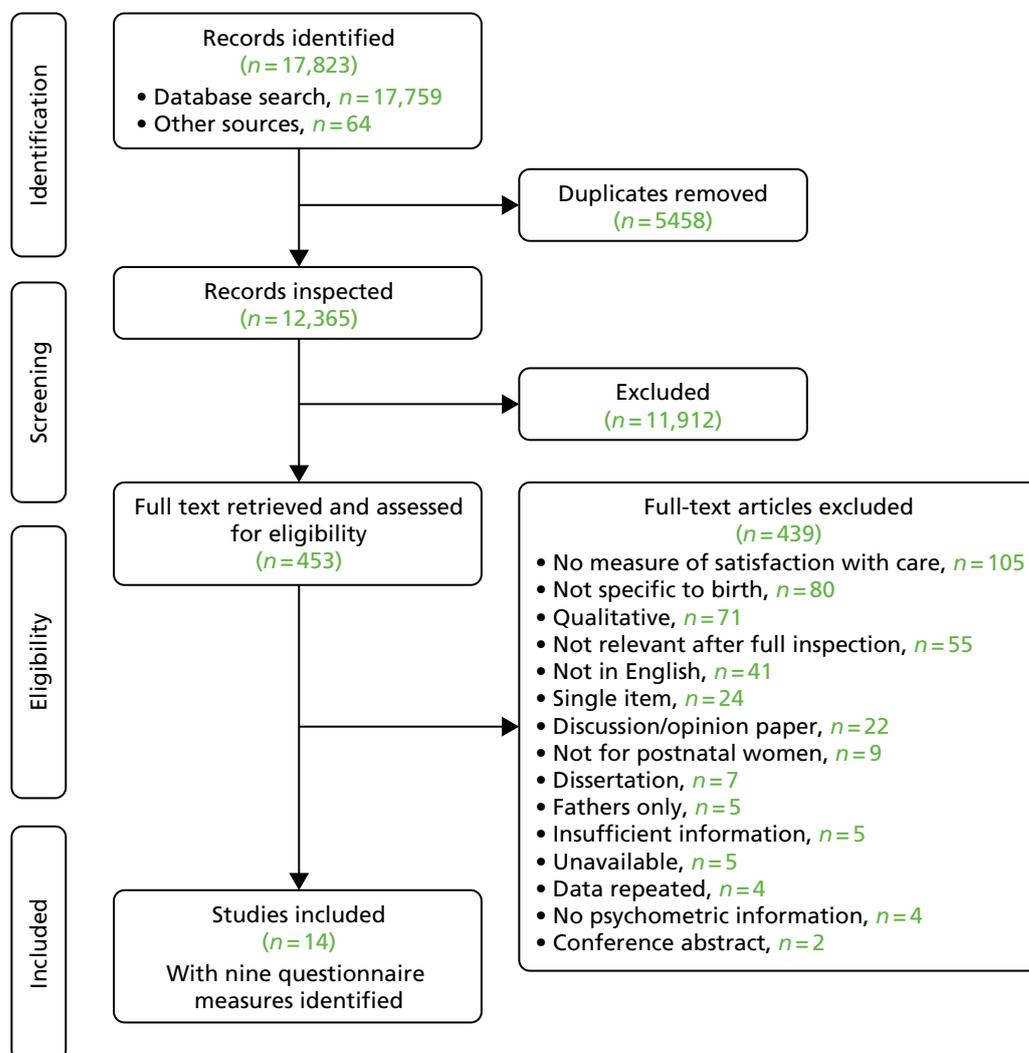


FIGURE 5 The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart for the comparative review. Reproduced from Sawyer *et al.*⁴³ © Sawyer *et al.*; licensee BioMed Central Ltd 2013. This article is published under license to BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

had tests of internal consistency, but only one reported test–retest reliability.⁴³ At least one aspect of validity was reported for all questionnaires, but none reported criterion validity.

Only two questionnaires assessed satisfaction with different aspects of care, as well as the perceived importance of these aspects of care. Three questionnaires were designed for particular types of births, two for operative births and one for uncomplicated vaginal birth. None of the nine questionnaires evaluated care for specific populations, such as parents of sick or preterm babies, or whose baby was stillborn. Parent experiences in these situations may be substantially different from giving birth to a healthy, term baby.

Preterm Birth experience and Satisfaction Scale questionnaire to measure parents' satisfaction with care during very preterm birth

Based on the qualitative interviews with parents, the review and discussion with relevant experts, we identified 97 potential questions in seven domains. Following screening by two experts, 30 items were chosen (27 in the maternal section and three in the partner section) for the draft questionnaire.⁴⁴ To check face validity, content validity and ease of comprehension the P-BESS was sent to nine parent representatives, following which minor changes were made to the wording.

We posted this 30-item questionnaire to 458 couples/single parents, and 147 were returned completed (32% of couples/single parents, 147 women and 107 partners). Of these 24 were excluded, largely as they were completed by partners who were not present at the birth, leaving 145 women and 85 partners. Initial screening removed three questions that were not performing well. Another three were removed because they did not significantly correlate with other questions. The remaining 21 questions in the maternal section were entered into the factor analysis and a further four questions were removed (see *Appendix 12*). The final factor analysis identified three factors with 17 questions for the maternal section: 'staff professionalism and empathy' [seven questions, mean 29.2, standard deviation (SD) 5.1], 'information and explanations' (seven questions, mean 27.9, SD 5.7), and 'confidence in staff' (three questions, mean 12.4, SD 2.5) (*Table 1*). The mean score for the total scale was 69.5 (SD 11.6), out of a possible range of 17–85. Rerunning the factor analysis with the addition of partner involvement questions confirmed that the three factors remained, with the addition of a fourth factor with the partner involvement questions.

The total scale and subscales had good reliability and individual items correlated well with the total scale. Reliability for the 'partner involvement' subscale was 0.72 but this increased to 0.91 with deletion of one question, which was therefore removed. Convergent validity was explored by comparing the scales with the two questions measuring overall satisfaction with care and the need for improvement. The total scale and three subscales were all moderately to strongly correlated with these items. A confirmatory factor analysis to check applicability to fathers showed that the scale was reliable ($\alpha = 0.93$), but the three subscales in women's responses were not applicable to partners and the three factor solution did not fit the partner's data well. One possible explanation for this is that fathers' experiences of preterm birth differ from mothers'.⁴⁴ We recommend that only the total score on satisfaction with care is used for partners. Total scores were related to higher levels of overall satisfaction and less need for improvements, indicating convergent validity for partners.

Successes

We achieved a good response to the invitation to be interviewed. The use of qualitative methods provides an in-depth insight into the experiences of parents who have had a very premature baby. The inclusion of fathers and bereaved parents also provides a valuable and unique perspective. Our data underline the importance of listening to women during preterm labour and of encouraging fathers to feel involved during the birth. Whenever possible, parents should be encouraged to visit the NICU before birth. If this is not possible, parents could be provided with a photograph of their baby in the neonatal unit before they visit.

TABLE 1 The P-BESS questionnaire: maternal section with 17 items and partner involvement section with two items

During the birth	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					

Instructions were provided as follows: this questionnaire asks you about your experiences and satisfaction with care at the birth of your premature baby. Please read each statement carefully and indicate the extent to which you agree or disagree with each question. If you had a caesarean section under general anaesthetic then we understand that some of these questions may be difficult to answer but please complete as best you can.

Subscales: Staff professionalism and empathy – items 2, 3, 4, 6, 7, 9 and 17; information and explanations – items 1, 5, 8, 11, 13, 15 and 16^R; confidence in staff – items 10^R, 12^R and 14^R; and partner involvement – items 18 and 19^R, reverse-scored items.

Parents who are worried about touching their baby should be reassured and taught to recognise infant behaviour in response to touch.

Having identified only two existing questionnaire measures of satisfaction with care during labour and childbirth, both designed for term birth, we developed a new tool for use by both parents following very preterm birth. This tool is the first specific to preterm birth. The total score may be useful to compare satisfaction with care during very preterm birth across hospitals and differing practices, and individual aspects of care can be evaluated using the separate subscales. We used this tool to measure satisfaction with care in the Cord pilot trial (see *Work Package 4*), and it has been translated into Spanish and Portuguese.

Challenges

Although the response rate for our qualitative interviews was good for this type of study, we received responses from parents whose baby was born only from two of the three hospitals, reducing the generalisability of our data. In addition, participants were mainly white, married women, which is not typical for very preterm birth. In common with other studies of satisfaction, parents may have been reluctant to criticise the professionals who took care of them and their preterm baby. This 'halo effect' may be even more pronounced for parents of premature babies, as the staff have been looking after their baby for many weeks.⁴⁴ Similarly, if women do not know what care during birth should be like they may just evaluate the status quo.^{156,157} Our study used in-depth interviews by a researcher not associated with the hospital, which should have helped to pick up relevant negative experiences.

The response rate for development of the questionnaire was relatively low, although again this is a good response for studies of this kind. The sample size was relatively small for a factor analysis, which limits the validation process. In addition, the sample was not representative of all parents who have a very preterm birth, as it included largely white, highly educated, married/cohabiting women and their partners. Finally, as the same factor structure was not identified in partners as in women, only the total score is recommended for use with partners, which means that the individual factors of care cannot be explored for them.

Implications for future research

Further research is needed to replicate our findings about parent experiences at very preterm birth, and to explore whether or not there is variation for parents from different backgrounds. For the P-BESS, further studies are needed to test the refined instrument in a larger, more representative sample of parents. Fathers of preterm or sick babies are a difficult group to recruit into research.¹⁵⁸ Our work highlights the importance of including them in research studies to ensure that their perspective is represented.

Our experience in conducting semistructured interviews with parents following very preterm birth also contributed to the design and conduct of an evaluation of parent and clinician experiences of neonatal care beside the mother (see *Work Package 3.5*), and of women and clinicians' experiences of the two-stage consent pathway in the Cord pilot trial (see *Work Package 4*).

Work package 3.3: measuring placental transfusion

Previous research into the physiology of placental transfusion has largely involved term births. It remains unclear how the volume and the duration of placental transfusion vary with gestation at birth, and what the optimal timing is for umbilical cord clamping for preterm births.

See *Appendix 13* for the unpublished report of this work.

Research aims

The aim of this work package was to measure the volume and the duration of placental transfusion for preterm births by weighing babies with the umbilical cord intact.

Methods for data collection

Recruitment was at three maternity units in England. Women likely to give birth to a live baby before 36 completed weeks' gestation were offered participation. At each site, research staff undertook an initial training phase recruiting women giving birth at term. At birth, the baby was placed on the weighing platform and wrapped in warm towels with the umbilical cord intact. We used high-quality pharmacy scales (Excellence XS Precision Balance Model XS8001L, Mettler Toledo, Im Langacher, Switzerland), which calculated an average weight twice every second, with data stored in a linked computer. Before the birth, scales were zeroed to allow for towels, probes and any other equipment. To ensure that the baby was no higher than the level of the woman's abdomen, the woman's bed was raised or lowered if necessary. The baby was monitored throughout weighing using saturation monitors.

Analysis

Characteristics of the women, events during labour and mode of birth were described for all women. Placental transfusion was assessed by change in weight over time, as 1 ml of blood weighs 1.05 g. For each birth, two authors (JD and SO) independently assessed the weight change by inspecting the graphs of weight against time, using information on the time of cord clamping and when the baby was touched. Differences were resolved by discussion. Owing to the small numbers recruited, data are described only as summary statistics were inappropriate.

Key findings

Of 97 women approached, 33 gave consent, of whom six had their baby weighed. Reasons why the baby was not weighed for the remaining 27 with consent were: term birth ($n = 10$), research staff not available as out of working hours ($n = 6$), birth too rapid ($n = 5$), cord too short ($n = 2$), consent withdrawn ($n = 2$), hardware problem ($n = 1$) and clinician decision ($n = 1$). For the six babies who were weighed, gestation was from 34⁺⁴ weeks to 36⁺⁵ weeks (*Figure 6*). Three were vaginal births and three were caesarean. The time of cord clamping ranged from 2 minutes to 3 minutes 57 seconds. For two babies, drying and applying probes led to a poor recording of weight for the first minute. An initial 10 seconds 'hands-off' period to give a baseline weight was therefore adopted. Weight change ranged from a 20-g decline to a 128-g increase. For one baby, weight change was continuing when the cord was clamped at 120 seconds; for another, weight change ceased at 2 minutes, and for the remaining four babies weight change appeared to continue for at least 3 minutes.

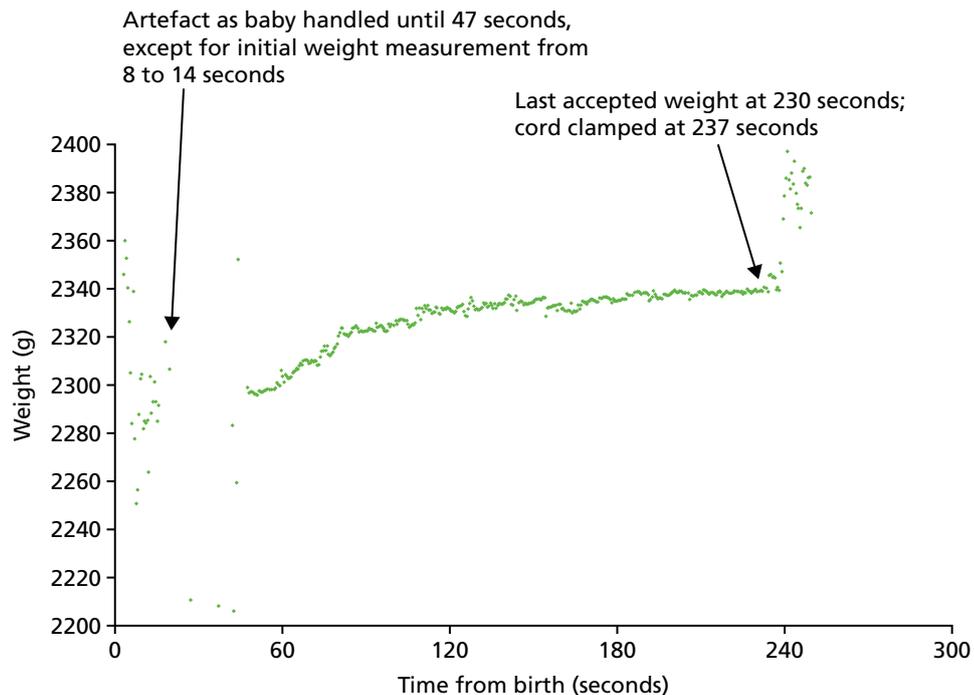


FIGURE 6 Caesarean section at 35⁺⁶ weeks, weight gain estimated at 51 g.

This study is small; nevertheless, as with term births, there appears to be variation in the volume and duration of placental transfusion and, for some, net flow is to the placenta rather than the baby. For preterm births, umbilical flow may continue for more than 3 minutes. As placental transfusion may have a role in stabilising the cardiorespiratory circulation during transition from the fetal to neonatal circulation, the duration of time that the cord is left unclamped and umbilical flow continues may be as, or possibly more, relevant than the volume of any net flow.^{49,159}

Challenges

Major challenges were recruitment and, when appropriate women were recruited, having enough time for research staff to arrive and prepare the equipment, made even more challenging as births were often out of hours. Despite considerable effort at each site, these challenges were only partly overcome.

Implications for future research

Despite the small numbers, these data contributed to evidence supporting the decision to wait at least 2 minutes before clamping the cord for the intervention arm in the Cord pilot trial (see *Work Package 4*). These data also suggest that the effect of delayed cord clamping may not simply be to allow more blood to reach the baby from the placenta, but rather to allow the changes from an in utero placental circulation to an ex utero lung one, to occur more gradually. Improved understanding of the physiology of placental transfusion at very preterm birth would help identify the optimal strategy for cord clamping. Better methods for assessing placental transfusion are required.^{46,72}

Work package 3.4: developing a Bedside Assessment, Stabilisation and Initial Circulatory Support trolley

Newborn resuscitation with an intact cord had been described previously,^{53,160} but with no agreed strategy for how to do this and little apparent uptake in clinical practice.⁶⁷ In 2010, a 1-day meeting led to the idea for a small mobile resuscitation trolley, the 'Bedside Assessment, Stabilisation and Initial Cardiorespiratory Support' (BASICS) trolley,⁶⁹ extending the concept of a simple platform.⁵³ This work package describes its subsequent development into a commercially available medical device.

See *Appendix 14* for the published report of this work.

Research aims

The aims of this work package were to develop a mobile trolley to provide newborn life support beside the mother, and with the umbilical cord intact, and to identify a commercial partner so that the trolley could be made more widely available.

Methods

A multidisciplinary team including clinical engineers, neonatologists, obstetricians, midwives and parent representatives met regularly to discuss and develop the design, using a prototype device based on an overbed hospital table with piped gasses, suction and a timer. Two simulated resuscitations provided assessment of functionality and practicality for both vaginal and caesarean births, following which the prototype was modified further.

A 'second-generation' prototype was developed in collaboration with Inditherm Medical (Rotherham, UK), a company specialising in the development and sale of neonatal equipment and devices. Following a third simulation to refine the design further, and certification with the Conformité Européenne (CE) logo, this was subsequently marketed as LifeStart™.

Key findings

The first prototype trolley was adapted from an overbed hospital table, which has a long base directly below the platform that slides under the bed, providing stability. However, modern operating tables and delivery beds have pedestal bases with little room beneath them. Therefore, the next prototype used a circular base, with larger wheels and enough weight to provide stability. This then led to the first commercially available trolley (*Figure 7*). The design struck a balance between trolley stability and reach of the platform. The platform is widest at the proximal end, allowing space for the baby's shoulders and to access the head. The distal end is narrower, allowing the platform to get close to the mother. The baby is kept warm with an electric heated mattress produced by Inditherm; the company already produced the CosyTherm© (Inditherm Medical) mattress for neonatal cots, and this was reshaped to fit the trolley platform. To allow the platform height to be adjusted to be level with the mother, the central pillar adjusts up and down via an electronic mechanism. The trolley also has a battery driven digital timer with alerts at 1 minute and at 5 minutes, for use during resuscitation.



FIGURE 7 First commercially available LifeStart trolley, October 2012. Reproduced from Thomas *et al.*¹⁶¹ © 2014 The Authors, licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License 4.0 (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated.

Medical gases for newborn resuscitation (air or oxygen) usually come from wall sockets; hoses connecting these sockets to the usual resuscitation equipment are short and tuck in against the wall. For a mobile trolley, long hoses connected to wall sockets create a trip hazard. Using small gas cylinders attached to the trolley was not possible at the time we developed the trolley, as the smallest size available for medical air was too large to attach to the trolley. Gasses are blended and the pressures are regulated using a Tom Thumb Infant Resuscitator® (Viamed, Keighley, UK) and an oxygen blender (Inspiration Health Care Ltd, Leicestershire, UK) attached to the back of the trolley, along with a suction bottle (Oxylitre Ltd, Manchester, UK). Other equipment is attached, as required, using two medical equipment rails on the central pillar.

Successes

This is the first mobile neonatal resuscitation unit designed to facilitate newborn resuscitation beside the mother, and with the umbilical cord intact. Our initial prototype was entered into the Medical Futures Innovation Awards in 2011 (www.medicalfutures.co.uk/) and awarded 'Best Redesign in Cardiovascular Medicine'. Further development has led to a successful commercial product, LifeStart, marketed in the UK and internationally, and cheaper than the usual equipment (around half to one-third of the cost). Regardless of timing of cord clamping, the trolley has a role in supporting neonatal care beside the mother and allowing her to share her baby's first moments.

Challenges

Feedback to the manufacturer led to further modifications. For example, the platform was lengthened to extend its reach, an important development as premature babies tend to have shorter cords than those born at term.

The trip hazard caused by piped gas from wall sockets has reduced acceptability of the trolley in clinical care. A medical air gas cylinder small enough for the trolley is now available and can be used following a local risk assessment (as it is not covered by the CE mark). A disadvantage of this solution is that the cylinder requires frequent refilling. Another less practical option is to put the large cylinder on a second trolley and move this to the bedside with the resuscitation trolley.

Resuscitation can be provided without a pressurised gas supply, using a bag, valve and mask system, and room air. Disadvantages of this method for preterm resuscitation are the inability to control inspiratory time or provide positive end expiratory pressure, and also that oxygen would not be available for those babies who fail to respond to resuscitation with air.

Implications for future research

Once a trolley was available for use, we introduced it into clinical service and conducted a service evaluation¹⁶¹ followed by qualitative interviews to explore the experiences and views of parents and clinicians of neonatal care at birth beside the mother, and of their experiences and views of the trolley (see *Work Package 3.5*).^{39,40} We also developed strategies for providing neonatal care beside the mother using the usual resuscitation equipment.¹⁶² As discussed in *Work package 3.5*, further research is needed to evaluate the clinical and psychological impact of neonatal care beside the mother and of providing care with the cord intact.

Work package 3.5: evaluating parents' and clinicians' views of neonatal care beside the mother

See *Appendices 15 and 16* for the published reports of this work.

Research aims

Our aims were to provide proof of concept that the trolley could be used in clinical practice, then to assess whether or not the trolley could be used as part of routine care within a busy tertiary care hospital, and whether or not it was acceptable to parents and to clinicians. Therefore, we aimed to conduct:

- a case study of first use of the trolley in clinical practice
- a questionnaire-based service evaluation
- qualitative semistructured interviews with parents and clinicians about their experiences.

Methods for data collection

First use of the trolley in clinical practice was for a baby born by caesarean section at 37 weeks' gestation who required an EXIT (Ex utero Intrapartum Treatment) procedure¹⁶³ at Liverpool Women's hospital. We delivered the baby's head and shoulders, while the chest and abdomen stayed inside the uterus, and administered tocolytics to maintain placental perfusion. Once a safe airway was achieved (by endotracheal intubation), the baby was born and the umbilical cord cut.

Following this the LifeStart trolley was introduced into clinical service at Liverpool. We conducted a service evaluation from March 2012 to October 2013.¹⁶¹ The trolley was available at births for which hospital policy required attendance of an advanced neonatal nurse practitioner or a paediatrician. As this was the first time that the trolley was available for routine clinical practice because its use was initially restricted to 'low-risk' births. This was extended to high-risk births after review of data from the first 20 births, which was satisfactory. Babies were assessed and resuscitated at birth according to hospital guidelines. Overall, 78 births were included in the evaluation. Data were from the clinical notes, including demographics, temperature of the baby after resuscitation, care provided on the trolley, whether or not there was a need to move the baby to a standard resuscitation platform, and any problems experienced. For 61 of these births, clinicians completed a questionnaire asking their views of care beside the mother and of using the trolley, and any views expressed by the women or their partners. This questionnaire was not completed for 17 births, as the women were recruited into the Cord pilot trial.

For the qualitative interviews, we recruited parents and clinicians between November 2012 and January 2014. Interviews were conducted by a female psychologist or one of three midwives trained in qualitative methods, using a standard schedule of open-ended questions. They were recorded and transcribed, and reporting complied with COREQ.¹⁵⁴

Fifty-six women and their birth partners who had initial neonatal care beside the mother were invited to participate, of whom 30 were interviewed (19 mothers, 10 partners and one grandmother).³⁹ We conducted 19 interviews, as 11 women chose to be interviewed with their birth partner. Five of the babies required advanced neonatal resuscitation at birth. If their baby had not received intervention at birth, it was explained to parents what this might involve, and they were asked about how they might feel about being so close if

this had been necessary. Interviews lasted approximately 30 minutes, and took place either in a private hospital room (17 women) or at the woman's home (two women). We extracted demographic data from the clinical notes.

Using purposive sampling, 26 clinicians who were present at a birth where initial neonatal care was beside the mother were invited to participate. All initially agreed to be interviewed; as six later declined, 20 were interviewed.⁴⁰ Most were neonatal specialist doctors or nurses (Table 2). Five had provided or observed advanced resuscitation beside the mother. Interviews lasted approximately 20 minutes, and took place in a private room on the neonatal unit.

Analysis

For the service evaluation, we assessed usability of the trolley based on the range of resuscitation procedures performed while babies were on it; the feasibility of resuscitation with the cord intact, based on the proportion who received this; and the acceptability to clinicians based on questionnaire responses. The only anticipated safety concern was hypothermia. We monitored unexpected safety issues using the Hospital Incident Reporting System.

The qualitative interviews ended when we achieved data saturation. We used inductive systematic thematic analysis to identify themes across interviews. Data were managed using NVivo software. We identified five themes in the parent interviews: (1) reassurance, (2) involvement of the family, (3) staff communication, (4) reservations and (5) experiences of the trolley. For the clinician interviews, we also identified five themes: (1) parents' involvement, (2) reservations about neonatal care at birth beside the mother, (3) practical challenges in providing neonatal care beside the mother, (4) comparison of the trolley with usual resuscitation equipment, and (5) training and integration into clinical routine.

TABLE 2 Characteristics of clinicians interviewed

Characteristics	n (%) (N = 20)
Profession	
Advanced neonatal practitioner	10 (50)
Consultant obstetrician	1 (5)
Consultant neonatologist	2 (10)
Neonatal nurse	1 (5)
Senior house officer (paediatrics)	4 (20)
Midwife	1 (5)
Senior registrar (paediatrics)	1 (5)
Role in providing neonatal care at birth	
Observer	2 (10)
Contributor	18 (90)
Trolley experience ^a	
Used once	9 (50)
Used more than once	9 (50)

a Missing data, n = 2.

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Key findings

Case report of the first use in clinical practice

Endotracheal intubation was at 7 minutes of age; at 8 minutes, the baby was born, the cord was clamped and cut and the baby was transferred to the trolley. At 15 minutes of age, the baby was moved to the standard resuscitation equipment and at 16 minutes the temperature was normal.

Service evaluation

Common delivery room resuscitation procedures were performed successfully for babies on the trolley, and none was moved to the standard resuscitation platform.¹⁶¹ All resuscitation interventions were performed with an intact cord, apart from umbilical venous catheterisation, which requires division of the cord. Immediate neonatal care with an intact umbilical cord was attempted for 61 births and was achieved for 43 (70%). For 18 births (30%), the cord was too short to allow the baby to reach the trolley. Births for which the cord was judged to be too short were no different in gestation or mode of birth to those with the baby on the trolley with the cord intact; two-thirds of these births took place during the first half of the study, which included fewer very low-birthweight babies. As experience increased, the proportion of babies able to receive care on the trolley with an intact cord also increased.

Only one baby had a temperature of < 36 °C and this baby was born at 30 weeks' gestation and their temperature was 36.4 °C at 10 minutes of age on the trolley; therefore, (s)he probably got cold during transfer to the neonatal unit. No serious adverse events related to the trolley were reported. A reported practical difficulty was the trip hazard due to hoses connecting the trolley to gas sockets on the wall. A partial solution was to attach a small size oxygen cylinder to the trolley, reducing the number of gas hoses.

Compared with conventional resuscitation equipment, clinicians rated the trolley as 'the same', 'better' or 'much better' for most aspects of care, and none rated it 'much worse'. Some rated the trolley as 'worse' than conventional resuscitation equipment for ease of access to the baby (15% of clinicians), ease of assessing the baby (10%) and ease of access to resuscitation equipment (18%). These issues seemed largely due to difficulty in getting sufficiently close to the operating table at caesarean section. There were also concerns about maintenance of the sterile field, about the sterile drapes covering the trolley obstructing the view of the airway management equipment, and that preparing the trolley for use in theatre was time-consuming. Two-thirds of clinicians rated the trolley as 'better' or 'much better' for ease of communication with parents, with a similar proportion rating the overall experience for parents as 'better' or 'much better'.

Parents' experiences of immediate neonatal care beside the mother

Parents reported that they liked having their baby close by and described feeling reassured by knowing what was going on.³⁹ At some births the woman was unable to see her baby, but the father (or other birth partner) could and relayed information about the baby, which reassured her. Parents reported feeling involved as a family, as they could see and sometimes touch their baby. By watching, parents felt that they understood what was happening to their baby, felt that they could see that staff were doing the best that they could, and felt part of their baby's care. One mother reported that having her baby so close gave some 'normality' and 'goodness' to a birth she otherwise experienced as unnatural. Some parents felt that seeing the initial neonatal care helped staff to communicate with them. Others said that they would have liked more explanation about what was going on and why, as this might have allayed some of their fears.

Parents whose babies had only low intensity interventions at birth, such as drying or receiving oxygen by mask, reported no reservations about watching. However, half of them said that they might have reservations if their baby needed more intensive intervention. No parent whose baby received intensive intervention, such as intubation or cardiac massage, expressed regrets about watching. These parents reported feeling scared or finding the intervention unpleasant to watch, but three out of five stated that it was 'fine' or 'nice'. A few parents suggested that they should be asked beforehand whether or not they would like to watch their baby's care at birth. Two were concerned that watching might have an impact on the staff in terms of adding pressure or distraction.

Of 11 parents who gave an overall opinion of the trolley, nine were favourable and two were unsure. The standard resuscitation equipment was also in the room, and some parents thought that this equipment looked 'scary', clinical or like their baby needed a lot of help or would be taken away. Two parents felt that the standard equipment looked 'more advanced'.

Clinicians' experiences of immediate neonatal care beside the mother

Eighteen clinicians mentioned that initial neonatal care at birth beside the mother allowed parents to see and touch their baby, and to see what the clinical team was doing.⁴⁰ They felt that this was especially important for babies subsequently admitted to the neonatal unit, in contrast with usual care, where the woman might not have been able to see her baby until she visited the neonatal unit. Some clinicians reported that parents were not able to see their baby at caesarean section because of the screen, or at an assisted vaginal birth when the trolley was positioned close to the perineum.

Almost half of the clinicians reported positive comments from parents about being close to their baby, which included one woman whose baby died soon after birth. None mentioned negative comments from parents. Four clinicians said that they felt that being near to the parents aided or increased their communication with them, three clinicians felt that being close made no difference, but one clinician said that communication was an issue of practice, not equipment. One clinician felt that when advanced resuscitation was required, a member of staff should be assigned to support parents.

Most clinicians had no reservations about being watched by parents, but five thought that staff with less experience might feel insecure about this. Clinicians varied in their views about the potential impact on parents of watching neonatal care at birth: five felt that it would be beneficial, four were unsure and two felt that seeing advanced resuscitation might be upsetting. Two clinicians suggested that parents are asked beforehand whether or not they wanted to watch.

Practical challenges at caesarean births were that parents were sometimes unable to see their baby and that scrubbing to enter the sterile field was perceived as a burden that took time out of already busy work days. Clinicians also noted that the trolley switches and controls were covered by the sterile drapes, making their use awkward. Other practical issues were: (1) for admission to the neonatal unit, the baby had to be moved to the standard equipment, and (2) the small platform size limited space for equipment. Problems with integration into clinical care included not having the trolley routinely available at a birth, or it not being set up in time. A common concern was that the trolley interfered with other staff members' space beside the mother. However, three clinicians reported no problems with space for other staff. Eighteen clinicians gave an overall evaluation of initial neonatal care beside the mother and using the trolley as positive or conditionally positive.

We also showed that the usual resuscitation equipment can easily be adapted to do this.^{70,162} Some clinicians, particularly those with less experience, may find it challenging to conduct neonatal resuscitation in such close proximity to parents. Although many will appreciate the opportunity this gives to communicate with parents about their baby, others may prefer to be away from parental scrutiny. Thus, successful introduction of neonatal care at birth beside the mother requires adequate training and support, and a multidisciplinary team approach.

Successes

As far as we are aware, the work reported here describes experiences at the first hospital to provide initial neonatal care beside the mother within routine clinical service. We have shown that all common resuscitation procedures can be provided this way, with reassurance that this is also safe. Although we used the mobile trolley designed for this purpose, the same care can be provided using the standard resuscitation equipment, as happened in the Cord pilot trial.⁷⁰ Although larger than the trolley, standard resuscitation equipment is easily moved alongside the mother, the side panel dropped to allow the mattress on which the baby is placed

to be moved closer to the mother, and the height adjusted. Using standard equipment has the advantages of being already available in the room or operating theatre, having the usual radiant heater, and requiring no equipment-specific training as staff are already familiar with its use. Data presented here on initial neonatal care beside the mother are therefore generalisable to settings in which care is provided using standard equipment, with the exception of specific practical issues with the trolley.

Although this requires further investigation, the positive view of a woman whose baby had care beside her and died shortly afterwards has important implications for bereavement.

Challenges

A practical concern about the trolley was the potential trip hazard, especially in the operating theatre, associated with the hose required for gas supply. Replacing one hose with a small oxygen cylinder fixed to the trolley has reduced this hazard. Removing the second hose requires a small air cylinder, which was not commercially available at the time. It is now available, but is not included in the CE mark. A concern about providing care with the cord intact at caesarean section is the potential to compromise the sterile field. Maintaining the sterile field and negotiation about space for the neonatal team at the operating table remain a challenge at caesarean births, especially in an emergency. Our experience is that this becomes easier as staff become familiar with providing this care.

Generalisability of these data is limited by recruitment of both parents and clinicians from a single hospital (where the trolley had been developed) with a particular interest in care beside the mother. Other limitations of the interviews with parents were that participants were not necessarily representative of the wider population, as they were primarily white, they were either married or living with their partner, the babies were all alive at the time of interview, and most babies had not required advanced resuscitation at birth. Parents may have been reluctant to criticise their care, but we mitigated this risk by having an interviewer who was not directly involved in their care or care of their baby.

Implications for future research

The work presented here should be repeated in other hospitals and should include using the standard resuscitation equipment as well as the mobile trolley to assess whether or not outcomes, experiences and costs are similar. Further research should include parents from more diverse backgrounds, those whose baby required advanced resuscitation and those whose baby died. Further research should also include follow-up of both parents and infants to assess any long-term impact.

The optimal study design for further evaluation would be a randomised trial comparing outcome for parents who are offered initial neonatal care beside the mother with the outcome for those offered traditional care only.

Work package 4: Cord pilot trial, a randomised trial of deferred cord clamping and initial neonatal care with cord intact versus immediate cord clamping and initial neonatal care after clamping for very preterm births

This work package was planned as an assessment of the feasibility of a large randomised trial based on recruitment for 1 year. As recruitment was extended for a further 11 months, we present outcomes by allocated group for all participants at hospital discharge and follow-up at 1 year for women and at the age of 2 years (corrected for gestational age at birth) for the children. In addition, parent and clinician experiences of the two consent pathways are described.

See *Appendices 17–23* for the unpublished and published reports of this work.

Research aims

The aim of the Cord pilot trial was to assess the feasibility of conducting a large multicentre randomised trial in the UK comparing deferred cord clamping and immediate neonatal care (if needed) with the cord intact, with immediate cord clamping and with immediate neonatal care after cord clamping for very preterm births. Recruitment was planned for 1 year and feasibility was assessed based on prespecified process measures, such as recruitment, compliance, completeness of data collection and participants' views.

At an interim review, the independent TSC agreed that feasibility criteria had been met and advised that recruitment continue while funding was sought for the full trial. Recruitment closed in February 2015, when this funding application was unsuccessful. For the planned full trial, joint primary outcomes were death before discharge and IVH (all grades), hence these outcomes were considered the primary outcomes for the extended pilot trial. As the two-stage consent pathway was an important addition to the trial protocol, we also conducted a qualitative evaluation of the alternative consent pathways.

Methods for data collection

Recruitment to this pragmatic trial was at eight UK tertiary maternity units: five had contributed to earlier work in the programme and three had not been involved and so were more typical of UK sites. Three parent representatives were coinvestigators, involved in identifying the research question, securing funding, and designing and conducting the study. Target recruitment for assessment of feasibility was 100–110 women over 1 year, based on target accrual of 16–18% of eligible births. As we planned this as a pilot, there was no formal power calculation.

Women expected to have a live birth before 32 weeks' gestation were potentially eligible. The intervention was umbilical cord clamping after at least 2 minutes and neonatal stabilisation and resuscitation, if needed, with the cord intact. Babies were placed onto a firm surface with access to resuscitation equipment; six sites used their usual resuscitation equipment moved alongside the woman's bed¹⁶² (153 women recruited) and two sites used the mobile trolley (108 women).⁶⁹ The control was cord clamping within 20 seconds and neonatal stabilisation and resuscitation, if needed, after clamping. For both groups, neonatal care was based on local unit policy and consistent with newborn life support guidelines.^{57,164}

For the assessment of feasibility we prespecified measures of feasibility. For the planned main trial, joint primary outcomes were death before discharge and IVH (all grades);¹⁶⁵ therefore, these were the main outcomes for the extended pilot trial. We adjudicated diagnosis of IVH. Secondary outcomes for the babies included severe IVH (grade 3 or 4),¹⁶⁵ a range of measures of neonatal morbidity and neurodevelopment in early childhood. Secondary outcomes for the women included complications of the third stage of labour, well-being and satisfaction with care at birth. Follow-up for women was by self-completed questionnaire at 2–3 months and again at 1 year, and for the children at the age of 2 years (corrected for gestation at birth) by parent-completed Ages and Stages Questionnaire (ASQ)¹⁶⁶ and an assessment at home using the Bayley Scales of Infant Development III (Bayley-III).¹⁶⁷ If no ASQ or Bayley-III data were available, we asked the site to complete an outcome form using routine clinical data. We agreed the statistical analysis plan for the extended study before unblinding the data.

Whenever possible, we offered women the usual written consent process (Figure 8). However, if birth was imminent and the attending clinician considered it appropriate, we offered women a brief explanation of the study and randomised those who said ‘yes’ (i.e. they gave oral assent). Before discharge from hospital, these women had an opportunity to discuss the study in detail and to give written consent for participation in follow-up. This two-stage process was developed in consultation with the NCT and Bliss.

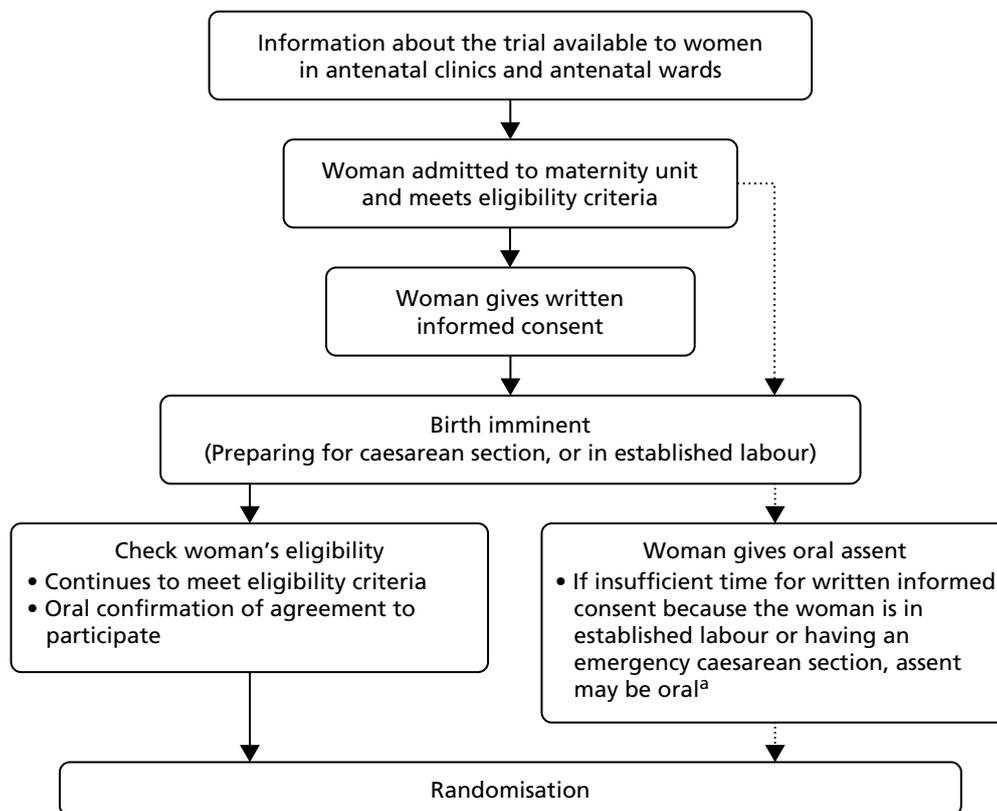


FIGURE 8 The two alternative consent pathways. a, Women approached to give oral assent in established labour or at emergency caesarean section only if the attending clinicians considered it to be appropriate. Women were not approached if there was insufficient time to give a brief verbal summary of the trial or if they did not speak fluent English and no translator was available. How long was required for oral assent depended on factors such as how much the woman already knew about the study, and her knowledge and wishes about care during the third stage. If recruitment was after oral assent, (1) women were approached before discharge to give written consent to participation in follow-up and (2) the chief investigator was notified of this within 15 days, and this recruitment was monitored by the TSC. Derived from Pushpa-Rajah *et al.*¹⁶⁸ © Pushpa-Rajah *et al.* 2014. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated.

Randomisation was by the attending clinicians, using sealed consecutively numbered opaque envelopes. Clinical staff were trained, with regular study-specific training provided at each site to as many neonatal staff, midwives, obstetricians and theatre staff as possible (see *Appendix 17*). We supported site training with film clips of simulations for providing immediate neonatal care with the cord intact, and of role-playing to offer consent via the two pathways. Multidisciplinary teamworking on site was essential for successful trial conduct.

We sent 179 women in the trial an invitation to participate in semistructured interviews. A total of 23 were interviewed (usual consent pathway, $n = 18$; two-stage pathway, $n = 5$). The interview schedule consisted of open-ended questions⁴² to explore the women's views and experiences of being offered participation. Interviews lasted approximately 30 minutes and took place either at their home or by telephone. We sent 20 clinicians who recruited women invitations for semistructured interviews, and interviewed 17 from seven sites. The interview schedule consisted of open-ended questions, to explore clinicians' views and experiences of offering participation.⁴¹ Interviews took place either in a private hospital room or by telephone. They lasted 20–30 minutes and were audio-recorded and transcribed. Reporting complied with COREQ.¹⁵⁴

Analysis

For the assessment of feasibility of a large trial, the prespecified outcomes are presented based on recruitment at 1 year. For participants in the extended pilot, analyses were based on the groups as randomly allocated (intention to treat). Women who gave birth after 35⁺⁶ weeks were not included in the analyses, as outcomes for these babies are different from those born very preterm. Where appropriate, results are presented as RR or risk difference with 95% CIs.

For the qualitative interviews, we used inductive thematic analysis using NVivo version 10 software.

Key findings

Feasibility of a large multicentre trial, based on recruitment for 1 year

Overall, the feasibility objectives were met. During the feasibility phase, we randomised 22% of women who gave birth before 32 weeks' gestation (varying from 9% to 43% between sites) (see *Appendix 17*). Factors in this variation included availability of the mobile trolley and of trained clinical staff. Sites already involved in the programme randomised their first participant more quickly than new sites; most sites randomised the first woman within 1 month of opening, whereas new sites took up to 5 months. Of the 125 women randomised, over one-quarter (29%, 36/125) were recruited using the two-stage oral assent pathway. Time from randomisation to birth was within half an hour for over one-third of women, and within 1 hour for over half; three-quarters of women gave birth within 2 hours of randomisation and only 6% gave birth > 1 day after randomisation. Recruitment was across the range of gestational age with approximately one-third before 28 weeks' gestation, one-third at 28–29 weeks' gestation and one-third at 30–31 weeks' gestation.

Compliance with the allocated intervention was good. In the intervention group, median time to cord clamping was 120 seconds (interquartile range 30–135 seconds), compared with 10 seconds (10–15 seconds) in the control group. Overall, 82% (111/135) of babies in the intervention arm had later cord clamping than the control arm (< 20 seconds). In the intervention group, the main reason for cord clamping before 2 minutes was the cord being too short. There were no obvious differences in compliance according to the mode of birth, or whether the site used usual equipment or the mobile trolley for neonatal care.

Fifteen babies (11%) died before discharge; this included three stillbirths all of whom were extremely premature and resuscitation at birth was attempted. Nine (60%) deaths (including one stillbirth) were of babies born < 26 weeks' gestation. Of liveborn babies, 51 (40%) had an IVH, of whom this was severe for eight (6%).

Results by allocated group, for all women randomised

Of 945 women approached, 472 (50%) gave consent and 261 (28%) were randomised (*Figure 9*).⁷¹ One-third of women were randomised before 28 weeks' gestation and two-thirds of women were randomised before 30 weeks. Just over half were women in their first pregnancy and a similar proportion had a caesarean birth. Compliance was good, with median time to cord clamping 120 seconds for women allocated to cord clamping after at least 2 minutes, and 11 seconds for those allocated to cord clamping within 20 seconds. Neonatal care was comparable between the two allocated groups.

There were no clear differences between the allocated groups in either of the primary outcomes (*Table 3*). Three-quarters of infants who died were born before 28 weeks' gestation. The three stillborn babies were all born before 28 weeks' gestation and resuscitation was attempted at birth. There were no clear differences between the allocated groups for any other outcome for the baby, or in any outcome for the mother.

Qualitative interviews about the consent pathways

Women's experiences were similar regardless of the consent pathway (see *Appendix 20*). Few showed a good understanding of randomisation, but how staff spoke to them when offering participation was important to women. They appreciated a calm manner, clear information with time to consider participation, and staff being warm and friendly and not making them feel pressured. Those recruited following oral assent reported being given less information about the trial, but felt that it was sufficient to make a decision regarding participation. Irrespective of the consent pathway, there were gaps in women's understanding of the trial. Unsurprisingly, the trial was a minor event in comparison to the birth of their baby and, once women had agreed to take part, often they did not give it further thought. Common reasons for agreeing to participate were contributing to research, that the trial might help their baby, and that it appeared to be low risk.

Overall, clinicians were supportive of the two-stage consent pathway (see *Appendix 19*). Over half discussed the importance of a team approach to inviting participation, regardless of which consent pathway was used. Clinicians were aware of the tension between the signed consent form as a record of the consent process and as a legal document proving consent was given. They viewed consent as a continual process and thought that different consent pathways could be appropriate for different trials. Some clinicians felt that in time-critical situations, oral assent had advantages over the usual consent process, as information was provided on a 'need-to-know' basis. There was some concern about the balance between time, information and understanding, for example how much information should be given for oral assent and how this is understood by women when birth is imminent. However, issues about the validity of consent applied to both pathways.

Follow-up of women up to 1 year

Response to the women's questionnaires was 76% (186/244) at 2–3 months, which dropped to 55% (133/242) at 1 year (see *Appendices 21 and 22*).¹⁶⁹ There were no clear differences between the groups for any responses, and responses were similar at the two time frames. Scores on the Hospital Anxiety and Depression Scale¹⁷⁰ were lower for depression than for anxiety on both questionnaires, and satisfaction with care at birth was high. Women were largely positive about their experiences of participation, with 92% answering 'definitely yes'¹⁶⁹ or 'probably yes' at 1 year to a question about whether or not they would participate again in the trial.¹⁷¹ Things women liked about the trial were good information about the study, caring staff and that their baby or others in the future might benefit from the research. Suggestions about what could have been improved in the trial including approaching women earlier in labour, and better communication about the study from staff.

Follow-up of children at the age of 2 years (corrected for gestation at birth)

Overall, data were available for 83% (218/262) of the children included in the follow-up (see *Appendix 23*). Children born to women allocated to cord clamping after at least 2 minutes and neonatal care, if required, with the cord intact had a lower risk of death or adverse neurodevelopmental outcome at the age of 2 years (corrected for gestation) (RR 0.61, 95% CI 0.39 to 0.96). However, although the response rate for follow-up was higher among those in the intervention group, neonatal morbidity at hospital discharge was higher for

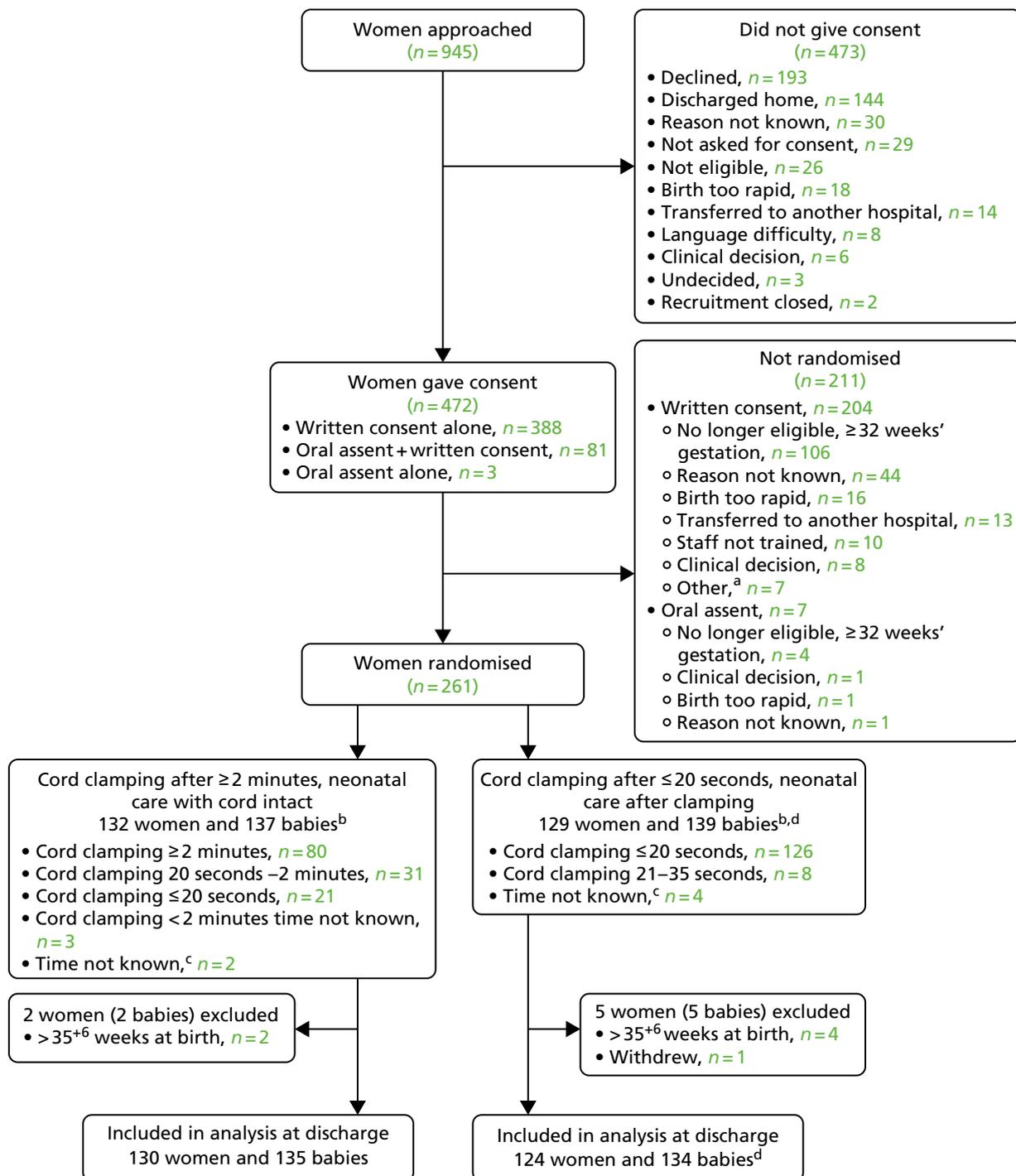


FIGURE 9 The CONSORT (Consolidated Standards of Reporting Trials) flow diagram for outcome to discharge from hospital. a, Woman changed her mind (n=2), intrauterine death (n=2), equipment failure (n=1), study closed (n=1), randomisation website failed (n=1). b, Compliance reported by baby. c, Birth at ≥36 weeks' gestation (all singleton pregnancies). d, One woman and her baby withdrew, data reported for mortality only. Reproduced from Duley *et al.*⁷¹ © Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted. This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: <http://creativecommons.org/licenses/by/4.0/>.

TABLE 3 Primary outcomes at discharge from hospital for all babies

	Clamp \geq 2 minutes + neonatal care with cord intact, <i>n</i> (<i>n</i> = 135)	Clamp \leq 20 seconds + neonatal care after clamping, <i>n</i> (<i>n</i> = 135) ^a	Risk ratio (95% CI)
Death	7 (5%)	15 (11%)	0.47 (0.20 to 1.11) ^b
Stillbirth	1	2	
Early neonatal death	3	7	
Late neonatal death	2	5	
Post neonatal death	1	1	
For babies who died, gestation at birth (weeks)			
30 – 31 ⁺⁶	–	1 ^c	
28 – 29 ⁺⁶	1	3	
26 – 27 ⁺⁶	–	4	
< 26	6	7	
Any IVH (grade 1–4) ^{d,e}	43 (32%)	47 (36%)	0.90 (0.64 to 1.26)
Alive at discharge	38	42	
Severe IVH (grade 3–4) ^d	6 (4%)	7 (5%)	

a Includes the baby of one woman who withdrew.

b Excluding death due to congenital malformation gives a RR of 0.50 (95% CI 0.21 to 1.20).

c Major congenital malformation, not known before birth.

d For live births: *n* = 134, clamp \geq 2 minutes; *n* = 132, clamp \leq 20 seconds.

e IVH diagnosis based on scan adjudication for 81 infants, scan report only for 8, and site data only for 1.

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children with no follow-up data available than for those with outcome data. Hence, this difference no longer achieved statistical significance after adjusting for missing data using multiple imputation (RR 0.69, 95% CI 0.44 to 1.09).

Successes

We conducted a substantial and successful pilot trial in a difficult clinical area, and demonstrated feasibility of conducting a large multicentre study. As the study was conducted within existing NHS clinical services, results are generalisable to similar settings.

A key limitation of previous trials is that they largely excluded babies who were likely to need immediate resuscitation at birth.¹⁷² We developed two successful strategies for recruiting such high-risk infants. First, for women allocated deferred clamping, neonatal stabilisation and resuscitation was available with the cord intact. This had the additional advantage that stabilisation was equivalent in the two intervention groups. Second, if birth was imminent, we could offer women the opportunity to participate using the two-stage consent pathway. We recruited one-quarter of women using this pathway – women and babies it would not otherwise have been possible to recruit. Qualitative interviews and questionnaire responses from the women suggest the two-stage consent pathway was acceptable in the trial.

Design and conduct of the Cord pilot trial drew on outputs from earlier parts of the programme, and the experience we developed of working as a multidisciplinary team. In particular, the strong patient and public involvement in the programme and in the trial was essential for changing the way neonatal care was provided for very preterm births, and for developing the two-stage consent pathway.

Our study is also the first cord clamping trial to use independent adjudication of cranial ultrasound scans, thereby reducing potential for bias and improved reliability in ascertainment of IVH.¹⁷³ Other successes were being the one of the first deferred cord clamping versus early cord clamping trials at preterm birth to report outcome for the women, and outcome for the children at 2 years of age (corrected for gestation at birth).

Challenges

Although we demonstrated feasibility and had strong support for the main trial, both from the independent oversight committees and from clinical sites keen to participate, we were not able to secure the necessary funding. The reason given by the funding board was that they had concerns over the timing of the study given other relevant trials that had yet to conclude.

When an external pilot trial is successful, transforming it into an internal pilot by continuing into the full trial may maximise efficiency and value for money, but our experience demonstrates it is a challenge to achieve.¹⁷⁴ Nevertheless, data from our trial will contribute to the design of any future trials,⁷² in particular through the planned prospective meta-analysis and the experience gained in delivering the intervention.

As for many perinatal trials, long-term follow-up of the children was challenging and it required a range of strategies. The importance of complete follow-up to minimise potential bias is underlined by the apparent difference between the allocated groups in response to follow-up and that children without follow-up data in the intervention group were higher risk than those for whom data were available.

Implications for future research

With appropriate planning and training, large multicentre trials of interventions around the time of preterm birth are feasible within existing maternity and neonatal services in the NHS. To improve the opportunity for participation, such trials should consider including the two-stage consent pathway. Nevertheless, this two-stage pathway merits further evaluation in a wider range of studies. Providing neonatal care beside the mother so that she can see and, if she wishes, touch her baby, also merits further evaluation in a wider range of clinical settings, and with follow-up to assess any long-term effects for parents or baby.

Since our trial was planned, new research has emerged that should be considered in planning new trials of timing of cord clamping. This includes work with pregnant sheep which has improved understanding of the physiology of transition from the fetal to neonatal circulation^{51,159,175,176} and the publication of other relevant trials including a large international trial.¹⁷⁷ The design of any future trial, including the interventions to be compared, should therefore be informed by the systematic review and meta-analysis based on individual participant data (IPD) planned in our final work package.

Work package 5: a prospective meta-analysis

Providing really reliable data on long-term safety and disability-free survival for children born very premature requires very large numbers. To achieve this, international collaboration is required and, therefore, we included planning a prospective meta-analysis as the final element of this programme. Our plan was that the first cycle of this analysis would inform the design of the main trial, should this go ahead. Although the time scale for this first cycle of analysis has been delayed beyond the end of this programme, nevertheless it will inform the design of any future large trial.

See *Appendices 24* and *25* for the unpublished reports of this work.

Research aims

The aims were to establish a collaborative group of triallists to conduct an IPD meta-analysis to assess whether timing of cord clamping and other strategies to alter placental transfusion at preterm birth influence (1) the composite outcome of death or serious morbidity at discharge from hospital and (2) disability-free survival in early childhood (aged 2–3 years). This work is referred to as Cord Clamping and Placental Transfusion at Preterm birth (CCPTP). The unexpected rapid increase in small randomised trials being published led to agreement by the CCPTP collaboration that, if sufficient funding is available, the planned prospective meta-analysis should be expanded to a retrospective IPD meta-analysis, with a nested prospective meta-analysis.

Methods for data collection

The CCPTP collaborative group of triallists was established and the protocol (see *Appendix 24*) discussed at the annual face-to-face meeting. The PROSPERO registration identifier is CRD42013004405. Following quarterly searches of trial registries, the chief investigators of studies potentially eligible for the prospective meta-analysis are contacted and invited to join the collaboration. Studies are included if they are randomised trials meeting the eligibility criteria and the investigator(s) are blind to outcome data by intervention group at the time that they agree to the CCPTP protocol.

Eligibility criteria are that participants gave birth (if women were randomised) or were born (if baby was randomised) before 37 completed weeks' gestation. Interventions are comparisons of alternative policies for timing of cord clamping, and other strategies to influence umbilical flow (e.g. lowering the baby below the level of the placenta, use of uterotonic drugs and umbilical cord milking or stripping). Studies are included if they compare strategies to maintain 'physiological' umbilical flow (i.e. none or minimal intervention) with strategies that aim to alter umbilical blood flow (e.g. using gravity by lowering the baby, cord milking or stripping). Studies comparing alternative strategies for influencing umbilical flow without a 'timing of cord clamping' arm will also be included.

Planned comparisons are:

1. Early cord clamping (short delay) versus deferred cord clamping (long delay).
2. Early cord clamping (short delay) versus umbilical cord milking or stripping.
3. Deferred cord clamping (long delay) versus umbilical cord milking or stripping.
4. Deferred cord clamping (long delay) plus umbilical cord milking or stripping versus early cord clamping (short delay).

As there is no consensus about the definition of 'early' and 'deferred' cord clamping, early clamping is defined whenever possible as within 30 seconds, and deferred clamping as after at least 1 minute. Trials that use different definitions will be included in the analysis.

As outcomes for babies born very preterm (< 32 weeks' gestation) are different for those born moderately preterm (32 to 37 weeks' gestation), separate analyses are planned for these two groups of infants. For those born < 32 weeks' gestation, primary outcomes are (1) death or serious morbidity at hospital discharge (serious morbidity is defined as one or more of severe IVH, necrotising enterocolitis, late onset sepsis, chronic lung disease and retinopathy of prematurity); (2) chronic lung disease; and (3) neurodevelopmental delay in early childhood. Secondary outcomes include individual items in the composite outcome and measures of neonatal morbidity and adverse neurodevelopmental outcome in early childhood.

For infants born at or after 32 weeks' gestation, the primary outcome is admission to NICU. Secondary outcomes are measures of neonatal morbidity, iron status in infancy, and adverse neurodevelopmental outcome in early childhood.

For the women, outcomes are complications of the third stage of labour, postpartum infection, breastfeeding and postnatal depression.

Analysis

The detailed statistical analysis plan will be developed and agreed before any analysis begins. Planned subgroup analyses are based on:

- participant-level characteristics – gestation at birth, whether singleton or multiple pregnancy, mode of birth and whether or not spontaneous onset of labour
- hospital-level characteristics – highest level of neonatal unit available at site, timing of uterotonic drug, timing of cord clamping, planned position of the baby relative to the placenta with the cord intact, and whether or not babies needing immediate resuscitation at birth were recruited.

To assess whether or not the results are robust to trial quality and different methods of analysis, the following sensitivity analyses are planned for the primary outcomes, if there are sufficient data: excluding studies with a high risk of bias; for comparison of early with deferred clamping, analysis weighted by observed between-arm difference in mean timing between the groups; analysis weighted by degree of separation in haemoglobin between the groups.

If a policy of deferred cord clamping appears to be beneficial, additional analyses will therefore explore the effects based on duration of allocated deferred cord clamping and, if the allocation was clamping after 20 to 30 seconds, whether or not neonatal care, if needed, was provided with the cord intact.

Successes

Currently we know of 53 trials, involving 11,811 infants (3020 for long-term outcomes). Our success in establishing the CCPTP collaboration emphasises the international interest in this topic. Annual collaborators meetings, held alongside neonatal conferences to minimise cost, have facilitated collaboration and biannual newsletters provide regular updates.

Success of the collaboration between the Nottingham Clinical Trials Unit and the National Health and Medical Research Council Clinical Trials Centre at the University of Sydney, which jointly support the secretariat for CCPTP, means that the first cycle of analysis is now planned for 2020 and funding has been secured to expand this to include a retrospective meta-analysis based on IPD, with a nested prospective meta-analysis

(see *Appendix 25*). The collaboration also changed its name to systematic review and network meta-analysis with individual participant data on Cord Management at Preterm birth (iCoMP).

Challenges

The main challenge for this project is common to all planned prospective meta-analyses: the time scale for analysis is unpredictable. Results for the large study planned for inclusion in CCPTP, the Australian Placental Transfusion Trial, were published later than anticipated,¹⁷⁷ as were results for the Cord pilot trial. Hence, the first cycle of analysis was not possible within the programme time scale. The number of new trials under way is accelerating, with 29 registered in the past 2 years. Many of these are relatively small and data analysis may have begun before the investigators agree the CCPTP protocol. Growing numbers being published risked undermining the relevance of a standalone prospective meta-analysis. Hence, we expanded the protocol to allow inclusion of a retrospective IPD meta-analysis, with network meta-analysis. Work commenced on this IPD in 2019.

Implications for future research

Placental transfusion at preterm birth is a current 'hot topic', with wide variation in clinical practice. This has led to a plethora of recent trials largely undertaken in isolation, with little standardisation of the intervention(s) being tested or the outcomes being collected. Value of these existing trials will be substantially enhanced by combining and fully utilising the IPD, as planned in CCPTP. Provision of individual participant data by each trial investigator will provide the required statistical power and enable reliable subgroup analyses to be undertaken.

Results of these analyses based on IPD from each trial will inform clinical practice and will identify the most promising intervention(s) for further evaluation. Co-ordinating international efforts in this way will also help achieve consensus on the most important clinical outcomes to assess in any future trials.

Conclusions

Our programme aimed to improve the quality of immediate care at very preterm birth, enhance family-centred care at birth and improve outcome for infants and their families. To do this, we conducted 10 projects grouped into five work packages. First, we identified and ranked the top research gaps for preterm birth. Then, to develop strategies for providing initial neonatal care at birth beside the mother at very preterm birth, we conducted a survey of practice, assessed parents' views of initial neonatal care beside the mother, improved understanding of the physiology of transition from fetal to neonatal circulation, systematically reviewed strategies for initial care and assessment at preterm birth, and developed a mobile newborn life support trolley. Finally, to generate the information to enable conduct of a large NHS trial comparing alternative policies for cord clamping at preterm births, we systematically reviewed ethics issues in recruiting preterm or sick infants to trials, conducted a feasibility pilot trial and developed the protocol for a prospective meta-analysis.

The prioritisation process ran in parallel to other work packages, as it was added in response to feedback from the funding board at stage 1 of the grant application process. Hence, the other work packages were not dependent on its outcomes. Although cord clamping did emerge as a top priority, we had already identified this as a priority via an informal process.

Central to the success of our programme was that service user representatives were partners throughout its planning and conduct. What worked well was being equal partners, rooted in a service user perspective, and being guided throughout by service user representatives who shared responsibility for the research. This allowed us to tackle emotive issues, such as immediate neonatal care at very preterm birth, and consent for participation in a clinical trial evaluating an intervention during labour at very preterm birth. Our service users came with an understanding of different research methods, but this should not be a prerequisite as good training could also be included. Our research team included experience and expertise in working with service users and their representatives. Vital to equal partnership is the support from those leading the research to specifically include service users who bring their personal experience to the project. The time commitment required did not prove a problem with this particular programme of research, but may well be a problem generally. In addition, our qualitative interviews with parents who had experienced very preterm birth were conducted early in the programme. The experiences these parents described informed our work, helping to ensure that it remained parent-focused throughout.

Providing care for the mother, her baby and other family members involves complex multidisciplinary teams. A substantive output from our programme has been to demonstrate that providing initial neonatal care at birth beside the mother is both feasible within the NHS and acceptable to parents and to clinicians. Our work is contributing to a shift in culture, for example the World Health Organization now recommends that ventilation can be started before cutting the umbilical cord, if the attending clinicians have experience in providing effective positive-pressure ventilation with the cord intact.⁷³ Although further evaluation is required, our data suggest that, with adequate training, preparation and support, parents and clinicians prefer care beside the mother rather than moving the baby away from the mother for assessment, stabilisation and resuscitation at birth.

Although this might seem to be a relatively simple change in practice, achieving it required a change in culture for care at the time of very preterm birth. When we planned this work, usual practice was to quickly clamp the umbilical cord and then move the baby either to the side of the room or to another room nearby. This requires little communication between the obstetric and the midwifery team responsible for the mother and the birth and the neonatal team responsible for the newborn infant. In contrast, providing immediate neonatal care beside the mother requires discussion in advance and negotiation about where to place the resuscitation equipment, who will stand where and who will support the mother and her partner so they understand what is happening. Parents and clinicians felt that this improved communication between them. Anecdotally, clinicians involved in the programme also felt that this

multidisciplinary working enhanced how they interacted with other clinical colleagues on the delivery suite, with wider benefits in terms of improved quality of care.

Another example of this change in culture is the change in attitude to the role of the mobile trolley. When we were planning the programme, the neonatologists we consulted were unanimous that developing this trolley, or a similar device, was essential if they were to provide neonatal care beside the mother. However, following consultation with the necessary disciplines about providing care beside the mother and with the umbilical cord intact, and having demonstrated that this is possible in clinical practice, opinion shifted. Working as a multidisciplinary team, we showed that it was also possible to adapt the existing equipment to provide neonatal care beside the mother.⁷⁰ This has the advantages of not needing to purchase new equipment and that staff are already familiar with its use. For the pilot trial, six out of the eight hospitals used existing equipment to provide the intervention and two hospitals chose to purchase the new mobile trolley.

Very preterm birth is a difficult time for parents and their experiences of care may differ from those having a term birth. Our P-BESS questionnaire may be useful to compare views and experiences across hospitals and differing practices for very preterm birth, whereas individual aspects of the care environment can be evaluated using the separate subscales.

Conducting randomised trials of interventions around the time of very preterm birth is particularly challenging, and in the past infants at highest risk have largely been excluded from trials.⁵⁵ To help ensure that recruitment to the Cord pilot trial was representative of the total population of very preterm births, we developed a two-stage consent pathway that allowed women for whom birth was imminent the opportunity to consider participation. This strategy is now recommended for use in other intrapartum trials by the Royal College of Obstetricians and Gynaecologists.⁸¹ The current informed consent process is laborious and a major barrier to conducting research on important, but time-sensitive, topics. The two-stage consent process should help to open neonatology and perinatology to making research participation more like the everyday clinical care. A similar approach may also be relevant in other emergency trials,¹⁷⁸ or in those for which recruitment is time critical. For example, it has been adapted for use in an acute stroke trial.⁸²

Part of the rationale for including a prospective meta-analysis in our programme was that a large trial was under way in Australia. That study compared cord clamping after at least 60 seconds and lowering the baby with clamping within 10 seconds, and results have just been reported for the 1634 babies randomised.¹⁷⁷ There was no clear difference in the composite primary outcome of death or serious morbidity at 36 weeks postmenstrual age, although fewer babies in the intervention group died (6.4% in delayed clamping group versus 9.0% in immediate clamping).¹⁷⁷ In the light of these new data, remaining research questions to address in future trials include whether or not stabilisation and resuscitation can safely be left until after cord clamping, even for those with apnoea and the very premature, and what is the optimal time for cord clamping at very preterm birth.^{72,179}

Our prioritisation process for preterm birth research is already influencing the UK research agenda. For example, the NIHR Health Technology Assessment programme has funded studies addressing topics in the top priorities, and Bliss, the charity for babies born premature or sick, has included the priorities in their strategy for research they support.

Limitations of our programme

Preterm birth is associated with factors such as lower socioeconomic status, ethnicity and maternal age. For our prioritisation process, despite implementing strategies to reach a representative population, respondents were primarily white and a relatively high proportion of respondents were homeowners and were therefore not representative of those most affected by preterm birth. This may limit relevance of the ranked priorities to other populations.

For the qualitative work on very preterm birth, limitations of our data were that participants in the interviews came from two hospitals in the south of England and they were mainly white married women; therefore, not typical for very preterm birth. For development of the P-BESS questionnaire, the sample size was relatively small for a factor analysis and, again, was unrepresentative.

Generalisability of our findings on neonatal care beside the mother is limited by recruitment of parents and clinicians from a single hospital with a particular interest in care beside the mother, and where the trolley had been developed. In addition, we were again not successful in recruiting parents for interview who were representative of the wider population with very preterm birth. Furthermore, the babies were all alive at the time of interview and most had not required advanced resuscitation at birth.

Finally, although our pilot trial demonstrated feasibility and had strong support for progression to the main trial, we were not able to secure the necessary funding. Hence, we have not been able to conduct a definitive trial.

Implications for health care

Providing initial neonatal care at birth beside the mother is feasible within the NHS, acceptable to parents and to clinicians, and both parents and clinicians felt that it improved communication. Although further evaluation is required, our data suggest that, with adequate training, preparation and support, parents and clinicians prefer care beside the mother rather than moving the baby away from the mother for assessment, stabilisation and resuscitation at birth. This has major implications for maternity services. Although this is a relatively simple change in practice, implementation of neonatal care beside the mother at birth requires a change in culture to multidisciplinary teamworking. Care beside the mother can be done either by adapting the usual resuscitation equipment or by using a mobile trolley specifically designed for the purpose.

The Cord pilot trial demonstrates that neonatal stabilisation and resuscitation can be provided with the umbilical cord intact, providing a practical and generalisable strategy for supporting continued umbilical flow at birth. Results of this trial add to the growing body of data from randomised trials suggesting that there is no need to rush to clamp the cord at very preterm birth. Although the optimal policy for cord clamping at very preterm birth remains unclear, waiting 20 to 30 seconds seems prudent.

Only a small proportion of births are very preterm, and parents' experiences of care during the birth can differ from those having a term birth. The P-BESS questionnaire was developed to assess experiences and satisfaction with care during very preterm birth and can be used by hospitals to assess their care, potentially identifying areas where care can be improved. A total score can be used to compare across hospitals and differing practices, whereas individual aspects of care can be evaluated using the subscales.

Recommendations for future research

- The 15 top research priorities should guide researchers and funding bodies when planning new research.
- When planning and funding preterm birth research, it may be relevant to consider not only the top 15 priorities but also the full list of 104 unanswered questions, the top 30 ranked by those affected by preterm birth and the top 30 ranked by health-care professionals.
- Future prioritisation processes, particularly those with a similar wide range of health-care professionals, should anticipate potential different perspectives and mitigate any imbalance where possible, and should report voting separately by 'service users' and health-care professionals. Health-care professionals who are also researchers should declare this potential conflict before participating in the prioritisation workshop, so that it can be taken into account.

- Important 'evidence gaps' for neonatal care at birth include pharmacological intervention for transition support or resuscitation of newborn infants, and the effectiveness of new, less invasive forms of airway management (and related issues regarding surfactant delivery).
- Since our programme started, both timing of cord clamping for very preterm births and providing neonatal care with the cord intact have become increasingly topical. New research has emerged, including the work conducted within this programme, which is changing opinion and clinical practice. Therefore, it would be timely to repeat a survey of practice.
- Further research is needed to replicate our findings about parent experiences at very preterm birth, and to explore whether or not there is variation for parents from different backgrounds.
- Further studies are needed to test the P-BESS questionnaire in a larger, more representative sample of parents.
- Fathers of preterm or sick babies are a difficult group to recruit into research. Our work highlights the importance of including them in research studies to ensure that their perspective is represented.
- Further research is needed to evaluate clinical outcomes, parent experiences and the costs of neonatal care beside the mother and of care with the cord intact. This should include a wider range of settings and using the standard resuscitation equipment as well as the mobile trolley. It should involve parents from more diverse backgrounds, those whose baby required advanced resuscitation, and those whose baby died. Future studies should also include follow-up of parents and infants.
- The optimal study design would be a randomised trial to compare outcomes (for children and parents) for parents offered initial neonatal care beside the mother, with outcomes for those offered traditional care.
- With appropriate planning and training, large multicentre trials of interventions around the time of preterm birth are feasible within existing maternity and neonatal services in the NHS.
- The two-stage consent pathway should be included in future perinatal trials to increase participation when there is little time in which to seek consent to participation. It also has potential to increase participation in other emergency or time-critical trials, but this merits further evaluation.
- Design of future trials comparing alternative policies for cord management should take account of results from our trial and the planned meta-analysis based on individual participant data from all relevant trials.

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Programme steering group

Lelia Duley (chairperson), Susan Ayers, Zoe Chivers, Jon Dorling, David Field, Gill Gyte, William McGuire, Chris Megone, Sam Oddie, Sandy Oliver, Jim Thornton, Andrew Weeks and Charles William Yoxall.

Programme management team

Lelia Duley, Charlotte Lloyd (2011–13), Virginia Portillo (2014–15), Sarah Somerset (2016–17), Sarah Smith (2011–13) and Ruth Fletcher (2014–16).

Thanks to Lindsay Armstrong-Buisseret for assistance with compiling this report.

Work package 1

James Lind Alliance Preterm Birth Priority Setting Partnership

This work would not have been possible without the organisations that contributed to the partnership, the people who responded to the survey and who voted on the priorities, and the participants in the final workshop. For the qualitative work on consensus development, thanks to Lizzie Oliver and Sarah Thum-Bonanno for transcribing the data, Sergio Grazio for technical support, members of the steering group, and delegates who attended the final workshop.

Ethics approval

Research Ethics Committee approval for the whole priority setting exercise was obtained from the Institute of Education (reference FCL 318), and for distribution of paper versions of the survey from the Liverpool Research Ethics Committee (reference 12/WA/0286).

Steering group

Sally Crowe (chairperson), Fiona Alderdice, Bev Chambers, Zoe Chivers, Anna L David, Sanjeev Deshpande, Irene Dowling, Lelia Duley, Chris Gale, Gill Gyte, Catherine P James, Jenny McNeill, Sandy Oliver, Andrew Shennan, Mark Turner and Seilin Uhm.

Consensus development for tackling technical and emotive challenges

Seilin Uhm and Sandy Oliver.

Work package 2.1

Evidence-based immediate care of the very preterm infant

This systematic overview is registered with PROSPERO CRD42012003038. It was conducted by Thirimon Moe-Byrne, Jennifer VE Brown, Mark Corbett and William McGuire.

Work package 2.2

Ethical issues in recruitment of preterm or sick infants to perinatal trials

This framework synthesis was conducted by Chris Megone, Eleanor Wilman, Sandy Oliver, Lelia Duley and Gill Gyte and Judith Wright.

Work package 3.1

Neonatal care at birth, a survey of current practice

This research would not have been possible without the neonatal units and staff who responded to the survey, and the participants who agreed to be interviewed. Thanks also to Richard A Parker from the Centre for Applied Medical Statistics, University of Cambridge, for statistical support for the survey.

Ethics approval

The survey was approved by the local research and development department at Bradford Teaching Hospitals NHS Foundation Trust but did not require ethics committee approval. The interview study was approved by the Rotherham sitting of National Research Ethics Committee 11/YH/0302.

Project team

Sam Oddie, Penny Rhodes and Yogen Singh.

Work package 3.2

Parents' views of care at preterm birth

This research would not have been possible without the parents who agreed to be interviewed and who so generously shared their experiences.

Ethics approval

The study received approval from the National Research Ethics Committee South East Coast – Kent. Reference: 11/LO/0143.

Project team

Susan Ayers, Jane Abbott, Leah Arnold, Lelia Duley, Gill Gyte, Heike Rabe, Gillian Russell and Alexandra Sawyer.

Work package 3.3

Measuring placental transfusion

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Ethics approval

The study received ethics approval from the London Riverside National Research Ethics Service Committee.

Project team

Jon Dorling, Sam Oddie, Bernard Schoonakker and Lelia Duley.

Work package 3.4

Developing a Bedside Assessment, Stabilisation and Initial Circulatory Support trolley

This research would not have been possible without contributions from a large number of people: a group who met at Worcestershire Royal Hospital to discuss ways of bedside resuscitation consisting of Susan Bewley (who coined the term 'BASICS'), Amanda Burleigh, Lelia Duley, Andrew Gallagher, Ann Marie Heuchan, David Hutchon, Rabia Imtiaz, David Odd and Andrew Weeks. David Hutchon, who convened the initial meeting, was a member of the team for the Medical Futures award in 2010, and provided input into the design of the BASICS trolley prototype, and identified Inditherm as a commercial partner. Inditherm and their managing director Nick Bettles for their work in developing the fully functional CE marked mobile resuscitaire from the initial prototype. Gill Gyte who attended the Liverpool design meetings and provided important input into the trolley design. Tony Fisher, Head of Department of Clinical Engineering at the Royal Liverpool University Teaching Hospital, who provided important advice about intellectual property as well as agreeing to develop the prototype in his department at a discounted cost.

Ethics approval

The commercially produced trolley (with CE mark) was subsequently introduced into clinical service at Liverpool Women's Hospital following approval from the Medical Devices Committee, the head of Research and Development, and the Clinical Director for the Neonatology Directorate.

Project team

Andrew Weeks, Peter Watt, Charles William Yoxall and Lelia Duley.

Work package 3.5

Evaluating parents' and clinicians' views of neonatal care beside the mother

This research would not have been possible without the clinicians who completed the service evaluation forms, and the parents and clinical staff who generously agreed to be interviewed and shared their experiences. Particular thanks to Louise Goodman, Gill Houghton, Heather Longworth and Angela Pascall for conducting the qualitative interviews.

Ethics approval

The service evaluation was approved by Trust governance procedures during the introduction of the trolley into clinical practise in Liverpool Women's Hospital. Ethics approval for the qualitative interviews was from the Yorkshire and Humber Research Ethics Committee (reference 12/YH/0321).

Project team

Charles William Yoxall, Andrew Weeks, Susan Ayers, Alex Sawyer, Sophia Bertullies, Lelia Duley and Margaret Thomas.

Work package 4

Cord pilot trial

This research would not have been possible without the women who participated in the trial, and their families, and the clinical and research staff at the sites. Particular thanks to Diane Whitham and Gill Bumphrey for preparation of the randomisation envelopes, and to Alec Whitham for making the mail boxes.

This study is registered as ISRCTN21456601.

Ethics approval

Ethics approval was from Nottingham REC 2 (National Research Ethics Service reference 12/EM/0283).

Cord Pilot Trial Collaborative Group***Nottingham Clinical Trials Unit***

Lelia Duley, Lindsay Armstrong-Buisseret (from November 2015), Brian Barnes, Lucy Bradshaw, Natalie Hutchings, Eleanor Mitchell, Angela Pushpa-Rajah (May 2013–July 2015) and Keith Whittaker.

Trial Management Group

Lucy Bradshaw, Jon Dorling, Lelia Duley, Eleanor Mitchell and Angela Pushpa-Rajah (chairperson).

Trial Steering Committee

Mike Clarke (chairperson), Lucy Bradshaw, Kate Branchett, Richard Cooke, Jon Dorling, Lelia Duley, Liz Goddard, Sara Kenyon, Angela Pushpa-Rajah and Philip Steer.

Data Monitoring Committee

Douglas Altman (chairperson), Declan Devane, Andrew Shennan and Ben Stenson.

Patient and public involvement

Jane Abbott (until June 2014), Zoe Chivers and Gill Gyte.

Cranial ultrasound adjudication

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Clinical advisors

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Women's and clinicians' views of the consent pathways

Celine Chhoa, Alexandra Sawyer, Susan Ayers, Angela Pushpa-Rajah and Lelia Duley.

Cord Pilot Trial Cranial Ultrasound Adjudication Collaborative Group***Working group***

Lindsay Armstrong-Buisseret, Lucy Bradshaw, Robert Dineen, Jon Dorling, Lelia Duley and Eleanor Mitchell.

Nottingham Clinical Trials Unit

Lelia Duley, Lindsay Armstrong-Buisseret, Brian Barnes, Lucy Bradshaw, Eleanor Mitchell and Keith Whitaker.

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Narendra Aladangady, Dushyant Batra, Robert Dineen, Jon Dorling, Joe Fawke, Louise Hattingh, Shoaib Khan, Bernard Schoonakker and Kiran Yajamanyam.

Follow-up of the women postnatally and at 1 year

Lindsay Armstrong-Buisseret, Lucy Bradsaw, Lelia Duley, Eleanor Mitchell, Alexandra Sawyer and Susan Ayers.

Follow-up of the children at 2 years of age

Lindsay Armstrong-Buisseret, Lucy Bradsaw, Jon Dorling, Lelia Duley, Samantha Johnson, Eleanor Mitchell, Rob Dineen and Kathryn Powers.

Work package 5***A prospective meta-analysis***

This systematic review and prospective meta-analysis is registered with PROSPERO CRD42013004405.

This research would not have been possible without the triallists who agreed to participate in the collaborative group. Particular thanks to Kylie Hunter for advice on the search strategy for ongoing trials.

Cord Clamping and Placental Transfusion at Preterm Birth Collaborative Group

Secretariat

Lelia Duley (chairperson), Lisa Askie, Alan Montgomery (from 2013), Min Yang (to 2016), Charlotte Lloyd (2011–13), Virginia Portillo (2014–15) and Sarah Somerset (2016–17).

Trialists and collaborators

Krishna Agarwal, Ola Andersson, John Bauer, Melchor Carbonell Socias, Sangkae Chamnanvanakij, Vikram Datta, Eugene Dempsey, Catalina De Paco Matallana, Monica Domingo Puiggros, Walid El-Naggar, Karen Fairchild, Neil Finer, Meena Garg, Alejandra Gurzman, Shigeharu Hosono, Omar Kamlin, Anup Katheria, John Kattwinkel, Justin Josephsen, Judy Mercer, G Ram Mohan John Simes, William Tarnow-Mordi, Tanai Trongkamonthum, Sundaram Venkateshan and Danielle Young.

Contributions of authors

Lelia Duley (Professor of Clinical Trials, University of Nottingham) substantially contributed to the design, methodology, data collection, analysis and reporting for all of the work packages. She was the grant holder, the chief investigator for the Cord pilot trial and chaired the programme steering group. She led the writing, revision and approval of the final report.

Jon Dorling (Associate Professor of Neonatology, University of Nottingham) substantially contributed to the design, methodology, data collection, analysis and reporting for the measuring placental transfusion work package (3.3), and the Cord pilot trial work package (4). He was a member of the programme steering group and contributed to the writing, revision and approval of the final report.

Susan Ayers (Professor of Maternal Health, City, University of London) led on the qualitative aspects of the programme. She substantially contributed to the design, methodology, data collection, analysis and reporting for the parents' views of care at preterm birth work package (3.2), and the evaluating parents' and clinicians' views of neonatal care beside the mother work package (3.5). She also led on the qualitative aspects of the Cord pilot trial work package (4). She was a member of the programme steering group and contributed to the writing, revision and approval of the final report.

Sandy Oliver (Professor of Public Policy, University College London) led the preterm birth priority setting work package (1) including supervising the doctor of philosophy (PhD) student, and substantially contributed to the design, methodology, data collection, analysis and reporting for the framework synthesis of ethics issues in recruitment of preterm or sick infants to perinatal trials work package (2.2). She was a member of the programme steering group and contributed to the writing, revision and approval of the final report.

Charles William Yoxall (Consultant Neonatologist, Liverpool Women's Hospital) substantially contributed to design and development of the BASICS trolley work package (3.4), and the design, methodology, data collection, analysis and reporting for the evaluating parents' and clinicians' views of neonatal care beside the mother work package (3.5) and the Cord pilot trial work package (4). He was a member of the programme steering group and contributed to the writing, revision and approval of the final report.

Andrew Weeks (Professor of International Maternal Health Care, University of Liverpool) substantially contributed to design and development of the BASICS trolley work package (3.4), and the design, methodology, data collection, analysis and reporting for the evaluating parents' and clinicians' views of neonatal care beside the mother work package (3.5) and the Cord pilot trial work package (4). He was a member of the programme steering group and contributed to the writing, revision and approval of the final report.

Chris Megone (Professor of Philosophy, University of Leeds) led the design, methodology, data collection, analysis and reporting for the framework synthesis of ethics issues in recruitment of preterm or sick infants to perinatal trials work package (2.2), and advised on development of the two-stage oral assent consent pathway in the Cord pilot trial work package (4). He was a member of the programme steering group and contributed to the writing, revision and approval of the final report.

Sam Oddie (Consultant Neonatologist, University of York) substantially contributed to the design, methodology, data collection, analysis and reporting for the neonatal care at birth work package (3.1), the measuring placental transfusion work package (3.3), and the Cord pilot trial work package (4). He was a member of the programme steering group and contributed to the writing, revision and approval of the final report.

Gill Gyte (NCT) provided patient and public involvement expertise across all work packages. In particular she substantially contributed to the design, methodology, data collection, analysis and reporting for the preterm birth priority setting work package (1), the framework synthesis of ethics issues in recruitment of preterm or sick infants to perinatal trials work package (2.2), the parents' views of care at preterm birth work package (3.2), design and development of the BASICS trolley work package (3.4), and the Cord pilot trial work package (4). She was a member of the programme steering group and contributed to the writing, revision and approval of the final report.

Zoe Chivers (Bliss) provided patient and public involvement expertise across all work packages. In particular she substantially contributed to the design, methodology, data collection, analysis and reporting for the preterm birth priority setting work package (1), and the Cord pilot trial work package (4). She was a member of the programme steering group and contributed to the writing, revision and approval of the final report.

Jim Thornton (Professor of Obstetrics and Gynaecology, University of Nottingham) supported the measuring placental transfusion work package (3.3) and substantially contributed to the design, methodology, data collection, analysis and reporting for the Cord pilot trial work package (4). He was a member of the programme steering group and contributed to the writing, revision and approval of the final report.

David Field (Professor of Neonatal Medicine, University of Leicester) substantially contributed to the design, methodology, data collection, analysis and reporting for the Cord pilot trial work package (4). He was a member of the programme steering group and contributed to the writing, revision and approval of the final report.

Alexandra Sawyer (Research Fellow, University of Brighton) substantially contributed to the design, methodology, data collection, analysis and reporting for the parents' views of care at preterm birth work package (3.2), the evaluating parents' and clinicians' views of neonatal care beside the mother work package (3.5), and the qualitative aspects of the Cord pilot trial work package (4).

William McGuire (Professor of Child Health, University of York) substantially contributed to the design, methodology, data collection, analysis and reporting for the evidence-based immediate care of the very preterm infant work package (2.1). He was a member of the programme steering group and contributed to the writing, revision and approval of the final report.

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Patient data

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

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Appendix 1 List of programme journal publications, with status and whether or not included in appendices

Work package 1

Duley L, Uhm S, Oliver S, Preterm Birth Priority Setting Partnership Steering Group. Top 15 UK research priorities for preterm birth. *Lancet* 2014;**383**:2041–2. See *Appendix 2*.

Oliver S, Uhm S, Duley L, Crowe S, David A, James CP, *et al*. Top research priorities for preterm birth: results of a prioritisation partnership between people affected by preterm birth and healthcare professionals. *Submitted, in peer review*. See *Appendix 3*.

Uhm S, Liabo K, Stewart R, Rees R, Oliver S. Patient and public perspectives shaping scientific and medical research: panels for data, discussions, and decisions. *Patient Intell* 2012;**4**:1–10.

Work package 2.1

Corbett MS, Moe-Byrne T, Oddie S, McGuire W. Randomisation methods in emergency setting trials: a descriptive review. *Res Synth Methods* 2016;**1**:46–54.

Moe-Byrne T, Brown JV, McGuire W. Naloxone for opiate-exposed newborn infants. *Cochrane Database Syst Rev* 2013;**2**:CD003483.

Work package 2.2

Wilman E, Megone C, Oliver S, Duley L, Gyte G, Wright JM. The ethical issues regarding consent to clinical trials with pre-term or sick neonates: a systematic review (framework synthesis) of the empirical research. *Trials* 2015;**16**:502. See *Appendix 6*.

Megone C, Wilman E, Oliver S, Duley L, Gyte G, Wright J. The ethical issues regarding consent to clinical trials with pre-term or sick neonates: a systematic review (framework synthesis) of the analytical (theoretical/philosophical) research. *Trials* 2016;**17**:443. See *Appendix 7*.

Work package 3.1

Singh Y, Oddie S. Marked variation in delivery room management in very preterm infants. *Resuscitation* 2013;**84**:1558–61. See *Appendix 8*.

Oddie S, Rhodes P, Very Preterm Birth Qualitative Collaborative Group. Barriers to deferred cord clamping in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2014;**99**:F391–4. See *Appendix 9*.

Work package 3.2

Sawyer A, Rabe H, Abbott J, Gyte G, Duley L, Ayers S, Very Preterm Birth Qualitative Collaborative Group. Parents' experiences and satisfaction with care during the birth of their very preterm baby: a qualitative study. *BJOG* 2013;**120**:637–43. See *Appendix 10*.

Arnold L, Sawyer A, Rabe H, Abbott J, Gyte G, Duley L, Ayers S, Very Preterm Birth Qualitative Collaborative Group. Parents' first moments with their very preterm babies: a qualitative study. *BMJ Open* 2013;**3**:e002487. See *Appendix 11*.

Russell G, Sawyer A, Rabe H, Abbott J, Gyte G, Duley L, Ayers S, Very Preterm Birth Qualitative Collaborative Group. Parents' views on care of their very premature babies in neonatal intensive care units: a qualitative study. *BMC Pediatr* 2014;**14**:230.

Sawyer A, Ayers S, Abbott J, Gyte G, Rabe H, Duley L. Measures of satisfaction with care during labour and birth: a comparative review. *BMC Pregnancy Childbirth* 2013;**13**:108.

Sawyer A, Rabe H, Abbott J, Gyte G, Duley L, Ayers S, Very Preterm Birth Collaborative Group. Measuring parents' experiences and satisfaction with care during very preterm birth: a questionnaire development study. *BJOG* 2014;**121**:1294–301. See *Appendix 12*.

Work package 3.4

Weeks AD, Watt P, Yoxall CW, Gallagher A, Burleigh A, Bewley S, *et al*. Innovation in immediate neonatal care: development of the Bedside Assessment, Stabilisation and Initial Cardiorespiratory Support (BASICS) trolley. *BMJ Innov* 2015;**1**:53–8. See *Appendix 14*.

Work package 3.5

Sawyer A, Ayers S, Bertullies S, Thomas M, Weeks AD, Yoxall CW, Duley L. Providing immediate neonatal care and resuscitation at birth beside the mother: parents' views, a qualitative study. *BMJ Open* 2015;**5**:e008495. See *Appendix 15*.

Yoxall CW, Ayers S, Sawyer A, Bertullies S, Thomas M, D Weeks A, Duley L. Providing immediate neonatal care and resuscitation at birth beside the mother: clinicians' views, a qualitative study. *BMJ Open* 2015;**5**:e008494. See *Appendix 16*.

Thomas MR, Yoxall CW, Weeks AD, Duley L. Providing newborn resuscitation at the mother's bedside: assessing the safety, usability and acceptability of a mobile trolley. *BMC Pediatr* 2014;**14**:135.

Work package 4

Duley L, Dorling J, Pushpa-Rajah A, Oddie SJ, Yoxall CW, Schoonakker B, *et al*. Randomised trial of cord clamping and initial stabilisation at very preterm birth. *Arch Dis Child Fetal Neonatal Ed* 2018;**103**:F6–F14. See *Appendix 18*.

Chhoa CY, Sawyer A, Ayers S, Pushpa-Rajah A, Duley L. Clinicians' views and experiences of offering two alternative consent pathways for participation in a preterm intrapartum trial: a qualitative study. *Trials* 2017;**18**:196. See *Appendix 19*.

Sawyer A, Chhoa C, Ayers S, Pushpa-Rajah A, Duley L. Women's views and experiences of two alternative consent pathways for participation in a preterm intrapartum trial: a qualitative study. *Trials* 2017;**18**:422. See *Appendix 20*.

Bradshaw L, Sawyer A, Armstrong-Buisseret L, Mitchell E, Ayers S, Duley L. Cord pilot trial, comparing alternative policies for timing of cord clamping before 32 weeks gestation: follow-up for women up to one year. *BMC Pregnancy Childbirth* 2019;**19**:78. See *Appendix 21*.

Bradshaw L, Sawyer A, Mitchell E, Armstrong-Buisseret L, Ayers S, Duley L. Women's experiences of participating in a randomised trial comparing alternative policies for timing of cord clamping at very preterm birth: a questionnaire study. *Trials* 2019;**20**:225. See *Appendix 22*.

Armstrong-Buisseret L, Powers K, Dorling J, Bradshaw L, Johnson S, Mitchell E, Duley L. Randomised trial of cord clamping at very preterm birth: outcomes at 2 years [published online ahead of print August 1 2019]. *Arch Dis Child Fetal Neonatal Ed* 2019. See *Appendix 23*.

Bradshaw LE, Pushpa-Rajah A, Dorling J, Mitchell E, Duley L. On behalf of the 'Cord Pilot Trial Collaborative Group'. Cord pilot trial: update to randomised trial protocol. *Trials* 2015;**16**:407.

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Batey N, Yoxall CW, Fawke JA, Duley L, Dorling J. Fifteen-minute consultation: stabilisation of the high-risk newborn infant beside the mother. *Arch Dis Child Educ Pract Ed* 2017;**102**:235–8.

Work package 5

Duley L, Askie L, Montgomery A, Hunter K, Barba A, Seidler AL, *et al*. Systematic review and network meta-analysis with individual participant data on Cord Management at Preterm Birth (iCoMP): study protocol. *Draft prepared for submission*. See *Appendix 25*.

Appendix 2 Top 15 UK research priorities for preterm birth

Duley *et al.*³¹ [https://doi.org/10.1016/S0140-6736\(14\)60989-2](https://doi.org/10.1016/S0140-6736(14)60989-2)

Appendix 3 Top research priorities for preterm birth: results of a prioritisation partnership between people affected by preterm birth and health-care professionals

Abstract

Background: We report a process to identify and prioritise research questions in preterm birth that are most important to people affected by preterm birth and healthcare practitioners in the UK.

Methods: Using consensus development methods established by the James Lind Alliance, unanswered research questions were identified using an online survey, a paper survey distributed in NHS preterm birth clinics and neonatal units, and through searching published systematic reviews and guidelines. Prioritisation of these questions was by online voting followed by a decision-making workshop of people affected by preterm birth and healthcare professionals.

Results: Overall 26 organisations participated. 386 people responded to the survey, and 636 systematic reviews and 12 clinical guidelines were inspected for research recommendations. From this a list of 122 uncertainties about the effects of treatment was collated: 70 from the survey, 28 from systematic reviews, and 24 from guidelines. After removing 18 duplicates, the 104 remaining questions went to a public online vote on the top 10. 507 people voted; 231 (45%) people affected by preterm birth, 216 (43%) health professionals, and 55 (11%) affected by preterm birth and also a health professional. Although the top priority was the same for all types of voter, there was variation in how other questions were ranked.

Questions ranked as 31-40 were reviewed by the Steering Group, taking into account voting preferences of people affected by preterm birth. The top 30 were then taken to the prioritisation workshop. A list of top 15 questions was agreed, but with some clear differences in priorities between people affected by preterm birth and healthcare professionals.

Conclusions: These research questions prioritised by a partnership process between service users and healthcare professionals should inform the decisions of those who plan to fund research. Priorities of people affected by preterm birth were sometimes different from those of healthcare professionals, and future priority setting partnerships should consider reporting these separately, as well as in total.

Background

Preterm birth has major impacts on survival, quality of life, psychosocial and emotional stress on the family, and costs for health services.¹ Improving outcome for these vulnerable babies and their families is a priority, and prioritising research questions is advocated as a pathway to achieve this.^{2,3}

Traditionally the research agenda has been determined primarily by researchers, either in academia or industry, who have used processes for priority setting that lack transparency.^{4,5} The James Lind Alliance has developed methods for establishing Priority Setting Partnerships between patient organisations and clinician organisations, which then identify and prioritise treatment uncertainties in order to inform publicly funded research.^{6,7}

We report the outcomes of a process to identify and prioritise research questions in preterm birth that are most important to people affected by preterm birth and healthcare practitioners in the United Kingdom and Ireland using methods established by the James Lind Alliance.⁸ This partnership differed from previous priority setting partnerships supported by the James Lind Alliance in that pregnancy is not an illness or disease, and that it involves at least two people (mother and child); in addition preterm birth can have life-long consequences for them, their families and for the health services and society. Our aim was first to identify unanswered questions about the prevention and treatment of preterm birth from people affected by preterm birth, clinicians and researchers. Then to prioritise those questions that people affected by preterm birth and clinicians agree are the most important.

Methods

The Preterm Birth Priority Setting Partnership was convened in November 2011, following an introductory meeting in July 2011. The partnership followed the four stages of the James Lind Alliance process (see Figure 1).⁶

Initiation

Organisations whose areas of interest included preterm birth were informed about the priority setting partnership and invited to participate in, or contribute to, the introductory workshop. Those who then joined the partnership are listed in Box 1. All participating organisations were asked to complete a declaration of interests, including disclosure of relationships with the pharmaceutical or medical devices industry. Subsequently a Steering Group was

convened, with members of participating organisations who volunteered to take on this role. This group was chaired by a representative from the James Lind Alliance (SC).

At the introductory workshop it was clear that many participants felt the scope of the partnership should be wider than was initially envisaged. Additional topics proposed for inclusion in the scope were uncertainties about the causes of preterm birth, about the prognosis following being born preterm, and about treatments long before birth. As widening the scope too far would risk leaving the prioritisation unachievable within a reasonable time frame and the existing resources, the Steering Group decided the scope would be restricted to uncertainties about treatments, to interventions during pregnancy and around the time of birth or shortly afterwards (taken up to the time of hospital discharge for the baby after birth).

Box 1: Partner organisations

Organisations representing people affected by preterm birth	Both service users' and clinicians' organisations	Clinicians' organisations
<ul style="list-style-type: none"> • Action on Pre-eclampsia • Bliss, the special care baby charity* • Irish Premature Babies* • Multiple Births Foundation • Cleft Lip and Palate Association • Irish Neonatal Health Alliance* • National Childbirth Trust* • Tiny Life* 	<ul style="list-style-type: none"> • Children's Trust • Tommy's 	<ul style="list-style-type: none"> • Association of Paediatric Anaesthetists of Great Britain and Ireland • British Academy of Childhood Disability* • British Association of Paediatric Surgeons • British Association of Perinatal Medicine • British Paediatric Pathology Group • British Maternal and Fetal Medicine Society* • Cochrane Neonatal Group • Department of Neonatal Medicine, Imperial College*

		<ul style="list-style-type: none"> • MCRN Neonatal Clinical Studies Advisory Group* • Neonatal Nurses Association • Obstetric Anaesthetists Association • Paediatric Intensive Care Society • Royal College of Anaesthetists • Royal College of Obstetrician and Gynaecologists* • UCL Institute of Women’s Health*
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* Organisations represented on the steering group

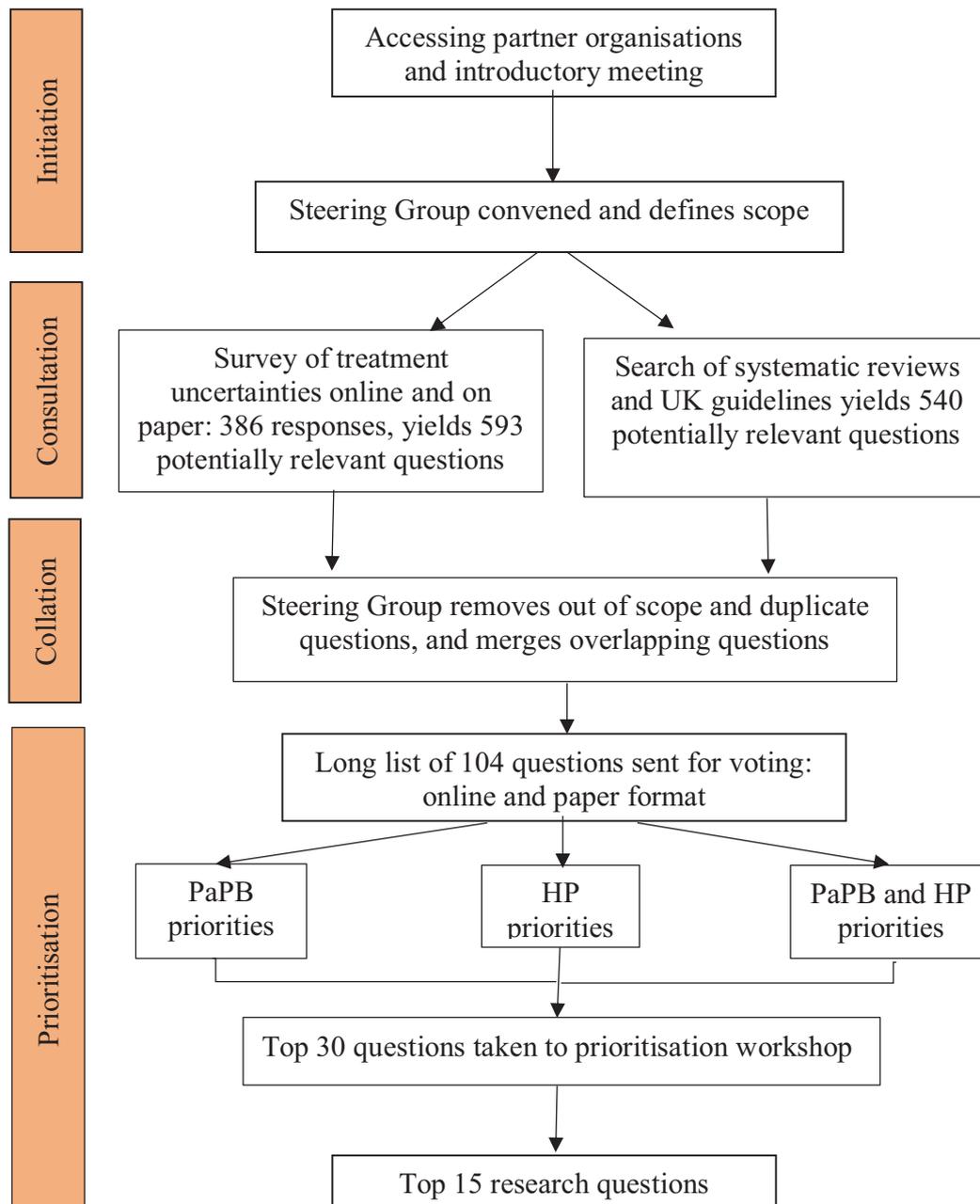
Consultation to gather research questions (treatment uncertainties)

Research questions were gathered from people affected by preterm birth, clinicians and researchers, using methods developed by the James Lind Alliance.⁷ First, a survey was distributed online, including through partner organisations, to ask for suggestions about preterm birth experiences, services or treatments which needed to be researched, any why the research would be important (see Appendix 1 for paper version of this survey). Respondents were asked to say if they were people with personal or family experiences of preterm birth, and/or if they were a health professional.

At an interim review of demographic data about home ownership and ethnicity from this survey there was concern that the respondents were not representative of the population at risk of preterm birth. To try and access a more high risk group, paper copies of the survey (see Appendix 1) were distributed at high risk specialist prematurity antenatal clinics at two tertiary level hospitals (University College London Hospital and Queen’s Medical Centre Nottingham), and to parents visiting their babies in three level 3 neonatal intensive care units (University College London Hospital and Chelsea and Westminster Hospital, London; Liverpool Women’s Hospital) between March and December 2012. The survey closing date was extended to allow time to implement these changes. Respondents were invited to provide an email address to be notified about voting to prioritise the questions.

In addition, research questions were identified by members of the steering group from systematic reviews of existing research and from national UK clinical guidelines (see Appendix 2 for the search strategy).

Figure 1: Flow chart of the JLA Preterm Birth Priority Setting Partnership



PaPB=people affected by preterm birth
HP=health professionals

Collation - checking and combining research questions

With support from an independent information specialist, submissions from the survey were formatted into research questions, which were checked against existing reviews and guidelines. Those already answered were removed. The remaining research questions were screened by the Steering Group, to remove those answered by a subsequent randomised trial or for which a large randomised trial was in progress, and those that were out of scope or unclear, and to combine similar research questions (see additional file 2). This left the final long list of unanswered research questions which was sorted into similar categories, ordered chronologically from before pregnancy to hospital discharge following birth.

Prioritisation of the research questions

Prioritisation was by a two-stage process using a modified Delphi with individual voting, followed by a face-to-face workshop using nominal group technique.⁷ First, the long list of unanswered research questions was made available online for public voting (from September to December 2013). Respondents were asked to pick the 10 they considered most important. Overall results and results by stakeholder group (people affected by preterm birth, health professional) were reviewed by the Steering Group to remove remaining repetition or overlap between questions. The final shortlist of 30 unanswered research questions to go forward to the prioritisation workshop was then agreed.

The aims of the prioritisation workshop were to agree a ranking for the short list, including the 'top10', and to consider next steps to ensure that the priorities are taken forward for research funding. Participants were invited from across the partnership, and included representatives from organisations representing both people affected by preterm birth and clinicians, parents of babies born preterm, and adults who were born preterm. Prior to the workshop, participants were sent the shortlist of unanswered research questions.

At the workshop (held in January 2014), after an introductory session participants were assigned to one of four small groups, each with a facilitator, to discuss ranking for each uncertainty. Groups were pre-specified in advance to include a mix of parents, people born preterm, clinicians and other health professionals. The groups were provided with a set of 30 large cards each printed with one shortlisted research question. On the reverse were examples of wording from the original submissions, and a breakdown of how people affected by preterm birth and healthcare professionals had scored that question in their voting. Following

discussion, these cards were placed in ranked order. Over the lunchtime break, rankings from the four groups were aggregated into a single ranking order. These aggregate rankings were presented at a plenary session, to demonstrate where there was existing consensus between groups, and where there were differences. Participants were then reconvened into three small groups, again pre-planned so each had a new mix of participants and retained a balance of backgrounds, to discuss the aggregate ranking. Similar processes were used as in the earlier small groups, with the aim of agreeing the top ten research questions and ranking all 30 questions. Aggregated ranking from the three small groups was taken to a final plenary session, with the 30 cards laid out on the floor in ranked order. Participants then debated and agreed the final ranking.

Results

Forty two organisations were approached and invited to participate in the priority setting partnership (see additional file 1); of these 26 accepted and joined partnership. Ten organisations were represented on the Steering Group; four representing those affected by preterm birth, and six representing health professionals (obstetricians and neonatologists) (see Box 1). Some Steering Group members were parents of infants born preterm, or had themselves been born preterm. The group also included four non-voting members: two researchers who co-ordinated the prioritisation partnership, one a clinical academic with a background in obstetrics and the other with expertise in public engagement in research; one charity representative, and one PhD student.

When the online survey closed it had been accessed by 1076 people, and completed by 349; an additional 37 paper survey forms were completed and returned. Hence a total of 386 people responded of whom 204 (53%) said that they were affected by preterm birth, 107 (28%) that they were health professionals, 43 (11%) that they were both affected by preterm birth and a health care professional, and 32 (8%) did not answer this question (Table 1). Of the 247 respondents affected by preterm birth, most 186 (75%) reported they were parents of a preterm baby, but some were grandparents and other family members.

Table 1: Characteristics of respondents to the survey gathering research questions, and to voting about priorities

	Gathering research questions n=386	Voting about priorities n=507
<i>Type of respondent</i>		
affected by preterm birth	204 (53%)	231 (45%)
healthcare professional	107 (28%)	216 (43%)
affected by preterm birth + healthcare professional	43 (11%)	55 (11%)
not known	32 (8%)	5 (1%)
<i>Gender</i>		
female	163 (42%)	422 (83%)
male	9 (2%)	76 (15%)
not known	214 (55%)	9 (2%)
<i>Ethnicity</i>		
white	159 (41%)	436 (86%)
Asian	4 (1%)	32 (6%)
black	9 (2%)	5 (1%)
Chinese	-	1 (<1%)
mixed	-	8 (2%)
not known	214 (55%)	25 (5%)
Home owner*	113 (46%)	

* For people affected by preterm birth only, n=247 gathering research questions

The 386 responses contained 593 potential research questions. Submissions were formatted into research questions, with similar submission combined into one question (see supplementary file 2), and screened to remove those already answered, out of scope or unclear (see supplemental file 3). Thirty eight submissions were removed as being outside the scope of this process. After merging similar questions and removing those that were fully answered, 70 unanswered questions were left from the survey.

The search of systematic reviews and clinical guidelines identified 540 potentially relevant questions. As there was such a large number, the Steering Group agreed a process to prioritise which would go forward to the next stage. Each member was asked to select the 60 questions from systematic reviews they considered to be most relevant and important. They then brought their list of 60 to a face-to-face meeting at which questions were only considered as potential priorities for the voting stage if they were supported by three or more members. This resulted in 28 questions from systematic reviews and 24 from clinical guidelines remaining in the process. Overall there were then 122 questions; as 18 of these overlapped with other questions they were merged to give a final 'long list' of 104 unanswered research questions (appendix 3).

The 104 questions on the long list were sent for an online public vote, with paper copies distributed to the same high risk antenatal clinics and neonatal units. Overall 507 people voted (448 online and 59 on paper); 231 (45%) said they had been affected by preterm birth, 216 (43%) that they were a health professional, and 55 (11%) that they were affected by preterm birth and also a health professional (table 1). Type of respondent was not known for 5 (1%) voters. Of the 271 who said they were a health professional (including those who had been affected by preterm birth themselves), 85 said they were an obstetrician, 51 a nurse, 44 a neonatologist, 24 a midwife, 4 a general practitioner, 32 were other health professionals and 31 preferred not to say. Of those who voted, 512 (87%) reported their ethnicity as white, and ethnicity was not known for 8 (2%). Responses were received from the four nations within the United Kingdom and the Republic of Ireland.

For public voting, the top priority (which treatments (including diagnostic tests) are most effective to predict or prevent preterm birth?) was the same for all three types of respondent (table 2), but there was considerable variation in how other questions were ranked. Several questions were in the overall top 10 for only one type of voter. Questions ranked overall as 1-40 in the public vote were reviewed by the Steering Group, taking into account the voting preferences of people affected by preterm birth and the overall balance of the topics. Four questions were removed: one had already been answered, one was being addressed by an ongoing trial, and two were merged with another broader question (all three being about infant feeding). A shortlist of the top 30 questions was then taken forward to the prioritisation workshop (see table 3).

The workshop to prioritise these 30 questions was attended by 34 participants; 13 parents or adults who had been born preterm and 21 health professions (neonatology, obstetrics, midwifery, speech therapy and psychology). Several of the health professionals also had personal experience of preterm birth. In addition, there were four facilitators (two from the James Lind Alliance and two non-voting members of the Steering Group), five observers (one from the James Lind Alliance, one from a research funding organisation in Canada, one from the Institute of Education University of London, and two who were non-voting members of the Steering Group).

During the prioritisation workshop, two questions were merged as it was agreed they overlapped, and the wording of a few others was modified for clarification. Following the first round of small group discussion, there was considerable variation in the top priorities between the four groups. Following the second round of small group discussion there was agreement about the top few priorities. During the final plenary discussion about the aggregated ranking there was consensus about the top seven questions, less consensus about the next three, and disagreement about those ranked as between 10 and 20. As it was not possible to achieve consensus about the top 10 questions within the timeframe, a proposal for agreeing a top 15 was agreed. Consensus about the top 15 was then achieved (table 3). This top 15 had some significant differences to the ranking following public voting. The most noticeable was two questions ranked 18 (How do stress, trauma and physical workload contribute to the risk of preterm birth, are there effective ways to reduce those risks and does modifying those risks alter outcome?) and 26 (What treatments can predict reliably the likelihood of subsequent infants being preterm?) at the workshop were ranked 3 and 4 respectively in the overall public vote (table 3), and 2 and 3 by service users in the public vote (table 2).

Table 2: For the public vote: top 10 research questions by type of voter (those in *italics* cells were in the top 10 for one type of voter only)

Type of respondent for public vote			
	Service user	Health professional	Service user & health professional
1	Which treatments (including diagnostic tests) are most effective to predict or prevent preterm birth?	Which treatments (including diagnostic tests) are most effective to predict or prevent preterm birth?	Which treatments (including diagnostic tests) are most effective to predict or prevent preterm birth?
2	What treatments can predict reliably the likelihood of subsequent infants being preterm?	What is the optimum milk feeding regimen, for preterm infants, including quantity and speed of feeding and use of donor and formula milks?	What is the optimum milk feeding regimen, for preterm infants, including quantity and speed of feeding and use of donor and formula milks?
3	How do stress, trauma and physical workload contribute to the risk of preterm birth, are there effective ways to reduce those risks and does modifying those risks alter outcome?	<i>Which treatments are most effective to prevent necrotising enterocolitis in preterm infants?</i>	How do stress, trauma and physical workload contribute to the risk of preterm birth, are there effective ways to reduce those risks and does modifying those risks alter outcome?

Type of respondent for public vote			
	Service user	Health professional	Service user & health professional
4	What should be included in packages of care to support parents and families / carers when a premature baby is discharged from hospital?	Which treatments are most effective to prevent pre-eclampsia (for example, progesterone, calcium, garlic etc)?*	What should be included in packages of care to support parents and families/carers when a premature baby is discharged from hospital?
5	What is the optimum milk feeding regimen, for preterm infants, including quantity and speed of feeding and use of donor and formula milks?	Which treatments are effective in preventing spontaneous preterm birth in women with twin and triplet pregnancies, especially in those at high risk of preterm birth?*	<i>What type of support is most effective at improving breastfeeding in NICU/SCBU/feeding clinics?</i>
6	Which treatments are most effective to prevent pre-eclampsia (for example, progesterone, calcium, garlic etc)?	<i>What methods are most effective to predict risk of preterm birth in order to allocate service provision?*</i>	What treatments can predict reliably the likelihood of subsequent infants being preterm?***

Type of respondent for public vote			
	Service user	Health professional	Service user & health professional
7	How can infection in preterm infants be better prevented? [‡]	<i>Is routine transvaginal scanning during pregnancy to detect short cervical length, and treatment, cost effective?*</i>	Is screening in the first trimester effective to help prevent preterm birth?***
8	Can screening of the placenta be effective to detect placenta abnormalities associated with preterm birth? [‡]	Is screening in the first trimester effective to help prevent preterm birth? [†]	Which treatments are most effective to prevent pre-eclampsia (for example, progesterone, calcium, garlic etc)?
9	<i>What is the best way to judge whether a baby is feeling pain (for example, by their face, behaviours or brain activities)?</i>	Does screening and treatment for Group B Streptococcus help to prevent preterm birth and neonatal morbidity and mortality? [†]	<i>Do preterm babies have better outcomes if their parents have roomed in?</i>
10	Is screening in the first trimester effective to help prevent preterm birth?	<i>What is the best time to clamp the umbilical cord for preterm babies?</i>	How can infection in preterm infants be better prevented?

*, **, †, ‡ these questions had the same number of votes within this type of voter category

Table 3: For the prioritisation workshop: final ranking for the 29 research questions (two questions were merged due to overlap) and overall ranking from the public vote

Rank following prioritisation workshop	Ranking from public vote
1 Which treatments (including diagnostic tests) are most effective to predict or prevent preterm birth?	1
2 How can infection in preterm infants be better prevented?	8
3 Which interventions are most effective <i>to prevent</i> necrotising enterocolitis in preterm infants?	9
4 What is the best treatment for life-threatening lung damage in preterm infants?	20
5 What should be included in packages of care to support parents and families / carers when a premature baby is discharged from hospital?	6
6 What is the optimum milk feeding strategy and guidance (including quantity and speed of feeding and use of donor and formula milk) for the best long-term outcomes of premature babies?	2
7 What is the best way to judge whether a baby is feeling pain (for example, by their face, behaviours or brain activities)?	14
8 Which treatments are most effective to prevent early onset pre-eclampsia?	5

Rank following prioritisation workshop		Ranking from public vote
9*	What emotional and practical support improves attachment and bonding, and does the provision of such support improve outcomes for premature babies and their families?	25/28*
10	Which treatments are most effective for premature rupture of membranes?	16
11	What is the best time to clamp the umbilical cord for preterm babies?	19
12	What type of support is most effective at improving breastfeeding in NICU/SCBU/feeding clinics?	12
13	Which treatments are most effective <i>to treat</i> necrotising enterocolitis in preterm infants?	22
14	Does specialist antenatal care for women at risk of preterm birth improve outcomes for mother and baby?	11
15	What are the best ways to optimise the environment (such as light and noise) in order to improve outcomes for premature babies?	26
16	Is screening in the first trimester effective to help prevent preterm birth?	7
17	Which treatments are effective in preventing spontaneous preterm birth in women with twin and triplet pregnancies, especially in those at high risk of preterm birth?	10

Rank following prioritisation workshop		Ranking from public vote
18	How do stress, trauma and physical workload contribute to the risk of preterm birth, are there effective ways to reduce those risks and does modifying those risks alter outcome?	3
19	Is routine transvaginal scanning during pregnancy to detect short cervical length, and treatment, cost effective?	18
20	What guidance and information is most useful for parents at risk of having preterm infants?	21
21	Does screening and treatment for Group B Streptococcus help to prevent preterm birth and neonatal morbidity and mortality?	15
22	What is the impact of length of orogastric / nasogastric feeding and reflux on early feeding development in preterm infants?	24
23	What methods are most effective to predict risk of preterm birth in order to allocate service provision?	17
24	Can screening of the placenta be effective to detect placenta abnormalities associated with preterm birth?	13
25	What is the best way to encourage Kangaroo Mother Care more by staff in NICU for parents?	23
26	What treatments can predict reliably the likelihood of subsequent infants being preterm?	4

Rank following prioritisation workshop	Ranking from public vote
27 Do parents of preterm infants benefit from an open approach to notes and ward rounds?	27
28 Do preterm babies have better outcomes if their parents have roomed in?	29
29 Which lifestyle changes including gym, bed rest, posture and sexual intercourse are effective to minimise the risk of preterm birth?	30
*two original questions merged	

Discussion

The unanswered research questions relevant to preterm birth identified during this process were prioritised in the United Kingdom and Ireland by people affected by preterm birth (parents, grandparents, adults who were born preterm, and others affected by preterm birth), by a range of health professionals, and by people who were both personally affected by preterm birth and a health professional. To our knowledge this is the first such process in preterm birth. People affected by preterm birth and health professionals had many shared priorities, but our process demonstrates that on some questions they have different perspectives. Priorities may also change over time and in different settings. Hence, although the top research priorities from this process should be considered by those who plan and fund research in this area, the full list of 104 unanswered questions is also relevant to decision-making about research funding. This is particularly true if we wish to make research more relevant to those whose lives have been affected by preterm birth, and the healthcare workers who care for them.

While several of the top priorities for research are broad topics already well recognised as important, such as what is the optimum milk feeding regimen for preterm infants and prevention of infection, others are indicative of areas previously underrepresented in research; for example packages of care to support families after discharge, and what is the role of stress, trauma and physical workload in the risk of preterm birth, and are there effective ways to reduce this risk and does this influence outcome. This is in keeping with findings from previous James Lind Alliance partnerships, which suggests and highlights the value of partnership and shared decision making with an inclusive stakeholder group with balanced representation of service users and clinicians.⁹

In line with the literature on consensus development¹⁰, the strengths of this preterm birth priority setting partnership include the large numbers of participants in the process, the range of stakeholders involved, the formality of the processes, the use of facilitators for face-to-face debate to ensure that all options were discussed and all participants had a chance to voice their views, providing feedback and repeating the judgement, and ensuring that judgements were made confidentially. The first three features applied to both the consultation and the workshop; the last applied only to the consultation. The change in priorities between the survey and the workshop deserves further investigation. Although the choice of individuals

within the professional groups represented is unlikely to have made a difference to the priorities,¹¹ difference in status across workshop participants may have.¹⁰

Preterm birth is associated with factors such as lower socio-economic status, ethnicity (such as African origin), and maternal age (being lower than 18 years or above 35 years).¹² Despite implementing strategies to reach a more representative population, our respondents remained primarily white and with a relatively high proportion of home owners, hence not representative of the population affected by preterm birth. This could limit generalisability of these priorities to other populations. A wide range of relevant health professionals participated in the public voting, including neonatologists, obstetricians, neonatal nurses, midwives, speech and language therapists, psychologists and general practitioners; strengthening generalisability.

Maintaining balanced representation between people affected by preterm birth and the different groups of health professionals for the final prioritisation workshop was challenging. This may have had implications for the final decisions, as happens in guideline development, where consensus development research concludes that differences in how groups are constituted (but not individual members) leads to different decisions.¹³ At our workshop differences in priorities between the various professional groups contributed to the difficulty in achieving consensus for a top 10 list, and to the two 'lost priorities' which although ranked in the top 5 at the public vote were not included in the final top 15.

The difficulty in agreeing a top 10 underlines the complexity of priority setting for research, particularly for topics such as preterm birth which involve mother and baby, as well as their wider family. This complexity and the differing priorities of different stakeholders make it important to publicise the top 30 list, and the full long list of 104 questions, as well as the top 15 priorities.¹⁴ Large changes in ranking following the public vote and the final prioritisation appeared to be related to difficulty in the perspective of people affected by preterm birth being heard in the large group session, and an imbalance between the different priorities of two key types of health professional (neonatologists and obstetricians). This was further complicated by some of the healthcare professionals also being researchers. Reporting of the process for prioritisation is therefore important for transparency, and to identify ways in which it could be improved. Future prioritisation processes, particularly those with a similar wide range of healthcare professionals, should endeavour to anticipate potential different

perspectives and mitigate any imbalance where possible, and should report voting separately by ‘service users’ and healthcare professionals. Similarly, whilst it may be appropriate to include healthcare professionals who are also researchers in prioritisation, this potential conflict of interest should be declared and taken into account.

This priority setting was limited to the United Kingdom and Ireland, and is therefore most readily generalisable to settings with a similar population and health system. Previous research prioritisation processes for preterm birth^{15,16} did not include people affected by preterm birth and were for low and middle income settings. The most recent neonatal prioritisation exercise in the UK did not include people affected by preterm birth and considered only medicines for neonates.¹⁷ Although unanswered research questions are universal, prioritisation of these questions depends on the local values, context and setting. Nevertheless, there are common priorities across these different settings and our prioritisation process in the UK, such as prevention of preterm birth, postnatal infection and lung damage.

Failure to take account of the views of users of research (i.e. clinicians and the patients who look to them for help) contributes to research waste.¹⁸ James Lind Alliance priority setting partnerships brings together ‘patients, carers and clinicians’ to identify unanswered research questions and to agree a list of the top priorities,¹⁹ which can then shape the health research agenda.²⁰⁻²² The aim is to ensure that those who fund health research, and also those who support and conduct research, are aware of what really matters to both patients and clinicians. In our priority setting partnership, people affected by preterm birth and the different groups of health care professionals had different priorities. This underlines the importance of this paper presenting the full list of 30 questions taken forward to the prioritisation workshop, and the respective priorities of people affected by preterm birth and health professionals, as well as the long list of 104 unanswered questions sent out for public voting.

Conclusions

We present the top 30 unanswered research questions identified and prioritised by the priority setting partnership, along with the full list of 104 questions. These include treatment and prevention as well as how care should be organised and staff training. They should be publicised to the public, to research funders and commissioners, and to those who support and conduct research.

People affected by preterm birth and health professionals sometimes had different priorities. Future priority setting partnerships should consider reporting the priorities of service users and healthcare professionals separately, as well as in total. Those with a wide range of healthcare professionals involved should anticipate potential different perspectives and mitigate any imbalance where possible. Healthcare professionals who are also researchers should declare this potential conflict before participating in prioritisation, so that it can be taken into account.

Declarations

Ethics approval

Research Ethics Committee approval for the whole priority setting exercise was obtained from the Institute of Education (reference FCL 318), and for distribution of paper versions of the survey from the Liverpool Research Ethics Committee (reference 12/WA/0286).

Consent for publication

Not applicable

Availability of data and material

Datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

None known

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Author's contributions

All authors were members of the steering group, and so planned the study, and reviewed data. SC chaired the steering group, and the final workshop. SU conducted the survey, managed the voting, and analysed the data. LD drafted the paper, with feedback from all authors. All authors agree the final draft.

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Appendix 4 Consensus development for tackling technical and emotive challenges: a case study of the James Lind Alliance Preterm Birth Priority Setting Partnership

Abstract

Background

Setting priorities for research requires engaging with technical and value-laden issues. Guidance developed by the James Lind Alliance (JLA) for priority setting draws on both formalised and tacit knowledge held by clinicians and service users. We aimed to assess how service users and clinicians interact when making collective-decisions about research, in particular how they interact and what makes some messages more persuasive.

Methods

An observational study of the Preterm Birth Priority Setting Partnership (PSP), including 13 meetings (12 steering group, one workshop) and two public consultations from 2011 to 2014. We used the Elaboration Likelihood Model of persuasion as a theoretical framework, and adopted an ethnographical approach with participant observation and discourse analysis. This included transcriptions, field notes and analysis of documentary records of meetings.

Results

The most frequently used route for persuasion was the ‘central pathway’; health care professionals were more likely to use this route while service users were more likely use peripheral route pathways. Communication patterns depended on the stage of group development. The steering group showed typical stages for group development: forming, storming, norming, performing and adjourning. When new participants joined for the workshop, the group returned to the ‘forming’ stage. This may have influenced quality of the consensus

Conclusions

Understanding these interactions may explain differences between public voting and the final workshop, and suggests ways to improve prioritisation for research.

Background

Guidance developed by the James Lind Alliance (JLA) for clinicians and service users making decisions collectively about research² is unusual in drawing on both formalised knowledge about structures, resources and procedures and tacit knowledge about interpersonal communication and support.³ We used the experience of the Preterm Birth Priority Setting Partnership⁴ to assess how participants interacted and influenced each other.

What we know about how people interact in committees with members from across organisational boundaries that make decisions about highly technical matters comes from health research, from experimental ‘laboratory’ studies in social psychology, and from observations in business administration.⁵ Larger groups allow greater diversity of membership, possibly enhancing the groups’ credibility and acceptance of its decisions.⁶ Varied membership brings more perspectives, alternatives and better performance. Increasing group size may offset the benefit of greater diversity, as reliability declines with more than six people, and there are diminishing returns over 12. Status is linked to participation in larger groups, and to influence in small groups. Formal methods appear to be better than informal methods, but the reasons are unclear. The role of the chair or group facilitator links to collective performance, being crucial for establishing inclusive practices, and an atmosphere of openness and trust.⁶⁻⁹ Discussion allows sharing and evaluation of knowledge; when time is short, less knowledge is shared and decisions are more the result of negotiating between prior preferences.¹⁰ When tasks involve judgments, rather than problem solving, status within the group influences decisions.⁶

This evidence is directly relevant to decision-making about research priorities. Two additional issues for research prioritisation involving service users and clinicians are i) the influence of different types of expertise, based on qualifications, experience or problem-solving skills¹¹, and ii) how arguments are framed and attitudes changed as consensus develops.^{12,13} The roles of logic and emotion in changing attitudes through one-way communication, such as a broadcasted political campaign or advertisement, have been investigated with the Elaboration Likelihood Model.^{14,15} This argues that messages to influence others take either a central route or a peripheral route. Central route messages include information, rational arguments and evidence. Peripheral route messages rely on receivers’ emotional responses to ‘authority’, ‘commitment’, ‘consistency’, ‘liking’,

‘reciprocation’, ‘scarcity’ and ‘social proof’.¹⁶ This model, adapted for interactive communication, offers a framework for analysing group discussion of technical and emotive issues in the context of inequalities of knowledge and status. We aimed to use this model to assess how service users and clinicians in the James Lind Alliance (JLA) Preterm Birth Priority Setting Partnership interacted when making collective-decisions about research priorities. In particular, to determine how they communicated when deciding research priorities together, and what made some messages more persuasive than others.

Methods

The preterm birth priority setting process took place from March 2011 to March 2014. Methods are published elsewhere.¹⁷ During this process, the partnership had two workshops (initial awareness, and final prioritisation), and 12 steering group meetings (nine face-to-face and three teleconferences). The study sample comprised those attending one or more of the steering group meetings, or the final workshop. We excluded the initial workshop, as it did not involve decision-making. The final workshop prioritised the top 30 research questions from public voting into a top 15. Meetings took place in either London or Nottingham, and involved three types of organisations: academic, clinical and charities.

This was a semi-ethnographical study¹⁸ with participant observation¹⁹ and discourse analysis²⁰ of steering group meetings and the final workshop. We used digital recording and transcription of discussions, field notes (for instance of non-verbal communication), and analysis of documentary records of meetings and steering group activities. At each event, participants were reminded about the recording and all consented. Voice recorded data were imported into software for qualitative data analysis (NVivo 10), transcribed by an independent researcher, and coded using an analytical framework based on the Elaboration Likelihood Model¹⁵ with peripheral cues adapted.¹⁶ Analysis therefore sought two different pathways of persuasion (central or peripheral) and their cues (authority, commitment, consistency, liking, reciprocation, social proof or scarcity).

Results

Use of central and peripheral pathways at steering group meetings and the workshop

At steering group meetings, members used the central route (n=281) more often than the peripheral route (n=221). This was consistent (table 1), regardless of timing of the meeting or type of discussion, supporting the assumption of the Elaboration Likelihood Model¹⁵ that

individuals with good cognitive ability (such as these steering group members) employ central routes for persuasion. Amongst peripheral cues, ‘social proof’ and ‘consistency’ were the most popular. During the workshop, ‘social proof’ was the most frequent cue (table 1); this relies on peer pressure, arguing ‘we do this in our group’.

Table 1: Persuasive pathways used during the steering group meetings and final workshop

	Frequency of use	
	Steering Group meetings	Final workshop
Peripheral route	221	40
Authority	18	6
Commitment	15	-
Consistency	39	5
Liking	2	1
Reciprocation	10	2
Scarcity	23	6
Social proof	42	23
Central Route	281	48

At the final workshop, health care professionals used central route pathways³³ more often than people effected by preterm birth (table 2). The association between type of speaker and the persuasive pathway was statistically significant ($p=0.017$, Pearson's Chi-square test). In other words, health care professionals were more likely to use central route pathways than service users, while service users were more likely to use peripheral route pathways.

Table 2: Association between type of speaker and use of persuasive pathway at the workshop

	Persuasive pathway		<i>Total</i>
	Central	Peripheral	
Health care professional	33	17	50
People effected by preterm birth	15	23	38
Total	48	40	88

At the workshop, for the peripheral route both types of speaker used ‘social proof’ more than other cues. They used this more often at the beginning of discussion, and more often by people effected by preterm birth than health care professionals (table 3). Some participants used ‘reversed’ social proof to persuade others, using arguments based on ‘we do not do it normally in our group so we should try it next time’.

Table 3: Peripheral route cues used at the final workshop, by type of speaker

	People effected by preterm birth	Health care professionals	<i>Total</i>
<i>Peripheral route cues</i>			
Authority	3	3	6
Commitment	-	-	-
Consistency	2	3	5
Liking	1	-	1
Reciprocation	-	2	2
Scarcity	2	4	6
Social proof	17	6	23
<i>Total</i>	<i>23</i>	<i>17</i>	<i>40</i>

Different contexts for discussion

Preliminary analysis of the first two steering group meetings suggested the patterns of persuasion differed depending on the context of discussion. When the discussion was about medical information (for example, prevalence of pre-eclampsia), participants were easily persuaded by information based on evidence. When it was about decision-making based on values (for example, the scope of the partnership), participants used different ways of persuasion. To investigate communication behaviour in different contexts, we needed to look at the types of discussion. It has been argued that there are four types of discussion; informational, dialectical, problematical and reflexive.²¹ During informational discussion, the facilitator encourages participants to speak, defers controversy, and lets participants know their ideas will not be evaluated. In problematical discussion, a problem-posing query has the participants consider the information and/or values needed to address the issue intelligently. In dialectical discussion, participants are requested to state opponents’ views accurately and

sympathetically. In reflexive discussion, participants discuss their own discussion in order to learn from the process.

Based on this classification, we coded transcripts based on whether the discussion was: informational, problematical or reflexive. We did not use ‘dialectical’ as it was not clear whether participants were taking a position to provoke thoughtful debate, or genuinely challenging an opponent’s views. Throughout the partnership process, informational (n=104) and problematical (n=169) were the main types of discussion, with problematical increasing as the partnership developed. For the first 18 months, during the first phase of partnership working (up to preparing the long list for public voting), there were no reflexive discussions. Reflexive discussions were identified later (n=9), but were few.

Persuasive pathways used for different types of discussion

For both informational and problematic discussion, people used more central route than peripheral route pathways (table 4). When using peripheral route messages to persuade others for informational discussion, participants tended to use all the peripheral cues (table 4). For problematical discussion, they used mostly ‘consistency’ or ‘social proof’. At steering group meetings ‘consistency’ was used more, while ‘social proof’ was used during the workshop. ‘Scarcity’ was used more frequently during the second phase of the priority setting process, when there was more time pressure.

Table 4: Persuasive pathways and cues, by type of discussion

	Type of discussion		
	Informational	Problematical	Reflexive
Central route	85	134	1
Peripheral route	39	79	3
Authority	6	9	1
Commitment	3	5	-
Consistency	5	23	-
Liking	-	1	-
Reciprocation	5	3	-
Scarcity	7	8	1
Social proof	4	24	1

Final prioritisation workshop

New participants joined the group for the workshop. They required explanation, information, time to understand the process of priority setting, and time to ask questions. Steering group members actively advocated the partnership process. They often responded to queries before facilitators could do so. As service users and clinicians themselves, steering group members were effective at providing credibility to the wider group. Participants at the workshop used ‘reciprocation’ during the consensus process. For example, for a topic with conflicting views, some people wanted to place it at the top of the list while others wanted to put it at the bottom. Often the group decided to place the topic in the middle of the list, to compromise.

It took time for new participants to contribute to discussions. There were four small groups in the morning, and three in the afternoon. Facilitators in the small groups began with introductions, and reminded participants of the purpose of the prioritisation and invited them to express their views. In the morning, for the first 15 minutes participants did not initiate discussion, they only responded to the facilitator. This was especially so for newly joined service users. During this time participants did not express strong views on a particular topic, rather they used ‘cushion words’ such as *‘if I understood correctly, [...]’* or *‘this is only my personal experience, [...]’*, and social proof cues, such as *‘in my charity (or in clinic), we do this in this way therefore [...]’*, appeared more frequently.

Subsequently, participants actively engaged, and often there were lively debates with conflicting views on a particular issue. When they came back after the lunch break and met different people in another small group, participants engaged immediately with the task. They were involved more actively in the topics they had failed to persuade others about in the morning. They came back with more developed arguments, and often paraphrased their opponent’s earlier argument.

Discussion

Throughout the partnership working process, participants were more likely to accept messages with a central route than those with a peripheral route. This supports the Elaboration Likelihood Model, which argues that if participants are ‘highly motivated’ and ‘have enough knowledge to understand the information’, messages with a central route are

more persuasive. Participants in the partnership were assumed to be ‘highly motivated’ and ‘have enough cognitive abilities’ to understand the process, as they had experience (either direct or indirect) and were willing to advocate for the group they represented.

The impact of peripheral route message is weak compared to central route messages.¹⁵ For example, participants might be persuaded for the short term but change their decision later;²² hence for a lasting impact, central routes are better than peripheral routes. During the final workshop, sometimes participants were assisted to use more central route (or evidence-based) arguments. For example, in one small group discussion, participants considered ‘how can infection in preterm infants be better prevented?’. Initially they decided not to prioritise this topic based on the assumption that ‘infection would be limited to the hygiene issues’. After clarifying that infection is also associated with brain injury, the group decided to prioritise the topic. If a peripheral route message was supported by a central routed message from another speaker, it became more persuasive. If logical arguments supported the peripheral route, it was more likely to be accepted.

At the workshop, participants had access to information about the public vote for that question; overall, and by service user and health care professional. After accessing this information, they used more central route arguments, rather than peripheral route ones. When participants could clearly state that the topic was an unanswered question, it became more persuasive. For example, questions on ‘Group B Strep’ and ‘environmental issues’ were prioritised within the small group discussions. However, topics such as ‘kangaroo care’ and ‘breastfeeding’ were moved down the ranking because participants thought that they were (partly) answered or being actively investigated.

The James Lind Alliance Guidebook highlights the importance of the facilitators’ role.² Throughout the prioritisation process, facilitators often paraphrased someone’s claims by using central route expressions, and these claims were likely to be accepted. Facilitators focused on the prioritisation process, particularly when time was short. When there was less time pressure, facilitators were able to explore further. Participants were able to review the outcomes of their collaborative work as they went along, and could ask questions. During these reflective discussions, participants mostly used central-route pathways. These claims were more effective, supporting the Elaboration Likelihood Model.

After the first 15 minutes of discussion, workshop participants were more likely to engage actively, and used more central-route messages. During the afternoon discussion, many used what they agreed in the morning as a cue to justify or support their arguments. In this way, participants used ‘social proof’ of the morning group. Participants reflected what they discussed in the morning, although they were reluctant to change the existing order because it was based on consensus from the small groups.

What factors made arguments more or less persuasive?

An argument was less persuasive when: a) it lacked a central-route pathway, b) it lacked urgency, c) broader questions subsumed narrower questions, d) participants thought that they knew the answer, e) participants did not like the answer they thought might ensue, and f) when survival was not at stake. An argument without a central-routed pathway was less likely to be accepted. When an argument did not have a central-routed pathway, discussion was more likely to move to another topic.

When the topic (research question) did not address either immediate investigation, or a serious health conditions, it was more likely to be rejected. Participants tended to treat physical conditions (such as brain injury) as more serious, while they tended to conceptualise psychological conditions (such as emotional impact, attachment and bonding) as less serious. With similar reasoning, workshop participants combined two questions with themes of ‘emotional and practical support’, and ‘attachment and bonding’ (table 5). For the first, original submissions from the public consultation focused on emotional impact for mothers experiencing preterm birth, how to offer them adequate support, and communication between parents and health care professionals, especially at the time of birth. For the second, original submissions were about communication between mother and infant caused by preterm birth, which could be related to health care professionals and hospitals, but mostly focused on long-term problems and consequences. In the public voting these two questions were both supported mainly by service users, the first ranked 28/104 and the second 25/104.¹⁷ The merged question was ranked 9 at the workshop (4) ‘*What emotional and practical support improves attachment and bonding, and does the provision of such support improve outcomes for premature babies and their families?*’. Although some service users still argued that the two questions differed in nature and origins, other participants were not convinced.

Table 5: Original submissions for the two questions merged during the workshop

What emotional and practical support should be included in a care bundle that aims to optimise outcomes of preterm birth?	Which treatments improve attachment and bonding and does the promotion of appropriate attachment and bonding improve outcomes?
<ul style="list-style-type: none"> • ‘The emotional effects on the mother of <i>having a preterm baby</i>’ (mother) • ‘More information available to parents <i>before the child is born and emotional support for while the child is in ICU</i>’ (parent) • ‘<i>Communication with parents: do parents who receive regular communications (both written and verbal) feel better prepared and supported during the hospital stay?</i>’ (father) • ‘The only problem I experienced was the lack of support for me [...]’ (mother of twins) 	<ul style="list-style-type: none"> • ‘Impact of early parental separation to emotional development’ (service user) • ‘Long term impact of being preterm on <i>later communication and feeding development - particularly social communication development long term impact on attachment and bonding in parents with preterm infants</i>’ (carer & speech/language therapist) • ‘Lacking in bonding with mother, being left <i>alone for periods of time without nurture or comfort</i>’ (mother) • ‘the area in a whole, time spend with family just after birth to bond’ (service user) • ‘Attachment issues between mother and baby during this traumatic experience’ (mother)

Some workshop participants were more likely to rank a question down if they felt that a similar or broader question was already high on the list. For example, screening for the placenta was considered covered by ‘general prevention’. Others pointed out the risk of de-prioritising questions because of an overarching question. Participants were more likely to move a question down if they personally did not have uncertainty. For example, a health care professional who argued against support for breastfeeding as a priority used the argument their hospital knew what to do and it worked.

Priorities from the public voting ‘lost’ during the workshop

Four research questions ranked in the top 10 after public voting were not included in the final top 15 (Table 6). Three (2-4 in table 6) were moved down because participants thought they were included in the overarching question on prevention of preterm birth (“*which treatments, including diagnostic tests, are most effective to predict or prevent preterm birth?*”), whereas the fourth (1 in table 6) was moved down because some participants argued ‘it sounded too similar to another question’. For two (1 and 3), participants raised questions about the effectiveness or adverse impact of the intervention. For example, arguing that if stress and physical work does cause stress, why cause additional stress by raising women’s concern about it, and the potential stress of screening.

Table 6: Ranking during prioritization for questions in the top 10 after public voting which finished outside the top 15

		Public voting	Final workshop		
			am	pm	final*
1	How do stress, trauma and physical workload contribute to the risk of preterm birth, are there effective ways to reduce those risks and does modifying those risks alter outcome?	3	22	19	19
2	What treatments can predict reliably the likelihood of subsequent infants being preterm?	4	27	27	27
3	Can screening of the placenta be effective to detect placenta abnormalities associated with preterm birth?	7	16	17	25
4	Which treatments are effective in preventing spontaneous preterm birth in women with twin and triplet pregnancies, especially in those at high risk of preterm birth?	9	18	18	18

*final ranking before two questions were merged

The question about ‘stress and physical workload’ remained controversial. Although ranked third after public voting, at the final workshop it ranked 22nd in the morning and 19th in the afternoon, and was not included in the final top 15. Some participants had difficulty accepting

this was a ‘research question’ because stress and physical workload do not have conventional treatments. Others commented it is difficult to define or standardise ‘stress’ and ‘workload’, potentially making research difficult. For example, one service user commented stress would be difficult to define as it is different for different people. Others argued that interventions to reduce physical workload, such as rest, are hard to accept as ‘treatment’. Some questioned whether stress and physical workload are associated with preterm birth. Service users who argued against this question referred to their own experiences, arguing either ‘I had stress and/or physical workload but I was fine’ or ‘I had preterm birth but did not have physical workload’. For example, one service user said *‘as a parent, I’ve been pregnant five times, lost the baby, had a miscarriage, had ectopic pregnancy so I can tick all of those things, [...], you are going to get lots of people saying yeah I had stress, the wider the question more than likely to get them voting, so for me, it is, can we identify these physical workload things? Having had an extremely stressful time, I still put it further down.’*

This tendency to relate to their own experiences risks over-estimating the accuracy of and/or relevance of past knowledge potentially leading to ‘hindsight bias’, also known as the ‘knew-it-all-along effect’.^{23,24} When someone clarified the issues by offering definitions or methods for the intervention, or outlining a group who might be high risk, participants tended to rank the question higher.

The final list of priorities combined outcome from two types of public consultation (Delphi survey, and workshop), designed to counterbalance each other. The ‘lost priorities’ reflect views from the wider public consultation, which may reflect views from a more representative population of those at risk of preterm birth than was possible to involve in the face-to-face workshop. The top ranked question throughout was an overarching question on prevention and prediction of preterm birth. Participants at the steering group meetings and the workshop discussed whether to keep this overarching question. The consensus from both discussions was to keep it, as it scored so high in the public vote. A consequence was that questions about specific interventions tending to be ranked down, based on the argument they were covered by this overarching question, contributing to the ‘lost priorities’.

Delphi versus Nominal Group Technique

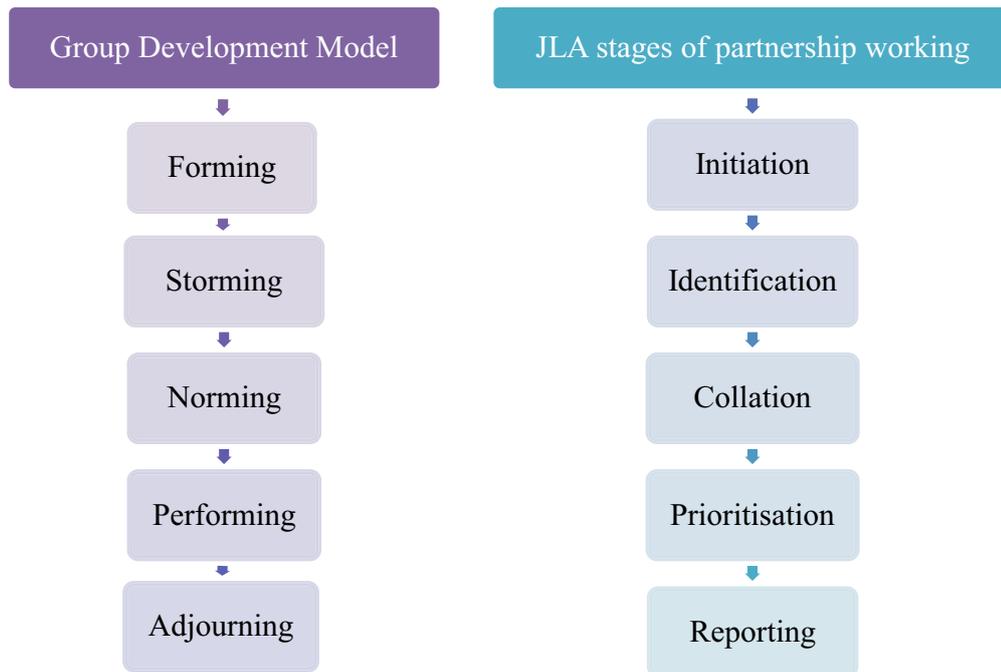
The preterm birth prioritisation used methods² which combine two iterative techniques for achieving consensus: Delphi and the Nominal Group Technique. The Delphi method involves

circulating questionnaires to individuals, sharing results with them, and then continuing to re-circulate and refine responses until consensus is reached.²⁵ The Nominal Group Technique prioritises within a group. Usually Delphi is used for forecasting. It takes longer to achieve consensus as data are shared over time,²⁶ but allows wide gathering views in different geographical areas. It is anonymous, preventing undue influence of individuals. Disadvantages were the difficulty of retaining participants, and that it may look less transparent than face-to-face meetings. A Delphi can be closed where a single set of individuals work toward consensus, or open where new people are brought in.²⁵ Nominal Group Technique requires members to meet face-to-face, giving opportunity for discussion and resolving differences of opinion, and is designed to ensure equal participation.²⁷ It can achieve consensus within a relatively short time, with members quantifying their opinions numerically. Sometimes smaller teams achieve numerical consensus, and these results are compiled.¹⁰ Disadvantages are the lack of flexibility in time and geography, and that face-to-face meetings need planning and resources.

Public consultation (survey and voting) for this partnership adapted Delphi methods to perform forecasting, this required time to think and research the topic (i.e. what are the research priorities for preterm birth?). The Nominal Group Technique helped the process of initiating and developing the steering group, and the final prioritisation. The final workshop combined the two methods by using outcomes from the public consultation and bringing new participants to the face-to-face meeting. The aim was to maximise the advantages of both methods, whilst minimising the disadvantages. However, the 'lost priorities' suggest it may have weakened the benefits of each method. One factor may have been that in the public voting the reasons for ranking by participants were not known.

Process of consensus development in the Preterm Birth Priority Setting Partnership

To understand the process of consensus development, we compared the Priority Setting Partnership to the five stages in the 'Group Development Model'²⁸: 'forming', 'storming', 'norming', 'performing' and 'adjourning'. This model argues that every group goes through these before becoming a self-reliant unit. At each stage, group dynamics change from inefficiency and uneasiness through to high performance. The five stages in the James Lind Alliance process have similarities to the Group Development Model. In particular 'forming' in the Group Development Model, is comparable to 'initiation', and 'adjourning'²⁹ is similar to 'reporting' (Figure 1).

Figure 1: Group Development Model versus JLA stages of partnership working

JLA=James Lind Alliance

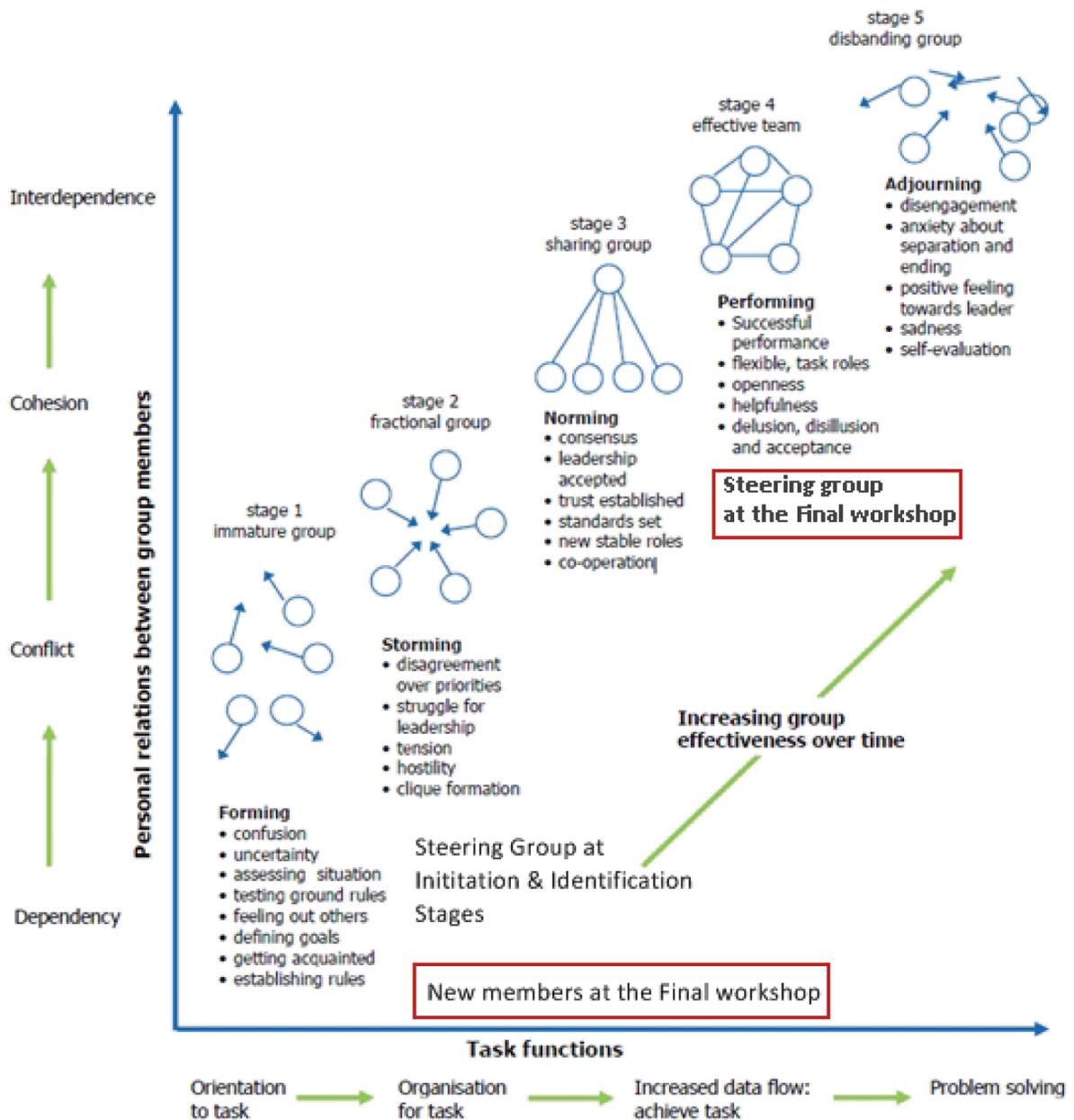
At 'initiation' of the partnership, participants had to form a steering group, and define the scope, timeframe and methods for priority setting. Steering group members looked outside for guidance and direction, while some felt anxious and were unsure of their roles. These characteristics are similar to those in the 'forming' or 'team building' in the Group Development Model.²⁸ Once the group completes 'forming', it moves onto 'storming' and 'norming'.²⁸ During 'storming', members feel comfortable expressing discontent and challenging other opinions; although this can be unpleasant, the process of challenging is necessary for group growth. At 'norming', the group have a common goal and mutual plan, and take responsibility for success in reaching that goal. In the JLA process, it was difficult to distinguish 'norming' and 'storming', as members were repeating 'storming' after 'norming'. This 're-norming' is perhaps due to the group having to perform multiple tasks, such as deciding the partnership scope and preparing the survey.^{30,31} At 'performing' group members are competent, autonomous and able to handle the decision-making process; a stage reached only by high-performing groups²⁸ and similar to 'prioritisation' in the JLA process.

At the final workshop, communication patterns were different between the steering group members and new participants. The steering group members had already reached 'performing'. When new participants joined the final workshop, the group returned to 'forming'. Members had to spend time getting to know each other, and defining their roles

and tasks. Therefore, those first fifteen minutes, when participants did not express views, can be interpreted as the ‘forming’ or ‘norming’ stages necessary for group development. The Group Development Model relates to task function and dependency of group members (Figure 2).¹ Initially, participants are scattered and show high dependency, so tasks at this stage should be introductory. As the group moves on to ‘storming’ and ‘norming’, it will experience conflict and cohesion; then as the group ‘performs’ members manage tasks effectively. Before the final workshop, steering group members had been through the ‘conflict’ and ‘cohesion’ process and were ‘interdependent’, so at the workshop they could work effectively. This caused discrepancy in group development between steering group members and new participants, and new participants were given tasks they were not yet ready for. This discrepancy may have influenced the quality of consensus at the workshop.

In conclusion, this study showed the complex issues when tackling research priorities with service users and clinicians. The Elaboration Likelihood Model helped understanding of how they interact and what elements makes some views more persuasive than others. Service users and clinicians had different priorities and used different communication styles to persuade others. Nevertheless, in general, messages using logical arguments (centrally routed) were more persuasive than emotional arguments (peripherally routed). While the role of facilitators were crucial, participants tended to share more direct messages after the first 15 minutes of each session. The steering group’s communication patterns were similar to stages in the Group Development Model, and this changed with new participants joining.

Figure 2: Stages of group development for the steering group and new participants (modified from ¹⁾)



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Appendix 5 Delivery room transition support for newborn infants: an overview of Cochrane reviews

Abstract

Background

Newborn infants who have delayed establishment of independent respiratory effort after birth may require transition support in the delivery room. Cochrane systematic reviews which summarise evidence for delivery room interventions are used to inform policy, practice and research. Our aim was to identify Cochrane reviews of delivery room transition support interventions, appraise their quality, and identify important gaps in the evidence.

Methods

We searched the Cochrane Database of Systematic Reviews (Issue 6, 2015) for reviews evaluating the effects of delivery room transition support for newborn infants. Review quality was assessed using the AMSTAR tool.

Results

Eighteen Cochrane reviews were identified. Broadly, these reviews assessed delivery room interventions for airway management, respiratory or circulatory support, supplemental oxygen or other drugs, and measures to prevent hypothermia or metabolic compromise. The overall quality of reviews was good, but the methodological quality of the included trials varied greatly. Most reviews assessed interventions to support the infant airway and breathing, and the strongest evidence of effect was for types and timing of surfactant replacement. Reviews of oxygen and other drug therapies identified few good quality trials to inform practice.

Conclusions

Existing Cochrane reviews provide good quality evidence to inform the airway and respiratory management of newborn infants in the delivery room. They also demonstrate gaps in the evidence with the need for further research, particularly with regard to circulatory support and pharmacological interventions.

Introduction

One-in-ten newborn infants has delayed establishment of independent respiratory effort after birth requiring delivery room resuscitation or transition support. Delivery room interventions to support newborn infants include airway, breathing and circulatory support, supplemental oxygen or other drugs, and measures to prevent hypothermia or metabolic compromise.¹⁻⁵ Increasingly consensus guidelines with recommendations for delivery room transition support are informed by evidence from Cochrane systematic reviews.^{6,7} The validity and utility of guidelines and policy recommendations are dependent on the quality of the included reviews. The methodological quality of Cochrane reviews in several areas of health care, including perinatal and neonatal, is variable.^{8,9} Low methodological quality introduces potential for bias. This work package aimed to describe the available Cochrane reviews evaluating delivery room interventions for newborn infants, assess their methodological quality and the validity of their findings, and identify important research gaps in the evidence. This chapter presents an overview (umbrella review) of systematic reviews evaluating immediate care and transitional support at birth for very preterm infants. The results supported guidance for initial neonatal care beside the mother, and also provided a context for determining how deferred cord clamping might be implemented in the Cord Pilot Trial reported in Chapter 11.

Methods

We undertook a systematic overview using the standard methods of the Cochrane Collaboration and the Centre for Reviews and Dissemination.^{10,11} We registered the overview on PROSPERO, the international prospective register of systematic reviews (registration number CRD42012003038).

Criteria for including reviews

We searched the Cochrane Database of Systematic Reviews Issue 6, 2015 for reviews examining any intervention for delivery room support of newborn infants. We did not include (i) reviews of interventions that are more usually or feasibly delivered following admission of the newborn infant to the neonatal unit, or (ii) reviews of delivery room interventions administered as part of routine practice to all infants. We did not apply any date limits. We searched the bibliographies of all relevant reviews for references to other related Cochrane Reviews. Two reviewers independently screened titles and abstracts of all records identified in the search, and assessed the full texts of any potentially relevant reports.

Data extraction

Two reviewers used piloted data extraction forms to collect information on quality characteristics, participants, treatment and control interventions, and outcomes.

Assessment of methodological quality of included reviews

Two authors assessed independently the methodological quality of included reviews across 11 domains used the AMSTAR tool (see box).^{12, 13} If necessary, we requested additional information to clarify methodology and results from the review authors. We resolved disagreements in the assessments and data extraction by consensus.

Box 1: AMSTAR questions

1. Was an 'a priori' design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Were published and unpublished studies eligible, irrespective of language of publication?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of the included studies provided?
7. Was the scientific quality of the included studies assessed and documented?
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
9. Were the methods used to combine the findings of studies appropriate?
10. Was the likelihood of publication bias assessed?
11. Was the conflict of interest stated?

We rated each criterion as 'Yes' (definitely done), 'No' (definitely not done), 'Unclear' or 'Not applicable' (NA). Criteria rated as 'Not applicable' were removed from the denominator, with appropriate adjustment to the ranking.

Risk of bias in the included trials

For each included trial, we extracted data from the Cochrane reviews' "risk of bias" tables on the risk of selection bias, detection bias and attrition bias.¹⁴

Results

We included 18 Cochrane reviews in this overview,¹⁵⁻³² and grouped them by type of intervention: airway or respiratory support interventions; surfactant replacement therapy for preterm infants with or at risk of respiratory distress syndrome; oxygen and other drugs for infants compromised at birth; strategies for timing of cord clamping at preterm birth.

Quality of included reviews

All of the reviews used methods consistent with those recommended in the Cochrane Handbook.¹⁰ Four reviews did not have any included trials and therefore could not be assessed for the relevant domains.^{16, 18, 25, 27} The overall quality of the other reviews assessed was high, based on the AMSTAR assessment (see Table 1). Most reviews failed to have a positive score in just one domain. The only common quality concern was that reviews did not explicitly assess the likelihood of publication bias, but most of these reviews did not include sufficient trials to allow assessment of funnel plot symmetry or statistical assessment with meta-regression.

Search strategy in the reviews

The reviews all searched the three major bibliographic databases (Medline, EMBASE, and The Cochrane Library), and they all described methods for identifying unpublished studies. The last search was after 2010 for seven reviews. Three reviews had last conducted searches in 2009, and the remainder had not had a search update since 2007 or earlier.

Primary outcomes in the reviews

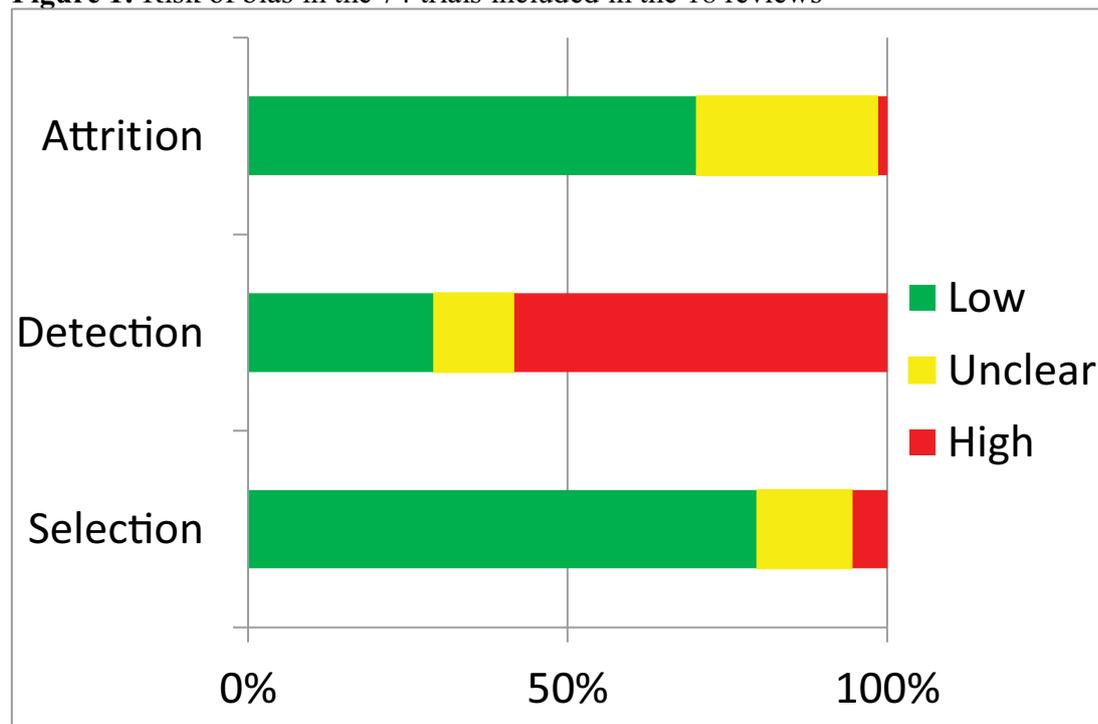
The most commonly pre-specified primary outcomes were death, incidence of chronic lung disease, and neuro-disability (18 of 20 reviews). Two reviews pre-specified surrogate outcomes such as physiological measures (heart rate, temperature) rather than infant-important primary outcomes. The available trial data provide limited evidence of the effects on other outcomes. There are few data on long term neuro-developmental outcomes.

Risk of bias in the included trials

All the reviews assessed the risk of bias for included trials by assessing the risk of selection bias (randomisation sequence and allocation concealment), detection bias (blinding of intervention and outcomes assessment), and attrition bias (complete or near-complete participant outcomes assessment). Of the 74 trials included in the reviews, 76% were

assessed as being at low risk of selection bias, 41% at low risk of detection bias, and 93% at low risk of attrition bias (Figure 1). The risk of detection bias and attrition bias was consistent across the types of interventions. The risk of selection bias varied; with 96% of surfactant replacement trials assessed to be at low risk of selection bias, compared with 45% of trials of circulatory, pharmacological or thermal support.

Figure 1: Risk of bias in the 74 trials included in the 18 reviews



Effects of the interventions

Airway or respiratory support interventions: Four reviews assessed devices and techniques for airway support in newborn infants with, or at risk of, respiratory compromise (table 1).¹⁵⁻¹⁸ Of these, two reviews did not find any eligible trials and one included only a single small trial.¹⁶⁻¹⁸ The fourth review assessed delivery room airway support for infants at risk of meconium aspiration, and included four trials with 2,884 participants.¹⁵ This review provides evidence that routine endotracheal intubation does not reduce mortality or morbidity in vigorous term babies with meconium staining compared with standard resuscitation, including oro-pharyngeal suction.

Table 1: Characteristics of reviews of airway or respiratory support interventions at birth

Review	Last search	Population	Intervention	Comparison	Primary outcomes	N=Trials (participants)
Halliday ¹⁵	2002	Non-asphyxiated term infants with meconium staining	Endotracheal intubation and airway aspiration at birth	Routine care determined by attending clinician	Death, meconium aspiration syndrome, air leak	4 (2884)
O'Donnell ¹⁶	2004	Receiving positive pressure ventilation at birth	PEEP	No PEEP	Death, Apgar scores	0 (0)
Grein ¹⁷	2004	Requiring intermittent positive pressure ventilation	Laryngeal mask airway for respiratory support	Bag-mask device or endotracheal tube for respiratory support	Time to heart rate >100/min or device inserted, placement attempts	1 (44)
Schmölzer ¹⁸	2010	Newborn infants who need resuscitation	Respiratory function monitoring in addition to clinical assessment	Clinical assessment alone	Death	0 (0)

PEEP = Positive end expiratory pressure

Surfactant replacement therapy for preterm infants with or at risk of respiratory distress syndrome: Eight reviews assessed the effects of different types of surfactant, different routes of administration, and different timing and thresholds for administration in preterm infants with or at risk of respiratory distress syndrome (table 2).¹⁹⁻²⁶ Two early reviews, originally published in 1997, provide strong evidence that for very preterm infants surfactant replacement reduced the risk of death by about 40%.^{19, 20} A related review provides evidence that natural surfactant is more effective than synthetic surfactant for reducing the risk of death.²¹ These reviews are now regarded as “complete” as further trials would be unlikely to change their conclusions.

Subsequent reviews examined various modifications of the intervention in the context of evolving practice, particularly the use of antenatal corticosteroids to enhance fetal lung maturation and the adoption of non-invasive ventilation modalities. The reviews found evidence that early surfactant administration with brief ventilation reduces the need for mechanical ventilation and associated morbidity, but that prophylactic (delivery room) surfactant administration is not more effective than delayed, selective administration when infants have prophylactic nasal continuous positive airway pressure support.^{24, 26} Uncertainty remains about the effects of newer synthetic surfactants that contain “surfactant protein mimics”, and of novel non-invasive delivery routes.^{22, 23}

Table 2: Characteristics of reviews of strategies for surfactant replacement therapy for infants with, or at risk of, respiratory distress syndrome

Review	Last search	Population	Intervention	Comparison	Primary outcomes	N=Trials (participants)
Soll ¹⁹	2009	Preterm infants with or at risk of RDS	Prophylactic protein-free synthetic surfactant	Placebo or no surfactant	Death, chronic lung disease	7 (1500)
Soll ²⁰	2010	Infants <30 weeks gestation	Prophylactic natural surfactant	Placebo or no surfactant	Death, chronic lung disease	9 (1256)
Soll ²¹	2000	Preterm infants with or at risk of RDS	Natural (animal derived) surfactant	Synthetic surfactant	Pneumothorax, patent ductus arteriosus, necrotising enterocolitis	11 (4657)
Pfister ²²	2007	Preterm infants with or at risk of RDS	Protein-containing synthetic surfactant	Natural surfactant	Death, chronic lung disease	2 (1037)
Pfister ²³	2009	Preterm infants with or at risk of RDS	Protein-containing synthetic surfactant	Synthetic surfactant (protein-free)	Death, chronic lung disease	1 (785)
Stevens ²⁴	2006	Preterm infants with or at risk of RDS	Prophylactic or early surfactant, followed by early extubation	“Conventional” treatment (surfactant administration and mechanical ventilation)	Death, need for mechanical ventilation, chronic lung disease	6 (1863)

Review	Last search	Population	Intervention	Comparison	Primary outcomes	N=Trials (participants)
Abdel-Latif ²⁵	2010	Infants < 32 weeks gestation	Pharyngeal instillation of surfactant before the first breath	Placebo, no treatment or intra-tracheal instilled surfactant	Death, chronic lung disease, neuro-disability	0 (0)
Rojas-Reyes ²⁶	2011	Very preterm infants	Prophylactic surfactant	Delayed (selective) surfactant treatment of RDS	Death, chronic lung disease	11 (4756)

RDS = respiratory distress syndrome

Oxygen and other drugs for infants compromised at birth: One review compared using air versus 100% oxygen for resuscitation of newborn infants at birth (table 3).³⁰ This review identified five trials (three of which were quasi-randomised), but concluded that insufficient evidence existed to support a recommendation for using either room air or 100% oxygen for resuscitation of newborn infants.

Three reviews assessed other drug interventions.²⁷⁻²⁹ Reviews of using adrenaline or sodium bicarbonate during resuscitation found insufficient trial data to determine effects.^{27,28} The review of naloxone for infants exposed transplacentally to opiate found nine trials but these did not assess the pre-specified, infant-important outcomes for the review.²⁹ One review examined interventions to prevent hypothermia in newborn very preterm infants.³¹ This review found evidence that various measures including plastic wraps or bags and warming mattresses reduce the risk of delivery room hypothermia in preterm infants, but found insufficient data to assess effects on infant morbidity and mortality.

Table 3: Characteristics of reviews of delivery room oxygen and other drugs for infants compromised at birth

Review	Last search	Population	Intervention	Comparison	Primary outcomes	N=Trials (participants)
Ziino ²⁷⁾	2010	Newborn with extreme bradycardia or apparent stillbirth	Epinephrine (adrenaline)	1. Placebo or no drug 2. Different doses or routes	Death or severe disability	0 (0)
Beveridge ²⁸	2006	Infants resuscitated at birth	Sodium bicarbonate	1. Placebo or no drug 2. Another alkalising agent	Death in the delivery room	1 (55)
Moe-Byrne ²⁹⁾	2013	Newborn with opiate exposure <i>in utero</i>	Naloxone	Placebo or no drug	Neonatal unit admission, breastfeeding not established	9 (316)
Tan ³⁰⁾	2005	Infants receiving IPPV at birth	Respiratory support using room air initially	Respiratory support using 100% oxygen initially	Death or severe disability	5 (1302)
McCall ³¹⁾	2009	Newborn preterm or low birth weight infants	Heat loss barriers, heated mattresses or skin-to-skin care	Routine thermal care (includes drying, wrapping, radiant heater or incubator)	Temperature on admission to neonatal unit	7 (400)

IPPV = intermittent positive pressure ventilation

Strategies for timing of cord clamping at preterm birth: One review assessed alternative strategies for timing of cord clamping for preterm births (Table 4).³² This review found evidence that deferring cord clamping for 30 to 120 seconds, rather than clamping before 30 seconds, reduced the need for blood transfusion or circulatory support and reduced the risk of intraventricular haemorrhage. Data from 13 of the 15 included trials did not identify a statistically significant effect on risk of death. Long-term neurodevelopmental outcomes were not reported.

Discussion

We identified 18 Cochrane reviews evaluating delivery room interventions for infants born very preterm: these included strategies for airway or respiratory support, surfactant replacement therapy, oxygen and other drugs for infants compromised at birth, and timing of cord clamping. Several effective interventions have been identified, particularly surfactant administration for preterm infants with or at risk of developing respiratory distress syndrome. However, many reviews highlight the paucity of trial data supporting even commonly used interventions.

Strengths and limitations of this overview

In general, the quality of these Cochrane reviews was high, as expected as the editorial process includes a published peer-reviewed protocol and a requirement to list all study characteristics and assessments. A potential concern is that many had not been updated within the past two years, as per Cochrane Collaboration guidelines. Of the 18 reviews, eight had not been updated within the past five years. The Cochrane Neonatal Group recognizes the challenges in keeping reviews up-to-date, and determines priorities for updating based on expert opinion and focused searches. Also, some reviews may be considered as “complete” or “dormant”, and no longer be updated as new or modified interventions become established.³³

Table 4: Characteristics of reviews of strategies for timing of cord clamping for preterm births

Review	Last search	Population	Intervention	Comparison	Primary outcomes	N=Trials (participants)
Rabe ³²	2011	Newborn preterm infants	Early cord clamping (< 30 seconds after birth)	Later (delayed) cord clamping	Death or severe disability (maternal postpartum haemorrhage)	15 (738)

Quality of the trials included in the reviews was variable. The potential contribution of methodological weaknesses to bias in trials and systematic reviews is well-described.³⁴ In particular, quasi-randomised trials and randomised trials with inadequate concealment of allocation tend to over-estimate effect size estimates compared with randomised trials with adequately concealed allocation.^{35,36} For example, the Cochrane review of lower versus higher oxygen concentrations for delivery room transition support found evidence that high oxygen (up to 100%) conferred important harms, including a higher risk of death.³⁰ These effects were no longer statistically significant when the three trials with inadequate sequence generation and concealment of allocation were excluded. For emergency trials, use of quasi-random methods may not increase selection bias, as assessed by baseline characteristics.³⁷

Trials that report a statistically significant effect are more likely to be submitted and accepted for publication than studies that do not.³⁸ Few reviews assessed the potential for publication bias, but most did not have enough trials for meaningful funnel plot asymmetry or regression testing. Prospective registration of trials aims to reduce publication bias and improve the quality of the conduct, analysis, and reporting of trials and systematic reviews.

For several reviews, it was unclear how the scientific quality of the included trials had informed the conclusions. No reviews used the GRADE approach to define the quality of the evidence with respect to risk of bias, directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias.³⁹ This may change as the Cochrane Collaboration has endorsed use of GRADE.

Implications for future research

Some reviews identified key “evidence-gaps”. These were mainly related to pharmacological intervention for transition support or resuscitation of newborn infants, and the effectiveness of new, less-invasive forms of airway management (and related issues regarding surfactant delivery).

Although the Cochrane reviews included in this overview in general focussed on clinically important primary outcomes such as death or chronic lung disease, few trials reported data for longer-term outcomes. Future trials should therefore assess the potential effects on disability and impairment. This is particularly important as delivery room interventions for newborn infants have the potential to have competing effects, that is, they may reduce mortality but with a consequent increase in the risk of disability.

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Table 1: AMSTAR quality assessment of reviews included in the overview

Review	<i>A priori</i> design provided	Duplicate study selection + data extraction	Compreh- ensive literature search	Published + unpublished studies included	List of included + excluded studies	Characteristics of included studies provided	Scientific quality of included studies assessed	Quality of included studies applied to conclusions	Appropriate methods for combining studies	Likelihood of publication bias	Conflict of interest stated	Score
<i>Airway or respiratory support interventions at birth</i>												
Halliday ¹⁴	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	Yes	9/10
O'Donnell ¹⁵	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	NA	NA	Yes	6/6
Grein ¹⁶	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	10/10
Schmölzer ¹⁷	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	NA	NA	Yes	6/6
<i>Surfactant replacement therapy for infants with, or at risk of, respiratory distress syndrome</i>												
Soll ¹⁸	Yes	Yes	Yes	Yes*	Yes	Yes	Yes	Yes	Yes	No	Yes	10/11
Soll ¹⁹	Yes	Yes	Yes	Yes*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11/11
Soll ²⁰	Yes	Yes	Yes	Yes*	Yes	Yes	Yes	Yes	Yes	No	Yes	10/11
Pfister ²¹	Yes	Yes	Yes	Yes*	Yes	Yes	Yes	Yes	Yes	No	Yes	10/11
Pfister ²²	Yes	Yes	Yes	Yes*	Yes	Yes	Yes	Yes	Yes	No	Yes	10/11
Stevens ²³	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	10/11
Abdel-Latif ²⁴	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	NA	NA	Yes	6/6
Rojas-Reyes ²⁵	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	10/11

Review	<i>A priori</i> design provided	Duplicate study selection + data extraction	Compreh- ensive literature search	Published + unpublished studies included	List of included + excluded studies	Characteristics of included studies provided	Scientific quality of included studies assessed	Quality of included studies applied to conclusions	Appropriate methods for combining studies	Likelihood of publication bias	Conflict of interest stated	Score
<i>Oxygen and other drugs for infants compromised at birth</i>												
Ziino ²⁶	Yes	Yes*	Yes	Yes	Yes	NA	NA	NA	NA	NA	Yes	6/6
Beveridge ²⁷	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	NA	No	Yes	7/10
Moe-Byrne ²⁸	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	10/11
Tan ³⁰	Yes	Yes	Yes	Yes*	Yes	Yes	Yes	Yes	Yes	No	Yes	10/11
McCall ³¹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	9/11
<i>Strategies for timing of cord clamping at preterm birth</i>												
Rabe ³²	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11/11

NA= not applicable

Appendix 6 The ethical issues regarding consent to clinical trials with preterm or sick neonates: a systematic review (framework synthesis) of the empirical research

See Wilman *et al.*⁷⁹ <https://doi.org/10.1186/s13063-015-0957-x>

Appendix 7 The ethical issues regarding consent to clinical trials with preterm or sick neonates: a systematic review (framework synthesis) of the analytical (theoretical/philosophical) research

See Megone *et al.*⁷⁸ <https://doi.org/10.1186/s13063-016-1562-3>

Appendix 8 Marked variation in delivery room management in very preterm infants

See Singh and Oddie.⁶⁸ <https://doi.org/10.1016/j.resuscitation.2013.06.026>

Appendix 9 Barriers to deferred cord clamping in preterm infants

See Oddie *et al.*⁶⁷ <https://doi.org/10.1136/archdischild-2014-305968>

Appendix 10 Parents' experiences and satisfaction with care during the birth of their very preterm baby: a qualitative study

See Sawyer *et al.*³⁶ <https://doi.org/10.1111/1471-0528.12104>

Appendix 11 Parents' first moments with their very preterm babies: a qualitative study

See Arnold *et al.*³⁷ <https://doi.org/10.1136/bmjopen-2012-002487>

Appendix 12 Measuring parents' experiences and satisfaction with care during very preterm birth: a questionnaire development study

See Sawyer *et al.*⁴⁴ <https://doi.org/10.1111/1471-0528.12925>

Appendix 13 Measuring placental transfusion at preterm birth

Abstract

Background

The physiology of placental transfusion for preterm births is poorly understood. Optimal timing of umbilical cord clamping at preterm birth is uncertain. This study aimed to assess the volume and duration of placental transfusion at preterm birth.

Methods

Women likely to have a healthy livebirth between 32 and 36 completed weeks gestation at three maternity units in England were eligible for recruitment. At birth, babies placed on high quality pharmacy scales (Mettler-Toledo) with the umbilical cord intact. The scales calculated an average weight twice every second, and were on a trolley beside the women. To ensure the baby was no higher than the level of the woman's abdomen, the bed or operating table was raised or lowered as necessary. The baby was monitored using temperature and saturation probes. Staff training was with term births.

Results

Six infants (range 34⁺⁴ to 36⁺⁵ weeks) were weighed; three were vaginal births and three caesarean. Cord clamping was between two minutes and three minutes 57 seconds. For two babies, weight was not well recorded in the first minute while they were dried and probes applied. Therefore, an initial 10 seconds 'hands-off' period was adopted to obtain the baseline weight. Weight change appeared to range from a 20g decrease to a 128g increase. Placental flow appeared to continue for at least two minutes for all six babies.

Conclusions

This study is small, nevertheless, there appears to be variation in the volume and duration of placental transfusion, and for some, net flow is to the placenta rather than the baby. For preterm births, placental transfusion may continue for longer than at term births.

Background

At birth, if the umbilical cord is not clamped blood flow between the baby and placenta may continue for several minutes.¹⁻⁴ This umbilical flow is part of the physiological transition from the fetal to the neonatal circulation, and for very preterm infants deferring cord clamping may improve resilience during this transition.⁵⁻⁷ 'Placental transfusion' refers to the net transfer of blood to the baby between birth and cord clamping.

Cord clamping before umbilical flow ceases may restrict neonatal blood volume and red cell mass, and/or interrupt transition from the fetal to neonatal circulation. For term births, umbilical flow usually continues for two minutes, but may continue for over five minutes.^{2,4} The mean volume of placental transfusion at term is 100 ml, which is 29 ml/kg birthweight and 36% of neonatal blood volume at birth.⁴ For preterm births, umbilical flow may continue for longer than for term births⁸ and is incomplete if the cord is clamped in 30-90 seconds.⁹ This corresponds with development during gestation, as at term two-thirds of the fetoplacental circulation is in the infant, whilst below 30 weeks a greater proportion is in the placenta.¹ Also, preterm, the umbilical vein is smaller than at term, uterine contraction less efficient, and the transition from fetal to the neonatal circulation may be slower.

To improve understanding of the physiology of placental transfusion and assess when might be the optimal time to clamp the cord for preterm births, we measured umbilical flow at preterm birth.

Methods

Women likely to have a healthy singleton livebirth between 32 and 36 completed weeks gestation at Nottingham City Hospital, Queen's Medical Centre (Nottingham) or Bradford Royal Infirmary were eligible for inclusion. Information about the study was given to women considered at risk of preterm birth. Eligible women were invited to participate either before labour, during the first stage of labour, or during preparation for caesarean section. Women who provided written consent were included. They were free to withdraw from the study at any time.

Staff training was with women having a term birth. Ethics approval required independent review of data from five term births before progressing to recruitment of women having a preterm birth. Following this review, the data monitoring committee agreed that women over

32 weeks gestation could be recruited. Recruitment from 28 weeks was planned, but not reached.

Procedure for weighing

Babies were weighed using digital scales (Mettler Toledo excellence XS precision balance Model: XS8001L, Im Langacher, CH-8606 Greifensee, Switzerland), which calculate an average weight twice every second, with data stored in a linked computer. Before the birth, the scales were zeroed to allow for the weight of any probes being used, a plastic tray and two towels (used to wrap the baby during weighing).

At birth, babies were placed on the scales with the cord intact. The attending clinician and parents were asked not to touch the baby, the cord, or the scales until weighing was complete. If anything was touched or knocked, this was recorded. The scale pan for vaginal births was level with either the bed or the woman's abdomen, and for caesarean births it was level with either the bed or the woman's thighs. Once delivered, the placenta was placed in a funnel to drain any residual placental blood. All other aspects of care were at the discretion of the attending clinician. The cord was clamped early if requested by the woman or a clinician.

In accordance with the recommendation of the ethics committee, temperature and oxygen saturation probes were used to assess temperature and heart rate respectively. For the first two preterm births, weight was not well recorded in the first minute while they were dried and probes applied. Therefore the temperature probe was no longer used, and the saturation probe applied after a 'hands-off' period of 10 seconds to establish the baseline weight.

Data collection

Parity and gestation at birth were recorded. For vaginal births, data were collected on whether labour was induced or augmented, the use of analgesia, the mode of delivery and maternal position during the second and third stage. For caesarean births, data were collected on the indication for caesarean section and the type of anaesthesia. For all women, timing of the uterotonic drug, time of cord clamping, maternal blood loss during the third stage, length of the third stage and use of controlled cord traction were recorded. For the baby, information was collected on the time of birth (delivery of buttocks for cephalic births, and head for breech births), temperature after cord clamping, need for resuscitation at birth and whether

admitted to the neonatal unit. In addition, a log was kept for each weighing, which included events such as the scales being knocked or the cord touched. All data were anonymous.

Statistical analysis

Characteristics of the women and events during labour were described for women who had a vaginal birth and those who had a caesarean birth. The scales were activated to record weight as the baby was born, providing the data for each child's weight against time. Although the use of statistical methods to determine the best approximation to the weight gain was intended, visual examination and estimation of weight gain was required due to artefacts in the data. Two authors (JD, SO) independently assessed the weight change by inspecting the graphs, with information on the timing of clamping and when the baby was being handled. Differences were resolved by discussion. Due to the small sample, only descriptive statistics were used. Volume of placental transfusion was calculated based on 1 ml of blood weighs weighing 1.05 g.

Results

From July 2012 to February 2013, 97 potentially eligible women were approached, 33 of whom gave consent. Of these six were included, with gestation from 34⁺⁴ to 36⁺⁵ weeks (Table 1). For the 27 women with consent for whom the baby was not weighed, reasons were: pregnancy progressed beyond 36 weeks (n=10); research staff not available at time of birth as out of working hours (n = 6); birth too rapid for equipment to be set up (n=5); cord too short (n =2); woman withdrew consent (n=2); hardware problem (n = 1; and clinician felt not clinically appropriate (n =1).

Table 1: Characteristics of the women and events during labour and birth

		n=6
Primigravid		3
Gestation at birth (weeks)	36 ⁺⁰ – 36 ⁺⁷	3
	35 ⁺⁰ – 35 ⁺⁷	2
	34 ⁺⁰ – 34 ⁺⁶	1
Induction of labour		2
Mode of birth		
vaginal		3
Caesarean		3
<i>Third stage of labour</i> clamping	oxytocin before cord	5
	oxytocin after cord clamping	1
Estimated blood loss (ml) (median, range)		330 (200, 600)
Manual removal of placenta		-
Residual placental volume (ml) (median, range)		11 (0, 40)
<i>Baby at birth</i>		
Temperature after cord clamping (°C) (mean, SD)		36.3 (0.46)
Resuscitation after clamping		2
tactile stimulation		1
facial oxygen		1
Admitted to special care baby unit		2

Of the six births included, three were vaginal and three caesarean (Table 1). Two of the caesarean births were during labour. All births were cephalic presentation. Time from birth to the baby being on the scales was within three seconds for the caesarean births, but up to 37 seconds for the vaginal births. The estimated weight change ranged from a 20 gm decrease to a 128 gm increase. This equates to between a 19 ml decrease and a 122 ml increase.

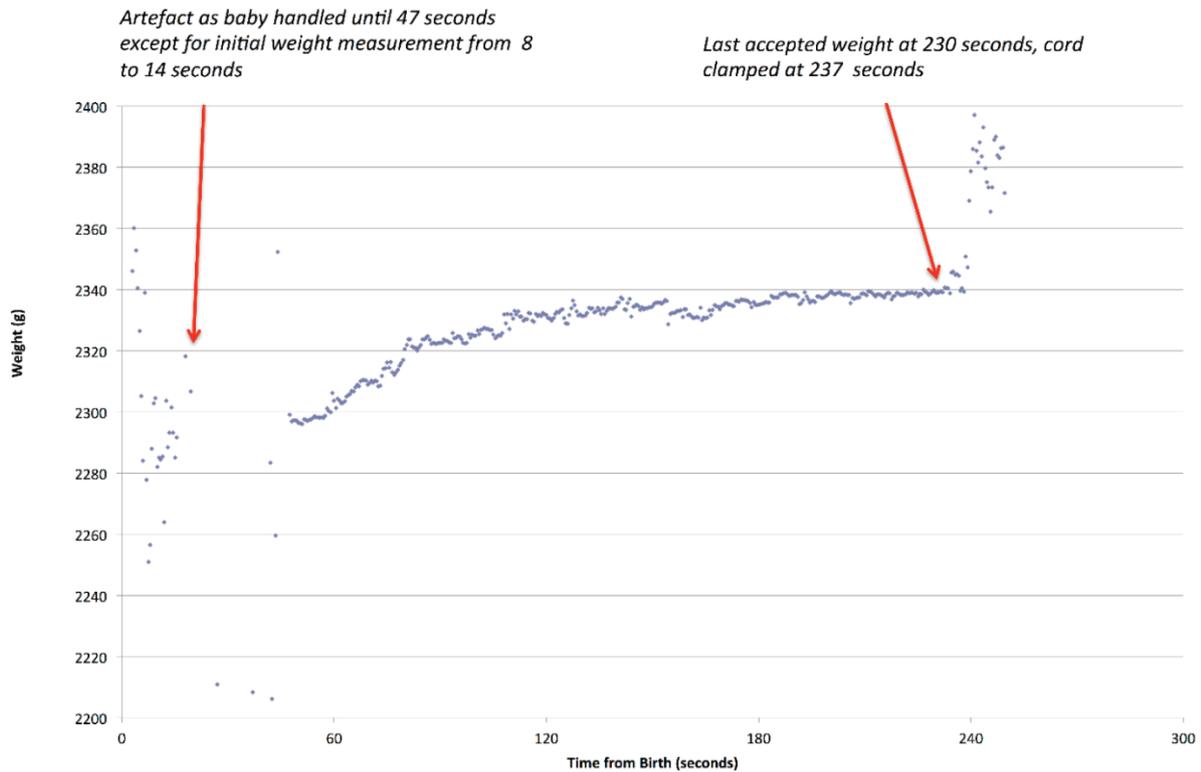
An example of weight change over time for one baby born at 35 weeks gestation is shown in Figure 1. For the remaining five babies, graphs are provided in the Supplementary material.

The time at which net placental flow appeared to cease was at or after two minutes for all six babies (see figure 1, and Supplementary material). For one baby the cord was clamped at two minutes but placental transfusion appeared to be continuing, for another weight change was static between two and three minutes, and for four babies umbilical flow appeared to continue for at least three minutes. For two babies net flow during the last minute before clamping appeared to be from the infant into the placenta.

Discussion

To assess the volume and duration of placental transfusion at preterm birth we weighed six premature infants before clamping the umbilical cord. Due to difficulties with recruitment and having research staff available out of hours we were only able to obtain data for a small number of births. Nevertheless, these data suggest that for preterm births placental transfusion may continue for longer than for term births. For five out of six babies weight change appeared to continue beyond two minutes, and for four beyond three minutes. The volume of transfusion was difficult to estimate. Handling the baby at birth to attach oxygen saturation and temperature probes led to considerable artefact in the weighing data.

Figure 1: Caesarean section at 35⁺⁶ weeks gestation. Weight gain estimated at 51 grams.



Although we improved on our speed of doing this, and started weighing the baby for 10 seconds before siting probes to obtain a better baseline weight, weight change was difficult to judge. As placental transfusion may have a role in stabilising the cardiorespiratory circulation during transition from the fetal to neonatal circulation, the duration of time the cord is left unclamped may be as, or possibly more, important than the volume of any net flow.^{5,7}

Despite the limitations of this study, these data helped inform the design of a pilot randomised trial of immediate versus deferred cord clamping at very preterm birth.¹⁰ This trial compared clamping within 20 seconds with clamping after at least two minutes.¹¹ Other future trials evaluating deferred cord clamping at preterm birth should consider an intervention of two minutes or more, and if necessary providing neonatal care with the cord intact.

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Supplementary Material

Figure A1: Caesarean section in labour, 35⁺⁶ weeks. Weight gain estimated at 14 grams.

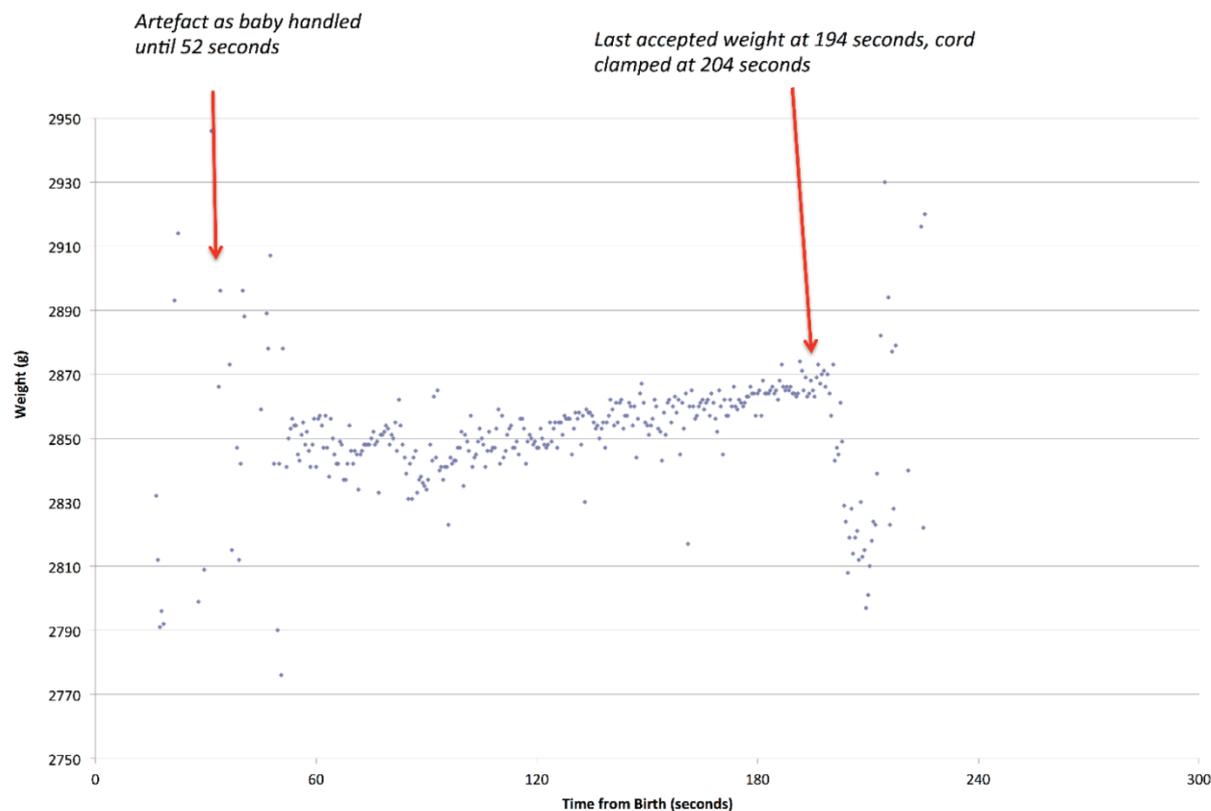


Figure A2: Induced labour with vaginal birth, 35⁺⁴ weeks. Weight gain estimated at 17 grams.

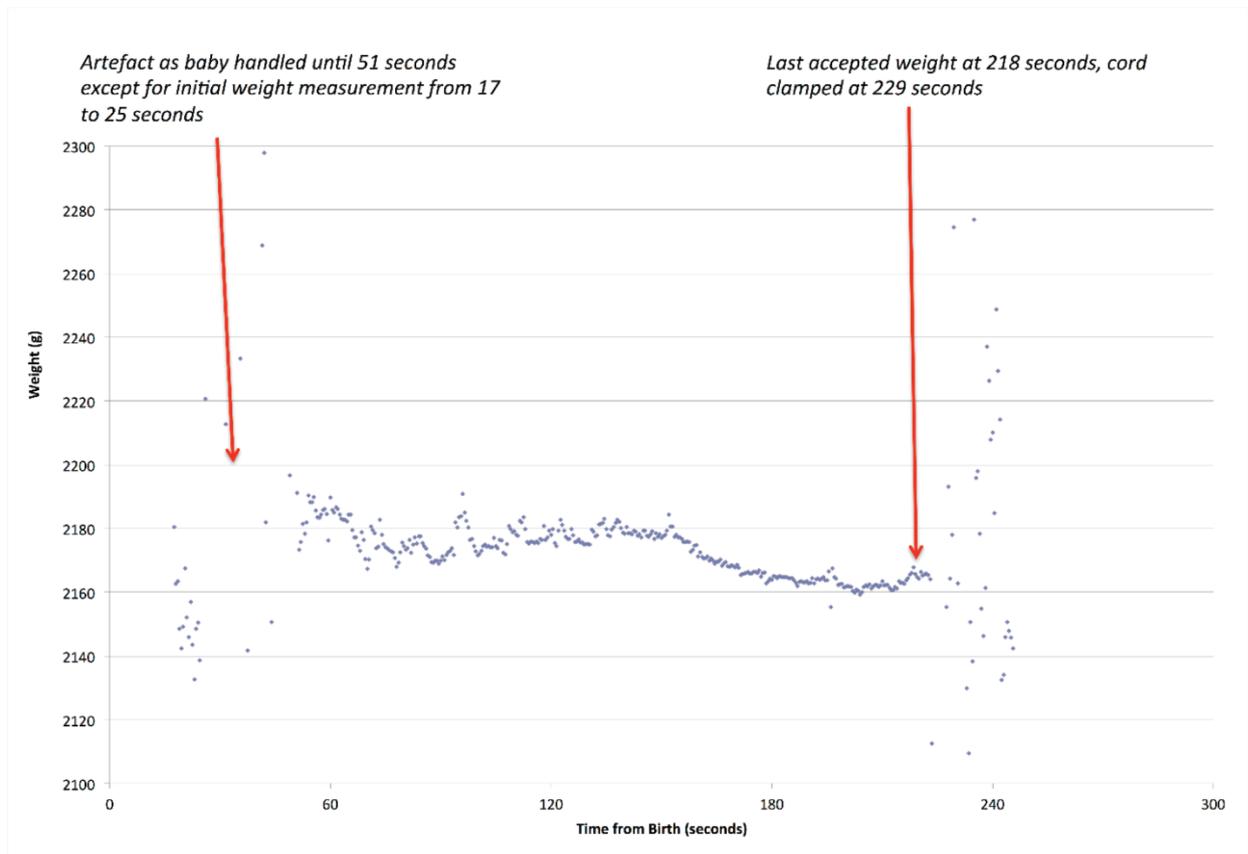


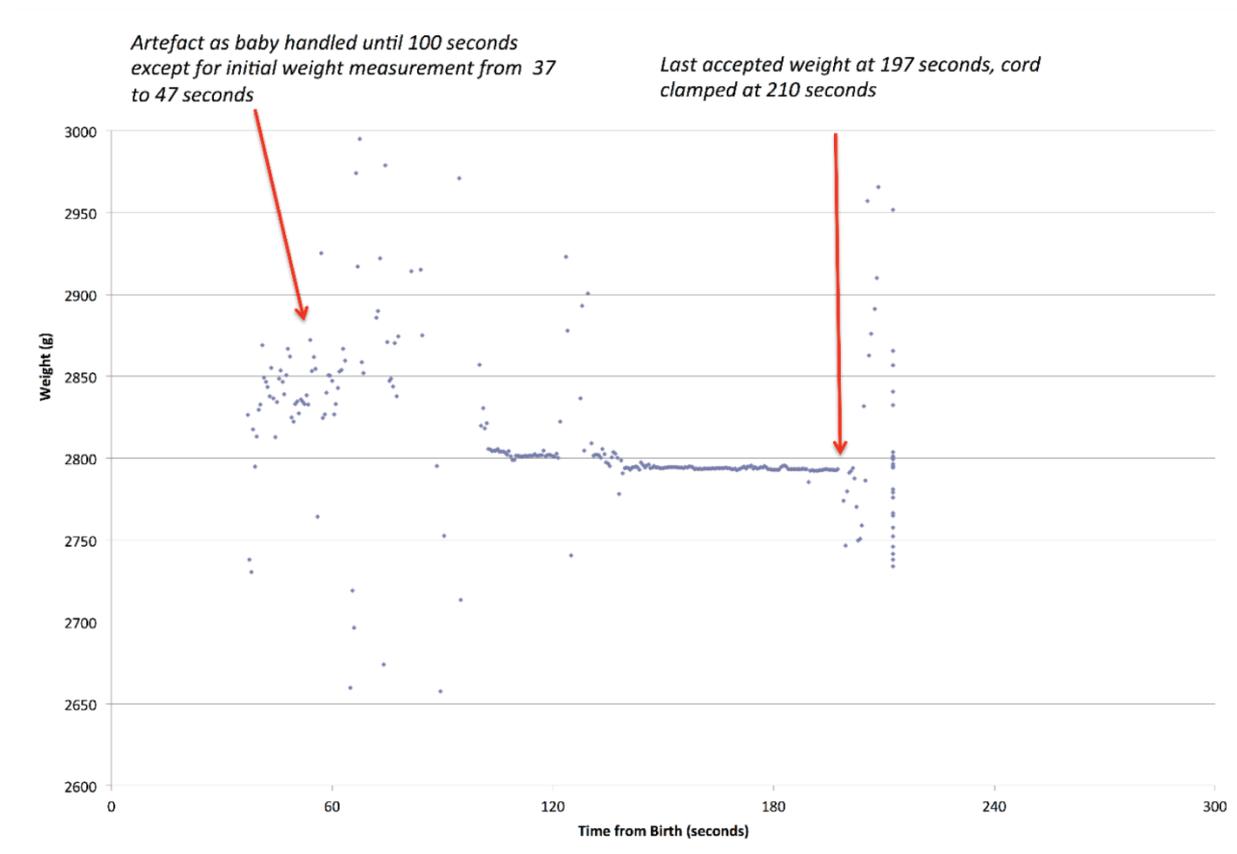
Figure A3: Vaginal birth, 36⁺¹ weeks. Weight loss estimated at 20 grams.

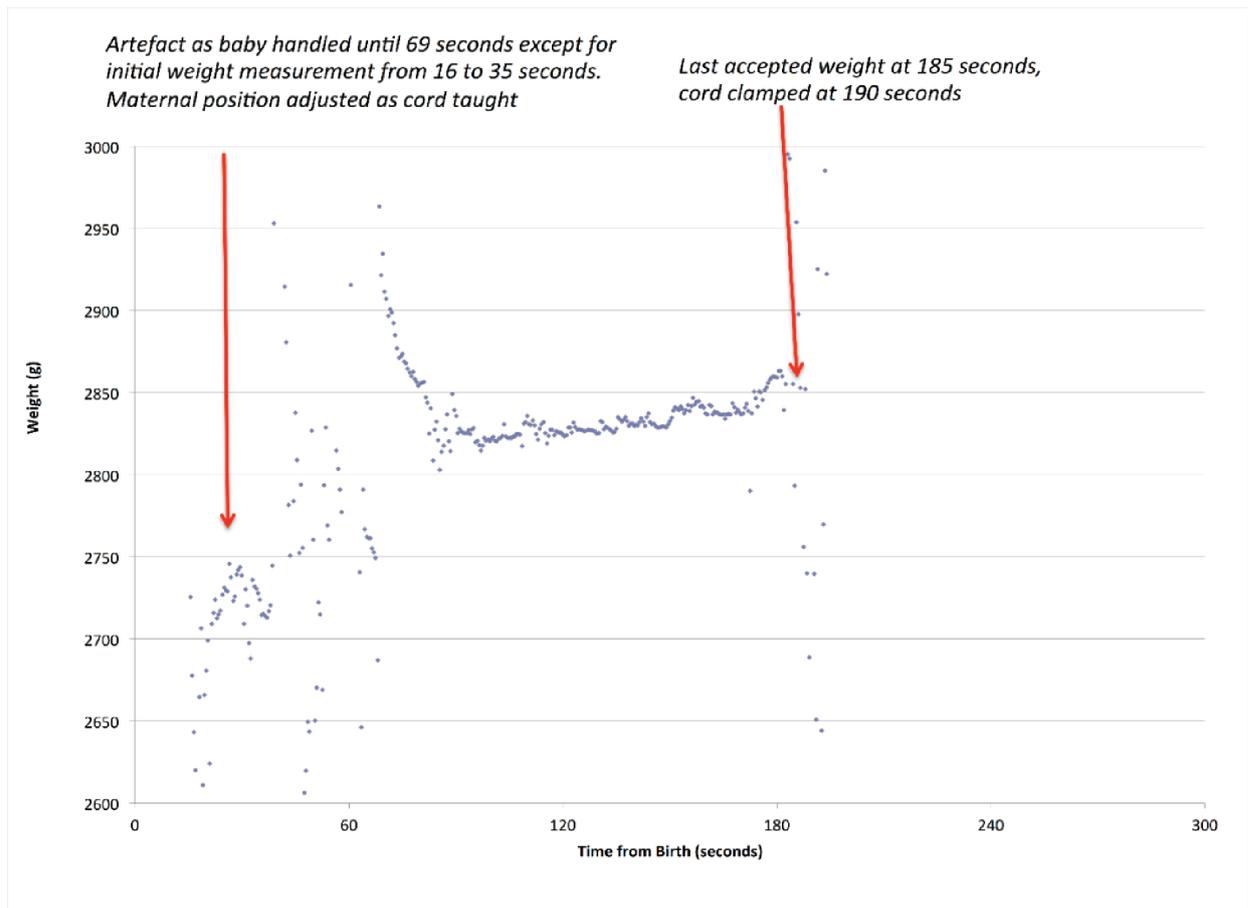
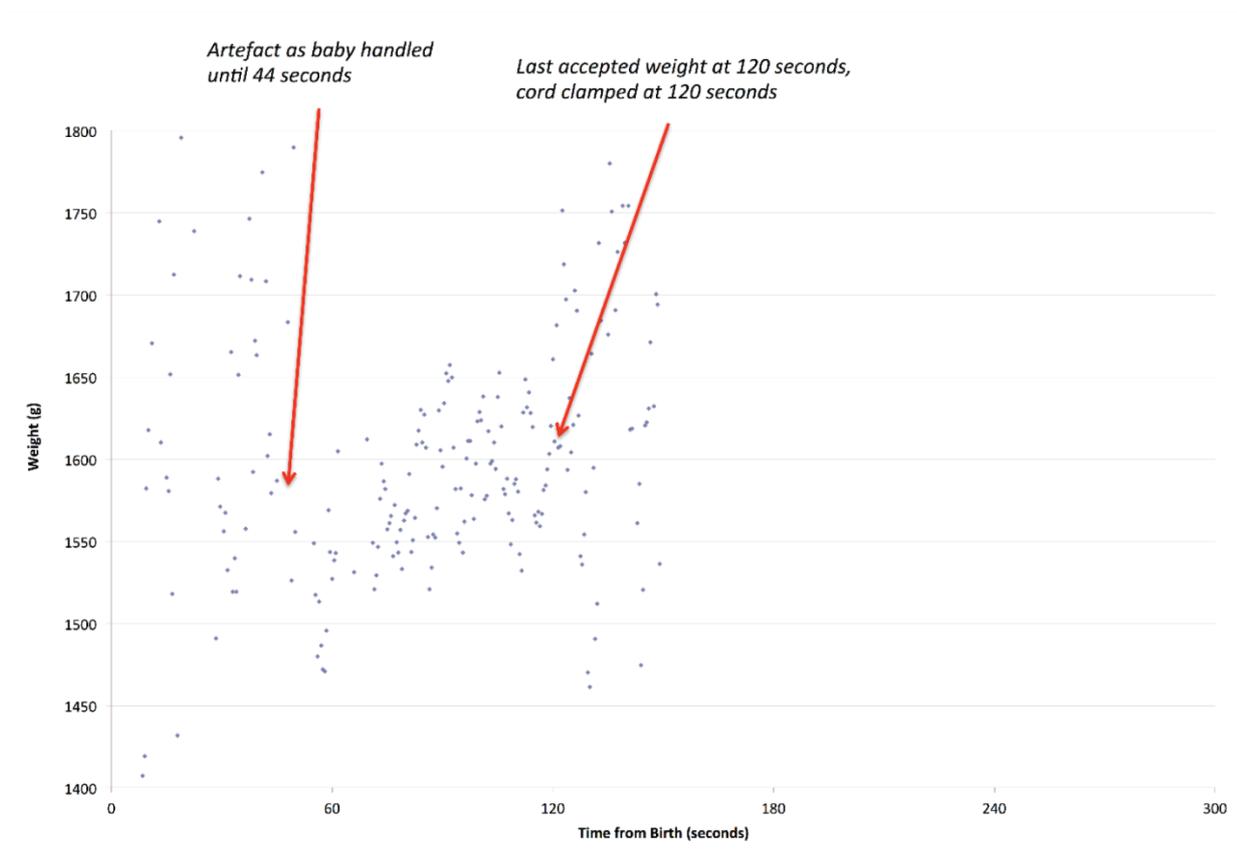
Figure A4: Vaginal birth, 36⁺⁵ weeks. Weight gain estimated at 128 grams.

Figure A5: Caesarean birth, 34⁺⁴ weeks. Weight gain estimated at 63 grams.

Appendix 14 Innovation in immediate neonatal care: development of the Bedside Assessment, Stabilisation and Initial Cardiorespiratory Support trolley

See Weeks *et al.*⁶⁹ <https://doi.org/10.1136/bmjinnov-2014-000017>

Appendix 15 Providing immediate neonatal care and resuscitation at birth beside the mother: parents' views, a qualitative study

See Sawyer *et al.*³⁹ <https://doi.org/10.1136/bmjopen-2015-008495>

Appendix 16 Providing immediate neonatal care and resuscitation at birth beside the mother: clinicians' views, a qualitative study

See Yoxall *et al.*⁴⁰ <https://doi.org/10.1136/bmjopen-2015-008494>

Appendix 17 Cord pilot trial: assessment of feasibility of a large trial

Abstract

Objectives

To assess feasibility of a large trial comparing alternatives policies for umbilical cord clamping and immediate neonatal care for very preterm births, based on recruitment for one year.

Methods

Women were eligible if expected to have a livebirth before 32 weeks at eight tertiary maternity units. Recruitment was available via two consent pathways. Randomisation (1:1), using sealed opaque numbered envelopes, was to either cord clamping after at least two minutes and immediate neonatal care with cord intact, or clamping within 20 seconds and neonatal care after clamping. Feasibility outcomes were measures of recruitment, compliance, acceptability and retention.

Results

Overall, 125 women were randomised over one year; with 22% (121/550) of births before 32 weeks randomised, of whom one third were before 28 weeks (39/121). Over a quarter of recruitment (29%, 36/125) was via the two-stage consent pathway. Compliance with the allocated intervention was good, with median time to clamping 120 seconds (IQR 30 to 135 seconds) for the deferred arm and 10 (10 to 15) for the early arm. Neonatal care with cord intact was provided for babies using both the mobile trolley (n=32), and the usual equipment (n=35).

Conclusions

A large multicentre trial comparing cord clamping after at least 2 minutes and immediate neonatal care, if needed, with cord intact versus clamping within 20 seconds and neonatal care after clamping is feasible in the UK.

Introduction

We conducted a pilot randomised trial to assess the feasibility of conducting a large multicentre randomised trial in the UK comparing alternative policies for timing of cord clamping and immediate neonatal care at birth. Having demonstrated feasibility recruitment continued beyond the planned one year.¹ This paper presents the assessment of feasibility based on the first twelve months of recruitment.

Methods

This was a pragmatic multicentre pilot randomised trial comparing alternative policies for cord clamping at very preterm birth. Recruitment was at eight UK tertiary maternity units, five of which (in Nottingham, Leicester, Bradford and Liverpool) had contributed to development work, and therefore were not necessarily typical of all UK sites. To ensure an adequate assessment of feasibility, we included three sites (in Wolverhampton, London and Aberdeen) with no previous involvement.

Ethics approval was by Nottingham REC 2(NRES reference 12/EM/0283). The sponsor is Nottingham University Hospitals NHS Trust. Coordination was by the Nottingham Clinical Trials Unit (NCTU). The protocol² and an update³ are published and summarised here.

Participants

Women were eligible if they were expected to have a livebirth before 32 weeks gestation, regardless of mode of birth or whether cephalic or breech presentation. Exclusion criteria were monochorionic twins (from an ultrasound scan) or clinical evidence of twin-twin transfusion syndrome; triplets or higher order multiple pregnancy; and known congenital malformation.

Interventions

We compared umbilical cord clamping after at least two minutes and immediate neonatal stabilisation and resuscitation, if needed, with the cord intact with usual care of clamping within 20 seconds and neonatal care after clamping. For the intervention group, babies were placed with the cord intact onto a firm surface with easy access to resuscitation equipment, either the usual equipment moved alongside the woman's bed⁴ or a mobile trolley designed for this purpose.⁵ At caesarean births the neonatal resuscitation equipment was covered with sterile drapes, and the neonatologist scrubbed and gowned. After cord clamping, neonatal

care continued either beside the mother or at the usual location (the side of the room or an adjacent room), at the discretion of the local clinicians. Until cord clamping, the baby was kept at the level of placenta (introitus or mothers' abdomen or, if a caesarean birth, the anterior thigh).

For the control group, babies were dried and/or wrapped at birth with all other neonatal care after cord clamping. For both groups other aspects of care, including administration of a prophylactic uterotonic drug, were at the discretion of the attending clinicians. Neonatal care was based on local unit policy and consistent with Resuscitation Council (UK) newborn life support guidelines.^{6,7} Standard equipment was used according to local practice.

Outcome measures

Feasibility outcome measures were to:

- Estimate the number of potential recruits in each centre
- Measure the recruitment rate
- Describe reasons for non-recruitment
- Measure the spectrum of gestational age and neonatal outcome among recruits
- Measure compliance with the trial interventions and describe factors in non-compliance
- Measure the completeness of data collection for main outcomes
- Record views of parents on randomisation and treatment procedures
- Measure loss to follow-up after discharge from hospital.

Data collection included clinical outcomes for the women and babies.¹ For example, for the baby death before discharge; intraventricular haemorrhage; periventricular leukomalacia; hypothermia; blood transfusion; other measures of serious neonatal morbidity; and neurosensory outcome at age 2 years (corrected for gestation at birth). For the woman, complications of the third stage of labour; wellbeing and satisfaction with care at birth; and their about participation in the trial.

Initially, we collected data on intraventricular haemorrhage (IVH) and other brain injury using the case report form completed at site. However, as we planned that IVH would be a primary outcome for the full trial, we adjudicated cranial ultrasound scan images and

compared these with the scan reports, to assess whether this would be necessary for a large trial.⁸ Adjudication was for all babies in the trial, not just those recruited during the first year, and is reported in detail elsewhere.⁹

Recruitment and consent pathways

Information about the study was available in the antenatal clinics and on antenatal wards. Women at risk of very preterm birth were invited to participate. They had the opportunity to ask questions, and whenever possible had at least 12 hours to consider participation. Those who agreed to participate gave written informed consent.

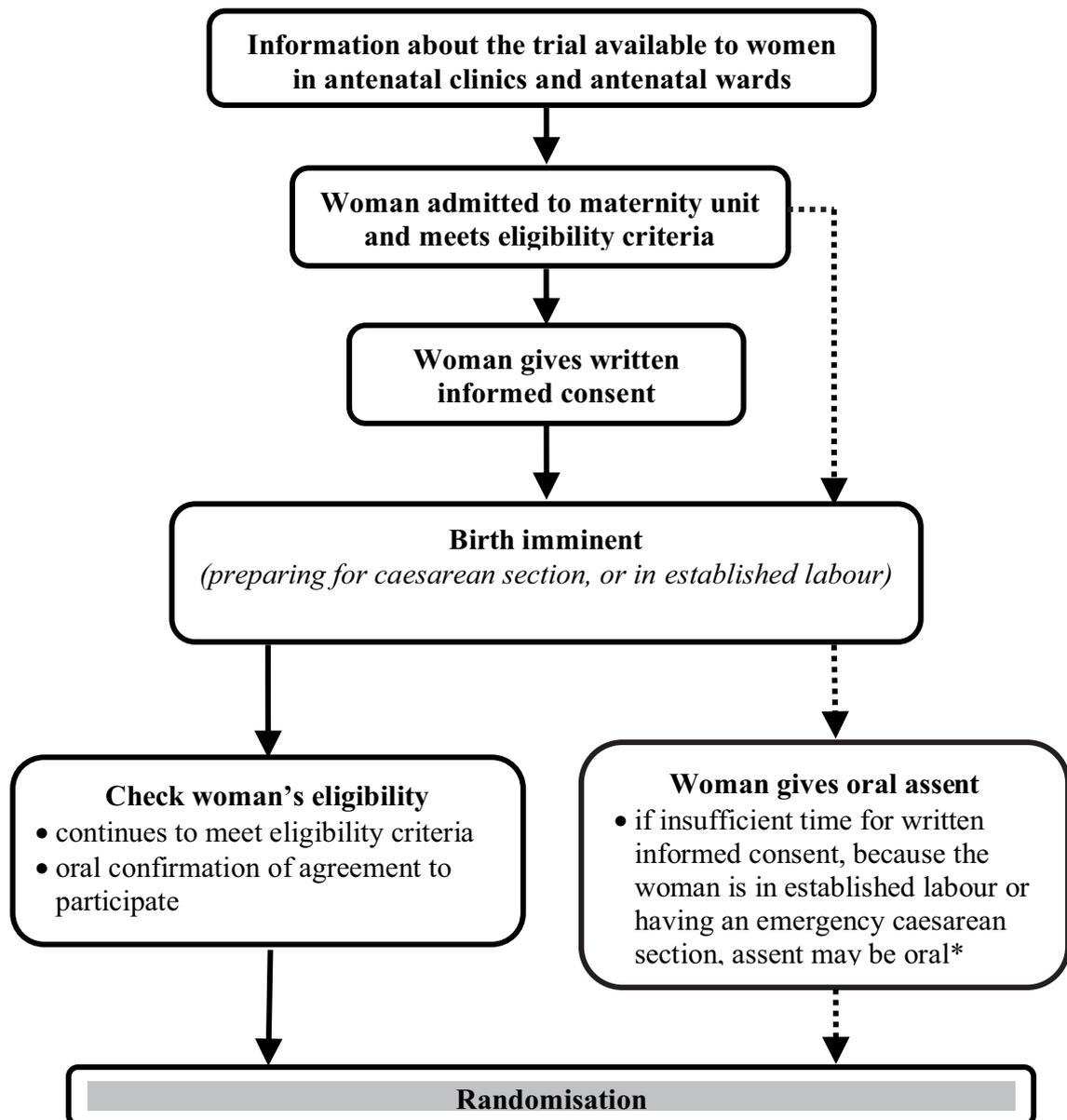
As very preterm birth can be rapid and unexpected, there may be insufficient time for the usual consent pathway. Therefore, we developed a two-stage oral assent consent pathway, in discussion with the National Childbirth Trust (NCT) and Bliss, the special care baby charity. This complies with recommendations from the Royal College of Obstetricians and Gynaecologists.¹⁰ If birth was imminent and the attending clinician considered it appropriate, we offered women a brief explanation of the study and invited participation. Those who said 'yes' (i.e. gave oral assent) were randomised.

Randomisation

Randomisation was by attending clinicians, who took the next sealed consecutively numbered opaque envelope from a ringbinder folder. Each maternity unit kept a central log of envelopes. Sequence generation (1:1) was by computer, stratified by site with balanced blocks of randomly varying size, created by NCTU. On the envelope was a reminder to check eligibility criteria, and a label to record the date, time, woman's initials, her date of birth and gestation. Once this label was completed, she was considered randomised, even if the envelope was not opened. Inside the envelope was a yellow card instructing when to clamp the cord, and a 'Birth Record' (plus a second for twins) for clinical staff to record information about the third stage of labour and neonatal care at birth. Used envelopes and yellow cards were placed in a locked mailbox, which was emptied regularly and details from each envelope entered into the online randomisation log.

Sample size

For the assessment of feasibility it was planned that eight large maternity hospitals would recruit for one year. Based on a total of 43,600 livebirths per year at these eight hospitals (average annual livebirths per unit 5-6,000) we expected 610 (1.4%)¹¹ livebirths to be before 32 weeks gestation. Target accrual was 16% to 18% of eligible births so we anticipated 100 to 110 women randomised in one year. As this was planned as a pilot trial there was no formal power calculation.

Figure 1: The two consent pathways

* Women approached to give oral assent in established labour or at emergency caesarean section only if the attending clinicians considered it appropriate. Women were not approached if there was insufficient time to give a brief verbal summary of the trial, or they did not speak fluent English and no translator was available. How long was required for oral assent depended on factors such as how much the woman already knew about the study, and her knowledge and wishes about care during the third stage.

If recruitment was after oral assent:

- women were approached before discharge to give written consent to participation in follow up
- Chief Investigator notified within 15 days, and monitoring by Trial Steering Committee

Site training and initiation

To prepare for the trial launch, we held a collaborators' meeting with representatives from each site. Key challenges addressed during the meeting were training in deferring cord clamping and neonatal care with the cord intact, and in the two consent pathways. Short film clips of simulations supported training in deferred cord clamping and neonatal care with cord intact. Roleplaying various scenarios for recruitment, with two actresses playing the women, supported training in the consent pathways.

As success of the trial depended on engagement by clinicians, the chief investigator or another clinician (obstetrician or neonatologist) accompanied the trial manager (or senior trial manager) on site initiation visits. These included training in the protocol and trial procedures, and a walk through of the participant pathway including the antenatal clinic and wards, labour suite, obstetric operating theatres, and neonatal unit. This was helpful for integrating the trial into local processes, and for raising its profile. Before opening to recruitment, sites were encouraged to agree how they would deliver neonatal care with cord intact for vaginal and caesarean births. We suggested training staff using simulation and/or at low risk births. To support training we provided film clips of the recruitment scenarios from the collaborators meeting, and of simulations for neonatal care with cord intact (both usual equipment and the trolley).

As randomisation was by the clinical staff, the local investigator and research nurse provided regular study specific training to relevant staff. We encouraged sharing of experiences between sites by newsletters, site visits and collaborators meetings.

Statistical analysis

Continuous data were summarised as mean with standard deviation and/or median with lower and upper quartiles. Categorical data were summarised as frequency counts and percentages. We excluded women (and their babies) randomised who gave birth after 35⁺⁶ weeks, as outcomes for these babies are different from those born very preterm. For each site, the number of births before 32 weeks, the number of women approached, consenting and randomised were described, along with reasons why women did not give consent or were not randomised if they had given consent. Baseline characteristics were described, along with compliance with the allocated intervention and reasons for non-compliance. For IVH we derived the worst grade for each baby. As this was a feasibility study, no analysis of outcome

by allocated group was planned. Analyses were conducted in Stata v13.1. No formal interim analysis was planned. An independent Data Monitoring Committee Data monitored data in confidence.

Results

Recruitment opened in March 2013, and for the feasibility assessment ended after 12 months (on 28th February 2014). Four sites randomised women within a month of opening to recruitment, two within two months, one within 4 months, and one 5 months. The sites not involved in the development work took longer to recruit their first participant. Issues contributing to delays included: concerns about having the neonatal equipment close to the sterile field at caesarean section (which led to one site largely recruiting vaginal births); research staff having limited time as they were running multiple studies; difficulties in building the necessary agreement between the neonatologists and obstetricians; and engagement of the local investigator.

We randomised 125 women, four of whom gave birth after 32 weeks gestation. This was 22% of women who gave birth before 32 weeks gestation, varying from 43% to 9% between sites. Factors in this variation were whether women having a caesarean birth were offered participation, availability of the trolley in the two sites using this equipment, and availability of clinical staff trained in the trial. Four hundred and thirty four women were approached: of whom 389 were offered usual consent and 45 the two-stage oral assent consent pathway (table 1). For those offered the usual consent pathway, almost half (184/389, 47%) gave consent, of whom almost half (89, 48%) were randomised. For women offered oral assent, most (38/45, 84%) gave assent, of whom almost all (36, 95%) were randomised. Thirty five women were randomised following oral assent only, as one woman gave written consent before randomisation. Of the women offered participation who did not give consent, almost half (101/212, 48%) declined, and a quarter (53/212, 25%) were discharged home (figure 2). For the women who gave consent but were not randomised, the main reason was pregnancy continuing beyond 32 weeks (63/97, 65%).

Table 1: Consent and randomisation for women offered participation, by site*(i) usual written consent pathway*

	Offered participation	Consent n (%)	Consent & randomised n (%)
Site 1	65	28 (43%)	10 (36%)
Site 2	58	37 (64%)	18 (49%)
Site 3	63	31 (49%)	12 (39%)
Site 4	66	21 (32%)	11 (52%)
Site 5	21	11 (52%)	6 (55%)
Site 6	92	42 (46%)	24 (57%)
Site 7	12	9 (75%)	4 (44%)
Site 8	12	5 (42%)	4 (80%)
Total	389	184 (47%)	89 (48%)

(ii) two-stage oral assent consent pathway

	Offered oral assent*	Gave oral assent**	Oral assent & randomised	Written consent after randomisation†
Site 1	7	6	6	6
Site 2	6	6	6	5
Site 3	9	5	5	5
Site 4	6	6	6	5
Site 5	2	2	2	2
Site 6	9	9	9	9
Site 7	1	1	1	1
Site 8	5	3	1	1
Total	45	38 (84%)	36 (95%)	34 (95%)

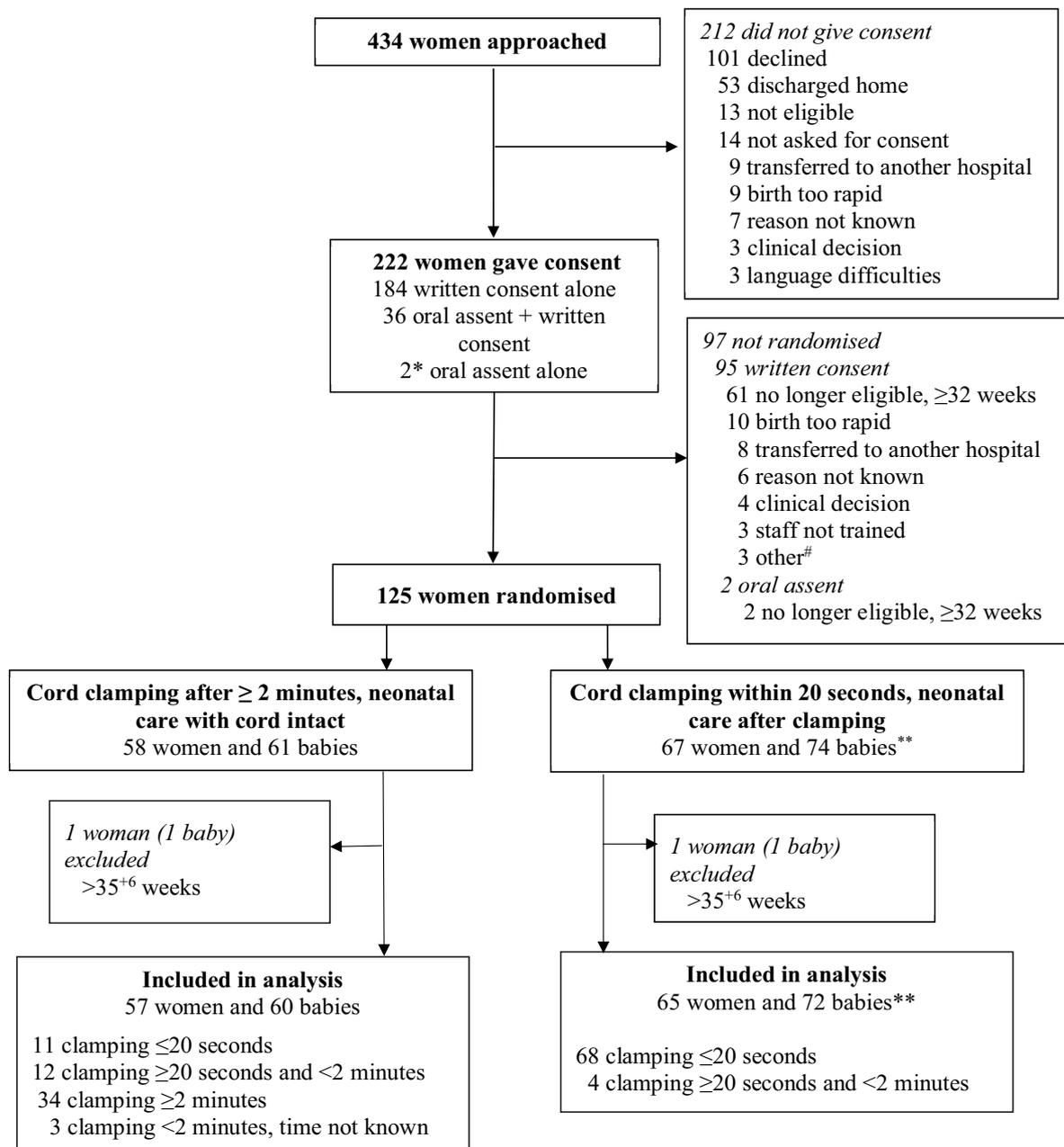
* Declined oral assent only recorded from July 2013

** 1 woman who gave oral assent also gave written consent before randomisation

† for 2 women written consent after randomisation was not obtained, as the baby died before discharge and they did not return for the counselling appointment

The 125 women randomised gave birth to 135 babies (figure 2). Two women randomised before 32 weeks gave birth at 38⁺² and 39⁺² weeks respectively, and were excluded from analysis. One woman withdrew the use of her and her baby's data, leaving 122 women and 132 babies for analysis (figure 2). Six sites used their usual resuscitation equipment (75 women randomised) and two the trolley (50 women).

The system of randomisation envelopes was popular at sites, and worked well. The only incorrect use was when a second envelope was taken in error for a second twin; data are presented according to the allocation in the first envelope. Five randomisation envelopes were taken from the folder but not used, reasons: second twin (2 women), birth too quick (1), gestation 35 weeks (1), and woman did not give birth and was discharged home (1).

Figure 2: Consort flow for the feasibility assessment based on one year of recruitment

* baby died before discharge and written consent was not obtained;

** 1 woman and her baby withdrew, data reported for mortality only;

intrauterine death (n=1), equipment failure (1), randomised after the end of the feasibility phase (1)

Baseline characteristics

The allocated groups were balanced at trial entry (table 2). Time from randomisation to birth was within half an hour for over a third of women, and within an hour for over half; three quarters of women gave birth within two hours of randomisation and eight gave birth more than one day after randomisation. Recruitment was across the range of gestational age with approximately one third before 28 weeks, one third 28 to 29 weeks, and one third 30 to 31 weeks. One woman was randomised in error, at 33 weeks. The earliest gestation at randomisation was 23⁺¹ weeks.

Table 2: Baseline characteristics for the women

	Clamp ≥ 2 minutes + neonatal care with cord intact n= 57 (%)	Clamp ≤ 20 seconds + neonatal care after clamping n=65 (%)
Oral assent	19 (33%)	16 (25%)
<i>Time from randomisation to birth</i>		
<30 min	22 (39%)	22 (34%)
≥ 30 min to <1 hour	12 (21%)	13 (20%)
≥ 1 hour to <2 hours	8 (14%)	13 (20%)
≥ 2 hours to <5 hours	5 (9%)	7 (11%)
≥ 5 hours to <12 hours	3 (5%)	5 (8%)
≥ 12 hours to <24 hours	2 (4%)	2 (3%)
≥ 24 hours	5 (9%)	3 (5%)
<i>Gestation at randomisation (weeks)</i>		
≥ 32	1 (2%)	-
30 to 31 ⁺⁶	19 (33%)	28 (43%)
28 to 29 ⁺⁶	16 (28%)	19 (29%)
26 to 27 ⁺⁶	10 (18%)	11 (17%)
<26	11 (19%)	7 (11%)

	Clamp \geq2 minutes + neonatal care with cord intact n= 57 (%)	Clamp \leq20 seconds + neonatal care after clamping n=65 (%)
Age (years), mean [sd]	30.5 [6.5]	29.4 [6.8]
Primiparous	31 (54%)	41 (63%)
Twin pregnancy	*4 (7%)	7 (11%)
<i>Pregnancy complications</i>		
prelabour rupture of membranes	22 (39%)	26 (40%)
anteartum haemorrhage/placenta previa	5 (9%)	12 (18%)
spontaneous onset of labour	12 (21%)	11 (17%)
chorioamnionitis	6 (11%)	10 (15%)
pre-eclampsia/pregnancy induced hypertension	14 (25%)	10 (15%)
CTG abnormalities/fetal distress	12 (21%)	10 (15%)
fetal growth restriction/small for gestational age	3 (5%)	5 (8%)
other	-	**5 (8%)
<i>In last week received:</i>		
magnesium sulphate	28 (49%)	20 (31%)
corticosteroids	52 (91%)	59 (91%)
<i>Caesarean section</i>	38 (67%)	36 (55%)
before labour	31	28
during labour	7	8
<i>Vaginal birth</i>	19 (33%)	29 (45%)
breech presentation	4	5

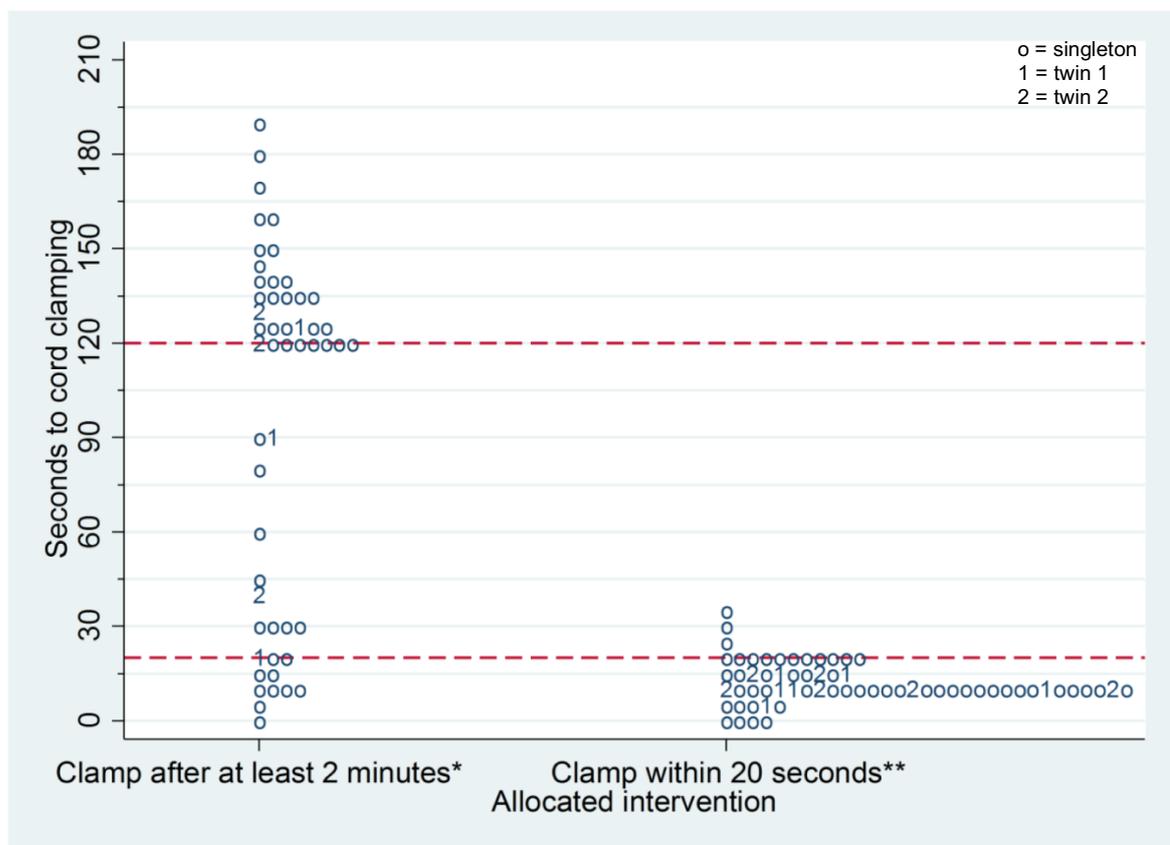
* For one woman, one twin known intrauterine death before randomisation. Data for this baby not included in any tables

**Abdominal pain (n=1), severe asthma (1), pyelonephritis (1), antiphosphate lipid syndrome (1) and not known (1).

Compliance with the allocated intervention

In the intervention group, cord clamping was after at least two minutes for 34 (56%) babies and after 20 seconds for 44 (77%) (Figure 3). Of the 27 babies in this group with cord clamping before two minutes, for 11 (42%) this was due to the cord being too short. For singleton births without a short cord, cord clamping was at two minutes or later for 69%, and after 20 seconds for 78%. Compliance in the control group compliance was high; for 68 babies (94%) cord clamping was within 20 seconds.

Figure 3: Time to cord clamping (seconds) for babies by allocated group



* 60 babies allocated to clamp cord after at least 2 minutes, seconds to cord clamping not known for 8 babies.

** 72 babies allocated to clamp cord within 20 seconds, seconds to cord clamping not known for 8 babies

In the deferred clamping group, there were no obvious differences in time to cord clamping according to equipment for providing immediate neonatal care (usual equipment or trolley), or whether vaginal or caesarean birth. As sites gained experience, compliance with deferred clamping seemed to improve, although numbers are small (data not shown). Three quarters of the babies were positioned level with the placenta. Almost all women (118/122, 97%) received a prophylactic uterotonic drug. Time of administering this, used to derive whether it was before or after cord clamping, was not recorded for 37 women.

Neonatal care was provided beside the mother for 67 babies, of whom 49 (82%) were allocated deferred clamping (table 3) (some were in the immediate clamping group, for whom neonatal care was after cord clamping). The usual resuscitation equipment was used for 35 babies, and the trolley for 32.

Table 3: Care given to the babies at birth, beside the mother and at the roomside

	Beside the mother	At the roomside	Location not known
baby in plastic bag/sheet	72*	39	-
airway suction	23	54	-
mask ventilation	44	54	1
CPAP	11	22	-
intubation attempted, but unsuccessful	12	22	-
intubation successful	28	55	-
supplemental oxygen	28	48	-
surfactant	22	48	-
cardiac massage	6	4	-
umbilical venous catheterisation	1	5	-

* some allocated to immediate clamping were placed in plastic bag beside mother, but received all other care at roomside

Outcomes at hospital discharge

Fifteen babies (11%) died before discharge; this included three stillbirths born extremely premature for whom resuscitation was attempted (table 4). Two thirds of deaths were of babies born before 26 weeks. One baby born at 30⁺⁴ weeks died during surgery for an undiagnosed abdominal mass (congenital anomaly).

Table 4: Death before discharge from hospital

	n=133* (%)
Died before discharge	15 (11%)
stillbirth	3
day 0-6	5
day 7-27	6
≥day 28	1

		n=133* (%)
Gestational age at birth (weeks)	30 ⁺⁰ – 31 ⁺⁶	1
	28 ⁺⁰ – 29 ⁺⁶	2
	26 ⁺⁰ – 27 ⁺⁶	3
	<26 ⁺⁰	9

* includes one woman who requested her data be removed from the analysis, data reported for death only

Of liveborn babies, 51 (40%) had an intraventricular haemorrhage of whom this was severe for eight (6%) (Table 5). Only one baby had a temperature below 35°C on admission to the neonatal unit. Almost half the babies had a blood transfusion, which was usually for anaemia.

Table 5: Outcome at discharge from hospital for livebirths

		n=129 (%)
<i>Brain injury</i> *	any IVH (grade 1-4)	51 (40%)
	severe IVH (grade 3-4)	8 (6%)
	periventricular leukomalacia	9 (7%)
	other**	10 (8%)
Heart rate < 100 at 1 minute		40 (31%)
	not known	2 (2%)
Temperature on admission to neonatal unit (°C) mean [sd]		36.8 [0.7]
	≤36°C	9 (7%)
	<35°C	1 (1%)
Blood transfusion (any)		61 (47%)
	for anaemia	58
	for hypotension	3
	other†	8

	n=129 (%)
Jaundice requiring treatment	117 (91%)
phototherapy	117
exchange transfusion	-
Polycythaemia requiring treatment	1 (1%)
intravenous fluids	1
Chronic lung disease [‡]	42 (36%)
Ventilation	97 (75%)
duration (days) median (25 th , 75 th centile)	3 (1, 10)
Necrotising enterocolitis (≥grade 2)	4 (3%)
x-ray with perforation or pneumatosis	4
laparotomy	2
Clinical sepsis	71 (55%)
positive culture + antibiotics ≥5 days	27
negative culture + antibiotics ≥5 days	44
Treatment for:	
patent ductus arteriosus	18 (14%)
retinopathy of prematurity ^{‡††}	6 (5%)
Duration of hospital stay (nights) ⁴ median (25 th , 75 th centile)	56 (36, 82)
Receiving mother's breast milk at discharge [?]	67 (57%)

* 124 babies had cranial scan, adjudication results available for 112. For 12 with no scan adjudication, report review/CRF was used: IVH (n=6), severe IVH (2)

** prominent subarachnoid spaces suggestive of atrophy (n=3), ventriculomegaly (2), periventricular echodensities (1), increased echogenicity of deep white matter (1), periventricular cyst (1), mega cisterna (1), porencephalic cysts (1)

[†] thrombocytopenia (n=2), pulmonary haemorrhage (2) NEC clinically unwell (1), internal bleeding (1), haemorrhage and clotting anomaly (1), and bradycardia (1)

[‡] for 118 babies who survived to 36 weeks postmenstrual age

^{††} information collected at 36 weeks postmenstrual age, discharge or death whichever happened first

[?] n=118 alive at discharge

Overall, one in ten women had blood loss of 1,000ml or more, and five in ten of 500 ml or more (table 6). A quarter had postpartum infection requiring parenteral antibiotics. Most women whose babies were alive when they were discharged were breastfeeding at discharge.

Table 6: Outcome at discharge from hospital for the women

		n=122 (%)
Postpartum haemorrhage	≥500 ml	58 (48%)
	≥1000 ml	12 (10%)
Blood transfusion		4 (3%)
<i>For vaginal births</i> (n=48)	manual removal of placenta	2 (4%)
	length of third stage >30 minutes	1 (2%)
Postpartum infection treated with parenteral antibiotics		28 (23%)
	pyrexia >38°C	5
Duration of hospital stay (nights) median (IQR)		4 (2, 6)
Expressing breast milk/breast feeding at discharge*		106 (91%)

IQR = interquartile range

* for 117 women whose babies were alive at the time of their discharge

Overall assessment of feasibility objectives

The independent Trial Steering Group (TSC) assessed progress against the feasibility objectives and recommended progression to the full trial (table 7). They felt assessment of the feasibility of long-term follow up was not necessary at this point, as this should be comparable to other similar trials. They advised that recruitment in the pilot sites continue whilst seeking funding, in order to maximise efficiency and value for money. Progression was “strongly supported” by the DMC.

Table 7: Feasibility assessment based on one year of recruitment

Feasibility objective	Outcome
Recruit 100-110 women at 8 sites over 12 months	<ul style="list-style-type: none"> Recruitment opened on schedule 125 women randomised across 8 sites 51% women approached gave consent (222/434) 56% women with consent randomised (125/222)
Recruit 16%-18% of women with livebirth <32 weeks gestation	<ul style="list-style-type: none"> 22% (121/550) births <32 weeks randomised 4 women recruited gave birth >32 weeks
Describe main reasons for non-recruitment	<ul style="list-style-type: none"> 23% approached declined participation (101/434), 12% discharged home (53/434) 97 with consent not randomised, reasons: 65% progressed >32 weeks (63/97), 8% transferred or discharged (8/97), 10% birth too rapid (10/97), and 4% a clinical decision (4/97)
Generalisable spectrum of gestational age, and outcome	<ul style="list-style-type: none"> 32% recruited <28 weeks (39/122) 15% recruited <26 weeks (18/122) 11% perinatal mortality
Compliance with trial interventions	<ul style="list-style-type: none"> Good compliance, endorsed by DMC Median time (seconds) to clamping 120 (IQR 30, 135) deferred arm vs 10 (10, 15) early arm Neonatal care provided with cord intact, so same care in both groups
Describe reasons for non-compliance	<ul style="list-style-type: none"> Deferred clamping: cord too short (11/60), clinical decision (7/60), staff error (2/60) Early clamping: staff error (2/72), baby born membranes intact (1/72), natural sequence of events (1/72)
Assess feasibility of oral assent consent pathway	<ul style="list-style-type: none"> Offered to 45 women, 84% (38/45) accepted 2 not randomised, progressed >32 weeks 36 randomised: 34 gave written consent. 2 not offered written consent, as baby died and they did not return for bereavement counselling appointment

Feasibility objective	Outcome
Assess acceptability of oral assent consent	<ul style="list-style-type: none"> • No issues reported in follow up questionnaires • Qualitative interviews with women and clinicians largely positive
Completeness of data collection for main outcomes	<ul style="list-style-type: none"> • 100% for death before discharge • 96% for IVH (124/129 livebirths with cranial ultrasound)
Women's view of participation	<ul style="list-style-type: none"> • 75% (91/122) response to questionnaire at 6-8 weeks • 94% (81/86 who completed this section) answered 'probably yes' or 'definitely yes' to '<i>if time suddenly went backwards, and you had to do it all over again, would you agree to participate in the Cord pilot trial</i>'

IQR=interquartile range

Discussion

The Cord pilot trial demonstrated feasibility of a large multicentre UK trial comparing deferred cord clamping and neonatal care, if needed, with the cord intact versus usual care. Nevertheless, we were unsuccessful in our attempt to transform this successful external pilot trial into an internal pilot, by continuing into the full trial.¹²

The trial was multicentre and conducted within existing clinical services, so widely generalizable to similar settings. Randomisation close to the time of birth was feasible, with over half the women giving birth within one hour of randomisation. We achieved good compliance with the allocated intervention. As this is a complex multidisciplinary intervention, maintaining compliance required regular training for clinical staff at sites, particularly following staff changes and rotations. We anticipate compliance would improve in a larger trial as, with sufficient units participating, a growing pool of trainees and other staff would have experience of deferring cord clamping and providing neonatal care with the cord intact. In addition, the cord being too short, a key reason for clamping before two minutes in the intervention arm, becomes less of a problem with more experience.

Mortality was 11.3% (15/133). As three babies were stillborn, livebirth mortality was 9.2% (12/130), comparable with UK data for 2012¹³ and suggesting a generalizable spectrum of babies was recruited. Our two-stage consent pathway allowed recruitment of women for whom birth was imminent and was largely supported by parents and clinicians.^{14,15} Resuscitation with the cord intact allowed us to recruit babies requiring resuscitation at birth. These two strategies mean high-risk women and infants were randomised.

Our independent adjudication of cranial ultrasound scans shows improved reliability of the diagnosis of IVH,⁸ suggesting that for trials where IVH is a main outcome criteria for diagnosis should be standardised and adjudication considered.

A practical problem was that babies were sometimes transferred to another hospital not participating in the trial. Although we were able to adapt our trial procedures to allow data collection for these babies, this was time consuming. For a large trial with many sites this would be a less common problem.

In conclusion, this pilot trial demonstrates that a large multicentre trial in the UK would be feasible. The two-stage consent pathway merits further evaluation, although our data support its use in future trials of cord clamping at preterm birth. Similarly, our data support provision of neonatal care beside the mother, although further evaluation of neonatal care with cord intact is required.

Acknowledgements

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Appendix 18 Randomised trial of cord clamping and initial stabilisation at very preterm birth

See Duley *et al.*⁷¹ <https://doi.org/10.1136/archdischild-2016-312567>

Appendix 19 Clinicians' views and experiences of offering two alternative consent pathways for participation in a preterm intrapartum trial: a qualitative study

See Chhoa *et al.*⁴¹ <https://doi.org/10.1186/s13063-017-1940-5>

Appendix 20 Women's views and experiences of two alternative consent pathways for participation in a preterm intrapartum trial: a qualitative study

See Sawyer *et al.*⁴² <https://doi.org/10.1186/s13063-017-2149-3>

Appendix 21 Cord pilot trial, comparing alternative policies for timing of cord clamping before 32 weeks' gestation: follow-up for women up to 1 year

See Bradshaw *et al.*¹⁶⁹ <https://doi.org/10.1186/s12884-019-2223-9>

Appendix 22 Womens' experiences of participating in a randomised trial comparing alternative policies for timing of cord clamping at very preterm birth: a questionnaire study

See Bradshaw *et al.*¹⁸⁰ <https://doi.org/10.1186/s13063-019-3325-4>

Appendix 23 Randomised trial of cord clamping at very preterm birth: outcomes at 2 years

See Armstrong-Buisseret, *et al.*¹⁸¹ <https://doi.org/10.1136/archdischild-2019-316912>

Appendix 24 Preterm cord clamping and placental transfusion prospective meta-analysis: protocol v1.0, dated 28 January 2013

Background

The primary objectives are to assess whether timing of cord clamping and other strategies to alter placental transfusion at preterm birth influence (i) the composite outcome of death or serious morbidity at discharge from hospital, and (ii) disability-free survival in early childhood (aged 2-3 years).

Methods

The Chief Investigators of potentially eligible studies will be contacted to invite them to collaborate in this prospective meta-analysis. Eligible trials identified in January 2013 are listed in Table 1. The Cord Clamping and other measures to influence Placental Transfusion at Preterm birth collaboration (CCPTP collaboration) will undertake this prospective meta-analysis using individual participant data according to the methods recommended by the Cochrane Collaboration Prospective Meta-Analysis Methods Group.¹

Criteria for potentially eligible studies

Study design: Studies will be included if they are randomised trials. Studies will be included if they are individual or cluster randomised. Quasi-random studies will be excluded.

Publication and unblinding of outcome data: Studies will only be included in the prospective meta-analysis if the investigator/s were blind to outcome data by intervention group at the time this protocol was agreed (i.e. when the objectives, aims and hypotheses, eligibility criteria, subgroup and sensitivity analyses, and main outcomes were agreed). If short term data are unblinded by allocation group but follow-up data remain blinded at the time the protocol is agreed, only the follow-up data from such trials will be included.

Types of participant: Participants will be women giving birth preterm (before 37 completed weeks gestation) and their babies. Studies will be eligible for inclusion if they recruited women and their babies, or babies alone.

Types of intervention: Studies will compare early or immediate cord clamping (standard care) with deferred cord clamping, with or without other strategies to influence placental transfusion (such as position of the baby whilst cord intact, use of uterotonic drugs, and umbilical cord milking). Studies will also be included if they compare any alternative strategies for influencing placental transfusion without a timing of cord clamping arm.

Studies evaluating collection and storage of residual placental blood that is then used for transfusion after birth will be excluded.

The comparisons included in the prospective meta-analysis will be:

1. Immediate cord clamping versus deferred cord clamping (trials with no cord milking in either allocated group)
2. Immediate cord clamping versus deferred cord (with subgroups by whether umbilical cord milking)
3. Immediate cord clamping versus umbilical cord milking
4. Umbilical cord milking versus deferred cord clamping

There is no consensus about the definition of ‘immediate’ and ‘deferred’ cord clamping. Whenever possible immediate clamping will be defined as within 20 seconds, and deferred clamping as at least 60 seconds. However, one objective of this PMA will be to explore the potential impact of alternative timings of cord clamping.

Types of outcome: Primary outcomes will be for the children:

- Death or serious morbidity at discharge from hospital. Serious morbidity will be defined as one or more of (i) brain injury on cranial ultrasound, (ii) necrotizing enterocolitis \geq Grade 2, (iii) late onset sepsis (>48 hr after birth), (iv) chronic lung disease, and (v) retinopathy requiring treatment
- Disability-free survival at age 2-3 years

Secondary outcomes will be:

For the women: postpartum haemorrhage (blood loss >500ml), any breast feeding, postnatal depression

For the children: Death, Brain injury on cranial ultrasound, Necrotizing enterocolitis \geq Grade 2, Late onset sepsis (> 48 hr after birth), Chronic lung disease, Retinopathy requiring treatment, Blood transfusion, Hypothermia, Jaundice requiring treatment, Long term neurodevelopment: cerebral palsy, neurosensory disability, deafness, blindness.

Search strategy for potentially eligible studies

We will identify ongoing trials that may be eligible by searching for published protocols in Medline and Embase, searching online registries of clinical trials, web searches of other sources, and personal contacts (for example by asking all collaborators to check conference abstracts). The Chief Investigators of ongoing trials will be invited to join the PMA provided the data remain blind and the study meets the eligibility criteria.

Assessment of study quality

Potentially eligible studies will be assessed for risk of bias using the criteria described in the Cochrane Handbook.

Planned subgroup analyses

To assess whether the results are comparable for different groups of infants, and for different levels of intervention, the following subgroup analyses will be conducted for the primary outcomes, if data are sufficient, based on:

For all comparisons:

- Gestation at birth: <37 completed weeks to 32 weeks; <32 weeks to 28 weeks, <28 weeks
- Type of pregnancy: singleton; multiple
- Mode of birth: caesarean; vaginal
- If caesarean birth, by type of anaesthesia: general anaesthesia, regional anaesthesia, type of anaesthesia not known

For comparisons of timing of cord clamping

- Timing of uterotonic drug: before cord clamping; after/at cord clamping
- Duration of deferred cord clamping: >30 seconds but ≤1 minute; >1 minute but ≤2 minutes; >2 minutes
- Whether cord milking: cord milking; no cord milking; not known whether cord milking

Planned sensitivity analyses

To assess whether results are robust to trial quality and different methods of analysis the following sensitivity analyses will be conducted for the primary outcomes, if data are sufficient:

- excluding studies with high risk of bias
- for trials comparing alternative strategies for timing of cord clamping: excluding studies where the mean difference between timing in the intervention arms was <45 seconds, or where the difference is not known
- comparing analyses using fixed effects and random effects models
- analysis of outcomes weighted by degree of difference between birth weights in treatment and control

Analysis plan

Analysis will include all randomised participants with available data and be based on intention-to-treat. Missing data will be described and reasons for missing data explored. The impact of missing data on conclusions about the comparative effects on the primary outcomes will be explored where possible (for example by using sensitivity analyses or imputation techniques). Multilevel models will be considered to examine how much variation in the outcomes is attributable by subgroup variables, and to estimate effect sizes with adjustment for subgroup variables as well as uncountable random effects among individual studies where necessary.⁵ The full analysis plan will be agreed by the Collaboration before any analyses are undertaken.

Project management

Membership of the CORD Collaboration will include representatives from each of the trials contributing data to the project, plus representatives from the project coordination group, and invited experts in IPD prospective meta-analysis. The project coordination group will be responsible for data management and analysis and communication within the Collaboration, including newsletters and email updates.

Ethics issues

Participants in the individual trials have previously consented to participation in their respective trial. The data will be available through an agreement between all Chief

Investigators of the included trials, and ethics approval for each of the trials has been given by their respective Research Ethics Committees. The trialists remain the custodians of their own data and retain the right to withdraw their data from the analysis at any time. Data will be de-identified before being shared with the CCPTP Collaboration.

Publication policy

Each trial has the right to publish the main results of their trial prior to the CCPTP Collaboration results being published. When publishing individual study results the authors for participating trials will acknowledge within the publication their involvement in the CCPTP Collaboration. Before publication of any CCPTP manuscripts, drafts will be circulated for comment, revision and approval by a nominated representative of each of the participating trials. Publications using these data will be authored on behalf of the CCPTP Collaboration, either with specific named authors, or on behalf of the Collaboration as a whole and names of other participating Collaborators will be listed in the Acknowledgements.

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Table 1: Trials eligible for collaboration in CCPTP at January 2013

Chief Investigator	Participants	Intervention	Primary outcome	Comparator
El-Nagare, W	70 infants <31 weeks gestation	Cord milking - infants in the cord-milked group will be placed at or below the level of the placenta, and about 20 cm of the umbilical will be vigorously milked towards the umbilicus three times before clamping the cord	Systemic blood flow as reflected by mean SVC flow measured by echocardiographic study at 4-6 hours after birth.	Immediate cord clamping at birth
Mercer, S	212 pregnant women in preterm labour between 24 and 31.6 weeks	Delayed cord clamping - at birth, the obstetrical provider delays the cord clamping for 45 sec while lowering the infant. At 45 sec the cord is milked once and then clamped and cut	Very low birth weight infants in the delayed cord clamping group will have better motor function at 18-22 months corrected age when compared with VLBW infants in the ICC group.[Time Frame: 18-22 months]	Immediate cord clamping at birth
Josephsen, J	80 pregnant women in preterm labour between	Cord milking - the neonate will be placed below the level of the placenta and approximately 20cm	• To evaluate and compare hemoglobin and hematocrit concentrations in extremely	Immediate Cord clamping at birth

Chief Investigator	Participants	Intervention	Primary outcome	Comparator
	24 0/7 and 27 6/7 weeks	of umbilical cord will be milked three times over 10-20 seconds total from the placental end to the neonate before clamping the cord	low birth weight infants (ELVW) after cord milking intervention to ELBW infants receiving immediate cord clamping • To evaluate and compare the incidence and numbers of blood transfusions after cord milking	
Katheria, A	60 Infants <32 weeks gestation	Cord milking – the delivering obstetrician will hold the infant below the mother's introitus at vaginal delivery or below the level of the incision at caesarean section and about 20cm of the cord will be milked over 2 seconds and repeated two additional times	Superior Vena Cava Flow. Researchers hypothesize that infants who receive umbilical cord milking (UCM) compared to infants who receive immediate cord clamping (ICC) will have higher SVC flow at 6 hours. [Time Frame: 6 hours]	Immediate cord clamping at birth without milking

Chief Investigator	Participants	Intervention	Primary outcome	Comparator
Datta, V	120 infants between 34 weeks 0 days to 36 weeks +6 days gestation	Delayed cord clamping - delayed by 30 to 60 seconds	Short term neurobehavioral outcome using N.A.P.I. (neurobehavioural assessment of preterm infant).	Early cord clamping within 20 sec
Mercer, J	212 pregnant women between 24 and 31.6 weeks at risk of delivery	1-Delayed cord clamping - delayed 30 to 45 seconds while the infant is held lower than the placenta. 2-Cord milking -At the end of the time, the cord is milked once and the cord is clamped. If the obstetrician feels he cannot delay the cord clamping, then the cord can be milked 2 to 3 times.	<ul style="list-style-type: none"> • Very low birth weight (VLBW) infants in the delayed cord clamping (DCC) group will have less intraventricular haemorrhage (IVH) compared to VLBW infants in the immediate clamped (ICC) group [Time Frame: December, 2012] <ul style="list-style-type: none"> • Very low birth weight infants in the delayed cord clamping group will have less late onset sepsis than those in the immediate clamping group 	Immediate cord clamping at birth

Chief Investigator	Participants	Intervention	Primary outcome	Comparator
			[Time Frame: December 2012]	
Hosono, S	566 infants between 24 and 28 weeks gestation	Cord milking - Umbilical cord is cut and clamped at 30cm from infants, baby is placed on a radiant warmer. Paediatrician then milks the umbilical cord once	1) the probability of not needing transfusion and death 2) amount of blood transfusion within the first 4 weeks	Early cord clamping within 30 seconds
Tarnow-Mordi, W	1600 pregnant women less than 30 weeks at risk of delivery	Delayed cord clamping - Infant held as low as possible below the level of the placenta for 60 seconds or more before cord clamped about 6 cm from the umbilicus.	Composite death and/or major morbidity at 36 weeks post menstrual age. Morbidity is defined by one or more of the following: Brain injury on ultrasound, Chronic lung disease, Severe retinopathy, Necrotising enterocolitis, Late onset sepsis. Timepoint: 36 weeks post menstrual age	Immediate cord clamping

Chief Investigator	Participants	Intervention	Primary outcome	Comparator
Tarnow-Mordi, W	100 pregnant women less than 32 weeks at risk of delivery	Autologous placental transfusion 1. Cord milking – Cord clamped and cut long (3 cm from the placenta or the introitus of the vagina) then untwisted and milked during resuscitation. 2. Delayed cord clamping - Infant place as low as possible below the level of the introitus or placenta for 30 – 60 seconds then cord clamped 6 cm from the umbilicus. If the baby is in extremis, the previous step is omitted and the cord is clamped immediately 6 cm from the umbilicus.	Haemoglobin concentration will be measured using arterial or venous or capillary blood on the neonatal intensive care unit blood gas analysis machine or hospital laboratory using any method pragmatically available. Timepoint: at 6 hours after birth	Immediate cord clamping

Chief Investigator	Participants	Intervention	Primary outcome	Comparator
		3. Delayed cord clamping plus milking - Infant held as low as possible below the level of the introitus or the placenta for 30 – 60 seconds then cord clamped and cut long before being handed to neonatal team. After the delay step, cord untwisted and milked during resuscitation		

Appendix 25 Systematic review and network meta-analysis with individual participant data on cord management at preterm birth: study protocol

Abstract

Introduction: Timing of umbilical cord clamping and other cord management strategies may improve outcomes at preterm birth. Trials comparing such strategies often recruit at different gestations and compare alternative policies, including immediate cord clamping, short (30 seconds), medium (45 seconds) or long deferrals (up to 5 minutes) and 'milking' the cord. Individual participant data (IPD) enables exploration of subgroups to give differential cord management recommendations for different groups of participants. Network meta-analysis (NMA) methods enable to compare and rank all available interventions using a combination of direct and indirect comparisons of multiple treatment options by integrating all the available data.

Objectives: 1) To evaluate the effectiveness of cord management strategies on neonatal mortality and morbidity overall and for different patient characteristics using IPD meta-analysis; and 2) to evaluate and rank the effect of different cord management strategies for preterm births on mortality using NMA.

Methods and analysis: Systematic search for all planned, ongoing and completed randomised controlled trials that compare alternative cord management policies (such as different timing of cord clamping and/or cord milking) at preterm birth (before 37 weeks' gestation). The trials will be identified by searching Medline, Embase, clinical trial registries, and other sources. IPD will be sought for all trials. First, deferred clamping and cord milking will be compared with immediate clamping in IPD meta-analyses. The primary outcome will be death (at any time). Secondary outcomes will include morbidities and harms. Effect differences will be explored for pre-specified subgroups of participants. Second, all identified cord management strategies will be compared and ranked in an IPD NMA for the primary outcome death, and differential treatments depending on participant characteristics will be identified using meta-regression and subgroup analyses. Inconsistency and heterogeneity will be explored.

Ethics and dissemination: Approved by the University of Sydney Human Research Ethics Committee (2018/886). Results will be relevant to clinicians, guideline-developers, policy-makers and the global research community, they will be disseminated to these groups through publications, conference presentations and media releases.

Registration

Keywords: Preterm birth, umbilical cord clamping, umbilical cord milking, placental transfusion, individual participant data meta-analysis, prospective meta-analysis, network meta-analysis

Introduction

Preterm birth is an important determinant of adverse outcome for the child, as well as the family and health services.¹ Each year, 15 million babies are born too soon (before 37 weeks gestation) and the number is rising.²⁻⁴ Of these, 1.1 million babies die, and preterm birth is now the second most common cause of death in children under five years of age.² Preterm birth is more common in low and middle-income countries.² There are stark inequalities in survival, with 95% survival in high-income countries compared to 30% in low-income countries for babies born at 28-32 weeks gestation.³ Worldwide, preterm birth is a risk factor for half of all neonatal deaths.³

For those born preterm who survive, morbidity and health service costs are high compared to babies born at term. In the UK, hospital stay lasts 85 times longer for babies born before 28 weeks than for term infants; and 16 times longer for those born at 28-31 weeks.⁵ Total cost to the UK public sector of very preterm birth (before 32 weeks) is estimated at £1 billion annually.⁶ Of very premature infants (<28 weeks) who survive, 5-10% develop cerebral palsy; and 25% develop neurosensory disability.¹ Those without severe disability have increased risk of developmental, cognitive, and behavioural difficulties.⁷⁻¹⁰ Teenagers and young adults born very preterm report poorer physical abilities and more chronic ill health than their peers born at term, although similar health-related quality of life.^{11,12} Prematurity and its sequelae may have a negative psychosocial and emotional impact on parents and families.¹ Even modest improvement in outcome would be of substantial benefit to the children, their families, and health services.

Neonatal transition and blood transfer in preterm infants

Net transfer of blood from the placenta to the baby is known as ‘placental transfusion’. If the umbilical cord is not clamped immediately at birth, blood flow between the baby and placenta may continue for a few minutes. Blood flow may continue without any net transfer, however, and sometimes net transfer may be to the placenta.¹³

As the baby is born, umbilical circulation slows and pulmonary vascular resistance falls, rapidly increasing pulmonary blood flow volume. Continued flow in the umbilical vein and arteries at birth may be part of the physiological mechanisms assisting the baby during this transition from fetal to neonatal circulation. For term births, umbilical blood flow may continue for up to five minutes or longer.^{14,15} For preterm births, umbilical blood flow may continue for longer,¹⁶ since a greater proportion of feto-placental circulating blood volume is still in the placenta (while at term two-thirds are in the infant with one third in the cord and placenta).¹⁷

Time of umbilical cord clamping

Animal and pilot human studies suggest that breathing and lung aeration before cord clamping can improve cardiovascular stability and oxygenation and reduce infant mortality, and intraventricular haemorrhage.¹⁸⁻²¹ Other animal and pilot studies suggest that initial respiratory support for up to 5 minutes before cord clamping results in improved blood pressure and cerebral oxygenation and reduced cerebrovascular impairment compared with immediate cord clamping.^{22,23} One potential mechanism of benefit of deferred clamping is allowing time for the infant to establish spontaneous breathing whilst still placentally supported, thus avoiding invasive interventions such as endotracheal intubation in the delivery room.

Without the assistance of video or extra equipment, clinicians record the time when the cord is clamped more accurately and consistently than the time when vigorous breathing begins. In unpublished data from an earlier study,²⁴ Katheria found that time of onset of breathing in preterm infants receiving gentle stimulation is related to time after birth – within a minute over 90% of preterm infants had begun spontaneous breathing ($r^2=0.91$, $P<0.001$) (personal communication). Thus the longer after birth the cord is clamped, the more likely is it that breathing has begun.

Cord milking

Cord milking (pinching the cord close to the mother and running the fingers towards the baby, usually several times) may be a way to increase preterm blood volume without deferring clamping.²⁵ However milking over-rides the infant's physiological control of its blood pressure and volume and disrupts umbilical flow. Animal data show that cord milking without allowing placental refill fails to provide placental transfusion, and milking can cause major haemodynamic disturbance.²⁶ A recent trial comparing deferred cord clamping with cord milking was stopped early in the subgroup of extremely preterm infants (23-27 weeks), as the incidence of severe intraventricular haemorrhage was higher in the cord milking group.²⁴ Hence, the effects of cord milking need further elucidation.

Other cord management issues

Initial neonatal care and stabilisation traditionally takes place on a resuscitation platform at the side of the room or in an adjacent room, away from the woman. For infants requiring resuscitation immediately at birth, this practice means the cord is usually clamped and cut immediately.

An alternate strategy is providing immediate neonatal care, including resuscitation if needed, with the cord intact beside the woman.^{27,28} The recent Cord pilot trial²⁹ showed that neonatal stabilisation and resuscitation with cord intact is feasible and acceptable to parents and clinicians.^{28,30-32}

Previous reviews of aggregate data

A 2012 Cochrane Review of timing of cord clamping for preterm births³³ included 15 trials, with 738 infants, one of which (with 40 infants) compared cord milking with immediate cord clamping.³⁴ There was heterogeneity in the timing of cord clamping and gestational age at recruitment, and data were insufficient for reliable conclusions about any of the primary outcomes of the review. A systematic review and meta-analysis published in 2018 (including 18 trials with 2834 participants) compared the effect of deferred (≥ 30 seconds) vs early (< 30 seconds) clamping in preterm infants, and found a reduction the primary outcome hospital mortality by 32% (Risk Ratio = 0.68, 95% Confidence Interval = 0.52-0.90).³⁵ The main outcomes of this systematic review are summarised in Table 1. There was heterogeneity in the definition of ‘early cord clamping’ ranging from immediate or less than 5 seconds to 25 seconds, and ‘late cord clamping, ranging from 30 seconds to 180 seconds, with most trials clamping after less than 60 seconds. Recruitment age varied from 22 weeks to 36+6 weeks. Most analyses of infant and maternal morbidity were substantially underpowered.³⁵ The review concludes that while there is high quality evidence that deferred cord clamping improves outcomes, individual participant data analyses of existing and new randomised controlled trials are urgently needed to further understand the benefits and potential harms of different cord management strategies, and to understand whether differential treatment options are advantageous for key subgroups of infants.³⁵

Current guidelines and practice for cord management at birth

These uncertainties in optimal cord clamping strategies are reflected in varying guidelines. The World Health Organisation (WHO) recommends late cord clamping³⁶ unless resuscitation is required, the National Institute for Health and Clinical Excellence (NICE) recommends waiting for 30 seconds to 3 minutes if mother and baby are stable,³⁷ and the International Resuscitation Council (ILCOR) recommends a delay in cord clamping of at least 1 minute. NICE recommends positioning the baby positioned at or below the level of the placenta whilst deferring clamping, whilst WHO and ILCOR make no such recommendations. If the baby is assessed as requiring resuscitation (which is the case in many preterm infants),³⁸ WHO recommends immediate clamping,^[39] NICE recommends to consider cord milking before clamping, and ILCOR

concludes that there is insufficient evidence to make any recommendations.³⁸ There is little information about actual practice for cord clamping.⁴⁰

The current study

Overall, there is uncertainty about the optimal cord management strategy which has led to wide practice variation. It is also unclear whether there should be differential cord management strategies for key subgroups of infants, e.g. those for which resuscitation and/or stabilisation is deemed necessary, extremely preterm infants, or those with growth restriction. This uncertainty has led to 112 planned, ongoing or published trials (in more than 15,000 preterm babies) that are comparing a range of cord management strategies. Individual participant data (IPD) meta-analysis is the gold standard for combining such trial data. IPD will provide larger statistical power for estimation of treatment effects of rarer secondary endpoints and will enable reliable subgroup analyses to examine hypotheses about differences in treatment effect, exploring interactions between treatment- and participant-level characteristics.⁴¹ A network meta-analysis (NMA) facilitates data synthesis when there is a range of interventions available and permits comparisons across all interventions, although some interventions may not have been directly compared in trials.⁴² Indirect evidence for these comparisons is obtained by inferring the relative effectiveness of two competing treatments through a common comparator.⁴³ Network meta-analysis produces estimates of relative effects for each intervention compared with every other intervention in the network. These effect sizes can be used to obtain rankings of the effectiveness of the interventions.⁴⁴ Using individual participant data in a network meta-analysis (as opposed to aggregate data) can improve precision, increase information, and reduce bias.⁴⁵

Objectives

The aims of this study are to:

- 1) evaluate the effectiveness of strategies of cord management on neonatal mortality and morbidity and to evaluate differential treatment by participant characteristics using individual participant data meta-analysis;
- 2) evaluate, compare and rank the effect of different cord management strategies for preterm births on mortality using network meta-analysis.

Methods and analysis

We will conduct a systematic review of randomised trials with individual participant data pairwise and network meta-analysis, and a nested prospective meta-analysis. The lead investigator for all

potentially eligible studies will be contacted and invited to collaborate and join the individual participant data Cord Management at Preterm birth (iCoMP) Collaboration. Eligible trials identified up to August 2018 are listed in Table 2. The Collaboration will undertake this project according to the methods recommended by the Cochrane Collaboration Individual Participant Data, Cochrane Multiple Interventions Group, and Prospective Meta-Analysis Methods Groups.^{41,46,47} The protocol is registered at PROSPERO, the International Prospective Register of Systematic Reviews.[48] PRISMA-IPD and PRISMA-NMA statements will be followed for reporting.

Eligibility criteria

Types of studies

Studies will be included if they are randomised trials, quasi-random studies will be excluded. Studies must compare at least two of the interventions of interest (defined below).

Trial participants

Participants will be women giving birth preterm (before 37 completed weeks' gestation) and/or their babies. Individually randomised studies will be eligible for inclusion if the unit of randomisation was either the woman, or the baby. Women and babies will be included regardless of whether mode of delivery was vaginal or Caesarean, and whether the birth was singleton or multiple. Babies will be included regardless of whether or not they received immediate resuscitation at birth.

Types of interventions and comparators

Part 1: individual participant data pairwise meta-analysis

For the pairwise meta-analysis we will include all trials that compare an intervention to enhance umbilical blood flow or allow more time for physiological transition to the comparator immediate cord clamping. This includes interventions assessing cord management strategies for timing of cord clamping, and other strategies to influence umbilical flow and physiological transition (such as lowering the baby below the level of the placenta whilst cord intact, and umbilical cord milking or stripping). Studies will be included if they compare strategies to maintain 'physiological' umbilical flow (i.e. none or minimal intervention) and placental transfusion, and if they examine strategies that aim to alter umbilical blood flow and placental transfusion (such as using gravity by lowering the baby, or cord milking or stripping). Trials will be included regardless of whether initial neonatal care is provided with the umbilical cord intact, or not.

Different strategies (i.e. cord clamping and milking) will be analysed in separate subgroups to assess comparability between the groups by assessing subgroup effects and heterogeneity. They will then be collapsed into one 'cord management intervention' group if they are deemed comparable based on the previous subgroup assessments. If they are deemed non-comparable they will be analysed and interpreted separately.

Part 2: individual participant data network meta-analysis

For the network meta-analysis we will include as interventions of interest cord management strategies for timing of cord clamping, and other strategies to influence umbilical flow and placental transfusion.

Thus, interventions of interest include:

- Immediate cord clamping (within 30 seconds)
- Short deferral of cord clamping (>30 to ≤ 45 seconds) without milking
- Medium deferral of cord clamping (45 to ≤ 90 seconds) without milking
- Long deferral of cord clamping (≥ 90 seconds) without milking
- Umbilical cord milking or stripping before cord clamping
- Umbilical cord milking or stripping after immediate cord clamping
- Umbilical cord milking or stripping after deferred cord clamping
- Physiological clamping after onset of breathing

If we identify other interventions not listed above we will include them if they are addressing cord management or related strategies to influence umbilical flow and placental transfusion. Again, trials will be included regardless of whether initial neonatal care is provided with the umbilical cord intact, or not. Studies evaluating collection and storage of residual placental blood that is then used for transfusion after birth will be excluded. All possible comparisons between eligible interventions are displayed in Figure 1.

Nodes that specify different timings of cord clamping were defined according to what timing is classified as immediate clamping, short deferral, medium deferral or long deferral according in the literature to date (as shown in Table 2), and after discussion with clinicians. Different timings are commonly compared in head-to-head comparisons, hence, their classification as different intervention nodes. Similarly, nodes that specify cord milking were classified after a review of current milking techniques described in the literature and after discussion with clinicians.

If insufficient data are available, categories will be collapsed where possible. For instance, milking before and after cord clamping could be collapsed into one single cord milking category, or medium and long delay could be collapsed into a medium to long delay category. We consider the interventions of interest to be jointly randomisable (i.e. a participant could, in principle, be randomised to any one of the interventions of interest).

Types of outcome measures

Included trials must report at least one of the clinical outcomes included in this review as specified in the ‘measures’ section below to be included.

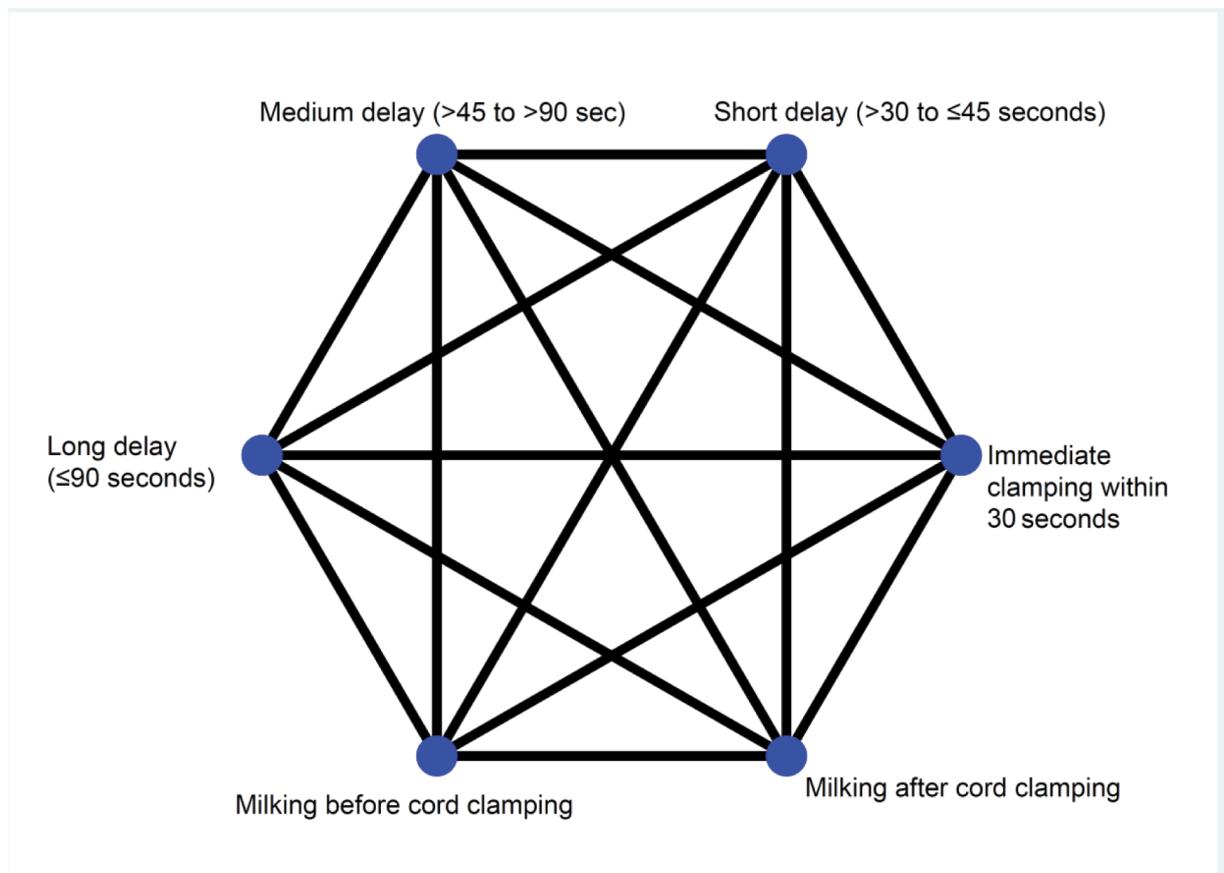


Figure 1. Network of possible comparisons between cord management interventions

Eligibility for nested prospective meta-analysis

Studies are only included in the nested prospective meta-analysis if the investigator/s were blind to outcome data by intervention group at the time the main components of the protocol (i.e. objectives, aims and hypotheses, eligibility criteria, subgroup and sensitivity analyses and main outcomes) were initially agreed in January 2015. Other planned or completed eligible trials will

be included in the first cycle of this IPD meta-analysis if their expected last participant enrolment is before end March 2019.

Information sources and search strategy

The search strategy to identify potentially eligible studies will include a search of the register of trials developed and maintained by the Cochrane Collaboration Pregnancy and Childbirth Review Group. The Cochrane Pregnancy and Childbirth Group's Trials Register contains trials identified from: monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL); weekly searches of MEDLINE (Ovid); weekly searches of Embase (Ovid); monthly searches of CINAHL (EBSCO); hand searches of 30 journals and the proceedings of major conferences; and weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts. Details of the search strategies for CENTRAL, MEDLINE, Embase and CINAHL, the list of hand searched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.⁴⁹ We will identify ongoing trials that may be eligible by searching for published protocols in Medline and Embase, searching online registries of clinical trials, and personal contacts (for example, by asking collaborators to notify any unregistered studies they are aware of). The Chief Investigators of eligible trials will be invited to join the iCoMP Collaboration. They will also be asked if they know of any further planned, ongoing or completed studies.

Selection of studies for inclusion in the review

Two members of the iCoMP Secretariat (see project management section below) will independently assess all the potentially eligible studies identified for inclusion. Disagreements will be resolved by discussion or, if required, by consulting a third member. Studies that are not willing or able to provide IPD will be synthesised where possible using aggregate data.

Data collection, management and confidentiality

Data receipt

De-identified, individual participant level data for each randomised participant will be provided by each participating trial. These data will be backed-up and stored in a secure, centralised database.

Data processing

Data checking: Range, internal consistency, consistency with published reports and missing items will be checked for each trial. Trial details such as randomisation methods and intervention timing will be cross-checked against any published reports, trial protocols and data collection sheets. Integrity of the randomisation process will be examined by reviewing the chronological randomisation sequence and pattern of assignment, as well as the balance of prognostic factors across treatment groups (taking into account stratification factors). Inconsistencies or missing data will be discussed with the individual trialists and any problems will be resolved by consensus. Each trial will be analysed individually and the resulting analyses and trial data will be sent to the trialists for verification before inclusion in the iCoMP database. All trial specific outcomes generated from the individual participant data will be cross-checked against published information via a series of crosstabs.

Data re-coding: The outcome data may have been collected in different formats within the different trials. Therefore, the de-identified data collected from each of the participating trials will be extracted and re-formatted into a commonly coded dataset.

Data transformation and collating: Once the data from each of the trials are finalised, it will be combined into a common dataset, but a trial identifier code for each participant will be retained. New variables will be created from the combined dataset as required to address the hypotheses to be tested.

Risk of bias assessment and quality of evidence appraisal

Eligible studies will be assessed for risk of bias using the criteria described in the Cochrane Handbook:⁵⁰ random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other bias. The quality of evidence will be assessed using the GRADE approach⁵¹ for the pairwise comparisons, and the rating approach suggested by Salanti and colleagues for network meta-analysis that is implemented in the CINeMA application.⁵²

Measures

Part 1: individual-participant data pairwise meta-analysis

Outcomes

All outcome measures are listed in Table 3. The primary outcome will be death of the baby at any time. As outcomes for babies born very preterm (before 32 weeks gestation) are different to those born moderately preterm (32 to 37 weeks), separate analyses will be conducted for these two groups of infants for the secondary outcomes. Where possible, definitions will be standardised, otherwise outcomes will be used as defined by the trialists. Secondary outcomes will include measures of neonatal and maternal morbidity, and health service use. There will be efficacy outcomes that cord management strategies, compared with immediate clamping, may improve such as death, late onset sepsis and severe intraventricular haemorrhage, and there will be safety outcomes reflecting potential risks of not clamping immediately such as postpartum haemorrhage, hypothermia and polycythaemia.

Covariates and subgroups

Subgroup analyses will be conducted for the primary outcome of death and key secondary outcomes, if sufficient data are available. All included covariates and subgroups are listed in Table 3. The comparative effects of alternative cord management strategies may vary depending on key infant risk factors, but also depending on the level and type of neonatal care available at the hospital of birth. Thus, there will be subgroup analyses based on participant-level characteristics and based on hospital-level characteristics. If data are insufficient for subgroup analysis, categories will be collapsed.

Table 3. Measures for individual participant data pairwise meta-analysis

Outcomes	
<i>For all infants</i>	
Primary outcome	<ul style="list-style-type: none"> • Death (at any time for follow-up duration of the included trials)
<i>For infants born before 32 weeks gestation</i>	
Key secondary outcomes	<ul style="list-style-type: none"> • Death (within 7 days) • Severe intraventricular haemorrhage on cranial ultrasound (grade 3-4) • Necrotizing enterocolitis \geq grade 2 (or trialist definition) • Late onset sepsis (where possible defined as clinical sepsis > 72 hour after birth) • Patent ductus arteriosus requiring treatment (medical and/or surgical) • Chronic lung disease (at 36 weeks postmenstrual age or trialist defined)
Other secondary outcomes	<ul style="list-style-type: none"> • All grades of intraventricular haemorrhage on cranial ultrasound • Respiratory support (mechanical ventilation, CPAP, low flow oxygen) • Duration of respiratory support • Retinopathy of prematurity requiring treatment (medical and/or surgical) • Drug treatment for hypotension • Blood transfusion (volume) • Hypothermia on admission to neonatal unit

	<ul style="list-style-type: none"> • Polycythaemia, haemoglobin, haematocrit • Jaundice requiring treatment • Birthweight • Length of stay in NICU • Long term developmental disability (assessed using the Bayley III, or similar tools): <ul style="list-style-type: none"> ○ cerebral palsy (severe, moderate, mild) ○ neurosensory disability (severe, moderate, mild) ○ deafness (severe, moderate, mild) ○ blindness (severe, moderate, mild)
<i>For infants born at or after 32 weeks gestation</i>	
Key secondary outcome	<ul style="list-style-type: none"> • Death (within 7 days) • Admission to Neonatal Intensive Care Unit (NICU)
Other secondary outcomes	<ul style="list-style-type: none"> • Length of stay in NICU • Duration of respiratory support (mechanical ventilation or CPAP) • Chronic lung disease (receiving supplemental oxygen at 36 weeks postmenstrual age) • Late onset sepsis (> 72 hour after birth) • Patent ductus arteriosus requiring treatment (medical and/or surgical) • Drug treatment for hypotension • Blood transfusion • Hypothermia on admission to neonatal unit or postnatal ward • Long term developmental disability (assessed using the Bayley III, or similar tools): <ul style="list-style-type: none"> ○ cerebral palsy (severe, moderate, mild) ○ neurosensory disability (severe, moderate, mild) ○ deafness (severe, moderate, mild) ○ blindness (severe, moderate, mild)
<i>For all women</i>	
Secondary outcomes	<ul style="list-style-type: none"> • Maternal death • Postpartum blood loss ≥ 500ml • Postpartum infection requiring antibiotics • Manual removal of placenta • Retained placenta (>30 minutes) • Not breast feeding when baby discharged from hospital • Postnatal depression • Blood transfusion
Covariates/ Subgroups	
<i>Based on participant-level characteristics</i>	
	<ul style="list-style-type: none"> • Gestation at birth: <37 completed weeks to 32 weeks; 28 to <32 weeks; 26 to <28 weeks, <26 weeks • Type of pregnancy: singleton; multiple • Mode of birth: caesarean before onset of labour; caesarean after onset of labour; vaginal • Spontaneous onset of labour: spontaneous onset or prelabour ruptured membranes; not spontaneous onset or prelabour ruptured membranes; not known whether spontaneous onset of labour or prelabour ruptured membranes • Time of breathing onset (seconds or before/after cord clamping/milking) • Assessed as needing resuscitation and/or stabilisation (yes/no) • Gender (male, female, uncertain/other) • Intrauterine growth restriction: yes, no (trialist defined) • Suspected maternal antenatal/intrapartum sepsis (trialist defined): yes/no

<i>Based on hospital / trial-level characteristics</i>	
	<ul style="list-style-type: none"> • Highest level of neonatal unit available at site: neonatal intensive care unit, neonatal unit (some capacity to provide ventilation), special care baby unit (no ventilation available), no neonatal unit or special care baby unit • Type of uterotonic drug (if any) • Planned timing of uterotonic drug: before cord clamping; after/at cord clamping; timing mixed or not known • Planned position of the baby relative to the placenta whilst cord intact: level with placenta (between level of woman's bed and her abdomen/anterior thigh); more than 20 cm below level of placenta; position mixed or not known • Need for immediate resuscitation at birth: infants requiring immediate resuscitation at birth excluded; infants requiring immediate resuscitation at birth included; unclear whether infants requiring immediate resuscitation at birth included or excluded • Type of consent

Part 2: individual participant data network meta-analysis

Outcome

The primary outcome for the network meta-analysis will be death of the baby at any time (during the follow-up duration of the trials).

Covariates and subgroups

All variables listed in Table 3 will be considered as covariates to improve consistency of the NMA model. There will be subgroup analyses comparing babies born before and after 32 weeks, and comparing babies in need of immediate resuscitation versus not in need of immediate resuscitation.

Data analysis

The full, detailed Statistical Analysis Plan will be agreed on by the Collaboration before any analyses are undertaken. Analyses will include all randomised participants with available data, and the primary analyses will be based on intention-to-treat without imputation of missing data. Missing data will be described and reasons for missing data explored. The impact of missing data on conclusions about the comparative effects on the primary outcomes may be explored in sensitivity analyses if appropriate.

Part 1: individual-participant data pairwise meta-analysis

For each outcome, a one-stage approach to analysis will be employed to include individual participant data from all eligible trials in a multilevel random or mixed effects regression model. Aggregate data will be included where individual participant data is unavailable. Heterogeneity of treatment effects across trials will be estimated using confidence and prediction intervals, with further inclusion in secondary models of participant-level and trial-level covariates to explain the sources of heterogeneity. Forest plots will be presented by trial for each of the primary outcomes, and for any secondary outcomes where there is evidence of heterogeneity across trials.

We will use a generalised linear modelling framework, with the choice of outcome distribution and link function dependent on outcome type. For example, binomial with log link will be used to estimate risk ratios for the binary primary outcome of death or serious morbidity, and Gaussian with identity link for differences in mean duration of ventilation, with log-transformation of the data if appropriate. We will follow a similar approach for secondary outcomes. For estimation of subgroup effects on the primary outcomes, we will present forest plots of pooled treatment effects according to pre-specified subgroup variables, and estimate effects by including appropriate interaction terms between subgroup variable and treatment arm in the regression models. The results of all comparative analyses will be presented using appropriate estimates of treatment effect along with 95% confidence intervals and two-sided p-values.

Part 2: individual participant data network meta-analysis

We will calculate a two-step random-effects network meta-regression model to compare and rank all available treatments using direct and indirect comparisons using a Bayesian model and assuming an independent interaction between treatment effects and covariates. We will obtain probability rankings of the effect of all interventions on the primary outcome death and for key secondary outcomes if data permits. If there are statistically significant interactions between covariates and treatment effects, we will provide probability rankings of intervention effects by subgroup for these covariates. Heterogeneity will be measured by the heterogeneity parameter τ^2 . Residual inconsistency will be measured by comparing effect estimates between the direct and indirect comparisons. A judgement of excessive heterogeneity or inconsistency would prevent the interpretation and reporting of the network meta-analysis.

Assessment of compliance with the allocated intervention

Compliance with the interventions will be described for each trial. For studies of early versus deferred cord clamping this will be based on i) the time to cord clamping in each allocated group and ii) the difference in time between early and deferred clamping. For studies comparing cord milking with no milking, this will be based on i) time to cord clamping in the allocated groups ii) reported compliance with cord milking in both groups.

Adjustments for multiple testing (to be added)

Planned sensitivity analyses

To assess whether results are robust to trial quality and different methods of analysis the following sensitivity analyses will be conducted for the primary outcome, if data are sufficient:

- Excluding studies with high risk of bias, defined as those assessed as high or unclear risk of bias for sequence generation and/or concealment of allocation, and/or high risk of bias for loss to follow up for pairwise and network meta-analysis;
- For trials comparing early cord clamping with deferred clamping: analysis of outcomes weighted by degree of separation between groups (observed between-arm difference in mean timing of clamping) for pairwise meta-analysis;
- Analysis of outcomes weighted by degree of separation in haemoglobin (at 24 hours) achieved between intervention and control groups for pairwise meta-analysis (as a surrogate for net placental transfusion);
- For trials with deferred cord clamping, we will perform an additional dose-response analysis assessing intended time of cord clamping deferral as a continuous variable;
- An exploratory analysis will be based, not as intention-to-treat, but on actual timing of cord clamping for individual participants for pairwise and network meta-analysis.

Project management

Membership of the iCoMP Collaboration will include representatives from each of the trials contributing data to the project, the Secretariat, and invited experts in individual participant data systematic reviews, network meta-analysis and prospective meta-analysis who will form an Advisory Group. The Secretariat will be responsible for data management and analysis and communication within the Collaboration, including newsletters and email updates.

Ethical issues

Participants in the individual trials have previously consented to participation in their respective trial. The data will be available through an agreement between all Chief Investigators of the included trials, and ethics approval for each of the trials has been given by their respective Research Ethics Committees. The trialists remain the custodians of their own data and retain the right to withdraw their data from the analysis at any time. Individual participant data will be de-identified before being shared with the iCoMP Collaboration. Ethics approval for this project has been granted by the University of Sydney Human Research Ethics Committee (Project number: 2018/886).

Publication policy <will be updated>

The key methods for this meta-analysis protocol were agreed by the iCoMP Collaborators in January 2015, before unblinding of any outcome data from the studies included in the nested prospective meta-analysis. This manuscript was discussed at the first iCoMP Collaborators meeting held at the Pediatric Academic Societies meeting in San Diego, in April 2015. At this meeting it was agreed the protocol should be expanded to a retrospective systematic review and individual participant data and network meta-analysis with a nested prospective meta-analysis. The protocol was then revised based on further discussion, and circulated to members of the collaborative group for further comment and agreement prior to submission.

Participating trialists in the prospective meta-analysis, when reporting results from their own trials, will endeavour to include a statement that their trial is part of this prospective meta-analysis in any published manuscripts or conference abstracts. Any reports of the results of this meta-analysis will be published either in the name of the collaborative group, or by representatives of the collaborative group on behalf of the iCoMP Collaboration, as agreed by members of the collaborative group. Reports will be circulated to the collaborative group for comments and approval before submission for publication.

Discussion

There is an urgency to conduct this systematic review and individual participant data pairwise and network meta-analysis so we can make sense of the many small trials now being undertaken,

inform clinical practice and identify the most promising interventions for further evaluation. This meta-analysis offers an opportunity to reliably test important hypotheses that cannot be resolved by any of the individual trials, either alone or in simple combination. Coordinating international efforts in this way will help achieve consensus on the most important substantive clinical outcomes to assess in any future trials. Unequivocal synthesized results, together with the identification of key determinants (e.g. effect modifiers) will be critical for translating evidence from the results of this meta-analysis into practice. Figure 2 gives an idea of the network of direct comparisons available from the trials that we have identified to date. We plan to complete study identification and individual participant data collection by mid-2019, and conduct the analysis and disseminate the results by end-2020.

This study is only possible because trialists around the world have agreed to collaborate to share the individual participant data from their cord management trials. This collaborative approach will enable us to move beyond the traditional ‘one-size-fits-all’ approach in medicine, towards precision medicine to find the optimal treatment from a range of treatment options for each individual woman and her baby, based on their individual characteristics and risk factors.

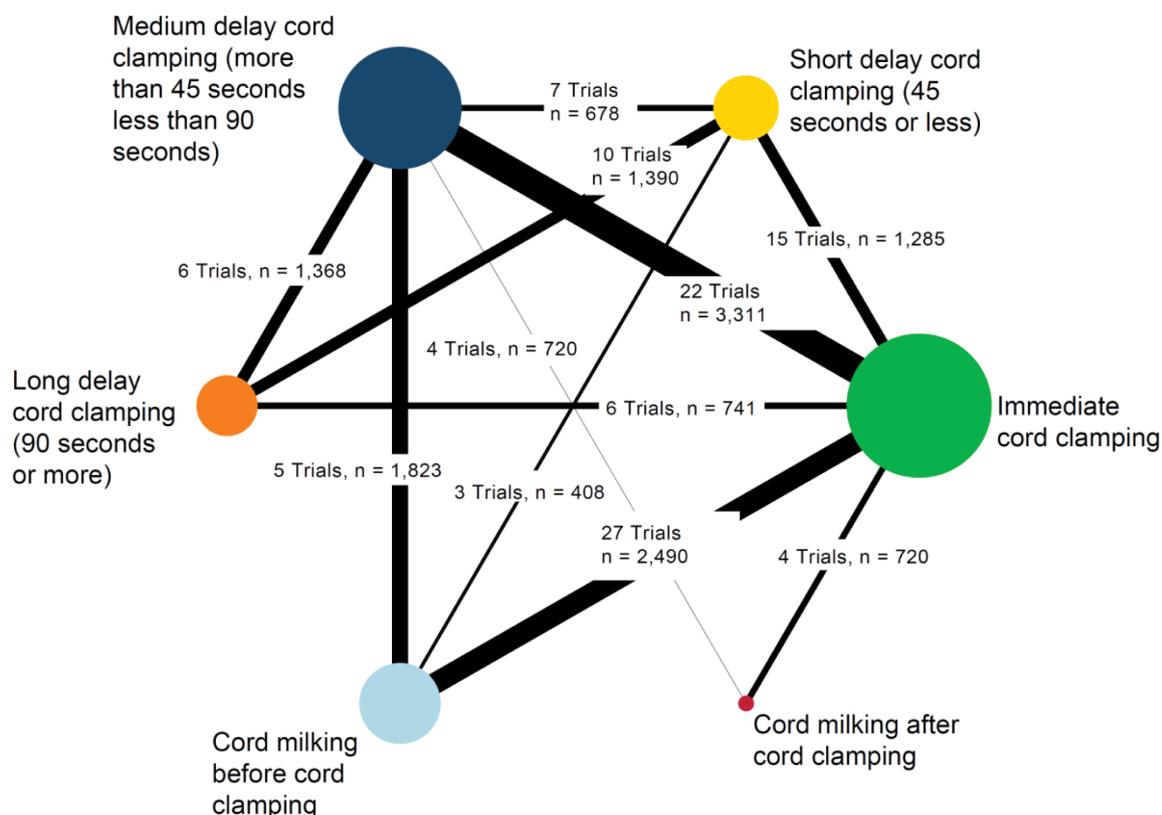


Figure 2. Illustration of network of currently available trials comparing different cord management strategies.

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Developing the protocol and establishing the collaborative group was supported by the UK National Institute of Health Research with a grant entitled The Preterm Birth Programme (number RPPG060910107). It presents independent research commissioned by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research funding scheme (RP-PG- 0609-10107). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. Funding for individual trials remains the responsibility of the trialists themselves. Funding to undertake the data collection and data analysis for the iCoMP Collaboration will be provided by the Australian National Health and Medical Research Council (APPID1163585).

<full list of iCoMP collaborators will be added>

List of abbreviations

iCoMP – individual participant data on **C**ord **M**anagement at **P**reterm birth

UK – United Kingdom

WHO – World Health Organization

NICE – National Institute for Health and Clinical Excellence

PRISMA – Preferred Reporting Items for Systematic Review and Meta-Analysis

IPD – individual participant data

NMA – network meta-analysis

CPAP – continuous positive airway pressure

NICU – neonatal intensive care unit

NIHR – National Institute for Health Research

Competing interests

None known.

Non-financial competing interests

<List of all collaborating CIs> are Chief Investigators for potentially eligible trials.

Authors' contributions <needs to be updated>

LD and LA conceived the idea. LD, ALS and LA drafted the protocol with input from all authors. All authors have agreed the final manuscript.

Acknowledgements

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Table 1: Fogarty review³⁵ of immediate versus deferred cord clamping for preterm births

Outcome	Number of trials	Number of participants	Risk ratio	95% confidence interval
<i>All infants born <37 wk</i>				
Hospital mortality	18	2538	0.68	0.52 to 0.90
Apgar score				
<4 at 1 minute	2	1600	0.82	0.67 to 1.00
<8 at 5 minutes	3	1683	1.03	0.91 to 1.17
Cardiorespiratory support at resuscitation	10	748	0.89	0.71 to 1.11
Intubation in the delivery room	6	532	0.96	0.82 to 1.13
Temperature on admission (°C, mean)	11	2317	-0.02 [§]	-0.07 to 0.3 [§]
Intraventricular haemorrhage				
any (grade 1 to 4)	19	2871	0.87	0.75 to 1.00
severe (grade 3 or 4)	11	2300	0.87	0.59 to 1.27
Periventricular leukomalacia	8	1977	0.71	0.39 to 1.27
Combined periventricular leukomalacia or porencephaly or echodense intraparenchymal lesions or ventriculomegaly	6	1920	0.77	0.56 to 1.06
Mechanical ventilation	9	686	0.95	0.84 to 1.07
Chronic lung disease ≥ 36 wk	7	1951	1.02	0.93 to 1.12
Patent ductus arteriosus	12	2397	0.96	0.84 to 1.09
Necrotising enterocolitis	12	2397	0.88	0.65 to 1.18
Late onset sepsis	10	2146	0.95	0.80 to 1.13
Severe retinopathy of prematurity	5	1893	0.74	0.51 to 1.07
Peak haematocrit %	2	1587	2.73 [§]	1.94 to 3.52 [§]
Blood transfusion	13	2595	0.81	0.74 to 0.87
Polycythemia (haematocrit >65%)	13	2529	2.65	1.61 to 4.37
Partial exchange transfusion	4	1743	0.14	0.01 to 2.74
Serum bilirubin peak (mean)	15	2358	4.43 [§]	1.15 to 7.71 [§]
<i>All infants born ≤28 wk gestation</i>				
Hospital mortality	3	996	0.70	0.51 to 0.95
Severe (grade 3 or 4) intraventricular haemorrhage	3	967	0.80	0.51 to 1.25
Chronic lung disease ≥ 36 wk	3	869	0.99	0.91 to 1.09
Necrotising enterocolitis	4	977	0.87	0.61 to 1.24
Late onset sepsis	3	925	1.07	0.87 to 1.31
Severe retinopathy of prematurity	2	839	0.72	0.47 to 1.09
Blood transfusion	2	941	0.91	0.85 to 0.97

[§] mean difference

SCBU=Special Care Baby Unit

Table 2: Eligible randomised trials to date for the pairwise and network meta-analysis with individual participant data on Cord Management at Preterm Birth (iCoMP) February 2019

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
Argentina ⁵³ (Carroli)	n/a	2016/2020	700	24-30 weeks GA	DCC – at 90 sec	Early cord clamping <30 sec	Sepsis (proven and very probable)
Australia ⁵⁴ (Badurdeen)	n/a	2018/2020	120 (not all preterm)	Infants greater than 32 weeks GA*	DCC: at least 1 minute	ICC	Average heart rate between 60-120 seconds after birth
Australia ⁵⁵ (McDonnell)	1997	1994/1994	46	26 to 33 weeks	DCC: 30 sec	ICC	Venous haematocrit
Australia ⁵⁶ (Kamlin)	n/a	2014/2015	27 (not all preterm)	32-42 weeks GA*	Arm 1: DCC - at 90-180 sec Arm 2: DCC – 10 sec after crying and breathing established	Early cord clamping <60 sec	Heart rate 90 sec after birth (measured by pulse oximetry and digital microphone enabled stethoscope)
Australia ⁵⁷ (Tarnow-Mordi)	n/a (Pilot for Tarnow-Mordi 2017)	2009/2010	100	<32 weeks GA	Arm 1: Cord milking - cord cut long (3 cm from placenta/introitus), milked during resuscitation Arm 2: DCC – at 30-60 sec infant below level of introitus/placenta. If baby in extremis, immediate clamping. Arm 3: DCC at 30 – 60 sec + milking	Immediate cord clamping within 10 sec	Haemoglobin 6 hours after birth
Australia ⁵⁸ (Tarnow-Mordi)	2017	2010/2019	1634	<32 weeks GA	DCC - ≥60 sec, baby positioned below placenta	ICC within 10 sec	Composite: Mortality or major morbidity (IVH, chronic lung disease, ROP, NEC, late onset sepsis) at 36 weeks

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
Austria ⁵⁹ (Urlesberger)	n/a	2018/2021	80 (not all preterm)	>=28 weeks*	DCC 30 cm, cord milking after long clamping at 30cm, 1x 10cm/sec	Standard care (cord cutting)	Cerebral blood volume (CBV) (within 15 min after birth) Changes in CBV (ml/100g brain)
Bangladesh ⁶⁰ (Yasmeen)	2015	2012/2013	40	Neonate delivered at less than 37 weeks of GA	DCC: cord clamped at 3 minutes	DCC: cord clamped at 1 minute	Haemoglobin (Hb), iron and ferritin
Canada ⁶¹ (El-Naggar)	2019	2011/2018	73	24-31 weeks GA	Cord milking x3, at or below the level of the placenta, ~20 cm milked, before clamping	ICC	Systemic blood flow (Superior vena cava flow at 4-6 hours)
Canada ⁶² (Murphy)	n/a	2007/2010	296	Singletons, 24-32 weeks GA	DCC – at 30-45 sec	ICC	Composite: IVH or late onset sepsis
China ⁶³ (Dai)	2014	n/a	31	Preterm infants	Wait until cord pulsation ceased	ICC: 5-10 sec	NA
China ⁶⁴ (Dong)	2016	n/a	90	<32 weeks	DCC: 45 sec	ICC: <10 sec	Routine blood test results, total amount of red blood cell transfusion, blood gas parameters, mean arterial pressure, bilirubin peak, total time of phototherapy, incidence rates of necrotizing enterocolitis, late-onset sepsis, intracranial haemorrhage, retinopathy, and bronchopulmonary dysplasia
China ⁶⁵ (Hao)	n/a	2018/2019	48	Preterm infants with GA of 30 to 31 + 6/7 weeks	UCM	DCC	Cerebral haemodynamics

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
China ⁶⁶ (Hu)	2015 (master's thesis)	n/a	120	28-35 weeks GA Vaginal birth	1. DCC 30 sec 2. DCC 60 sec 3. DCC 120 sec	ICC < 10 sec	Haematocrit and haemoglobin levels at 24 hours and 1 week after birth
China ⁶⁷ (Hua)	2010	2009/2011	176 (49 of those preterm)	Any GA*	<u>Normal birth</u> Arm 1: DCC – wait until cord ceases pulsing Arm 2: DCC – at 90 sec <u>Asphyxia</u> Arm 1: DCC – wait until cord ceases pulsing, resuscitate on bed site with cord intact	<u>Normal birth</u> Immediate clamping <10 sec <u>Asphyxia</u> Immediate clamping <10 sec, resuscitate after on irradiation table	Haemoglobin 1 month after birth
China ⁶⁸ (Li)	2018	2017/2017	102	Neonates who were delivered vaginally between 28 0/7 and 36 6/7 week and complicated by premature prolonged rupture of membranes	UCM: milked four times at a speed of 10cm/sec, then clamped	ICC: clamped and cut immediately	Incidence of certain or probable infection in neonates
China ⁶⁹ (Liu)	n/a	2019/2019	948 (not all preterm)	Neonates with GA between 34 weeks 0 day and 38 weeks 6 days*	DCC: 60 sec	ICC: within 10 sec	Rate of respiratory distress within 24 hours after birth
China ⁷⁰ (Shi)	2017	n/a	60 preterm (and 460 term)	Single foetus deliveries*	DCC	ICC 5-10 sec	Hemoglobin (newborn cord blood & after 24 h), neonatal complications, bleeding volume, third labour time, incidence of placental adhesion and peeling
China ⁷¹ (Xie)	n/a	2017/2019	300	Singletons, <34 weeks GA	UCM: X2-3, 25cm/2 sec, below placenta level, before clamping	ICC	Concentrations of Haemoglobin & Haematocrit, serum ferritin level (48 hours after birth)

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
Egypt ⁷² (Allam)	n/a	2018/2019	210	Premature babies at 30-34 weeks GA	ECC: first 5 sec	DCC: until cord stops pulsing or 1-2min	Fetal haemoglobin, neonatal death
Egypt ⁷³ (Nour 2017a)	n/a	2017/2019	90	Preterm infant <34 weeks GA	UCM: cord milked three times at 10cm/sec	ICC	Peripheral venous CD34 at admission
Egypt ⁷⁴ (Nour 2017b)	n/a	2017/2018	90	Preterm infant <34 weeks GA	Group A: ICC, with placental insufficiency Group B: DCC, with placental insufficiency	Normal placenta with DCC: 60 sec	Peripheral venous CD34 at admission
Germany ⁷⁵ (Nelle)	1998	n/a	19	PT <1500g*	DCC: 30 sec, 30 cm below placenta	ICC	Mean Blood Pressure (mmHg, Dinamap), left ventricular output (LVO, ml/kg/min), mean cerebral blood flow velocity (CBFV) in the Arteria carotis interna (ACI, m/s; Doppler-ultrasound), hemoglobin (Hb, g/dl), hematocrit (Hct, %), systemic and cerebral hemoglobin transport (HbT), systemic vascular resistance (SVR; mmHg/kg/min-1)
Germany ⁷⁶ (Rabe 2011)	2011	2006/2008	40	<33 weeks	DCC: 45 sec	DCC: 20 sec	Feasibility, effects on post-partal adaption and anaemia of prematurity
India ⁷⁷ (Agarwal)	2018	2013/2014	100	<34 weeks GA	DCC: at 120 sec	ICC \leq 30 sec	Hyperbilirubinemia and polycythemia within first 7 days

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
India ⁷⁸ (Aghai 2014)	2018	2014/2016	101 (not all preterm)	>35 weeks GA, baby depressed*	UCM: X3 before cord clamping, below placenta level	ICC	Feasibility (Number neonates cord milking), resuscitation efforts (ventilation, intubation, chest compression), short term resuscitation outcomes (5 min Apgar, severity Hypoxic Ischemic Encephalopathy, blood gas 1 hour)
India ⁷⁹ (Aghai 2018)	n/a	2018/2020	1400 (not all preterm)	Depressed neonates born between 35-42 weeks*	UCM: milked four times, milking 30cm over 2 sec	ICC: immediately after birth	Number of infants with moderate to severe HIE or death
India ⁸⁰ (Anusha)	n/a	2017/2019	148	Neonates with birth weight less than 1500g*	DCC: 30 sec	ICC: within 10 sec	Haemodynamic stability, haematological status, serum ferritin, and requirement of blood transfusion
India ⁸¹ (Bhriyuvanshi)	n/a	2017/not specified	236	Neonate > 28 weeks GA, requiring resuscitation*	UCM: milked three times towards baby at 10cm/sec, then clamped	ICC: within 30 sec	Haemoglobin (Hb) and hematocrit (Hct)
India ⁸² (Chopra)	2018	2013/2015	142	growth retarded babies (IUGR) born at and above 35 weeks of GA*	DCC: 60 sec	ICC: 10 sec	Hemoglobin and ferritin levels
India ⁸³ (Datta)	2017	2012/2013	120	34-36 weeks GA	DCC: at 30-60 sec	ICC: <20 sec	Neurobehavioural Assessment of Preterm Infant (NAPI) at 37 weeks post-conceptual age
India ⁸⁴ (Dhaliwal)	2014	n/a	300	34-37 weeks GA	DCC: 60 sec	ICC: <10 sec	Risk of neonatal mortality & abnormal neurological examination at 40 weeks GA
India ⁸⁵ (Dipak)	2017	2013/2014	78	27-31 weeks GA	1. DCC: 60 sec DCC 60 sec with intramuscular ergometrine	ICC: 10 s	Hematocrit 4 h after birth

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
India ⁸⁶ (George/Isac)	n/a	2017/2018	180 (not all preterm)	Mothers with a period of gestation between 34 and 40 6/7 *	UCM: milking whole length at 10cm/sec, three times, then clamped	ICC: no details	Infant haemoglobin (Hb) and hematocrit (Hct)
India ⁸⁷ (Gupta)	n/a	2018/2020	110	Preterm newborn babies born at <34 weeks	DCC	ICC	Ferritin and PCV
India ⁸⁸ (Ram Mohan)	2018	2014/2015	54	Preterm, requiring resuscitation	UCM: 20-25 cm umbilical cord x3, within 30 sec of birth	No milking	Haemoglobin at 6 weeks
India ⁸⁹ (Ranjit)	2015	2010/2010	100	30-36 ⁶	ICC	DCC: >2min	Hematocrit and serum ferritin, at 6 weeks
India ⁹⁰ (Kumar Mangla/ Thukral)	n/a	2016/2016	84 (not all preterm)	Late preterm and term neonates*	Deferred UCM: cord clamped at 60 sec	UCM: Cord milking in 10 sec	Venous haematocrit at 48 hours of life
India ⁹¹ (Upadhyay 2010)	2013	2010/2011	170 (not all preterm)	>35 weeks GA*	UCM	Non UCM	Haemoglobin and serum ferritin at 1 and 1.5 months
India ⁹² (Upadhyay 2013)	2015	2013/2014	200	32-36 weeks GA, vaginal or caesarean	UCM: X3, 10cm/sec	ICC: <30 sec	Haemoglobin and ferritin at 1.5 months
India ⁹³ (Varanattu)	n/a	2018/2019	250	Preterm infants <32 weeks GA	UCM: milked three times over 20 sec period towards infant at 20cm/2sec with 2 second pause between.	ICC: clamped immediately	Haemoglobin levels at birth and IVH (incidence and severity)
India ⁹⁴ (Venkateshan)	2018	2012/2013	434	30-33 weeks GA	DCC: 60 sec below placenta. If baby depressed, immediate clamping keeping cord long, milked x3 during resuscitation	ICC: within 10 sec	Mortality and/or abnormal neurological examination at 40 weeks postnatal age
Iran ⁹⁵ (Armanian)	2017	2015/2015	60	≤34 weeks GA	DCC: at 45 sec	ICC: <10 sec	Time of cord clamping

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
Iran ⁹⁶ (Haghshenas)	2017	2014/2015	54	<32 weeks GA, caesarean, birth weight < 1500g	DCC: at 30-45 sec	ICC: <10 sec	IVH (days 3 to 7), survival infant (up to 28 days)
Iran ⁹⁷ (Hemmati)	n/a	2012/2013	114	26-34 weeks GA	DCC: at 30-45 sec	ICC: 10-15 sec	IVH, 3-4 and 7-10 days
Iran ⁹⁸ (Mirzaeian)	n/a	2017/2018	160	Neonates with a GA of 28 to 34 weeks	UCM: milked three times in 20 sec	ICC	Amount of transfused blood, bilirubin levels
Iran ⁹⁹ (Sekhavat)	2008	n/a	52	Infants born 26-34 weeks GA	DCC: 30-60 sec	ICC: 10-15 sec	higher blood pressure (BP), hematocrit (Hct) and blood glucose (BS)
Iran ¹⁰⁰ (Shahgheibi)	n/a	2017/2018	90	Women with preterm labour	DCC: 180 sec	DCC: 30 sec	Blood parameters, weaning from ventilator, NICU discharge time
Ireland ¹⁰¹ (Dempsey)	n/a	2015/2016	45	<32 weeks GA	Arm 1: DCC – at 60 sec on mobile resuscitation trolley at/below placenta level Arm 2: UCM – Cord stripped 3 times at 20cm/2 sec at/below placenta level	ICC: <20 sec	Neonatal: Brain activity (6 & 12 hours post-partum, EEG and NIRS) Maternal: hemoglobin at 24-36 hours post-partum
Israel ¹⁰² (Kugelman)	2007	2004/2005	65	<35 weeks GA	DCC: 30-45 sec	ICC: 5-10 sec	initial serum complement (C3 and C4) and immunoglobulins (IgG, IgM)
Japan ²⁵ (Hosono 2008a)	2008	2001/2002	40	24-28 weeks GA, singletons	UCM: 20 cm of the cord, 2-3x, before clamping, 20cm/2sec	ICC	Probability of not needing transfusion, determined by Kaplan–Meier analysis number of RBC transfusions
Japan ¹⁰³ (Hosono 2008b)	n/a	2008/2016	566	24-28 weeks GA	UCM: cord cut 30 cm from infant, cord milked x1	ICC: <30 sec	1) Probability needing transfusion and death 2) Amount of blood transfusion first 4 weeks

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
Korea ¹⁰⁴ (Song)	2017	2012/2015	66	Neonate delivered between 24 0/7 and 32 6/7 weeks	UCM: milked four times at speed of 20cm/2sec, with 2sec pause between	ICC: immediately after delivery	Short term safety: Apgar score, prevalence of hypothermia, early intubation, initial blood gas analyses, bilirubin levels, duration of phototherapy, use of cross-transfusion, and respiratory distress.
Nepal ¹⁰⁵ (Andersson)	2017	2014/2017	540 (not all preterm)	34-41 weeks GA*	DCC: at ≤180 sec	ICC: ≤30 sec	Haemoglobin at 8±1 months
Nepal ¹⁰⁶ (Ashish KC)	n/a	2016/2016	1510 (not all preterm)	Singletons, ≥33 weeks GA*	DCC: at ≥180 sec	ECC: <60 sec	Neonatal heart rate continuously until 10 min after birth and at 1,3&5 min
Netherlands ¹⁰⁷ (Te Pas)	n/a	2019/2020	660	<30 weeks GA	Physiology-based cord clamping (PBCC): Resuscitation with cord intact, clamp when infant is stable (heart rate >100 bpm, oxygen>80%, supplemental oxygen <40%)	DCC: 30-60 sec, clamping before resuscitation	Intact survival at NICU discharge (without cerebral injury (IVH ≥ grade 2 and/or PVL ≥ grade 2 and/or periventricular venous infarction) and/or NEC (Bell stage ≥ 2)
Netherlands ¹⁰⁸ (Ultee)	2008	n/a	37	34 to 36 weeks GA	DCC: 3 min	ICC: <30 sec	haemoglobin and ferritin levels (at 10 weeks)
Pakistan ¹⁰⁹ (Malik)	2013	2009-2009	80	30-37 weeks GA	DCC: 120 sec	DCC: 30 sec	Hematocrit
Saudi Arabia ¹¹⁰ (Al-Wassia)	n/a	2017/2019	180	Preterm infants <32 weeks GA	UCM: milked 20cm segment over 2-3 sec three times	DCC: 60 sec	IVH

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
Saudi Arabia ¹¹¹ (Gomaa)	n/a	2016/2018	200	Infants 23 to 34 + 6/7 weeks GA	DCC: 45-60 sec before clamping, with baby at level or below placenta	UCM: milked 4-5 times from maternal end of cord to baby abdomen, 2 sec pause between milking	Haematological parameters of neonates - hematocrit (Hct) level
South Africa ¹¹² (Hofmeyr 1988)	1988	n/a	38	<35 weeks	DCC: 1 min & ergometrine	ICC	PVH/ IVH
South Africa ¹¹³ (Hofmeyr 1993)	1993	n/a	86	<2000 g birthweight*	DCC 1-2 min	ICC	PVH/ IVH
South Africa ¹¹⁴ (Tiemersma)	2015	2012/2012	102 (not all preterm)	Birth weight <2500g ± 500g*	DCC: at 2-3 minutes	ICC: within 30 sec	Haemoglobin at 2 months
Spain ¹¹⁵ (De Paco Matallana)	n/a	2011/2014	100	24- 34 weeks GA	DCC: at 45-60 sec	ICC: <10 sec	Neonatal haemoglobin, haematocrit and bilirubin levels (within 7 days after birth)
Spain ¹¹⁶ (Domingo Puiggrós)	n/a	2014/2016	40	<34 weeks GA, caesarean	UCM: X3 at 20 cm/2sec	DCC: 30 sec	Haemoglobin (at 1 and 24 hours)
Spain ¹¹⁷ (Leal)	2019	n/a	138	24 + 0/7 until 36 + 6/7 weeks	UCM	ICC	Red blood cell transfusion, phototherapy
Spain ¹¹⁸ (Socias)	n/a	2014/2017	150	26-32 weeks GA	DCC – at 30-60 sec	ICC: <30sec	Red blood cell transfusions (number & volume), IVH, postpartum haemorrhage
Switzerland ¹¹⁹ (Baenziger)	2007	1996/1997	39	24-32 weeks	DCC: 60-90 sec, below placenta	ICC: <20 sec	Cerebral oxygenation
Taiwan ¹²⁰ (Shen)	n/a	2015/2019	100	Preterm infants born at less than 30 weeks GA	UCM: milked one time, 20cm section at speed of 10cm/sec and clamped at 2-3cm.	ICC and no milking	Neonate's hemoglobin, hematocrit, and mean arterial pressure at admission
Thailand ¹²¹ (Chamnanvanakij)	2017	2015/2016	46	25-34 weeks GA	UCM: X3-4 , 30 cm, before clamping	DCC: at 60 sec	Haematocrit level (2 hours after birth)

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
Thailand ¹²² (Jomak)	n/a	2018/2018	110	Singleton preterm pregnancy at 24 weeks to 36 + 6 /7 weeks GA	ICC	DCC	Hematocrit (Hct)
Thailand ¹²³ (Mungkornkaew)	2015	2014/2014	200 (not all preterm)	Singleton, GA 34-42 weeks*	DCC: 2 minutes	DCC: 1 minute	Fetal hematocrit, hemoglobin and microbilirubin
Thailand ¹²⁴ (Panichkul)	n/a	2015/2016	170	34-36 weeks GA	DCC: at 60 sec	ICC: at 10 sec	Haematocrit 2 hours after birth
Thailand ¹²⁵ (Ruangkit)	2019	2016/2017	100	Multiples, 28-36 weeks GA	DCC: at 30-60 sec	ECC: <10 sec	Haematocrit level at birth
Thailand ¹²⁶ (Salae)	2016	2014/2015	86	34-36 weeks GA	DCC: at 2 minutes	ECC: within 30 sec	Haematocrit at 48 hours
Thailand ¹²⁷ (Tanthawat)	n/a	2016/2016	40	<32 weeks GA	UCM: Cut cord at 30cm, cord milking x1, 10cm/sec.	ECC: <10 sec	Haemoglobin and Haematocrit level at admission
Turkey ¹²⁸ (Alan)	2014	2011/2013	44	≤32 weeks GA ≤1500 g	UCM: at 25-30 cm, X3, 5cm/s, below placenta level	ICC: <10 sec	Packed red blood cell (PRBC) transfusion and hematologic and hemodynamic parameters
Turkey ¹²⁹ (Gokmen)	2011	2008/2009	42	<32 weeks GA	DCC: 30-45 sec	ICC: 5-10 sec	peripheral hematopoietic progenitor cells (HPCs) and haematological parameters
Turkey ¹³⁰ (Kilicidag)	2015	2012/2013	54	PT ≤ 32 weeks GA	UCM: X4 before clamping (20cm/2sec)	ICC	absolute neutrophil counts (ANCs) and the neutropenia frequency
Turkey ¹³¹ (Silahli)	2018	2015/2016	75	<32 weeks GA	UCM: at 20 cm, 3x, before clamping	ICC <10s	Thymic size
UK ¹³² (Aladangady)	2006	n/a	46	24-32 ⁶ weeks GA	DCC: 30-90 sec, below placenta, oxytocic agent, with ventilation/ resuscitation if necessary	ICC	Infants' blood volumes.

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
UK ¹³³ (Duley)	2017	2013/2017	260	<32 weeks GA	DCC: after at least 2 min	ECC: <20 sec	Feasibility: Recruitment, compliance, retention, completeness data, patient views
UK (Holland)	Not published	1998/2001		<33 weeks' gestation	DCC 40-90 s	ICC (?)	Median arterial/alveolar PO2 ratio over the first 24 hours of life
UK ¹³⁴ (Kinmond)	1993	n/a	36	27-32 weeks GA, vaginal delivery	Conventional management (ICC): 10 sec median	DCC 30 sec, 20 cm below placenta	Initial packed cell volume, peak serum bilirubin concentrations, red cell transfusions, respiratory impairment
UK ¹³⁵ (Rabe)	2011	2006/2008	58	Singletons, <34 weeks GA	UCM	DCC: Slight deferral in cord clamping time	Acceptability of cord clamping methods
UK ¹³⁶ (Weeks)	n/a	n/a (protocol, not funded/started to date)	7242 (not all preterm)	All births*	DCC: clamped once it has stopped pulsating or at least 5 minutes after birth	ICC: within 30 sec of birth	Developmental delay and/or behaviour problem
USA ¹³⁷ (Backes)	2016	2009/2013	40	22.5-27.6 weeks	DCC: 30-45 sec, Below placenta	ICC: 5-10 sec	Safety, feasibility, haematological and circulatory outcomes
USA ¹³⁸ (Bauer)	n/a	2014/2019	400	24-29 weeks GA	Arm 1: DCC – at 45 sec and indomethacin within 6hrs Arm 2: DCC – at 45 sec and placebo within 6hrs	Arm 3: ICC and indomethacin Arm 4: ICC and placebo	Survival at 38 weeks with no severe IVH (grades 3/4) or PVL
USA ¹³⁹ (Berens)	n/a	2018/2019	100 (not all preterm)	>35 weeks GA*	DCC: 60 sec	ECC: <15 sec	Neonatal bilirubin level [Time Frame: 24 hours after birth]

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
USA ¹⁴⁰ (Bienstock)	n/a	2011/2013	22	24 - 32 weeks GA	UCM: X4 over 10 min	ICC	Haemoglobin (within 24 hours of birth and through NICU stay)
USA ¹⁴¹ (deVeciana)	2013	2009/2011	113	Singletons, 24-28 weeks GA	UCM: 10cm, immediately after delivery	ICC	Red blood cell transfusion (within 28 days of life)
USA ¹⁴² (Driggers)	n/a	2011/2013	2	Infants delivered at 24 to 28 + 6/7 weeks GA	DCC: 30 sec UCM: milking four times in 10 sec	ICC	Adverse neonatal event: composite of bronchopulmonary dysplasia, NEC, grade 3 or 4 IVH or PVL, or death
USA ¹⁴³ (Elimian)	2014	2006/2011	200	Singletons, 24-34 weeks GA	DCC: at 30-35 sec	ICC: <5 sec	Need for blood transfusion
USA ¹⁴⁴ (Garg)	n/a	2016/2018	5	<32 weeks GA	UCM: X2, before clamping	ICC	Cerebral oxygenation and function (first 24 hours of life)
USA ¹⁴⁵ (Josephsen)	n/a	2012/2016	64	24-27 weeks GA	UCM: below level of placenta and ~20 cm cord milked x3 over 10-20 sec before clamping	ICC	Haemoglobin and haematocrit concentrations (within 4 hrs birth) Incidence and number blood transfusions until discharge
USA ¹⁴⁶ (Katheria 2011)	2014	2011/2013	60	<32 weeks GA	UCM: milking X3, below placenta, about 20 cm of cord over 2 sec	ICC	Superior vena cava flow at 6 hours
USA ¹⁴⁷ (Katheria 2013)	2015 & 2017	2013/2018	197	23-31 weeks GA	UCM: X4 at 20 cm/2 sec	DCC – at 45-60 sec	Superior vena cava flow at <12 hours
USA (Katheria 2017)	n/a	2017/2022	1200	Infants 23 to 32 + 6/7 weeks GA	UCM: milking four times at 20cm/2sec	DCC: at least 60 sec	Incidence of IVH or death

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
USA (Katheria 2019)	n/a	2019/2020	1000 (not all preterm)	Non-vigorous newborns born between 35-42 weeks GA*	UCM: milking four times, entire umbilical length over 2 sec.	ICC: average 20 sec	Admission to NICU
USA ¹⁴⁸ (Kattwinkel)	n/a	2016/2021	940	23-28 weeks GA	Assisted Ventilation (face mask, Continuous Positive Airway Pressure or Positive Pressure Ventilation) prior to DCC at 120 sec	DCC: 30-60 sec, assisted ventilation only after cord clamping	IVH on head ultrasound (7-10 days)
USA (Krueger)	2015	2012/2013	67	Singletons, 22-31 ⁶ weeks GA	DCC: (30 sec) with cord milking	DCC: (30 sec) without cord milking	Initial fetal hematocrit
USA ¹⁴⁹ (Martin)	n/a	2012/2014	72	Singletons, 23-37 weeks GA	Arm 1: DCC – at 60 sec Arm 2: DCC – at 40 sec	ECC: 20 sec	IVH number and severity (15 months)
USA ¹⁵⁰ (Mercer 2003a)	2003	1998/2001	32	24 to 32 weeks GA	DCC: 30-45 sec	ICC: 5-10 sec	Initial blood pressure
USA ¹⁵¹ (Mercer 2003b)	n/a	2003/2006	58	Singletons, <34 weeks gestation	DCC: 30-45 sec, below placenta	ICC	Acceptability of cord clamping methods
USA ¹⁵² (Mercer 2006)	2006	2003/2004	72	<32 weeks GA	DCC:30-45 sec	ICC: 5-10 sec	bronchopulmonary dysplasia (BPD) and suspected NEC (SNEC)
USA ¹⁵³ (Mercer 2008)	2011 & 2016 & 2018	2008/2014	211	24-31 weeks GA	DCC & UCM - 30 - 45 sec, below placenta level, cord milking x1 at end of time, before clamping. If clamping cannot be deferred, cord milked x2-3	ICC: <10 sec	IVH, late onset sepsis
USA ¹⁵⁴ (Oh)	2011	2000/2001	54	Singletons, 24-27 weeks GA	DCC: at 30-45 sec	ICC: <5 sec	Number of infants enrolled in the pilot within 6 months
USA ¹⁵⁵ (Perlman)	n/a	2015/2019	150	28-34 weeks GA	DCC: at 60 sec	DCC: at 30 sec	Haematocrit 1 hour after birth

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
USA ¹⁵⁶ (Smith)	n/a	2014/2018	240	23-34 weeks GA	UCM: X4, before clamping, below placenta level	DCC: at 30 sec, below placenta level	Haemoglobin & Haematocrit in NICU (~50 days)
USA (Strauss)	2008	n/a	158	Neonates ≤36 weeks GA	DCC: 60 sec	ICC	Red blood cell volume/mass, per biotin labelling
USA (Yared/Young)	n/a	2015/2016	39	Very low birth weight (500 to 1500 grams)*	DCC: at 60 sec	DCC: at 30 sec	IVH (during NICU admission up to 6 months)
Thailand Pongmee 2010	2010 (abstract)		43	<35 weeks GA	Milking 2x along 30 cm after cutting	ICC	Initial haematocrit, need for blood transfusion, morbidity
Medina 2014				Premature neonates	DCC		Haemodynamic parameters

* only those born <37 weeks gestation eligible

NEC = necrotising enterocolitis; GA = gestational age; DCC = deferred cord clamping; ROP = retinopathy of prematurity; IVH = intraventricular haemorrhage; PVL = periventricular leukomalacia; EEG = electroencephalogram; NIRS = near-infrared spectroscopy; cm = centimetres; sec = seconds, NICU = Neonatal intensive care unit; UCM = umbilical cord milking; ECC = early cord clamping; ICC = immediate cord clamping

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