# Caring for babies born too soon:

# perspectives from high and low resource settings

Eleanor J Mitchell

Associate Professor of Clinical Trials, Nottingham Clinical Trials Unit

School of Medicine, University of Nottingham

2021

Thesis submitted for the degree of Doctor of Philosophy

December 2021

“It always seems impossible until it’s done”

- Nelson Mandela

*For all the small and sick babies around the world - you are not forgotten*

## ACKNOWLEDGMENTS

There are many people to thank and acknowledge, but I'd like to start with some personal reflections. I have never particularly believed I'm academic: I left school at the age of sixteen, didn't study A levels and didn't go to university. I've had the privilege of working with many great people over the years who have supported me professionally and encouraged me to continue learning and be inquisitive. Having studied part-time for an undergraduate degree whilst working in my early twenties, I never thought I'd study again, particularly as a working Mum. Yet here I am in my early forties having had the support and encouragement to pursue an academic career and write this thesis. To my 16-year-old self, believe in yourself, surround yourself with amazing people who are a joy to work with and work hard, and you'll achieve your dreams.

I don't want this to sound like an Oscar speech, but there are many, many people to thank. To Mike and Sally Doherty – thank you for giving your "3rd daughter" my first research job, for believing in me and supporting me to do a business degree, I am eternally grateful. Thank you to Lelia Duley who led the first perinatal study I worked on and gave me my first opportunity working in global health – you definitely gave me the bug! To Jon Dorling for giving me my first glimpse into the world of neonatology and for introducing me to Shalini Ojha. To Lucy Bradshaw for holding my hand and showing me the ropes when the statistics got too hard and for always being patient. To Phoebe Pallotti for putting up with my many imposter syndrome moments and for teaching me how to do qualitative data analysis. To the many members of the team at the hospitals in Kenya, India, Uganda and Pakistan – in particular Zahida Qureshi and Jacque Opira at Kenyatta National Hospital. Working on global health studies is extremely challenging but very rewarding and I have had the opportunity to meet some wonderful people during these studies.

Huge thanks to my colleague and friend, Shalini Ojha. We make a great team and I am eternally grateful to you for believing in me: long may our working partnership and friendship continue. You're a joy to work with. Thank you for all your words of wisdom and support throughout this journey. To the many other neonatologists with whom I have had the opportunity to work with – must be something about the specialty, but

I've never met a neonatologist whom I didn't like! Of course, thank you to all the parents and infants who have participated in the studies, both UK and abroad.

Thank you to Jane Daniels, Alan Montgomery and Kate Walker who gave me encouragement to move my academic career forwards and to do this PhD, and for your advice throughout. I am super proud of the work we do at the Nottingham Clinical Trials Unit and hope we'll continue to design and conduct excellent research studies for a long time to come.

To my children, James and Lucy, for putting up with me when I've been stressed, away on long-haul trips for the global health studies and trying to juggle too many things at once – now do you believe I am a scientist?! Thank you to my lovely Mum and Dad who are always there to support in any way they can. Finally, thank you to Diane for your unwavering, eternal love. You were right. I can do it.

Lastly, I'd like to briefly reflect upon the COVID-19 pandemic that has sadly had such a catastrophic effect on so many lives and changed the world we live in. Much of this thesis, outwith the published works, was written during many months of lockdown and for that, I am grateful to the pandemic for putting a temporary pause on life allowing me to write this.

# TABLE OF CONTENTS

**ACKNOWLEDGMENTS** ..... **3**

**TABLE OF CONTENTS** ..... **5**

**LIST OF FIGURES** ..... **7**

**LIST OF TABLES** ..... **8**

**LIST OF IMAGES** ..... **9**

**LIST OF APPENDICES** ..... **10**

**ABBREVIATIONS** ..... **11**

**1. EXTENDED ABSTRACT** ..... **16**

1.1 Introduction, aims and outline of thesis ..... 16
1.1.1 Introduction ..... 16
1.2.1 Aims ..... 16
1.1.3 Objectives ..... 17
1.1.4 Outline of the thesis ..... 18

1.2 Preterm birth – "where you're born matters" ..... 20
1.2.2 Global disparity in neonatal mortality rate ..... 21
1.2.3 Global efforts to reduce neonatal mortality ..... 22
1.2.4 Importance of focussing on prematurity and low-birth weight infants ..... 24

1.3 Essential newborn care of infants ..... 25
1.3.1 Kangaroo Mother Care (KMC) ..... 26
1.3.2 Thermal regulation ..... 27
1.3.3 Resuscitation ..... 28
1.3.4 Infection management ..... 29
1.3.5 Nutrition and feeding ..... 30
1.3.6 Summary ..... 31

1.4. Part 1: Early Warning scores (published works 1, 2) ..... 32
1.4.1 Background, existing evidence and gaps in knowledge ..... 32
1.4.2 Objectives ..... 37
1.4.3 Methods ..... 37

1.5 Part 2: Timing of umbilical cord clamping (published works 3) ..... 41
1.5.1 Background, existing evidence and gaps in knowledge ..... 41
1.5.2 Objective ..... 43
1.5.3 Methods ..... 44

1.6 Part 3: High quality and efficient neonatal trials (published works 4-6) introduction ..... 46
Part 3a: 1.7.1 Background to the FEED1 Trial ..... 49
1.7.2 Objectives ..... 50
1.7.3 Methodological considerations in the FEED1 Trial ..... 51

1.8 Part 3B: Consent in neonatal trials (published works 5) ..... 57
1.8.1 Background, existing evidence and gaps in knowledge ..... 57
1.8.2 Objective ..... 63
1.8.3 Methods ..... 64

1.9 Part 3C: Training of staff working on clinical trials (published works 6) ..... 68
1.9.1 Background, existing evidence and gaps in knowledge ..... 68

1.9.2 Objectives ..... 71
1.9.3 Methods ..... 72

**2. THE PUBLISHED WORKS ..... 78**

PAPER 1: Feasibility of using an Early Warning score for preterm or low-birth weight infants in a low resource setting: results of a mixed-methods study at a national referral hospital in Kenya ..... 79

PAPER 2: Parents, healthcare professionals and other stakeholders' experiences of caring for babies born too soon in a low-resource setting: a qualitative study of essential newborn care for preterm infants in Kenya ..... 80

PAPER 3: Identifying women giving birth preterm and care at the time of birth: a prospective audit of births at six hospitals in India, Kenya, Pakistan and Uganda ..... 81

PAPER 4: The FEED1 Trial: Protocol for a randomised controlled trial of full milk feeds versus intravenous fluids with gradual feeding for preterm infants (30-33 weeks gestational age) ..... 82

PAPER 5: Implementing two-stage consent pathway in neonatal trials ..... 83

PAPER 6: Evaluation of an enhanced training package to support clinical trials training in low and middle income countries (LMICs): experiences from the Born Too Soon Optimising Nutrition study ..... 84

**3. DISCUSSION ..... 85**

3.1 Objectives reviewed ..... 85

3.2 Contribution to knowledge and impact ..... 93

3.3 Critical review and recommendations for future research ..... 95
3.3.1 Part 1: Early warning scores ..... 98
3.3.2 Part 2: Timing of umbilical cord clamping ..... 103
3.3.3 Part 3a: High quality and efficient neonatal trials: design and methodological aspects of the FEED1 trial ..... 106
3.3.4 Part 3B: High quality and efficient neonatal trials: consent in neonatal trials ..... 110
3.3.4 Part 3C: High quality and efficient neonatal trials: training staff working in clinical trials ..... 112

**4. CONCLUSIONS ..... 116**

**REFERENCES ..... 118**

**APPENDICES ..... 129**

# LIST OF FIGURES

Figure 1 - Global causes of neonatal death (death within first 28 days of life) in 2017[6] ..... 20
Figure 2 - Neonatal Mortality rate 1999-2019 in countries included in this thesis..... 22
Figure 3 - United Nations Sustainable Development Goals (2016) [13] ..... 23
Figure 4 - Key aspects of essential newborn care ..... 25
Figure 5 - Causes of neonatal deaths in Kenya in 2018 ..... 29
Figure 6 - National Early Warning Score [64]..... 32
Figure 7 – Newborn Early Warning Track and Trigger (NEWTT)[69]..... 34
Figure 8 - Levels of Evidence-based medicine ..... 47
Figure 9 - Themes identified from framework synthesis[120] ..... 57
Figure 10 - FEED1 participant pathway..... 62
Figure 11 - Example of an oral assent conversation (post-natal)..... 66
Figure 12 - QR code for animation to support an oral assent conversation ..... 67
Figure 13 - Enhanced training package in Born Too Soon Optimising Nutrition Study..... 72

# LIST OF TABLES

Table 1 – Authors' contributions ..... 14
Table 2 - Preterm birth and neonatal mortality rate ..... 21
Table 3 - FEED1 Trial PICO ..... 51
Table 4 - FEED1 Trial eligibility criteria ..... 52
Table 5 - Themes identified from qualitative sub-study[122, 123] ..... 60
Table 6 - Initiatives to support implementation of the two-stage consent pathway ..... 65
Table 7 - Minimal information to include in an oral assent conversation in FEED1 ..... 65
Table 8 - Questionnaires to evaluate the training package ..... 75
Table 9 - Objectives reviewed ..... 86
Table 10 - Strengths and limitations of the research ..... 95

# LIST OF IMAGES

Image 1 - Mother and baby doing KMC ..... 26
Image 2 - Networking meeting in Kenya, July 2019 ..... 39
Image 3 - Born Too Soon Optimising Nutrition Study, training sessions in India and Kenya, December 2019 ..... 73

# LIST OF APPENDICES

1 – Cord Pilot Trial: protocol publication

2 – Cord Pilot Trial: results at outcome at discharge publication

3 – Cord Pilot Trial: results at 2 years publication

4 - Feed1 oral assent baseline survey questions

5 – Feed1 oral assent additional documentation

6 – Questionnaires to evaluate the enhanced training package

## ABBREVIATIONS

| | |
|---|---|
| CI | Confidence Interval |
| COVID | Corona Virus disease |
| CPAP | Continuous Positive Airway Pressure |
| CSV | Comma Separated Value |
| CTU | Clinical Trials Unit |
| DCC | Delayed Cord Clamping |
| DBM | Donor Breast Milk |
| ECRIN | European Clinical Research Infrastructure Network |
| EWS | Early Warning Score |
| FEED1 | Fluids Exclusively Enterally from Day 1 Trial |
| GCP | Good Clinical Practice |
| GCRF | Global Challenges Research Fund |
| HIC | High income country |
| HIE | Hypoxic Ischaemic Encephalopathy |
| HRB-TMRN | Health Research Board – Trials Methodology Research Network |
| HTA | Health Technology Assessment |
| ICH | International Conference on Harmonisation |
| ICTMC | International Clinical Trials Methodology Conference |
| IQR | Inter Quartile Range |
| IV | Intravenous |
| KMC | Kangaroo Mother Care |
| LBW | Low Birth Weight |
| LMIC | Low and Middle Income Country |
| LMP | Last Menstrual Period |
| LOS | Late Onset Sepsis |
| MD | Mean Deviation |
| MDG | Millennium Development Goal |
| MOEWS | Modified Obstetric Early Warning System |
| MRC | Medical Research Council |
| NCTU | Nottingham Clinical Trials Unit |
| NEC | Necrotising enterocolitis |

| | |
|---|---|
| NEWS | National Early Warning Score |
| NEWTT | Neonatal Early Warning Track and Trigger System |
| NHS | National Health Service |
| NICU | Neonatal Intensive Care Unit |
| NIHR | National Institute for Health Research |
| NMR | Neonatal Mortality Rate |
| NPV | Negative Predictive Value |
| PEEP | Positive End-Expiratory Pressure |
| PEWS | Paediatric Early Warning Score |
| PICO | Population, Intervention, Control, Outcome |
| PPI | Patient and Public Involvement |
| PPV | Positive Predictive Value |
| QR | Quick Response Code |
| RCOG | Royal College of Obstetricians and Gynaecologists |
| RCP | Royal College of Physicians |
| RCT | Randomised Controlled Trial |
| RDS | Respiratory Distress Syndrome |
| SCAMP | Standardised Concentrated Additional Macronutrients Parenteral Nutrition in very preterm infants trial |
| SDG | Sustainable Development Goals |
| SIFT | Speed of Increasing milk Feeds trial |
| SIV | Site Initiation Visit |
| SPIRIT | Standard Protocol Items: Recommendations for Interventional Trials |
| STEPS | Strategies for Trial Enrolment and Participation Study |
| SWAT | Study Within a Trial |
| TGHN | The Global Health Network |
| TMG | Trial Management Group |
| TMRP | Trials Methodology Research Partnership |
| UI | Uncertainty Interval |
| UK | United Kingdom |
| UKAMB | UK Association of Milk Banks |
| UKCRC | United Kingdom Clinical Research Collaboration |

| | |
|---|---|
| UKRI | United Kingdom Research and Innovation |
| UN | United Nations |
| UNICEF | United Nations Children's Fund |
| VLBW | Very Low Birth Weight |
| WHO | World Health Organisation |

**Table 1 – Authors' contributions**

The numbers in each box correspond with the number of the published works included in the thesis. For ease, these are listed below as footnotes. Authors are given in alphabetical order, by surname.

| Authors' initials | Original idea / conception | Study design | Study coordination (inc. set-up, training, oversight/ management) | Data acquisition | Data analysis | Results interpretation | Wrote first draft of manuscript | Edited versions of manuscript |
|---|---|---|---|---|---|---|---|---|
| ELEANOR MITCHELL | 1, 2, 5, 6 | 1-6 | 1-6 | 6 | 1, 2, 5, 6 | 1-3, 5-6 | 1-6 | 1-6 |
| Jalemba Aluvaala | | | 6 | | | 6 | | 6 |
| Josie Anderson | | 4 | 4 | | | | | 4 |
| Santosh Benjamin | | | 3 | 3 | | 3 | | 3 |
| Lucy Bradshaw | | | 6 | | 1, 6 | 1, 6 | | 1, 6 |
| Jane Daniels | | | 1, 6 | | | 1, 2, 6 | | 1, 2, 6 |
| James Ditai | | | 3 | 3 | | 3 | | 3 |
| Jon Dorling | 4 | 4 | 4-5 | | | 5 | | 4-5 |
| Lelia Duley | 3 | 3 | 3 | | | 3 | 3 | 3 |
| Chris Gale | | 4 | 4, 5 | | | | | 4, 5 |
| Peter Godolphin | | | | | 3 | 3 | | 3 |
| George Gwako | | | | 1 | | 1, 2 | | 1, 2 |
| Rachel Haines | | | 4 | | | | | 4 |
| Mark Johnson | | 4 | 4, 5 | | | | | 4, 5 |
| Charlotte Kenyan | | 4 | | | | | | 4 |
| Violet Kimani | | | 2 | 2 | | 2 | | 2 |
| Ashok Kumar | | | 6 | | | 6 | | 6 |
| William McGuire | | 4 | 4, 5 | | | | | 4, 5 |
| Garry Meakin | | | 4 | | | | | 4 |
| Hema Mistry | | 4 | 4 | | | | | 4 |
| Alan Montgomery | | 4 | 4 | | | | | 4 |
| Shabeen Naz Masood | | | 3 | 3 | | 3 | | 3 |
| Sam Oddie | | 4, 5 | 4, 5 | | | 4, 5 | | 4, 5 |
| Reuben Ogollah | | 4 | 4 | | | | | 4 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Shalini Ojha | 4 | 1, 4, 8 | 1, 4-6 | | | 1, 2, 5, 6 | | 1, 2, 4-6 |
| Mary Oliver | | 6 | 1, 2, 6 | | 2 | 1, 2, 6 | | 1, 2, 6 |
| Sam Ononge | | | 3 | 3 | | 3 | | 3 |
| Jacqueline Opira | | | 1, 2, 6 | | | 1, 2, 6 | | 1, 2, 6 |
| Alfred Osoti | | | | 1 | | 1, 2 | | 1, 2 |
| Phoebe Pallotti | | 2, 4 | 1, 2, 6 | | 2 | 1, 2, 6 | | 1, 2, 4, 6 |
| Christopher Partlett | | 4 | 4 | | | | | 4 |
| Zahida Qureshi | | | 1-3, 6 | 1, 3 | | 1-3, 6 | | 1-3, 6 |
| Richard Swinden | | | 6 | 6 | | 6 | | 6 |
| Kate Walker | | 4 | | | | | | 4 |
| Fredrick Were | | | 1-2, 6 | 1 | | 1, 2, 6 | | 1, 2, 6 |
| Diane Whitham | | 3 | 3 | | | 3 | | 3 |

- Paper 1: Feasibility of using an Early Warning score for preterm or low-birth weight infants in a low resource setting: results of a mixed-methods study at a national referral hospital in Kenya
- Paper 2: Parents, healthcare professionals and other stakeholders' experiences of caring for babies born too soon in a low-resource setting: a qualitative study of essential newborn care for preterm infants in Kenya
- Paper 3: Identifying women giving birth preterm and care at the time of birth: a prospective audit of births at six hospitals in India, Kenya, Pakistan and Uganda
- Paper 4: The FEED1 trial: protocol for a randomised controlled trial of full milk feeds versus intravenous fluids with gradual feeding for preterm infants (30-33 weeks gestational age).
- Paper 5: Implementing two-stage consent pathway in neonatal trials
- Paper 6: Evaluation of an enhanced training package to support clinical trials training in low and middle income countries (LMICs): experiences from the Born Too Soon Optimising Nutrition Study

# 1. EXTENDED ABSTRACT

## 1.1 Introduction, aims and outline of thesis

### *1.1.1 Introduction*

This thesis contains six publications on the topic of interventions for infants who are born prematurely, i.e. before 37 weeks gestation, in high and low resource settings. Prematurity is the leading cause of death in the first month of life[1]. Death from 'neonatal conditions' is the fifth leading cause of **all** deaths worldwide and the **leading** cause of all deaths in low resource settings[2]. Evaluating interventions to reduce neonatal mortality is critical to reduce this alarming statistic.

### *1.2.1 Aims*

To examine a range of interventions for neonatal care and the management of preterm birth, both in high and low resource settings, and to explore some of the challenges in conducting neonatal studies, in the United Kingdom (UK) and in low and middle income countries (LMICs).

Specific research questions are:

- Is it feasible to implement an early warning score in neonatal units in LMICs?
- What are the barriers and facilitators to essential newborn care in LMICs?
- Is it feasible to conduct a clinical trial comparing timing of cord clamping at preterm birth?*
- What are current practices at the time of preterm birth in LMICs?
- What are the methodological considerations when designing a clinical trial (The FEED1 Trial*) of a feeding intervention for preterm infants?
- What strategies are required to implement a two-stage consent pathway in neonatal intervention studies?
- Does an enhanced training package improve researchers' knowledge of clinical trials?

Of the research questions above, two studies (indicated with an asterisk above) are in line with three of the top fifteen research priorities for preterm birth. A Priority Setting Partnership, involving people affected by preterm birth (e.g. parents) and healthcare professionals in the UK and Republic of Ireland, was conducted using methods established by the James Lind Alliance[3]. The top fifteen research priorities included:

- How can infection in preterm babies be better prevented?
- 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?
- Which interventions are most effective to prevent necrotising enterocolitis in premature babies?
- When is the best time to clamp the umbilical cord in preterm birth?

In addition, a similar priority setting exercise, involving global experts, was published in 2016[4]. The top ten priorities for improving newborn health and birth outcomes by 2025 (ranked by 91 experts) included the following, both addressed in the published works contained in this thesis:

- Can simple clinical algorithms used by child health workers identify and refer neonates with signs of infection and consequently reduce newborn mortality?
- How can quality of care during labour and birth be improved to reduce intrapartum stillbirths, neonatal mortality and disability?

### *1.1.3 Objectives*

The thesis is sub-divided into three specific themes, all of which are introduced within this extended abstract. The objectives for each theme are outlined in the relevant section. In addition, two further sub-sections are included in this chapter, for context, both of which are relevant to the overall theme and sub-themes: “Preterm birth – “where you’re born matters” and “essential newborn care”.

### *1.1.4 Outline of the thesis*

**Part One: Early Warning Scores**

**Paper 1** presents developmental work undertaken in Kenya to determine if a neonatal early warning score could be useful in a low resource setting. The results of a single-centre observational study are presented. This is the first report of a neonatal early warning score in a low-resource setting.

**Paper 2** presents a qualitative study where I engaged with both stakeholders and women and their families to elicit opinions on essential newborn care of preterm infants, as part of the developmental work to establish if a neonatal early warning score could be useful in a low resource setting.

**Part Two: Timing of Umbilical cord clamping**

**Paper 3** presents the results of an international prospective audit of timing of umbilical cord clamping in four low and middle income countries.

In addition, for background information, three publications are included as appendices (1-3). These papers present the Cord Pilot trial (protocol paper, outcomes at discharge and two-year follow-up), conducted in the UK, investigating the feasibility of conducting a clinical trial evaluating deferred cord clamping. I played a significant role and made a major contribution to the design and conduct of this trial.

**Part Three: High quality and efficient neonatal trials**

***This part is split into parts 3A-C.***

**Paper 4** is the protocol for a large, multi-centre randomised controlled trial of feeding strategies for preterm infants in the UK (FEED1 Trial). Some of the methodological aspects of designing a high-quality trial of a feeding intervention for preterm infants are discussed.

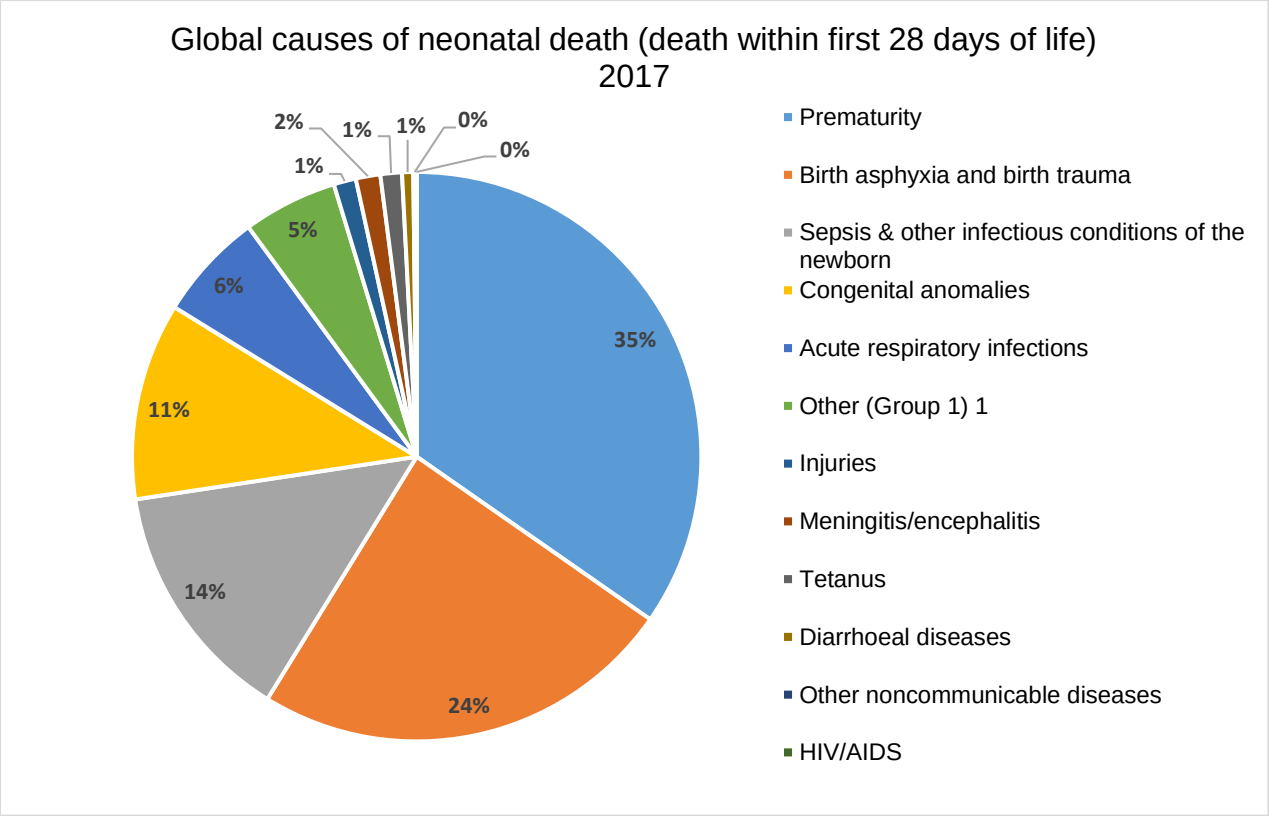
**Paper 5** presents challenges and solutions in the implementation of a two-stage consent pathway in a neonatal trial, including opinions of clinicians in the FEED1 Trial.

**Paper 6** presents the results of a study to evaluate a training package to increase the clinical trials knowledge and skills of researchers involved in a neonatal study conducted in Kenya and India.

### 1.2 Preterm birth – "where you're born matters"

Globally, 15 million babies are "born too soon", i.e. preterm (birth before 37 weeks of gestation) every year[5], equating to around 10% of all births globally. Prematurity is the leading cause of perinatal mortality and morbidities[1]. Over a third (35%) of neonatal mortality (death within the first 28 days of life) is due to complications of preterm birth (Figure 1).

**Figure 1 - Global causes of neonatal death (death within first 28 days of life) in 2017[6]**




[1] Other (group 1) is remainder of all causes of death

### *1.2.2 Global disparity in neonatal mortality rate*

This thesis includes research undertaken in several low and/or low-middle income countries and the UK, a high-income country (HIC), as defined by the World Bank who use the country's economy to classify each country[(7)].

There is wide variation in the proportion of infants born preterm and their outcomes, dependent on their place of birth. In Asia and Sub-Saharan Africa, 22% of all births are preterm, contributing to 80% of all preterm births globally[(5)]. Mortality for a preterm infant born in a LMIC setting is 12 times higher than in Europe[(8)].
Table 2 shows data on current preterm birth and neonatal mortality rates for the countries included in the research within this thesis. For context, global and regional (according to the United Nations Children's Fund (UNICEF) region definitions) rates are also included.

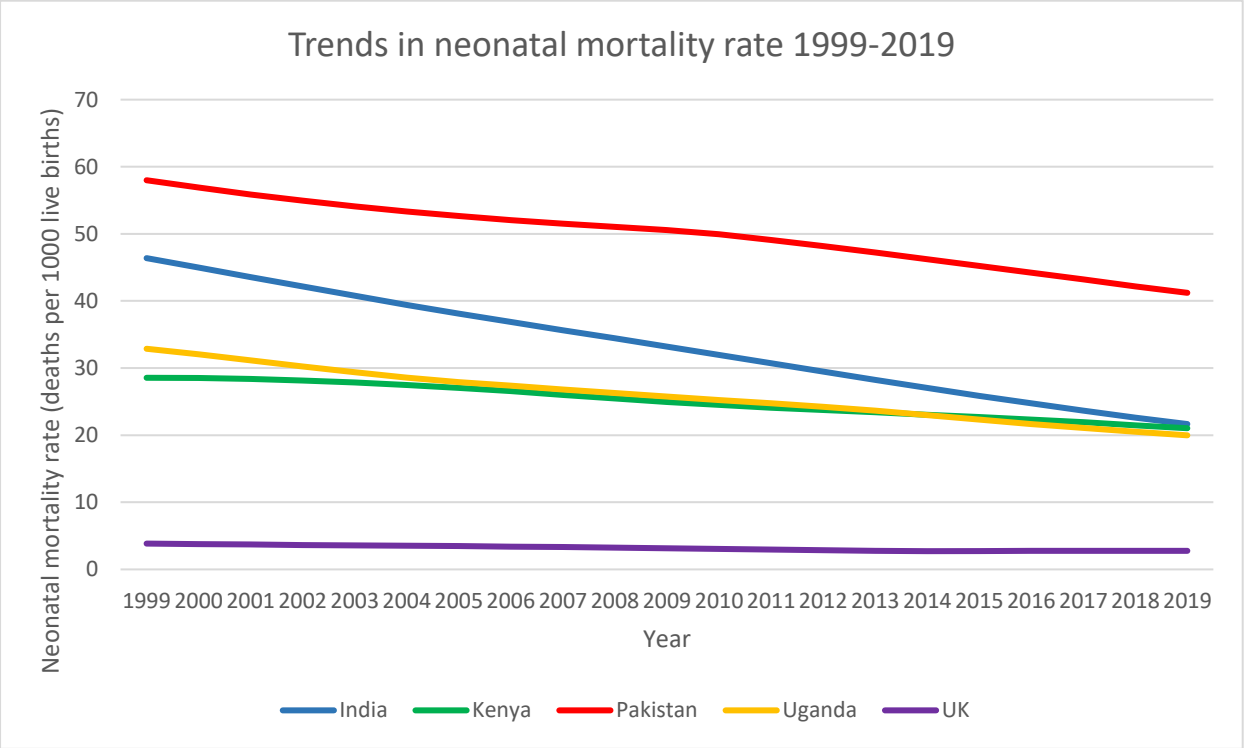
**Table 2 - Preterm birth and neonatal mortality rate**

| Country | Economic classification[1] | Preterm births rate (per 100 live births) (UI)[2] | Proportion of global preterm births (%) | Neonatal mortality rate (deaths per 1000 live births)[3] (range) |
|---|---|---|---|---|
| Global | n/a | 10.6% (9.0-12.0) | 100% | 17.7 (16.9-19.1) |
| Sub-Saharan Africa | n/a | 12.0% (8.6-16.7) | 28.2% | 27.7 (25.6-31.6) |
| Asia | n/a | 10.4% (8.7-11.9) | 52.9% | 24.5 (22.4-26.9)[4] |
| Europe | n/a | 8.7 (6.3-13.3) | 4.7% | 2.8 (2.5-3.0) |
| UK | High income | 7.0% (6.4-7.8) | 0.6% | 2.6 (2.3-2.9) |
| Kenya | Lower middle income | 8.64% (6.3-11.3) | 1.1% | 19.6 (14.5-26.5) |
| India | Lower middle income | 13.6% (11.1-16.1) | 18.5% | 22.7 (20.1-25.3) |
| Uganda | Low income | 6.6% (4.1-10.0) | 1.2% | 19.9 (14.9-26.5) |
| Pakistan | Lower middle income | 8.4% (5.6-11.9) | 3.9% | 42.0 (33.4-52.1) |

[1] data from the World Bank June 2019
[2] data from the World Health Organisation. UI = Uncertainty interval
[3] data from the UN Inter-agency Group for Child Mortality Estimation 2018[(9)]
[4] regional classifications differ to those indicating preterm birth rate. For Asia, this includes data for Central and Southern Asia.

Although the neonatal mortality rate has improved, there is wide variation between countries. In some countries the rate of change is slow. For example, over the last 20 years, Kenya's neonatal mortality rate has only reduced from 28.5 per 1000 live births in 1999 to 21 per 1000 live births in 2019. Many countries' rates are considerably higher than the target of 12 per 1000 live births (Figure 2).

**Figure 2 - Neonatal Mortality rate 1999-2019 in countries included in this thesis**




### *1.2.3 Global efforts to reduce neonatal mortality*

Reducing child mortality was one of the eight Millennium Development Goals outlined by the United Nations (UN)[10] yet whilst the universal childhood mortality rate has reduced, the rate has been slower to decline in children aged 1-59 months[11]. In the joint World Health Organisation (WHO) and UNICEF report "Every Newborn: An Action Plan to End Preventable Deaths", goal 1 is to end preventable newborn deaths, which account for 44% of all causes of childhood deaths under the

age of five[12]. The publications contained in this thesis meet the top three strategic objectives of this global action plan:

- strengthen and invest in care during labour, birth and the first day and week of life
- improve the quality of maternal and newborn care
- reach every woman and newborn to reduce inequalities

In 2016, the UN published the Sustainable Development Goals (SDGs)[13] and called for all countries to develop a global partnership to tackle issues that affect people and the planet on a global scale (Figure 3).

**Figure 3 - United Nations Sustainable Development Goals (2016)** [13]




SDG 3 relates to health: “ensure healthy lives and promote well-being for all at all ages”. There are a range of targets and indicators to assess each SDG. Target 3.2 aligns with the UNICEF “Every Newborn” report, with the additional target of all countries aiming to reduce neonatal mortality to at least as low as 12 per 1000 live births. In 2019, the UN Secretary General published its latest SDG progress report[14], reporting that around 2.5 million infants had died from preventable causes within the first month of life; a crucial period for child survival. Although the global neonatal mortality rate has continued to decline, it is still 18 per 1000 live births,

indicating significant progress is needed to reach the target of 12 per 1000 live births in the next decade.

Of the lower middle income and low income countries included in the research all but Uganda have now developed national newborn action plans, aligned with the “Every Newborn” milestone, and defined newborn mortality reduction targets[15].

### *1.2.4 Importance of focussing on prematurity and low-birth weight infants*

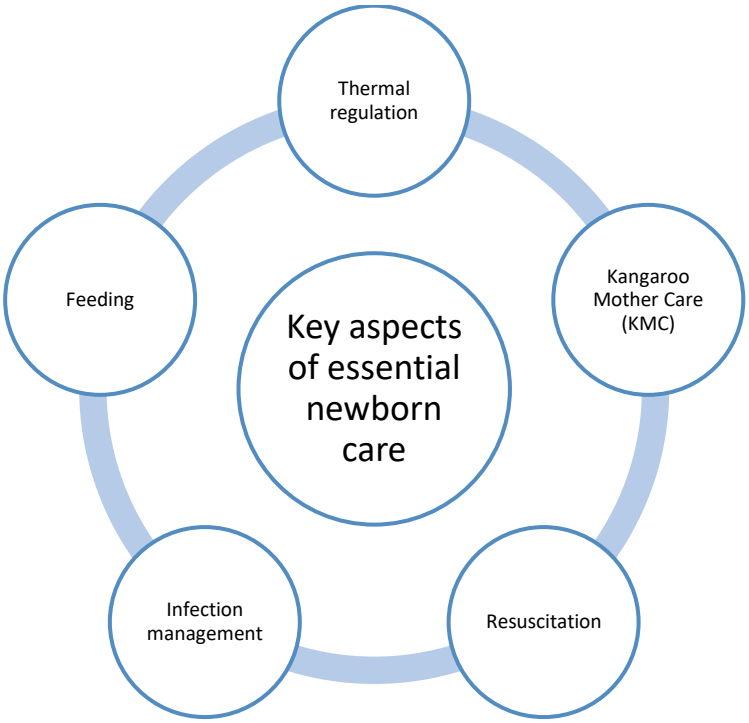
The research contained in this thesis focuses on infants born before 37 weeks gestation – the internationally recognised cut-off for term and preterm infants, as defined by WHO[16]. In some countries, particularly those with lower resources, determining gestational age of an infant can be difficult due to lack of technology such as ultrasonography. It is common for gestational age to be predicted antenatally using the woman’s self-report of last menstrual period (LMP)[17]. Postnatally, in many countries the infant’s birthweight is used to predict gestational age. Therefore, low-birth weight (LBW) infants are also included in some of the studies presented in this thesis, as these infants are also likely to be preterm.

Infants born preterm are not only at higher risk of death than infants born at term (>37 weeks gestation), particularly in lower resource settings, but they are at higher risk of many complications, both short and long-term. To meet targets to reduce mortality due to prematurity, outlined in section 1.2.3, evidence-based interventions are vital. Simple, cost-effective interventions are urgently required to be developed, evaluated and implemented. This is important in all settings, but of particular importance in LMICs where mortality and morbidity rates are much higher and yet resources are much more limited, than in high-income settings. Implementation of evidence-based interventions to reduce neonatal mortality and morbidities is needed at scale to tackle this global issue. Reducing the preterm birth mortality rate is, of course, essential. However, reducing the short, medium and long-term complications that many preterm infants experience is also of utmost importance. All infants should be given the opportunity to survive *and* thrive. High quality, efficient studies are required to test these simple interventions.

### 1.3 Essential newborn care of infants

WHO provide recommendations for the care of newborn infants in the first week of life[18] and, specifically, evidence-based recommendations to improve outcomes for preterm infants[19]. For preterm or LBW infants (<2500g), essential newborn care consists of several components (Figure 4). Whilst these international guidelines have been adopted in many LMICs, it is unclear how well they have been implemented. Kangaroo mother care, thermal regulation, resuscitation, infection management and feeding are introduced in this section.

**Figure 4 - Key aspects of essential newborn care**



### *1.3.1 Kangaroo Mother Care (KMC)*



*Image 1 - mother and baby doing KMC (consent kindly provided)*

KMC involves an infant being carried, usually by the mother, though fathers and other family members can also participate, with skin-to-skin contact (image 1). It comprises three main components: thermal care, support for exclusive breastfeeding and early recognition and response to complications[20]. KMC, when compared to standard care, has also been shown to substantially reduce neonatal mortality in preterm infants and those weighing <2000g (RR 0.49; 95% confidence interval (CI) 0.29-0.82)[21]. This meta-analysis included 15 studies (9 RCTs, 6 observational studies), all of which were conducted in LMICs. In addition to a reduction in neonatal mortality, five RCTs included suggested significant reductions in serious morbidities, defined as severe infection such as sepsis, necrotising enterocolitis (NEC) and severe pneumonia, for infants weighing <2000g (RR 0.34; 95% CI 0.17-0.65). KMC also reduces hypothermia (section 1.3.2).

Despite its proven benefits, KMC is often not practiced regularly. Several barriers to its facilitation have been identified, including lack of space and privacy, staff shortages and lack of education[22]. However, international groups including WHO and the KMC Acceleration partnership are advocating for international roll-out in order for KMC to become the standard of care for newborns, and moreover that KMC be added as a health management information system indicator, to collect data and report progress[23]. In Kenya, Save the Children International and the Ministry of Health are working with county governments to implement this evidence-based intervention. It has been reported that by 2018, KMC had been implemented in 24 of 47 counties in Kenya, though this is anecdotal evidence[24]. Where county roll-out has been successful, neonatal mortality has been halved and longer term benefits have also been seen, such as monthly mother's support groups being initiated[15].

### *1.3.2 Thermal regulation*

Maintaining an infant's temperature is the foremost aspect of newborn care. Since infants regulate temperature much less efficiently than adults, they are at high risk of hypothermia and hyperthermia, both of which are associated with mortality and morbidities. A temperature of 36.5-37.5°c is in the normothermic range and WHO define a temperature of 36-36.4°c as cold stress, 32.0-35.9°c as moderate hypothermia and <32°c as severe hypothermia[25]. Infants who experience hypothermia in the newborn period are at risk of respiratory distress syndrome and severe infection and are less likely to feed properly. Hyperthermia (i.e. a temperature >37.5°c) can indicate severe infection, i.e. sepsis, and infants with hypoxic-ischaemic encephalopathy (HIE) who develop hyperthermia are at higher risk of their brain injury worsening[26]. Lowest rates of neonatal adverse outcomes have been shown to be associated with temperatures of 36.5-37.2°c at the time of admission to the Neonatal Intensive Care Unit (NICU) in a Canadian Study[27]. It is essential to identify infants at risk of hypo or hyperthermia early and implement corrective measures, such as placing the infant in KMC to achieve and maintain normal temperature. A Cochrane review showed that provision of KMC in LBW infants in comparison to conventional neonatal care resulted in a reduction in the risk of hypothermia (18 studies, 2751 infants, RR 0.34, 95% CI 0.17-0.67)[28]. A subsequent systematic review comparing KMC with conventional care also found a reduction in hypothermia (124 studies, 214,385 infants, RR 0.22; 95% CI 0.12-0.41)[29]. WHO recommends that KMC be initiated for all stable newborn infants who weigh 2000g or less at birth and be provided as close to continuous as possible. For infants who are unstable or stable infants who cannot be given KMC, radiant warmers or incubators should be used to provide a thermo-neutral environment. A Cochrane review (25 studies, 2433 infants) published after WHO published its recommendations also showed that using the preventive measure of a plastic bag or wrap within the first ten minutes of life compared to routine care, reduced hypothermia on admission to the Neonatal Intensive Care Unit (NICU) (RR 0.67; 95% CI 0.62-0.72)[30]. Whilst there is substantial evidence demonstrating that hypothermic infants are at greater risk of complications and international guidance recommends a variety of preventive measures, infants often remain cold due to inadequate resources in LMICs, lack of neonatal-specific training and inadequate staff numbers. For example, at the

Kenyatta National Referral Hospital in Kenya, the labour suite is located several floors away from the newborn unit. Due to inadequate equipment and staff shortages, preterm infants are often carried, wrapped in a sheet or blanket, and arrive cold.

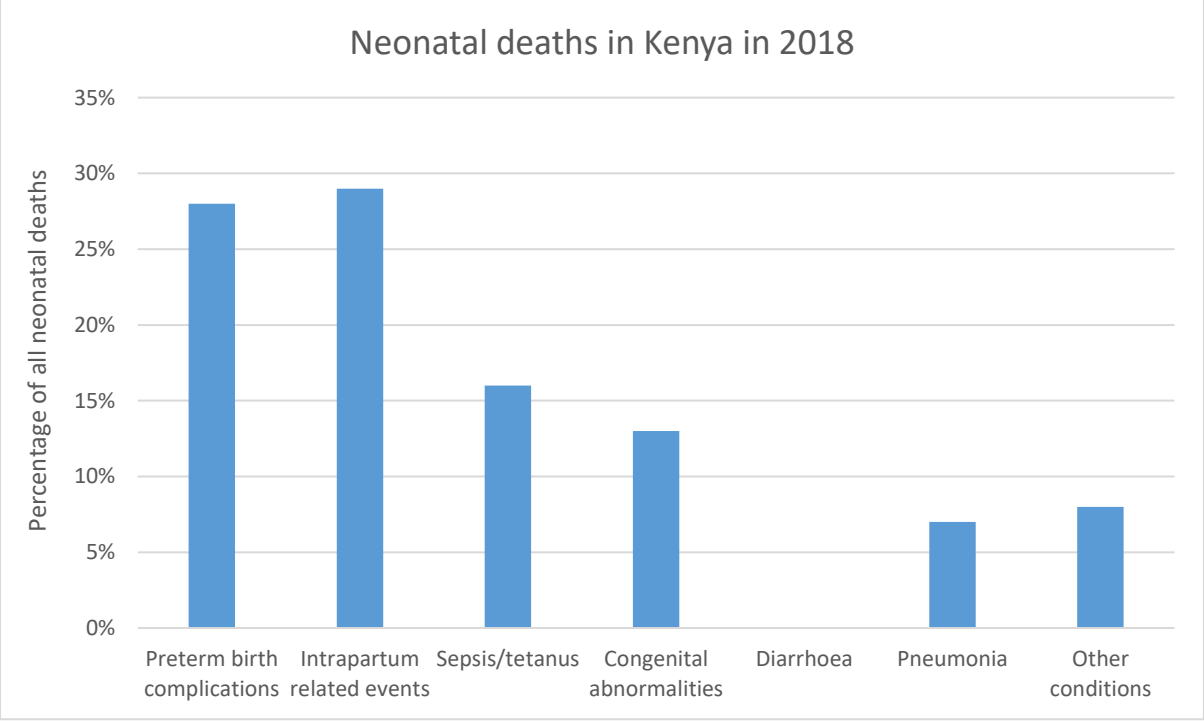
### *1.3.3 Resuscitation*

Neonatal mortality in preterm infants is highest in the early neonatal period. In 2013, 36% of all infant deaths occurred in the first 24 hours of life, with a further 73% in the first 7 days of life[31]. Resuscitation is often required at the time of preterm birth; Aziz et al evaluated ante and intra-partum risk factors predicting an increased need for resuscitation and found that birth at <36 weeks gestation was one such risk factor[32]. Preterm infants are also at higher risk of developing respiratory distress syndrome (RDS) than term infants[33] due to lung immaturity. Starting resuscitation within one minute of birth for infants not breathing or gasping for breath features in international guidelines and involves the ABC approach of checking the airway, breathing and circulation, with a practitioner administering ventilation breaths and chest compressions if required. In high-income settings, guidelines advocate a range of methods for newborn life support such as positive end expiratory pressure (PEEP), continuous positive airway pressure (CPAP) and a variety of other assisted ventilation devices[34]. Due to resource constraints these methods may not be always available or feasible in lower resource settings. Interventions that are developed for the management of preterm birth need to ensure infants who require resuscitation can receive this in line with international guidelines. In 2010, the American Academy of Pediatrics launched the Helping Babies Breathe (HBB) programme which teaches birth attendants how to care for newborn infants at the time of birth, specifically babies who are not breathing and need extra support[35]. It focuses on the “golden minute” – the first sixty seconds after birth. A systematic review that examined changes in neonatal resuscitation practices after the HBB programme had been implemented showed that whilst there were no changes in the use of stimulation, suction or bag and mask ventilation overall, there was a significant increase in use of bag and mask ventilation in the golden minute (4 studies, RR 2.67; CI 2.17-3.28)[36].

### *1.3.4 Infection management*

Preterm infants are at increased risk of serious infection[37-39]. Neonatal sepsis is a leading cause of death in preterm and LBW infants and monitoring infants for signs of bacterial infection and subsequent treatment with antibiotic therapy is part of international guidelines[18]. In Kenya, sepsis/tetanus was the cause of death for 16% of all neonatal deaths in 2018 (Figure 5)[40]. However, since prematurity is a complex problem, it is often difficult to extrapolate a primary cause of death, since many infants die due to multiple diagnoses caused by preterm birth. It is therefore likely that far more deaths were due to sepsis, as a complication of prematurity, than the 16% shown in Figure 5, and these data should be interpreted with caution.

**Figure 5 - Causes of neonatal deaths in Kenya in 2018**




Sepsis can broadly be categorised into either early onset sepsis (EOS) (commonly defined as infection <72 hours since birth[41, 42]), or late onset sepsis (LOS)[43], however various case definitions are used and there is a lack of consensus amongst experts[44]. In HICs, such as the UK, diagnosis is often confirmed by a positive blood or cerebrospinal fluid culture, though infants are also treated with antibiotics for cases of clinically suspected sepsis[45]. However, in LMICs, blood and cerebrospinal

fluid cultures are often unavailable routinely, making diagnosis and ascertainment of the true incidence of sepsis very challenging. Along with other benefits described in sections 1.3.1 and 1.3.2, KMC has shown to reduce severe neonatal infection by 44% (RR 0.56; 95% CI 0.4-0.78 - data from 7 studies, 1343 infants)[19]. The Every Newborn Action Plan aims to ensure that at least half of all newborns worldwide with possible serious bacterial infection will receive antibiotic therapy by 2020 and 75% by 2025.

### *1.3.5 Nutrition and feeding*

Maternal breast milk is the recommended 'gold-standard' nutrition to provide to preterm and LBW infants[46]. Its nutritional composition includes macronutrients (e.g. proteins, fats, and carbohydrates) and micronutrients (e.g. vitamins and immunoglobulins)[47], though content may differ depending upon stage and length of lactation time, and how it is stored[46].

Despite evidence demonstrating that maternal breastmilk is 'best for baby', feeding has been recognised as a major health challenge for preterm infants and suboptimal feeding is linked to higher risks of mortality, infections and adverse neuro-developmental outcomes[48]. Several factors have been recognised as challenges in feeding preterm infants: medical factors such as physiological immaturity, environmental factors such as the highly medicalised environment of the neonatal unit and parental factors such as delays in production of full breast milk[49].

A large surveillance study of infants admitted to 163 UK neonatal units over a 2-year period showed that very preterm infants (28-32 weeks gestation) who are fed with formula milk, rather than maternal breast milk, are more likely to develop adverse outcomes, including necrotising enterocolitis and infection[50]. NEC is a serious inflammatory bowel condition in preterm infants and is a leading cause of death. Large, influential international organisations such as WHO and UNICEF, actively promote breastmilk as the best source of nutrition for all infants and young children. Initiatives such as the Global Monitoring Framework for maternal, infant and young child nutrition[51], to track breastfeeding rates globally, have been implemented and

UNICEF's Baby Friendly Initiative supports' families and practitioners in breastfeeding.

Feeding methods for preterm infants include feeding maternal breast milk, formula milk and/or donor breast milk (from another woman – either independently or a family member, such as grandmother) enterally – i.e. via a naso-gastric (NG) tube directly into the infant's stomach. Infants are also fed parenteral nutrition, which is intravenous (IV) fluids containing glucose and some electrolytes.

Feeding preterm and LBW infants has been the subject of several large-scale RCTs[52-56]. In addition, several Cochrane systematic reviews have been undertaken on the broad subject of nutrition for preterm infants[57-59]. An important question that has troubled neonatologists has been when to introduce milk feeds to preterm infants and, once initiated, how fast to then increase the volume of the milk feed, mainly due to fears over increasing the risk of NEC. More information on feeding preterm infants is provided in section 1.7.1, which focuses on the FEED1 Trial.

### *1.3.6 Summary*

In summary, preterm birth is a global problem that requires a global effort to tackle it. Since the largest number of preterm infants are born and die in LMICs, most efforts should be focussed there. Given these countries are resource-limited, simple, cost-effective, evidence-based interventions are essential if substantial improvements are to be made. Interventions and technologies that have been developed and/or used in high-income settings such as the UK could be useful in LMICs. However, by their very definition, LMICs do not have the same available resources as HICs, and it is likely changes would be required before testing and/or implementing any intervention in a LMIC. Conducting research in LMICs can be challenging and it is therefore imperative that any research conducted is efficient and encourages capacity-development, for researchers in LMICs to develop research skills to enable them to contribute to the global agenda of reducing neonatal mortality.

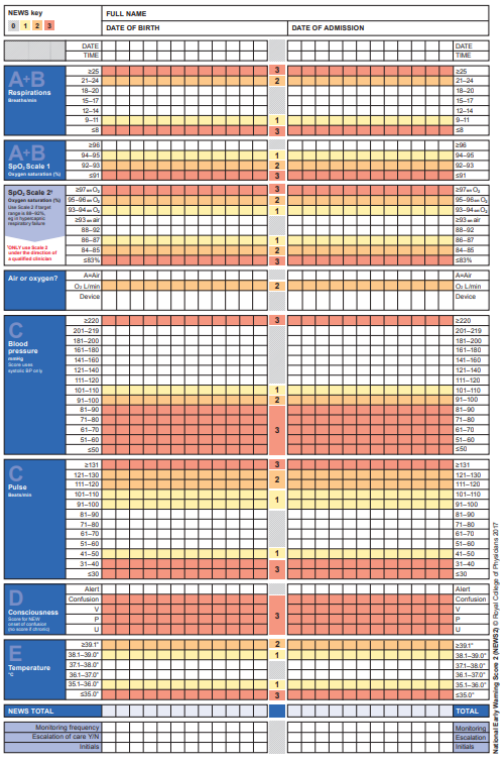
## 1.4. Part 1: Early Warning scores (published works 1, 2)

### *1.4.1 Background, existing evidence and gaps in knowledge*

#### Background

Early warning scores (EWS) have been used in a variety of adult clinical areas in HICs for over two decades[60-62]. They are usually a paper-based document with a traffic light system where vital signs (e.g., temperature, respiratory rate, heart rate) are plotted, depending on the value, to a red, amber of green zone. The EWS visually alerts clinicians to a patient that may require additional management[63]. Figure 6 gives a visual example of an adult early warning score used in the UK.

**Figure 6 - National Early Warning Score [64]**




Reproduced from: *Royal College of Physicians. National Early Warning Score (NEWS) 2: Standardising the assessment of acute-illness severity in the NHS.* Updated report of a working party. London: RCP, 2017[1]

[1] The national early warning score is known as (NEWS), however for the purpose of this thesis, NEWS relates to the neonatal early warning score (below).

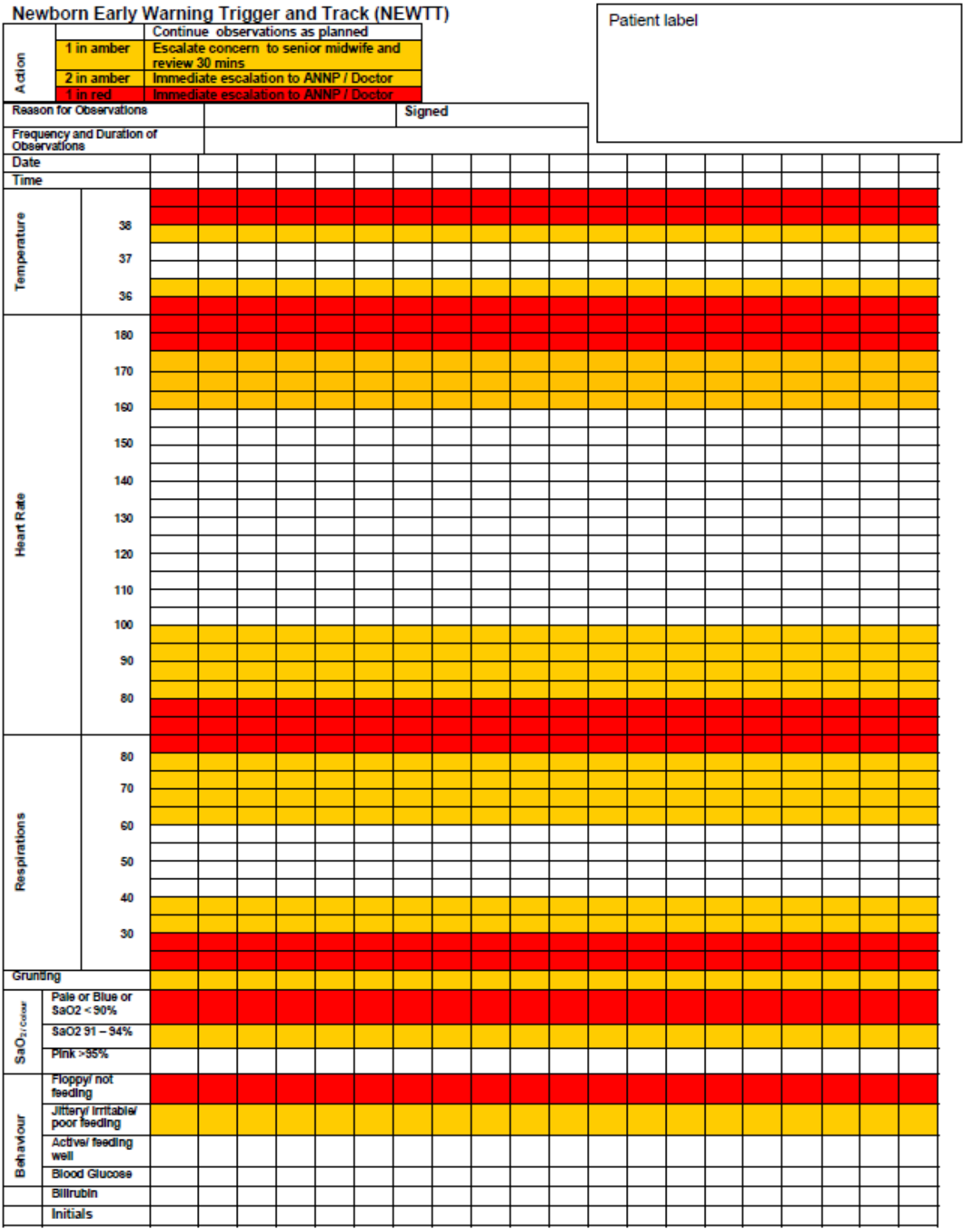
#### Neonatal early warning scores

In neonatal care, however, there have been fewer EWSs developed, and they are less routinely used. A review of EWS for newborn infants was published in 2017, which included any articles that involved infants <6 months of age, included

reference values for physiological parameters (including respiratory rate and heart rate), as well as other definitions of deviations from “normal”[65]. In total four full neonatal early warning scores (NEWS), were identified. Additionally, three other articles were included, though one was based upon infants with cardiac problems and two were not full EWS. Of the four full NEWS, all included temperature, respiratory rate and heart rate, though reference values differed, and two of the reviews only included term infants. This non-systematic review proposed a need for the development of a validated EWS, with acceptable sensitivity and specificity in different gestational age groups, to be used on postnatal wards and NICUs with both term and preterm infants. This is consistent with the conclusion of a single-centre matched case control study in Australia which included infants >34 weeks gestation[66]. In this study, three NEWS were compared to evaluate whether a trigger and escalation of care would have hypothetically taken place, compared with the hospital’s standard observation tool. The authors concluded that a one-size approach does not fit all and that vital signs’ reference values should be modified depending on the gestational age of the infant; this is important due to the significant differences in the physiology and neurology of infants born at different gestational ages[67]. A subsequent systematic review (10 studies) that explored this further also concluded that reference ranges for newborns should be adapted dependent upon the infants’ gestational age[68].

One EWS, described in Mortensen’s review, was developed by The British Association for Perinatal Medicine (BAPM) who published the “Newborn Early Warning Track and Trigger (NEWTT): a framework for practice in 2015[69] (Figure 7). It was designed to be used for infants who are not admitted for higher-dependency care where continuous monitoring is already undertaken. Whilst adoption of this in the UK is unclear, there is anecdotal evidence that it is used by neonatal teams.

**Figure 7 – Newborn Early Warning Track and Trigger (NEWTT)[69]**



## Newborn Early Warning Trigger and Track (NEWTT)

**At Risk Infants – Please tick box as appropriate. Record reason for observation, frequency and duration overleaf .**

**Sepsis**

- Infants fulfilling NICE (2012) criteria ☐
- PROM > 18hours Preterm ☐
- PROM > 24 hours Term ☐
- Maternal Temperature > 38°C ☐
- Chorioamnionitis ☐
- Maternal GBS in vaginal swab/ or MSU ☐
- Confirmed invasive GBS sepsis in previous baby ☐

**Intrapartum**

- Meconium Stained Liquor (requiring intervention ☐
- Cord arterial pH ≤ 7.1 ☐
- Base Excess ≥ - 12mmol/l ☐
- APGAR ≤ 7 at 5 minutes ☐
- Other – Specify reason

.....

**Metabolic : Blood Sugar Monitoring**

- Maternal Diabetes ☐
- Maternal β Blockers ☐
- Birthweight <2nd centile ☐

Other – Specify reason

.....

**Other**

- IPPV > 5 minutes ☐
- Maternal pethidine < 6 hours before delivery ☐
- < 37 weeks gestation ☐

Other – Specify reason .....

**Weight on 2nd centile in Kg.**

| GA | Boys | Girls |
|---|---|---|
| 35 | 1.65 | 1.60 |
| 36 | 1.90 | 1.80 |
| 37 | 2.10 | 2.00 |
| 38 | 2.30 | 2.20 |
| 39 | 2.50 | 2.45 |
| 40 | 2.65 | 2.60 |
| 41 | 2.8 | 2.75 |
| 42 | 2.9 | 2.85 |

**Infants that need immediate review by Doctor /ANNP**

- Jaundice < 24 hours
- Bilious Vomiting
- Abnormal Movements
- Hypoglycaemia
- Apnoea

**These criteria are a guide only to increase surveillance on infants of potential concern. It can be expanded upon to meet local requirements and guidelines.**

*Reproduced with kind permission from the British Association of Perinatal Medicine (BAPM)*

**Neonatal early warning scores in LMICs**

Whilst international guidelines for the provision of essential newborn care exist, they do not provide a clear framework, nor act as clinical prediction tool for easy monitoring of infants in the same way an EWS does. Alongside the potential advantages already outlined, an EWS also enables recording of patients' vital signs in a systematic and standardised way. This standardisation may also improve communication between teams and individuals caring for a patient[65], which could be of particular benefit in LMICs where staffing and resources are limited.

The EWS included in Mortensen's review were all developed in HICs where continuous vital sign monitoring is standard. However, no published EWS for neonates have been developed in LMICs and to the best of our knowledge are not currently used. Unlike preterm infants in HICs, infants born in low resource settings don't have access to continuous high-dependency monitoring and could benefit the most from closer monitoring and early detection of adverse signs.

**Early warning scores in other clinical areas in LMICs**

In paediatric medicine, a scoping review of paediatric early warning scores (PEWS) was undertaken in resource limited settings[70]. Eight studies conducted in seven LMICs were reviewed concluding that it is possible for successful implementation of an early warning score in these settings, urging for further research to be conducted for PEWS to be modified to local resources and context. Overall, the scores documented on the PEWS accurately identified children with a higher severity of illness and two of the studies showed a reduction in clinical deterioration [71, 72].

In obstetrics early warning scores have been adapted for use in LMICs. The Modified Obstetric Early Warning Score (MOEWS) identifies deteriorating clinical condition of women in labour and has been shown to be feasible to implement in resource poor settings[73]. In this quasi-experimental before-after study, conducted at a government referral hospital in Zimbabwe, the MOEWS (developed and used in the UK) was implemented as a quality improvement initiative and was viewed positively amongst staff, including midwives and obstetricians, who found the chart easy to evaluate "at a glance". In addition, an early warning score was introduced in a hospital in Pakistan, where it was evaluated prospectively in 200 high-risk women experiencing

an emergency Caesarean section, to prompt nurses and junior clinicians to escalate care if the mother's health deteriorated[74]. Feedback from nurses was positive, stating they found it easy to use and authors recommended its continued use, due to its simplicity and structured scoring system.

### *1.4.2 Objectives*

To develop an early warning track and trigger system for preterm infants, by:

- Conducting a prospective observational study of current practice for preterm (born at <37 weeks) or low birth-weight (<2500g) infants at a national hospital in Kenya
- Identifying barriers and facilitators to providing essential newborn care by conducting in-depth interviews of healthcare professionals and other stakeholders
- Gaining a contextual understanding of the experiences of essential newborn care provided to their infants, by undertaking focus groups with mothers and their families.

### *1.4.3 Methods*

**Observational study**

A single-centre observational study was undertaken at a tertiary referral hospital in Kenya to assess current practice in provision of essential newborn care. This was conducted as part of a longer programme of work in the development of an EWS for use in a low resource setting. However, before embarking upon a larger-scale project to assess the feasibility and acceptability of an EWS, it was important to understand the provision of care and physiological characteristics of preterm infants in this setting.

The Kenyatta National Referral hospital was chosen as the centre for two main reasons 1) their high preterm birth rates (18.3%)[75], which is higher than other facilities in Kenya. Neonatal care facilities within the hospital are extremely overstretched and overcrowded, with low patient to staff ratios and it was therefore considered useful to conduct the research here, on the basis that if an overcrowded

facility could adopt an EWS, it may be possible elsewhere and 2) existing collaborations with the research team. Although observational data were collected in a previous study (publication 3) in this hospital, this had focussed on care at the time of birth, rather than the infant's admission on the newborn unit. A cross-sectional observational study was the most appropriate study design to understand care and characteristics of preterm infants in this setting. This epidemiological descriptive design enables measurement of outcomes and determinants of health over a short, pre-specified period of time and is an inexpensive research method[76]. Collecting data in this way will help to understand the characteristics and outcomes of the infants in this setting, which is vital before planning any interventional study that may be conducted in the future to investigate the effectiveness of early warning scores on mortality and serious morbidities.

An alternative approach to understanding the provision of care in this setting, would have been to conduct a survey of current practice and ask healthcare professionals to complete this. However, this methodology would not be appropriate as there is the potential risk of recall bias. Healthcare professionals may provide the responses they perceive they should. For example, if they were asked a question about whether infants receive KMC in their setting, they may answer "yes", given that their guidelines stipulate infants should receive KMC. However, guidance is not always followed and therefore not all infants may receive KMC. Moreover, this methodology would not enable detailed data collection of infants' clinical signs. Conducting a prospective observational study enabled collection of current detailed data and was the most appropriate methodology for this purpose.

A team of eight research midwives collected data prospectively over an eight-week period using routine clinical records available on the labour suite, postnatal wards and newborn unit and data were entered onto a web-based study-specific database. Descriptive analyses were conducted using Stata version 15® (Timberlake). Missing data were not imputed nor estimated. Instead, denominators for each datapoint are presented.

## National stakeholder meeting

Following the completion of the observational study (publication one) and parallel qualitative study (publication two) a large stakeholder meeting was organised to discuss the results and ascertain opinions on the possibility of using an EWS in Kenya (Image 2). The meeting enabled seeking opinions en masse, which was important for two reasons: 1) enabled us to consider the views of a wide-range of stakeholders, 2) if an EWS is to be implemented in the future, early “buy-in” of relevant stakeholders, particularly those at policy-level, is crucial. The stakeholder meeting was organised at a central location in Nairobi and a variety of stakeholders, all with an interest in neonatal care and outcomes, were invited by the Kenyan Ministry of Health. Following presentations of the observational and qualitative studies, the 78 stakeholders were asked to work in small groups to discuss possible advantages and disadvantages of using a neonatal EWS in Kenya.

**Image 2 - Networking meeting in Kenya, July 2019**



## Qualitative study

Running concurrently with the observational study, a qualitative study was conducted at the Kenyatta National Referral Hospital. This included focus groups with mothers and their family members and in-depth interviews with stakeholders, including a range of healthcare professionals and policy-makers. The qualitative study was undertaken to understand the barriers and facilitators to the provision of essential newborn care in Kenya. Whilst seeking these opinions could have been done on a

larger scale via surveys (e.g., a survey of all women in the postnatal wards, newborn unit or labour suite over a specific duration of time), this method would have missed the richness of data that can be collected during a qualitative study. Focus groups were chosen to elicit the views of mothers and family members, since it was felt participants may feel more comfortable expressing themselves in small groups due to potential issues with hierarchical power structures if 1:1 interviews were conducted. For logistical reasons, due to staff availability, conducting focus groups with healthcare professionals and policy-makers was not practical. Therefore, 1:1 in-depth interviews with healthcare professionals and policy-makers were conducted. A thematic network analysis[77] was undertaken; this is a way of identifying emergent themes from data in a systematic way, by coding and organising themes to improve internal validity.

## 1.5 Part 2: Timing of umbilical cord clamping (published works 3)

### *1.5.1 Background, existing evidence and gaps in knowledge*

At the time of birth, blood continues to transfer from the mother's circulatory system to the neonatal circulatory system via the umbilical cord; a process known as 'placental transfusion'. Early studies investigating this phenomenon in term infants have shown that the volume and duration of placental transfusion varies but have averaged around 100ml blood, which is around 20-30% of blood volume and red cell mass at birth[78]. In a more recent prospective observational study, 26 term infants were weighed, with the umbilical cord still intact, immediately after birth (mean time 16 seconds for infant to be placed on weighing scales from recorded time of birth)[78]. The results from this study corroborated studies undertaken previously, showing 110ml of blood (95% CI; 69-152) continues to flow from mother to infant with the cord intact. There have been fewer studies investigating placental transfusion in preterm infants. As part of a large national programme of work investigating care and outcomes at very preterm birth (known as "the preterm birth programme"), a small study investigated this[79]. Recruitment into the study was very challenging and as a result only 6 preterm infants (gestational age $34^{+4}$-$36^{+5}$ weeks$^{days}$) were able to be weighed with the cord still intact. The volume and duration of placental transfusion varied between infants (ranging from a 20g decrease to a 128g increase) in keeping with the earlier studies conducted in term infants. Placental transfusion is important as it facilitates transition from the mother's circulation to the neonatal circulation. In preterm infants, particularly those born at earlier gestations, this could be even more important as they are more likely to have poorer outcomes than infants born at later preterm or term gestations. Clamping the umbilical cord immediately after birth was standard practice in the UK for many years, though the exact time at which to clamp in order for the mother and infant to benefit most has been contested and is still unclear[80]. In a Cochrane review undertaken prior to the Cord Pilot Trial being undertaken (appendices 1-3) (15 trials, 738 infants born at 24-36 weeks gestation), the maximum delay in cord clamping was 180 seconds[81]. The review showed promising results for infants with delayed cord clamping (DCC) for several outcomes: less transfusions for anaemia (RR 0.61; 95% CI 0.46-0.81), less intraventricular haemorrhage (all grades) (RR 0.59; 95% CI 0.41-0.85) and lower risk of NEC (RR

0.62; 95% CI 0.43-0.90). No clear differences between groups were seen for most other outcomes, including the primary outcome of infant death. However, in many of the studies included in the review, reporting of data on outcomes to hospital discharge was incomplete and confidence intervals were wide. In addition, only one small study, including 58 children, included data after discharge from hospital. The review concluded that the data were insufficient for reliable conclusions about the comparative effects on any of the primary outcomes included in the review, thus more evidence was needed to assess the effect of DCC on important neonatal and maternal outcomes.

The decision on the optimal time to clamp the cord must be balanced with the need for the infant requiring neonatal care and stabilisation, which traditionally has been provided elsewhere in the delivery room once the cord has been clamped. A more family-centred approach to provision of neonatal care was developed during the preterm birth programme, which involved the development of a bedside trolley (BASICS) to provide neonatal assessment and stabilisation at the mother's side[82]. This innovation also enabled DCC to be offered to women, thus enabling placental transfusion to continue whilst neonatal care was being provided.

The Cord Pilot Trial was conducted as part of the larger preterm birth programme in the UK. Three publications (appendices 1-3) arising from this trial are included for background information to the research included in this thesis, which focusses on conducting feasibility work to determine whether it was possible to conduct a clinical trial comparing timing of cord clamping policies in LMICs. These publications present the published protocol, maternal and neonatal outcomes at the time of infant discharge from hospital and neonatal outcomes at 2-years corrected gestational age[1].

[1] *I played a significant role as part of the multidisciplinary team who designed and conducted the Cord Pilot Trial. My role, as Senior Trial Manager, was to lead all trial management activities including obtaining approvals, training of site staff and preparation of trial documentation. I was an active member of the Trial Management Group (TMG), responsible for the day-to-day running of the trial. I was involved in the interpretation of the results, writing of the publications and dissemination of results to trial sites, participants and the wider perinatal community.*

Delayed umbilical cord clamping in preterm infants could have a greater impact on neonatal mortality and morbidity in LMICs. It is a relatively simple intervention that doesn't require expensive equipment. Conducting a randomised trial comparing early and delayed clamping would be important, however before conducting any trial, developmental work is required. Whilst the Cord Pilot trial was being conducted in the UK, given the stark contrasts in settings, it was agreed that earlier feasibility work, to understand current practice, was required.

### *1.5.2 Objective*

The overall aim was to assess whether conducting a large multicentre randomised trial comparing timing of cord clamping policies at preterm births is possible in LMICs. Specific objectives were to assess current practices for management of the third stage of labour, and for care at the time of birth for preterm infants in LMICs by:

- assessing prospectively the accuracy of estimated gestation at birth and birthweight (using either Ballard or Dubowitz scores)
- describing the methods used for assessment of gestation and estimated birthweight
- describing current practice for timing of cord clamping at preterm and term births
- estimating the proportion of births either between 28-34 weeks gestation or 1-2 kg birthweight
- identifying the proportion of births either between 28-34 weeks or 1-2 kg birthweight that can be identified before birth
- describing the clinical staff present at the birth of preterm or low birthweight babies
- describing current practice for care of the preterm or low birthweight baby in the delivery room, and outcome at hospital discharge
- identifying the proportion of preterm and low birthweight babies admitted to the neonatal unit or paediatric ward, and serious neonatal morbidity

### *1.5.3 Methods*

We conducted an international, prospective audit to determine current clinical practice at the time of birth for preterm and term infants in six hospitals in five LMICs (India, Pakistan, Kenya, Uganda). This methodology was chosen for the same reasons outlined as for the observational EWS study (section 1.4.3); prospective observational data collection enabled detailed data collection at the time of birth and was the most appropriate methodology to understand current practice.

Sites were asked to collect data on all births during a series of pre-specified time periods, to ensure a representative sample (day and night, week days, weekends, different staff shifts). Due to resource availability, it was not possible to collect data 24/7. “Outborn” births (births occurring before arrival at the hospital) were excluded. The aim was to collect data for at least 30 preterm births at each site. For this study, preterm was defined as births between $28^{+0}$-$33^{+6}$ weeks gestation and/or birthweight of 1-1.99kg. To collect data on around 30 preterm births, it was anticipated between 500-700 births would be included at each site.

All sites participated in a 3-day training visit. This was conducted within the hospital for all sites, with the exception of Pakistan. Three members of staff from the site in Pakistan (including the Principal Investigator) travelled to Kenya to participate in the site training visit, due to the University of Nottingham’s travel advice to avoid travelling to Pakistan. Apart from Pakistan, site staff included obstetricians, neonatologists, paediatricians, research nurses/midwives and clinical nurses/midwives. Before data collection commenced, ethical approval was sought, according to local requirements, by each participating site.

Data were collected using simple, paper data collection forms which were subsequently entered onto a study-specific, secure, password-protected database designed by staff at the Nottingham Clinical Trials Unit. Data were collected on all infants, with additional data collected for infants who met our definition of preterm. To collect information on births that may have been excluded from the audit, a record of births was maintained on each labour suite for the duration of the audit. This captured basic data on all births (mode of delivery, gestation at birth, birthweight and

pregnancy outcome) and whether their data were included in the audit or not. For the purposes of a future neonatal clinical trial, it was important to know the gestational age of the newborn. Cord clamping is an intervention conducted on the labour suite before gestational age assessment of the newborn is undertaken. It was therefore important to assess the accuracy of antenatal methods (e.g. last menstrual period, antenatal ultrasound) of determining gestational age. The positive predictive value (PPV) and negative predictive value (NPV) of being preterm, in accordance with our definition, were calculated and presented. All other analyses were presented descriptively and performed in Stata.

## 1.6 Part 3: High quality and efficient neonatal trials (published works 4-6) introduction

This part is split into three sub-sections (parts A-C):

- Part A focuses on important design and methodological considerations in the FEED1 trial
- Part B follows by exploring consent pathways in neonatal trials, using the FEED1 trial as an exemplar
- Part C focuses on clinical trials training for clinicians and researchers conducting neonatal trials in LMICs

To introduce the topic, I provide background information about the importance of conducting *high-quality* and *efficient* neonatal trials.

### Inefficiencies in clinical trials

Evidence-based medicine is making use of the best available evidence in decision making when caring for and treating patients[83]. Various hierarchies or levels of evidence have been contested over several decades, though it is generally accepted that randomised controlled trials (RCTs) provide a high level of evidence[84] (Figure 8). Despite the RCT's ability to provide high level evidence to inform clinical decision-making, it is well known they can be expensive and inefficient. Twenty-five years ago, Altman made the case for conducting high quality medical research calling for "less research, better research, and research done for the right reasons"[85]. He and others have reported that many studies lack methodological rigour and are inefficient in their conduct[86]. Examples of such inefficiencies are broad ranging from poor design, lack of trial registration, lack of reporting and incorrect outcome measures. Additionally, there is a plethora of evidence that many trials fail to reach their recruitment target or fail to collect primary outcome data and thus have insufficient power to answer the research question[87-91]. Though the need for conducting efficient trials was recognised several decades ago, it is currently acknowledged that approaches are urgently needed to make trials more efficient and cheaper[92, 93]. The need to conduct efficient clinical trials to answer research questions that are important to patients, clinicians, healthcare policy-makers and commissioners has

been acknowledged within the clinical trial community, with a range of initiatives[94-97] being established. There is a growing body of evidence of methodological research undertaken to improve the design and conduct of RCTs.

**Figure 8 - Levels of Evidence-based medicine**

| Level | Type |
|---|---|
| 1a | Systematic review with homogeneity of RCTs |
| 1b | Individual RCT with narrow confidence intervals |
| 1c | All or none case-series |
| 2a | Systematic review with homogeneity of cohort studies |
| 2b | Individual cohort study (including low quality RCT, e.g. <80% follow-up) |
| 2c | "Outcomes research", ecological studies |
| 3a | Systematic review with homogeneity of case-control studies |
| 3b | Individual case-control study |
| 4 | Case series (and poor quality cohort and case control studies) |
| 5 | Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" |

*Oxford Centre for Evidence-Based Medicine: Levels of evidence (March 2009). Available at www.cebm.ox.ac.uk*

## Cost of clinical trials

The UK's largest health research funder, NIHR, spent £317 million across its spectrum of funding programmes in 2018-2019[98]. Between April 2011 and December 2019, the entire spend on 4650 research projects across all clinical areas was over £3000 million[99]. It is unclear how much of this spend was on neonatal research, however £171 million was spent on reproductive health and childbirth studies, across 259 research studies (approximately 5% of the entire portfolio), which includes studies of the newborn[100]. These figures do not include training or fellowship awards, which often include embedded studies or trials and therefore are likely to underestimate the overall number of projects and amount of money spent. The real-cost of conducting a poor quality and/or inefficient trial is unknown: there have been studies that have reported the number of trials requiring time only or time and cost extensions[87, 89], the most recent of which showing that almost half of all trials funded by the NIHR during a six year period required an extension of some kind. However, the indirect costs of such inefficiencies and research waste to the research community and society as a whole are unknown and difficult to quantify. It

is therefore imperative that trials are conducted to a high-quality standard and are as efficient as possible.

**Efficient neonatal trials**

The arguments for conducting efficient trials in neonatal medicine are similar to those described above which relate to efficient trials across all clinical specialities. Modi has recently argued that to address uncertainties in newborn health a number of important steps are required to improve research efficiency and impact and that research can be considered efficient if studies are of “high quality, conducted rapidly, at reasonable cost and with minimal burden on investigators and participants”[92].

### *Part 3a: 1.7.1 Background to the FEED1 Trial*

A Cochrane review compared slower advancement of feeds (24 ml/kg/day) with faster advancement of feeds in very preterm (<32 weeks) or very LBW (<1500g) infants[58]. This large review (10 studies, 3753 infants) included studies which were considered methodologically robust. Results did not show an increase in NEC or all-cause mortality in faster advancement of feeds. Around three quarters of the infants (n=2804) included in the review were from the Speed of Increasing Milk Feeds Trial (SIFT)[52], which compared slow advancement of enteral feeding (18ml/kg) with faster advancement (30ml/kg). This showed no significant between-group difference in the primary outcome of survival without moderate or severe neurodevelopmental disability at 2 years corrected for gestational age. In addition, there was no evidence of between-group differences for the important secondary outcomes of NEC and late-onset sepsis (microbiologically confirmed or clinically suspected). Infants started the intervention at a median of 4 days old and the authors recommended further research be undertaken to address the issue of feeding infants' larger increments in the first few hours and days after birth.

A further Cochrane review (6 trials, 526 infants) compared early full enteral feeding with delayed/gradual introduction of enteral feeds in preterm and LBW infants. All included studies were conducted in the 2010s in India, and most infants were VLBW, born at 28-34 weeks gestation. The review concluded there remains uncertainty on the effectiveness and safety of full enteral feeds due to insufficient data, and the authors assessed the quality of evidence as low with included studies having methodological weaknesses[101]. Despite this, the review gave promising evidence that full milk feeds may reduce length of hospitalisation. Five of the six studies reported the duration of hospital stay[102-106]; meta-analysis showed that infants in the full enteral feeding group had a shorter length of hospital stay than infants in the delayed/gradual feeding group (mean deviation (MD) -3.07 days; 95% CI -4.13 to -2.02). In addition, infants in the full enteral feeding group regained birth weight sooner than infants in the delayed/gradual feeding group (MD -3.42 days; 95% CI -4.31 to -2.53). Whilst this demonstrates promising evidence that full milk feeds may be beneficial, these data should be interpreted with caution, due to the limited amount of data and methodological weaknesses. In addition, the meta-analysis

comparing time to regain birth weight was not pre-specified and done post-hoc. Finally, four of the six studies included in the review reported invasive infection. When data was meta-analysed, there was no between group difference (RR 0.72; 95% CI 0.36-1.46) though three studies did demonstrate a reduction in invasive infection. However, the studies were under-powered to detect a clinically significant difference[103, 105, 106]. The Cochrane review provides evidence that fast feeding is safe and beneficial, though it remains unclear whether providing infants their full fluid requirements solely as enteral feeds, without using IV fluids or parental nutrition – a strategy known as 'full milk feeds' - is safe.

To compare full milk feeds enterally with gradual milk feeding, the Fluids Exclusively Enteral from Day 1 (FEED1) trial has been funded by the National Institute for Health Research (NIHR) (Ref: NIHR HTA 17/94/31) in the UK. More information about the trial can be found at www.feed1.ac.uk.

In clinical trials, it is standard practice to publish the trial protocol in a peer-reviewed journal before the trial recruitment period ends[107, 108]. Indeed, many journals now refuse to publish a trial protocol after recruitment ends and publishers of trial results commonly expect to see a published protocol, along with evidence of prospectively registering the trial on a public registry[109]. This is to ensure transparency with respect to trial methods and analyses, ensuring they are pre-planned and not data-driven. The published protocol (publication 4) includes detailed methods, which are therefore not repeated in this extended abstract; instead, some of the design and methodological considerations are presented.

### *1.7.2 Objectives*

The objective of the FEED1 trial is to investigate whether full milk feeds initiated in the first 24 hours of life, in infants born between 30-33 weeks gestation, reduce the length of hospital stay, when compared to IV fluids and gradual milk feeding (table 3).

The trial is ongoing and therefore the objective for the FEED1 trial has not yet been met. The specific objective for this section of the thesis is to explore some of the design and methodological considerations in the FEED1 trial.

**Table 3 - FEED1 Trial PICO**

| | |
|---|---|
| **Population** | • Infants born between 30-33 weeks gestation |
| **Intervention** | • Full milk feeding from day 1 |
| **Control** | • Parenteral nutrition/IV fluids with gradual milk feeding, as per usual local practice |
| **Outcome** | • Length of hospital stay<br>• A range of secondary outcomes as given in full in paper 4 |

### *1.7.3 Methodological considerations in the FEED1 Trial*

The FEED1 Trial is a large multi-centre, open, parallel, randomised controlled superiority trial that is currently being conducted in approximately 40 neonatal units in the UK. A randomised controlled trial is the most appropriate robust methodology to answer the clinical research question and minimise bias. This methodology enables us to test whether an intervention provides benefit or harm. In a randomised trial, the research team/healthcare professional/parent cannot choose their intervention of choice. Instead, participants are randomly allocated to a treatment which reduces the effect of selection bias. Well designed and conducted RCTs produce high-quality evidence and are the 'gold standard' for testing healthcare interventions[84, 110].

In the FEED1 Trial, infants meeting the eligibility criteria (Table 4) are randomised to either:

- Full milk feeds from day 1[2] or
- Parenteral nutrition/IV fluids with gradual milk feeding, as per usual local practice

**Table 4 - FEED1 Trial eligibility criteria**

| Inclusion criteria | Exclusion criteria |
|---|---|
| Infants born between $30^{+0}$ and $32^{+6}$ gestation (weeks/$^{days}$) inclusive | Infants with known congenital abnormalities of the gastrointestinal tract or other congenital conditions that make enteral feeding unsafe |
| Infants born <3 hours (180 minutes) old (since recorded time of birth) | Infants who are small for gestational age (birth weight <$10^{th}$ centile) and evidence of reversed end-diastolic flow on antenatal umbilical artery Doppler ultrasound |
| | Mother has participated in the trial during a previous pregnancy |

**Infant age at the time of randomisation**

Several factors were taken into consideration when making the decision to only include infants who are <3 hours old. The time period was selected after wide consultation with neonatologists, including members of the UK Neonatal Nutrition (N3) Network[(111)]. Three hours is the maximum length of time neonatologists agreed they could wait before needing to give the infant fluids. It is also in-keeping with the time it takes to complete delivery room stabilisation, transfer to the neonatal unit and complete the admission process. Enabling feeding to commence soon after birth will

[2] *For the purpose of this trial, 'full milk' is all feeds and fluid requirements being given as milk from day 1, starting at 60 ml/kg/day, increasing as per the infant's fluid requirements in line with standard practice. The definition of reaching full enteral milk feeds is when the infant receives at least 140 ml/kg/day of milk for three consecutive days.*

also minimise potential contamination between the intervention and control groups in the trial.

It has been important to strike a balance between infants not waiting too long before receiving any fluids and ensuring it would be possible to detect a difference between the two randomised groups. If a longer time-window was given (e.g., infants could be randomised if <24 hours old), fluids may have started; possibly resulting infants in the 'full milk' group receiving IV fluids, which is part of the 'gradual milk' group. Therefore, enabling feeding to commence soon after birth should minimise potential contamination between the two groups. Since the trial opened, the TMG has closely monitored the reasons for ineligibility into the trial, including whether it has not been possible for sites to randomise infants quickly, within 3 hours of birth. Whilst we have held discussions about the possibility of extending this time window beyond 3 hours, for more infants to be eligible for participation, currently eligibility criteria remain the same, to maintain clear differences between the two randomised groups.

**Choice of milk**

As described in section 1.3.5, maternal breast milk is the gold-standard nutrition for preterm infants. It was therefore important that in a trial of a feeding intervention for preterm infants, every attempt was made to prioritise mother's breast milk being used. To address concerns by clinicians and parents that the trial may naturally increase the use of formula by starting full milk feeds sooner (i.e. sometimes before the mother is able to produce the full milk volume) it was important to explore the use of donor breast milk (DBM). As FEED1 is a pragmatic trial[112], the trial was designed to mimic usual practice as much as possible and it was agreed that sites should use the type of milk they would usually use in clinical practice, i.e. if a site already has access to DBM, they should continue to use this. Whilst developing the trial, a visit to the Hearts Milk Bank (https://humanmilkfoundation.org/hearts-milk-bank/), part of the Human Milk Foundation, was undertaken. This was an important part of determining feasibility of the trial and discussions included the process for sites gaining access to DBM should they opt for this, and, given the potential greater demand for DBM, as a direct result of the trial, whether there would be sufficient supplies of DBM nationally. We have worked closely with a representative from the Hearts Milk Bank, who also represents the UK Association of Milk Banks (UKAMB) throughout. In addition, for

sites who were interested in supplementing mother's breast milk with donor milk, we have facilitated discussions with the relevant milk bank.

Furthermore, whilst designing the trial, two surveys were designed and conducted (unpublished) to ascertain opinions of neonatologists (n=49) and parents (n=334) in aspects of our proposed trial. The clinicians' survey included questions on the use of donor breast milk within the hospital they were based and whether the hospital had UNICEF Breastfeeding Friendly Initiative accreditation (https://www.unicef.org.uk/babyfriendly/accreditation/). Once the trial was funded, these questions were also included at the time of conducting site selection. Whilst we didn't include specific questions about the choice of milk in the parents' survey, in a free-text open-ended question designed to capture any other thoughts about the proposed trial, many parents commented about the importance of feeding with breast milk. Throughout the development and conduct of the FEED1 trial, we have emphasized the message that the first choice of milk will always be mother's milk and that there is no involvement, of any kind, of any manufacturers of formula milk.

**Choice of primary outcome – length of infant hospitalisation**

Initial discussions whilst developing the FEED1 trial focussed on whether it would be possible to power the trial on important clinical outcomes, including NEC and/or late-onset sepsis. Both NEC and sepsis are life-threatening conditions and of huge importance to clinicians and parents. However, since the incidence of both conditions is relatively low in the UK, it would not be feasible since many thousands of infants would be required. This is further discussed in section 3.3.3.

Attention then turned to the next most appropriate choice of primary outcome. Given the evidence described in section 1.7.1 that full milk feeds *may* result in a shorter length of hospital stay in the studies conducted in India, this was explored in the UK context. In England and Wales, around 6000 infants are born between 30 and 33 weeks' gestation taking up the greatest capacity of cots on neonatal intensive care units[113]. Similarly in Scotland, where data is recorded differently and reported separately to other areas in the UK, over 3500 infants weigh <2.5 kg at birth and it is estimated 5.6% of all live births are at 28-31 weeks[114]. Reducing the length of time an infant spends in hospital and normalisation/ de-medicalisation of care, is hugely

important to parents who have told us this during patient and public involvement (PPI) activities whilst designing the trial. Due to the large numbers of infants born between 30 and 33 weeks in the UK, even a modest reduction in length of hospital stay would increase cot capacity in neonatal units. Infant care on a neonatal unit in the UK costs approximately £450 per day[115] – thus a reduction in length of hospital stay (for infants born at 30-33 weeks gestation) by just one day could result in a National Health Service (NHS) cost-saving of around £2.8 million annually. In addition to important NHS savings, parents could also benefit financially: they currently spend around £282 per week whilst their infant is in hospital, in addition to loss of working days[116]. The combination of potential cost savings for the NHS and families, in addition to the emotional benefits of reducing length of hospital stay, make this an important outcome.

**Consent pathways**

Mothers can be approached and asked to consider their infant participating in several ways. Firstly, during their routine neonatal antenatal counselling appointment, which is offered to all families who are expecting to have a preterm birth. They are approached by a research midwife who explains the trial and goes through a full participant information sheet. The woman can ask questions and, if willing, provides written informed consent. If she prefers to take time to consider participation, written informed consent can be obtained at the next antenatal appointment. However, preterm birth can be unexpected and therefore not all women will know they are having a baby prematurely and therefore may not have been approached about their infant participating in the trial. These women are approached either during labour or shortly afterwards. This can be an emotionally fraught and potentially difficult time and therefore an alternative consent pathway is in place. Women are approached by a member of the clinical team who gives the minimal important information about the trial and asks the mother if they are willing for their infant to participate. The mother does not need to read the participant information sheet or sign the written informed consent form; instead, her verbal agreement is sufficient, providing this is clearly documented in the clinical records. This process is called “oral assent”. This allows feeding to commence in a short space of time and means women aren’t being over-burdened with trial information at a difficult time. Full written informed consent is required as a follow-up, though this

can be done several days later (ideally within 72 hours). This two-stage consent pathway is described in detail in part 3b (publication 5).

**Randomisation**

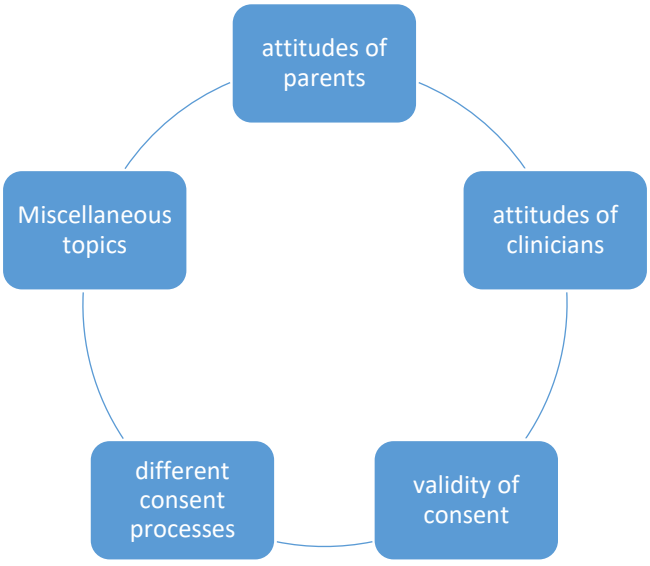
Once the infant has been born and either written informed consent or oral assent is obtained, providing the infant meets the eligibility criteria (Table 3), the mother is randomised. The unit of randomisation is the mother since when undertaking prior PPI activities, mothers of multiple infants told us that they would not like to feed their infants differently. Therefore, all infants born to one mother will be fed using the same strategy. Randomisation is undertaken using a secure online web-based system, using a 1:1 ratio. The randomisation software includes a minimisation algorithm, with a random element, to ensure balance between important prognostic factors: hospital; single or multiple birth; gestational age at birth; birthweight centile; whether IV fluids were started prior to randomisation. Randomisation must take place within three hours of the infant's recorded time of birth and is indeed one of the eligibility criteria, as previously described.

## 1.8 Part 3B: Consent in neonatal trials (published works 5)

### *1.8.1 Background, existing evidence and gaps in knowledge*

Having a preterm infant can be a stressful and emotional time for parents[117, 118] and it is therefore important to ensure that neonatal clinical trials are designed to not add additional stress, thus minimising the burden to them. Informed consent is an underpinning principle of research ethics and ICH-GCP specifies that participants must give their consent for participation prior to any research activities take place[119]. In the context of neonatology, consent must be given by a parent or someone with parental responsibility (agreement by only one parent is required). A systematic review was conducted to focus on the ethical issues concerning consent in neonatal research[120]. This included 49 published articles (with full-text available in English) that met the inclusion criteria of reporting any empirical research/analysis/commentary concerning i) consent, participation or recruitment for neonatal research (relevant to clinical trials), ii) parental decision-making for treatment of, or research with, sick or preterm neonates, iii) parental decision making for birth/labour, iv) methodology in emergency/urgent neonatal research, v) alternative ways of gaining consent for neonatal research. Several themes emerged from the framework synthesis (Figure 9).

**Figure 9 - Themes identified from framework synthesis[120]**



Parents and clinicians acknowledged the requirement for a consent form, but also shared the view that holding discussions about trial participation at a difficult time added to stress and anxiety. Overall parental understanding about trial participation was variable between studies, questioning the validity of the consent they provided, though acknowledgment was given to the timing of the approach and the effect that may have on parental understanding of the trial. Several consent processes were included in the studies reviewed and all appeared to have pros and cons. The authors concluded that there was no acceptable process for consent in neonatal research and that development of an ethically acceptable alternative process was required to conduct neonatal studies.

**Development of an alternative consent process**

The Cord Pilot trial (appendices 1-3) randomised women during labour. For many women where preterm birth was expected, they had been approached about study participation during their routine antenatal or neonatal counselling appointments. However, given that preterm birth is often rapid and unexpected, this was not always possible. It was important we considered the process by which these women could participate in the study. Based upon the results from the systematic review of ethical issues concerning consent in neonatal research, a two-stage consent pathway was developed and used in the trial. The development of the pathway is described in the published protocol (appendix 1). In brief, the process allowed women to be approached antenatally and written informed consent given, as is standard in many clinical trials. However, for women who were admitted to the labour suite where preterm birth was imminent, women were approached about the trial and gave their oral assent if they were willing to participate. This involved the clinician explaining the minimal information about the trial required to allow the woman to decide about participation. As this trial was evaluating an intrapartum intervention (third stage of labour), women were unable to withdraw from the intervention part of the trial subsequently. However, it was important that, for women who agreed to participate via the oral assent pathway, subsequent written consent was collected for their data to be used subsequently. Women were approached by research midwives at the eight participating hospitals at a convenient point following delivery to complete the consent form. To make the process as simple as possible for the site staff, the consent form was on one A4 sheet of paper. Page 1 was the written informed

consent form and overleaf was a documented record of an oral assent conversation if one had taken place. This meant that all documentation relating to the woman's consent discussion was together. In their clinical governance advice on obtaining valid consent in perinatal research where consent is time critical, the Royal College of Obstetricians and Gynaecologists (RCOG) recognise that in acute circumstances, it may not be appropriate to provide full study information at a time of labour complications (including rapid unexpected preterm birth)[121]. The two-stage consent pathway now features in their guidance, and they recommend researchers may wish to consider this process for their own studies.

**Opinions of the two-stage consent pathway**

As the two-stage consent pathway was new in the Cord Pilot trial and perinatal trials generally, it was important to understand the views and experiences of those who used it, i.e., the women who were approached for participation and the clinicians who made the approach and discussed the study with the woman. An embedded qualitative sub-study was undertaken within the Cord Pilot Trial[122, 123]. In total 23 women and 17 clinicians were interviewed about their experiences of the two-stage consent pathway. The themes identified from the qualitative interviews are summarised below in Table 5.

**Table 5 - Themes identified from qualitative sub-study**[122, 123]

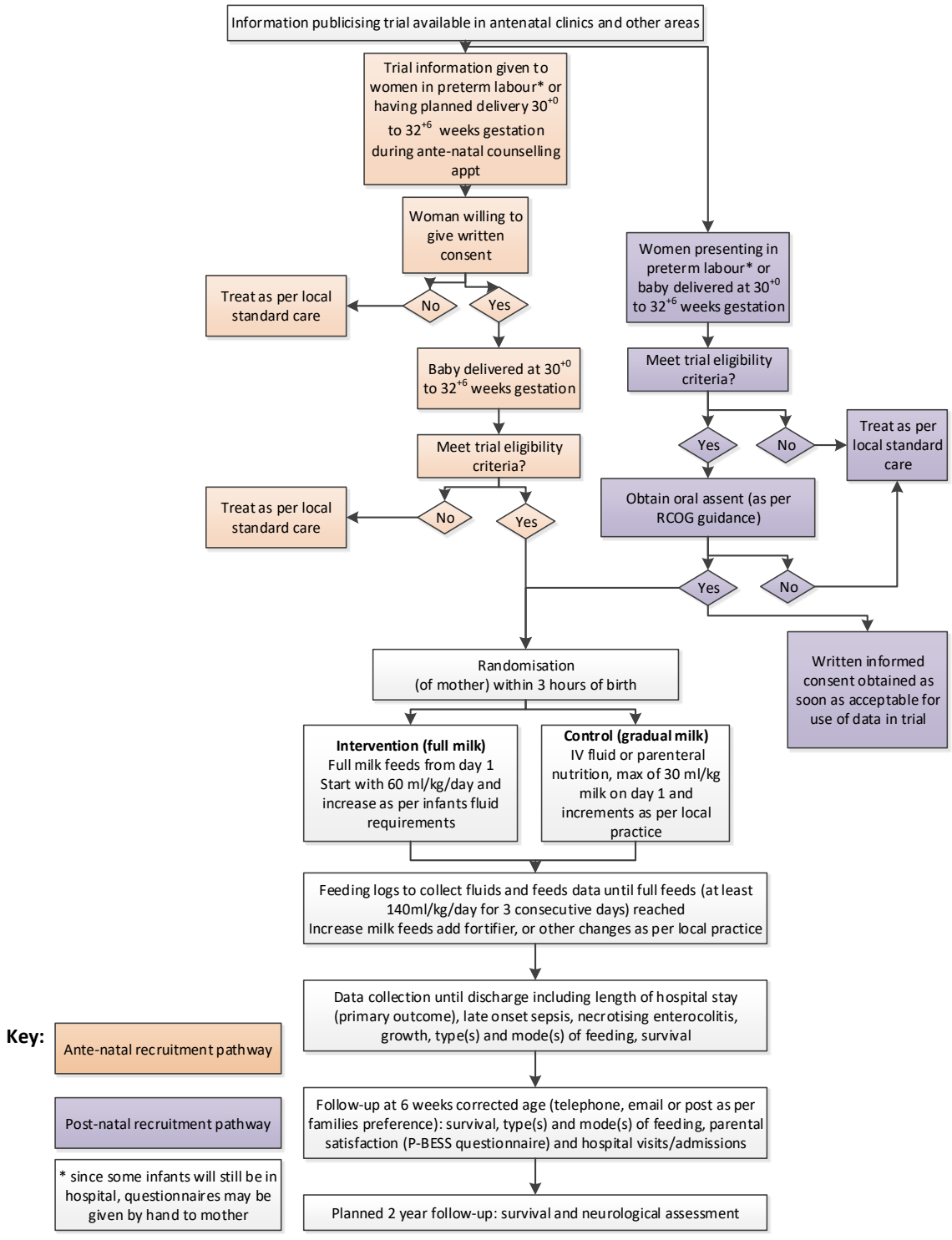
| ***Themes identified from interviews with women*** |
|---|
| 1. Understanding of the implications of randomisation<br>2. Importance of staff offering participation<br>3. Information about the trial and time to consider participation<br>4. Trial secondary in women's minds<br>5. Reasons for agreeing to take part in the trial |
| ***Themes identified from interviews with clinicians*** |
| 1. Team approach to offering participation<br>2. Consent form as a record<br>3. Consent and participation as a continual process<br>4. Different consent pathways for different trials<br>5. Balance between time, information and understanding<br>6. Validity of consent |

Overall, clinicians and women liked the two-stage consent pathway. Women recognised that they did not have much time to consider participation but understood that was because of the situation rather than "anyone's fault". Some clinicians expressed concern about the lack of documentation (i.e., a standard consent form) for women agreeing to participate via the oral assent pathway. However, women did not share these concerns and felt that the clinicians' providing minimal, clear information made it easier to consider participation. Importantly women were positive about their experience of being invited to participate in the trial, regardless of whether they gave written informed consent or oral assent. Some clinicians had concerns about the lack of standardisation information given to a woman and most clinicians felt there was minimal information that must be included in an oral assent conversation; randomisation, details about the intervention itself and the risks, and the women's right to decline participation or withdraw subsequently from the study. Importantly, clinicians supported a two-stage consent pathway for similar trials of a low-risk intervention. It was concluded that the two-stage process should be considered for future trials, though required further development and evaluation.

**Implementing the two-stage consent pathway in other trials**

The FEED1 Trial (publication 4) has since adopted the two-stage consent pathway (Figure 10). The trial has ethical approval for women to be approached either antenatally, during labour or postnatally. If women are approached antenatally, full written informed consent is undertaken. If women are approached during labour, either written informed consent or oral assent is undertaken, depending upon the stage of labour. For women approached postnatally, oral assent is undertaken.

## Figure 10 - FEED1 participant pathway




*women presenting in preterm labour may be consented via the antenatal or postnatal pathway. Clinician discretion will be used to determine the most appropriate method.

Given the concerns raised by clinicians in the qualitative sub-study described previously, the importance of full training on the consent pathway was recognised. Participating sites in the FEED1 Trial were either trained during a group training session (with other sites) or an individual site initiation visit (SIV), as part of the embedded SWAT to investigate clinical trials training. Regardless of training method, clinicians and site research staff had a dedicated training session on the two-stage consent pathway, including opportunities for site staff to ask questions or express any concerns they may have.

Based upon ad-hoc feedback from sites to the FEED1 trial manager and/or Chief Investigator (either verbal or email), it was clear that during the initial recruitment phase of the trial, many clinicians and research staff felt apprehensive about the process. They shared concerns similar to those described by clinicians in the qualitative study within the Cord Pilot Trial - mainly the lack of documentation for the oral assent process and lack of clarity on what information should be included in an oral assent conversation. It was clear that whilst the development of the two-stage pathway was worthwhile, further work was required to **implement** this successfully into other trials and develop the process further.

### *1.8.2 Objective*

To implement a series of interventions to support implementation of the two-stage consent pathway in the FEED1 Trial.

It had originally been intended to evaluate whether the interventions implemented (described in section 1.8.3, table 6) had led to clinicians feeling more supported in the process. However, due to the Covid-19 pandemic, it was not possible to undertake this evaluation. The FEED1 trial was temporarily paused and, following re-opening, activity has been slow to start due to reduced staffing. Amidst a global pandemic, whilst the NHS is in crisis, is not an appropriate time to undertake this survey. Evaluation will take place at a later date.

### *1.8.3 Methods*

To understand clinicians' views of the two-stage consent pathway to know how to support them, shortly after recruitment started (October 2019) all sites participating in the FEED1 trial at the time (February 2020) were sent a short online survey (appendix 4). Twenty-eight responses were received in total and twenty of these were from site staff who had no experience of taking oral assent in FEED1 or any previous trials. These clinicians (n=20) were asked to report how confident they felt at taking oral assent using a ten-point scale (0 = not confident at all, 10 being extremely confident). Only seven (35%) clinicians reported a score of between 8-10, with most clinicians (n=11, 55%) reporting a score of 5-7. As expected, the likes and dislikes of the process were similar to those given during the previous Cord Pilot trial and ad-hoc feedback from FEED1 sites. Almost all respondents (n=26, 93%) reported that they liked that the oral assent process allowed them to approach women for participation in a trial during a stressful and sensitive period, when full informed consent might not be practical. Clinicians also liked that the process helped with recruitment into the trial when there is limited time to enter a participant (n=23, 82%). Three quarters of clinicians (n=16) didn't like that the process was unfamiliar, acknowledging they were more familiar in taking written informed consent, and nine (43%) felt unsure about how much information to give in an assent conversation. Clinicians were asked about the support they might find helpful with the oral assent process. Eighteen (72%) clinicians felt that seeing other people having an oral assent conversation would be helpful and seventeen (68%) felt that peer support within the site team would also be helpful.

Given concerns raised during training visits, ad-hoc feedback and the survey results described above, several initiatives were implemented (Table 6). Each initiative is now described in turn.

**Table 6 - Initiatives to support implementation of the two-stage consent pathway**

| |
|---|
| 1. Production of two-stage consent pathways document |
| 2. Hosted interactive webinar for all site staff |
| 3. Produced video showing various oral assent conversation scenarios |
| 4. Oral assent animation provided to women to support decision-making |

### Provision of consent pathways document

Firstly, a short document (appendix 5), focussing entirely on the consent pathway, was written, and circulated to all sites. The document included background to the process, the principles to be followed, the "minimal information" to include in an oral assent conversation (Table 7) and example wording of what a conversation might include (Figure 11).

**Table 7 - Minimal information to include in an oral assent conversation in FEED1**

| |
|---|
| **"You do not have to take part" –** It is a choice to participate; parents can decline a non-standard approach to management |
| **Feeding strategy:** That the proposed study involves non-standard management. The variation from standard management is in the domain of feeding baby – whether to feed milk only, or to incrementally introduce milk in combination with intravenous fluids |
| **"The computer decides"** – In order for it to be a fair test, the computer decides, at random, the feeding strategy |
| **Research –** having explained the above, this is called research |
| **Documentation –** We must still do some paperwork, but can do this later and this is "allowed" |

**Figure 11 - example of an oral assent conversation (post-natal)**

*Your baby is doing well and is ready to have milk. With babies like yours we usually start with a little milk and increase it over a few days. While we increase the milk, we give fluids in the vein to ensure baby has enough fluid.*

*An alternative is to give all the fluids as milk and fully feed your baby from today. This may help your baby and be more comfortable. We think that as your baby is doing well, it would be safe to give all milk.*

*For babies like yours, we do not know which of these two approaches is better. We are comparing them – we let the computer decide which way to feed baby, and see which is best. We want to propose that your baby joins our comparison of treatments – is that OK with you?*

*If baby does join in our comparison of treatments ('research'), we can sort out all the paperwork in the next few days (the "committee" says that's OK). If you don't want baby to join in, that's fine.*

**Support and training via a webinar**

Secondly, an interactive webinar was presented by me and a consultant neonatologist (who was a co-investigator on both the Cord Pilot Trial and the FEED1 Trial). The content of the webinar included similar information to that included in the document, however offered sites an opportunity to ask questions and hold discussions between themselves. A short role-play exercise was also carried out so that clinicians could hear an example of an oral assent conversation. The webinar was audio-recorded and a link to this then circulated to all participating sites. Initial feedback from the webinar and clinicians felt that including examples of scenarios of oral assent conversations was helpful.

**'Oral assent scenarios' video**

Thirdly, a series of short videos was produced. Following a short introduction, these showed several different examples of a clinician approaching a woman to have an oral assent conversation about participation in the FEED1 Trial. For authenticity, the role of the woman was played by a mother who had experience of giving birth to an infant at 31 weeks gestation (i.e., representative of the trial population). The role of the clinician was conducted by the consultant neonatologist who had also co-presented the webinar. Several scenarios were included to demonstrate to clinicians

that there is no “script” when having an oral assent conversation. Instead, clinicians should tailor their conversation to the needs of the woman, whilst ensuring the minimal information required is included. A link to the videos was circulated to all sites and placed on the FEED1 website.

**Animation for parents**

Finally, a short animation was produced. The purpose of this was two-fold: (i) to offer parents an additional way of receiving information about participation in the trial which may be easier to understand during a stressful and sensitive time, (ii) to provide clinicians support with a standardised way of giving information to women about the trial. The intention was that the animation was in *addition* to an oral assent conversation, rather than *instead of*. The animation included the minimal information required for the women to help make a decision about participation.

The webinar, oral assent videos and animation are all available at www.feed1.ac.uk. The animation can also be accessed via a QR code (Figure 12).

**Figure 12 - QR code for animation to support an oral assent conversation**

QR code and link to FEED1 assent animation

https://youtu.be/wTyq_ZXcw78

FEED1

FLUIDS EXCLUSIVELY ENTERAL FROM DAY 1

## 1.9 Part 3C: Training of staff working on clinical trials (published works 6)

### *1.9.1 Background, existing evidence and gaps in knowledge*

**Current practice and why training is important**

Designing and conducting a clinical trial to a high quality standard requires expertise which, in some countries, is enshrined in law, stating that staff working on clinical trials have appropriate training to enable them to conduct their role to a high standard[119, 124]. Training is often focussed around the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) training, which is a standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials. This standard, originating in the 1940s as a result of the Nuremberg Code, serves to protect the rights, safety and wellbeing of research participants and the scientific credibility of clinical trial data[125]. A survey conducted by the European Clinical Research Infrastructure Network (ECRIN) showed that GCP training was provided in all but one of the eleven member countries and in many countries this is supplemented with study-specific training, though this was often non-standardised and optional in some countries[126]. All participating countries were high-income settings. In the UK, a systematic review reported studies investigating trials training for recruiting staff where there was a link to RCT recruitment[127]. This included seventeen studies and showed that overall whilst training programmes were well received, there appeared to be no specific link to increased recruitment rates, patient understanding of the trial, satisfaction or levels of informed consent. It concluded that recruiter training programmes need to be developed to lead to improved recruitment and consent rates in RCTs. Methods for training can vary, though there is a paucity of evidence in evaluating these training methods. To add to this scarce evidence base, I have designed and implemented a Study Within a Trial (SWAT), which is a self-contained research study, nested within a trial, to evaluate or explore an alternative way of delivering or organising a particular trial process[128]. This SWAT, embedded within the FEED1 Trial (publication 4) aims to compare group-based training of trial site staff with individual site initiation training and whether the type of training impacts upon a range of defined core performance metrics[129]. The results of this SWAT are not presented in this thesis since work is ongoing.

The UK has several clinical trials training programmes in place, usually offered by universities or large funding bodies, such as NIHR, and in addition has a well-established clinical trial infrastructure. The UKCRC Clinical Trials Units (CTUs) Network comprises 53 registered CTUs and registration is based upon ensuring several quality criteria are met. One such criterion is that there is a presence of "a core team of expert staff to develop studies". Other groups and networks exist which support researchers designing and conducting studies with their ongoing professional development to conduct high-quality trials.

**Clinical Trials training in low-resource settings**

In the context of conducting studies in low-resource settings, it is less clear what standards are in place for staff designing and conducting clinical trials. Some resources are available, such as The Global Health Network (TGHN). This Network, established in 2009 by researchers at the University of Oxford, is a platform to enable research by sharing knowledge and methods. The TGHN website contains many resources, such as groups in specialist areas, but in the context of this thesis, of relevance is the Global Health Training Centre: https://globalhealthtrainingcentre.tghn.org/. This online training centre aims to provide research staff in a variety of roles, regions and clinical areas, a range of 'how to' training materials in order to conduct high quality research. Whilst these resources are welcomed, the capacity to conduct locally-led clinical trials in low-resource settings is limited[130, 131]. A qualitative study which included focus-group discussions and interviews with a range of stakeholders conducted in three LMICs (Ethiopia, Cameroon and Sri Lanka), found several barriers to undertaking clinical trials. One barrier identified was "knowledge and technical skills to undertake trials"; participants identified that the lack of skilled research staff was in part due to lack of attention to research methods in undergraduate and postgraduate curriculums. In addition, they felt that the capacity to teach clinical trials was limited. The study concluded that multiple, coordinated interventions are needed to establish the conditions needed to conduct research, particularly clinical trials, thus building capacity in LMICs [132].

In 2018, Rosala-Hallas published the results of a priority-setting exercise considering the methodological research agenda for global health trials[133]. This study, which

included over 300 participants from different research methods disciplines and across several continents, used the Delphi survey method[134] to gain consensus on the top priorities for research methods research in LMICs. The second highest priority was methods relating to training of research staff, including cost-effective methods, blended learning and the incorporation of new technologies.

**Research-capacity building in LMICs**

Clinicians and researchers based in LMICs are best placed to conduct research into the challenges that face the people of the country in which they reside. However, for these individuals to gain the skills and experience required to conduct studies tackling important health challenges, research capacity-building is essential. Beran et al published a call to action in 2017 which focused on obligations for funders, researchers and governments in HICs and LMICs in order to ensure that research capacity-building is not neglected[135]. Since this publication, progress has been made in some of these areas, though there is still a long way to go. There are currently a number of strategies in place to help build research capacity building which I will describe in brief here. Funders of clinical research in the UK, including NIHR and UKRI-MRC, provide funding for conducting research in LMICs. It is a requirement that applications are co-developed by researchers in the UK and the LMIC in which the research is proposed, and that all applications include research-capacity building activities. Examples of such activities include providing research training to people in LMICs, research qualifications (including conducting post-graduate studies), mentoring less experienced members of the team, including requests for funding for conference attendance, and ensuring a fair and equitable publication policy. In addition, specific programmes to fund individuals to focus on research leadership in LMICs have been developed, including the African Research Leaders call offered by the UKRi-MRC, which is intended for *"rising star individuals who will lead high quality research on key global health issues pertinent to sub-Saharan Africa"*. Embedding PhD training into research studies was viewed as a positive example in two case studies of research-capacity building initiatives in Ethiopia and Central African Republic[136]. Some UK universities also provide training in clinical trials, specifically focussing on training individuals from LMICs, including the London School of Hygiene and Tropical Medicine which offers different levels of

training by distance learning (https://www.lshtm.ac.uk/study/courses/masters-degrees/clinical-trials-online).

In previous studies I have designed and conducted in low-resource settings, the focus has been to deliver study-specific training delivered via classroom teaching, rather than general research skills training aimed at building capacity amongst clinicians and researchers in LMICs. Paper 6 within this thesis presents a study aimed at investigating whether an enhanced training package, which includes elements of the 'train-the-trainer' approach, to teach clinical trials to researchers and clinicians improves knowledge of clinical research in clinicians and researchers in LMICs. The 'train-the-trainer' approach is an effective way of spreading training in healthcare and involves an individual or small group receiving training, who then provide training to a larger group of people[137-139]. This approach could be an effective method for providing global health clinical trials training and has not been evaluated previously.

### *1.9.2 Objectives*

I co-led the Born Too Soon Optimising Nutrition study which was conducted in Kenya and India in 2019-2020. Part of this project was to assess the feasibility of conducting the FEED1 Trial (published works 4) in LMICs. This project was part of an interdisciplinary Global Challenges Research Fund (GCRF) grant which included several interlinked studies, including a focus on research capacity-building.

The objectives of the capacity-building component of the project, which I led, were to:

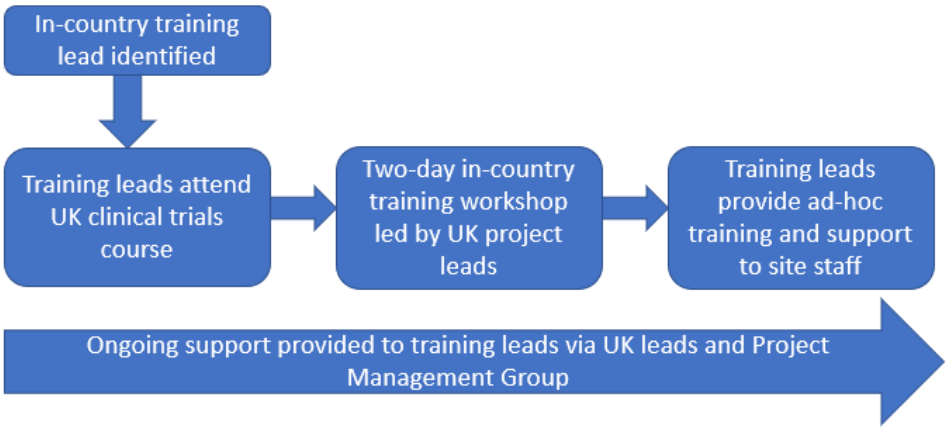
1. Provide clinical trials training for designated "trainers" at each participating institution
2. To test the effectiveness of an enhanced training package to provide training to researchers and clinicians, including elements of the 'train the trainer' approach

### *1.9.3 Methods*

Methods are described in detail in published works 6. Two hospitals participated in the project: Kenyatta National Hospital, Nairobi, Kenya and Sir Sunderlal Hospital, Banaras Hindu University, Varanasi, India. These were selected based upon existing collaborations and contacts, and their prior research experience. The two hospitals provide alternative contexts: the Kenyatta National Hospital is a national referral hospital in Kenya's densely populated capital city, Nairobi. It is closely linked to the University of Nairobi and its staff have conducted numerous research studies in the past. Its neonatal unit is frequently over-occupied due to the number of neonates requiring additional care after birth. In contrast, the Sir Sunderlal Hospital in Varanasi serves a much smaller population, and its staff have less experience in conducting neonatal research, particularly clinical trials.

The enhanced training package included several components (Figure 13) which are now described in turn.

**Figure 13 - Enhanced training package in Born Too Soon Optimising Nutrition Study**




**Fundamentals of Clinical Trials course**

An individual from each country was identified to take responsibility for ensuring research staff and the wider clinical team were appropriately trained to conduct the Optimising Nutrition Study. Each team chose to nominate a clinician (one

neonatologist and one paediatrician) for the training lead role. Both training leads attended the Fundamentals of Clinical Trials course, run by the Nottingham Clinical Trials Unit (NCTU) UK in November 2019 (www.nctu.ac.uk/short-courses/index.aspx). This is a 5-day face-to-face course which teaches the basics of clinical trial design and conduct and is delivered by members of NCTU staff with expertise in this area. In addition to the individual professional development benefits of attending the course, attendance also gave them skills to increase their understanding of clinical trials and thus teach others, within the wider research and clinical teams at their hospitals, as part of the Born Too Soon Optimising Nutrition Study.

**In-hospital training sessions**

Following attendance at the course in November 2019, a two-day training workshop at each hospital in December 2019 was conducted, led by myself and co-lead, Ojha (Image 3). The training workshop was attended by the training leads, members of the research team within each hospital and the wider clinical team, including neonatal doctors and nurses. The workshop utilised a range of training methods including classroom-based lectures, facilitated and unfacilitated group discussions and hands-on data collection and data entry practice. Ample time was included for attendees to ask questions, highlight potential study delivery issues and discuss possible solutions.

**Image 3 - Born Too Soon Optimising Nutrition Study, training sessions in India and Kenya, December 2019**



### Additional training support

In addition to the two training methods described above, the training leads were responsible for providing additional ad-hoc training and support to other healthcare workers and researchers at their site. Training leads and in-country study coordinators were encouraged to maintain regular contact with the study team in the UK who were able to provide ongoing support and mentorship. In addition, the training leads attended a virtual Project Management Group meeting, held monthly, where issues and potential solutions were discussed.

### Evaluation of the enhanced training package

Prior to the delivery of training material, each attendee was asked if they'd be willing to participate in the training sub-study and, if so, to complete a written informed consent form. Once consent was provided, participants completed short paper questionnaires (Table 8). Questionnaires can be seen in full in appendix 6.

**Table 8 - Questionnaires to evaluate the training package**

| Questionnaire name | Description of questionnaire | Number of questionnaire items | Questionnaire completion timepoints |
|---|---|---|---|
| Demographic details | Basic demographics (gender, age, job title, clinical area) | 4 | Baseline only |
| Research experience | Any research experience, number and type of research studies worked on, previous research training received, tasks conducted on a research study | 6 | Baseline only |
| Protocol-specific questions | Born Too Soon Optimising Nutrition Study protocol questions. Highest mark available = 10. | 8 multiple-choice items | Baseline / end of study |
| Informed consent and ICH-GCP | Questions reproduced from TGHN training resource. Questions scored as a percentage. Pass mark = ≥80%. | 13 (informed consent) and 31 (ICH-GCP), all multiple-choice items | Baseline / end of study |

Each participant gave their consent to be contacted subsequently, by a method that suited them (e.g. WhatsApp, Skype) to discuss their views and opinions on training methods. Paper questionnaires were returned to the UK and data subsequently entered onto a Microsoft Excel spreadsheet.

The questionnaires (Table 8) were then repeated at the end of the study (November 2020). For logistical and cost reasons, rather than asking participants to complete paper questionnaires, an electronic version of the questionnaires was built, using JISC surveys©. The link was emailed to all participants and one-two reminders sent to non-responders, with ad-hoc reminders given by in-country coordinators.

The protocol-specific questionnaire and informed consent/ICH-GCP questionnaires were scored at the end of the study. Actual scores and percentages were entered into a .CSV file. All data were imported into Stata version 15 for analyses. Data from the demographic and previous research experience questionnaire are presented descriptively. Descriptive statistics are also presented for the protocol-specific questionnaire and informed consent/ICH-GCP questionnaire. In addition, mean differences in scores and 95% CIs are also reported, for participants who completed questionnaires at both time intervals.

The outcomes of interest are i) the proportion of participants who pass the Global Health Network ICH-GCP course and informed consent module, ii) the proportion of researchers who have an increased understanding of the study protocol.

*All references for this extended abstract can be found at the end of the thesis*

## 2. THE PUBLISHED WORKS

Herein follows publications 1-6. Since these published works were large, often international, collaborations, there are a large number of authors on each paper, reflecting the contributions they made to the research. Authors' contributions are described at the beginning of the thesis (table 1).

**PAPER 1: Feasibility of using an Early Warning score for preterm or low-birth weight infants in a low resource setting: results of a mixed-methods study at a national referral hospital in Kenya**

BMJ Open

# Feasibility of using an Early Warning Score for preterm or low birthweight infants in a low-resource setting: results of a mixed-methods study at a national referral hospital in Kenya

Eleanor J Mitchell [1], Zahida P Qureshi,[2] Fredrick Were,[3] Jane Daniels,[1] George Gwako,[2] Alfred Osoti,[2] Jacqueline Opira,[4] Lucy Bradshaw,[1] Mary Oliver,[5] Phoebe Pallotti,[6] Shalini Ojha [7,8]

**To cite:** Mitchell EJ, Qureshi ZP, Were F, *et al*. Feasibility of using an Early Warning Score for preterm or low birthweight infants in a low-resource setting: results of a mixed-methods study at a national referral hospital in Kenya. *BMJ Open* 2020;**10**:e039061. doi:10.1136/bmjopen-2020-039061

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-039061).

Received 02 April 2020
Revised 11 September 2020
Accepted 22 September 2020

Check for updates

© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

**Correspondence to**
Eleanor J Mitchell;
Eleanor.Mitchell@nottingham.ac.uk

## ABSTRACT

**Introduction** Fifteen million babies are born prematurely, before 37 weeks gestational age, globally. More than 80% of these are in sub-Saharan Africa and Asia. 35% of all deaths in the first month of life are due to prematurity and the neonatal mortality rate is eight times higher in low-income and middle-income countries (LMICs) than in Europe. Early Warning Scores (EWS) are a way of recording vital signs using standardised charts to easily identify adverse clinical signs and escalate care appropriately. A range of EWS have been developed for neonates, though none in LMICs. This paper reports the findings of early work to examine if the use of EWS is feasible in LMICs.

**Methods** We conducted an observational study to understand current practices for monitoring of preterm infants at a large national referral hospital in Nairobi, Kenya. Using hospital records, data were collected over an 8-week period in 2019 on all live born infants born at <37 weeks and/or <2500 g (n=294, 255 mothers) in the first week of life. Using a chart adopted from the EWS developed by the British Association of Perinatal Medicine, we plotted infants' vital signs. In addition, we held group discussions with stakeholders in Kenya to examine opinions on use of EWS.

**Results** Recording of vital signs was variable; only 63% of infants had at least one temperature recorded and 53% had at least one heart rate and respiratory rate recorded. Stakeholders liked the traffic-light system and simplicity of the chart, though recognised challenges, such as staffing levels and ability to print in colour, to its adoption.

**Conclusion** EWS may standardise documentation and identify infants who are at higher risk of an adverse outcome. However, human and non-human resource issues would need to be explored further before development of an EWS for LMICs.

## Strengths and limitations of this study

- This is the first study exploring the possibility of using a neonatal early warning score in a low-resource setting.
- The opinions of a wide range of stakeholders, including senior policy-makers and clinicians, are included.
- Detailed data on preterm and low birthweight infants' vital signs were recorded for the first 7 days of life, though was limited to what was routinely recorded.
- The tool includes physiological reference ranges for term and late preterm infants, whereas we studied preterm or low birthweight infants.
- Data collection was limited to a tertiary referral hospital in Nairobi, however, many preterm infants in low-resource settings are cared for in centres with much larger constraints.

## BACKGROUND

Globally, 15 million babies are born prematurely[1]; more than 80% in sub-Saharan Africa (12.3% of all births).[1] Mortality for a preterm infant born in a low-income or middle-income country (LMIC) is eight times higher than in Europe.[2] Among the causes of neonatal mortality (NMR), prematurity remains the biggest killer with 35% of all neonatal deaths attributed to preterm birth or its complications.[3] The United Nations Sustainable Development Goals recognise the need to significantly improve outcomes for newborn infants and have a strategic vision to end preventable newborn deaths, with all countries aiming to reduce the NMR to at least 12 per 1000 live births.[4]

In Kenya, where the most recent NMR was 19.6 per 1000 live births,[5] infants born prematurely should be managed in accordance with national and international guidance for essential newborn care,[6–8] though this may not always reflect what happens in practice. Guidance includes a range of evidence-based

BMJ Open: first published as 10.1136/bmjopen-2020-039061 on 28 October 2020. Downloaded from http://bmjopen.bmj.com/ on April 1, 2021 by guest. Protected by copyright.

recommendations for care in the first week of life, for example, provision of Kangaroo Mother Care (KMC) for all clinically stable infants weighing <2000 g, which is recommended for hypothermia prevention.[6 8 9] The World Health Organisation (WHO) estimates that >80% of moderate to late (32–37 weeks) preterm infants could survive with the provision of essential newborn care.[10]

Early Warning Scores (EWS) are a way of quickly and easily identifying adverse clinical signs and are often used in adult populations in a variety of clinical areas,[11] however, they are less commonplace for neonatal care. A review by Mortensen *et al*[12] identified seven EWS systems for neonates, including the Newborn Early Warning Trigger and Track (NEWTT) Framework, developed in the UK by the British Association for Perinatal Medicine[13] for infants primarily on postnatal wards with little or no increased surveillance (online supplemental material 1). While this framework states that the chart should be triggered for 'high-risk' infants, only late preterm infants ($34–36^{+6}$ weeks) are considered due to the fact most preterm infants born in the UK at earlier gestations are admitted for higher-dependency neonatal care with continuous monitoring. Infants who could most benefit from closer monitoring and early detection of adverse signs, particularly in low-resource settings where continuous monitoring is not available in neonatal units, are preterm or low birthweight infants. Indeed Mortensen *et al*'s review stated that of the four systems published in full, two only included term babies weighing >2500 g. The authors concluded that none of the available systems at the time considered 'high-risk' infants who had been admitted for neonatal care and recommended modifications be made to existing systems. For example, the reference ranges included in the NEWTT were based on neonatal physiological parameters in term and late preterm infants and adjustments may need to be made based on gestational age.[14] To the best of our knowledge, there are no published EWS from low-resource settings such as Kenya nor are such systems currently utilised. All available scoring systems were developed in high-income countries where continuous vital sign monitoring in neonatal units is standard, yet there is evidence, within an obstetric setting, that an EWS system is feasible and possible to implement in a low-resource setting.[15]

In keeping with other EWS systems, the NEWTT adopts a traffic-light scoring system. An infant's vital signs are recorded on to a single page. If a measurement is in the red zone or there are two recordings in the amber zone, the attending nurse is alerted and immediate escalation to a review by a suitably qualified practitioner is required. The purpose of such a strategy is to alert healthcare professionals to the potential of deterioration in the condition of a high-risk infant and give them an opportunity to intervene with appropriate care.

The aim of this study was to investigate whether an EWS system in preterm and low birth weight infants could be implemented in a low-resource setting such as Kenya.

## METHODS

### Observational study

In order to understand the characteristics of infants born in this setting, first we conducted an observational study at the Kenyatta National Hospital (KNH), a tertiary referral hospital, in Nairobi, Kenya. Data were collected during an 8-week period in March to April 2019 from routinely recorded data. No interventions nor study specific actions in response to observations were required and management of the infants followed usual practice. All infants born at KNH, during the study period, who were <37 weeks gestational age and/or <2500 g at birth were included. Data were collected from birth until day 7 or discharge/death. Outborn infants (not born at KNH and admitted postnatally) were excluded.

Research midwives, trained during a 3-day workshop, collected data using paper data collection booklets. Maternal and infant characteristics were collected and all vital signs recordings (temperature, heart rate and respiratory rate) in the infant's clinical notes were collected. All data were entered into a password-protected study-specific database (Macro (Elsevier)) by the study coordinator. Data quality checks were undertaken remotely by the UK team. Maternal and infant characteristics were summarised descriptively using the mean, SD, minimum and maximum for continuous variables and frequency counts and percentages for categorical variables along with the number of observations. Analyses were conducted in Stata V.15 (StataCorp). Data on temperature, heart rate and respiratory rate were retrospectively plotted onto graphs representing the NEWTT system, showing values that were within the red, amber and green zones, using the reference ranges specified in the NEWTT.

No informed consent was sought from parents since the study was observational and participants were not subjected to any intervention.

### Stakeholder meeting

In order to understand possible barriers and facilitators to the use of an early warning track and trigger system in Kenya, a stakeholder meeting was held in July 2019 in Nairobi. This was attended by 78 delegates from a range of organisations (online supplemental material 2). Delegates were split into groups of approximately 8–10 and asked to consider and feedback: (1) what they did and did not like about an early warning track and trigger system, (2) what would need to be in place to enable its use and (3) what are the perceived barriers to its use. Feedback was written by groups using flipchart paper and verbal feedback given. A narrative thematic analysis[16] was conducted and themes were identified from the feedback provided.

### Patient and public involvement

Patients and the public were not involved in the design or conduct of this study. However, non-government organisations and charities representing patients and the public were involved in the stakeholder meeting.



BMJ Open: first published as 10.1136/bmjopen-2020-039061 on 28 October 2020. Downloaded from http://bmjopen.bmj.com/ on April 1, 2021 by guest. Protected by copyright.

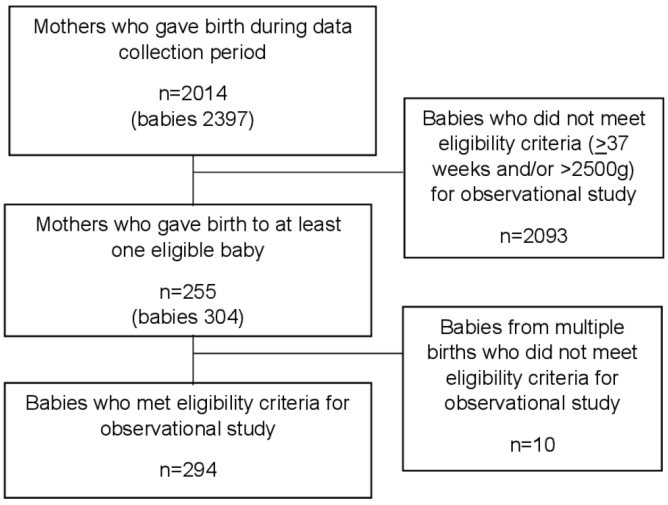



**Figure 1** Study flow diagram.

## RESULTS

### Observational study

Data were collected between 5 March 2019 and 30 April 2019 on the labour suite, postnatal wards and newborn unit of the participating hospital. During the data collection period 2397 infants were born in KNH (figure 1). 294 infants (255 mothers) (14.6%) met the eligibility criteria of being born at <37 weeks gestation and/or weighing <2500 g. Ten infants, from multiple births, were subsequently excluded as they did not meet the eligibility criteria. Two hundred and six infants were from singleton pregnancies, 82 from twin pregnancies and 6 from triplet pregnancies.

The mean (SD) age of the mother was 28 (6) years and just under half were educated to secondary/high school level (124/255, 49%). Infants' characteristics are included in table 1.

### Recording of vital signs (heart rate, respiratory rate, temperature, in clinical records)

Very few infants had vital signs recorded in the first hour of life (table 1) and KMC was not recorded as having been initiated in any of the 180 clinically stable infants soon after birth.

The number of recorded observations per infant per day was analysed (table 2). On day 1, less than half of the infants (136/294, 46%) had at least one temperature recording, 130/294 (44%) had at least one heart rate recording and 129/294 (44%) had at least one respiratory rate recording. The number of infants with at least one recording in each of the domains increased throughout the hospital admission: on day 7, 86/104 (83%) of infants had at least one temperature recording, 85/104 (82%) had at least one heart rate recording and 83/104 (80%) had at least one respiratory rate recording. This also includes infants who were then discharged on or died on day 7 (n=9), in addition to the 95 infants who remained in hospital. For these 95, each infant had a mean (SD) of 18 (5.1) temperature recordings, 18 (6.8) heart rate recordings and 17 (6.6) respiratory rate recordings throughout their admission.

Over the entire study period, 185/294 (63%) infants had at least one temperature recorded, 156/294 (53%) had at least one heart rate recording and 155/294 (53%) had at least one respiratory rate recording. Retrospectively, each recording for each domain (temperature, heart rate,

**Table 1** Characteristics of infants <37 weeks gestational age and/or <2500 g at birth born at the Kenyatta National Hospital in March to April 2019

| Characteristic | Total (n=294) |
|---|---|
| Sex: no (%) of females | 135 (54) |
| Mode of delivery—n (%) | |
| Vaginal | 123 (42) |
| Elective caesarean section | 3 (1) |
| Emergency caesarean section | 168 (57) |
| Delayed cord clamping (n=14; 280 unknown) | 0 (0) |
| Birth weight (g) mean (SD) | 1977 (603) |
| Head circumference (cm) (n=19) Mean (SD) | 32.6 (2) |
| Length (cm) (n= 4) mean (SD) | 36.0 (5) |
| Estimated gestational age at birth—n (%) | |
| <28 weeks | 26 (9) |
| 28–32+6 weeks | 70 (24) |
| 33–36+6 weeks | 123 (42) |
| >37 weeks | 73 (25) |
| Unknown | 2 (<1) |
| Gestational age estimation based upon—n (%) | |
| First trimester ultrasound | 14 (5) |
| Clinical assessment | 30 (10) |
| Last menstrual period and/or clinical assessment (mother) | 242 (82) |
| Dubowitz and New Ballard score | 6 (2) |
| Unknown | 2 (<1) |
| No (%) of babies who required resuscitation at birth (n=287) | 110 (37) |
| Type of resuscitation—not mutually exclusive (n=110) | |
| Stimulation only | 12 (11) |
| Ventilation | 91 (83) |
| Continued ventilation | 36 (33) |
| Advanced resuscitation | 4 (4) |
| No (%) of babies who received maternal breast feeding within one hour of birth (n=260) | 39 (13) |
| No of babies who had initiation of Kangaroo Mother care soon after birth (stable babies only) (n=180) | 0 (0) |
| No (%) of babies who had temperature within one hour of birth* | 10 (3) |
| No (%) of babies who had heart rate at birth* | 58 (20) |
| No (%) of babies who had respiratory rate at birth* | 70 (24) |

*Recorded in clinical records.

BMJ Open: first published as 10.1136/bmjopen-2020-039061 on 28 October 2020. Downloaded from http://bmjopen.bmj.com/ on April 1, 2021 by guest. Protected by copyright.

Table 3 Subsequent temperature recordings for 92 infants who had an initial temperature recorded of <36°C

| Temperature (°C) | <4 hours (n=25) (27%) | 4–6 hours (n=26) (28%) | >6 hours (n=41) (46%) |
|---|---|---|---|
| <36 | 10 (40%) | 7 (27%) | 12 (29%) |
| 36 to <36.5 | 5 (20%) | 5 (19%) | 11 (27%) |
| 36.5 to 37.5 | 9 (36%) | 11 (42%) | 15 (37%) |
| >37 to 38 | – | 3 (12%) | 3 (7%) |
| >38 | 1 (4%) | – | – |

respiratory rate) was mapped to a single red, amber or green zone on the UK NEWTT by the researchers. These recordings were not charted on the NEWTT in real time by the clinical staff and we did not collect data on what action(s), if any, were taken in response to a red or amber recording. Although, the NEWTT indicates escalation of care for one recording in the red zone or two recordings in the amber zone, we only included single recordings since it was impossible to know whether an action was taken after one single amber recording.

97/185 (52.4%) had at least one temperature recording in the moderate hypothermic range (<36°C) and 145/185 (78.4%) had at least one recording between 36°C and 36.49°C. Of the 97 infants who had a recorded temperature of <36°C, 92 had any subsequent temperature recording, almost half (41/92, 46%) of which were taken >6 hours later (range 30 min to 46 hours). Of those, 29 infants' (32%) subsequent temperature remained <36°C (table 3).

Tachycardia, defined as a heart rate of >161 beats/minute, was noted in 98/156 infants (62.8%), and 34/156 (21.8%) had at least one recording >175 beats per minute (red zone). High respiratory rate (>80 breaths/min; red zone) was recorded, at least once, in 24/155 (15.5%) and 109/155 (70.3%) had at least one recording of 61–80 bpm (upper amber zone). A respiratory rate of <30 breaths/min (red zone) was recorded at least once in 9/155 (6%) and 73/155 (47%) had at least one recording of 30–39 breaths/min (lower amber zone). Figure 2 shows recordings for the 95 infants who were still in hospital at day 7 plotted onto colour-coded graphs representing the NEWTT's reference ranges.

## Stakeholder meeting

Seventy eight stakeholders attended the 1-day meeting to discuss the development of this tool in a low-resource setting such as Kenya. Stakeholder types are shown in online supplemental material 2. Feedback groups contained a variety of stakeholder types. The main themes that emerged from stakeholder discussions were (1) simplicity and ease of use of the tool, (2) sustainability and resource and (3) training and implementation. Example quotes are included for each theme.

### Simplicity and ease of use

Stakeholders reported they liked the coloured traffic-light system since this enabled easy interpretation of the data, recognition of need for action and earlier identification of danger signs.

'The colours are good and explains why'.

'It would be easy to identify infants at risk'.

Several stakeholders also commented they liked the combined presentation of several vital signs on one chart, rather than having lots of paper notes which can easily become untidy or misplaced. One policy-maker commented that '[the chart's] simplicity would make universal coverage easier'. Some also considered whether it would be possible to digitise the system, for example, by creating an app, though recognised while this would negate the use for coloured printing, it would not relieve issues with availability of resources.

### Sustainability and resources

Several stakeholders commented that although they liked the traffic-light system approach, it may be difficult to print the document since colour printing is expensive and often not available.

'Printing coloured is a challenge'

The main concerns for the majority of stakeholders were the availability of healthcare staff to make and document the recordings. It was recognised that such

Table 2 Number of infants with vital signs recordings (temperature, heart rate, respiratory rate) per day for the 7-day data collection period

| Day | Babies in hospital | At least one temperature recording, (%) | At least one heart rate recording, (%) | At least one respiratory rate recording, (%) |
|---|---|---|---|---|
| 1 | 294 | 136 (46) | 130 (44) | 129 (44) |
| 2 | 272 | 165 (61) | 139 (51) | 139 (51) |
| 3 | 222 | 147 (66) | 130 (59) | 128 (58) |
| 4 | 194 | 127 (65) | 119 (61) | 119 (61) |
| 5 | 139 | 110 (79) | 107 (77) | 107 (77) |
| 6 | 115 | 90 (78) | 89 (77) | 90 (78) |
| 7 | 104 | 86 (83) | 85 (82) | 83 (80) |

BMJ Open: first published as 10.1136/bmjopen-2020-039061 on 28 October 2020. Downloaded from http://bmjopen.bmj.com/ on April 1, 2021 by guest. Protected by copyright.

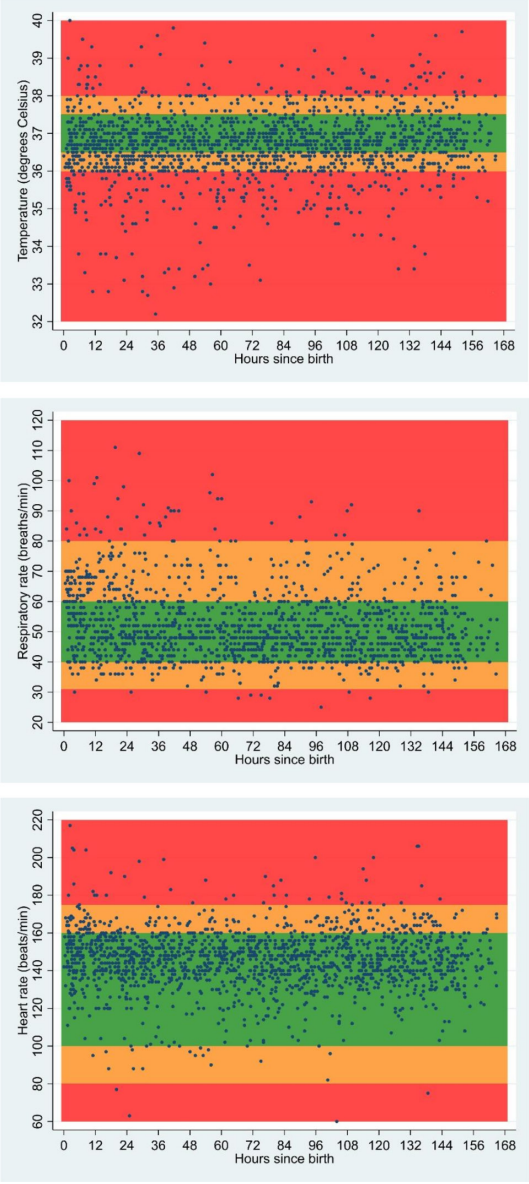



**Figure 2** Vital sign recordings of preterm, low birthweight infants born and admitted to a tertiary referral hospital in Kenya for first 7 days of life (n=95) data from infants who were in hospital at day 7. Each dot represents a vital sign recording. Since infants had multiple vital signs recordings during their admission, they could have several values across each of the colour zones at multiple time points. Graph adapted from NEWTT (Newborn Early Warning Trigger and Track).

a system would be acceptable if it replaced the current system of recording vital signs but would not be acceptable as additional workload. Further to this the major barrier to implementation of this or any similar EWS was recognised as the lack of resources, both staff and interventions, to be able appropriately escalate the care of those infants who would be identified as sick. The early warning track and trigger system requires immediate escalation to a more senior neonatologist if a value falls into a red zone or two values in an amber zone; stakeholders felt this may not be possible given staffing levels on neonatal units in this setting.

> 'We have low staff:patient ratios. This [EWS] has very intense observational needs in a staff-constrained set-up'

### Training and implementation

Some stakeholders felt that staff working on the newborn/neonatal unit may not like it since it may 'feel like more work' although others recognised that while initial resistance may be encountered this could be overcome by educating staff members of the potential value of such a system. Many stakeholders commented that training on its use would be paramount, which should include not only how to complete the tracking system and trigger escalation, but its potential to reduce neonatal mortality. A non-governmental organisation representative commented that while implementing such a system may be a good idea, it would 'require national level harmonisation' and that a close working relationship with the Ministry of Health would be important, since it would need to be endorsed at both a national and organisational level.

> 'It should be integrated into existing tools and the curriculum'.

> 'Harmonise/integrate this with existing tools to avoid double work'.

## DISCUSSION

This is the first study exploring the possibility of using a neonatal EWS in LMICs. EWSs are recommended for use in routine practice in the UK[13] and may have the potential for supporting early recognition of unwell infants.[17] However, before any practice can be transferred from one healthcare setting to another it is important to test the feasibility of implementing the practice in the target setting.[18]

EWSs are predicated on regular recordings of vital signs. At KNH, local guidelines stipulate newborn infants should have vital signs checked every 4–6 hours,[19] however, our study demonstrates that the routine recording of vital signs in infants' notes was infrequent; only half had any heart or respiratory rate recordings and around two thirds had any temperature recording during their admission. Indeed even for the infants with a low temperature (<36°C) that would be in the red zone on an EWS, many of them did not have a subsequent temperature recorded within 4–6 hours. Interestingly, the number of infants with at least one recording increased during their admission. This could be because fewer infants remained in hospital throughout the 7 days and those that remained are more likely to be infants who are unwell and require longer hospital care. It is likely, therefore, that these infants were prioritised by the staff and monitored more closely. The first 24 hours of life for an infant are critical and 25%–45% of all neonatal deaths occur in this



BMJ Open: first published as 10.1136/bmjopen-2020-039061 on 28 October 2020. Downloaded from http://bmjopen.bmj.com/ on April 1, 2021 by guest. Protected by copyright.

period[20]; it is of importance, then, that less than half of infants in the observational study had vital signs recorded on day 1 of life and only a very small handful of infants had any vital signs recorded within the first hour of life. These findings are in-keeping with other studies, for example, about 40% infants had vital signs chart available in the Nairobi Newborn Study, which was a retrospective review of 33 neonatal facilities in Nairobi City County.[21] In addition, none of the 180 stable infants had KMC initiated shortly after birth, despite clear evidence that KMC, when compared with standard care, reduces neonatal mortality in preterm infants and infants weighing <2000 g.[22] It will be important to ensure that early implementation of KMC is considered in the further development of an EWS in this setting.

Our study included detailed data on preterm and LBW infants' vital signs' recordings, which included temperature, for the first 7 days of life. Keeping newborn infants warm is a key aspect of essential newborn care.[23] Hypothermia is common in all newborns, particularly preterm and LBW infants, regardless of country of birth. In a large systematic review of neonatal hypothermia[24] prevalence ranged from 32% to 85% in 21 hospital-based studies in Africa and Asia (with the exception of one study which reported 8% prevalence[25]). Temperature data collected in our study is consistent with other studies reporting hypothermia. Infants' temperatures ranged from 32.1°C to 40°C. Of the 2249 recorded temperatures during the 7-day data collection period, over one-third (859/2249, 38%) were <36.4°C. Almost one-third of infants who had a recorded temperature of <36°C, had a subsequent temperature recording of <36°C. If infants were more closely monitored and care escalated if a low temperature was identified, for example, by using simple colour-coded chart such as an EWS, it may be possible for action to be taken sooner, thus potentially preventing further hypothermia.

A standardised template, such as an EWS chart, could support better record keeping. Stakeholders identified that the simple traffic-light system could be easily adaptable to local practice. However, concerns about lack of resources weighed heavily in their minds. This included lack of material resources such as inability to print in colour and the larger issue of shortfalls in numbers of healthcare professionals available for newborn care. The lack of adequate resources for neonatal care in Kenya is well documented.[21 26] In such situations, our results show that any new intervention is likely to be useful only if it does not increase the workload of the healthcare staff.

The Nairobi Newborn Study[21] suggested that implementation of standardised medical and nursing notes could improve care. A priority setting exercise to improve global newborn health recommended that the development of simple clinical algorithms to refer neonates with signs of infection and consequently reduce newborn mortality was a top priority.[27] Although currently there is no evidence that using neonatal EWS improves outcomes in LMICs, research in closely related clinical areas is encouraging: in Ethiopia, the introduction of a Modified Obstetric Early Warning Score (MOEWS) in a referral hospital, improved practice in several domains.[28]

The desired improvement in outcomes can only be achieved from EWSs if there is an appropriate escalation of care when required. In this study, infants' vital signs were retrospectively plotted to the red and amber zones on the NEWTT, using data available via clinical records. Whether clinical action was taken as a result of an adverse vital sign is unknown since these data were not collected. We are, therefore, only able to report the number of infants who may have hypothetically triggered an escalation of care, by the fact a value was plotted to a single red or amber zone. Since the observational study was undertaken to understand current practice, the NEWTT was applied without any modifications. The physiological parameters used therefore pertain to term or late preterm infants and further work will be required to modify these parameters to be more suitable for use in preterm and low birthweight infants. For example, since respiratory rates and heart rates are likely higher in preterm infants than term or late term infants, the need for escalation of care may be overestimated, using the current unmodified version of the NEWTT.

At the stakeholder meeting, the lack of adequately trained medical and nursing staff was again seen as an impediment to such escalation, particularly if the practice were to be implemented widely. The KNH is a tertiary referral centre. Most preterm infants in LMICs including within Kenya are cared for in centres with significantly larger constraints than the KNH. In this context, it is worth considering if the use of EWSs may enable staff to identify patients with greater need sooner and hence facilitate more efficient use of limited resources. A suitably adapted neonatal EWS, using physiological parameters relevant to preterm infants, could replace existing documentation systems and may improve the situation by replacing a cumbersome process of documentation with a more streamlined method.

This is the first study investigating the possibility of using a neonatal EWS in LMICs. We used mixed-methods to explore current practice, and report the opinions of a range of relevant stakeholders into understanding the potential use of neonatal EWS in Kenya. However, we recognise our study has some limitations. First, the study was conducted in a large tertiary hospital which is relatively well resourced. As this is an exploratory study, our aim was to scope current practice and explore the possibility of using EWS in KNH before considering the bigger challenge of rolling it to more remote settings. We used the existing NEWTT chart, designed for term and late preterm infants (rather than all preterm infants), to plot vital signs. Outcome data in large datasets are needed to determine whether the thresholds that define the red and amber zones are applicable to all preterm and low birthweight babies. We limited data collection to what is currently routinely recorded. The next step would be to test the feasibility of replacing the current system of



BMJ Open: first published as 10.1136/bmjopen-2020-039061 on 28 October 2020. Downloaded from http://bmjopen.bmj.com/ on April 1, 2021 by guest. Protected by copyright.

documenting vital signs with an EWS chart to explore if such tools can improve documentation without an unacceptable increase in workload. Further work is planned and will include emphasis on training for the use of EWSs.

Use of MOEWS in obstetrics in LMICs has highlighted the need of a 'partnership approach' and leadership from local teams.[28] Our findings include the possibilities of resistance to change in keeping with the adoption theory, which proposes that any group consists of a mixture of 'innovators, early adopters, early majority, late majority, laggards' and resistance to change is expected.[29] There are several steps outlined in innovation research that are transferable to this healthcare context; 'relative advantage', 'compatibility', 'complexity', 'trialability', 'observability'.[29] In the context of implementing a neonatal EWS, emphasising relative advantage (eg, ease of use); ensuring that the new system 'fits' (compatibility); supporting with easily accessible training (complexity); having a period of trialling before implementing (trialability); and being clear to staff about any outcomes (observability) could facilitate adoption. The follow-up of implementation of MOEWS in Ethiopia showed that attitudes to new practice improved over time.[28]

## CONCLUSION

Development of neonatal EWS in LMICs requires testing the acceptability and feasibility of recording vital signs using locally adapted neonatal EWS charts. Further work is required to ensure that such charts facilitate monitoring of vital signs without increasing workload. A partnership approach with local leadership and training programmes incorporating the principles of the adoption theory are vital. This preparatory work must precede any clinical trials investigating whether implementation of neonatal EWS could reduce neonatal mortality in LMICs.

**Author affiliations**
[1]Nottingham Clinical Trials Unit, School of Medicine, University of Nottingham Faculty of Medicine and Health Sciences, Nottingham, UK
[2]Department of Obstetrics and Gynaecology, University of Nairobi, Nairobi, Nairobi, Kenya
[3]Department of Paediatrics and Child Health, University of Nairobi, Nairobi, Nairobi, Kenya
[4]Kenya Paediatric Research Consortium (KEPRECON), Nairobi, Kenya
[5]School of Education, University of Nottingham, Nottingham, UK
[6]School of Health Sciences, University of Nottingham, Nottingham, UK
[7]Division of Graduate Entry Medicine, School of Medicine, University of Nottingham Faculty of Medicine and Health Sciences, Nottingham, UK
[8]Neonatal Unit, University Hospitals of Derby and Burton NHS Foundation Trust, Derby, UK

**Twitter** Eleanor J Mitchell @eleanor_mitch

**Acknowledgements** We would like to thank the team of research midwives at the Kenyatta National Hospital for their assistance in data collection. We also thank everyone who attended the networking event for their input. Thank you to staff at the Nottingham Clinical Trials Unit for their input: Lisa Evans and Charlotte Gidman (data management), Daniel Simpkins (database programming).

**Contributors** EJM was the overall principal investigator and conceived the idea and wrote the first draft of the manuscript. SO was the overall clinical lead. ZPQ was the principal investigator and JO was the Study Coordinator in Kenya. GG and AO provided obstetric expertise and facilitated data collection. FW was the lead neonatologist in Kenya. LB undertook statistical analyses. JD provided mentorship to the research group. PP provided midwifery expertise. MO assisted with qualitative analysis. All authors contributed to the manuscript and approved the final draft.

**Funding** The observational study was funded by a Global Challenges Research Fund (GCRF) pump-priming grant by the University of Nottingham (ref RIS 630122). The stakeholder meeting was funded by an in-country networking event grant by the University of Nottingham (ref RIS 630131).

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** The study was conducted with full ethical approval from the joint Kenyatta National Hospital-University of Nairobi Ethics Research Committee (ref P772/11/2018) and the Faculty of Medicine and Health Sciences Research Ethics Committee at the University of Nottingham (ref 161–1812).

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available on reasonable request to the corresponding author.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

**ORCID iDs**
Eleanor J Mitchell http://orcid.org/0000-0002-6998-4533
Shalini Ojha http://orcid.org/0000-0001-5668-4227

## REFERENCES

1 Chawanpaiboon S, Vogel JP, Moller A-B, *et al*. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Health* 2019;7:e37–46.
2 Blencowe H, Cousens S, Oestergaard MZ, *et al*. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet* 2012;379:2162–72.
3 World Health Organisation. Child causes of death 2000-2017. Available: https://www.who.int/healthinfo/global_burden_disease/estimates/en/index2.html [Accessed 7 Feb 2020].
4 United Nations. UN sustainable development goals. Available: https://sustainabledevelopment.un.org/ [Accessed 14 Feb 2020].
5 UNICEF. UNICEF child mortality estimates: regional and global neonatal mortality rate. Available: http://data.unicef.org [Accessed 25 Jul 2019].
6 Republic of Kenya Ministry of Health. Basic paediatric protocol 4th edition 2016.
7 World Health Organisation. *Pregnancy, childbirth, postpartum and newborn care: a guide for essential practice*. 3rd edn, 2015.
8 World Health Organisation. WHO recommendations on interventions to improve preterm birth outcomes 2015.
9 Conde-Agudelo A, Díaz-Rossello JL. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. *Cochrane Database Syst Rev* 2016:CD002771.
10 World Health Organisation. Born too soon: the global action report on preterm birth 2012.
11 Gerry S, Birks J, Bonnici T, *et al*. Early warning scores for detecting deterioration in adult hospital patients: a systematic review protocol. *BMJ Open* 2017;7:e019268.
12 Mortensen N, Augustsson JH, Ulriksen J, *et al*. Early warning- and track and trigger systems for newborn infants: a review. *J Child Health Care* 2017;21:112–20.



BMJ Open: first published as 10.1136/bmjopen-2020-039061 on 28 October 2020. Downloaded from http://bmjopen.bmj.com/ on April 1, 2021 by guest. Protected by copyright.

13 British Association of Perinatal Medicine. British association of perinatal medicine. newborn early warning trigger and track (NEWTT): a framework for practice. British association of perinatal medicine 2015;17.
14 Paliwoda M, New K, Bogossian F. Neonatal early warning tools for recognising and responding to clinical deterioration in neonates cared for in the maternity setting: a retrospective case-control study. *Int J Nurs Stud* 2016;61:125–35.
15 Merriel A, Murove BT, Merriel SWD, *et al*. Implementation of a modified obstetric early warning system to improve the quality of obstetric care in Zimbabwe. *Int J Gynaecol Obstet* 2017;136:175–9.
16 Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol* 2006;3:77–101.
17 Roland DMJ, Connolly G. The newborn early warning (new) system: development of an at-risk infant intervention system. *Infant* 2010;6:116–20.
18 Ridde V. Need for more and better implementation science in global health. *BMJ Glob Health* 2016;1:e000115.
19 Murphy GAV, Omondi GB, Gathara D, *et al*. Expectations for nursing care in newborn units in Kenya: moving from implicit to explicit standards. *BMJ Glob Health* 2018;3:e000645.
20 Lawn JE, Cousens S, Zupan J. Lancet neonatal survival steering T. 4 million neonatal deaths: when? where? why? *Lancet* 2005;365:891–900.
21 Murphy GAV, Gathara D, Mwachiro J, *et al*. Effective coverage of essential inpatient care for small and sick newborns in a high mortality urban setting: a cross-sectional study in Nairobi City County, Kenya. *BMC Med* 2018;16:72.
22 Lawn JE, Mwansa-Kambafwile J, Horta BL, *et al*. 'Kangaroo mother care' to prevent neonatal deaths due to preterm birth complications. *Int J Epidemiol* 2010;39:i144–54.
23 World Health Organisation. Thermal protection of the newborn: a practical guide 1997.
24 Lunze K, Bloom DE, Jamison DT, *et al*. The global burden of neonatal hypothermia: systematic review of a major challenge for newborn survival. *BMC Med* 2013;11:24.
25 Sodemann M, Nielsen J, Veirum J, *et al*. Hypothermia of newborns is associated with excess mortality in the first 2 months of life in Guinea-Bissau, West Africa. *Trop Med Int Health* 2008;13:980–6.
26 Aluvaala J, Nyamai R, Were F, *et al*. Assessment of neonatal care in clinical training facilities in Kenya. *Arch Dis Child* 2015;100:42–7.
27 Yoshida S, Martines J, Lawn JE, *et al*. Setting research priorities to improve global newborn health and prevent stillbirths by 2025. *J Glob Health* 2016;6:010508.
28 Moore J, Thomson D, Pimentil I, *et al*. Introduction of a modified obstetric early warning system -(-MOEWS-)- at an Ethiopian referral hospital: a feasibility assessment. *BMJ Open Qual* 2019;8:e000503.
29 Allen E. *Diffusion of innovations*. New York: Simon & Schuster, 2003.


BMJ Open: first published as 10.1136/bmjopen-2020-039061 on 28 October 2020. Downloaded from http://bmjopen.bmj.com/ on April 1, 2021 by guest. Protected by copyright.

**PAPER 2: Parents, healthcare professionals and other stakeholders' experiences of caring for babies born too soon in a low-resource setting: a qualitative study of essential newborn care for preterm infants in Kenya**

BMJ Open

# Parents, healthcare professionals and other stakeholders' experiences of caring for babies born too soon in a low-resource setting: a qualitative study of essential newborn care for preterm infants in Kenya

Eleanor J Mitchell [1], Phoebe Pallotti,[2] Zahida P Qureshi,[3] Jane P Daniels,[1] Mary Oliver,[4] Fredrick Were,[5] Alfred Osoti,[3] George Gwako,[3] Violet Kimani,[6] Jacqueline Opira,[6] Shalini Ojha [7,8]

**To cite:** Mitchell EJ, Pallotti P, Qureshi ZP, *et al*. Parents, healthcare professionals and other stakeholders' experiences of caring for babies born too soon in a low-resource setting: a qualitative study of essential newborn care for preterm infants in Kenya. *BMJ Open* 2021;**11**:e043802. doi:10.1136/bmjopen-2020-043802

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-043802).

Received 13 August 2020
Accepted 05 May 2021

Check for updates

© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

**Correspondence to**
Eleanor J Mitchell;
Eleanor.Mitchell@nottingham.ac.uk

## ABSTRACT

**Objectives** Prematurity is the leading cause of global neonatal and infant mortality. Many babies could survive by the provision of essential newborn care. This qualitative study was conducted in order to understand, from a family and professional perspective, the barriers and facilitators to essential newborn care. The study will inform the development of an early warning score for preterm and low birthweight infants in low and middle income countries (LMICs).

**Setting** Single-centre, tertiary referral hospital in Nairobi, Kenya.

**Participants** Nineteen mothers and family members participated in focus group discussions and 20 key-informant interviews with professionals (healthcare professionals and policy-makers) were conducted. Focus group participants were identified via postnatal wards, the newborn unit and Kangaroo Mother Care (KMC) unit. Convenience and purposive sampling was used to identify professionals.

**Outcome measures** Understanding facilitators and barriers to provision of essential newborn care in preterm infants.

**Results** From 27 themes, three global themes emerged from the data: mothers' physical and psychological needs, system pillars and KMC.

**Conclusion** Meeting mothers' needs in the care of their babies is important to mothers, family members and professionals, and deserves greater attention. Functioning system pillars depended on a standardised approach to care and low cost, universally applicable interventions are needed to support the existing care structure. KMC was effective in both meeting mothers' needs, supporting existing care structures and also provided a space for the resolution of the dialectical relationship between families and hospital procedures. Lessons learnt from the implementation of KMC could be applied to the development of an early warning score in LMICs.

## Strengths and limitations of this study

- This is the first report of parents', healthcare professionals' and wider stakeholders' views of essential newborn care in the context of development of an early warning score in low and middle income countries.
- A wide range of parents were recruited to ensure a wide range of opinions were elicited.
- Parents were recruited from a single, large national referral hospital, though some healthcare professionals had previous experience outside of this hospital.

## BACKGROUND

Globally, 15 million infants are born prematurely (before 37 weeks gestation), the leading cause of neonatal mortality and morbidity.[1] More than 60% of all preterm births occur in sub-Saharan Africa[2] and over a third of all neonatal deaths are due to preterm birth complications.[3] In Kenya, the preterm birth rate is 8.6 per 1000 live births[1] and neonatal mortality rate (NMR) is 20.9 deaths per 1000 live births,[4] currently double the global goal of an NMR of <10 deaths per 1000 live births by 2035.[3] In this setting, preterm infants should be managed in accordance with national and international evidence-based guidance for essential newborn care,[5 6] including strategies for thermoregulation, resuscitation, feeding, Kangaroo Mother Care (KMC) and infection management. More than 80% of all preterm births occur between 32 weeks and 37 weeks gestation and most babies could survive with the provision of essential newborn care.[2]

BMJ Open: first published as 10.1136/bmjopen-2020-043802 on 23 June 2021. Downloaded from http://bmjopen.bmj.com/ on June 24, 2021 by guest. Protected by copyright.

This study is part of a wider programme of work developing an early warning score (EWS) for use in preterm and low birthweight (LBW) infants in low and middle income countries (LMICs). An EWS is used by healthcare professionals (HCPs) to document vital signs in a standardised way. While they are used for adults in a variety of clinical areas,[7–9] there are few EWSs for newborn infants and none developed or used in LMICs.[10] An EWS identifies vital signs that require closer monitoring and escalation of care which could result in a reduction in mortality and other serious morbidities. Before adopting an intervention developed for a high-resource setting in an LMIC, it is important to explore the current provision of care for the LMIC setting and to ensure the opinions of parents and HCPs are considered.

The aims of this study were to gain a contextual understanding of parents', HCPs' and other stakeholders' experiences of essential newborn care in Kenya, to understand barriers and facilitators to caring for a preterm or LBW infant in a low-resource setting and to consider both in the development of an EWS.

## METHODS

This qualitative study was conducted at a large tertiary referral hospital in Nairobi (Kenyatta National Hospital (KNH)). Focus group discussions (FGDs) with mothers and family members were conducted in parallel to key informant interviews (KIIs) with a range of stakeholders involved in care of or management of preterm or LBW infants. FGDs were chosen for mothers and family members to reduce the risk of a potential power imbalance between participants and the researcher. A trusted staff member (clinical matron) was also invited to the FGDs to support the parents. Furthermore, the collaborative aspects of care were the focus of this study, involving both the relationships between the parents and the HCPs, but also the 'community' of mothers with sick babies. FGDs were the most appropriate methodology to capture this dynamic. KIIs were chosen for stakeholders for organisation and convenience reasons. The study was conducted with full ethical approval from the joint KNH–University of Nairobi Ethics Research Committee (reference number: P772/11/2018) and the Faculty of Medicine and Health Sciences Research Ethics Committee at the University of Nottingham (reference number: 161-1812) and is reported in accordance with the consolidated criteria for reporting qualitative research (COREQ).[11]

### Recruitment

Training in interview techniques was provided to the team by PP, EJM and SO. Potential mothers and families were identified by a clinical matron on postnatal wards, the newborn unit and KMC unit. Mothers of different ages, different duration of hospital stay and singleton and multiple pregnancies were invited to ensure a diverse sample. Participant information sheets were provided in English or Kiswahili. Convenience and purposive sampling was used to recruit HCPs via the labour suite, postnatal wards and newborn unit. External stakeholders, including policy-makers and non-government organisation (NGO) representatives, were purposively sampled and invited to participate in an interview. Participants' involvement was somewhat determined by their availability, though the research team made efforts to accommodate an interview at a mutually convenient time. All participants gave their written informed consent prior to taking part.

### Data collection

All data collection was undertaken by VK, a Kenyan female social scientist educated to PhD level with over 40 years' experience, during March and April 2019. Two FGDs, each lasting around 90 minutes, were conducted at KNH. The interview guide consisted of prompts to explore mothers' and family members' views of essential newborn care for a premature baby (online supplemental material 1). Face-to-face KIIs lasted around 60 min. All discussions were audio-recorded and transcribed. No identifiable data were included on the transcripts.

### Analysis

Thematic network analysis (TNA) was used.[12] TNA is a way of coding, organising and identifying emergent themes from the data in a systematic way and improves the internal validity of the results by employing systematic and repeatable methods. Global themes emerged from the grouping of organising themes into more abstracted and/or structural categories and was done by both analysts in collaboration. The philosophical underpinnings of this study are relational dialectic theory[13] as a pragmatic but nuanced way of identifying effective clinical interventions, which would work within the human context of neonatal care in a less resourced setting where much of the burden of basic nursing care rests on the mothers. Understanding what is fairly pragmatic data through this epistemological lens allowed the researchers to elucidate the spaces where communication and relationship between mothers and HCPs are either enabled or prevented. This understanding also removes the concept of 'blame' of failures in care from either side, preferring a more salutogenic approach to designing protocols and practices which support collaborative working.[14] Data from FGDs and KIIs were analysed together in order to consider consistent themes and gaps between the two. Table 1 shows an example of a coding tree. Initial coding was undertaken independently by EJM and PP before being moderated by a third reviewer (MO). Analyses were conducted using NVivo V.12 (QSR international). Initial codes were organised into organising and global themes in accordance with the stages of TNA.

The study is strengthened by the fact that data collection and analyses were performed by teams in Kenya and the UK, since concepts are developed from a more etic perspective. However, although one of the senior academic analysts has substantial clinical experience in

BMJ Open: first published as 10.1136/bmjopen-2020-043802 on 23 June 2021. Downloaded from http://bmjopen.bmj.com/ on June 24, 2021 by guest. Protected by copyright.

**Table 1** Example of the coding tree

| Global theme | Organising theme | Basic semantic code |
|---|---|---|
| Mother's physical and psychological needs | Impact on wider family and community | ► Impact of children on mother not being at home<br>► Long inpatient stay<br>► Involvement of other siblings<br>► Emotional impact of preterm death on siblings<br>► Impact on siblings has led to drop in educational performance<br>► Anxiety to mothers around leaving older siblings at home<br>► Impact on other children and family<br>► Preterm birth impacts on other children<br>► Daddy panics about mum's health<br>► Involvement of dads and wider family<br>► Less involvement from daddy<br>► Partner anxiety about premature baby<br>► 'You are not a burden' family member perspective |

a similar setting, the lack of lived experience in the exact context means that more nuanced cultural understandings may well have been missed as a result. However, all results were discussed with the wider team (Kenya and the UK). The positionality of the researchers was discussed at each stage of data collection and analysis. Thought was given particularly to the potential influence of the interviewer in terms of their familiarity with some participants (HCPs) and potential deference of either the researcher or participants, depending on the relationship therein.

### Role of funding source

The funder had no role in the collection, analysis or interpretation of data, writing of the report or decision to submit the paper for publication.

### Patient and public involvement

Patients and the public were not involved in the design or conduct of this study. However, the views of parents and stakeholders involved in this study will help to shape future research in this area.

## RESULTS

### Participants

Focus groups: 19 mothers were invited and all agreed to participate in the FGD; three of which were accompanied by the infant's father and two by other family members (mother-in-law and sister). All mothers had experience of their infant being on the newborn unit and 10 also had experience of the postnatal ward. Infants of the participants were born between 27 weeks and 34 weeks gestation and, on average had spent 20 days in hospital since birth. Participants' characteristics are shown in table 2.

**Table 2** Focus group participant characteristics

| Focus group | Gestational age (weeks) of infant | Experience of post-natal ward | Infant's length of stay (days) at time of focus group discussion |
|---|---|---|---|
| 1 | 34 | No | 18 |
| | 29 | Yes | 26 |
| | 34 | No | 12 |
| | 32 | No | 30 |
| | 32 | Yes | 30 |
| | 32 | Yes | 19 |
| | 32 | No | 17 |
| | 33 | No | 9 |
| | 29 | Yes | 23 |
| 2 | 27 | Yes | 10 |
| | 32 | No | 47 |
| | 30 | No | 7 |
| | 31 | Yes | 33 |
| | 31 | No | 16 |
| | 31 | Yes | 44 |
| | 32 | No | 14 |
| | 33 | Yes | 10 |
| | 28 | Yes | 10 |
| | 34 | Yes | 13 |

KIIs: 31 stakeholders were invited to participate and 20 KIIs were conducted. Stakeholder characteristics are given in table 3.

## THEMES

In total, 153 basic semantic codes emerged from the data, which were then synthesised into 27 organising codes. Three global themes emerged from the organising codes: (1) mothers' physical and psychological needs, (2) system pillars and (3) KMC. The organising codes for each global theme are shown in figures 1–3.

The three themes were emergent from the process of analysing the organising themes into overarching categories, which were either more abstracted in terms of concepts (for instance, the wider issue of mothers' biopsychosocial needs) or structures of care. An example of how the third global theme, KMC, emerged is given in table 4.

### Global theme 1: mothers' physical and psychological needs

This theme reflected the met and unmet needs of mothers, families and the wider community, while the baby was in hospital.

Mothers and fathers were generally positive about the support and communication from staff and their own communities, though there was also a recurrent theme of basic physical needs being unmet. This included a lack



BMJ Open: first published as 10.1136/bmjopen-2020-043802 on 23 June 2021. Downloaded from http://bmjopen.bmj.com/ on June 24, 2021 by guest. Protected by copyright.

**Table 3** KIIs participant characteristics

| Participant number | Stakeholder type | Years of professional experience |
|---|---|---|
| 1 | Policy-maker | 9 |
| 2 | NGO representative | 28 |
| 3 | Obstetrician | 43 |
| 4 | Paediatrician | 50 |
| 5 | Paediatrician | 35 |
| 6 | Obstetrician | 12 |
| 7 | NGO representative | 13 |
| 8 | Obstetrician | 15 |
| 9 | Nurse | 7 |
| 10 | Nurse | 23 |
| 11 | Neonatal Nurse | 20 |
| 12 | Neonatal Nurse | 27 |
| 13 | Neonatal Nurse | 4 |
| 14 | Nurse | 20 |
| 15 | Neonatal nurse | 20 |
| 16 | Neonatal nurse | 9 |
| 17 | Nurse | 4 |
| 18 | Nurse | 3 |
| 19 | Nurse | 25 |
| 20 | Nurse | 14 |

KIIs, key informant interviews; NGO, non-government organisation.




**Figure 1** Global theme 1: mothers' physical and psychological needs.




**Figure 2** Global theme 2: system pillars.

of available food and drink, feeling unsafe while moving around the hospital at night and a scarcity of places to sleep.

> 'the mother must feed well in order to produce milk. Like the mothers here, we have a schedule to feed the babies and then do kangaroo care for about an hour. Every two hours the routine is repeated. Most of the time the schedules coincide with meal times … . You go back to the ward and there's no food!' (Mother, FGD 2)




**Figure 3** Global theme 3: Kangaroo Mother Care.

BMJ Open: first published as 10.1136/bmjopen-2020-043802 on 23 June 2021. Downloaded from http://bmjopen.bmj.com/ on June 24, 2021 by guest. Protected by copyright.

Table 4 An example of how the third global theme, KMC, emerged

| Basic codes | Organising themes |
|---|---|
| Kangaroo care helps mum cope | Mothers being in control of care |
| KMC as a simple intervention | Valuing and training mothers |
| Low-tech solutions to lack of high-tech solutions | Conceptual and physical facilities |
| Simple interventions | Staff parent communication |
| KMC can be seen as a primitive practice | International agenda |
| Encouragement that KMC helps baby grow | Cultural beliefs |
| High-level strategy helped develop KMC (including generational effects) | Essential newborn care |
| KMC=mother and baby bond | Impact on wider family and community |
| KMC allows mum to always be with baby | |
| KMC keeps your baby warm | |
| KMC and feeding | |
| Better brains—ongoing development | |
| Importance of baby staying with mum | |
| KMC improves weight gain | |
| Role of KMC in infection reduction | |

KMC, Kangaroo Mother Care.

Impact of extended inpatient stays on the wider families were noticeably absent from the KIIs but referred to frequently in the FGD data.

> 'My first child is twelve-year-old and is at home. I delivered preterm twins about a month ago. One died on the third day and I was called to see the body before they removed him. My child was informed I delivered twins but he did not get to see them. Children are not allowed in this unit. He keeps wondering when I will go back home. I worry a lot about my child.' (Mother, FGD 2)

One of the most positive themes was the value placed on the mothers' care (and in some cases, other family members) of the baby. The newborn unit is crowded and the staff to patient ratio is low, so training and valuing the mothers input is a pragmatic solution, but the concept of maternal love and the importance of the mother baby bond also added an extra emotional and spiritual dimension to this theme.

> 'We feel included in everything to do with our baby care. We alert the nurse if baby seems uncomfortable. You get used to your baby. And if you have any question, you ask nurse or matron.' (Mother, FGD 1)

The impact on and support of the wider community was seen as key. The mother's absence from the home and the community costs (direct and indirect) was noted but families and staff also spoke of the importance of support and training from their communities.

> 'We intervene at grassroots level. We provide guidelines and capacity building through training at community level.' (Participant 2, KII)

Cultural aspects of the conceptualisation of preterm birth led some mothers to feel stigmatised, but where community and wider support was given, families felt the outcomes were better for all.

> 'When I delivered this baby even my husband was anxious, let me say disappointed. He stated, 'why did you deliver this one?' This is 'Mtoto wa kisirani.' … (meaning an ill-fated baby).' (Mother, FGD 1)

### Global theme 2: system pillars

This theme refers to the intra-hospital and pan-Kenyan organisation of care for premature and LBW babies. Much of this data is taken from the KIIs though mothers and families did comment on the structures of care within their units.

Using the 'Too Much Too Soon, Too Little Too Late (TLTL)' model,[15] we initially examined the data on resources allocated to the care of premature babies. Overall, the Kenyan context seemed to indicate that the latter (TLTL) was the most problematic in terms of both the incidence of preterm birth and the survival rate thereafter. Stakeholders discussed resource issues at length, particularly in regards to differences between rural and urban (and tertiary and primary) care settings.

> 'If we have to reduce infant deaths we must ensure mothers are aware of danger signs. This can be addressed during ANC clinics. For example, if a mother notices spotting they should go for check-up.' (Participant 7, KII)

Facilities were mentioned by almost all stakeholders, irrespective of role or years of experience. The crucial issue in preterm care seemed to be physical space, with nurseries being overcrowded and thus adequate monitoring and infection control being almost impossible to reliably achieve.



BMJ Open: first published as 10.1136/bmjopen-2020-043802 on 23 June 2021. Downloaded from http://bmjopen.bmj.com/ on June 24, 2021 by guest. Protected by copyright.

'I mean in the cots in unit X. Some babies have long legs, so they have to be folded in order to share the limited space with others. The baby cannot sleep freely as they are squeezed.' (Mother, FGD 2)

Stakeholders discussed recent technological and care protocol advances in neonatal care and the adoption across Kenya. Newer equipment and medicines seemed to be mostly available in the urban units, but adaptations in rural areas were also discussed.

'I would like this simple technology to continue, particularly in facilities that are not well equipped. Then put a sufuria [cooking pot] of boiling water at a corner of the room. The humidity acts like an incubator.' (Participant 3, KII)

More strategic stakeholders discussed that national and international training programmes were constantly rolled out, and while staff retention was a problem, upskilling of existing staff was felt to be on an upward trajectory.

'We developed a curriculum for training for use. Right now our staff is in [a region] developing training curriculum. We have trained over 9000 health care staff in the past three to four years.' (Participant 1, KII)

Finally, the implementation of new and existing protocols and the roll-out of new technology and training, in line with key global priorities, was discussed by all stakeholders.

'As we evolved now we have ventilators and at [the hospital] we have even mechanical ventilators. We also have CPAP [continuous positive airway pressure] machines.' (Participant 4, KII)

### Global theme 3: KMC

KMC units were identified as a valued and useful intervention in the FGDs and the KIIs alike.

For mothers and families, being an integral part of the infant's care on a KMC unit was seen as psychologically supportive. They felt more positive about the baby's chances of survival, more comfortable balancing their own needs with the needs of their feeding baby and more involved in their wider care.

'When a baby is weighed today, there is an increase from yesterday's weight and tomorrow weight will be higher than today. I attribute this to kangaroo care. The mother is always with her baby. The baby grows fast.' (Mother, FGD 1)

Furthermore, 'baby wearing' was seen as culturally acceptable and considered a normal way to care for any infant, normalising the practice and easing the transition from hospital to home.

'In our traditional setting, we don't like pushing our babies as they look in empty space [a pram]. We like direct contact with our babies. In this setting then Kangaroo mother care is commendable and embraced much more easily.' (Participant 3, KII)

Participants also referred to the benefits of KMC in alleviating infrastructure and resource issues and the wider Government strategy for roll-out of KMC.

'You can look at it from the infrastructure. Incubators are obviously inadequate for the number of babies needing them …, but KMC is skin to skin and need no regulation.' (Participant 7, KII)

## DISCUSSION

This study gives voice to mothers and families, HCPs, and wider stakeholders in Kenya. Its results empower them to be heard and understood such that any further plans to improve the care for preterm and LBW infants in this setting are built on their priorities. The emergent themes are discussed here in the context of the development of an EWS for preterm infants in LMICs, with the third global theme, 'KMC', considered an exemplar of an intervention which meets the needs' of the two previous global themes. Public partnership and stakeholder engagement in research and quality improvement initiatives are of particular importance in low resource settings, since it encourages participation from previously marginalised populations.[16] The results of this study were shared with a group of 78 stakeholders with a key interest in preterm birth.

Participants in the KIIs discussed the importance of the development and implementation of simple interventions and initiatives supported by the government, ensuring that such initiatives were aligned with national and global priorities for newborn health. If an EWS was developed for use in an LMIC, it would, therefore, be important to ensure 'buy-in' from a wide range of stakeholders, including the state. Consistent and standardised approaches to the provision of healthcare for newborn infants was considered important. Any effective interventions should be scaled up rapidly to all groups within countries, in line with the WHO's goal to provide universal health coverage and to enable progress towards the Sustainable Development Goals by 2030.[17] KII participants commented on lack of infant monitoring and poor documentation on the newborn unit. This is consistent with an observational study conducted by the same team showing record-keeping was poor with many infants' having few vital signs recorded[18] and a previous newborn study in Nairobi showing that vital signs charts were only completed for around a third of infants.[19] These issues are not uncommon in low-resource settings. A qualitative study of health facility leaders in Ethiopia also found that human resource issues such as training and staffing levels are critical in caring properly for preterm infants.[20]

Mothers, other family members and HCPs all placed importance on the mother's involvement in their newborn infant's care and, in particular, the communication



BMJ Open: first published as 10.1136/bmjopen-2020-043802 on 23 June 2021. Downloaded from http://bmjopen.bmj.com/ on June 24, 2021 by guest. Protected by copyright.

between the HCP and the mother. The EWS provides a standardised method of monitoring infants, which could also provide more focused communication between the HCP and mother. It could serve as a visual aid to the mother, so she can easily see how her baby is doing; however, this would need to be done with care and sensitivity to avoid causing undue anxiety. Communication with parents would be an essential element to be included in the provision of training provided to HCPs.

The third global theme that emerged was KMC, an evidence-based intervention commonly practiced in this setting, which was considered an exemplar where the resources and issues of each group, and the tensions between them, are met in and answered by the KMC unit. From a staff and system perspective, KMC units alleviated some of the resource challenges in the Kenyan context. Fewer incubators and fewer interventions with feeding and infection control were necessary and participants felt that babies were usually discharged home earlier. Importantly, KMC is strongly supported by the government who are working with NGOs to roll-out this initiative more widely across the country. From a strategy perspective, KMC is an established priority and included in national guidance.[21] The emergence of KMC as a strong theme demonstrated that any new intervention developed must be suitably adopted to support uninterrupted KMC.

The key principles of relational dialectics, contradictions, totality, process and praxis, whereby seemingly opposing needs, views and ontological perspectives, are processed and brought to agreement and then practically implemented[13] are met in this study. If, as the mothers do so much of the 'work' of nursing a sick baby, one sees them as colleagues as well as patients of the HCPs, understanding the blending of roles and relationships inherent in this may well open spaces of both better communication and a better mutual meeting of needs and responsibilities. The principal exemplar of this is in the provision of KMC units, which served both mothers' physical and psychological needs, reduced the burden of care and interventionist medicine on the healthcare system both on a unit and hospital level and allowed more discussion and co-production of care between mothers and HCPs on the unit. In this way, the physical existence of the KMC unit, as opposed to the practice of KMC itself, becomes vital for enabling this relational collaboration to exist in the 'openness' it engenders.[14] The enthusiasm and praise for the KMC unit is seen clearly in the data from all stakeholders and this can be seen as a practical and as an emotive value placed on that, which makes the participants feel at ease and feel successful in their shared goals of the babies' care.[13]

KMC units are highly valued, from a mother's perspective, ensuring use,[22] they meet national and international guidelines for the care of premature and LBW babies[23] and they use existing resources—beds, nurses and mothers.[24] However, roll-out of facility-based KMC, at scale, is not without challenges. A systematic review of implementation of KMC from a health systems perspective (86 studies) identified a range of barriers and enablers, including buy-in from staff, availability of training and resources and time to train and provide KMC.[25] Research focusing on the implementation of KMC is indeed in the top 10 research priorities for improving newborn health and birth outcomes by 2025.[26] This is in contrast to the possible difficulties in implementing an intervention on newborn units, which relies heavily on having adequate resources in place and, in particular, the availability of senior clinicians to see acutely unwell infants and expensive technology to support thermoregulation, infection control and infant feeding. This issue was discussed in our meeting of 78 stakeholders in Kenya, all of whom are involved in the care or provision of care for newborn infants. While the majority of stakeholders were positive about the concept of EWS, human resource issues were seen as a key barrier that would need to be overcome for successful implementation.[18] In addition, there is a strong evidence base for KMC. Studies have shown it improves outcomes for neonates, especially preterm and LBW babies,[27 28] which in turn reduces the financial and strategic burden on paediatric services as a whole in this context. Therefore, mothers, HCPs and policymakers can clearly see value and benefit in its provision and implementation. For an EWS to be implemented widely across LMICs, in addition to the potential benefits of standardised record-keeping and visual simplicity of such a chart, evidence would need to be generated in its ability to reduce neonatal mortality and morbidities. Further work has been funded to examine the feasibility and acceptability of implementing the EWS on several newborn units in Kenya and the key themes drawn from this study will ensure that the next step of this programme of work considers the views of mothers, families, HCPs and other stakeholders. If feasibility is demonstrated, then a study to investigate the possible clinical benefits would be warranted.

This is the first study to report views on the provision of newborn care in the context of the development of an EWS for preterm and LBW infants in LMICs. A limitation of the study is that mothers and families were recruited from a single national tertiary referral hospital and, therefore, may not represent wider views. However, many HCPs who were interviewed, while based at KNH, also had clinical experience outside of this single hospital, in addition to the wider expertise of two representatives at a national level.

In summary, while, at least theoretically, an EWS could potentially reduce neonatal mortality and serious morbidities, this is, as yet, unknown. If these potential benefits of an EWS were to be demonstrated in future studies, many of the issues identified in this study, including lack of space and overcrowding on newborn units, lack of trained neonatal staff and family involvement and communication, could be met. Results from this study may also help to identify areas for improvement in the provision of essential newborn care in a low-resource setting. For example, developing strategies to improve

BMJ Open: first published as 10.1136/bmjopen-2020-043802 on 23 June 2021. Downloaded from http://bmjopen.bmj.com/ on June 24, 2021 by guest. Protected by copyright.

communication between mothers and HCPs and ways in which interventions, shown to be effective, can be rolled out rapidly across different levels of healthcare.

## CONCLUSIONS

Ensuring the needs of parents, HCPs and policy-makers in the development of any intervention is important. A range of issues emerged that will be important to consider in the development and potential implementation of an EWS and lessons can be learnt from the emergent theme of KMC. KMC is already widely accepted as a gold standard intervention to increase newborn survival, especially in the preterm and LBW populations.[28] This paper adds the valuable perspective that KMC units may also help to alleviate system pressures, both within units and in a national health provision and is invaluable to mothers and families in terms of their physical and psychological well-being.

## RESEARCH IN CONTEXT

### Evidence before this study

In the context of the development of an EWS, we conducted a literature search using PubMed in June 2018 for studies on neonatal EWSs, using the search terms 'early warning score' and 'neonatal early warning score'. We identified only a small handful of publications relating to neonatal EWS and one non-systematic review of available EWS; however, none were from LMICs. We found no studies which included the views of parents in the development of an EWS.

### Added value of this study

This is the first study to importantly include the views and opinions of parents, family members, HCPs, policy-makers and non-government representatives in the context of the provision of newborn care and development of an EWS. A range of issues, important to parents/family members and stakeholders should be considered if an EWS were to be implemented, including: ensuring a consistent and standardised approach to newborn care, communication between parents and HCPs, and parental involvement in the newborn's care. KMC was viewed positively by all participants and should be considered as an exemplar in the development of other initiatives to improve newborn care.

### Implications of all the available evidence

The perspectives of a wide range of stakeholders, including parents and wider family members, should be considered in the development of an intervention designed to improved newborn care. In the context of an LMIC setting, where KMC is a commonplace, any new intervention implemented should be considered alongside KMC. Further research is required to test the feasibility and acceptability of an EWS in hospitals in LMICs.

**Author affiliations**
[1]Nottingham Clinical Trials Unit, University of Nottingham, Nottingham, UK
[2]Maternal Health and Wellbeing Research Group, School of Health Sciences, University of Nottingham, Nottingham, UK
[3]Department of Obstetrics and Gynaecology, University of Nairobi, Nairobi, Kenya
[4]School of Education, University of Nottingham, Nottingham, UK
[5]Department of Paediatrics and Child Health, University of Nairobi, Nairobi, Kenya
[6]Kenya Paediatric Research Consortium, Nairobi, Kenya
[7]Population and Applied Health Sciences, School of Medicine, University of Nottingham, Nottingham, UK
[8]Neonatal Unit, University Hospitals of Derby and Burton NHS Foundation Trust, Derby, UK

**Twitter** Eleanor J Mitchell @eleanor_mitch

**Acknowledgements** We thank all participants and our funders.

**Contributors** EJM was the principal investigator; conceived the idea, analysed data and wrote the first draft of the manuscript. PP analysed data and had a major role in writing the manuscript. SO was the clinical lead for the study. MO moderated analysed data. ZPQ was the lead at the Kenyatta National Hospital (KNH), supported by JO who provided study coordination. Qualitative data collection was undertaken by VK. FW, AO and GG all provided clinical input at KNH. JD provided mentorship to the team. All authors contributed to interpretation of the data, draft manuscripts and approved the final version of the manuscript prior to submission.

**Funding** University of Nottingham Global Challenges Research Fund (GCRF) (Ref: RIS 630122).

**Competing interests** SO declares grants from NIHR. No other conflicts of interest are declared by the authors.

**Patient consent for publication** Not required.

**Ethics approval** Ethical approval was granted by the joint Kenyatta National Hospital–University of Nairobi Ethics Research Committee (reference number: P772/11/2018) and the Faculty of Medicine and Health Sciences' Research Ethics Committee at the University of Nottingham (reference number: 161-1812).

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request to the corresponding author.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

**ORCID iDs**
Eleanor J Mitchell http://orcid.org/0000-0002-6998-4533
Shalini Ojha http://orcid.org/0000-0001-5668-4227

## REFERENCES

1 Chawanpaiboon S, Vogel JP, Moller A-B, *et al*. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Health* 2019;7:e37–46.
2 World Health Organisation. Born too soon: the global action report on preterm birth; 2012.
3 World Health Organisation. Every newborn: an action plan to end preventable deaths; 2014.
4 Unicef child mortality estimates: regional and global neonatal mortality rate. Available: http://data.unicef.org [Accessed 25 July 2019].

BMJ Open: first published as 10.1136/bmjopen-2020-043802 on 23 June 2021. Downloaded from http://bmjopen.bmj.com/ on June 24, 2021 by guest. Protected by copyright.

5 Republic of Kenya Ministry of Health. Basic paediatric protocol. January; 2016.
6 World Health Organisation. Pregnancy, childbirth, postpartum and newborn care: a guide for essential practice; 2015.
7 Morgan R L-WF. An early warning scoring system for detecting developing critical illness. *Clin Intensive Care* 1997;8.
8 Goldhill DR, McNarry AF. Physiological abnormalities in early warning scores are related to mortality in adult inpatients. *Br J Anaesth* 2004;92:882–4.
9 Gao H, McDonnell A, Harrison DA, *et al*. Systematic review and evaluation of physiological track and trigger warning systems for identifying at-risk patients on the ward. *Intensive Care Med* 2007;33:667–79.
10 Mortensen N, Augustsson JH, Ulriksen J, *et al*. Early warning- and track and trigger systems for newborn infants: a review. *J Child Health Care* 2017;21:112–20.
11 Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care* 2007;19:349–57.
12 Attride-Stirling J. Thematic networks: an analytic tool for qualitative research. *Qualitative Research* 2001;1:385–405.
13 Baxter LA. *A dialectical perspective of communication strategies in relationship development*. Handbook of Personal Relationships: Wiley, 1988.
14 Baxter LA, Bridge K. Blended relationships: friends as work associates. *Western journal of communication* 1992;56:200–25.
15 Miller S, Abalos E, Chamillard M, *et al*. Beyond too little, too late and too much, too soon: a pathway towards evidence-based, respectful maternity care worldwide. *Lancet* 2016;388:2176–92.
16 Cohen ERM, Masum H, Berndtson K, *et al*. Public engagement on global health challenges. *BMC Public Health* 2008;8:168.
17 Boerma T, Requejo J, Victora CG, *et al*. Countdown to 2030: tracking progress towards universal coverage for reproductive, maternal, newborn, and child health. *Lancet* 2018;391:1538–48.
18 Mitchell EJ, Qureshi ZP, Were F, *et al*. Feasibility of using an early warning score for preterm or low birthweight infants in a low-resource setting: results of a mixed-methods study at a national referral hospital in Kenya. *BMJ Open* 2020;10:e039061.
19 Murphy GAV, Gathara D, Mwachiro J, *et al*. Effective coverage of essential inpatient care for small and sick newborns in a high mortality urban setting: a cross-sectional study in Nairobi City County, Kenya. *BMC Med* 2018;16:72.
20 Usman AK, Wolka E, Tadesse Y, *et al*. Health system readiness to support facilities for care of preterm, low birth weight, and sick newborns in Ethiopia: a qualitative assessment. *BMC Health Serv Res* 2019;19:860.
21 Repulic of Kenya Ministry of Health. Kangaroo mother care clinical implementation guidelines; 2016.
22 World Health Organisation Department of Reproductive Health and Research. Kangaroo mother care: a practical guide; 2003.
23 World Health Organisation. Recommendations on interventions to improve preterm birth outcomes; 2015.
24 Campbell-Yeo ML, Disher TC, Benoit BL, *et al*. Understanding kangaroo care and its benefits to preterm infants. *Pediatric Health Med Ther* 2015;6:15–32.
25 Chan G, Bergelson I, Smith ER, *et al*. Barriers and enablers of kangaroo mother care implementation from a health systems perspective: a systematic review. *Health Policy Plan* 2017;32:1466–75.
26 Yoshida S, Martines J, Lawn JE, *et al*. Setting research priorities to improve global newborn health and prevent stillbirths by 2025. *J Glob Health* 2016;6:010508.
27 Boundy EO, Dastjerdi R, Spiegelman D, *et al*. Kangaroo mother care and neonatal outcomes: a meta-analysis. *Pediatrics* 2016;137:e20152238.
28 Conde-Agudelo A, Díaz-Rossello JL. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. *Cochrane Database Syst Rev* 2016;8:CD002771.


BMJ Open: first published as 10.1136/bmjopen-2020-043802 on 23 June 2021. Downloaded from http://bmjopen.bmj.com/ on June 24, 2021 by guest. Protected by copyright.

**PAPER 3: Identifying women giving birth preterm and care at the time of birth: a prospective audit of births at six hospitals in India, Kenya, Pakistan and Uganda**

BMC Pregnancy and Childbirth

RESEARCH ARTICLE Open Access

# Identifying women giving birth preterm and care at the time of birth: a prospective audit of births at six hospitals in India, Kenya, Pakistan and Uganda

Eleanor J. Mitchell[1*], Santosh Benjamin[2], Sam Ononge[3], James Ditai[4], Zahida Qureshi[5], Shabeen Naz Masood[6], Diane Whitham[1], Peter J. Godolphin[1], Lelia Duley[1] and on behalf of the "iCord Collaborative Group"

## Abstract

**Background:** Globally, 15 million infants are born preterm each year, and 1 million die due to complications of prematurity. Over 60% of preterm births occur in Sub-Saharan Africa and south Asia. Care at birth for premature infants may be critical for survival and long term outcome. We conducted a prospective audit to assess whether women giving birth preterm could be identified, and to describe cord clamping and neonatal care at hospitals in Africa and south Asia.

**Methods:** This prospective audit of livebirths was conducted at six hospitals in Uganda, Kenya, India and Pakistan. Births were considered preterm if between $28^{+0}$ and $33^{+6}$ weeks gestation and/or the birthweight was 1.00 to 1.99 kg. A pre-specified audit plan was agreed with each hospital. Livebirths before 28 weeks gestation with birthweight less than 1.0 kg were excluded. Data were collected on estimated and actual gestation and birthweight, cord clamping, and neonatal care.

**Results:** Of 4149 women who gave birth during the audit, data were available for 3687 (90%). As 107 were multiple births, 3781 livebirths were included, of which 257 (7%) were preterm. Antenatal assessment correctly identified 148 infants as 'preterm' and 3429 as 'term', giving a positive predictive value of 72% and negative predictive value of 97%. For term births, cord clamping was usually later at the two Ugandan hospitals, median time to clamping 50 and 76 s, compared with 23 at Kenyatta (Kenya), 7 at CMC (India) and 12 at FBH/LNH (Pakistan). At the latter two, timing was similar between term and preterm births, and between vaginal and Caesarean births. For all the hospitals, the cord was clamped quickly at Caesarean births, with Mbale (Uganda) having the highest median time to clamping (15 s 'term', 19 'preterm'). For preterm infants temperature on admission to the neonatal unit was below 35.5 °C for 50%, and 59 (23%) died before hospital discharge.

**Conclusions:** Antenatal identification of preterm birth was good. Timing of cord clamping varied between hospitals, although at each there was no difference between 'term' and 'preterm' births. For premature infants hypothermia was common, and mortality before hospital discharge was high.

**Keywords:** Low and middle income countries, Cord clamping, Prospective audit, Neonatal care, Preterm birth

* Correspondence: eleanor.mitchell@nottingham.ac.uk
[1]Nottingham Clinical Trials Unit, University Of Nottingham, Nottingham, UK
Full list of author information is available at the end of the article

© The Author(s). 2020 **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. 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 in a credit line to the data.

## Background

Being born preterm (before 37 weeks gestation) has 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]. Globally, around 15 million infants are born preterm each year, of whom more than 1 million die due to complications of prematurity [4, 5]. Over 80% of preterm births occur in sub-Saharan Africa and south Asia [5]. Twelve percent of newborns in low income settings are preterm compared to 9% in high income countries [5]. Amongst children born very preterm (before 32 weeks) who survive, morbidity is particularly high compared to those born at term [3]; in Europe, for example, around 5% develop cerebral palsy, and those without severe disability have a two-fold or greater increased risk for developmental, cognitive, and behavioural difficulties [1, 2]. These impairments may persist into adolescence and early adulthood [6, 7]. Reducing the morbidity and mortality associated with preterm birth is a priority [4, 8].

Care at birth, particularly for infants born preterm or sick, may be critical for survival and long term outcome. Optimal timing for umbilical cord clamping for both term and preterm births is controversial [9]. Traditionally, immediate cord clamping was widely implemented as part of active management of the third stage of labour [10]. For healthy term births, the evidence now supports a more liberal approach to delaying cord clamping [11], and WHO recommends clamping between 1 and 3 min [12]. Delayed cord clamping allows longer for the cardiorespiratory changes that occur at birth as the neonatal circulation is established, hence it may potentially be of greater benefit for preterm infants with immature lungs and myocardium [13]. For preterm births the evidence on when is best to clamp the cord is unclear, however, and trials have largely been conducted at births before 32 to 34 weeks in settings with access to neonatal intensive care [14, 15]. Yet delayed cord clamping may have additional advantages in low resource settings where neonatal care is limited or unavailable [16].

Our objectives were to describe care at the time of preterm birth in low and middle income hospital settings, and to assess whether a randomised trial of alternative policies for timing of cord clamping at preterm birth might be feasible. Assessment of gestation in many maternity units in low and middle income settings often relies primarily on menstrual history and clinical examination. Therefore, we conducted a prospective audit to assess whether women giving birth preterm could be identified, and to describe timing of cord clamping and neonatal care.

## Methods

This prospective audit was conducted between May and September 2015 at six hospitals in four low and middle income countries: Mulago National Referral Hospital, Kampala and Mbale Regional Referral Hospital in Uganda; Kenyatta National Hospital, Nairobi, Kenya; Christian Medical College (CMC), Vellore, India; and Fatima Bai Hospital and Liaquat National Hospital (FBH/LNH), Karachi, Pakistan. These hospitals were selected based on their interest in conducting a randomized trial evaluating alternative strategies for the timing of cord clamping at preterm birth. Hospitals varied in terms of available resources and funding/management structures, though this was not considered for selection purposes. At one hospital (Mbale), a neonatal unit was in the process of being established and there was no capacity for mechanical ventilation. The other five hospitals had some form of neonatal unit with some capacity to provide mechanical ventilation. All the hospitals had busy maternity units, with high levels of preterm birth and perinatal mortality. Ethics approval for each hospital was obtained according to local requirements. The study was observational, with all aspects of care being according to local practice.

For the purpose of this audit, we focused on preterm births associated with high mortality and morbidity. Therefore, we considered births as preterm if they were between $28^{+0}$ weeks and $33^{+6}$ weeks gestation or the birthweight was 1.00 kg to 1.99 kg; and as 'term' if they were $34^{+0}$ weeks or above and birthweight was 2 kg or more. We used 34 weeks as the upper gestational age cut off as above this mortality is low and the infants usually do not require admission to a neonatal unit. As menstrual history is often unknown, and can be unreliable for assessing gestation, and a dating ultrasound scan is not usually available, we included birthweight as a surrogate for gestation, a common practice at the participating hospitals and more widley in low and middle income countries. For all infants admitted to a neonatal unit we requested a gestational age assessment using either the Dubowitz [17] or New Ballard [18], whichever was in local practice.

The aim was to collect data for at least 30 preterm births at each hospital, which we estimated would require surveillance of 500–700 births. Continuous surveillance was not realistic in these settings, so we agreed a pre-specified plan for when the audit would be conducted within each hospital. To ensure a representative sample, this included day and night, weekdays and weekends, and was across different staff shifts. During each pre-specified audit period all livebirths on the delivery unit were eligible to be included. Births before the woman arrived on the delivery unit, stillbirths, and livebirths before 28 weeks gestation with birthweight less than 1 kg were excluded. Before the audit began at each hospital, the local staff who would be conducting the study attended 3 days of training in study procedures.

As time of cord clamping and some other delivery room care is not usually recorded in the clinical notes, this included training in observing the birth, timing events with a stop watch, and recording the information. Staff were also trained in how to extract relevant information from the clinical notes onto our data collection forms, and to enter the data onto the database.

During each pre-specified audit period, we collected data on: estimated gestation and how this was estimated (last menstrual period (LMP), clinical assessment, and/or dating ultrasound scan as per local practice); estimated birthweight and how this was estimated (clinical assessment or ultrasound scan); assessment of gestation after birth, and how this was assessed (LMP, clinical assessment, dating ultrasound scan, a Dubowitz [17] or New Ballard [18] assessment); birthweight; and timing of cord clamping. For births that met our criteria for preterm we also collected data on: neonatal care at birth; admission to the neonatal unit or paediatric ward, and duration of stay; serious neonatal morbidity, and outcome at discharge from hospital. Delivery unit records were checked for eligible births missed during the audit period, and for these data were collected on gestation at birth, birthweight, and mode of birth.

Data were anonymous, with each woman and her infant(s) identified by a unique study ID. At each hospital, data were entered into a secure online database developed and maintained by the Nottingham Clinical Trials Unit.

### Analysis

For each hospital we described: births missed during the audit period; estimated gestation at birth and birthweight, (and how these were estimated, i.e. LMP, clinical assessment, dating ultrasound scan); timing of cord clamping for 'preterm' and 'term' births; the number of births identified as preterm before birth; clinical staff present at these preterm births; neonatal care provided at birth and after birth; and serious neonatal morbidity. Mortality was described both overall and per site; analysis by timing of cord clamping and mortality was not performed due to the observational study design and risk of bias. We classified neonatal units as: Level 1 if they had no access to ventilation support, Level 2 if there was limited access to ventilation support, and Level 3 if they provided neonatal intensive care including the capacity to provide prolonged mechanical ventilation [19, 20]. Level 3 units were available at the hospitals in India, Kenya and Pakistan, but not in Uganda.

For assessment of gestation before birth, we calculated the positive predictive value (PPV) and negative predictive value (NPV) of being preterm. If data were missing for either gestation or birthweight, then the single measure (gestation or birthweight) was used. If data for both gestation and birthweight was missing, the infant was excluded from the PPV/NPV calculation. We conducted three sensitivity analyses: using only infants with complete data for gestation and birthweight; categorising infants with missing birthweight solely on gestation; and assuming that all infants with missing data were born at term.

Variables were described as median (interquartile range) or mean (standard deviation) when continuous, and N (%) when categorical. All analyses were performed in Stata version 14.2 or later.

## Results

Overall, 4149 women gave birth during the audit period; 399 of these births were not observed; for 74 women this was because she was known to be having a stillbirth (Fig. 1).

Of the 325 women with a livebirth for whom no audit data were available, 7 (2%) had a preterm birth, 241 (74%) a spontaneous vaginal birth, 80 (25%) caesarean section and 4 (1%) a vaginal breech or instrumental birth. Audit data were available for 3750 (90%) women, of whom 63 were excluded (Fig. 1). Of the 3687 women included in the audit, 3580 had a singleton pregnancy and 107 a multiple pregnancy. For five women who had a multiple pregnancy, at least one infant was eligible and included in the audit and at least one infant was not eligible (based on birthweight or stillbirth).In the audit, 3687 women gave birth to 3781 live newborns, of whom 257 were 'preterm' and 3524 were 'term' (Fig. 1).

Before birth an estimate of gestation was available for 99% of the women; for three quarters this was based on the LMP and/or clinical assessment (Table 1). For one in five women the estimate of gestational age was based on a dating ultrasound scan, but these women were mostly in CMC (India) and FBH/LNH (Pakistan). Of the 227 births considered preterm at the time of birth, 181 (80%) had a neonatal assessment for gestational age. Overall birthweight was estimated before birth for a quarter of the infants, but this ranged from 3% of births in Mbale (Uganda) to 90% in CMC (India). For almost three quarters of the infants with an estimated birthweight (652/900, 72%), this estimate was based on clinical assessment alone (Table 2).

Comparing antenatal assessment with assessment of gestation and birthweight after birth for the 3740 infants with these data available, 148 (4%) were correctly identified as preterm and 3429 (92%) were correctly recognised as term (Fig. 2 and *Supplementary material*, Table S1). This corresponds to a PPV of 72% and NPV of 97% for assessment before birth. The three sensitivity analyses produced identical PPV's, with NPV only differing for one sensitivity analysis to 96%.

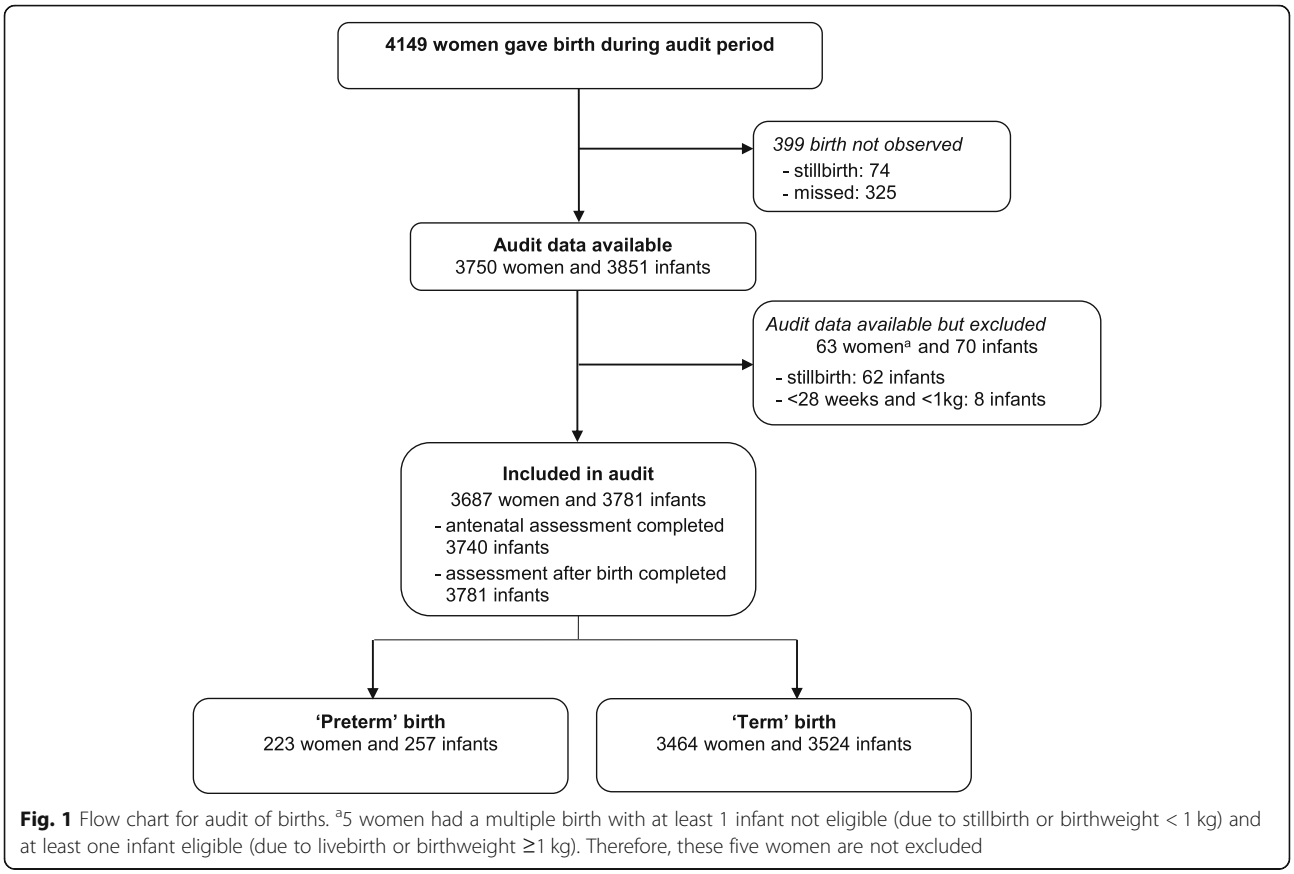



**Fig. 1** Flow chart for audit of births. [a]5 women had a multiple birth with at least 1 infant not eligible (due to stillbirth or birthweight < 1 kg) and at least one infant eligible (due to livebirth or birthweight ≥1 kg). Therefore, these five women are not excluded

**Table 1** For all livebirths included in the audit, estimated gestation before birth and assessment of gestation after birth

| | CMC (*n* = 692) | | Mulago (*n* = 958) | | Mbale (*n* = 772) | | Kenyatta (*n* = 992) | | FBH/LNH (*n* = 273) | | Total (*n* = 3687) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Estimated before birth*** | 691 | (99%) | 957 | (99%) | 770 | (99%) | 954 | (96%) | 272 | (99%) | **3644** | **(99%)** |
| *Method* | | | | | | | | | | | | |
| LMP and/or clinical assessment | 191 | (28%) | 855 | (89%) | 742 | (96%) | 921 | (93%) | 169 | (62%) | **2878** | **(78%)** |
| Dating ultrasound scan alone | 211 | (30%) | 55 | (6%) | 21 | (3%) | 31 | (3%) | 37 | (14%) | **355** | **(10%)** |
| Dating ultrasound scan + other | 289 | (42%) | 47 | (5%) | 7 | (1%) | 2 | (< 1%) | 66 | (24%) | **411** | **(11%)** |
| *Gestation (weeks)* | | | | | | | | | | | | |
| < 28 | – | – | 11 | (1%) | 4 | (1%) | 10 | (1%) | 3 | (1%) | **28** | **(1%)** |
| 28–$33^{+6}$ | 14 | (2%) | 52 | (5%) | 26 | (3%) | 36 | (4%) | 17 | (6%) | **145** | **(4%)** |
| ≥ 34 | 677 | (98%) | 894 | (93%) | 740 | (96%) | 908 | (92%) | 252 | (92%) | **3471** | **(94%)** |
| ***Assessed after birth*** | | | | | | | | | | | | |
| *Gestation (weeks)* | | | | | | | | | | | | |
| < 28 | – | – | 3 | (< 1%) | – | – | 3 | (< 1%) | 2 | (1%) | **8** | **(< 1%)** |
| 28–$33^{+6}$ | 15 | (2%) | 67 | (7%) | 10 | (1%) | 29 | (3%) | 15 | (5%) | **136** | **(4%)** |
| ≥ 34 | 677 | (98%) | 888 | (93%) | 762 | (99%) | 960 | (97%) | 256 | (94%) | **3543** | **(96%)** |
| ***Neonatal assessment done[a]*** | -[b] | | 81 | | 32 | | 45 | | 23 | | **181** | |

All data are N (%)
*LMP* Last menstrual period
[a]Neonatal Assessments were only done for births thought to be preterm, CMC (*n* = 39), Mulago (*n* = 82), Mbale (*n* = 32), Kenyatta (*n* = 49), FBH/LNH (*n* = 25), Total (*n* = 227)
[b]Not reported as only done for the infants for whom the neonatologist thought there was a discrepancy between before and after birth assessments

**Table 2** For all livebirths in the audit, birthweight estimated before birth and actual birthweight

| | CMC (*n* = 703) | | Mulago (*n* = 993) | | Mbale (*n* = 787) | | Kenyatta (*n* = 1018) | | FBH/LNH (*n* = 280) | | Total (*n* = 3781) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Birthweight estimate*** | 632 | (90%) | 89 | (9%) | 22 | (3%) | 51 | (5%) | 106 | (38%) | **900** | **(24%)** |
| *Method* | | | | | | | | | | | | |
| Clinical assessment | 619 | – | 5 | – | – | – | 1 | – | 27 | – | **652** | **–** |
| Ultrasound scan | 13 | – | 84 | – | 22 | – | 50 | – | 79 | – | **248** | **–** |
| *Estimate (kg)* | | | | | | | | | | | | |
| < 1.00 | – | – | – | – | 1 | – | – | – | 2 | – | **3** | **–** |
| 1.00–1.99 | 36 | – | 15 | – | – | – | 12 | – | 15 | – | **78** | **–** |
| 2.00–2.99 | 354 | – | 17 | – | 8 | – | 16 | – | 56 | – | **451** | **–** |
| > 3.00 | 242 | – | 57 | – | 13 | – | 23 | – | 33 | – | **368** | **–** |
| ***Actual birthweight*** *(kg)* | | | | | | | | | | | | |
| < 1.00 | – | – | 6 | (1%) | 1 | (< 1%) | 1 | (< 1%) | 1 | (< 1%) | **9** | **(< 1%)** |
| 1.00–1.99 | 45 | (6%) | 68 | (7%) | 35 | (4%) | 52 | (5%) | 16 | (6%) | **216** | **(6%)** |
| 2.00–2.99 | 327 | (47%) | 303 | (31%) | 318 | (40%) | 323 | (32%) | 108 | (39%) | **1379** | **(36%)** |
| > 3.00 | 331 | (47%) | 616 | (62%) | 433 | (55%) | 642 | (63%) | 155 | (55%) | **2177** | **(57%)** |

All data are N (%)

Just over one third (37%) of the total births were by Caesarean section (Table 3), ranging from 22% at Mbale (Uganda) to 61% at FBH/LNH (Pakistan). For term births, cord clamping was usually later at the two hospitals in Uganda, with median time to clamping 50 and 76 s, compared with 7 s at CMC (India) and 12 s at FBH/LNH s (Pakistan). At these two latter hospitals, timing of cord clamping was similar between 'term' and 'preterm births', and between vaginal and Caesarean births (Table 3). For all the hospitals, the cord was clamped quickly at Caesarean births, with Mbale (Uganda) having the highest median time to clamping of 15 s for term birth and 19 s for preterm births (Table 4, and *Supplementary material*, Figure S1).

For the 130 preterm infants born vaginally, one member of staff was present at the birth for 90, and for all

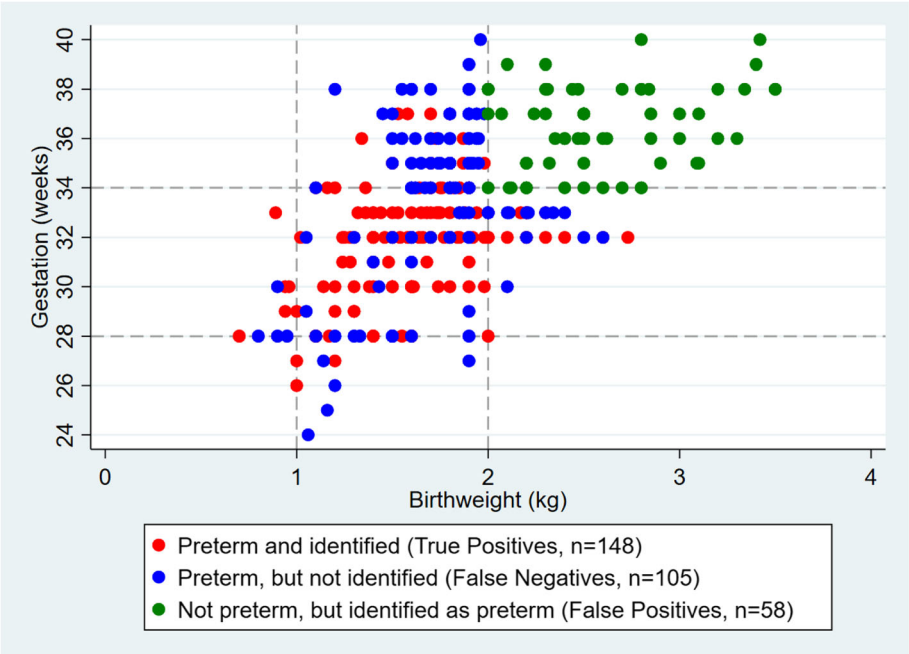



**Fig. 2** Identification of infants born preterm using antenatal assessments and confirmation using postnatal assessment

**Table 3** Mode of birth and timing of cord clamping for 'term' and 'preterm' births

| | CMC (*n* = 703) | | Mulago (*n* = 993) | | Mbale (*n* = 787) | | Kenyatta (*n* = 1018) | | FBH/LNH (*n* = 280) | | Total (*n* = 3781) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***'Term'*** | 657 | | 900 | | 750 | | 961 | | 256 | | **3524** | |
| Caesarean section | 202 | (31%) | 312 | (35%) | 165 | (22%) | 423 | (44%) | 155 | (61%) | **1257** | **(36%)** |
| Vaginal | 455 | (69%) | 588 | (65%) | 585 | (78%) | 538 | (56%) | 101 | (39%) | **2267** | **(64%)** |
| ***Time of cord clamping (seconds)*** | | | | | | | | | | | | |
| Median {25, 75} | 7 | {5, 11} | 49.5 | {11, 87.5} | 75.5 | {37, 109} | 23 | {9, 49} | 12 | {8.5, 17} | **22** | **{8, 69}** |
| *Caesarean section:* Median {25, 75} | 5 | {4, 6} | 8 | {5, 12} | 15 | {11, 24} | 9 | {6, 14} | 10 | {8, 15} | **8** | **{5, 14}** |
| *Vaginal:* Median {25, 75} | 8 | {6, 12} | 76.5 | {50, 109.5} | 87 | {62, 120} | 43.5 | {25, 62} | 15 | {11, 20} | **52** | **{17, 88}** |
| ***'Preterm'*** | 46 | | 93 | | 37 | | 57 | | 24 | | **257** | |
| Caesarean section | 37 | (80%) | 35 | (38%) | 7 | (19%) | 32 | (56%) | 16 | (67%) | **127** | **(49%)** |
| Vaginal | 9 | (20%) | 58 | (62%) | 30 | (81%) | 25 | (44%) | 8 | (33%) | **130** | **(51%)** |
| ***Time of cord clamping (seconds)*** | | | | | | | | | | | | |
| Median {25, 75} | 5 | {4, 7} | 28 | {7, 59} | 75 | {47, 109} | 12 | {8, 42} | 10.5 | {7, 15.5} | **16** | **{6, 52}** |
| *Caesarean section:* Median {25, 75} | 4 | {4, 6} | 6 | {5, 9} | 19 | {13, 30} | 10 | {6, 11} | 9.5 | {6.5, 14} | **7** | **{4, 11}** |
| *Vaginal:* Median {25, 75} | 7 | {6, 9} | 50 | {29, 70} | 83 | {61, 129} | 46 | {27, 69} | 14 | {8, 36.5} | **51** | **{27, 79}** |

All data are N (%) unless otherwise stated

but three births this was a midwife (data not shown). A paediatrician or neonatologist was present for just over a quarter of all preterm births (67, 26%), and for the majority this was in CMC (India) (45, 98%) or FBH/LNH (Pakistan) (19, 79%). Of these preterm infants, 230 (89%) had some neonatal care in the delivery room, the most common being wrapped in plastic or Embrace (www.embraceinnovations.com) (52%), airway suction (54%) and oxygen (54%) (data not shown).

Thirteen (5%) of the preterm infants were taken to the postnatal ward and not admitted to a neonatal unit (Table 4). For the preterm infants, temperature on admission to the neonatal unit or postnatal ward was below 35.5 °C for 50%, with FBH/LNH (Pakistan) the only hospital with no temperatures at this level. Infants appeared coldest in Mulago, where 27 (29%) had a temperature below 34.5 °C. Use of respiratory support varied considerably between hospitals, ranging from 11% of preterm infants in CMC (India) to 96% of those in Mulago (Uganda) (Table 4). Length of stay in the neonatal unit and hospital also varied between hospitals, with median stay of 1 day in Mbale (Uganda) and 8.5 days in CMC (India) (Table 4). Almost a quarter of the preterm infants died before hospital discharge (59, 23%), with mortality ranging from 2% in CMC (India) to 58% at Kenyatta (Kenya).

## Discussion

In order to conduct research to improve the quality of delivery room care for preterm infants it is important to be able to correctly identify those likely to be born preterm. In this prospective audit conducted in delivery units at a range of hospitals in low and middle income countries, we found that using information from antenatal assessments of estimated gestational age and birthweight resulted in reasonable identification of those giving birth preterm (based on our definition using gestational age and/or birthweight). Overall, the PPV was 72% and NPV 97%. Timing of cord clamping varied between hospitals, although within each hospital there was no real difference between timing of cord clamping for 'term' and 'preterm' births. At all hospitals, for caesarean births cord clamping was largely immediate (within 30 s). For vaginal births, cord clamping was usually immediate at CMC (India) and FBH/LNH (Pakistan), and usually deferred at Mulago and Mbale in Uganda and Kenyatta (Kenya). With the exception of FBH/LNH (Pakistan), hypothermia following preterm birth was common, with half the preterm infants having a temperature below 35.5 °C, and 14% below 34.5 °C on admission to the neonatal unit. Although the numbers are relatively small, our study also confirms the high mortality associated with preterm birth in these settings.

Recently, the evidence base for alternative policies for timing of cord clamping at very preterm birth has increased, including publication of a large international trial co-ordinated from Australia [21] and our own UK trial [22]. A recent systematic review (18 trials, 2834 infants) concluded that 'delayed clamping reduced hospital mortality' [15]. There was no clear impact on neonatal or maternal morbidity, but the review was 'substantially underpowered' for these outcomes. The review authors also highlighted the need for follow up of the infants in childhood. However, relatively few births included in this review occurred in low and middle income settings; as six studies conducted in Iran [23], India [24, 25], South

**Table 4** For 'preterm' infants, admission to neonatal unit, care in the neonatal unit and outcome at discharge

| | CMC ($n = 46$)[a] | | Mulago ($n = 93$) | | Mbale ($n = 37$) | | Kenyatta ($n = 57$) | | FBH/LNH ($n = 24$)[a] | | Total ($n = 257$)[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Level of neonatal care after birth** | | | | | | | | | | | | |
| Postnatal ward | 1 | (2%) | 2 | (2%) | 7 | (19%) | 1 | (2%) | 2 | (8%) | **13** | **(5%)** |
| Neonatal unit, Level 1 | – | – | – | – | 30 | (81%) | – | – | 7 | (29%) | **37** | **(14%)** |
| Neonatal unit, Level 2 | 30 | (65%) | 91 | (98%) | – | – | 55 | (96%) | – | – | **176** | **(68%)** |
| Neonatal unit, Level 3 | 14 | (30%) | -[b] | – | -[b] | – | 1 | (2%) | 14 | (58%) | **29** | **(11%)** |
| **Temperature on admission (°C)** | | | | | | | | | | | | |
| Mean [SD] | 36.1 | [0.7] | 34.7 | [0.8] | 35.6 | [0.9] | 35.5 | [0.8] | 37 | [0.2] | **35.5** | **[1.0]** |
| < 34.5 | – | – | 27 | (29%) | 6 | (16%) | 3 | (5%) | – | – | **36** | **(14%)** |
| 34.5–35.4 | 8 | (17%) | 52 | (56%) | 7 | (19%) | 26 | (46%) | – | – | **93** | **(36%)** |
| 35.5–36.4 | 21 | (46%) | 14 | (15%) | 18 | (49%) | 19 | (33%) | 1 | (4%) | **73** | **(28%)** |
| 36.5–37.4 | 14 | (30%) | – | – | 5 | (14%) | 6 | (11%) | 20 | (83%) | **45** | **(18%)** |
| ≥ 37.5 | 1 | (2%) | – | – | – | – | 2 | (4%) | – | – | **3** | **(1%)** |
| Not known | 2 | (4%) | – | – | 1 | (3%) | 1 | (2%) | 3 | (13%) | **7** | **(3%)** |
| **Respiratory support** | | | | | | | | | | | | |
| Any respiratory support | 5 | – | 89 | – | 8 | – | 52 | – | 5 | – | **159** | **–** |
| *Type of support and duration (days)* | | | | | | | | | | | | |
| Oxygen | 1 | – | 71 | – | 4 | – | 46 | – | – | – | **122** | **–** |
| Median {25, 75} | 1 | {1, 1} | 2 | {1, 3} | 3 | {3, 3.5} | 4 | {3, 6} | – | – | **3** | **{2, 4}** |
| CPAP | 4 | – | 46 | – | 1 | – | 2 | – | – | – | **53** | **–** |
| Median {25, 75} | 4 | {2.5, 5} | 2 | {1.5, 4} | 2 | {2,2} | 3 | {3, 3} | – | – | **2** | **{2, 4}** |
| *Ventilation* | 1 | – | 1 | – | 3 | – | 5 | – | 5 | – | **15** | **–** |
| Median {25, 75} | 2 | {2, 2} | 1 | {1, 1} | 4 | {3, 7} | 3 | {3, 5} | 1 | {1, 3} | **3** | **{1, 5}** |
| **Cranial ultrasound** | 13 | – | 2 | – | – | – | – | – | – | – | **15** | **–** |
| IVH | 5 | – | 1 | – | – | – | – | – | – | – | **6** | **–** |
| **Duration of stay in neonatal care (days)*** | | | | | | | | | | | | |
| Median {25, 75} | 8.5 | {5, 25.5} | 4 | {2, 7} | 1 | {1, 4} | 5 | {2.5, 22} | 3 | {1, 6} | **4.5** | **{2, 8}** |
| Min, max | 1, 66 | | < 1, 47 | | < 1, 19 | | < 1, 102 | | < 1, 16 | | **< 1, 102** | |
| < 1 | – | – | 4 | (4%) | 5 | (14%) | 6 | (11%) | 3 | (13%) | **18** | **(7%)** |
| 1–2 | 3 | (7%) | 20 | (22%) | 16 | (43%) | 8 | (14%) | 7 | (29%) | **54** | **(21%)** |
| 3–6 | 12 | (26%) | 42 | (45%) | 9 | (24%) | 17 | (30%) | 7 | (29%) | **87** | **(34%)** |
| 7–14 | 12 | (26%) | 24 | (26%) | 5 | (14%) | 5 | (9%) | 3 | (13%) | **49** | **(19%)** |
| ≥ 15 | 17 | (37%) | 3 | (3%) | 1 | (3%) | 20 | (35%) | 1 | (4%) | **42** | **(16%)** |
| **After leaving neonatal care, discharged** | | | | | | | | | | | | |
| Home | 36 | (78%) | 85 | (91%) | 29 | (78%) | 54 | (95%) | 12 | (50%) | **216** | **(84%)** |
| To another ward in the hospital | 8 | (17%) | 8 | (9%) | 7 | (19%) | 2 | (4%) | 9 | (38%) | **34** | **(13%)** |
| Not known | 2 | (4%) | – | – | 1 | (3%) | 1 | (2%) | 3 | (13%) | **7** | **(3%)** |
| **Outcome at discharge from hospital** | | | | | | | | | | | | |
| Early neonatal death (0–6 days) | 1 | – | 12 | – | 3 | – | 27 | – | 4 | – | **47** | **–** |
| Late neonatal death (7–27 days) | – | – | 4 | – | 1 | – | 5 | – | 1 | – | **11** | **–** |
| Post neonatal death (> 27 days) | – | – | – | – | – | – | 1 | – | – | – | **1** | **–** |

All data are N (%) unless otherwise stated

[a]One women at CMC and one women at FBH/LNH were transferred to different hospitals, resulting in missing outcome data

[b]Level 3 neonatal care is not provided in Uganda

Africa [26, 27] and Thailand [28] recruited a total of 507 infants, and the international trial included 71 infants recruited in Pakistan [21]. Also, it is likely that these studies were conducted in hospitals with access to a neonatal unit, and with neonatal care available in the delivery room. The comparative effects, both benefits and harms, associated with alternative policies for timing of cord clamping at preterm birth, particularly if very preterm, may be different in settings with limited access to neonatal care. Further evaluation in settings with limited or no access to neonatal care is therefore merited.

This study has shown that women giving birth preterm can be identified in these settings, and so conducting a randomised trial evaluating delivery room interventions for these births would potentially be feasible. Improving assessment of gestational age before birth would increase the proportion of potentially eligible women correctly identified. A future trial design would need to consider the implications of the PPV and NPV reported here and anticipate the inclusion of some births that were thought to be preterm and so randomised, but after birth are assessed as being term.

Despite conducting the audit in places with a warm climate, a surprisingly high proportion of the preterm infants were cold by the time they arrived at the neonatal unit. Keeping newborns warm, particularly those born preterm, is a key element in newborn life support [29], as this reduces morbidity [30, 31]. Common strategies on maternity units in high income settings, such as drying and the use of plastic wraps or bags and external heat sources, are largely unavailable on delivery units in low income settings. Evaluation of low cost interventions to reduce hypothermia, including staff training and availability of appropriate towels or cloths for drying and wrapping the infant following preterm birth in such settings is clearly a priority.

Cranial ultrasound scans were performed on a small number of infants at two of the hospitals in our study. This is not surprising as such scans are often unavailable in low and middle income settings [32].

Strengths of this study are that data were collected prospectively, with births observed to collect information not routinely available in the clinical notes; that we ensured a representative sample of all births was included; that data were available for 90% of births; and that we included a range of hospitals from four countries in low and middle income settings from four countries in Africa and south Asia. Limitations are that although the study was observational, conducting it may have changed care, as at some sites delivery unit midwives were trained to conduct the audit. Therefore they might also have been doing clinical shifts providing care at births included in the audit. Also, just the presence of an observer may have influenced care. As is common for audit data collected from clinical records, we were not able to assess the quality of these data. As our definition of preterm included birthweight, infants who were small for gestational age may potentially have been misclassified, although if a neonatal assessment was available this misclassification could be avoided. Finally, the hospitals contributing data may not be typical of wider practice within each country. Nevertheless, we consider that we included a representative range of units within low and middle income settings where conducting research at the time of preterm birth is feasible.

## Conclusions

Identification of women having a preterm birth, using our definition based on gestational age and/or birthweight, was good, with a PPV of 72% and a NPV of 97% based on antenatal assessment. Therefore conducting research, including randomised trials, to improve the quality of delivery room care for very preterm births would be feasible in hospitals in low and middle income countries. Timing of cord clamping varied between hospitals, although within each hospital there was no difference between 'term' and 'preterm' births. For caesarean births cord clamping was largely immediate. For vaginal births, timing varied. This variation in practice suggests a randomised trial comparing alternative policies for cord clamping may be feasible. The high levels of hypothermia amongst infants born preterm also suggests that implementing strategies to ensure these infants are kept warm following birth should be a priority. Given the high level of variation in practice in the delivery room and neonatal units, conducting quality improvement initiatives to promote high quality newborn care is also important.

## Supplementary information

**Supplementary information** accompanies this paper at https://doi.org/10.1186/s12884-020-03126-0.

**Additional file 1: Figure S1.** Timing of cord clamping for term and preterm births by mode of delivery.

**Additional file 2: Table S1.** Identification of preterm and term infants in the audit.

### Abbreviations

IVH: Interventricular haemorrhage; CMC: Christian Medical College; FBH/LNH: Fatima Bai Hospital and Liaquat National Hospital; LMP: Last menstrual period; PPV: Positive predictive value; NPV: Negative predictive value

### Acknowledgements

Thanks to all staff at the participating hospitals for their support of the study, and to Jennifer White for administrative support and Lucy Bradshaw for statistical advice.
CMC: Manish Kumar, Nirmala M, Nayana John
Mulago: Phiona Tukamushabe
Mbale: Isina Glades
University of Nairobi/Kenyatta National Hospital: Nereah Ojanga, Grace Wangombe, Julietta Kilonzo, Jacqueline Muthoni Opira

FBH/LNH: Shabana Rizvi, Dr. Humaira Tahseen, Dr. Fatima Bibi, Misbah Saleem, Dr. Bushra Rafique

*iCORD Collaborative Group*

Nottingham Clinical Trials Unit: Diane Whitham, Eleanor J Mitchell, Peter J Godolphin, Lelia Duley

CMC: Santosh Benjamin, Dr. Jiji Mathews, Dr. Manish Kumar, Dr. K Anil Kuruvilla, Ms. Nirmala M, Ms. Nayana John.

Mulago: Sam Ononge, Mariam Nabwire, Rose Mary Byenkya, Emilly Nakinja, Grace Engeu Ariokot, Sarah Namuddu

Mbale: James Ditai, Stephen Waiswa, Macreen Mudoola, Auma Proscovia, Julian Abesco, Susan Magoba

University of Nariobi /Kenyatta National Hospital: Zahida Qureshi, Dr. Alfred Osoti, Prof Rachel Musoke, Raheli Mukhwana

FBH/LNH: Shabeen Naz Masood, Zehra Naqvi, Haleema A Hashmi, Samina Shamim, Dr. Syed Kashif Abbas Zaidi, Dr. Yasir Masood

### Authors' contributions

DW drafted the protocol, co-ordinated the audit, contributed to the data analysis and wrote the first draft of the paper. EJM co-ordinated the audit, contributed to revision of and finalised the paper. SB was responsible for the audit at CMC. SO was responsible for the audit at Mulago. JD was responsible for the audit at Mbale. ZQ was responsible for the audit at Kenyatta. SNM was responsible for the audit at FBH/LNH. PJG analysed the data, and assisted with drafting the paper. LD conceived the study, designed the audit, drafted the protocol, and contributed to analysis of the data, and revision of the paper. All authors contributed to the protocol, and approved the final version of the paper.

### Funding

Medical Research Council (UK) Development Grant (MR/M017397/1). PJG was funded for this summary of independent research by the National Institute for Health Research (NIHR)'s Doctoral Research Fellowship Programme (DRF-2016-09-057). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. The funder had no role in study design, collection, analysis or interpretation of the data.

### Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

### Ethics approval and consent to participate

Ethics approval was obtained from the following committees: Kenyatta National Hospital/University of Nairobi Ethics Research Committee (P224/04/2015); IRB (Silver, Research and Ethics Committee) of Christian Medical College, Vellore (9945); Ethical Review Committee Liaquat National Hospital (LNH), Karachi (App#0199 LNH-ERC); Ethical Review Board Fatima Bai Hospital (FBH), Karachi (RD-045-APP-RB-0023-2015); Research Ethics Committee Uganda National Council for Science Technology (#HS 1791); Makerere University College of Health Sciences School of Medicine IRB (REC 2015–041). No administrative permissions or licenses were required by the teams to access the data.

This was an observational audit of current practice and therefore there were no regulatory requirements to obtain consent to participate from any of the participating countries.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

### Author details

[1]Nottingham Clinical Trials Unit, University Of Nottingham, Nottingham, UK. [2]Christian Medical College, Vellore, India. [3]Makerere University College of Health Science, Kampala, Uganda. [4]Sanyu Africa Research Institute, Mbale, Uganda. [5]University of Nairobi, Nairobi, Kenya. [6]Isra Medical University, Karachi-Campus, Karachi, Pakistan.

Received: 26 July 2018 Accepted: 21 July 2020
Published online: 31 July 2020

### References

1. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet. 2008;371(9608):261–9.
2. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJS. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. JAMA. 2002;288(6):728–37.
3. Zeitlin J, Draper ES, Kollee L, Milligan D, Boerch K, Agostino R, et al. Differences in rates and short-term outcome of live births before 32 weeks of gestation in Europe in 2003: results from the MOSAIC cohort. Pediatrics. 2008;121(4):e936–44.
4. March of Dimes P, Save the Children, WHO. Born too soon: the global action report on preterm birth. Geneva: World Health Organisation; 2012.
5. Chawanpaiboon S, Vogel JP, Moller AB, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. Lancet Glob Health. 2019;7(1):e37–46. https://doi.org/10.1016/S2214-109X(18)30451-0.
6. Anderson P, Doyle LW. Neurobehavioral outcomes of school-age children born extremely low birth weight or very preterm in the 1990s. JAMA. 2003;289(24):3264–72.
7. Aarnoudse-Moens CS, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. Pediatrics. 2009;124(2):717–28.
8. The Lancet. The unfinished agenda of preterm births. Lancet. 2016;388(10058):2323.
9. Duley L, Dorling J, Gyte G. When should the umbilical cord be clamped? BMJ. 2015;351:h4206.
10. Begley CM, Gyte GML, Devane D, McGuire W, Weeks A. Active versus expectant management for women in the third stage of labour. Cochrane Database Syst Rev. 2015;(3):CD007412. https://doi.org/10.1002/14651858.CD007412.pub4.
11. McDonald SJ, Middleton P, Dowswell T, Morris PS. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. Cochrane Database of Syst Rev. 2013(7):CD004074. https://doi.org/10.1002/14651858.CD004074.pub3.
12. WHO. Guideline: delayed umbilical cord clamping for improved maternal and infant health and nutrition outcomes. Geneva: World Health Organisation; 2014.
13. Kluckow M, Hooper SB. Using physiology to guide time to cord clamping. Semin Fetal Neonatal Med. 2015;20(4):225–31.
14. Rabe H, Gyte GM, Díaz-Rossello JL, Duley L. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. Cochrane Database Syst Rev. 2019;9(9):CD003248. https://doi.org/10.1002/14651858.CD003248.pub4 Published 2019 Sep 17.
15. Fogarty M, Osborn DA, Askie L, Seidler AL, Hunter K, Lui K, et al. Delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis. Am J Obstet Gynecol. 2018;218(1):1–18.
16. Manley BJ, Owen LS, Hooper SB, Jacobs SE, Cheong JLY, Doyle LW, et al. Towards evidence-based resuscitation of the newborn infant. Lancet. 2017;389(10079):1639–48.
17. Dubowitz L, Ricciw D, Mercuri E. The Dubowitz neurological examination of the full-term newborn. Ment Retard Dev Disabil Res Rev. 2005;11(1):52–60.
18. Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard score, expanded to include extremely premature infants. J Pediatr. 1991;119(3):417–23.
19. British Association of Perinatal Medicine. Categories of care 2011. 2011.
20. American Academy of Pediatrics Committee on F, Newborn. Levels of neonatal care. Pediatrics. 2012;130(3):587–97.
21. Tarnow-Mordi W, Morris J, Kirby A, Robledo K, Askie L, Brown R, et al. Delayed versus immediate cord clamping in preterm infants. N Engl J Med. 2017;377(25):2445–55.
22. 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(1):F6–F14.
23. Armanian A, Ghasemi Tehrani H, Ansari M, Ghaemi S. Is "delayed umbilical cord clamping" beneficial for premature newborns? Int J Pediatr. 2017;5:4909–18.

24. Datta BV, Kumar A, Yadav R. A Randomized Controlled Trial to Evaluate the Role of Brief Delay in Cord Clamping in Preterm Neonates (34-36 weeks) on Short-term Neurobehavioural Outcome. J Trop Pediatr. 2017;63(6):418–24. https://doi.org/10.1093/tropej/fmx004.
25. Ranjit T, Nesargi S, Rao PS, Sahoo JP, Ashok C, Chandrakala BS, Bhat S. Effect of early versus delayed cord clamping on hematological status of preterm infants at 6 wk of age. Indian J Pediatr. 2015;82:29.
26. Hofmeyr GJ, Bolton KD, Bowen DC, Govan JJ. Periventricular/intraventricular haemorrhage and umbilical cord clamping. Findings and hypothesis. S Afr Med J. 1988;73(2):104–6.
27. Hofmeyr GJ, Gobetz L, Bex PJ, Van der Griendt M, Nikodem C, Skapinker R, et al. Periventricular/intraventricular hemorrhage following early and delayed umbilical cord clamping. A randomized controlled trial. Online J Curr Clin Trials. 1993;Doc No 110:[2002 words; 26 paragraphs].
28. Tanprasertkul C, Salae R, Somprasit C, Bhamarapravatana K, Suwannarurk K. Efficacy of delayed versus immediate cord clamping in late preterm newborns following normal labor: a randomised control trial. BJOG. 2016; 123:86–7.
29. Wyllie J, Bruinenberg J, Roehr CC, Rudiger M, Trevisanuto D, Urlesberger B. European resuscitation council guidelines for resuscitation 2015: Section 7. Resuscitation and support of transition of babies at birth. Resuscitation. 2015;95:249–63.
30. Lyu Y, Shah PS, Ye XY, Warre R, Piedboeuf B, Deshpandey A, et al. Association between admission temperature and mortality and major morbidity in preterm infants born at fewer than 33 weeks' gestation. JAMA Pediatr. 2015;169(4):e150277.
31. McCall EM, Alderdice F, Halliday HL, Vohra S, Johnston L. Interventions to prevent hypothermia at birth in preterm and/or low birth weight infants. Cochrane Database Syst Rev. 2018(2):CD004210. https://doi.org/10.1002/14651858.CD004210.pub5.
32. Ballot DE, Agaba F, Cooper PA, Davies VA, Ramdin T, Chirwa L, et al. A review of delivery room resuscitation in very low birth weight infants in a middle income country. Matern Health Neonatol Perinatol. 2017;3(1):9.

## Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

**Ready to submit your research? Choose BMC and benefit from:**

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

**At BMC, research is always in progress.**

**Learn more** biomedcentral.com/submissions



**PAPER 4: The FEED1 Trial: Protocol for a randomised controlled trial of full milk feeds versus intravenous fluids with gradual feeding for preterm infants (30-33 weeks gestational age)**

Mitchell et al. Trials (2022) 23:64
https://doi.org/10.1186/s13063-021-05994-z

Trials

STUDY PROTOCOL Open Access

# The FEED1 trial: protocol for a randomised controlled trial of full milk feeds versus intravenous fluids with gradual feeding for preterm infants (30–33 weeks gestational age)

Eleanor J. Mitchell[1*], Garry Meakin[1], Josie Anderson[2], Jon Dorling[3], Chris Gale[4], Rachel Haines[1], Charlotte Kenyan[5], Mark J. Johnson[3], William McGuire[6], Hema Mistry[7], Alan Montgomery[1], Sam Oddie[8], Reuben Ogollah[1], Phoebe Pallotti[9], Christopher Partlett[1], Kate F. Walker[10] and Shalini Ojha[10,11]

## Abstract

**Background:** In the UK, approximately 8% of live births are preterm (before 37 weeks gestation), more than 90% of whom are born between 30 and 36 weeks, forming the largest proportion of a neonatal units' workload. Neonatologists are cautious in initiating full milk feeds for preterm infants due to fears of necrotising enterocolitis (NEC). There is now evidence to dispute this fear. Small studies have shown that feeding preterm infants full milk feeds enterally from birth could result in a shorter length of hospital stay, which is important to parents, clinicians and NHS services without increasing the risk of NEC. This trial aims to investigate whether full milk feeds initiated in the first 24 h after birth reduces the length of hospital stay in comparison to introduction of gradual milk feeding with IV fluids or parenteral nutrition.

**Methods:** FEED1 is a multi-centre, open, parallel group, randomised, controlled superiority trial of full milk feeds initiated on the day of birth versus gradual milk feeds for infants born at $30^{+0}$ to $32^{+6}$ (inclusive) weeks gestation. Recruitment will take place in around 40 UK neonatal units. Mothers will be randomised 1:1 to full milk feeds, starting at 60 ml/kg day, or gradual feeds, as per usual local practice. Mother's expressed breast milk will always be the first choice of milk, though will likely be supplemented with formula or donor breast milk in the first few days. Feeding data will be collected until full milk feeds are achieved (≥ 140 ml/kg/day for 3 consecutive days). The primary outcome is length of infant hospital stay. Additional data will be collected 6 weeks post-discharge. Follow-up at 2 years (corrected gestational age) is planned. The sample size is 2088 infants to detect a between group difference in length of stay of 2 days. Accounting for multiple births, this requires 1700 women to be recruited. Primary analysis will compare the length of hospital stay between groups, adjusting for minimisation variables and accounting for multiple births.

* Correspondence: eleanor.mitchell@nottingham.ac.uk
Sponsor contact details: University Hospitals of Derby and Burton NHS Foundation Trust: dhft.sponsor@nhs.net
[1]Nottingham Clinical Trials Unit, Building 42, University Park, University of Nottingham, Nottingham NG7 2RD, UK
Full list of author information is available at the end of the article

© The Author(s). 2022 **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. 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 in a credit line to the data.

**Discussion:** This trial will provide high-quality evidence on feeding practices for preterm infants. Full milk feeds from day of birth could result in infants being discharged sooner.

**Trial registration:** ISRCTN ISRCTN89654042. Prospectively registered on 23 September 2019: ISRCTN is a primary registry of the WHO ICTRP network, and all items from the WHO Trial Registration dataset are included.

**Keywords:** Clinical trial, Protocol, Preterm infant, Feeding, Neonatal, Full milk, Enteral feeding

## Background

In preterm infants, early establishment of enteral feeding is associated with reduced sepsis, improved growth [1] and enhanced neurodevelopment [2]. Achieving full milk feeds sooner and improving growth without infection or necrotising enterocolitis (NEC) may help the infant be ready for home earlier, reducing the length of hospital stay. Despite evidence to the contrary [3], clinicians often delay initiating feeds or increment feeds slowly due to fear of NEC. The recently completed Speed of Increasing milk Feeds Trial (SIFT) provides firm evidence from over 2800 infants that faster advancement of milk feeds does not increase the risk of NEC even in the most premature infants [4]. In this large, multi-centre trial comparing fast (30 ml/kg/day) vs. slow (18 ml/kg/day) feed increments in 2804 infants born before 32 weeks gestation, the risks of NEC or death were not increased by the faster increment in feeds. Faster fed infants achieved full feeds quicker and received intravenous (IV) fluids for fewer days. A recent Cochrane review assessing advancement of feed volumes in preterm infants concluded that slow advancement of enteral feed volumes results in several days of delay in establishing full milk feeds and may increase the risk of invasive infection [1] possibly due to increased iatrogenic infections from a longer duration of IV line placement.

These results indicate that there may be benefit from a faster approach to feeding. In infants between $30^{+0}$ to $32^{+6}$ weeks this could be achieved by providing their full fluid requirements solely as enteral feeds from day of birth without using IV fluids or parenteral nutrition, i.e. "full milk" feeds from the day of birth. A Cochrane review on early full enteral feeding in preterm infants included 6 randomised controlled trials involving 601 stable infants weighing between 1000 and 1500 g at birth [5]. A meta-analysis of length of hospital stay (4 studies, 398 infants) showed a mean difference of − 2.26 days in infants given early full enteral feeds. There was no difference in incidence of NEC. However, all studies were conducted in India and had a moderate to high risk of bias in several areas when assessed for methodological rigour. One small study included in the review included 46 infants (birth weight 1200–1500 g; mean gestation 31 weeks) who were randomised to receive full milk from one hour after birth or IV fluids and slow feed increments (20 ml/kg/d) [6]. They found that infants randomised to full milk feeding regained birth weight quicker, had improved growth at discharge, shorter duration of hospital stay and fewer cases of sepsis without an increased risk of NEC. Additionally, in a trial of 180 infants, Nangia et al. showed a mean difference of − 3.6 days in time taken to reach full enteral feeds in infants fed early enteral feeds and a reduction of 4.1 days in length of hospital stay [7]. These findings suggest it is potentially safe and may be better to start full milk feeds on the day of birth without increasing the risk of NEC and possibly reducing the risk of sepsis. An observational study also showed that implementing full milk feeds from birth is feasible and acceptable, with the infants receiving full enteral milk feeds having significantly fewer cases of NEC and sepsis, less antibiotics, less parenteral nutrition and a shorter average hospital stay [8]. These studies were all conducted in India where the preterm population, healthcare resources, infrastructure and delivery systems as well as treatments and risk factors are different to that in the UK. There have been no studies in the UK or other similar high resource settings investigating the strategy of feeding preterm infants "full milk" feeds from day of birth.

### Justification for study population

In 2018, in England and Wales, there were 656,925 live births of which 51,864 (7.9%) were preterm (born before 37 completed weeks gestation) [9]. Providing optimal nutrition is a cornerstone of neonatal care and the subject of many recent research studies including SIFT [4], ADEPT [10], NEON [11] and SCAMP [12]. These and other similar studies focus on extremely preterm infants (born before 30 weeks) at highest risk of adverse outcomes (death or NEC). However, more than 90% of preterm infants are born at or after 30 weeks, including the 12% of preterm infants who are eligible for FEED1. More mature preterm infants (≥ 34 weeks) typically do not require special care. Infants born at 30, 31 or 32 weeks comprise over 40% of preterm infants routinely admitted to neonatal units (in 2018 there were 5879 infants in this group in England and Wales) and form the largest proportion of workload for neonatal services. Treatments that reduce length of stay in this group of preterm infants could therefore impact the largest number of infants in neonatal units and their families.

### Justification for comparators

Infants that are fully milk fed need less monitoring and could be moved to lower dependency care. Adequate enteral nutrition could promote weight gain and reduce the risk of infections, potentially making infants ready for home sooner and reducing the length of hospital stay. This would make scarce higher dependency cots for sicker infants more readily available and avoid transferring infants further afield to access resources.

Strategies that aim to safely achieve a shorter hospital stay could improve care for all infants who require neonatal care. Full milk feeds may also reduce the cost of care by decreasing use of parenteral nutrition and IV fluids and reducing iatrogenic infections. Preterm birth is associated with long-term morbidities and large lifetime financial costs, placing strain on NHS finances and social care resources. Full milk feeds may improve nutrition and reduce morbidities such as sepsis, thereby improving neurodevelopmental outcomes and lifelong quality of life for this large group of infants. Such an approach that improves the care of preterm infants whilst simultaneously reducing the cost of care would achieve the NHS "Five Year Forward View" aim of achieving efficiency savings whilst maintaining and improving quality of care and safety [13]. There are also potential benefits for mothers and families from a less medical model of care, with opportunities for involvement in care, shorter mother-infant separation and improved satisfaction and mental health outcomes.

The FEED1 Trial addresses three of the top six research priorities identified by the James Lind Alliance [14]:

- "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 infants?
- How can infection in preterm infants be better prevented?
- Which interventions are most effective to prevent necrotising enterocolitis in premature infants?"

This paper is reported in accordance with the Standard Protocol Items: Recommendations for Interventional trials (SPIRIT) guidelines [15].

### Objectives

To determine whether, in infants born at $30^{+0}$ to $32^{+6}$ weeks gestation, full milk feeds initiated in the first 24 h after birth reduces the length of infant hospital stay in comparison to IV fluids or parenteral nutrition with gradual milk feeding.

## Methods/design

This is a multi-centre, open, parallel group, randomised (1:1) controlled superiority trial of full milk feeds versus gradual milk feeds. Mothers and infants will be recruited from around 40 neonatal units in the UK. A list of participating sites can be found at www.feed1.ac.uk. The full protocol and other trial documentation, including participant information sheets and consent forms, can also be found on the trial website. An embedded Study Within a Trial (SWAT) is also included which is investigating methods of training sites. Details of the SWAT can be found on the SWAT repository [16, 17] and will be reported separately.

### Eligibility

Inclusion criteria include (i) infants born at $30^{+0}$ to $32^{+6}$ weeks gestation (inclusive) and ii) infants < 3 h (180 min) old (since recorded time of birth). Infants requiring respiratory support (such as via continuous positive airway pressure) or other supportive treatments will be included in the study if the clinician is in equipoise about the infant being randomised to either the "full milk" or the "gradual milk" arm. Similarly, well infants should only be included if the attending clinician is in equipoise about the best feeding regime and the infant being randomised to either "full milk" or "gradual milk" groups. Exclusion criteria include (i) infants with known congenital abnormalities of the gastrointestinal tract or other congenital conditions that make enteral feeding unsafe, (ii) infants who are small for gestational age (SGA) (birth weight < $10^{th}$ centile) and have evidence of reversed end-diastolic flow on antenatal umbilical artery Doppler ultrasound and (iii) mothers who have participated in the trial during a previous pregnancy.

### Interventions

For infants in the full milk group (intervention), fluids will be started as milk at 60 ml/kg/day, increased as per their individual requirements and in line with standard neonatal practice. The choice of feeding intervals will be determined by local policy and clinician's preference. Wherever possible, mother's expressed breast milk will always be the first preference for infant milk feeds. It is likely that mother's breast milk will need to be supplemented with additional milk, i.e. either infant formula milk or donor breast milk in the first few days. The decision as to the type of milk used will be made by the mother and the site, in line with the site's local policy. For infants in the gradual milk group (control), fluids will be given in accordance with standard practice at the site. This may include milk feeds, starting at a maximum of 30 ml/kg/day on day 1 with a minimum of 30 ml/kg/day of supplementary IV fluids or parenteral nutrition. Adherence to the randomised allocation will be monitored

on a regular basis by the Trial Management Group. Due to the pragmatic nature of this neonatal feeding trial, there are no prohibited interventions or concomitant medications.

### Outcomes

The primary outcome is length of infant hospital stay. Since hospitals could apply different discharge criteria, a secondary outcome of time until objective discharge criteria are met has also been included. The statistician, blinded to treatment allocation, will use the date at which each infant first met all three of the following criteria: (i) current weight ≥ 1700 g, (ii) infant is able to take at least one full suck feed assessed as adequate and (iii) infant has been off additional temperature support for ≥ 24 h. Daily data will be collected to determine the day on which the infant achieved all the three features to determine the time until objective discharge criteria are met. The primary and all secondary outcomes, including the five elements (domain, specific measurement, specific metric, method of aggregation and time point) as defined by Saldanha et al [18], are listed in Table 1.

Outcome measures included have been guided by the Core Outcomes in Neonatology (COIN) core outcome set [22]. Discussions are ongoing to obtain separate funding to collect longer-term follow-up data at 2 years corrected gestational age. In addition, the research team are in discussions with researchers based in other countries, such as Canada and Australia, to set-up parallel studies. This will be to provide sufficient power to assess outcomes of NEC and sepsis; these outcomes occurred in 1% and 12% of infants retrospectively in the SIFT Trial among those who would have been eligible for FEED1.

### Sample size and recruitment

Our sample size calculation has been based upon detecting a between group difference in means of length of stay of 2 days. Input from our parent representatives suggests that from a family perspective even a short reduction in length of hospital stay could make a huge difference to parents. In addition, from a cost-saving perspective, a reduction in length of stay of 2 days for this population of infants could result in £5.6 m annual savings for the NHS in England and Wales and > 12,000 days of increased neonatal cot capacity.

Data from audits and previous studies suggest that the distribution of length of hospital stay in this population is approximately normal. To detect a difference in means of 2 days between the two groups with 90% power, 1:1 allocation and 5% two-sided significance requires 1778 infants, assuming a standard deviation of 13 [23, 24]. Allowing for 2% non-collection of the primary outcome data due to death, no consent for data collection after oral assent and infants remaining in hospital at the end of data collection and accounting for clustering will require 2088 infants and recruitment of approximately 1770 women. The inflation to account for clustering assumes that 15% and 1.4% of pregnancies will be twin and triplets respectively and that the intracluster correlation coefficient for length of hospital stay for infants from the same pregnancy is 0.82 [4].

### Participant enrolment and consent

The flow of women and infants throughout the trial is shown in Fig. 1. As the infant must be randomised within three hours of birth, a time during which the woman is recovering from giving birth and that is emotionally fraught and potentially difficult for families, a two-stage consent pathway will be used. Wherever possible, women will be approached antenatally and asked to consider participation in the trial. At around the time of antenatal counselling consultation, women will be given study information, have the opportunity to discuss the study and ask questions and give full written informed consent if they are willing to do so. For these women, once they have given birth, infant eligibility will be checked and the infant(s) will be entered into the trial, unless the mother expresses that she has changed her mind. For some women, receiving information and providing consent antenatally may not be possible due to the rapid and unexpected nature of preterm birth. During labour and postnatally, these women can be approached via an oral assent pathway. This involves a member of the neonatal team inviting the woman to participate and giving the minimal information required to make a decision. A shorter, simplified participant information sheet and/or a short animation film may be used to support this discussion. The decision to participate will be documented in the medical notes and full written informed consent will be obtained later (ideally ≤ 72 h). This two-stage consent pathway has been used successfully in a previous neonatal trial [24] and features as part of guidance from the Royal College of Obstetricians and Gynaecologists (RCOG) [25]. Sites will be fully trained in the two-stage consent pathway and will be provided with a range of supplementary materials to support oral assent conversations which include a recorded webinar, video showing examples of discussions and additional documentation. Women are asked to give their optional consent to be contacted for longer-term follow-up of their infant(s) and for later educational outcomes.

### Randomisation and blinding

The unit of randomisation is the mother to ensure that a mother-infant(s) dyad is treated as a unit. This will

**Table 1** Primary and secondary outcome measures

| Domain | Specific measurement | Specific metrics | Method of aggregation | Time point |
|---|---|---|---|---|
| **Primary outcome** | | | | |
| Length of hospital stay | Date of hospital discharge | Difference between the date the infant is discharged and date of randomisation | Mean and standard deviation (SD), per group | Hospital discharge |
| **Secondary outcomes** | | | | |
| Survival | Date of death as recorded on eCRF.<br>Date of death as recorded on eCRF | Death between date of randomisation and date of hospital discharge.<br>Death between date of randomisation and 6 weeks corrected gestational age | Proportion of infants alive, per group.<br>Proportion of infants alive, per group | Hospital discharge<br>6 weeks corrected gestational age |
| Microbiologically confirmed (positive blood/cerebrospinal fluid culture) or clinically suspected late-onset sepsis | Presence of confirmed or suspected late-onset sepsis on microbiology report and recorded in eCRF[1] | Microbiologically confirmed late-onset sepsis between date of randomisation and hospital discharge | Proportion of infants with microbiologically confirmed late-onset sepsis, per group | Hospital discharge |
| Necrotising enterocolitis (NEC) (Bell's stage 2 or 3) [19] | Presence of NEC (stage 2 or 3) recorded on eCRF[1] | Diagnosis of NEC (stage 2 or 3) between date of randomisation and hospital discharge | Proportion of infants with NEC (stage 2 or 3), per group | Hospital discharge |
| Time taken to maintain full milk feeding | Full milk feeds reached, defined as at least 140 ml/kg/day for three consecutive days[2], as recorded on eCRF | Derived from the date the infant achieves full feeds, recorded on CRF, and date of randomisation | Mean (and SD) and/or median (and IQR), per group | During hospital admission, in accordance with criteria for reaching full milk feeds |
| Time to regain birth weight | Birth weight regained, as recorded on eCRF | Derived from the date the infant regains birth weight and date of randomisation | Mean (and SD) and/or median (and IQR), per group | During hospital admission |
| Growth of infant | Growth *Z* scores (length, weight and head circumference), corrected for gestational age as per UK-NICM growth charts [20] | Derived from growth *Z* scores, expected date of delivery and infant sex | Mean (and SD) and/or median (and IQR), per group | Hospital discharge |
| Breast-feeding | Infant being breast-fed, as recorded on CRF. Infant being breast-fed, as recorded on 6-week parent-completed questionnaire | Infant being breast-fed at time of hospital discharge. Infant being breast-fed at 6 weeks (corrected gestational age) | Proportion of infants breast-feeding, per group. Proportion of infants breast-feeding, per group | Hospital discharge. 6 weeks corrected gestational age |
| Breast milk feeds | Infant being fed mother's breast milk, as recorded on eCRF. Infant being fed mother's breast milk, as recorded on 6-week parent-completed questionnaire | Infant being fed mother's breast milk at time of hospital discharge. Infant being breast fed mother's breast milk at 6 weeks (corrected gestational age) | Proportion of infants being fed mother's breast milk, per group. Proportion of infants being fed mother's breast milk, per group | Hospital discharge. 6 weeks, corrected gestational age |
| Number of days of cannulae | Number of days of peripheral cannula and IV cannulae inserted, as recorded on eCRF | Number of days of peripheral cannula and IV cannulae inserted, until infant reaches full milk feeds | Mean (and SD) and/or median (and IQR), per group | Date infant reaches full milk feeds, whilst in hospital |
| Number of days of infant receiving parenteral nutrition | Number of days of infant receiving parenteral nutrition, as recorded on eCRF | Number of days of infant receiving parenteral nutrition until hospital discharge | Mean (and SD) and/or median (and IQR), per group | Hospital discharge |
| Number of central venous lines inserted | Number of central venous lines, including umbilical and percutaneous or surgically inserted venous lines), as recorded on eCRF | Number of central venous lines between date of randomisation and date of hospital discharge | Mean (and SD) and/or median (and IQR), per group | Hospital discharge |
| Number of central line days | Number of days infant has a central line, as recorded on eCRF | Number of central line days between date of randomisation and date of hospital discharge | Mean (and SD) and/or Median (and IQR), per group | Hospital discharge |

**Table 1** Primary and secondary outcome measures *(Continued)*

| Domain | Specific measurement | Specific metrics | Method of aggregation | Time point |
|---|---|---|---|---|
| Time until objective discharge criteria are met | Objective discharge criteria, as recorded on eCRF | Derived from the date the objective discharge criteria is met and date of randomisation | Mean (and SD) and/or median (and IQR), per group | During hospital admission |
| Length of neonatal unit stay | Length of stay in (i) neonatal intensive care, (ii) high dependency care, (iii) special care, (iv) translational care, as recorded on eCRF | Derived from days spent in each type of neonatal unit between date of randomisation and date of discharge | Mean (and SD) and/or median (and IQR), per group | Hospital discharge |
| Retinopathy of prematurity (ROP) | Diagnosis of ROP, as recorded on eCRF | Diagnosis of ROP between date of randomisation and date of hospital discharge | Proportion of infants with ROP, per group | Hospital discharge |
| Chronic lung disease (CLD) | Diagnosis of CLD, as recorded on eCRF | Diagnosis of CLD between date of randomisation and date of hospital discharge | Proportion of infants who are mechanically ventilated or on nasal CPAP or in supplemental oxygen at 36 weeks corrected gestational age, per group | Hospital discharge |
| Brain injury | Diagnosis of intraventricular haemorrhage (grade 3 or 4), periventricular leukomalacia or hydrocephalus (requiring a shunt) on cranial ultrasound, recorded on eCRF | Diagnosis of brain injury (as per definitions) between date of randomisation and date of hospital discharge | Proportion of infants with recorded evidence of brain injury (grade 3 or 4 intraventricular haemorrhage, periventricular leukomalacia or hydrocephalous requiring shunt, per group | Hospital discharge |
| Blood glucose/ hypoglycaemia | Number of blood glucose tests, as recorded on eCRF.<br>Number of blood glucose tests indicating hypoglycaemia (< 2.2 mmol/L).<br>Number of blood tests indicating severe hypoglycaemia (< 1.0 mmol/L) | Number of blood glucose tests, between date of randomisation and date of hospital discharge.<br>Number of blood glucose tests < 2.2 mmol/L, between date of randomisation and date of hospital discharge.<br>Number of blood glucose tests < 1.0 mmol/L between date of randomisation and date of hospital discharge | Mean (and SD) and/or median (and IQR), per group.<br>Mean (and SD) and/or median (and IQR), per group.<br>Mean (and SD) and/or median (and IQR), per group | Hospital discharge.<br>Hospital discharge.<br>Hospital discharge |
| Hospital visits | Number of hospital visits, including day care and overnight admissions, as recorded on 6-week parent-completed questionnaire | Number of hospital visits between date of hospital discharge and 6 weeks corrected gestational age | Mean (and SD) and/or median (and IQR), per group | 6 weeks corrected gestational age |
| Parental satisfaction and wellbeing | Preterm birth experience and satisfaction scale (P-BESS) [21], completed by parents | P-BESS total score (and subscales for interpersonal care, information and explanations, lack of confidence in staff) at 6 weeks corrected gestational age | Mean (and SD) and/or median (and IQR), per group | 6 weeks corrected gestational age |

[1]Indeterminate cases will be subject to a blinded endpoint review to make a final determination
[2]Infants who are partially or exclusively breast fed will be considered to have achieved full enteral milk feeds if their intake of milk (breast feeding plus measured volume of additional milk) is considered equivalent to full enteral milk feeds

also enable antenatal consent and facilitate early commencement of the intervention. In addition, it will ensure that siblings from multiple pregnancies are assigned to the same group. Parents have told us this is important to them as they would not like to feed their infants differently unless there was a medical reason to do so. Randomisation will be performed on a 1:1 ratio, using a secure web-based system, developed and maintained by the Nottingham Clinical Trials Unit (NCTU), which will conceal allocation sequence. Randomisation will use a minimisation algorithm, with a random element, to ensure balance on important prognostic factors: neonatal unit, single or multiple birth, gestational age at birth, birth weight centile and whether IV fluids were started prior to randomisation. Randomisation will be undertaken by the principal investigator, clinician or other study team member within three hours from the recorded time of birth. This is to ensure infants randomised to full milk feeds can receive the intervention with minimal risk of receiving IV fluids and should help prevent contamination between groups.

It is not possible to blind investigators and families due to the nature of the intervention. Unblinding is therefore not relevant as this is an open-label trial. However, the trial statistician will remain blinded throughout the trial. To objectively assess the primary outcome, a

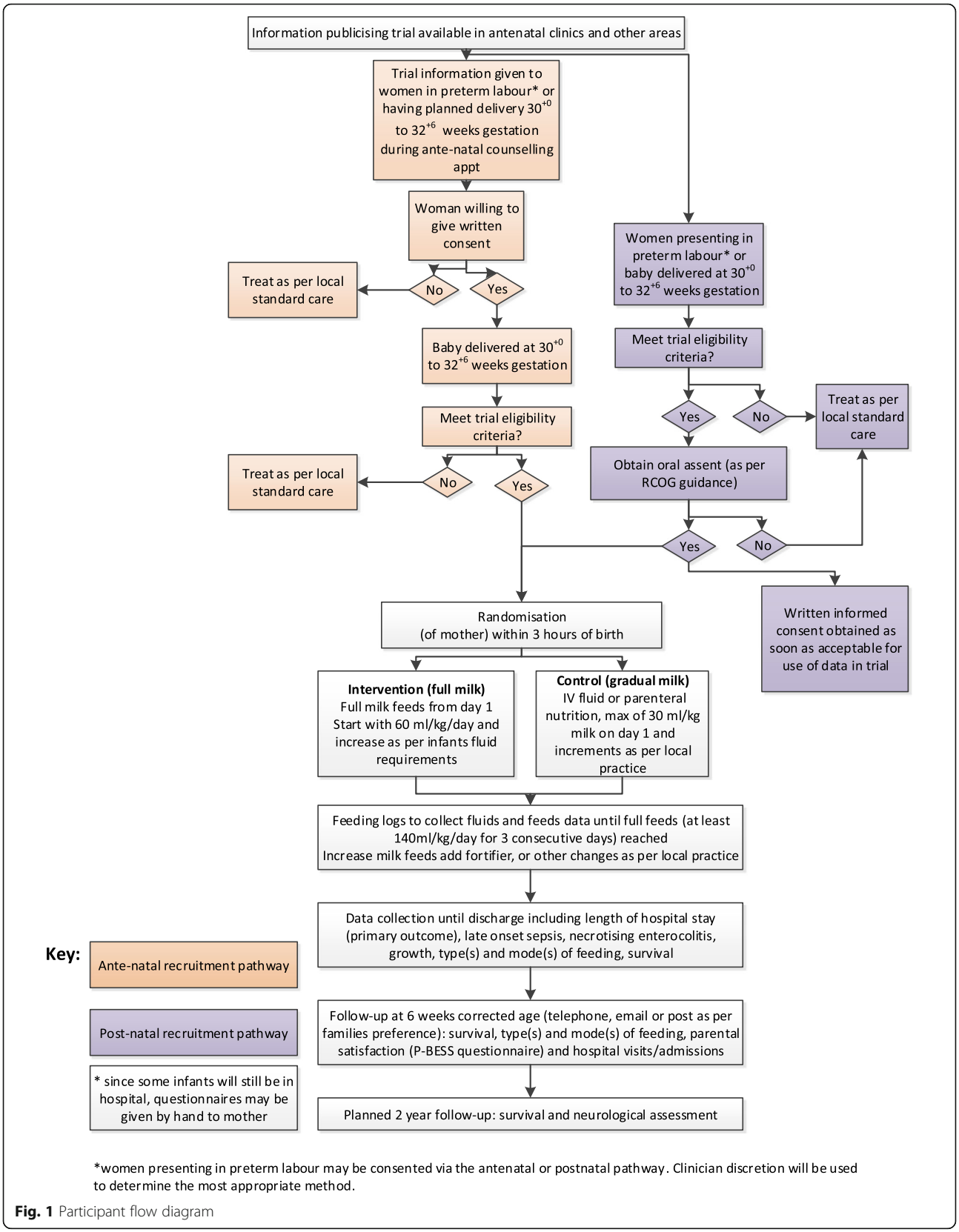



**Fig. 1** Participant flow diagram

secondary outcome measure to objectively assess discharge criteria is included and a blinded endpoint review committee (BERC) will also be established to examine cases of late-onset sepsis and necrotising enterocolitis where the diagnosis is unclear.

### Trial assessments and procedures

All trial assessments and procedures are outlined in Table 2. Most outcome data will be collected during the infant's hospital admission. A daily feeding log will be completed until the infant receives at least 140 ml/kg/day of feeds, sustained for 3 consecutive days. For infants who are transferred to another hospital, i.e. a continuing care site, a paper transfer pack will accompany the infant with information on trial participation and data collection will continue. To collect data at 6 weeks corrected gestational age, an online questionnaire (or paper if preferred) will be sent to women; reminders will be sent to increase response-rates.

No laboratory specimens will be collected specifically for the trial. Any samples taken are in line with usual care and results will only be recorded in the eCRF if relevant (e.g. blood glucose, late-onset sepsis).

No specific provision has been included for the care of infants outside of the trial; clinical care will be as per usual care, in line with the pragmatic nature of the trial.

### Adverse events

As adverse events are commonly encountered in preterm infants receiving neonatal care, they will be recorded in the infant's medical notes as per usual practice, from the commencement of the randomised feeding strategy until hospital discharge. Adverse reactions are thus collected as outcomes and will not need to be reported separately via an adverse event reporting process. Blood glucose levels will be monitored routinely for all infants, recorded in the trial eCRF and provided in meeting reports to the independent data monitoring committee (DMC). Coding of adverse events (e.g. MedDRA) will not be undertaken. Serious adverse events (SAEs), including death, will be reported as such by the principal investigator, or delegate, reporting within 24 h of being made aware of the event, using an SAE form, sent via email to a dedicated SAE reporting mailbox at NCTU. Reporting will be aligned with the standard operating procedure (SOP) at the Nottingham Clinical Trials Unit. The chief investigator, or delegate (neonatologist), has responsibility for the review of all SAEs, to assess causality. Late-onset sepsis (microbiologically confirmed or clinically suspected), necrotising enterocolitis (Bell's stage 2 or 3) or other known complications of prematurity will not be reported as serious adverse events. Only SAEs that are deemed to be related to the trial interventions will be followed up until resolution. If an SAE is unexpected, it will be classified as a SUSAR (serious unexpected suspected adverse reaction). All SUSARs will be reported by NCTU to the ethics committee within 15 days of being notified, and all principal investigators will be notified. The DMC will review all reported SAEs and neonatal outcome data at regular intervals throughout the trial, in line with the DMC charter.

Insurance and indemnity for infants and NHS trial staff is covered within the NHS Indemnity arrangements for clinical negligence claims in the NHS. No special compensation arrangements apply to this trial, though parents may have recourse to the NHS complaints procedure.

### Data management

All trial data will be collected by site staff delegated to do so and entered onto a trial specific database (eCRF) with infants only identified by their unique trial number and initials. Using MACRO (Elsevier), the database will be developed and maintained by NCTU staff. Access to the database will be restricted and secure. Sites will be provided with paper workbooks to assist them with data collection. Missing or spurious data will be queried in a timely manner throughout the trial, in accordance with the trial data management plan. To facilitate contact with families at 6 weeks corrected gestational age, contact details will be collected and entered into an online secure system, developed and maintained by NCTU staff. This data is held separately to the deidentified trial data collected. Access to contact details is restricted to those involved in the follow-up phase, as authorised by the chief investigator.

### Statistical analysis

Analysis and reporting of the trial will be in accordance with the Consolidated Standards of Reporting Trials (CONSORT) [26] guidelines. All analyses will be outlined in a detailed Statistical Analysis Plan agreed prior to database lock. No interim analyses are planned. The primary comparative analyses will be conducted according to randomised allocation with due emphasis on confidence intervals for between-group comparisons.

The primary outcome will be analysed using linear mixed models to compare the mean length of hospital stay between groups, adjusting for minimisation variables and accounting for the correlation between outcomes for infants born from a multiple pregnancy. The estimated between group effect will be presented using the difference in means, with a 95% confidence interval. Secondary outcomes will be analysed similarly using appropriate multilevel regression models, dependent on the type of outcome variable. The between group effect will be reported using

**Table 2** Schedule of assessments

| | TRIAL PERIOD | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Antenatal pathway | Postnatal pathway | Treatment period | | | | | Follow-up |
| **TIMEPOINT** | **Before birth** | **After birth** | **Day$_1$** | **Day$_2$** | **Day$_3$** | **Etc.** | **Discharge** | **6 weeks corrected age** |
| **ENROLMENT:** | | | | | | | | |
| **Eligibility screen** | X | X | | | | | | |
| **Informed consent** | X | | | | | | | |
| **Oral assent**[1] | X[1] | X[1] | | | | | | |
| **Randomisation** | | | X | | | | | |
| **Informed consent**[2] | X[2] | X[2] | | | | | | |
| **Baseline data** | | | X | | | | | |
| **INTERVENTIONS:** | | | | | | | | |
| **Full enteral feeds or Gradual feeds** | | | X | X | X | X | | |
| **ASSESSMENTS:** | | | | | | | | |
| **Daily feeding log** | | | X | X | X | X | | |
| **Number of painful procedures** | | | X | X | X | X | | |
| **Discharge criteria** | | | X | X | X | X | X | |
| **Late-onset Invasive Infection**[3] | | | X[3] | X[3] | X[3] | X[3] | | |
| **Gut Signs**[4] | | | | | | X[4] | | |
| **DISCHARGE DATA:** | | | | | | | | |
| **Growth (z scores - weight, length, and head circumference)** | | | | | | | X | |
| **FOLLOW-UP:** | | | | | | | | |
| **Healthcare visits** | | | | | | | | X |
| **Types and modes of feeding** | | | | | | | | X |
| **Parental satisfaction (p-BESS)** | | | | | | | | X |

[1] *Women who present in the late stages of labour or who have already given birth should be consented first via oral assent followed by later written informed consent*

[2] *Women who given oral assent trial should provide written consent within 72 hours of providing oral assent, where possible*

[3] *Each episode of microbiologically-confirmed or clinically-suspected late-onset invasive infection should be reported throughout the treatment period until hospital discharge*

[4] *To be reported if this infant has received at least 5 days of treatment for gut signs, if they are transferred with gut signs, or if they have died from gut signs*

an appropriate effect estimate along with a corresponding 95% confidence interval.

The primary approach to between-group comparative analyses will be by modified intention-to-treat (i.e. including all participants who have been randomised and without imputation of missing outcome data). In particular, the primary analysis will exclude the small number of deaths that might occur before discharge, but sensitivity analysis will be performed by imputing the primary outcome with the worst observed length of stay for infants who died prior to discharge to check that this does not influence the findings. A further sensitivity analysis will assess the effect of compliance with the allocated feeding strategy through complier average causal effect (CACE) analysis.

Appropriate interaction terms will be included in the primary regression analyses to conduct subgroup analyses according to gestation at birth and birth weight centile, but this analysis will be regarded as exploratory as the study is not powered to detect interactions. Interpretation of any subgroup effects will be based on the treatment-subgroup interaction and 95% confidence interval.

A within-trial economic analysis will be conducted from an NHS and personal social services perspective. Resource data will be collected prospectively and unit costs will be obtained from routine sources. The main cost-effectiveness analysis will be based on the cost per reduction in days in care. A longer-term projection of costs and benefits will be estimated through decision analytical modelling. Appropriate sensitivity analyses will be undertaken to account for any uncertainty.

### Monitoring and governance

An independent DMC will review unblinded trial data, including safety data, on an intermittent basis. The role of the DMC is outlined in a charter, available upon request, which outlines their terms of reference. Overall independent oversight will be provided by a trial steering committee (TSC).

On-site monitoring will not be conducted routinely throughout the trial. Instead, regular central monitoring of trial data will be undertaken and this data will be used to assess if sites have met any triggers to activate a triggered monitoring visit. The Trial Management Group (TMG) are responsible for reviewing central monitoring reports and agreeing if triggered on-site monitoring visits are required. Any trial conduct audits will be carried out by the sponsor as per their local auditing plans.

### Protocol amendments

Any amendments to the protocol will be managed in line with standard operating procedures at the NCTU. A decision to make an amendment to the protocol will be taken by the Trial Management Group, and changes to the protocol and/or trial documentation will reviewed by the trial sponsor and funder. It is the responsibility of the trial manager, or delegate, to submit the protocol and/or trial documentation for review by the ethics committee and to participating sites. Once an amendment is approved, all documentation relating to the amendment will be sent to Principal Investigators. The trial registry will remain up-to-date throughout the trial, by the trial manager or delegate.

### Patient and public involvement (PPI)

Our research team includes a parent who has experience of having a preterm infant, born at 31 weeks gestation, and the research manager for Bliss, the UK's largest premature and sick baby charity, who represent parents with experience of preterm birth. In addition to our immediate research team PPI members, we have a group of three parents who provide additional parent input, and a PPI member on the independent trial steering committee. We involved parents throughout the design stage of this trial and continue to do so whilst it is being conducted.

### Dissemination

The results of the FEED1 trial will be shared widely. Participants will receive a lay newsletter, with input from PPI members, unless they have expressed they do not wish to receive this. The results will be made publicly available via the trial website. Participating sites will receive a summary of the results. The trial results will be submitted to a high-impact peer-reviewed scientific journal and to international and national neonatal and paediatric conferences. Results will also be disseminated via social media platforms, including the NCTU Twitter page, FEED1 Trial Twitter page and partner organisations including Bliss. Any requests for data sharing of trial data will be handled in line with the standard operating procedure at the NCTU.

## Discussion

This is a pragmatic trial that has had strong patient and public involvement input from the outset. Having a preterm infant is a stressful, emotional experience and it has therefore been crucial for us to ensure the views of preterm infants are represented and that parents find the trial acceptable. The results of this trial will provide high-quality evidence on feeding practices for preterm infants of 30–33 weeks gestation. Infants in the intervention group may be discharged from hospital sooner and parents have told us that even a small reduction in the length of hospital stay is important to them. In addition, a reduction in length of stay could result in increased cot capacity on neonatal units and a potential cost saving of £5.6.8 million annually (based upon a reduction of 2 days). Full milk feeds from birth may be an

intervention that improves outcomes and care of preterm infants and their families whilst simultaneously reducing the cost of NHS care.

Since trial conception one challenge has been with respect to the type of milk available to the infant, since the intervention involves feeding infants full volumes of milk from day of birth. As in standard practice, the first choice will always be the mother's own milk unless there are medical contraindications or the mother chooses to feed her infant with formula milk. It is likely for some infants that mother's own milk may not be sufficient in volume during the first few days of life. For infants in the intervention arm, where this is the case, formula milk or donor breast milk will be used to replace the intravenous fluids or parenteral nutrition. Mothers will be supported in breast feeding and full milk feeding with mother's expressed breast milk will be established as soon as sufficient volumes are available. Breast feeding will be supported and encouraged in both arms of the trial. Information is included about the benefits of breast feeding in all study information. There is no involvement of any kind by any formula milk manufacturers or related organisations in this trial. Several outcomes related to breastfeeding are included. In addition, we will also undertake additional exploratory analyses to compare the primary outcome and key secondary outcomes between infants who have received donor breast milk and preterm formula milk to supplement mother's breast milk.

## Trial status

Protocol version 1.3, dated 14 May 2020. Recruitment opened on 15 October 2019 and is expected to continue until September 2022 at the earliest. Recruitment paused on 20 March due to the COVID19 pandemic and restarted on 3 July 2020.

### Abbreviations

BERC: Blinded endpoint review committee; CLD: Chronic lung disease; DMC: Data monitoring committee; eCRF: Electronic case report form; IQR: Interquartile range; IV: Intravenous; LOS: Late-onset sepsis; NCTU: Nottingham Clinical Trials Unit; NEC: Necrotising enterocolitis; NHS: National Health Service; ROP: Retinopathy of prematurity; SD: Standard deviation; SWAT: Study Within a Trial; TMG: Trial Management Group; TSC: Trial steering committee; UK-NICM: United Kingdom Neonatal and Infant Close Monitoring

### Acknowledgements

We would like to acknowledge all parents and infants participating in the trial and the neonatal units involved in recruiting participants and data collection. Thank you to the independent trial steering committee and data monitoring committee. Finally, thank you to our trial sponsor, the University Hospitals of Derby and Burton NHS Foundation Trust, and the Nottingham Clinical Trials Unit, who are the trial coordinating centre.

### Authors' contributions

EM is the lead trial methodologist and wrote the first draft of the manuscript. SO is the chief investigator and supported by JD conceived the idea and led the funding proposal. GM is the trial manager and trial management oversight is provided by RH. JA represents Bliss, the UK's largest charity for premature and sick infants. CG, MJ, WM and SO are neonatologists and are involved in training sites. CK is a parent representative. HM is the health economist. AM is the Nottingham Clinical Trials Unit Director and provides overall trial oversight. CP is the trial statistician and statistical oversight is provided by RO. PP provides midwifery expertise and KW provides obstetric expertise. All authors have contributed to the writing and critiquing of the manuscript for important intellectual content and have read and approved the final manuscript.

### Funding

This study is funded by the National Institute for Health Research (NIHR) [Health Technology Assessment programme (project reference 17/94/31)]. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. The funder had no role in the design of this study and will have no role in the analysis, interpretation of data or decision to submit results in the future.

### Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study. Anonymised participant data will be made available, upon request, in accordance with the NCTU standard operating procedure after publication of trial results.

## Declarations

### Ethics approval and consent to participate

Ethical approval was granted by the East Midlands – Derby Research Ethics Committee on 13 September 2019 (Ref: 19/EM/0258). Written informed consent to participate will be obtained from all participants.

### Consent for publication

Not applicable

### Competing interests

The authors declare that they have no competing interests.

### Author details

[1]Nottingham Clinical Trials Unit, Building 42, University Park, University of Nottingham, Nottingham NG7 2RD, UK. [2]Bliss, 4th Floor Maya House, 134-138 Borough High Street, London SE1 1LB, UK. [3]Department of Neonatal Medicine, University Hospital Southampton NHS Foundation Trust and NIHR Biomedical research Centre Southampton, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton SO16 6YD, UK. [4]Neonatal Medicine, School of Public Health, Faculty of Medicine, Imperial College London, Chelsea and Westminster Hospital campus, London SW10 9NH, UK. [5]c/o Nottingham Clinical Trials Unit, Building 42, University Park, University of Nottingham, Nottingham NG7 2RD, UK. [6]Centre for Reviews and Dissemination, University of York, A/B Block, Alcuin College, York YO10 5DD, UK. [7]Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry CV4 7AL, UK. [8]Department of Neonatal Medicine, Bradford Teaching Hospitals NHS Foundation Trust, Duckworth Lane, Bradford BD9 6RJ, UK. [9]Division of Midwifery, School of Health Sciences, University Park, University of Nottingham, Nottingham NG7 2RD, UK. [10]Population and Applied Health Sciences, School of Medicine University of Nottingham, University Park, Nottingham NG7 2RD, UK. [11]Neonatal Unit, University Hospitals of Derby and Burton NHS Foundation Trust, Uttoxeter Road, Derby DE22 3DT, UK.

Received: 12 April 2021 Accepted: 30 December 2021
Published online: 20 January 2022

### References

1. Oddie SJ, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. Cochrane Database Syst Rev. 2017;8(8):CD001241. https://doi.org/10.1002/14651858.CD001241.pub7.
2. Belfort MB, Ehrenkranz RA. Neurodevelopmental outcomes and nutritional strategies in very low birth weight infants. Semin Fetal Neonatal Med. 2017;22(1):42–8. https://doi.org/10.1016/j.siny.2016.09.001.
3. Morgan J, Bombell S, McGuire W. Early trophic feeding versus enteral fasting for very preterm or very low birth weight infants. Cochrane Database Syst Rev. 2013;3:CD000504. https://doi.org/10.1002/14651858.CD000504.pub4.

4. Abbott J, Berrington J, Bowler U, et al. The Speed of Increasing milk feeds: a randomised controlled trial. BMC Pediatr. 2017;17(1):39. https://doi.org/10.1186/s12887-017-0794-z.
5. Walsh V, Brown JVE, Copperthwaite BR, Oddie SJ, McGuire W. Early full enteral feeding for preterm or low birth weight infants. Cochrane Database Syst Rev. 2020;12(12):CD013542. https://doi.org/10.1002/14651858.CD013542.
6. Sanghvi KP, Joshi P, Nabi F, Kabra N. Feasibility of exclusive enteral feeds from birth in VLBW infants > 1200g-an RCT. Acta Paediatr. 2013;102(7):e299–304. https://doi.org/10.1111/apa.12254.
7. Nangia S, Vadivel V, Thukral A, Saili A. Early Total enteral feeding versus conventional enteral feeding in stable very-low-birth-weight infants: a randomised controlled trial. Neonatology. 2019;115(3):256–62. https://doi.org/10.1159/000496015.
8. Nangia S, Bishnoi A, Goel A, Mandal P, Tiwari S, Saili A. Early total enteral feeding in stable very low birth weight infants: a before and after study. J Trop Pediatrics. 2018;64(1):24–30. https://doi.org/10.1093/tropej/fmx023.
9. Office of National Statistics (ONS gov.uk). 2018 live births: birth characteristics. 2019. https://www.ons.gov.uk/releases/birthcharacteristicsenglandandwales2018. Accessed 12 Oct 2020.
10. Leaf A, Dorling J, Kempley S, McCormick K, Mannix P, Linsell L, et al. Early or delayed enteral feeding for preterm growth-restricted infants: a randomized trial. Pediatrics. 2012;129(5):e1260–8. https://doi.org/10.1542/peds.2011-2379.
11. Uthaya S, Liu XX, Babalis D, Dore CJ, Warwick J, Bell J, et al. Nutritional Evaluation and Optimisation in Neonates: a randomized, double-blind controlled trial of amino acid regimen and intravenous lipid composition in preterm parenteral nutrition. Am J Clin Nutr. 2016;103(6):1443–52. https://doi.org/10.3945/ajcn.115.125138.
12. Morgan C, Herwitker S, Badhawi I, Hart A, Tan M, Mayes K, et al. SCAMP: standardised, concentrated, additional macronutrients, parenteral nutrition in very preterm infants: a phase IV randomised, controlled exploratory study of macronutrient intake, growth and other aspects of neonatal care. BMC Pediatr. 2011;11(1):53. https://doi.org/10.1186/1471-2431-11-53.
13. NHS England. Five Year Forward View 2016. https://www.england.nhs.uk/wp-content/uploads/2014/10/5yfv-web.pdf [accessed 16.10.20]
14. Duley L, Uhm S, Oliver S. Preterm Birth Priority Setting Partnership Steering G. Top 15 UK research priorities for preterm birth. Lancet. 2014;383(9934):2041–2. https://doi.org/10.1016/S0140-6736(14)60989-2.
15. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200–7. https://doi.org/10.7326/0003-4819-158-3-201302050-00583.
16. Northern Ireland Network for Trials Methodology SWAT repository. https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/FileStore/Filetoupload,959223,en.pdf. [accessed 16.10.20]
17. Meeting abstracts from the 5th International Clinical Trials Methodology Conference (ICTMC 2019). Trials 20, 579. 2019. https://0-doi-org.brum.beds.ac.uk/10.1186/s13063-019-3688-6.
18. Saldanha IJ, Dickersin K, Wang X, Li T. Outcomes in Cochrane systematic reviews addressing four common eye conditions: an evaluation of completeness and comparability. PLoS One. 2014;9(10):e109400. https://doi.org/10.1371/journal.pone.0109400.
19. Holman RC, Stoll BJ, Curns AT, Yorita KL, Steiner CA, Schonberger LB. Necrotising enterocolitis hospitalisations among neonates in the United States. Paediatr Perinat Epidemiol. 2006;20(6):498–506. https://doi.org/10.1111/j.1365-3016.2006.00756.x.
20. Royal College of Paediatrics and Child Health (RCPCH). UK-WHO growth charts: neonatal and infant close monitoring (NICM). 2013. https://www.rcpch.ac.uk/resources/uk-who-growth-charts-0-4-years. Accessed 3 Dec 2021.
21. Sawyer A, Rabe H, Abbott J, Gyte G, Duley L, Ayers S, et al. Measuring parents' experiences and satisfaction with care during very preterm birth: a questionnaire development study. BJOG-Int J Obstet Gynaecol. 2014;121(10):1294–301. https://doi.org/10.1111/1471-0528.12925.
22. Webbe J, Brunton G, Ali S, Duffy JM, Modi N, Gale C. Developing, implementing and disseminating a core outcome set for neonatal medicine. BMJ Paediatr Open. 2017;1(1):e000048. https://doi.org/10.1136/bmjpo-2017-000048.
23. Kwok TC, Dorling J, Ojha S. Multicentre prospective observational study of feeding practices in 30–33 weeks preterm infants. BMJ Paediatr Open. 2017;1(1):e000040. https://doi.org/10.1136/bmjpo-2017-000040.
24. 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 Childhood Fetal Neonatal Ed. 2018;103(1):F6–F14. https://doi.org/10.1136/archdischild-2016-312567.
25. Royal College of Obstetricians and Gynaecologists (RCOG). Obtaining valid consent to participate in perinatal research where consent is time critical. 2016. https://www.rcog.org.uk/globalassets/documents/guidelines/clinical-governance-advice/clinical-guidance-6a-2016.pdf. Accessed 16 Oct 2020.
26. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. JAMA. 1996;276(8):637–9. https://doi.org/10.1001/jama.1996.03540080059030.


## Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

**Ready to submit your research? Choose BMC and benefit from:**

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

**At BMC, research is always in progress.**

**Learn more** biomedcentral.com/submissions



## PAPER 5: Implementing two-stage consent pathway in neonatal trials

OPEN ACCESS

# Implementing two-stage consent pathway in neonatal trials

Eleanor Mitchell [1], Sam J Oddie [2], Jon Dorling,[3] Chris Gale [4], Mark John Johnson [3,5] William McGuire,[6] Shalini Ojha [7,8]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/archdischild-2021-322960).

For numbered affiliations see end of article.

**Correspondence to**
Eleanor Mitchell, Nottingham Clinical Trials Unit, School of Medicine, University of Nottingham, Nottingham NG7 2UH, UK;
eleanor.mitchell@nottingham.ac.uk

Received 3 August 2021
Accepted 2 December 2021

Check for updates

© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY. Published by BMJ.

**To cite:** Mitchell E, Oddie SJ, Dorling J, *et al*. *Arch Dis Child Fetal Neonatal Ed* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/archdischild-2021-322960

## ABSTRACT

Perinatal trials sometimes require rapid recruitment processes to facilitate inclusion of participants when interventions are time-critical. A two-stage consent pathway has been used in some trials and is supported by national guidance. This pathway includes seeking oral assent for participation during the time-critical period followed by informed written consent later. This approach is being used in the fluids exclusively enteral from day one (FEED1) trial where participants need to be randomised within 3 hours of birth. There is some apprehension about approaching parents for participation via the oral assent pathway. The main reasons for this are consistent with previous research: lack of a written record, lack of standardised information and unfamiliarity with the process. Here, we describe how the pathway has been implemented in the FEED1 trial and the steps the trial team have taken to support sites. We provide recommendations for future trials to consider if they are considering implementing a similar pathway. Trial registration number: ISRCTN89654042.

### What is already known on this topic?

- Alternative consent pathways, including oral assent for intervention administration, have been developed in perinatal clinical trials and are supported by national guidance.
- In previous qualitative research, the two-stage consent pathway has shown to be acceptable to parents and healthcare professionals, although some concerns were noted.

### What this study adds?

- While the two-stage consent pathway is acceptable to healthcare professionals, in the FEED1 trial some recruiters have been hesitant to approach parents to seek oral assent for a variety of reasons.
- This paper provides practical guidance on the implementation of a two-stage consent pathway in a neonatal trial, in order to support recruiters at clinical trial sites.

## BACKGROUND

Informed consent of participants is a prerequisite for ethical conduct of a clinical trial. In neonatal trials, usually the parents provide consent on behalf of the infant. Studies show most parents believe they ought to make the decision about whether their child participates in research.[1] Many neonatal trials require time-critical consent, for example, when randomisation is required soon after birth or during acute illness. Parents may be approached antenatally, provided with information about potential participation and then provide consent if the infant's eligibility is confirmed after birth. This is not always feasible in trials involving preterm infants because preterm birth can be unpredictable. Obtaining valid, informed consent during emergencies or sensitive periods such as when a women has just had an unplanned premature delivery can be difficult and cause stress and emotional distress.[2]

A systematic review that evaluated ethical issues in consenting for clinical trials of preterm or sick neonates (49 studies) concluded that none of the methods available at the time was adequate and alternative approaches were required.[1] A two-stage consent pathway was developed, in conjunction with NCT ( www.nct.org.uk) and Bliss (www.bliss.org.uk), in a clinical trial comparing timing of umbilical cord clamping in very preterm infants and evaluated qualitatively.[3] This two-stage pathway includes oral assent for randomisation and participation followed by written consent for ongoing use of data. Oral assent was used when there was no opportunity to approach women during the antenatal period, for example, when preterm birth was unpredicted and imminent. This involved obtaining verbal agreement prior to participation and is different to deferred consent, where participants are not approached until after intervention administration as in some emergency medicine trials.[4] The two-stage process aligns with guidance from the UK Health Research Authority that states that the research consent process should be iterative (https://www.hra.nhs.uk/planning-and-improving-research/best-practice/informing-participants-and-seeking-consent/).

Balancing the complex ethical issues of consent with recruitment can be challenging but is crucial to get right. For clinical trial data to be relevant to the neonatal population of interest, it is important that alternative consent pathways are used. Mother and infant dyads who may not have had the opportunity to consent antenatally are then given the opportunity to participate.[5]

The two-stage pathway developed for the Cord Pilot Trial was acceptable to parents and clinicians.[3] Although women approached about trial participation reported receiving less information, most felt it was sufficient for decision-making. Clinicians expressed some concerns about how much information to give and the lack of a consent form as a record of the



Arch Dis Child Fetal Neonatal Ed: first published as 10.1136/archdischild-2021-322960 on 23 December 2021. Downloaded from http://fn.bmj.com/ on November 24, 2022 at University of Nottingham. Protected by copyright.

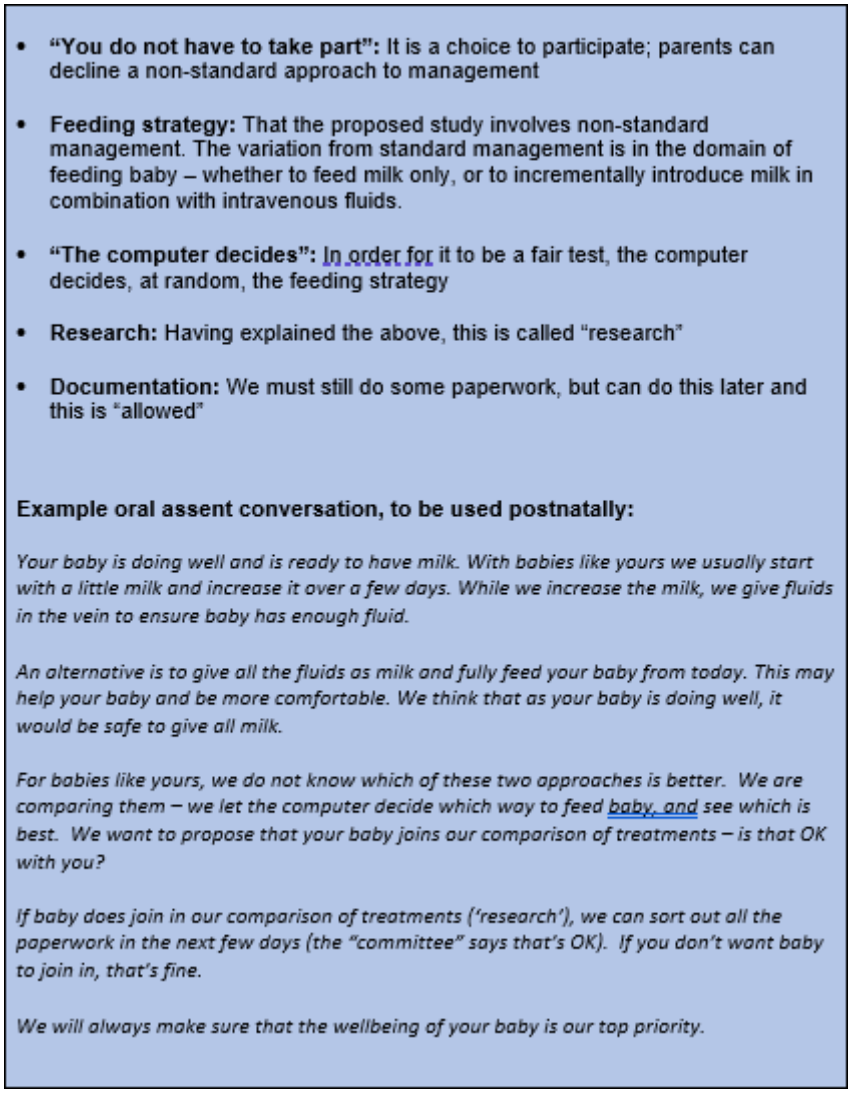



**Figure 1** Minimum important information required during an oral assent conversation and example discussion. Created by authors Mitchell and Oddie, permission for reuse granted.

discussion. The two-stage pathway now features in guidance by the Royal College of Obstetricians and Gynaecologists on obtaining consent for perinatal research (https://www.rcog.org.uk/globalassets/documents/guidelines/clinical-governance-advice/clinical-guidance-6a-2016.pdf).

FEED1 is a randomised, multicentre clinical trial comparing feeding full enteral milk feeds from day 1 with gradual milk feeding in infants born at $30^{+0}$–$32^{+6}$ weeks' gestational age. Participants are randomised within 3 hours of birth to ensure the allocated feeding strategy is implemented as soon after birth as possible. This period is often stressful and emotional for parents and taking consent can be challenging. A two-stage consent pathway was followed for antenatal consent or oral assent followed by later written consent to make the process less burdensome to families and more feasible for those approaching about consent. The approach was supported by the FEED1 parent and public involvement group and Bliss, the UK's largest charity for babies born prematurely or sick. This pathway is relatively new in UK neonatal trials and generated some apprehension among those less familiar with the process.

Here, we provide examples of how the two-stage consent pathway is being implemented in the FEED1 trial and suggest recommendations for adopting similar approaches in future studies.

## Implementation and training

The consent pathway is discussed during site training including the background, simulations with role-play, interactive discussions and guidance on the minimal information needed for an oral assent conversation. Two co-investigators who were part of the team that developed the pathway lead this. All training materials are freely available via the trial website (www.feed1.ac.uk).

## Supporting documents

A short document (online supplemental material 1) describing the background with references to supporting national guidance and details of the ethical approval has been prepared and made freely available to sites via the trial website. The minimum important information to include in an oral assent conversation is given in figure 1 with an example discussion.

## Trial webinars

Co-investigators conduct webinars for the sites where assent/consent scenarios are discussed with role-play exercises and exploration of any emerging concerns from the trial recruiters. Webinars are recorded and disseminated to all sites.



Arch Dis Child Fetal Neonatal Ed: first published as 10.1136/archdischild-2021-322960 on 23 December 2021. Downloaded from http://fn.bmj.com/ on November 24, 2022 at University of Nottingham. Protected by copyright.

### Consent scenarios

Several videos of role-play scenarios of oral assent conversations between clinicians and parents were professionally filmed. The parent 'actor' was the parent of a preterm infant. These have been distributed to sites and are available on YouTube and the trial website.

### Oral assent animation for parents

In response to clinicians reporting that the oral assent pathway was impeded by the lack of standardised information and uncertainty about how much information to include in an oral assent conversation, an ethically approved animation for parents, describing the trial, was developed in collaboration with parent partners. It has been distributed to sites with QR code-cards enabling instant access using any internet-enabled device and is available on the trial website.

### Q&A sessions with recruiting sites

The trial team hold monthly meetings with site staff to discuss emerging issues and share experiences. Quarterly clinical discussion forums are also held where, in addition to discussion on other trial issues, the consent process is discussed. Recruiters are given the opportunity to raise barriers and facilitators to approaching parents and conducting oral assent discussions.

## ONGOING APPROACH TO TRIAL DELIVERY AND CONDUCT

These processes have been developed during the initial phase of recruitment. The trial team work in an iterative manner, adapting the training material and support provided to sites as per the feedback from the recruiters and parent and public partners. Strategies will be evaluated though site feedback has been positive, particularly with respect to the oral assent animation which has been well received by parents.

## RECOMMENDATIONS FOR FUTURE RESEARCH

Previous research has shown that the two-stage consent pathway is acceptable to parents and clinicians. The FEED1 experience demonstrates that sites require support and resources to implement the pathway successfully. A detailed description of the process should be included in the trial protocol and full ethical approval is mandatory. Early engagement with public and parent partners in developing easily accessible study information resources is crucial. Additionally, 'buy in' from the clinical teams that will recruit and deliver the trial is needed early. This should be supported with training and ongoing engagement activities. Free and easily accessible training materials and use of multimedia resources helps disseminate training.

Such resources can be adapted for other clinical trials, particularly perinatal-neonatal research. Evaluation of the strategies implemented in FEED1 is planned when recruitment is complete. Understanding clinicians' and parents' views and analysis of recruitment data achieved by the different pathways will improve our understanding of using assent/consent pathways to make clinical trials more accessible to all potential participants.

**Author affiliations**
[1]Nottingham Clinical Trials Unit, School of Medicine, University of Nottingham, Nottingham, UK
[2]Department of Neonatal Medicine, Bradford Teaching Hospitals NHS Foundation Trust, West Yorkshire, UK
[3]Department of Neonatal Medicine, University Hospital Southampton NHS Foundation Trust, Southampton, UK
[4]Neonatal Medicine, School of Public Health, Faculty of Medicine, Imperial College London, London, UK
[5]NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK
[6]Centre for Reviews and Dissemination, University of York, York, UK
[7]Population and Applied Health Sciences, School of Medicine, University of Nottingham, Nottingham, UK
[8]Neonatal Unit, University Hospitals of Derby and Burton NHS Foundation Trust, Derby, UK

**Twitter** Eleanor Mitchell @eleanor_mitch, Chris Gale @DrCGale, Mark John Johnson @MarkJohnson800 and Shalini Ojha @shaliniojha7

**Acknowledgements** The authors would like to thank Alex Wilkinson Media (https://alexwilkinson.media/) for creating the video and animated content described in this manuscript. The authors would also like to thank all recruiting hospitals and, importantly, the families who have agreed to participate in the FEED1 trial to date.

**Collaborators** This article is written on behalf of the FEED1 trial collaborative group (in alphabetical order): Josie Anderson (Bliss), Jon Dorling (University Hospital Southampton NHS Foundation Trust), Chris Gale (Imperial College, London), Rachel Haines (University of Nottingham), Mark Johnson (University Hospitals Southampton NHS Foundation Trust), Charlotte Kenyan (PPI contributor), William McGuire (University of York), Alan Montgomery (University of Nottingham), Eleanor Mitchell (University of Nottingham), Garry Meakin (University of Nottingham), Hema Mistry (University of Warwick), Sam Oddie (Bradford Teaching Hospitals NHS Foundation Trust), Reuben Ogollah (all University of Nottingham), Phoebe Pallotti (all University of Nottingham), Christopher Partlett (all University of Nottingham), Shabina Sadiq (all University of Nottingham), Shalini Ojha (University of Nottingham and University Hospitals of Derby and Burton NHS Foundation Trust), Kate Walker (all University of Nottingham).

**Contributors** EM is a co-investigator on the FEED1 trial, has co-led activities to support clinicians in the use of the two-stage consent pathway and wrote the first draft of the manuscript. SJO is a clinical co-investigator and has co-led consent pathway support. SO is the Chief Investigator for the FEED1 trial, supported by JD who conceived the idea and led the funding proposal. CG, MJJ and WMcG are all clinical co-investigators who support FEED1 sites. All authors have reviewed the manuscript for important intellectual content and approved the final version.

**Funding** The FEED1 trial is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (project reference 17/94/31).

**Disclaimer** The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. The funder had no role in the design of this study and will have no role in the analysis, interpretation of data or decision to submit results in the future.

**Competing interests** The authors declare receiving grant funding to conduct the FEED1 trial. CG declares receiving funding via the MRC for a Clinician Scientist Fellowship, which supported his salary over the time spent on this work.

**Patient and public involvement statement** The FEED1 Trial team includes a parent co-investigator, a representative from Bliss charity and a parent and public involvement group. Parents' views have been included since the conception of the study.

**Patient consent for publication** Not applicable.

**Ethics approval** Ethical approval for the FEED1 trial was granted by East Midlands—Derby Research Ethics Committee on 13 September 2019 (ref 19/EM/0258). Parents give their oral assent or informed consent for their infant to participate before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data sharing not applicable as no datasets generated and/or analysed for this study.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: https://creativecommons.org/licenses/by/4.0/.

**ORCID iDs**
Eleanor Mitchell http://orcid.org/0000-0002-6998-4533
Sam J Oddie http://orcid.org/0000-0001-8701-4912



Arch Dis Child Fetal Neonatal Ed: first published as 10.1136/archdischild-2021-322960 on 23 December 2021. Downloaded from http://fn.bmj.com/ on November 24, 2022 at University of Nottingham. Protected by copyright.

Chris Gale http://orcid.org/0000-0003-0707-876X
Mark John Johnson http://orcid.org/0000-0003-1829-9912
Shalini Ojha http://orcid.org/0000-0001-5668-4227

## REFERENCES

1 Wilman E, Megone C, Oliver S, *et al*. 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.
2 Walsh V, Oddie S, McGuire W. Ethical issues in perinatal clinical research. *Neonatology* 2019;116:52–7.
3 Duley L, Dorling J, Ayers S, *et al*. Improving quality of care and outcome at very preterm birth: the preterm birth research programme, including the cord pilot RCT. *Programme Grants Appl Res* 2019;7:1–280.
4 Woolfall K, Frith L, Dawson A, *et al*. Fifteen-minute consultation: an evidence-based approach to research without prior consent (deferred consent) in neonatal and paediatric critical care trials. *Arch Dis Child Educ Pract Ed* 2016;101:49–53.
5 Owen LS, Davis PG. Parental consent and neonatal delivery room trials: walking an ethical tightrope. *Arch Dis Child Fetal Neonatal Ed* 2021;106:116–7.

Arch Dis Child Fetal Neonatal Ed: first published as 10.1136/archdischild-2021-322960 on 23 December 2021. Downloaded from http://fn.bmj.com/ on November 24, 2022 at University of Nottingham. Protected by copyright.

**PAPER 6: Evaluation of an enhanced training package to support clinical trials training in low and middle income countries (LMICs): experiences from the Born Too Soon Optimising Nutrition study**

# Evaluation of an enhanced training package to support clinical trials training in low and middle income countries (LMICs): experiences from the Born Too Soon Optimising Nutrition study

Eleanor J Mitchell[1], Jalemba Aluvaala[2], Lucy Bradshaw[1], Jane Daniels[1], Ashok Kumar[3], Jacqueline Opira[4], Mary Oliver[5], Phoebe Pallotti[6], Zahida Qureshi[7], Richard Swinden[1], Fredrick Were[2], Shalini Ojha[8,9]

Corresponding author: Eleanor Mitchell, Nottingham Clinical Trials Unit, Building 42, University Park, Nottingham, NG7 2RD. Eleanor.mitchell@nottingham.ac.uk

[1] Nottingham Clinical Trials Unit, University of Nottingham, Nottingham, NG7 2RD, UK

[2] Department of Paediatrics and Child Health, University of Nairobi, Nairobi, Kenya

[3] Department of Paediatrics, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

[4] Kenya Paediatric Research Consortium (KEPRECON), Nairobi, Kenya

[5] School of Education, University of Nottingham, Nottingham, NG7 2RD, UK

[6] School of Health Sciences, University of Nottingham, Nottingham, NG7 2RD, UK

[7] Department of Obstetrics & Gynaecology, University of Nairobi, Kenya

[8] Population and Lifespan Sciences, School of Medicine, University of Nottingham, UK

[9] Children's Hospital, University Hospitals of Derby and Burton NHS Trust, Derby, UK

## ABSTRACT

### Background

Training is essential before working on a clinical trial, yet there is limited evidence on effective training methods. In low and middle income countries (LMICs), developing and evaluating training methods is a high priority.

### Methods

We explored whether an enhanced training package in a neonatal trial in LMICs, utilising elements of the “train-the-trainer” approach, altered clinicians and researchers’ clinical trials knowledge. The package included a lead “trainer” attending an introductory course on clinical trials and other staff attending in-country training sessions at each hospital. To assess effectiveness of the package, several questionnaires were completed at the start and end of the study.

### Results

Thirty participants received training and completed baseline questionnaires. Around three quarters had previously worked on a research study, yet only half had received training. Nineteen participants completed questionnaires at the end of the study period. Only marginal increases were seen in questionnaire scores at the end of the study period. Few participants ‘passed’ the informed consent and ICH-Good Clinical Practice (GCP) modules (pass mark $\geq$80%). Participants who reported having prior research experience scored higher in questionnaires before the start of the study period.

### Conclusions

This is the first report evaluating a clinical trial training package in a neonatal trial in LMICs. Due to the Covid-19 pandemic, there was a significant time lapse between training and study start, which likely impacted upon scores reported here. The package did not impact upon

questionnaire scores. Given the burden of disease in LMICs, developing and evaluating high-quality training is critical.

**Key words:** clinical trials, training, LMICs, global health, ICH-GCP

## BACKGROUND

Individuals who work on clinical trials should be appropriately qualified and have received training that is relevant and proportionate to their role in accordance with the principles of ICH-Good Clinical Practice (GCP) and national policies and regulations [1, 2]. However, there is limited research evaluating clinical trial training methods and programmes both within UK [3] and even less in low-and-middle income countries (LMICs). In a priority-setting exercise to identify the top priorities for methodological research in trials conducted in LMICs, training of research staff was rated the second highest priority [4]. In particular, finding purposeful and cost-effective training methods and using blended learning approaches were highlighted. Only 60% of the participants of this global survey, who were from LMICs, had received any clinical trials training. The lack of research capacity is reflected in research outputs for example, Africa bears 25% of the global burden of diseases, yet produces only 2% of global research outputs [5].

Groups such as The Global Health Network (www.tghn.org) and many UK-funders of global health research advocate that research projects should include sustainable research capacity-building. Increasing opportunities to provide high-quality training to enhance capacity in LMICs is an essential step towards creating an equitable, global research community.

The “train the trainer” approach where a small group is trained to, in turn, disseminate training to larger groups is known to be an effective way to spread training in the healthcare sectors [6-8]. In addition, blended approaches i.e., using a variety of methods, further increase dissemination of curricula [9]. We conducted two literature searches in June 2019 and March 2021 and found no studies evaluating such approaches in the context of clinical trials. A study has been developed which utilises a train-the-trainer approach to teaching African-American community leaders in the USA about cancer clinical trials in order to increase public engagement and participation in clinical trials, though is yet to be evaluated [10].

The aim of this study was to explore whether an enhanced training package, which includes elements of the 'train the trainer' approach, altered clinicians and researchers' clinical trials knowledge in clinical researchers involved in a study in LMICs.

## METHODS

The "Born Too Soon: Optimising Nutrition" project was conducted from 1 August 2019 to 31 December 2020, to investigate feeding strategies for preterm infants admitted for neonatal care (reported separately). The project included a prospective observational study, a feasibility randomised controlled trial, and a qualitative study involving healthcare professionals and parents. The study was conducted in two hospitals: The Kenyatta National Hospital, Nairobi, Kenya and the Sir Sunderlal Hospital, Varanasi, India. Both are large teaching hospitals, affiliated with universities. The team in Kenya had prior research experience [11-14] whilst the team in India self-described as having limited experience in conducting research studies, in particular clinical trials.

### *Enhanced training package*

The enhanced training package included several components. Firstly, a designated "trainer" identified from each participating site, undertook a 5-day training course on clinical trials' design and conduct ("Fundamentals of Clinical Trials", Nottingham Clinical Trials Unit: https://www.nctu.ac.uk/short-courses/index.aspx). The trainers (i) were responsible for disseminating training and providing support to other healthcare professionals and researchers at their site; (ii) had access to support and mentorship from experienced researchers based at the project coordinating centre in the UK and (iii) disseminated the study protocol and other documents to all site staff.

Secondly, project leads (EJM and SO) provided in-person training to all site staff in Kenya and India in December 2019. This training consisted of two full-day sessions including training on the study protocol, Good Clinical Practice, research governance, and data

collection. Training was delivered via a range of methods including lectures, small group discussions, Q&A sessions and data entry workshops. Learning was put into practice by mock patient screening and data collection on the Newborn Units. Participants included healthcare professionals (doctors, nurses, midwives) and study personnel (coordinator, data entry personnel).

The study was due to open shortly after the in-person training sessions. However, this was hampered by delays in receiving ethics approval shortly followed by the declaration of the Covid-19 global pandemic in March 2020. The Born too soon: optimising nutrition study was paused whilst clinical staff focussed on clinical care and research staff were redeployed to clinical work, eventually opening for data collection in August 2020. Due to constraints within the funding, it was not possible for all personnel to be retrained. Instead, ad-hoc retraining was provided to the training leads and the UK and Kenya study coordinators worked closely together, answering any queries from the wider team.

***Evaluation of training package***

Participants were asked for their consent to participate in the study reported here. Study information was provided, and a consent form completed prior to the in-person training session. Participants were asked to complete four paper questionnaires: demographics details; research experience; protocol-specific questions; and questions about informed consent and ICH-GCP. The introduction to Informed consent and ICH-GCP questionnaires were taken from materials publicly available via The Global Health Network training centre (https://globalhealthtrainingcentre.tghn.org/) while the others were developed by the project team (supplementary material 1, 2). Baseline questionnaires were returned to the UK and data entered onto a MS Excel® spreadsheet.

At the end of the project, electronic versions (using JISC surveys©) of the protocol-specific questionnaire, ICH-GCP and Introduction to informed consent questionnaires were sent to the participants. The survey opened on 20 November 2020 and closed on 18 December

2020. Two email reminders were sent to encourage completion during this time. Data was downloaded from JISC as a .CSV file.

### *Evaluation instruments*

The protocol-specific training questionnaire included eight multiple choice response questions, with the highest mark available being 10. The Introduction to informed consent questionnaire (13 items) and the ICH-GCP questionnaire (31 items) both had multiple choice response questions. In accordance with the TGHN training resource, questionnaires were scored as a percentage; a pass mark was 80% or above.

### *Statistical analysis*

Data are reported overall and per country. Participant characteristics and previous research experience are summarised descriptively using frequency counts and percentages. The responses to the protocol-specific questionnaire, introduction to informed consent and ICH-GCP questionnaires are summarised descriptively using the mean, standard deviation (SD) and minimum, maximum values; reported overall and per country. For participants who completed questionnaire sets at both time-points, mean differences in scores and 95% confidence intervals (CI) are reported. Exploratory analyses were conducted to check for differences in questionnaire scores in individuals who self-reported prior research experience and those who did not. Statistical analyses were undertaken in Stata version 15 (Stata Corp LLC, Texas).

## RESULTS

Thirty participants (17 in Kenya, 13 in India) attended the in-country training sessions in December 2019 including 14 (46%) nurses and 13 (43%) doctors (Table 1).

**Table 1: Participant demographics**

| | Overall n=30 (%) | Kenya n=17 (%) | India n=13 (%) |
|---|---|---|---|
| Gender | | | |
| Male | 7 (23) | 4 (24) | 3 (23) |
| Female | 23 (77) | 13 (76) | 10 (77) |
| Age | | | |
| 16-25 | 3 (10) | 1 (6) | 2 (15) |
| 26-34 | 8 (27) | 1 (6) | 7 (54) |
| 35-44 | 9 (30) | 7 (41) | 2 (15) |
| 45-54 | 2 (7) | 2 (12) | 0 (0) |
| 55+ | 7 (23) | 6 (35) | 1 (8) |
| missing | 1 (3) | 0 (0) | 1 (8) |
| Job Title | | | |
| Professor | 3 (10) | 2 (12) | 1 (8) |
| Paediatrician | 2 (7) | 2 (12) | 0 (0) |
| Consultant | 1 (3) | 1 (6) | 0 (0) |
| Nurse | 10 (33) | 4 (34) | 6 (46) |
| Associate Professor | 2 (7) | 1 (6) | 1 (8) |
| Study coordinator | 1 (3) | 1 (6) | 0 (0) |
| Data clerk | 1 (3) | 1 (6) | 0 (0) |
| Nurse manager/chief nurse/coordinator | 4 (13) | 3 (18) | 1 (8) |
| Lecturer | 1 (3) | 1 (6) | 0 (0) |
| Social scientist | 1 (3) | 1 (6) | 0 (0) |
| Junior (resident) doctor | 4 (13) | 0 (0) | 4 (31) |
| Clinical area | | | |
| Obstetrics | 1 (3) | 1 (6) | 0 (0) |
| Neonatology | 21 (70) | 9 (53) | 12 (92) |
| Midwifery | 2 (7) | 2 (12) | 0 (0) |
| General nursing | 2 (7) | 2 (12) | 0 (0) |
| NA | 3 (10) | 3 (18) | 0 (0) |
| Missing | 1 (3) | 0 (0) | 1 (8) |

As shown in Table 2, almost three-quarters had previously worked on a research study (n=22, 73%) yet only half (n=11, 50%) had received any research training previously. Most had experience of observational or questionnaire-based studies and only 8/22 (36%) had worked on a clinical trial.

**Table 2: Previous research experience**

| | n=30 (%) |
|---|---|
| Previously worked on a research study before | |
| Yes | 22 (73) |
| No | 8 (27) |
| | n=22 (%) |
| Number of research studies previously worked on | |
| 1-3 | 12 (55) |
| 4-6 | 2 (9) |
| 7-10 | 1 (4) |
| 10+ | 6 (28) |
| Don't remember | 1 (4) |
| Last time worked on a research study | |
| Currently | 15 (68) |
| In the last year | 3 (14) |
| More than a year ago | 4 (19) |
| Types of studies previously worked on – *all that applied ticked* | |
| Observational (no intervention) | 15 (68) |
| Clinical trial | 8 (36) |
| Questionnaire-based study | 15 (68) |
| Case studies | 1 (5) |
| Don't know | 1 (5) |
| Qualitative | 2 (10) |
| Systematic review | 1 (5) |
| Previously received research training | |
| Yes | 11 (50) |
| No | 10 (45) |
| Missing | 1 (5) |
| Tasks undertaken in previous research studies - *all that applied ticked* | |
| Overall study responsibility as Principal Investigator | |
| Study coordination / management | 10 |
| Obtaining consent from participants | 10 |
| Recruiting participants | 11 |
| Data collection | 10 |
| Data entry | 12 |
| Data analysis | 11 |
| Reporting | 8 |
| | 10 |

Of the 30 participants who completed the questionnaires at the start of the study, 19 (63%; 16 in Kenya, 3 in India) completed the questionnaires at the end of the study period. Overall, scores for each questionnaire were higher at the end of the study period, as compared to the scores at the start of the study. The largest differences were seen in questionnaires completed by the team in India (Supplementary Table 1). Only 3 (10%) participants 'passed' (i.e., scored >80%) the consent questionnaire before the start of the study, and 4 (21%) passed at the end of the study period. No participants 'passed' the ICH-GCP questionnaire before the start of the study and only 1 (5%) passed at the end of the study period.

For the 19 participants who completed both sets of questionnaires, small mean increases were seen in scores at the end of the study period compared to before (Table 3).

**Table 3: Differences in questionnaire scores before and at the end of the study period for participants who completed both questionnaire sets**

| | **Before (n=19)** | **After (n=19)** | **Difference in means (SD), 95% CI** |
|---|---|---|---|
| Protocol-specific<br>Mean score (SD) | 5.6 (1.8) | 5.8 (2.6) | 0.2 (2.1),<br>-0.8 to 1.2 |
| Introduction to informed consent<br>Mean score (SD) | 64 (17) | 69 (14) | 5 (12),<br>0.6 to 11.1 |
| ICH-Good Clinical Practice<br>Mean score | 53 (9.4) | 56 (14) | 3.2 (12.7),<br>-2.9 to 9.3 |

Staff who self-reported as having previous research experience (n=22) scored higher in each questionnaire before the start of the study period, than those who had no prior research experience (n=8) (Table 4). Almost all staff with no prior research experience were in India (n=7, 88%).

**Table 4: Differences in questionnaire scores before start of study period between staff with and without prior research experience**

| | Staff with prior research experience[1] | Staff without prior research experience[1] |
|---|---|---|
| | n=22 | n=8 |
| Protocol-specific<br>Mean score (SD)<br>min, max | 6.0 (1.6)<br>3, 8 | 3.4 (1.9)<br>2, 6 |
| Introduced to informed consent<br>Mean score (SD)<br>min, max | 62 (18)<br>23, 85 | 41 (10)<br>30, 62 |
| ICH-Good Clinical Practice<br>Mean score (SD)<br>min, max | 50 (13)<br>11, 67 | 31 (12)<br>17, 50 |

[1] *Self-reported at time of completion of previous research experience questionnaire*

## DISCUSSION

It is not possible to determine, from this study, whether an enhanced training package can improve knowledge of research methods and governance. Though there was a marginal improvement in mean questionnaire scores, we found that scores did not increase statistically significantly between start and end of the study period. The study was compromised due to the Covid-19 pandemic and poor completion rate of questionnaires at the end of the study period, particularly in India, which limited the overall sample.

The Global Health Network Training centre classifies a 'pass' mark as ≥80% for the introduction to informed consent questionnaire and ICH-GCP questionnaire. In this study the mean scores were substantially lower than this at both time-points but improved by the end of the study (from 56% and 69% for informed consent, and from 45% and 56% for ICH-GCP). Whilst an increase was seen in scores, they remained low in both settings, indicating that additional training, incorporating alternative methods, with refresher training are required in future studies. The biggest gains in questionnaire scores were in questionnaires completed by participants in India, particularly in the consent questionnaire; with a difference in means of 19 between the beginning and end of the study period. This could perhaps reflect that the team in India were research naïve and had not previously participated in research training of this nature. However, this result should be interpreted with caution since only three participants in India completed the questionnaires at the end of the study period; these three participants were very involved in the conduct of the study which could explain the larger increase in scores as they were working on the study on a daily basis, unlike other participants who had a less active role.

A strength of this study is that, to the best of our knowledge, this is the first time a clinical trials training package has been evaluated for use in a global health neonatal trial. However,

we recognise there are some limitations. The substantial delay between in-person training in December and the start of data collection, some nine months later, imposed by the Covid-19 pandemic, meant evaluation of the training package was extremely difficult.

We did not assess immediate impact of the training. An additional set of questionnaires at the end of the initial training session could have provided additional information and comparison to assess gain or decline in knowledge over the study period. Finally, very few staff (n=3) in India completed the questionnaires at the end of the study period. This could be in part due to the type of staff that attended the original training session and completed baseline questionnaires: the majority were nurses who, by the time the study started, were moved from the project to work clinically for the pandemic response.

These results demonstrate the need for training for researchers in LMICs, both for individual studies and generically to increase research capacity. This is arguably even more critical since substantial cuts have been made to global health funding by the UK government[15]. For research to be conducted where need is greatest enabling researchers and health workers in LMICs to acquire research and research management skills is essential. Adapting the approach described here, by including additional training sessions throughout the study and providing the “trainers” with more standardised training tools for them to replicate the training when required, could be helpful for the future. During the Covid-19 pandemic, research teams have adapted training materials to enable virtual training sessions, since much travel between countries has been prohibited. Whilst this reduces the cost and environmental impact of in-person training conducted in LMICs by research teams outside of the setting, we strongly believe a blended approach is required. In-person training is important to understand the context and to enable detailed interactions between staff, to pick-up on issues that may need further input. Training packages designed to improve the skills of research teams in LMICs should continue to be evaluated, both in order to upskill staff in LMICs and to add to the trials methodology evidence-base. Researchers at the Global Health Network are in the process of developing a core curriculum, via the Essential

Research Skills Project (https://globalresearchmethods.tghn.org/methodology-projects/essential-research-skills-training-curriculum/), developed by analysis of training needs surveys, workshops and a Delphi survey, and the content from this curriculum could be utilised to support training in global health studies in the future.

## CONCLUSIONS

The Covid-19 pandemic substantially affected the study, due to a lengthy delay between training and the study opening, and staff, particularly in India, being redeployed to clinical work. These results should therefore be interpreted with caution. Only small differences were seen in questionnaire scores assessing the study team's overall knowledge of the study protocol, informed consent and ICH-GCP. For informed consent and ICH-GCP, scores were lower than the pass mark of 80% outlined by TGHN, at the start and end of the study period. Further research is needed to evaluate clinical trials training packages in LMICs.

## List of abbreviations

ICH-GCP – International Conference on Harmonisation-Good Clinical Practice

GCP – Good Clinical Practice

LMIC – low and middle income countries

NCTU – Nottingham Clinical Trials Unit

TGHN – The Global Health Network

CI – Confidence interval

## DECLARATIONS

## Ethics approval and consent to participate

Ethical approval was received by the joint Kenyatta National Hospital-University of Nairobi Ethics Research Committee (ref: P980/12/2019) on 28 February 2020 and the University of Nottingham Faculty of Medical and Health Sciences ethics committee (ref: 433-912) on 25 February 2020.

## Consent for publication

Not applicable

## Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author upon reasonable request

## Competing interests

No competing interests have been declared.


## Funding

The study was funded by the University of Nottingham Global Challenges Research Fund (GCRF) (ref:  RIS 214513).


## Authors' contributions

EJM conceived the idea, designed the study, analysed data and wrote the first draft of the manuscript. MO helped design the study. SO was the Chief Investigator for the overall project. LB provided support with statistical analyses. FW and AK were Principal Investigators at each site, supported by JA and ZQ. In addition, JA and AK were the "trainers" at each site. JO and RS were study coordinators in Kenya and the UK respectively. PP and JD were members of the wider Born Too Soon: Optimising Nutrition team and contributed to ongoing management of the project. All authors helped draft and critique the paper for important intellectual content, and approved the final manuscript.

## Acknowledgements

Many thanks to all staff who participated in the in-country training sessions and who participated in this study by completing questionnaires. Thank you to Joanna Green and Maeve Fitzpatrick, who administer the University of Nottingham Global Challenges Research Fund (GCRF), for their sound advice throughout the project, particularly in relation to 'pause' in activity due to Covid-19. Thank you to the course tutors at the Nottingham Clinical Trials Unit who taught on the 5-day course in November 2019.

## References

1. Health Research Authority. UK Policy Framework for Health and Social Care Research. 2021.

2. European Union Clinical Trials Directive 2001/20/EC, (2001).

3. Townsend D, Mills N, Savović J, Donovan JL. A systematic review of training programmes for recruiters to randomised controlled trials. Trials. 2015;16(1):432.

4. Rosala-Hallas A, Bhangu A, Blazeby J, Bowman L, Clarke M, Lang T, et al. Global health trials methodological research agenda: results from a priority setting exercise. Trials. 2018;19(1):48.

5. Kasprowicz VO, Chopera D, Waddilove KD, Brockman MA, Gilmour J, Hunter E, et al. African-led health research and capacity building- is it working? BMC Public Health. 2020;20(1):1104.

6. Yarber L, Brownson CA, Jacob RR, Baker EA, Jones E, Baumann C, et al. Evaluating a train-the-trainer approach for improving capacity for evidence-based decision making in public health. BMC Health Services Research. 2015;15(1):547.

7. Riley C, Spies LA, Prater L, Garner SL. Improving Neonatal Outcomes Through Global Professional Development. Advances in neonatal care : official journal of the National Association of Neonatal Nurses. 2019;19(1):56-64.

8. de Beurs DP, de Groot MH, de Keijser J, Mokkenstorm J, van Duijn E, de Winter RF, et al. The effect of an e-learning supported Train-the-Trainer programme on implementation of suicide guidelines in mental health care. Journal of affective disorders. 2015;175:446-53.

9. Pearce J, Mann MK, Jones C, van Buschbach S, Olff M, Bisson JI. The Most Effective Way of Delivering a Train-the-Trainers Program: A Systematic Review. Journal of Continuing Education in the Health Professions. 2012;32(3):215-26.

10. Blakeney N, Michaels M, Green M, Richmond A, Long D, Robinson WS, et al. Collaborative development of clinical trials education programs for African-American community-based organizations. Journal of cancer education : the official journal of the American Association for Cancer Education. 2015;30(2):400-6.

11. Mitchell EJ, Benjamin S, Ononge S, Ditai J, Qureshi Z, Masood SN, et al. Identifying women giving birth preterm and care at the time of birth: a prospective audit of births at six hospitals in India, Kenya, Pakistan and Uganda. BMC Pregnancy Childbirth. 2020;20(1):439.

12. Mitchell EJ, Qureshi ZP, Were F, Daniels J, Gwako G, Osoti A, et al. Feasibility of using an Early Warning Score for preterm or low birthweight infants in a low-resource setting: results of a mixed-methods study at a national referral hospital in Kenya. BMJ Open. 2020;10(10):e039061.

13. Woman Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet. 2017;389(10084):2105-16.

14. Widmer M, Piaggio G, Nguyen TMH, Osoti A, Owa OO, Misra S, et al. Heat-Stable Carbetocin versus Oxytocin to Prevent Hemorrhage after Vaginal Birth. N Engl J Med. 2018;379(8):743-52.

15. Ian Sample, Science Editor. UK scientists warn of catastrophic impact of funding cuts. The Guardian. 2021 31 March 2021. https://www.theguardian.com/science/2021/mar/31/uk-scientists-funding-cuts-grants-foreign-aid [accessed 5 April 2021]

**Supplementary Table 1 – Questionnaire scores before and at the end of the study period[1]**

| | BEFORE STUDY PERIOD | | | END OF STUDY PERIOD | | |
|---|---|---|---|---|---|---|
| Per site | **Both** | **Kenya** | **India** | **Both** | **Kenya** | **India** |
| | n=30 | n=17 | n=13 | n=19 | n=16 | n=3 |
| Protocol-specific | | | | | | |
| Mean score (SD) | 5.3 (2.0) | 5.6 (1.6) | 5 (2.4) | 5.8 (2.6) | 5.8 (2) | 6.3 (5.5) |
| Min, max | 2, 8 | 3,8 | 2, 8 | 3, 10 | 3, 9 | 9, 10 |
| Introduction to informed consent | | | | | | |
| Mean score (SD) | 56 (18) | 65 (15) | 45 (17) | 69 (14) | 70 (12) | 64 (24) |
| Min, max | 23, 85 | 38, 85 | 23, 85 | 39, 92 | 54, 92 | 39, 85 |
| ICH-GCP | | | | | | |
| Mean score (SD) | 45 (16) | 54 (8) | 34 (16) | 56 (14) | 58 (14) | 48 (18) |
| Min, max | 11, 67 | 39, 67 | 11, 67 | 28, 83 | 33, 84 | 28, 61 |

[1] *Scoring for each questionnaire: (1) Protocol-specific questionnaire, maximum score available = 10; (2) Introduction to informed consent questionnaire, scored as a percentage (TGHN pass mark = ≥80%); (3) ICH-GCP questionnaire, scored as a percentage (TGHN pass mark = ≥80%).*

# 3. DISCUSSION

## 3.1 Objectives reviewed

To recap, the overall aim of this thesis is to evaluate a range of interventions for neonatal care and the management of preterm birth, both in high and low resource settings, and to explore some of the challenges in conducting neonatal trials, in the UK and in LMICs.

The need for simple, cost-effective interventions is clear. To reduce mortality rates and improve the life course for infants born preterm, the development and testing of interventions is urgently required. For interventions that are shown to be effective, rapid implementation at scale is also needed. Table 9 summarises the objectives of the thesis and whether they have been met.

**Table 9 - Objectives reviewed**

| Thesis part | Published works | Objectives | How the objective has been met |
|---|---|---|---|
| 1: Early Warning Scores | 1, 2 | To utilise data collected in this study to develop an early warning track and trigger system for preterm infants, by:<br>• Conducting a prospective observational study of current practice for preterm (37 weeks) or low birth-weight (<2500g) infants at a national hospital in Kenya<br>• Identifying barriers and facilitators to providing essential newborn care by conducting in-depth interviews of healthcare professionals and other stakeholders<br>• Gaining a contextual understanding of the experiences of essential newborn care provided to their infants, by undertaking focus groups with mothers and their families. | Published works 1 and 2 report the results of the prospective observational study and qualitative study (interviews with healthcare professionals/stakeholders and focus groups with mothers/families). Data collected from both studies has highlighted that an early warning score could be useful in newborn units in Kenya. The observational study has shown that recording of vital signs and record-keeping is generally poor and that a simple intervention, such as an early warning score, could provide a standardised, streamlined approach to vital sign monitoring, thus enabling adverse outcomes to be spotted earlier and acted upon. The effects of an EWS on neonatal mortality and serious morbidities remains unknown and requires evaluation, ideally in a RCT. The qualitative study, conducted in parallel, has demonstrated the importance of ensuring that the development of an early warning score must consider the mother's needs, in addition to the "system" needs of health professionals in the newborn unit. Kangaroo Mother Care (KMC) can be considered an |

| | | | |
|---|---|---|---|
| | | | exemplar as an intervention, shown to reduce neonatal mortality, that is being more widely implemented, where lessons could be learnt if an early warning score were to be implemented in the future. In addition, further opinions of a neonatal early warning score, gained via the meeting with 80 stakeholders, have been reported in Published work 1. |
| 2: Timing of umbilical cord clamping | 3 | The overall aim is to assess whether conducting a large multicentre randomised trial comparing timing of cord clamping policies at preterm births is possible in LMICs. Specific objectives are to assess current practices for management of the third stage of labour, and for care at the time of birth for preterm infants in LMICs by:<br><br>• assessing prospectively the accuracy of estimated gestation at birth and birthweight (using either Ballard or Dubowitz) whichever is used locally | Published works 3 reports the iCord study; a multi-centre prospective observational study conducted in five hospitals in four LMICs (India, Kenya, Pakistan, Uganda). This study demonstrated that it may be possible to conduct a study comparing timing of cord clamping in LMICs and highlighted the importance of understanding local practices as part of feasibility work before conducting a clinical trial. However, as a subsequent systematic review reported that deferring cord clamping reduces mortality, a randomised trial of timing of cord clamping in LMICs is no longer required. As in the UK, it is now essential that this simple, cost-effective intervention is rolled out at scale. Future research could focus on whether deferred cord clamping has subsequently been implemented and, if not, the reasons for this. |

| | | | |
|---|---|---|---|
| | | • describing the methods used for assessment of gestation and estimated birthweight<br>• describing current practice for timing of cord clamping at preterm and term births<br>• estimating the proportion of births either between 28-34 weeks gestation or 1-2 kg birthweight<br>• identifying the proportion of births either between 28-34 weeks or 1-2 kg birthweight that can be identified before birth<br>• describing the clinical staff present at the birth of preterm or low birthweight babies<br>• describing current practice for care of the preterm or low birthweight baby in the delivery room, and outcome at hospital discharge | |

| | | | |
|---|---|---|---|
| | | • identifying the proportion of preterm and low birthweight babies admitted to the neonatal unit or paediatric ward, and serious neonatal morbidity | |
| 3A – High quality and efficient neonatal trials: design/methodological aspects of the FEED1 trial | 4 | To explore some of the design and methodological considerations in the FEED1 trial | Clinical trials are challenging to design and conduct and can be costly. It is therefore imperative to ensure due attention is given to the methodological aspects when designing and conducting a trial. The trial is ongoing at the time of writing, but there have been several key methodological decisions that have required full consideration, including the choice of primary outcome, the time at which randomisation occurs, the choice of milk and clinical equipoise. These considerations are described in detail in this part. |
| 3B – High quality and efficient neonatal trials: consent in neonatal trials | 5 | To implement a series of interventions to support implementation of the two-stage consent pathway in the FEED1 Trial.<br><br>*It had originally been intended to evaluate whether the interventions implemented had led to clinicians feeling more supported in the process. However, due to the Covid-19* | After the FEED1 Trial opened to recruitment, it quickly became clear that recruiting clinicians required additional support in the two-stage consent pathway, particularly in having an oral assent conversation with a family approached about participation. In addition to ad-hoc feedback received from trial sites and discussions during site training, a short online survey showed that clinicians who were unfamiliar with the process of oral assent felt apprehensive about |

| | | | |
|---|---|---|---|
| | | *pandemic, it has not been possible to undertake this evaluation. The FEED1 trial was temporarily paused and, following re-opening, activity has been reduced due to reduced staffing. Amidst a global pandemic, whilst the NHS is in crisis, is not an appropriate time to undertake this survey. Evaluation will take place later.* | approaching a family to have an oral assent conversation. A specific issue was a concern about the lack of standardised information to give to a parent. Survey respondents felt that seeing other people having an oral assent conversation and peer-support from other recruiting clinicians at the site would be helpful.<br><br>Four strategies have been implemented into the FEED1 trial to support recruiting clinicians. These include additional documentation, interactive webinars and support sessions for sites, professionally filmed examples of oral assent conversations and a professionally produced animation, aimed at parents, to support an oral assent discussion. Further evaluation of these strategies will be undertaken when it is possible to do so, in view of the ongoing Covid-19 pandemic. |
| 3C – High quality and efficient neonatal trials: training of staff working on clinical trials | 6 | Within the Born Too Soon Optimising Nutrition project, conducted in Kenya and India, to: | A training lead at each participating institution was identified and they attended the Fundamentals of Clinical Trials training course in the UK in November 2019. Both training leads, who were clinicians, gave positive feedback about |

| | | | |
|---|---|---|---|
| | | 1. Provide clinical trials training for designated “trainers” at each participating institution<br>2. To test the effectiveness of an enhanced training package to provide training to researchers and clinicians, including elements of the “train the trainer” approach | their attendance and felt attending the course enhanced their knowledge about clinical trials.<br><br>An enhanced training package was implemented into the Born Too Soon Optimising Nutrition study. This included the training leads attending the Fundamentals of Clinical Trials course (above), clinicians and research team members participating in a two-day in-country workshop, led by the UK project leads, and ongoing training and support provided by the training leads and via the UK team. A range of questionnaires were completed at baseline and at the end of the study period to assess effectiveness of the training package. The questionnaires included baseline characteristics of the participants, including their previous research experience, knowledge questions relating to the Born too Soon Optimising Nutrition protocol and questionnaires developed by The Global Health Network: ICH-GCP and Informed Consent. Overall, the study showed that the enhanced training package marginally improved knowledge of research methods and governance, though there were no statistically significant differences in mean |

| | | | |
|---|---|---|---|
| | | | scores between the start and end of the study. The Covid-19 pandemic substantially impacted upon this study, since there was a long delay between the training taking place and the study starting, which is likely to have impacted upon the results of this evaluation. |

### 3.2 Contribution to knowledge and impact

This thesis contains six published works on the broad theme of interventions for the management of preterm birth in low and high resource settings and the importance of conducting efficient neonatal clinical trials. Five of the six papers are published (1-5). Paper 6 has been submitted for publication.

Papers 1 and 2 are the first reports of a neonatal early warning score in the context of a LMIC. Collectively, these papers provide the starting point in understanding whether an early warning score for preterm infants could be feasible and acceptable in a low resource setting. The observational study and input from the stakeholder meeting demonstrated that record-keeping in newborn units is poor and that the provision of standardised documentation, with easy-to-follow algorithms, would be welcomed. The clinical data collected in the observational study was consistent with previous studies showing a high mortality rate in preterm infants. In addition, infants were often cold – identifying babies with low temperatures earlier, by using an early warning score, could, in the future, reduce mortality. This work, funded by the University of Nottingham Global Challenges Research Fund (GCRF), has led to further grant funding from the UKRI (UK Research & Innovation) MRC (Medical Research Council). The next step in this longer programme of work is described in the recommendations for future research section of the thesis.

Paper 3 reports the feasibility of conducting a clinical trial comparing policies of timing of cord clamping in LMICs; again, this is the first report of such data. As previously described, a definitive trial is no longer warranted since a large systematic review has reported that deferring the timing of cord clamping reduces mortality in preterm infants. The Cord Pilot Trial (appendices 1-3) contributed the second highest number of participants to this large systematic review, as described in section 3.3.2. Data on practices at the time of birth, including the timing of cord clamping, from LMICs is scarce. This is in part due to, in many areas, having less research capacity than in high-income settings and less resources (human and non-human) to collect robust data. Therefore, the iCord study (paper 3), which reports current practices at the time of birth in five hospitals within four LMICs, greatly adds to this scarce evidence-base.

Paper 4 is the published protocol for the FEED1 Trial. This trial is the largest randomised controlled trial of full milk feeds in preterm infants of 30-33 weeks gestation ever conducted and once completed, will provide vital data on whether feeding preterm infants full milk feeds from day 1 reduces the length of hospital admission, in addition to a range of secondary outcomes, outlined in the publication.

Paper 5 reports the practical steps required to implement a two-stage consent pathway in a neonatal trial. Previous studies have focussed on the development of an alternative consent pathway for neonatal trials and qualitative evaluation of the pathway. This paper acknowledges the need for a two-stage consent pathway but recognises challenges in its implementation in practice. It provides readers guidance on strategies that could be implemented to support recruiting clinicians in future neonatal clinical trials. This is important if we are to reduce research waste and conduct efficient clinical trials, which are vital in answering important clinical questions relevant to the neonatal population. All resources developed for the FEED1 Trial, to support the two-stage consent pathway, are publicly accessible via the trial website.

Paper 6 reports the findings of an embedded methodological sub-study within the Born Too Soon Optimising Nutrition Project. Whilst clinical trials training resources exist, evidence on effective approaches to providing such training is scarce. Conducting studies to evaluate training methods in clinical trials conducted in LMICs is in the top 10 priorities for global health trials methodology research. This study is the first study to evaluate a clinical trials training package in a global health neonatal trial. Although an enhanced training package was implemented, statistically significant differences were not seen in questionnaire mean scores before and at the end of the study. The study clearly demonstrates that for high quality global health studies to be conducted, substantial investment into training of clinicians and researchers must be factored in when developing global health studies. This is evident by mean scores for ICH-GCP and informed consent training being considerably lower than the ‘pass’ mark of 80%, stipulated by The Global Health Network. Given the study was significantly disrupted by the Covid-19 pandemic, further evaluation into assessing methods to provide clinical trials training to clinicians and researchers in LMICs is warranted.

### 3.3 Critical review and recommendations for future research

In this section, each part of the thesis is critically reviewed and recommendations for future research are given. Strengths and limitations of each study are included in the published works themselves and further summarised in Table 10.

**Table 10 - Strengths and limitations of the research**

| Part | Publication | Strengths | Limitations |
|---|---|---|---|
| 1: Early warning scores | 1, 2 | • The observational study is the first report of the development of a neonatal EWS in LMICs<br>• The stakeholder meeting enabled us to elicit opinions of a wide range of stakeholders<br>• The qualitative study is the first report of a wide range of stakeholders' views of essential newborn care, in the context of the development of a EWS in LMICs | • The observational and qualitative studies were conducted in a single centre only (a tertiary referral hospital) and is therefore not representative of the care preterm infants receive in other health facilities in Kenya, though wider policy-makers were included in the qualitative study<br>• Data collected in the observational study was limited to routinely recorded data, thus leading to missing data |
| 2: Timing of umbilical cord clamping | 3 | • Data were collected prospectively in several LMIC settings (five hospitals in four countries) | • Data was limited to routinely recorded data<br>• Clinical staff may have altered their behaviours and care due to the study |

| | | | |
|---|---|---|---|
| | | • The data collected greatly adds to the scarce evidence base in understanding practices at the time of preterm birth in LMICs | being conducted, i.e. the Hawthorne effect [140] |
| 3a: High quality and efficient neonatal trials: design/methodological aspects of the FEED1 trial | 4 | • This is the first trial comparing full milk feeds at day 1 with gradual milk feeding in preterm infants born at 30-33 weeks gestation<br>• The trial is multi-centre, pragmatic and is being conducted in approximately 40 hospitals around the UK<br>• Parents have influenced the trial design and conduct throughout, via patient and public involvement (PPI) activities, therefore making the trial more relevant to families<br>• The protocol provides detailed methods outlining important methodological considerations | • Due to the Covid-19 pandemic and the resultant pause on recruitment, the trial results will not be available when originally expected |
| 3b: High quality and efficient neonatal trials: consent in neonatal trials | 5 | • This is the first report of the practical aspects of implementation of a two-stage consent pathway in a neonatal trial<br>• Practical guidance is provided to future researchers conducting neonatal clinical trials | • Although the opinions of recruiting clinicians were collected at baseline, it has not yet been possible to ascertain opinions after implementing additional support, due to the Covid-19 pandemic |

| | | | |
|---|---|---|---|
| | | where there may be benefit from including a two-stage consent pathway | |
| 3c: High quality and efficient neonatal trials: training of staff working in clinical trials | 6 | • This is the first evaluation of an enhanced training package in a neonatal trial conducted in LMICs<br>• Existing training resources, freely available via TGHN, were utilised in the study, enabling comparisons to be made with these data and future studies | • The Covid-19 pandemic led to long delays between training and the study starting, which is likely to have impacted upon the evaluation of the enhanced training package<br>• The follow-up rate for questionnaires at the end of the study was poor, despite several reminders. This was a particular problem in India where only a small number of participants completed both sets of questionnaires, making interpretation of the data difficult |

### *3.3.1 Part 1: Early warning scores*

There is a paucity of evidence of the development and use of neonatal early warning scores. One (non-systematic) published review reviewed the seven scores publicly available at the time, though concludes that none of the scores currently available considered high-risk infants, e.g. infants born preterm who are admitted for neonatal care. Preterm infants born in high-income settings, such as UK, are usually admitted for neonatal care and, as such, continuous monitoring of vital signs is usually standard. However, in LMICs, continuous vital sign monitoring is not available, due to a scarcity of human and non-human resources. Newborn units in LMICs frequently do not have access to technology and equipment such as incubators and, where they are available, they may be scarce. For example, it is not uncommon for unrelated infants to share incubators, thus increasing the chance of infection and other life-threatening conditions.

In the first part of our longer programme of work on early warning scores in LMICs, we conducted an observational study of current practice for preterm and low-birth weight infants. This was an important first step in gaining an understanding of the clinical characteristics of the infants born in this setting and to understand some of the processes that occur on the newborn unit of a large tertiary hospital in Kenya.

The first 24 hours of an Infant's life are critical; most neonatal mortality happens within the first 24 hours and mortality rates reduce as infants get older[31]. It is therefore important to note that in the observational study, evidence-based interventions such as Kangaroo Mother Care were not initiated in the first hour of birth for any of the 180 clinically stable infants. Moreover, important vital signs monitoring (temperature, heart rate and respiratory rate) was poor throughout the study. Only 3% of infants (10/294) had a recorded temperature, 20% (58/294) had a recorded heart rate and 24% (70/294) had a recorded respiratory rate in the first hour of life. On day 1 of birth (i.e., the day the infant was born), less than half of all infants had at least one temperature recording, heart rate recording and respiratory rate recording. The study collected data for up to 7 days or until hospital discharge or death. Over the entire study period, around two thirds of infants had at least one temperature recorded (185/294, 63%) whilst just over half had at least one heart rate

(156/294, 53%) and respiratory rate (155/294, 53%) recording. Whilst these are shocking figures, they are unsurprising. It has been documented previously that record-keeping in hospitals in Kenya is poor[141, 142] largely due to a lack of resources and inadequate health systems. A simple way of identifying infants who are at higher risk of an adverse outcome, such as an early warning score, could provide staff on newborn units in LMICs an effective way of recording vital signs monitoring. Our data on temperature is consistent with previous studies that have shown that preterm infants can be cold and ensuring they are kept warm must be a priority. Of the 185 infants who had at least one temperature recorded, more than half (97/185, 52%) had at least one recording in the moderate hypothermic range, defined as <36°c. Despite being moderately hypothermic, only 92 infants then had a subsequent temperature recorded and almost half (41/92, 46%) were taken >6 hours later, though this varied, ranging from 30 minutes to 46 hours. Around a half of these infants' (41/92, 46%) remained moderately hypothermic. National and local guidelines stipulate that preterm and low-birth weight infants should have vital signs monitored every 4 hours. An early warning score has the advantage of clearly identifying a vital sign that requires further monitoring and, dependent upon the value, escalation to a more senior member of staff. It is plausible therefore that if the temperatures for these infants had been documented on an early warning score, by a member of staff on the newborn unit, that action could have been taken more swiftly potentially preventing further harm to the infant.

By their very definition, LMICs have less resources available than HICs. Therefore, it is important that any intervention designed to improve healthcare and health systems is simple and doesn't require additional resources, since these are already scarce. The data collected in the observational study were presented at a stakeholder meeting of 78 individuals, in Kenya, with an interest in preterm birth. Attendees included a wide range of stakeholders including neonatologists, neonatal nurses, obstetricians, representatives from non-government organisations (e.g. charities) and policy-makers such as the Ministry of Health. Following presentation of the observational and qualitative study results, stakeholders were invited to discuss and consider whether an early warning score could be a useful tool that may improve neonatal mortality and morbidity in the future. Overall stakeholders were enthusiastic and liked the concept of the early warning score, in particular the simplicity of a

paper-based document that utilises a traffic-light approach to identifying infants who may be at higher risk of an adverse outcome. However, the issue of lack of resources was discussed at length. Stakeholders recognised the non-human resource implications – e.g. the ability to print in colour when ink and paper may be scarce and the human resource implications. An EWS not only requires a healthcare professional to document infant monitoring using the traffic-light system, escalation to a more senior member of staff is also required. The latter presents the biggest problem; certainly in Kenya where there are a lack of trained neonatal doctors and nurses[142]. One stakeholder articulated the issue perfectly when they stated "We have low staff to patient ratios. This [EWS] has very intense observational needs in a staff-constrained set-up". This clearly demonstrates the need to ensure the feasibility and acceptability of the EWS is fully tested on newborn units in LMICs. The EWS must not create additional work for a resource-constrained setting. This concept was mirrored in the final theme that was elicited from the stakeholder meeting; training and implementation. Stakeholders recognised that training in use of the EWS is paramount, not only in the documentation itself but in the escalation, i.e. the "trigger" part of the EWS relies upon. In addition, "buy-in" from senior policy-makers, such as the Ministry of Health, would be paramount in order to roll-out any initiative and to ensure work is not duplicated.

When developing or adapting any healthcare intervention, it is important to understand the views of a range of individuals. This is particularly important in low resource settings when considering quality improvement initiatives, since it encourages participation from populations who may have previously been marginalised. Opinions were sought via discussions during the stakeholder meeting described above and in addition, via in-depth interviews with nineteen mothers and family members and twenty stakeholders. The qualitative study was conducted in parallel with the observational study and focussed on the experiences of essential newborn care in Kenya. Three themes emerged from data collected during interviews: (i) mothers' physical and psychological needs, (ii) system pillars and (iii) Kangaroo Mother Care (KMC). "Mothers' physical and psychological needs" concerned itself with the needs of mothers, families and the wider community after having a preterm infant who is in hospital. "System pillars" reflects newborn care in the context of the hospital organisation and wider country initiatives. Finally, KMC

reflects KMC units, available in low resource settings and the importance of KMC in the care of a preterm infant. Here, KMC is seen as an exemplar intervention and lessons learnt from the development and implementation of this evidence-based initiative could be applied to the EWS. The qualitative study showed that having a standardised approach to newborn care is important and findings were also consistent with the observational study that there is a lack of monitoring and poor documentation on the newborn unit. An EWS could provide healthcare professionals with a simple, standardised way of routinely recording observations and could also facilitate better communication between healthcare professionals and parents, which participants identified as important.

To understand whether implementing an EWS is feasible and acceptable to healthcare professionals based on newborn units, funding has been secured to conduct a further mixed-methods study. In this new study, the NEWTT, developed in the UK, will be adapted to the Kenyan setting and used in the newborn units of three hospitals in Kenya. Each hospital provides a different level of health facility. Healthcare professionals will be asked to use this for all eligible infants (<37 weeks gestation and/or <2.5kg birthweight) over a 6-week period. To understand feasibility, we will collect data on the proportion of infants for whom the EWS was used, the proportion of EWS "triggers" that were acted upon (e.g., if a temperature was recorded in a high-risk red zone, was this then escalated to a more senior member of staff) and the consequences of the actions taken of reviews triggered by the EWS. To understand acceptability, and determine barriers and facilitators to the EWS, after the data collection period described above has ended, healthcare professionals will be asked to participate in a semi-structured interview. The theoretical framework of acceptability[143] will be applied since this is highly relevant in this context.

Further steps in this programme of work will be determined by the results of the next study, however it is envisaged that if the EWS is shown to be feasible and acceptable to healthcare professionals, it will then be important to conduct a randomised clinical trial to investigate whether an EWS reduces mortality and morbidity in preterm and low-birth weight infants. This is likely to be a cluster trial, where hospitals are randomised to using an EWS or not. A pilot-phase to the randomised clinical trial will be important. This will either be conducted beforehand,

in order to pilot clinical trial procedures to determine if it is possible to conduct a randomised trial in this area, or as an embedded “internal pilot” at the beginning of the trial[144]. An embedded process evaluation will also be considered since it will be important to understand barriers and enablers to implementation of the EWS, should it demonstrate effectiveness.

### *3.3.2 Part 2: Timing of umbilical cord clamping*

The iCord study (publication 3) was designed as part of early feasibility work prior to potentially conducting a clinical trial comparing alternative cord clamping policies. The study reports on practices at the time of preterm birth and showed there was wide variability in the timing of cord clamping in term (n=3524) and preterm (n=257) infants within and between participating sites. In preterm infants, the median time of cord clamping was 16 seconds (IQR 6-52), and practice varied between countries, with the two hospitals in Uganda waiting the longest. Infants born in these settings, who are more likely to die because of their prematurity, could potentially benefit the most from delayed cord clamping.

This study was conducted concurrently with the Cord Pilot trial in the UK (appendices 1-3). Data from the Cord Pilot trial (276 infants) was included in a subsequent systematic review and meta-analysis (18 trials, 2834 infants)[145]; the second largest trial to contribute data (12.8% weighting). This provided high quality evidence that delayed clamping reduced hospital mortality (risk ratio, 0.68; 95% CI 0.52-0.90). For this reason, despite showing promise that it was possible to collect data at the time of birth in the LMICs included in the iCord study, it was no longer necessary to conduct a clinical trial comparing timing of cord clamping in preterm infants.

Despite the publication of the systematic review and meta-analysis, there remain unanswered questions in this area of research. Firstly, the trials included in the systematic review used a variety of definitions of delayed cord clamping, ranging from >30 seconds to ≥120 seconds. This means that the difference between the intervention and control groups in trials comparing early clamping (<30 seconds) and delayed clamping (>30 seconds) is very small and arguably a between group difference may be difficult to detect. In addition placental transfusion can continue for up to two minutes and, in some cases, continues up to five minutes[78]. Therefore, a longer delay, e.g. ≥120 seconds seems more biologically plausible to show a potential effect between the two groups. The authors of the systematic review performed several pre-specified sub-group analyses, including comparing the effects of the duration of delayed cord clamping. There was no significant sub-group

difference for mortality or other important secondary outcomes such as severe intraventricular haemorrhage. Despite evidence to suggest delayed clamping reduces mortality, the optimum time to clamp the cord is still unclear and there would be benefit in comparing different durations in future trials[80].

The UK Cord Pilot Trial was conducted as part of a larger programme of work on improving the quality of care and outcomes at very preterm birth. An important aspect in designing the trial was developing ways which made it possible to provide newborn care, including resuscitation, with the umbilical cord still intact, for infants in the delayed cord clamping group. As previously described, the BASICS trolley was designed during this programme of work. In addition, our team also developed a way of adapting a standard resuscitaire, available in all UK labour suites, to allow stabilisation of the infant with the cord still intact. This was not without challenges. Challenges included practicalities such as the umbilical cord being too short to allow the infant to be placed on the trolley, having the trolley easily accessible in theatres for deliveries by Caesarean section, and apprehension from clinicians' at "performing" resuscitation in front of parents. An interview-study with twenty clinicians who were present when the trolley was used to provide neonatal care at the bedside further describes these challenges[146]. Qualitative research was also undertaken to assess parents' views and experiences of care at the bedside using a mobile trolley, and to understand whether witnessing their baby being resuscitated, with the cord still intact, had any negative impact to the parents[147]. Though only conducted as a single-centre study, 30 participants were interviewed and parents were overall positive about the bedside trolley and the provision of bedside neonatal care. Parents felt reassured that the baby was close to them and liked that it allowed a family-centred approach. However, some negative emotions were also described, including the potential impact on staff and communication between staff and parents.

Whilst the systematic review has provided high-quality evidence that delayed cord clamping reduces all-cause infant mortality before discharge, all trials (other than the Cord Pilot trial) either clamped the cord before resuscitation of the infant or did not report these data. The Cord Pilot trial has demonstrated it is possible to provide newborn care, including resuscitation, with the cord intact, thus enabling delayed cord clamping to be offered. This is important since the infants who require

resuscitation are often the sickest and therefore could potentially benefit the most from delayed cord clamping.

Despite evidence provided by the systematic review, in a subsequent survey reporting current practices in timing of cord clamping in LMICs, only 60% of participants reported practicing DCC for stable infants[148]. For unstable infants, requiring resuscitation, only 6% reported practicing DCC. In addition, only just over a third of participants (36%) reported being aware of having any guidelines in place with respect to timing of cord clamping in their hospital. Whilst these survey data are based on a small sample only (n=70 from 10 LMICs), they indicate that further work is needed to embed DCC into routine practice in LMICs. This work could focus on outstanding research questions, as described, and/or quality improvement initiatives. The survey reported that 13% of participants were aware of ongoing related quality improvement projects. One such project is being conducted at hospitals in Uganda. A team at the University of Liverpool have designed the BabySaver (https://www.sanyuresearch.org/babysaver/) which is a low-cost resuscitation unit, allowing neonatal care to be delivered at the bedside, with the cord intact. Evaluation of the BabySaver is ongoing.

### *3.3.3 Part 3a: High quality and efficient neonatal trials: design and methodological aspects of the FEED1 trial*

Whilst there have been some smaller clinical trials investigating initiating full milk feeds from day 1 in preterm infants, these have been conducted in India where healthcare provision is very different. FEED1 will be the largest randomised clinical trial to produce high-quality evidence on whether full milk feeds from day 1 reduces the length of hospital stay for infants born between 30-33 weeks gestation. The trial received full ethical approval on 13 September 2019 and was prospectively registered to an international clinical trial registry. Recruitment commenced on 15 October 2019 and is expected to continue to at least September 2024. Results of the trial were expected to be available by January 2023, however the Covid-19 pandemic, the resultant pause and subsequent slow re-start has led to the trial requiring additional time to complete, discussed more below. Although the trial is ongoing, there have been some challenges, which are now discussed.

Firstly, the type of milk a preterm infant receives has been a challenging aspect since the idea for the trial was conceived. Some healthcare professionals believe that the FEED1 intervention will promote feeding with formula milk, rather than mother's breast milk. Mothers commonly take several days to produce the volume of milk the infant needs, yet the FEED1 intervention involves feeding infants full milk volumes from day 1 following birth. The first choice of type of milk will always be the mother's own milk, as in standard practice. However, for infants in the intervention group of the trial, if sufficient volumes of mother's milk are not available, this will be supplemented by formula milk or donor breast milk. This means that infants in the intervention group should always be fed milk, whereas UK standard care is to currently provide nutrition via intravenous fluids or parenterally. Once sufficient volumes of mother's milk are produced, mothers will be supported in expressing breast milk and breastfeeding will be encouraged for all infants in the trial, regardless of their allocated group. As described in section 1.7.3, whilst designing the trial, we worked with representatives from the UK Association of Milk Banks (UKAMB) who fully support the trial. In addition, discussions with Bliss, the UK's largest charity for babies born premature or sick, and our patient and public involvement (PPI) representatives, has been key in us alleviating any concerns that healthcare

professionals may have about the type of milk used. Finally, there is no involvement, of any kind, of any manufacturers of formula milk in the trial.

Secondly, some clinicians have found the consent pathway challenging. This is due to many clinicians having never entered a participant into a trial having only gained oral assent, rather than full written informed consent. Several initiatives have been implemented to alleviate these concerns. These are discussed in sections relating to Part 3B of this thesis and are not repeated here.

Thirdly, in March 2020, approximately six months after trial recruitment commenced, the World Health Organisation announced the COVID-19 respiratory virus as a global pandemic[149]. The trial funder, the National Institute for Health Research (NIHR), issued guidance that clinical care should take precedence over clinical research and a large proportion of clinical research studies in the UK were temporarily paused. The FEED1 Trial paused to recruitment on 20 March 2020, in line with national guidance, to allow research teams to be redeployed to clinical roles within the NHS and to alleviate the pressure of additional research activity. After 15 weeks on pause, the trial re-opened to recruitment on 3 July 2020. However, many hospitals around the UK have had reduced research capacity and have been asked to prioritise COVID-19 research studies. This has had a detrimental effect on recruitment into the trial, though this is constantly monitored by the Trial Management Group. A two-year time-extension request has been submitted to the trial funders in order to meet recruitment targets.

Finally, an ongoing challenge in the FEED1 trial is one of equipoise amongst recruiting clinicians. Clinical equipoise refers to uncertainties of the relevant benefits and harms of an intervention being tested in a clinical trial[150]. It is a foundation on which a clinical trial should be built – if equipoise doesn't exist, i.e. there is already clear evidence on the benefits and harms of an intervention, a clinical trial is not warranted since the question has already been answered. Whilst some clinicians in recruiting sites may have their own equipoise, this does not equate to all clinicians sharing this view. Some clinicians may, despite the lack of evidence, believe that feeding full milk feeds to preterm infants is either beneficial or harmful. Lack of equipoise can affect recruitment into a clinical trial since clinicians may believe they

already know the best treatment/intervention strategy for a patient, thus declining to randomise potential participants. However, in the FEED1 trial a specific concern is adherence to the intervention and the potential for clinical equipoise changing over time. The TMG is closely monitoring data on adherence to the randomised allocation (intervention or control group), since it appears that some infants randomised to the control group (gradual milk feeds) are then fed full milk feeds (intervention group). Whilst this is a pragmatic trial whereby analyses will be conducted using the intention-to-treat principle, it is important to ensure mitigations are in place to try to prevent this from happening. The importance of feeding infants as per their randomised allocation is covered in depth during site training and the topic of equipoise has also been covered in several clinical Q&A sessions which are held with sites. Importantly the data is being monitored monthly in order to take swift action as and when required. In sites where this appears to be a particular problem, this is discussed with the site Principal Investigator and their team and sites are reminded about the importance of feeding as per the infant's randomised allocation. It would be interesting for a future methodological project to explore clinical equipoise within the FEED1 trial and other, similar, neonatal trials to investigate whether there are shifts in equipoise over time.

If the FEED1 Trial demonstrates that full milk feeds from day 1 reduces the length of hospital stay by even a modest amount, this could dramatically improve parents' experiences and make significant cost-savings to the NHS. Whilst a reduction in hospital length of stay is important for the reasons outlined in section 1.7.3, interventions to reduce late-onset sepsis and NEC, both of which can be fatal, are of major clinical and parental importance. Incidence of late-onset sepsis in the UK is 17.9/1000 neonatal unit admissions (all gestations), though primarily diagnosed in preterm infants (<37 weeks gestation) [45]. For infants born at 30-33 weeks gestation (i.e. the FEED1 population), the incidence of NEC is low at $\leq$1%[50]. Given the estimated incidence of these fatal preterm complications, the UK trial would not be statistically powered to investigate a reduction in late-onset sepsis and NEC, however, these are clinically important secondary outcomes and data on incidence within the trial is being collected. It would be unfeasible to conduct the FEED1 trial in the UK alone, if the primary outcome were late-onset sepsis or NEC, since many thousands of infants would be required, and the study would take too long to

complete. Future research could include replicating the study in other high-income settings, with similar healthcare systems, and subsequently sharing participant data to conduct a prospective individual participant data meta-analysis[151]. Pooling data in this way could give adequate power to evaluate if the FEED1 intervention is effective at reducing late-onset sepsis and NEC.

In LMICs, the incidence of late-onset sepsis and NEC is unclear though expected to be significantly higher than in high-income settings[152]. Both outcomes are of huge clinical concern in LMICs since they are the cause of death for many infants. Therefore, in the future, conducting the FEED1 Trial in LMICs could be practice changing. Before any intervention developed in a high-income setting is then evaluated in a LMIC, it is crucial to undertake feasibility work. The Born Too Soon Optimising Nutrition study (briefly described in part 3C) has been funded to test the feasibility of conducting the trial in Kenya. Data from this study should also help to understand the incidence of late-onset sepsis and NEC in this setting, which would be important when designing a clinical trial in the future. The study has recently completed though is outwith this thesis.

Future research focussing on the FEED1 intervention could also include qualitative studies to understand the barriers and facilitators to initiating full milk feeds from day 1 in preterm infants. This would be important to ensure that, if the trial does demonstrate a reduction in length of stay for infants in the full milk feeds group, this change could be implemented into clinical practice quickly.

### *3.3.4 Part 3B: High quality and efficient neonatal trials: consent in neonatal trials*

The need for alternative approaches to consent in neonatal clinical trials has been clearly described in previous studies[120, 153]. During labour and the hours immediately after birth are an extremely stressful and emotional time periods for parents, particularly if the baby is preterm and/or sick. It may not be appropriate therefore to approach a parent to seek their written informed consent for their newborn to participate in a clinical trial. This leads to an additional challenge: by not approaching parents of a newborn who is eligible to participate in a neonatal clinical trial, the trial results could be considered less generalisable to the newborn population of interest. Using alternative approaches to consent enables newborns whose parents may not have been approached antenatally to be included[154, 155].

The development of a two-stage consent pathway in the Cord Pilot Trial was an important step in addressing this issue[156]. Women could be approached either antenatally, using the traditional written informed consent approach, or during labour to seek a woman's oral assent for participation, followed by written informed consent (for ongoing use of the mother-infant dyad's data) at a later date. Qualitative work found the pathway to be acceptable to parents and clinicians[122, 123]. However, there is no evidence on *how* to implement such a pathway, enabling inclusion of newborns irrespective of the time point of approaching parents about their newborn participating. The work presented in this thesis is important for triallists designing and conducting neonatal trials in the future. It is important that the practicalities on how a trial is operationalised are considered at an early stage by members of the multi-disciplinary team needed to deliver a trial[157].

Once the two-stage consent pathway had been included in the FEED1 Trial and sites were opened to recruitment, it quickly became clear, via ad-hoc communications, that whilst clinicians broadly supported its use, there was apprehension about approaching parents to seek their oral assent for their newborn to participate in the trial. This was corroborated by the results of the online survey, conducted shortly after the trial had opened to recruitment, which showed that three quarters of clinicians didn't like this

unfamiliar process and 43% were unsure about how much information to include in an oral assent conversation.

The strategies used to implement and embed the two-stage consent pathway into the FEED1 trial have been described in section 1.8.3. In the future, it will be interesting to evaluate use of the oral assent component of the pathway: did use increase over the recruitment period? did use differ between sites and between staff type? Did use increase after the strategies were implemented? Did use of oral assent affect retention in the trial or alter response rate to subsequent questionnaires and two-year neurodevelopmental outcome data. It will also be interesting to evaluate recruiting clinicians' views on the *implementation* of the pathway: did they use the additional resources? Were the resources helpful? What additional strategies may have been helpful? The survey undertaken in February 2020 could be repeated to gain understanding if clinicians' confidence in using the pathway had improved. A repeat survey had been planned, but unfortunately has been postponed given the significant delays in the trial to date because of the ongoing Covid-19 pandemic. Additionally, qualitative work could be undertaken to gain a deeper understanding of clinicians' views of the pathway and, importantly, the steps taken to implement and embed it within the recruiting site. Finally, it will be interesting to explore the views of parents about the pathway and whether the parent-facing resources developed for having an oral assent conversation (e.g. the short information sheet and animation) were helpful in their decision-making process.

### *3.3.4 Part 3C: High quality and efficient neonatal trials: training staff working in clinical trials*

Clinical trials are complex scientific research studies that should be conducted to a high quality to reduce research waste and answer important clinical questions. Ensuring staff who work on clinical trials, irrespective of their role, have the appropriate training and expertise is critical. Inadequate training and skills of clinical trials staff can lead to poor quality trials being conducted, resulting in resource waste (financial and non-financial). It is also unethical to recruit participants to a clinical trial that fails to answer the clinical question because it has been conducted poorly. Whilst it is unlikely that no one would argue the *need* for clinical trials staff to be adequately trained, there is little evidence on *how* best to do this. Legislation and the quality standards for conducting clinical trial varies between countries. In the UK, and other high-income countries, it is the law that clinical trials staff receive adequate training prior to them working on a trial. However, this is less clear in LMICs and previous research has identified the need for capacity-building programmes and adequate training programmes for researchers[132, 133].

The study embedded within the Born Too Soon Optimising Nutrition study, conducted in Kenya and India, is the first study evaluating an approach to clinical trials in a neonatal clinical trial conducted in LMICs. The previous research experience of the thirty participants (i.e. clinicians and researchers who participated in the study's training sessions) was limited: 50% of staff who had previously worked on a research study had received *any* research training, shockingly this includes staff who had previously worked on a clinical trial.

In this study, scores of questionnaires completed at baseline and end of the study were compared. Scores, for all questionnaires, before the study started varied, but overall were low. Unsurprisingly, scores for participants who had previous research experience were higher for all questionnaires. The TGHN questionnaire scores were much lower than the 80% pass rate they stipulate (introduction to informed consent: 56%, ICH-GCP: 45%) and the protocol-specific questionnaire mean score was 5.3/10. Though, particularly for the protocol-specific questionnaire, this is unsurprising since they had yet to be trained on specific aspects of the study. However, though scores

improved slightly at the end of the study, they remained strikingly low and no statistically significant differences were seen in scores before and at the end of the study. The TGHN scores remained lower than the 80% pass mark (introduction to informed consent: 69%, ICH-GCP: 56%) and the protocol-specific questionnaire score increased only marginally to 5.8/10. There could be several explanations for this which will now be explored.

Firstly, the enhanced training package itself may have been insufficient to see marked improvements in questionnaire scores. The training package was designed to include several components, including generic clinical trials training and study-specific training, and a variety of training methods were used. However, a large component of the training package hinged upon the availability, skills and experience of the training leads identified in the participating sites. Both sites chose a clinician to undertake the "trainer" role. However, upon reflection it may have been better to identify a separate member of the team, who had dedicated time built into a training lead role, rather than a member of staff with a busy clinical workload. A train-the-trainer approach relies upon the trainer to be able to provide adequate training to other members of this team and in this study, this may not have been possible due to lack of capacity and the understandable prioritisation of clinical workload.

The two-day training visits in Kenya and India were conducted using a variety of training methods and included a significant amount of time for open discussions and Q&A sessions. These sessions were largely led by me: a white, female researcher based in a high-income country. Substantial attention was given to attempting to make the training sessions as open and inclusive as possible. All attendees were actively encouraged, on multiple occasions, to discuss training material, identify issues and ask questions, and care was taken to address any language barriers. They were frequently asked if content was understood before moving on to subsequent materials. However, the power imbalance between global health researchers in HICs and LMICs is well documented[158, 159]. Despite efforts to create an equitable partnership, it could be that participants in the training session did not feel able to question the UK researchers. This is difficult to acknowledge though necessary to move forwards. In future, including the attendees in the design of the training sessions and having

sessions led by members of the research team at the LMIC, may go some way to reduce the perceived power imbalance.

The study has two substantial limitations which may have affected two separate, though linked, components. Firstly, there was a substantial length of time between the training sessions (UK and in-country) and the start of the study. This was due to delays in receiving ethical approval and the start of the Covid-19 pandemic. The study was about to start when the pandemic was declared by the World Health Organisation[149]. Participants at the training session had to not only conduct the study amidst a global pandemic but may well have forgotten content of the training sessions in the nine months between receiving training and the start of the study. Unfortunately, whilst training support was given remotely and via the training leads, re-training of research teams was not possible within the constraints of the funding and project timescales. Secondly, not all participants completed questionnaires at the end of the study. This was a particular problem in India where only three of seventeen participants (18%) completed the second set of questionnaires, despite reminders via various methods on several occasions. The reason for this could be explained by the fact that these three participants were much more actively involved in the study conduct, whereas others took on a much smaller role. In addition, many of the nurses who had attended the training understandably had to prioritise clinical workload which had increased due to the pandemic.

This study has shown that the enhanced training package resulted in marginal increases in questionnaire scores before and at the end of the study period, though these were not statistically significant and still remained lower than expected 'pass' rates from TGHN. In future global health studies, it will be important to consider the optimum timing for conducting training, though in this instance we were constrained by the pandemic. Content and format should be carefully considered, discussed between the multi-country team and training sessions led by a combination of UK and LMIC researchers who have appropriate expertise. If study timelines allow, it may be useful to consider developing a mandatory training programme which must be *passed* (rather than merely *completed*) before the member of staff commences any research activity.

The TGHN have recently conducted a study to develop the “Evidence-led Research Skills Training Curriculum”[160]. This study included several stages including an initial knowledge gap analysis, a Delphi survey and stakeholder workshop. Over 7000 researchers and health workers were involved in its development, worldwide. The project concluded with holding an implementation workshop to discuss how best to implement the curriculum that had been developed and convert this into relevant training resources. The curriculum includes a framework with 13 modules covering all aspects of the research cycle. The authors of the resultant report conclude that:

*“delivering training aligned with this curriculum framework will help promote and ensure that research should be safe, ethical and robust, and that local teams are equipped with lasting research skills, community engagement and management practices that will advance and support their careers”.*

Discussions held within the implementation workshop included the need for offering multiple options for training delivery, including using a “train the trainer” approach. It is clear that further research into the most effective training packages for researchers based in LMICs, linked to this curriculum, remains warranted and researchers should consider using mixed-methods in future studies. Though we had intended to interview researchers who had participated in the training, to gain deeper insight into their opinions on the training sessions, this was not possible due to the time constraints and the ongoing pandemic.

# 4. CONCLUSIONS

This thesis includes research conducted to tackle the global problem of neonatal mortality and serious morbidity, underpinned by research to evaluate ways to improve the quality and efficiency of clinical trials.

The clinical interventions evaluated are all theoretically simple interventions and can be summarised, in lay terms, as:

- Using a paper chart that uses a traffic light system to highlight when a baby is getting sicker
- Feeding babies born prematurely full milk feeds sooner
- Waiting a bit longer before clamping the umbilical cord after a baby is born

None of these interventions, at first glance, are hugely complicated or rely upon expensive equipment. This makes them relevant to a range of settings but could make the biggest difference and be particularly attractive to LMICs. The interventions evaluated were developed in HICs and should not simply be applied to a LMIC, which may have a very different culture, healthcare system and needs. All of these 'simple' interventions rely upon a systems-based approach to their evaluation and implementation. For example, the research undertaken to understand if it is possible to use an early warning score (developed in a HIC) in a LMIC has shown that, whilst theoretically possible, ensuring full consideration of current healthcare systems and Newborn Unit staffing is critical. The tracking of vital signs, using an EWS, is, in itself, helpful, since it could improve record-keeping, however it is the 'triggering' of an escalation to a more senior member of staff and thus, improving monitoring, that could make a difference to the infant's outcome. Without appropriate staffing to support the EWS, it is unlikely that using this version of a paper chart will make a substantial difference to outcomes.

Neonatal mortality and serious morbidity remain a huge burden, particularly in LMICs. To address the issue and meet SDG targets, studies to evaluate potential life-saving interventions must be prioritised. Researchers in HICs and LMICs should work

together, as equal partners, to co-develop clinical trials. Ensuring research teams receive appropriate training to conduct the trials is essential for them to be designed and delivered to a high standard. Robust feasibility work is also essential in the research pipeline and evaluation of interventions, as demonstrated in the EWS studies (papers 1 and 2) and the iCord study (paper 3). Where interventions are shown to be effective, efforts to implement them are critical, as seen in the example of Kangaroo Mother Care in the qualitative study to understand essential newborn care in Kenya.

With a coordinated global effort, underpinned by strong methodological research, high quality, efficient neonatal clinical trials, in HICs and LMICs, should be conducted to tackle the significant global burden of preterm birth, neonatal mortality and serious illness.

# REFERENCES


1. World Health Organisation. Child Causes of death 2000-2017. 2018. [accessed 7 February 2020]

2. World Health Organisation. Leading causes of death globally 2020 https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. [accessed 29 August 2021]

3. Oliver S, Uhm S, Duley L, Crowe S, David AL, James CP, et al. Top research priorities for preterm birth: results of a prioritisation partnership between people affected by preterm birth and healthcare professionals. BMC Pregnancy and Childbirth. 2019;19(1):528.

4. Yoshida S, Martines J, Lawn JE, Wall S, Souza JP, Rudan I, et al. Setting research priorities to improve global newborn health and prevent stillbirths by 2025. J Glob Health. 2016;6(1):010508.

5. Chawanpaiboon S, Vogel JP, Moller AB, Lumbiganon P, Petzold M, Hogan D, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. Lancet Glob Health. 2019;7(1):e37-e46.

6. Data and Analytics Section; Division of Data Analytics, Planning and Monitoring, UNICEF. Child Mortality Estimates. UNICEF 9 September 2020 [accessed 6 December 2020]

7. The World Bank [definitions of economic status of countries]. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups. [accessed 5 April 2020]

8. Zaidi AK, Huskins WC, Thaver D, Bhutta ZA, Abbas Z, Goldmann DA. Hospital-acquired neonatal infections in developing countries. Lancet. 2005;365(9465):1175-88.

9. United Nations. UN Inter-agency Group for Child Mortality Estimation. https://childmortality.org [accessed 5 April 2020]

10. United Nations. Millenium Development Goals. https://www.un.org/millenium-goals [accessed 5 April 2020]

11. United Nations. MDG Monitor: Tracking the millenium development goals http://www.mdgmonitor.org/mdg-4-reduce-child-mortality/2016 [accessed 5 April 2020]

12. World Health Organisation. Every Newborn: An Action Plan to End Preventable Deaths. 2014.

13. United Nations. UN Sustainable Development Goals https://sustainabledevelopment.un.org/. [accessed 14 February 2020]

14. United Nations Secretary General. Special edition: progress towards teh Sustainble Development Goals. 8 May 2019.

15. World Health Organisation and UNICEF. Reaching Every Newborn National 2020 MIlestones: 2018 progress report. 2018.

16. World Health Organisation, Geneva. Preterm Birth 2018 https://www.who.int/news-room/fact-sheets/detail/preterm-birth#:~:text=Preterm%20is%20defined%20as%20babies,(32%20to%2037%20weeks). [accessed 6 December 2020]

17. Lee ACC, Blencowe H, Lawn JE. Small babies, big numbers: global estimates of preterm birth. The Lancet Global Health. 2019;7(1):e2-e3.

18. World Health Organisation. Pregnancy, Childbirth, Postpartum and Newborn Care: a guide for essential practice. 3rd edition. 2015.

19. World Health Organisation. WHO recommendations on interventions to improve preterm birth outcomes. 2015. [accessed 24 March 2020]

20. Charpak N, Gabriel Ruiz J, Zupan J, Cattaneo A, Figueroa Z, Tessier R, et al. Kangaroo Mother Care: 25 years after. Acta Paediatrica. 2005;94(5):514-22.

21. Lawn JE, Mwansa-Kambafwile J, Horta BL, Barros FC, Cousens S. 'Kangaroo mother care' to prevent neonatal deaths due to preterm birth complications. Int J Epidemiol. 2010;39 Suppl 1(Suppl 1):i144-i54.

22. Morgan MC, Nambuya H, Waiswa P, Tann C, Elbourne D, Seeley J, et al. Kangaroo mother care for clinically unstable neonates weighing </=2000 g: Is it feasible at a hospital in Uganda? J Glob Health. 2018;8(1):010701.

23. Healthy Newborn Network. KMC Acceleration Partnership. https://www.healthnewbornnetwork.org/kap/ [accessed 17 January 2021]

24. County Innovation Challenge Fund. Kangaroo Mother Care: lessons learnt from the path to scale in Kenya. 2018. https://options.co.uk/sites/default/files/kangaroo_mother_care.pdf [accessed 17 January 2021]

25. World Health Organisation. Thermal Control of the Newborn: a practical guide. 1993.

26. Laptook A, Tyson J, Shankaran S, McDonald S, Ehrenkranz R, Fanaroff A, et al. Elevated temperature after hypoxic-ischemic encephalopathy: risk factor for adverse outcomes. Pediatrics. 2008;122(3):491-9.

27. Lyu YY, Shah PS, Ye XY, Warre R, Piedboeuf B, Deshpandey A, et al. Association Between Admission Temperature and Mortality and Major Morbidity in Preterm Infants Born at Fewer Than 33 Weeks' Gestation. Jama Pediatr. 2015;169(4).

28. Conde-Agudelo A, Diaz-Rossello JL. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. Cochrane Db Syst Rev. 2016(8).

29. Boundy EO, Dastjerdi R, Spiegelman D, Fawzi WW, Missmer SA, Lieberman E, et al. Kangaroo Mother Care and Neonatal Outcomes: A Meta-analysis. Pediatrics. 2016;137(1):e20152238.

30. McCall EM, Alderdice F, Halliday HL, Vohra S, Johnston L. Interventions to prevent hypothermia at birth in preterm and/or low birth weight infants. The Cochrane database of systematic reviews. 2018;2(2):CD004210-CD.

31. Oza S, Cousens SN, Lawn JE. Estimation of daily risk of neonatal death, including the day of birth, in 186 countries in 2013: a vital-registration and modelling-based study. The Lancet Global Health. 2014;2(11):e635-e44.

32. Aziz K, Chadwick M, Baker M, Andrews W. Ante- and intra-partum factors that predict increased need for neonatal resuscitation. Resuscitation. 2008;79(3):444-52.

33. Edwards MO, Kotecha SJ, Kotecha S. Respiratory distress of the term newborn infant. Paediatric respiratory reviews. 2013;14(1):29-36; quiz -7.

34. Wyllie J, Bruinenberg J, Roehr CC, Rudiger M, Trevisanuto D, Urlesberger B. Resuscitation and Support of Transition of Babies at Birth. Notfall Rettungsmed. 2015;18(8):964-83.

35. American Academy of Pediatrics. Helping Babies Breathe: The golden minute 2010 [Available from: https://internationalresources.aap.org/Resource/Home. [accessed 16 January 2021]

36. Budhathoki SS, Gurung R, Ewald U, Thapa J, Kc A. Does the Helping Babies Breathe Programme impact on neonatal resuscitation care practices? Results from systematic review and meta-analysis. Acta paediatrica (Oslo, Norway : 1992). 2019;108(5):806-13.

37. Escobar GJ, McCormick MC, Zupancic JAF, Coleman-Phox K, Armstrong MA, Greene JD, et al. Unstudied infants: outcomes of moderately premature infants in the neonatal intensive care unit. Archives of Disease in Childhood - Fetal and Neonatal Edition. 2006;91(4):F238-F44.

38. Kinney HC. The Near-Term (Late Preterm) Human Brain and Risk for Periventricular Leukomalacia: A Review. Seminars in Perinatology. 2006;30(2):81-8.

39. Wang ML, Dorer DJ, Fleming MP, Catlin EA. Clinical Outcomes of Near-Term Infants. Pediatrics. 2004;114(2):372-6.

40. Masaba BB, Mmusi-Phetoe RM. Neonatal Survival in Sub-Sahara: A Review of Kenya and South Africa. J Multidiscip Healthc. 2020;13:709-16.

41. Cummings JJ. The Well-Appearing Newborn at Risk for Early-Onset Sepsis: We Can Do Better. Pediatrics. 2017;139(3):e20164211.

42. Simonsen KA, Anderson-Berry AL, Delair SF, Davies HD. Early-onset neonatal sepsis. Clin Microbiol Rev. 2014;27(1):21-47.

43. Wynn JL. Defining neonatal sepsis. Curr Opin Pediatr. 2016;28(2):135-40.

44. Wynn JL, Wong HR, Shanley TP, Bizzarro MJ, Saiman L, Polin RA. Time for a neonatal-specific consensus definition for sepsis. Pediatr Crit Care Med. 2014;15(6):523-8.

45. Cailes B, Kortsalioudaki C, Buttery J, Pattnayak S, Greenough A, Matthes J, et al. Epidemiology of UK neonatal infections: the neonIN infection surveillance network. Archives of Disease in Childhood - Fetal and Neonatal Edition. 2018;103(6):F547-F53.

46. Brown JVE, Walsh V, McGuire W. Formula versus maternal breast milk for feeding preterm or low birth weight infants. The Cochrane database of systematic reviews. 2019;8(8):CD002972-CD.

47. Ballard O, Morrow AL. Human milk composition: nutrients and bioactive factors. Pediatr Clin North Am. 2013;60(1):49-74.

48. Dutta S, Singh B, Chessell L, Wilson J, Janes M, McDonald K, et al. Guidelines for Feeding Very Low Birth Weight Infants. Nutrients. 2015;7(1):423-42.

49. Crapnell TL, Rogers CE, Neil JJ, Inder TE, Woodward LJ, Pineda RG. Factors associated with feeding difficulties in the very preterm infant. Acta paediatrica (Oslo, Norway : 1992). 2013;102(12):e539-e45.

50. Battersby C, Longford N, Mandalia S, Costeloe K, Modi N. Incidence and enteral feed antecedents of severe neonatal necrotising enterocolitis across neonatal networks in England, 2012–13: a whole-population surveillance study. The Lancet Gastroenterology & Hepatology. 2017;2(1):43-51.

51. World Health Organisation, Geneva. Global Targets Tracking Tool https://www.who.int/tools/global-targets-tracking-tool. [accessed 31 January 2021]

52. Dorling J, Abbott J, Berrington J, Bosiak B, Bowler U, Boyle E, et al. Controlled Trial of Two Incremental Milk-Feeding Rates in Preterm Infants. New England Journal of Medicine. 2019;381(15):1434-43.

53. Griffiths J, Jenkins P, Vargova M, Bowler U, Juszczak E, King A, et al. Enteral lactoferrin supplementation for very preterm infants: a randomised placebo-controlled trial. The Lancet. 2019;393(10170):423-33.

54. Leaf A, Dorling J, Kempley S, McCormick K, Mannix P, Linsell L, et al. Early or Delayed Enteral Feeding for Preterm Growth-Restricted Infants: A Randomized Trial. Pediatrics. 2012;129(5):e1260-e8.

55. Morgan C, Herwitker S, Badhawi I, Hart A, Tan M, Mayes K, et al. SCAMP: standardised, concentrated, additional macronutrients, parenteral nutrition in very preterm infants: a phase IV randomised, controlled exploratory study of macronutrient intake, growth and other aspects of neonatal care. BMC Pediatrics. 2011;11(1):53.

56. Uthaya S, Liu X, Babalis D, Doré CJ, Warwick J, Bell J, et al. Nutritional Evaluation and Optimisation in Neonates: a randomized, double-blind controlled trial of amino acid regimen and intravenous lipid composition in preterm parenteral nutrition. Am J Clin Nutr. 2016;103(6):1443-52.

57. Brown JVE, Embleton ND, Harding JE, McGuire W. Multi-nutrient fortification of human milk for preterm infants. Cochrane Db Syst Rev. 2016(5).

58. Oddie SJ, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. Cochrane Db Syst Rev. 2017(8).

59. Quigley M, Embleton ND, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. The Cochrane database of systematic reviews. 2018;6(6):CD002971-CD.

60. Morgan R L-WF. An early warning scoring system for detecting developing critical illness Clinical Intensive Care. 1997;8(100).

61. Goldhill DR, McNarry AF. Physiological abnormalities in early warning scores are related to mortality in adult inpatients. Brit J Anaesth. 2004;92(6):882-4.

62. Gao H, McDonnell A, Harrison DA, Moore T, Adam S, Daly K, et al. Systematic review and evaluation of physiological track and trigger warning systems for identifying at-risk patients on the ward. Intens Care Med. 2007;33(4):667-79.

63. Gerry S, Bonnici T, Birks J, Kirtley S, Virdee PS, Watkinson PJ, et al. Early warning scores for detecting deterioration in adult hospital patients: systematic review and critical appraisal of methodology. BMJ. 2020;369:m1501.

64. Royal College of Physicians (RCP). National Early Warning Score (NEWS) 2: Standardising the assessment of acute-illness severity in the NHS. Updating report of a working party. London; 2017.

65. Mortensen N, Augustsson JH, Ulriksen J, Hinna UT, Schmolzer GM, Solevag AL. Early warning- and track and trigger systems for newborn infants: A review. J Child Health Care. 2017;21(1):112-20.

66. Paliwoda M, New K, Bogossian F. Neonatal Early Warning Tools for recognising and responding to clinical deterioration in neonates cared for in the maternity setting: A retrospective case–control study. International Journal of Nursing Studies. 2016;61:125-35.

67. Reardon H, Wilson JL, Graham B. Physiological deviations of the premature infant: with Summary of Principles of Care. AMA American Journal of Diseases of Children. 1951;81(1):99-138.

68. Paliwoda M, New K, Davies M, Bogossian F. Physiological vital sign ranges in newborns from 34 weeks gestation: A systematic review. International Journal of Nursing Studies. 2018;77:81-90.

69. British Association of Perinatal Medicine. Newborn early warning trigger and track (NEWTT): A framework for practice. 2015:17.

70. Brown SR, Martinez Garcia D, Agulnik A. Scoping Review of Pediatric Early Warning Systems (PEWS) in Resource-Limited and Humanitarian Settings. Front Pediatr. 2019;6:410-.

71. Agulnik A, Mora Robles LN, Forbes PW, Soberanis Vasquez DJ, Mack R, Antillon-Klussmann F, et al. Improved outcomes after successful implementation of a pediatric early warning system (PEWS) in a resource-limited pediatric oncology hospital. Cancer. 2017;123(15):2965-74.

72. Olson D, Preidis GA, Milazi R, Spinler JK, Lufesi N, Mwansambo C, et al. Task shifting an inpatient triage, assessment and treatment programme improves the quality of care for hospitalised Malawian children. Tropical Medicine & International Health. 2013;18(7):879-86.

73. Merriel A, Murove BT, Merriel SWD, Sibanda T, Moyo S, Crofts J. Implementation of a modified obstetric early warning system to improve the quality of obstetric care in Zimbabwe. Int J Gynecol Obstet. 2017;136(2):175-9.

74. Sheikh S, Qureshi R, Nausheen S, Sikandar R. Implementation of warning tool to improve maternal newborn health outcomes in a developing country. J Pak Med Assoc. 2017;67(1):111-5.

75. Wagura P, Wasunna A, Laving A, Wamalwa D, Ng'ang'a P. Prevalence and factors associated with preterm birth at kenyatta national hospital. BMC Pregnancy Childbirth. 2018;18(1):107.

76. Coggan D RG, Barker DJP. Epidemiology for the uninitiated. Chapter 8: Case-control and cross-sectional studies. 4th edition ed: The BMJ; 1997.

77. Attride-Stirling J. Thematic networks: an analytic tool for qualitative research. Qualitative Research 2001;1(3):385-405.

78. Farrar D, Airey R, Law G, Tuffnell D, Cattle B, Duley L. Measuring placental transfusion for term births: weighing babies with cord intact. BJOG: An International Journal of Obstetrics & Gynaecology. 2011;118(1):70-5.

79. Duley L, Dorling J, Ayers S, Oliver S, Yoxall CW, Weeks A, et al. Improving quality of care and outcome at very preterm birth: the Preterm Birth research programme, including the Cord pilot RCT. Programme Grants for Applied Research. Southampton (UK)2019.

80. Rabe H, Gyte GML, Díaz-Rossello JL, Duley L. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. Cochrane Db Syst Rev. 2019(9).

81. Rabe H, Diaz-Rossello JL, Duley L, Dowswell T. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. Cochrane Db Syst Rev. 2012(8).

82. 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 Pediatrics. 2014;14(1):135.

83. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ (Clinical research ed). 1996;312(7023):71-2.

84. Howick J C, I, Glaszio P, Greenhalgh T, Heneghan C, Liberati A, Moschetti I, Phillips B, Thornton H. The 2011 Oxford CEBM Evidence Levels of Evidence (Introductory document): Oxford Centre for Evidence-Based Medicine. 2011 https://www.cebm.net/index.aspx?o=5653.

85. Altman DG. The scandal of poor medical research. BMJ. 1994;308(6924):283-4.

86. Chalmers I. Current Controlled Trials: an opportunity to help improve the quality of clinical research. Trials. 2000;1(1):3.

87. Campbell MK, Snowdon C, Francis D, Elbourne D, McDonald AM, Knight R, et al. Recruitment to randomised trials: strategies for trial enrolment and participation study. The STEPS study. Health Technol Asses. 2007;11(48).

88. Healy P, Galvin S, Williamson PR, Treweek S, Whiting C, Maeso B, et al. Identifying trial recruitment uncertainties using a James Lind Alliance Priority Setting Partnership – the PRioRiTy (Prioritising Recruitment in Randomised Trials) study. Trials. 2018;19(1):147.

89. Sully BGO, Julious SA, Nicholl J. A reinvestigation of recruitment to randomised, controlled, multicenter trials: a review of trials funded by two UK funding agencies. Trials. 2013;14(1):166.

90. Treweek S, Lockhart P, Pitkethly M, Cook JA, Kjeldstrøm M, Johansen M, et al. Methods to improve recruitment to randomised controlled trials: Cochrane systematic review and meta-analysis. BMJ Open. 2013;3(2):e002360.

91. Brueton VC, Tierney JF, Stenning S, Meredith S, Harding S, Nazareth I, et al. Strategies to improve retention in randomised trials: a Cochrane systematic review and meta-analysis. BMJ Open. 2014;4(2):e003821.

92. Modi N. Improving the Efficiency and Impact of Clinical Research: A Game Changer for 21st Century Neonatology. Neonatology. 2020:1-4.

93. Van Calster B, Wynants L, Riley RD, van Smeden M, Collins GS. Methodology over metrics: current scientific standards are a disservice to patients and society. J Clin Epidemiol. 2021.

94. MRC-NIHR Trials Methodology Research Partnership (TMRP) https://www.methodologyhubs.mrc.ac.uk/about/tmrp/. [accessed 24 May 2020]

95. Trial Forge. https://www.trialforge.org/ [accessed 24 May 2020]

96. Clinical Trials Transformation Initiative. https://www.ctti-clinicaltrials.org/. [accessed 24 May 2020]

97. Health Research Board Trials Methodology Research Network. https://www.hrb-tmrn.ie/. [accessed 24 May 2020]

98. National Institute for Health Research. Annual report 2018-2019. 2019.

99. National Institute for Health Research. NIHR Open Data Award HRCS Health Categories Coding and apportionment. 1.4.2011-31.12.209 [accessed 24 May 2020]

100. UK Clinical Research Collaboration HRCS Online. UKCRC Health Research Classification System. 2020. https://hrcsonline.net/health-categories/ [accessed 24 May 2020]

101. Walsh V, Brown JV, Copperthwaite BR, Oddie SJ, McGuire W. Early full enteral feeding for preterm or low birth weight infants. Cochrane Db Syst Rev. 2020(12).

102. Bora R, Murthy NB. In resource limited areas complete enteral feed in stable very low birth weight infants (1000–1500 g) started within 24 h of life can improve nutritional outcome. The Journal of Maternal-Fetal & Neonatal Medicine. 2017;30(21):2572-7.

103. Chetry. A randomised control trial comparing initiation of total enteral feeds on 1st day of life with standard feeding regimen in very low birth weight infants born between 30-34 weeks gestation and 1000-1500g. E-PAS abstract. 2014;2930:442.

104. Jagoo M AN, Dabas V, Talukdar B, Kumari S, editor Early total verus gradual advancement of early nutrition in healthy preterm very low birth weight neonates in a tertiary care nursery: a randomised control trial. Pediatrics Academic Societies Annual Meeting; 2017 6-9 May 2017; San Francisco (CA).

105. Nangia S, Vadivel V, Thukral A, Saili A. Early Total Enteral Feeding versus Conventional Enteral Feeding in Stable Very-Low-Birth-Weight Infants: A Randomised Controlled Trial. Neonatology. 2019;115(3):256-62.

106. Sanghvi KP, Joshi P, Nabi F, Kabra N. Feasibility of exclusive enteral feeds from birth in VLBW infants >1200 g--an RCT. Acta Paediatr. 2013;102(7):e299-304.

107. Altman DG, Furberg CD, Grimshaw JM, Rothwell PM. Lead editorial: Trials – using the opportunities of electronic publishing to improve the reporting of randomised trials. Trials. 2006;7(1):6.

108. Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. Annals of Internal Medicine. 2013;158(3):200-7.

109. De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. CMAJ. 2004;171(6):606-7.

110. Guyatt GH, Sackett DL, Sinclair JC, Hayward R, Cook DJ, Cook RJ. Users' guides to the medical literature. IX. A method for grading health care recommendations. Evidence-Based Medicine Working Group. Jama. 1995;274(22):1800-4.

111. Neonatal Nutrition Network (N3). Available from: https://neonatalnutritionnetwork.org/. [accessed 26 April 2020]

112. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ : British Medical Journal. 2015;350:h2147.

113. Office of National Statistics, UK. Birth characteristics in England and Wales. 2018. [accessed 23 May 2020]

114. Public Health Scotland. Live births in Scottish hospitals by birthweight and gestation. https://www.isdscotland.org/Health-Topics/Maternity-and-Births/Publications/data-tables.asp?id=1285; 2016 [accessed 23 May 2020]

115. NHS England. National Cost Collection: National Schedule of NHS Costs - Year 2018-19 - NHS trust and NHS foundation trusts. 2020. https://www.england.nhs.uk/national-cost-collection/ [accessed 31 January 2021]

116. Bliss. It's not a game: the very real costs of having a premature or sick baby. 2014.

117. Arnold L, Sawyer A, Rabe H, Abbott J, Gyte G, Duley L, et al. Parents' first moments with their very preterm babies: a qualitative study. BMJ open. 2013;3(4):e002487.

118. Ionio C, Colombo C, Brazzoduro V, Mascheroni E, Confalonieri E, Castoldi F, et al. Mothers and Fathers in NICU: The Impact of Preterm Birth on Parental Distress. Eur J Psychol. 2016;12(4):604-21.

119. ICH Harmonised Guideline Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6 ICH Consensus Guideline, (2016).

120. 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(1):502.

121. Royal College of Obstetricians and Gynaecologists (RCOG). Obtaining Valid Consent to Participate in Perinatal Research Where Consent is Time Critical: Clinical Governance Advice No 6a. 2016.

122. 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(1):196.

123. 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(1):422.

124. European Union Clinical Trials Directive 2001/20/EC, (2001).

125. Vijayananthan A, Nawawi O. The importance of Good Clinical Practice guidelines and its role in clinical trials. Biomed Imaging Interv J. 2008;4(1):e5-e.

126. Magnin A, Iversen VC, Calvo G, Čečetková B, Dale O, Demlova R, et al. European survey on national training activities in clinical research. Trials. 2019;20(1):616-.

127. Townsend D, Mills N, Savović J, Donovan JL. A systematic review of training programmes for recruiters to randomised controlled trials. Trials. 2015;16(1):432.

128. Treweek S, Bevan S, Bower P, Campbell M, Christie J, Clarke M, et al. Trial Forge Guidance 1: what is a Study Within A Trial (SWAT)? Trials. 2018;19(1):139.

129. Meeting abstracts from the 5th International Clinical Trials Methodology Conference (ICTMC 2019). Trials. 2019;20(1):579.

130. Lang T, Siribaddana S. Clinical trials have gone global: is this a good thing? PLoS medicine. 2012;9(6):e1001228-e.

131. Dye C BT, Evans D, et al. The World Health Report 2013: Research for universal health coverage. 2013.

132. Franzen SRP, Chandler C, Siribaddana S, Atashili J, Angus B, Lang T. Strategies for developing sustainable health research capacity in low and middle-income countries: a prospective, qualitative study investigating the barriers and enablers to locally led clinical trial conduct in Ethiopia, Cameroon and Sri Lanka. BMJ open. 2017;7(10):e017246-e.

133. Rosala-Hallas A, Bhangu A, Blazeby J, Bowman L, Clarke M, Lang T, et al. Global health trials methodological research agenda: results from a priority setting exercise. Trials. 2018;19(1):48.

134. Dalkey N, Helmer O. An Experimental Application of the DELPHI Method to the Use of Experts. Management Science. 1963;9(3):458-67.

135. Beran D, Byass P, Gbakima A, Kahn K, Sankoh O, Tollman S, et al. Research capacity building-obligations for global health partners. The Lancet Global Health. 2017;5(6):e567-e8.

136. Adegnika AA, Amuasi JH, Basinga P, Berhanu D, Medhanyie AA, Okwaraji YB, et al. Embed capacity development within all global health research. BMJ Global Health. 2021;6(2):e004692.

137. de Beurs DP, de Groot MH, de Keijser J, Mokkenstorm J, van Duijn E, de Winter RF, et al. The effect of an e-learning supported Train-the-Trainer programme on implementation of suicide guidelines in mental health care. Journal of affective disorders. 2015;175:446-53.

138. Riley C, Spies LA, Prater L, Garner SL. Improving Neonatal Outcomes Through Global Professional Development. Advances in neonatal care: official journal of the National Association of Neonatal Nurses. 2019;19(1):56-64.

139. Yarber L, Brownson CA, Jacob RR, Baker EA, Jones E, Baumann C, et al. Evaluating a train-the-trainer approach for improving capacity for evidence-based decision making in public health. BMC Health Services Research. 2015;15(1):547.

140. Noland EW. Hawthorne Revisited. By Henry A. Landsberger. Ithaca, New York: The New York State School of Industrial and Labor Relations, 1958, 132 pp. $3.50. Social Forces. 1959;37(4):361-4.

141. Murphy GAV, Gathara D, Mwachiro J, Abuya N, Aluvaala J, English M, et al. Effective coverage of essential inpatient care for small and sick newborns in a high mortality urban setting: a cross-sectional study in Nairobi City County, Kenya. BMC Med. 2018;16(1):72.

142. Murphy GAV, Gathara D, Abuya N, Mwachiro J, Ochola S, Ayisi R, et al. What capacity exists to provide essential inpatient care to small and sick newborns in a high mortality urban setting? - A cross-sectional study in Nairobi City County, Kenya. Plos One. 2018;13(4):e0196585.

143. Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. BMC Health Services Research. 2017;17(1):88.

144. Eldridge SM, Lancaster GA, Campbell MJ, Thabane L, Hopewell S, Coleman CL, et al. Defining Feasibility and Pilot Studies in Preparation for Randomised Controlled Trials: Development of a Conceptual Framework. Plos One. 2016;11(3):e0150205-e.

145. Fogarty M, Osborn DA, Askie L, Seidler AL, Hunter K, Lui K, et al. Delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis. Am J Obstet Gynecol. 2018;218(1):1-18.

146. Yoxall CW, Ayers S, Sawyer A, Bertullies S, Thomas M, D Weeks A, et al. Providing immediate neonatal care and resuscitation at birth beside the mother: clinicians' views, a qualitative study. BMJ Open. 2015;5(9):e008494.

147. Sawyer A, Ayers S, Bertullies S, Thomas M, Weeks AD, Yoxall CW, et al. Providing immediate neonatal care and resuscitation at birth beside the mother: parents' views, a qualitative study. BMJ Open. 2015;5(9):e008495.

148. Payne L, Walker KF, Mitchell EJ. Timing of umbilical cord clamping for preterm infants in low-and-middle-income countries: A survey of current practice. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2021;264:15-20.

149. The World Health Organisation. WHO Director-General's opening remarks at the media briefing on COVID-19: 11 March 2020 https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. [accessed 4 June 2020]

150. Freedman B. Equipoise and the ethics of clinical research. N Engl J Med. 1987;317(3):141-5.

151. Seidler AL, Hunter KE, Cheyne S, Ghersi D, Berlin JA, Askie L. A guide to prospective meta-analysis. BMJ. 2019;367:l5342.

152. Fleischmann-Struzek C, Goldfarb DM, Schlattmann P, Schlapbach LJ, Reinhart K, Kissoon N. The global burden of paediatric and neonatal sepsis: a systematic review. The Lancet Respiratory Medicine. 2018;6(3):223-30.

153. Walsh V, Oddie S, McGuire W. Ethical Issues in Perinatal Clinical Research. Neonatology. 2019;116(1):52-7.

154. Owen LS, Davis PG. Parental consent and neonatal delivery room trials: walking an ethical tightrope. Archives of Disease in Childhood - Fetal and Neonatal Edition. 2021;106(2):116-7.

155. Sloss S, Dawson JA, McGrory L, Rafferty AR, Davis PG, Owen LS. Observational study of parental opinion of deferred consent for neonatal research. Archives of Disease in Childhood - Fetal and Neonatal Edition. 2020:fetalneonatal-2020-319974.

156. Duley L, Dorling J, Ayers S, Oliver S, Yoxall CW, Weeks A, et al. Improving quality of care and outcome at very preterm birth: the Preterm Birth research programme, including the Cord pilot RCT. 2019;7:8.

157. Farrell B, Kenyon S, Shakur H. Managing clinical trials. Trials. 2010;11.

158. Nafade V, Sen P, Pai M. Global health journals need to address equity, diversity and inclusion. BMJ global health. 2019;4(5):e002018-e.

159. Busse C, August E. Addressing power imbalances in global health: Pre-Publication Support Services (PREPSS) for authors in low-income and middle-income countries. BMJ Global Health. 2020;5(2):e002323.

160. De La Horra A FdCN, Baker B, Dahal P, Launois P, Maher D, Lang T. Developing an evidence-led essential research skills training curriculum. Geneva: World Health Organisation; 2022.

# APPENDICES

Pushpa-Rajah et al. Trials 2014, 15:258
http://www.trialsjournal.com/content/15/1/258

APPENDIX 1: Cord Pilot Trial published protocol

TRIALS

STUDY PROTOCOL Open Access

# Cord pilot trial - immediate versus deferred cord clamping for very preterm birth (before 32 weeks gestation): study protocol for a randomized controlled trial

Angela Pushpa-Rajah[1], Lucy Bradshaw[1], Jon Dorling[2], Gill Gyte[3], Eleanor J Mitchell[1], Jim Thornton[4], Lelia Duley[1*], on behalf of the Cord Pilot Trial Collaborative Group

## Abstract

**Background:** Preterm birth is the most important single determinant of adverse outcome in the United Kingdom; one in every 70 babies (1.4%) is born before 32 weeks (very preterm), yet these births account for over half of infant deaths.

Deferring cord clamping allows blood flow between baby and placenta to continue for a short time. This often leads to increased neonatal blood volume at birth and may allow longer for transition to the neonatal circulation. Optimal timing for clamping the cord remains uncertain, however. The Cochrane Review suggests that deferring umbilical cord clamping for preterm births may improve outcome, but larger studies reporting substantive outcomes and with long-term follow-up are needed. Studies of the physiology of placental transfusion suggest that flow in the umbilical cord at very preterm birth may continue for several minutes. This pilot trial aims to assess the feasibility of conducting a large randomised trial comparing immediate and deferred cord clamping in the UK.

**Methods/Design:** Women are eligible for the trial if they are expected to have a live birth before 32 weeks gestation. Exclusion criteria are known monochorionic twins or clinical evidence of twin-twin transfusion syndrome, triplet or higher order multiple pregnancy, and known major congenital malformation. The interventions will be cord clamping within 20 seconds compared with cord clamping after at least two minutes. For births with cord clamping after at least two minutes, initial neonatal care is at the bedside. For the pilot trial, outcomes include measures of recruitment, compliance with the intervention, retention of participants and data quality for the clinical outcomes.

Information about the trial is available to women during their antenatal care. Women considered likely to have a very preterm birth are approached for informed consent. Randomisation is close to the time of birth. Follow-up for the women is for one year, and for the children to two years of age (corrected for gestation at birth). The target sample size is 100 to 110 mother-infant pairs recruited over 12 months at eight sites.

**Trial registration:** ISRCTN21456601, registered on 28 February 2013.

**Keywords:** pilot, randomised trial, preterm birth, umbilical cord clamping, neonatal care at the bedside

* Correspondence: lelia.duley@nottingham.ac.uk
[1]Nottingham Clinical Trials Unit (NCTU), Nottingham Health Science Partners, C Floor, South Block, Queens Medical Centre, Derby Road, Nottingham NG7 2UH, UK
Full list of author information is available at the end of the article

BioMed Central

© 2014 Pushpa-Rajah et al.; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (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.

## Background

In the UK, infant mortality (deaths in the first year of life) for babies born very preterm (before 32 weeks gestation) is 144/1000 live births, compared to 1.8/1000 for those born at term (38 to 41 weeks) [1]. Very preterm birth accounts for 1.4% of live births in the UK, but 51% of infant deaths [1]. For infants born before 28 weeks, duration of hospital stay is 85 times longer than for term births, and hospital inpatient costs are £15,000 higher; for those born at 28 to 31 weeks, it is 16 times longer and £12,000, respectively [2].

Morbidity amongst children born very preterm is also high compared to those born at term. Of very preterm infants who survive, 5 to 10% develop cerebral palsy, and those without severe disability have a twofold or greater increased risk for developmental, cognitive, and behavioural difficulties [3,4]. Of babies born before 28 weeks, a quarter of survivors have neurosensory disability, such as cerebral palsy, severe developmental delay, blindness or deafness [5]. Surviving children have higher levels of dysfunction in a range of measures of cognition, behaviour and functioning [5], impairments that persist into adolescence and early adulthood [6,7]. Teenagers and young adults born very preterm also report poorer physical abilities and more chronic ill health and functional limitation than their peers born at term, although self-reporting of health-related quality of life is similar [8,9]. Prematurity and its sequelae have an enormous negative psychosocial and emotional impact on parents and families [5,10].

### Placental transfusion

Placental transfusion is the transfer of blood between the placenta and the baby at birth. For term births, this blood flow is usually complete by two minutes, but may continue for up to five minutes. The mean volume of placental transfusion for term births is 100 ml, which is around 29 ml/kg birth weight and 36% of neonatal blood volume at birth [11]. For preterm births, placental transfusion may take longer [12], and may be incomplete if the cord is clamped within 30 to 90 seconds [13]. This seems logical, as at term, two-thirds of the feto-placental circulation is in the infant, whilst below 30 weeks gestation, a greater proportion is in the placenta [14]. Also, the umbilical vein is smaller than at term, and uterine contraction less efficient. Cord clamping before placental transfusion is complete may restrict neonatal blood volume and red cell mass, and interrupt transition from the fetal to neonatal circulation.

As the baby is born, umbilical circulation slows and pulmonary vascular resistance falls, rapidly increasing pulmonary blood flow. This is the beginning of transition from the fetal to the neonatal circulation. For infants born too early, the mechanisms for these circulatory changes may not be fully developed and so may take longer. Continued flow in the umbilical vein and arteries at birth may be part of the physiological mechanisms assisting the baby as it makes the transition from fetal to neonatal circulation. Restricting this flow by immediate cord clamping may limit the baby's ability to deal with this transition. If there is insufficient circulating blood volume to fill the expanding pulmonary vasculature, an infant may compensate by reducing flow to the peripheral circulation and/or to organs such as the kidney. Whilst most healthy babies at term may adapt without major consequences, for those born preterm or with their cardio-respiratory circulation already impaired, there may be substantive consequences.

Over 20 years ago it was first suggested that restricting placental transfusion by immediate clamping for preterm babies might increase the risk of intraventricular haemorrhage [15]. Possible mechanisms for this increase were suggested to be hypovolaemia, and/or increased fluctuation in blood pressure following the abrupt transition to a neonatal circulation.

Cord milking (pinching the cord close to the mother and running the fingers towards the baby, usually several times) has been suggested for preterm births as a means to increase neonatal blood volume without deferring cord clamping [16]. Cord milking over-rides the infant's physiological control of its own blood volume and blood pressure, however, and disrupts umbilical blood flow.

#### Systematic review: immediate versus deferred cord clamping

The Cochrane Review of timing of cord clamping for preterm births [17] includes 15 trials, with 738 infants recruited between 24 and 36 weeks gestation. Immediate cord clamping ranged from 5 to 20 seconds, although several studies did not state the duration. Deferred clamping ranged from 31 to 120 seconds for births before 34 weeks; one study recruiting between 34 weeks and 36 weeks gestation used 180 seconds. The few studies that reported a rationale for how long to defer clamping said it had been a balance between allowing placental transfusion, and what was perceived as an acceptable delay in neonatal care. One small trial (40 mother-infant pairs) compared cord milking with immediate cord clamping [16]. Many outcomes are reported by only a few studies, so there is potential for reporting bias.

No trials reported outcome for the women. Primary outcomes for the infants were death, death or neurodisability at two years of age, ultrasound diagnosis of grade 3 or 4 intraventricular haemorrhage, and periventricular leukomalacia. Death before discharge from hospital was reported in 13 trials, and there was no clear difference between the groups (Table 1). No studies have reported death or neurodisability at two years of age. There was no clear difference between the

**Table 1 Immediate versus deferred cord clamping for preterm births: effects for infants**

| Outcome | Number of trials | Number of participants | Risk ratio | 95% confidence interval |
|---|---|---|---|---|
| Death | 13 | 668 | 0.63 | 0.31 to 1.28 |
| intraventricular haemorrhage | | | | |
| any (grade 1 to 4)) | 10 | 539 | 0.59 | 0.41 to 0.85 |
| severe (grade 3 or 4) | 6 | 305 | 0.68 | 0.23 to 1.96 |
| periventricular leukomalacia | 2 | 71 | 1.02 | -0.52 to 5.56 |
| temperature on SCBU admission (°C)[a] | 3 | 143 | 0.14[a] | -0.03 to 0.31[a] |
| Transfusion | | | | |
| for anaemia | 7 | 392 | 0.61 | 0.46 to 0.81 |
| for hypotension | 4 | 130 | 0.52 | 0.24 to 1.11 |
| number of transfusions[a] | 5 | 210 | -1.26[a] | -1.87 to −0.64[a] |
| mean arterial pressure[a] | | | | |
| at birth | 2 | 97 | 3.52[a] | 0.60 to 6.45[a] |
| at 4 hours | 2 | 111 | 2.49[a] | 0.26 to 4.72[a] |
| inotropes for low blood pressure | 4 | 158 | 0.42 | 0.23 to 0.77 |
| necrotising enterocolitis | 5 | 241 | 0.62 | 0.43 to 0.90 |
| serum bilirubin peak[a] | 7 | 320 | 15.01[a] | 5.62 to 24.40[a] |
| jaundice requiring phototherapy | 3 | 180 | 1.21 | 0.94 to 1.55 |
| oxygen supplementation at 36 weeks | 5 | 209 | 0.69 | 0.42 to 1.13 |

[a]mean difference.
SCBU, special care baby unit.

groups in either severe intraventricular haemorrhage or periventricular leukomalacia.

Infants allocated to deferred cord clamping had fewer diagnoses of any intraventricular haemorrhage than those allocated to immediate clamping (Table 1). There was no clear difference between the groups in the three trials reporting temperature on admission to the special care baby unit. Deferred cord clamping was associated with less transfusion for anaemia, but there was no clear difference in transfusion for hypotension. Deferred clamping was also associated with higher mean arterial blood pressures at birth and at four hours of age, and less requirement for inotropes. It was also associated with a reduction in the risk of necrotising enterocolitis. Infants allocated deferred cord clamping had higher serum bilirubin, but there was no clear difference in jaundice requiring phototherapy in the three trials reporting this outcome. There was no clear difference between the groups in oxygen requirement at 36 weeks postmenstrual age.

Follow-up at age seven months (corrected for gestation at birth) was reported for one study, which recruited 72 infants. Of these, five died before seven months and nine were lost to follow-up. There was no overall difference between the groups in Bayley Scales of Infant Development-II.

The review concludes that 'to reliably compare strategies for influencing placental transfusion we need large high-quality trials, with sufficient power to reliably assess clinically relevant differences in important outcomes' [17].

### Initial care at birth for very preterm infants: at the bedside or at the room side

Initial neonatal care and stabilisation takes place on a resuscitaire. Traditionally, this is at the side of the room, or in an adjacent room. Disadvantages of these locations are that they necessitate immediate cord clamping, and that often the woman and her partner are not able to see or touch their baby at birth [18,19]. If cord clamping is deferred this should not necessarily mean that neonatal care is also deferred. Strategies for providing neonatal care and stabilisation of the baby at the bedside have now been developed. Parents' views following initial care at the bedside have been positive [20]. Evaluation of the views of clinicians is also positive, although there are initial issues around training, practical arrangements for preparing and moving the equipment, and making space at the bedside [20]. The experience of providing initial neonatal care at the bedside has been positive, and it is now part of standard care in some hospitals.

Providing neonatal care for very premature infants at the bedside allows the woman and her partner to share the first moments of their child's life [21,22], if they wish to, and is therefore potentially a more family-centred approach. 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 parents [10] and is an NHS priority [23]. Providing neonatal care at the bedside has parallels with family presence during resuscitation of adults and children, which is preferred by families and appears to be beneficial [24-28].

### Current practice for timing of cord clamping at very preterm births

In the UK, 57% of obstetricians report clamping the cord within 20 seconds for very preterm births [29]. Just 15% of midwives and 5% of obstetricians reported that they routinely record when the cord was clamped in the medical notes. Guidelines for care during the third stage of labour make various recommendations, and it is often not clear how these should be applied to very preterm babies, many of whom will require neonatal care at birth [30-32].

### Why a trial is needed now

Current evidence is that for very preterm births, timing of cord clamping, and other strategies to influence placental transfusion, may improve outcome at hospital. But the trials are small, and overall there is high risk of bias. The effects on substantive outcomes and long-term neurodevelopment remain uncertain. Assessing alternative strategies for timing of cord clamping has been identified as a research priority by service users [33], researchers [17,34,35], obstetricians [29], midwives [29], 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, unpublished), NICE [30,36], and the Royal College of Obstetricians and Gynaecologists [21].

Our primary hypothesis is that for children born before 32 weeks gestation immediate cord clamping is associated with higher death or neurosensory disability at two years of age (corrected for gestation at birth) than deferred cord clamping. A trial to test this hypothesis would need to be large and multicentre. This protocol is for a pilot trial to assess the feasibility such a study.

## Methods/Design

This study is a pragmatic multicentre pilot randomised trial comparing alternative strategies for cord clamping at very preterm birth.

### Participants

Women are eligible for the study if they are expected to have a live birth before 32 weeks gestation, regardless of mode of birth or whether cephalic or breech presentation.

Exclusion criteria are monochorionic twins (from an ultrasound scan) or clinical evidence of twin-twin transfusion syndrome, triplets or higher order multiple pregnancy, or known major congenital malformation.

### Interventions

There is no consensus about the definition of immediate or deferred cord clamping, or about the optimal timing of cord clamping for very preterm birth. We have chosen our interventions based on current practice [29], the interventions reported in the trials included in the Cochrane review [17], consultation with neonatologists, and our work measuring the volume and duration of placental transfusion [11,37].

The interventions are cord clamping within 20 seconds or cord clamping after at least two minutes.

For both groups, while the cord is intact, the baby should be at the level of the placenta, and should not be lifted above the level of the mothers' abdomen. All other aspects of care are at the discretion of the attending clinicians, including administration of a prophylactic uterotonic drug.

For deferred cord clamping, care for the baby is provided at the mother's bedside. For immediate clamping care is either at the bedside or at the side of the room, at the discretion of the attending clinicians. In both cases the baby receives the same care at birth, just in different places. Neonatal care is based on local unit policy and consistent with newborn life support guidelines [32,38]. Standard equipment is used for both groups according to local practice, including plastic sheets or bags (depending on gestation and local practice), towels and any other equipment such as hats, warming mattress or overhead heaters, and saturation monitors.

For neonatal care at the bedside, babies are placed onto a firm surface next to the mother's bed or to the operating theatre table, with easy access to necessary equipment. This is achieved either by moving the conventional resuscitaire alongside the woman's bed [39] or by using a small specialised mobile trolley (for example the BASICS trolley) [40].

### Outcome measures

To assess the feasibility of a large multicentre trial, the outcomes for this pilot trial are as follows:

1. number of women recruited in each hospital;
2. proportion of potentially eligible women recruited;
3. reasons for non-recruitment (medical, parental, logistic, other);
4. spectrum of gestational age and neonatal outcome among recruits;
5. compliance with the trial interventions, and reasons for non-compliance;
6. completeness of data collection for main outcomes;
7. views of women and their partners on recruitment, randomisation and the interventions' and
8. proportion lost to follow.

Clinical outcomes for infants and women likely to be used in the main trial will also be collected. These are death or neurosensory disability at age two years (corrected for gestation at birth) as primary outcome. Secondary outcomes for the baby are death, blood transfusion, intraventricular haemorrhage (grade 3 to 4), periventricular leukomalacia, hypothermia, respiratory distress syndrome, ventilation, necrotizing enterocolitis, treatment for hyperbilirubinemia, duration of hospital stay and neurosensory delay at age 2 years (corrected for gestation at birth).

Secondary outcomes for the women are postpartum haemorrhage, infection, depression, and breast feeding/expressing.

Outcome for the women is assessed at discharge from hospital, by a self-completed (either handed out in hospital or sent by post) questionnaire at four to eight weeks, and by self-completed postal questionnaire at one year. For the babies, outcome is assessed at 36 weeks postmenstrual age, at discharge from hospital, and at age 2 years (corrected for gestation at birth). This assessment at age two includes an Ages and Stages Questionnaire [41], the PARCA-R (Parent Report of Children's Abilities-revised) questionnaire [42], and a Bayley Scales of Infant Development III [43]. This Bayley assessment is blind to the allocated group.

### Sample size

Eight large maternity hospitals are included in this pilot trial, with an estimated total of 43,600 live births per year (5 to 6,000 average annual live births per unit). In the UK, 1.4% of live births are before 32 weeks gestation [1]; we, therefore, expect 610 potentially eligible births and anticipate recruitment of between 100 and 110 women (16 to 18% accrual) over 12 months.

### Randomisation

Randomisation is in a 1:1 ratio, stratified by hospital. Sequence generation uses computer-generated, random permutated balanced blocks of randomly varying size, created by the Nottingham Clinical Trials Unit (NCTU) in accordance with their standard operating procedure. Concealment of allocation is by sealed consecutively numbered opaque envelopes. These envelopes are held in a ring binder randomisation folder, which is kept in a secure place that is easily accessible for the delivery suite. Envelopes are removed in consecutive order by tearing the next one out of the randomisation folder at the punch holes. At the time of removing the folder, whoever takes it initials and dates the folder log. On the front of each envelope is a reminder to check eligibility, and a label to be completed *before* the envelope is opened. This label records the date, time, woman's initials, her date of birth, and her gestation. Once this information is complete, the woman is considered to be randomised, even if the envelope is not opened.

The envelopes contain a yellow card stating when the cord should be clamped; stickers for the woman and baby's medical notes (indicating they are in the trial); and a Birth Record (plus a second to be used for twin births) to be completed at the time of birth and filed in the baby's medical notes. The Birth Record asks for information about care during the third stage of labour and initial neonatal care. Each delivery suite has a Cord Pilot Trial secure mailbox. After each randomisation, the randomisation envelope and the yellow allocation card are posted into this mailbox. The mailbox is checked daily by the research midwife/nurse. Details from the randomisation envelope are then entered into the online randomisation log maintained by the NCTU, and the envelope is filed with the woman's Case Report Form.

If an envelope is taken from the randomisation folder but not used, the discarded envelope is posted unopened into the Cord Pilot Trial mailbox. These unused and discarded envelopes are notified to NCTU, and the envelopes returned to NCTU. All randomisation envelopes, both opened and unopened, are accounted for by the NCTU. Envelopes used out of order or tampered with will be recorded and reported.

### Trial entry and recruitment

General information about the trial, such as summary information leaflets and study posters, is available on antenatal clinics and antenatal wards. These introduce the trial and explain how women can access more information if they wish. To avoid causing unnecessary anxiety this information makes clear that only around 1 in 70 women give birth before 32 weeks gestation. Women who would like more information are offered the parent information sheet, which is more detailed.

Women in the antenatal clinics, antenatal wards or a high risk antenatal clinic, who are at a high risk of having a birth at less than 32 weeks gestation are offered the parent information sheet. They have an opportunity to discuss the study with their family and partner. If a woman decides to participate in the trial, written informed consent is taken. Whenever possible, at least 12 hours is given for the woman to consider participating in the trial. If a woman does not participate, this decision will not influence her clinical care.

If a woman who has consented to participate in the trial is in established labour, or is being prepared for a caesarean section, her gestation and willingness to participate are checked. If she still meets the inclusion criteria she is randomised (Figure 1). Randomisation near to the time of birth should ensure that women enrolled into the trial give birth before 32 weeks gestation. However, if a woman is randomised but does not give

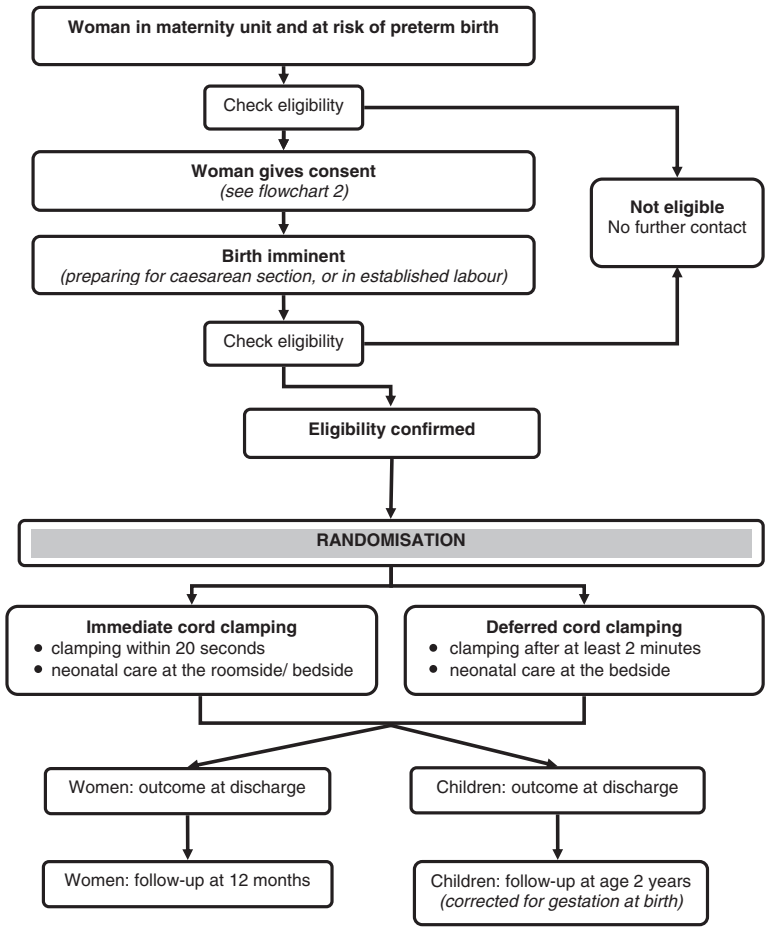



**Figure 1 Participant flow.** This figure shows the participants' pathway through the trial.

birth until after 32 weeks gestation, she remains in the trial.

If there is insufficient time to gain written consent before randomisation, and the attending clinician feels it is appropriate, these women will be asked verbally if they would like to participate in the trial. After a brief summary of the study as well an opportunity to ask questions, the woman is asked if she would like to participate in the trial. If she agrees, she is then randomised (Figure 2). This is recorded in her medical notes, and the clinician taking consent completes a form. Before discharge from hospital, the woman is approached for written consent to use her and her baby's data, and for participation in follow-up. If a woman declines oral assent, she is not randomised.

This process for oral assent was developed in discussion with the National Childbirth Trust (NCT) and Bliss, the special care baby charity. It is also in line with recommendations on valid consent for research while in labour from the Royal College of Obstetricians and Gynaecologists [44].

### Follow-up of participants

At discharge from hospital, outcome data for the women and babies are collected from the medical notes, along with contact details to facilitate follow-up. Women are asked to complete a questionnaire at four to eight weeks. If the baby is still in hospital this is given to them by the research midwife/nurse, or if the baby is no longer in hospital, it is posted to their home address. The questionnaire includes the Hospital Anxiety and Depression Scale (HADS) [45], questions asking the women about their and her babies' care and their experience in hospital, and asks women about their experience of participating in the CORD Pilot trial. There is also a section asking women about their baby's feeding (removed if the baby died). When the child is one year old, a birthday card is sent along with a second questionnaire asking the same questions. A stamped addressed envelope is provided to return questionnaires.

When the baby is 2 years old (corrected for gestation at birth), the parents/carers are contacted to arrange a neurodevelopment assessment for the child, using the

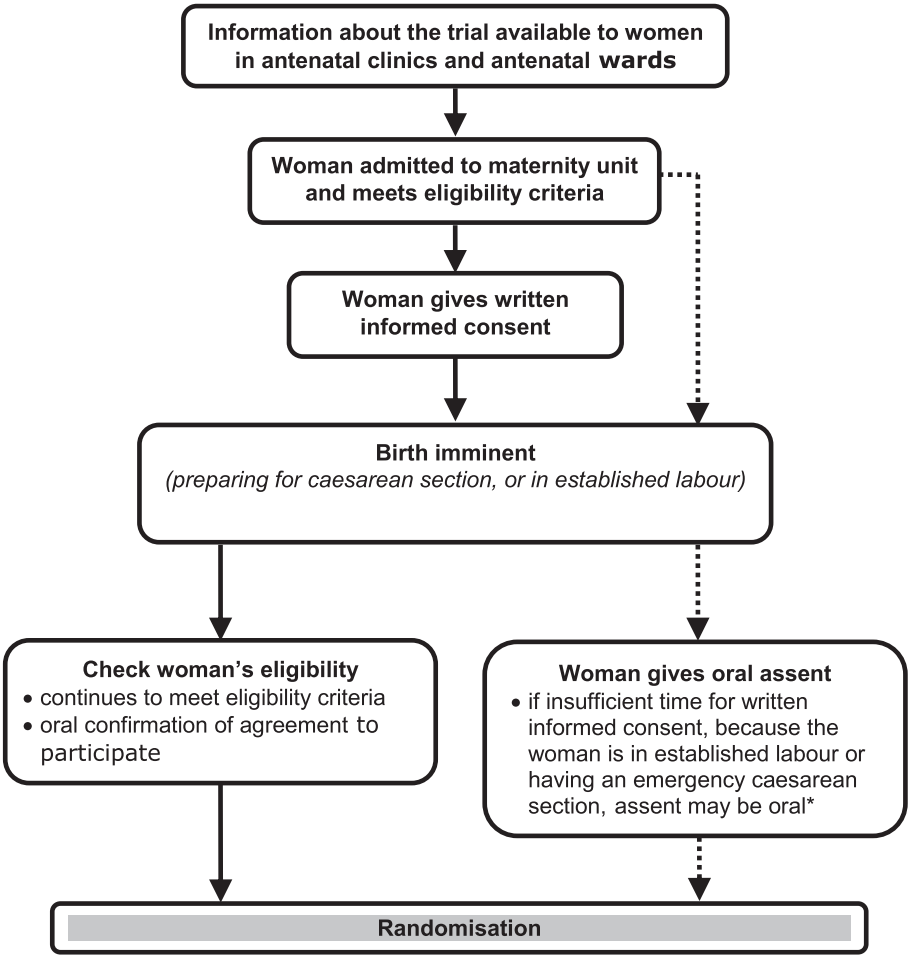



**Figure 2 Consent pathways.** This figure shows the two different consent pathways used within the trial.

Bayley Scales of Infant Development III. Four weeks before this assessment, the family are sent the Ages and Stages Questionnaire by post [41], and asked to complete and return this before the assessment (using a prepaid envelope). The assessment is by a trained practitioner either at home or in a clinic, whichever is preferred by the family. During the visit, the parents are asked to complete the Parent Report of Children's Abilities - Revised (PARCA-R) [42].

For all questionnaires, if there is no response a reminder is sent after two weeks. If there is still no response after another two weeks, the coordinating centre telephone to offer the opportunity to complete the questionnaire over the telephone. If no telephone number is available another postal reminder is sent. Stamped addressed envelopes are provided for all questionnaires.

Women and babies are also 'flagged' with the Health and Social Care Information Centre, through the Medical Research Information Service. This allows identification of deaths after discharge from hospital and movement out of the NHS, information that helps prevent inappropriate

contact with the family and also reduces losses to follow-up.

### Adverse events

This study includes babies who are high risk for adverse outcomes, and so adverse events that could be influenced by the trial interventions are being collected as outcomes for the study.

Although neonatal or infant death is one of the outcomes for this study, death before discharge from hospital is considered as a serious adverse event (SAE). Any unexpected and serious adverse event, for either the woman or the baby, considered to be potentially related to the study interventions will also be reported as a SAE. Any SAE that is not a death will be followed until there is resolution or the event is considered stable.

All SAEs are reported to the Chief Investigator. The Chief Investigator will submit, every six months for the duration of recruitment to the trial or on request, a safety report to the Data Monitoring Committee, which will include all reported SAEs.

### Site set-up and training

Site set-up and training includes a range of strategies, such as collaborators meetings, site initiation visits, video and simulations, slide sets, and site monitoring visits. Training in providing neonatal care at the bedside is provided for all clinical staff, including neonatologists, obstetricians, and midwives.

### Feasibility criteria for progression to the main trial

The final decision about progression to the main trial will be made by the independent Trial Steering Committee, in consultation with the Data Monitoring Committee. The pre-specified criteria for feasibility are based on:

1. recruitment of at least 50% of target at 12 months. But, if recruitment is below 80% of target, there will need to be clear and achievable strategies for overcoming identified barriers thereby improving recruitment.
2. at least 80% of women in each group receiving the intervention to which they had been allocated during the final six months of recruitment (as compliance may be lower in the early stages of a feasibility study). For a proportion of births it is anticipated that the cord will be too short to allow initial care at the bedside, and so for these infants in the deferred arm cord clamping may be before 2 minutes. For example, in a study requiring babies to be placed on weighing scales with the cord intact, of 33 term births for 5 (15%) the cord was too short to allow the baby to be placed on the scales [11]. For the deferred arm, feasibility criteria will be considered to be met if 80% of infants with adequate cord length had cord clamping after at least 2 minutes.
3. the difference between the two groups in median time to cord clamping is at least 45 seconds.

### Data management and trial monitoring

Data are entered as they accumulate into a trial specific database developed and maintained by the NCTU. Access to the database will be restricted and secure. All trial data are anonymised by use of unique participant trial numbers. Data quality is checked using criteria for out-of-range and consistency, and checks for conflicting data within and between data collections forms. Missing data and data queries are referred promptly back to the recruiting site for clarification.

For the follow-up phase, identifiable information about participants will be held in a separate database to the trial data. Access to this information will be restricted to those involved in the follow up phase, as authorised by the Chief Investigator.

Trial monitoring is by central statistical monitoring combined with site visits. Central statistical monitoring is used to monitor patterns of recruitment at sites, reasons for non-recruitment of potentially eligible women, characteristics of women recruited, gestation at recruitment, and time of recruitment. It is also to assess compliance with the protocol, such as eligibility and compliance with the trial interventions. Each site has at least one monitoring visit; timing of this visit is influenced by recruitment, data quality, and compliance with the protocol and study procedures.

The Chief Investigator is the custodian of the data. The trial is conducted in compliance with the current revision of the Declaration of Helsinki (last amendment October 2008), with relevant regulations, and with MRC Guidelines for Good Clinical Practice in Clinical Trials, [46] which is based on International Conference on Harmonisation (ICH) guidelines for good clinical practice (GCP) (CPMP/ICH/135/95) July 1996.

### Data analysis

Eligibility, recruitment and retention through the study will be presented in a CONSORT flow diagram to show the number of eligible women, the number approached for participation (split according to written consent and oral assent), the number of women (and their babies) randomised into the two groups, and completion of follow-up of the outcomes for the main study. Reasons for eligible women not providing consent and for those who have given consent not being randomised will be described, when known. The time between oral assent and randomisation will be analysed to check that this method of consent is being used appropriately. Reasons

for loss to follow-up after discharge from hospital will also be presented, where known.

Baseline characteristics of the women (age, previous pregnancy history, reason for preterm birth) and the baby at birth (gestational age at birth, baby gender and birth weight) will be presented descriptively split by allocated group. Continuous data will be summarised in terms of the mean, standard deviation and/or median, lower and upper quartiles, minimum and maximum with the number of observations. Categorical data will be summarised in terms of frequency counts and percentages. The number of missing values will be presented where applicable.

Compliance with the intervention will be assessed by summarising the median time to cord clamping in the two groups, the difference in median time to cord clamping between the two groups, and the proportion of women receiving the allocated intervention. Reasons for non-compliance with the allocated intervention will be tabulated. Compliance will be assessed for the first six months of recruitment and for the second six months, as our hypothesis is that compliance will improve over time. The number (and percentage) of babies receiving bedside or room side care and the type of care given in each location in the two groups will be described.

Outcomes will be described for women at discharge, at four to eight weeks, at 1 year, and for babies at discharge and at 2 years. Any unexpected serious adverse events for either the women or the baby will also be described. This description of outcome will be for both groups combined, not by allocated group. If feasibility is demonstrated, and the trial progresses to a main study outcome by allocated group will remain confidential to the Data Monitoring Committee. It would then contribute to the sample size for the main trial.

The woman's views about whether participation in the Cord Pilot Trial will be tabulated overall, and split by characteristics that may influence the women's views about participating in the study. These characteristics are prespecified as allocated group, death of the baby, whether oral assent was used, maternal age at recruitment, gestation at recruitment less than 30 weeks, severe post-partum haemorrhage, postnatal depression, length of stay in a special care baby unit longer than six weeks and whether participants needed a reminder to complete the questionnaires.

### Archiving

Data and all appropriate study documentation will be stored for a minimum of 10 years after completion of the trial, including the follow-up period. The trial master file and trial documents held by the Chief Investigator on behalf of the sponsor will be archived in secure archive facilities at Nottingham University Hospitals NHS Trust. This archive will include all trial databases and associated meta-data encryption codes.

### Trial management

Day-to-day management of the trial is the responsibility of the Trial Management Group (TMG), which meets at least every two months and more often if required. Trial oversight is by an independent Trial Steering Committee. Safety of trial participants is monitored an independent Data Monitoring Committee, who report to the Trial Steering Committee. Trial coordination is through the NCTU.

### Ethics approval

Approval for this study was granted by the Nottingham 2 Research Ethics Committee (NRES reference 12/EM/0283).

### Sponsor

Nottingham University Hospitals NHS Trust acts as the main sponsor for this trial. Delegated responsibilities are assigned to the NHS trusts taking part. Standard NHS Indemnity applies.

## Discussion

Recruitment to the Cord Pilot Trial began in March 2013 and will close on 28 February 2014. Assessment of the feasibility outcomes when recruitment is complete will inform the decision about progressing to a large multicentre trial in the UK.

## Trial status

Recruitment to the Cord Pilot Trial is ongoing. The feasibility assessment is based on recruitment from 1 March 2013 to 28 February 2014. Recruitment is being continued in pilot sites whilst main trial funding is sought.

#### Abbreviations

ASQ: Ages and Stages Questionnaire; HADS: Hospital Anxiety and Depression Scale; ICH GCP: International Conference on Harmonisation for good clinical practice; MRC: Medical Research Council; NCT: National Childbirth Trust; NCTU: Nottingham Clinical Trials Unit; NIHR: National Institute of Health Research; NRES: National Research Ethics Service; PARCA-R: Parent Report of Children's Abilities-revised; RCOG: Royal College of Obstetricians and Gynaecologists; SAE: serious adverse event; TMG: Trial Management Group.

#### Competing interests

The authors declare that they have no competing interests.

#### Authors' contributions

LD conceived the study and is the chief investigator and project lead. JD, JT, GG made substantial contributions to the conception and design of the work, revised this work critically for important intellectual content and approved the final version to be published. LB will provide statistical support to the study and conduct the data analysis. LD and LB drafted this work, revised it critically for important intellectual content and approved the final version to be published. AP is the Trial Manager and EJM is the Senior Trial Manager. Both AP and EJM will be responsible for the acquisition and interpretation of data for the trial, and both have drafted this work and approved the final version to be published. LD, GG and JT are grant holders, and JD is a collaborator on the grant application. All authors read and approved the final manuscript.

#### Acknowledgements

Thanks to Gill Bumphrey and Diane Whitham for their invaluable help in developing the randomisation system.

**Funding**
The Cord Pilot Trial is funded by the National Institute of Health Research (Reference RPPG060910107): Improving quality of care and outcome at very preterm birth. This paper presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research funding scheme (RP-PG-0609-10107). The views expressed in this paper are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

**Source of funding for authors**
A Pushpa-Rajah, L Bradshaw, J Dorling, EJ Mitchell, J Thornton J and L Duley are all employed by the University of Nottingham. External funding for all authors on this project is funded by the National Institute of Health Research (NIHR) Improving quality of care and outcome at very preterm birth, under the Programme Grants for Applied Research funding scheme (RP-PG-0609-10107).

**Cord pilot trial collaborative group**
*NCTU co-ordinating team:* Lelia Duley (chief investigator), Lucy Bradshaw (statistician), Eleanor Mitchell (senior trial manager), Lucinda Murphy (data manager), Angela Pushpa-Rajah (trial manager), and Keith Whitaker (database programmer).
*Trial management group:* Lelia Duley, Lucy Bradshaw, Jon Dorling, Eleanor Mitchell, and Angela Pushpa-Rajah (chair).
*Trial Steering Committee*: Mike Clarke (chair), Richard Cooke, Sara Kenyon, Philip Steer, Liz Goddard, and Kate Branchett.
*Data Monitoring Committee*: Doug Altman (chair), Declan Devane, Andrew Shennan, and Ben Stenson.
*Protocol development group:* Lelia Duley (chair), Jon Dorling, Alex Erven, David Field, Gill Gyte, Sam Oddie, and Jim Thornton.
Collaborating centres:
*Aberdeen Maternity Hospital*:
Medhat Ezzat, Annie Robertson, and Donna Nelson.
*Bradford Royal Infirmary*:
Sam Oddie and Kelly Young.
*City Hospital, Nottingham:*
Bernard Schoonakker, Carys Smith, and Dush Batra.
*Homerton University Hospital, London*:
Narendra Aladengady, Amit Kanhari, and Elaine Van Der Pool.
*Leicester Royal Infirmary*:
Joe Fawke, Marie Hubbard, and Tommy Mousa.
*Liverpool Women's Hospital*:
Bill Yoxall, Margaret Peake, and Andrew Weeks.
*New Cross Hospital, Wolverhampton*:
David Churchill, Melanie Sutcliffe, and Tilley Pillay.
*Queens Medical Centre, Nottingham*:
Jon Dorling, Gill Kirkwood, and Yvonne Hooton.

**Author details**
[1]Nottingham Clinical Trials Unit (NCTU), Nottingham Health Science Partners, C Floor, South Block, Queens Medical Centre, Derby Road, Nottingham NG7 2UH, UK. [2]Neonatal Unit, Queens Medical Centre, Derby Road, Nottingham NG7 2UH, UK. [3]National Childbirth Trust, Alexandra House, Oldham Terrace, Acton, London W3 6NH, UK. [4]Maternity, Nottingham City Hospital, Hucknall Road, Nottingham NG5 1 PB, UK.

Received: 27 February 2014 Accepted: 28 May 2014
Published: 30 June 2014

**References**

1. Moser K, Macfarlane A, Chow YH, Hilder L, Dattani N: **Introducing new data on gestation-specific infant mortality among babies born in 2005 in England and Wales.** *Health statistics Q Off National Statistics* 2007, **35:**13–27.
2. Petrou S, Mehta Z, Hockley C, Cook-Mozaffari P, Henderson J, Goldacre M: **The impact of preterm birth on hospital inpatient admissions and costs during the first 5 years of life.** *Pediatrics* 2003, **112:**1290–1297.
3. Zeitlin J, Draper ES, Kollee L, Milligan D, Boerch K, Agostino R, Gortner L, Van Reempts P, Chabernaud JL, Gadzinowski J, Bréart G, Papiernik E, and the MOSAIC research group: **Differences in rates and short-term outcome of live births before 32 weeks of gestation in Europe in 2003: results from the MOSAIC cohort.** *Pediatrics* 2008, **121:**e936–e944.
4. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJS: **Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis.** *JAMA* 2002, **288:**728–737.
5. Saigal S, Doyle LW: **An overview of mortality and sequelae of preterm birth from infancy to adulthood.** *Lancet* 2008, **371:**261–269.
6. Aarnoudse-Moens CS, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J: **Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children.** *Pediatrics* 2009, **124:**717–728.
7. Anderson P, Doyle LW: **Neurobehavioral outcomes of school-age children born extremely low birth weight or very preterm in the 1990s.** *JAMA* 2003, **289:**3264–3272.
8. Saigal S, Stoskopf B, Boyle M, Paneth N, Pinelli J, Streiner D, Goddeeris J: **Comparison of current health, functional limitations, and health care use of young adults who were born with extremely low birth weight and normal birth weight.** *Pediatrics* 2007, **119:**e562–e573.
9. Saigal S, Stoskopf B, Pinelli J, Streiner D, Hoult L, Paneth N, Goddeeris J: **Self-perceived health-related quality of life of former extremely low birth weight infants at young adulthood.** *Pediatrics* 2006, **118:**1140–1148.
10. POPPY Steering Group: *Family-Centred Care In Neonatal Units. A Summary Of Research Results And Recommendations From The POPPY Project.* London: NCT; 2009.
11. Farrar D, Airey R, Law GR, Tuffnell D, Cattle B, Duley L: **Measuring placental transfusion for term births: weighing babies with cord intact.** *BJOG Int J Obstetrics Gynaecol* 2011, **118:**70–75.
12. Saigal S, O'Neill A, Surainder Y, Chua LB, Usher R: **Placental transfusion and hyperbilirubinemia in the premature.** *Pediatrics* 1972, **49:**406–419.
13. Aladangady N, McHugh S, Aitchison TC, Wardrop CA, Holland BM: **Infants' blood volume in a controlled trial of placental transfusion at preterm delivery.** *Pediatrics* 2006, **117:**93–98.
14. Dawes GS: **Chapter 13**. In *Foetal and Neonatal Physiology: A Comparative Study of the Changes at Birth.* Chicago: Year Book Medical Publishers; 1968.
15. Hofmeyr GJ, Bolton KD, Bowen DC, Govan JJ: **Periventricular/ intraventricular haemorrhage and umbilical cord clamping. Findings and hypothesis.** *South African Med J* 1988, **73:**104–106.
16. Hosono S, Mugishima H, Fujita H, Hosono A, Minato M, Okada T, Takahashi S, Harada K: **Umbilical cord milking reduces the need for red cell transfusions and improves neonatal adaptation in infants born at less than 29 weeks' gestation: a randomised controlled trial.** *Arch Dis Child Fetal Neonatal Ed* 2008, **93:**F14–F19.
17. Rabe H, Diaz-Rossello JL, Duley L, Dowswell T: **Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes.** *Cochrane Database Syst Rev* 2012, **8:**CD003248.
18. Arnold L, Sawyer A, Rabe H, Abbott J, Gyte G, Duley L, Ayers S: **Parents' first moments with their very preterm babies: a qualitative study.** *BMJ Open* 2013, **3:**e002487.
19. Sawyer A, Rabe H, Abbott J, Gyte G, Duley L, Ayers S: **Parents' experiences and satisfaction with care during the birth of their very preterm baby: a qualitative study.** *BJOG* 2013, **120:**637–643.
20. Thomas M, Weeks A, Duley L, Yoxall B: **Providing newborn resuscitation at the mother's bedside: assessing the safety, usability and acceptability of a mobile trolley.** *BMC Pediatr* 2014, **14:**135.
21. Royal College of Obstetricians and Gynaecologists (RCOG) Scientific Advisory Committee: **Clamping of the umbilical cord and placental transfusion.** London, UK: 2009. http://www.rcog.org.uk/files/rcog-corp/uploaded-files/SIP_No_14.pdf.
22. Wyllie J, Niermeyer S: **The role of resuscitation drugs and placental transfusion in the delivery room management of newborn infants.** *Semin Fetal Neonatal Med* 2008, **13:**416–423.
23. Department of Health: *Toolkit For High Quality Neonatal Services.* London, UK: Department of Health; 2009.
24. Critchell CD, Marik PE: **Should family members be present during cardiopulmonary resuscitation? A review of the literature.** *Am J Hospice Palliative care* 2007, **24:**311–317.
25. Boie ET, Moore GP, Brummett C, Nelson DR: **Do parents want to be present during invasive procedures performed on their children in the emergency department? A survey of 400 parents.** *Ann Emerg Med* 1999, **34:**70–74.
26. Robinson SM, Mackenzie-Ross S, Campbell Hewson GL, Egleston CV, Prevost AT: **Psychological effect of witnessed resuscitation on bereaved relatives.** *Lancet* 1998, **352:**614–617.

27. Moons P, Norekval TM: **European nursing organizations stand up for family presence during cardiopulmonary resuscitation: a joint position statement.** *Prog Cardiovasc Nurs* 2008, **23:**136–139.
28. Resuscitation Council: *Should Relatives Witness Resuscitation?* London, UK: Resuscitation Council; 1996.
29. Farrar D, Tuffnell D, Airey R, Duley L: **Care during the third stage of labour: a postal survey of UK midwives and obstetricians.** *BMC Pregnancy Childbirth* 2010, **10:**23.
30. National Institute for Health and Clinical Excellence: *Intrapartum Care: Care Of Healthy Women And Their Babies During Childbirth.* London: National Institute for Health and Clinical Excellence; 2007.
31. WHO: *WHO Recommendations for the Prevention of Postpartum Haemorrhage.* Geneva: World Health Organization; 2006.
32. Perlman JM, Wyllie J, Kattwinkel J, Atkins DL, Chameides L, Goldsmith JP, Guinsburg R, Hazinski MF, Morley C, Richmond S, Simon W, Singhal N, Szyld E, Tamura M, Velaphi S, Neonatal Resuscitation Chapter Collaborators: **Part 11: Neonatal resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations.** *Circulation* 2010, **122:**S516–S538.
33. Gyte G: **NCT evidence based briefing. Third stage labour. Part 2: Active management of third stage.** *New Digest* 2006, 22–28. http://www.nct.org.uk/sites/default/files/related_documents/EBB%20Third%20Stage%20part%202%20ND36.pdf.
34. Hutton EK, Hassan ES: **Late vs early clamping of the umbilical cord in full-term neonates: systematic review and meta-analysis of controlled trials.** *JAMA* 2007, **297:**1241–1252.
35. Rabe H, Reynolds G, Diaz-Rossello J: **A systematic review and meta-analysis of a brief delay in clamping the umbilical cord of preterm infants.** *Neonatol* 2008, **93:**138–144.
36. NICE: *Caesarean Section.* London: National Institute for Health and Clinical Excellence; 2011.
37. Batey N, Dorling J, Oddie S, Schoonakker B, Grace N, Duley L, on behalf of the Very Preterm Birth Collaborative Group: **Placental transfusion in preterm infants: how long does the transfusion last?** Oporto, Portugal: European Society for Pediatric Research; 2013. Available at p148 of https://www.eiseverywhere.com/file_uploads/9206db9fe962868d47f709b38365ec5e_9349_abstract_book_-_25sett13-it-it.pdf.
38. Richmond S, Wyllie J: **European Resuscitation Council Guidelines for Resuscitation 2010 Section 7. Resuscitation of babies at birth.** *Resuscitation* 2010, **81:**1389–1399.
39. Schoonakker BDJ, Dorling J, Oddie S, Batra D, Grace N, Duley L: **Bedside resuscitation of preterm infants with cord intact is achievable using standard resuscitaire.** Oporto, Portugal: European Society for Pediatric Research; 2013. Available at p430 of https://www.eiseverywhere.com/file_uploads/9206db9fe962868d47f709b38365ec5e_9349_abstract_book_-_25sett13-it-it.pdf.
40. Weeks AD, Peake M, Yoxall W: **The Bedside Assessment, Stabilisation and Initial Cardiorespiratory Support (BASICS) trolley: enabling neonatal resuscitation with an intact cord.** Liverpool: RCOG World Congress; 2013:24–26.
41. Squires J: **Ages and Stages Questionnaires.** In *Ages and Stages Questionnaires.* 3rd edition. Baltimore, MD: Brookes Publishing Co; 2009.
42. Johnson S, Wolke D, Marlow N: **Developmental assessment of preterm infants at 2 years: validity of parent reports.** *Dev Med Child Neurol* 2008, **50:**58–62.
43. Bayley N: *Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III).* London, UK: Pearson Assessment; 2005.
44. Royal College of Obstetricians and Gynaecologists (RCOG): **Obtaining Valid Consent For Research While In Labour.** London, UK: 2010. http://www.rcog.org.uk/files/rcog-corp/CGAObtainingConsentResearchLabour0810.pdf.
45. Zigmond AS, Snaith RP: **The hospital anxiety and depression scale.** *Acta Psychiatr Scand* 1983, **67:**361–370.
46. Medical Research Council: *MRC guidelines for good clinical practice in clinical trials.* London, UK: 1998.

doi:10.1186/1745-6215-15-258
**Cite this article as:** Pushpa-Rajah *et al.*: Cord pilot trial - immediate versus deferred cord clamping for very preterm birth (before 32 weeks gestation): study protocol for a randomized controlled trial. *Trials* 2014 **15**:258.

**Submit your next manuscript to BioMed Central and take full advantage of:**

- **Convenient online submission**
- **Thorough peer review**
- **No space constraints or color figure charges**
- **Immediate publication on acceptance**
- **Inclusion in PubMed, CAS, Scopus and Google Scholar**
- **Research which is freely available for redistribution**

Submit your manuscript at
www.biomedcentral.com/submit

BioMed Central

Downloaded from http://fn.bmj.com/ on September 27, 2017 - Published by group.bmj.com
ADC-FNN Online First, published on September 18, 2017 as 10.1136/archdischild-2016-312567


OPEN ACCESS

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

APPENDIX 2: Cord Pilot Trial: results at outcome at discharge publication

Lelia Duley,[1] Jon Dorling,[2] Angela Pushpa-Rajah,[3] Sam J Oddie,[4] Charles William Yoxall,[5] Bernard Schoonakker,[6] Lucy Bradshaw,[1] Eleanor J Mitchell,[1] Joe Anthony Fawke,[7] on behalf of the Cord Pilot Trial Collaborative Group

[1]Nottingham Clinical Trials Unit, Queen's Medical Centre, University of Nottingham, Nottingham, UK
[2]Early Life Research Group, Queen's Medical Centre, University of Nottingham, Nottingham, UK
[3]Department of Dermatology, Guy's Hospital, London, UK
[4]Centre for Reviews and Dissemination, Hull York Medical School, University of York, Heslington, York, UK
[5]Neonatal Unit, Liverpool Women's Hospital, Liverpool, UK
[6]Neonatal Intensive Care Unit, City Hospital, Nottingham, UK
[7]Neonatal Unit, Leicester Royal Infirmary, Leicester, UK

**Correspondence to**
Professor Lelia Duley, Nottingham Clinical Trials Unit, Queen's Medical Centre, University of Nottingham, Nottingham, NG7 2UH, UK; lelia.Duley@nottingham.ac.uk

Received 21 December 2016
Revised 19 June 2017
Accepted 23 June 2017

## ABSTRACT

**Objectives** For very preterm births, to compare alternative policies for umbilical cord clamping and immediate neonatal care.

**Design** Parallel group randomised (1:1) trial, using sealed opaque numbered envelopes.

**Setting** Eight UK tertiary maternity units.

**Participants** 261 women expected to have a live birth before 32 weeks, and their 276 babies.

**Interventions** Cord clamping after at least 2 min and immediate neonatal care with cord intact, or clamping within 20 s and immediate neonatal care after clamping.

**Main outcome measures** Intraventricular haemorrhage (IVH), death before discharge.

**Results** 132 women (137 babies) were allocated clamping ≥2 min and neonatal care cord intact, and 129 (139) clamping ≤20 s and neonatal care after clamping; six mother-infant dyads were excluded (2, 4) as birth was after $35^{+6}$ weeks, one withdrew (death data only available) (0, 1). Median gestation was 28.9 weeks for those allocated clamping ≥2 min, and 29.2 for those allocated clamping ≤20 s. Median time to clamping was 120 and 11 s, respectively. 7 of 135 infants (5.2%) allocated clamping ≥2 min died and 15 of 135 (11.1%) allocated clamping ≤20 s; risk difference (RD) −5.9% (95% CI −12.4% to 0.6%). Of live births, 43 of 134 (32%) had IVH vs 47 of 132 (36%), respectively; RD −3.5% (−14.9% to 7.8%). There were no clear differences in other outcomes for infants or mothers.

**Conclusions** This is promising evidence that clamping after at least 2 min and immediate neonatal care with cord intact at very preterm birth may improve outcome; a large trial is urgently needed.

**Trial registration** ISRCTN 21456601.

## What is already known on this topic?

- If the umbilical cord is not clamped flow continues for longer than previously thought, and cord pulsation does not correlate with umbilical flow.
- A short delay in cord clamping may reduce the risk of intraventricular haemorrhage and improve outcome in preterm babies.
- Previous small trials excluded babies requiring resuscitation at birth.

## What this study adds?

- Neonatal stabilisation and resuscitation can be provided with the cord intact.
- Giving neonatal care with the cord intact may improve outcome for the infants born very preterm.
- The effect of resuscitating preterm babies with an intact cord needs to be addressed in a large multicentre trial.

## INTRODUCTION

At birth, if the umbilical cord is not clamped blood flow between baby and placenta may continue for several minutes.[1–3] This umbilical flow is part of the physiological transition from the fetal to the neonatal circulation; clamping the cord too soon may restrict the infant's ability to cope with this transition.[2 4–8] A short delay in cord clamping may increase neonatal blood volume, a longer delay of several minutes may have more substantive advantages, such as smoother cardiorespiratory transition and more stable blood pressure, which for very preterm infants (<32 weeks gestation) may reduce the risk of intraventricular haemorrhage.[9 10] Concerns about deferring (delaying) cord clamping include exacerbating jaundice, polycythaemia, delayed respiratory support and hypothermia.

The relevant Cochrane review suggests that for infants born preterm deferring cord clamping may improve outcomes at hospital discharge.[11] However, the 15 trials included were small and have a high risk of bias. None were prospectively registered, and they reported different outcomes, so the possibility of selective outcome reporting is high. Also, data on long-term safety are sparse. Importantly, these studies excluded infants requiring resuscitation at birth, and for very preterm births most trials deferred clamping for <60 s. Guidelines for very preterm birth make various recommendations about when to clamp the cord,[12–14] and advise that clamping should not be delayed if neonatal resuscitation is required.[14 15] Evaluating timing of cord clamping at very preterm birth is a research priority, particularly for infants requiring resuscitation at birth.[15–17]

Our hypothesis is that for very preterm births a policy of cord clamping after at least 2 min and providing immediate neonatal care with cord intact, rather than usual care of clamping within 20 s and neonatal care after clamping, improves outcome for the infants without adverse effects for

**To cite:** Duley L, Dorling J, Pushpa-Rajah A, *et al*. *Arch Dis Child Fetal Neonatal Ed* Published Online First: [*please include* Day Month Year]. doi:10.1136/archdischild-2016-312567



Copyright Article author (or their employer) 2017. Produced by BMJ Publishing Group Ltd (& RCPCH) under licence.

Downloaded from http://fn.bmj.com/ on September 27, 2017 - Published by group.bmj.com



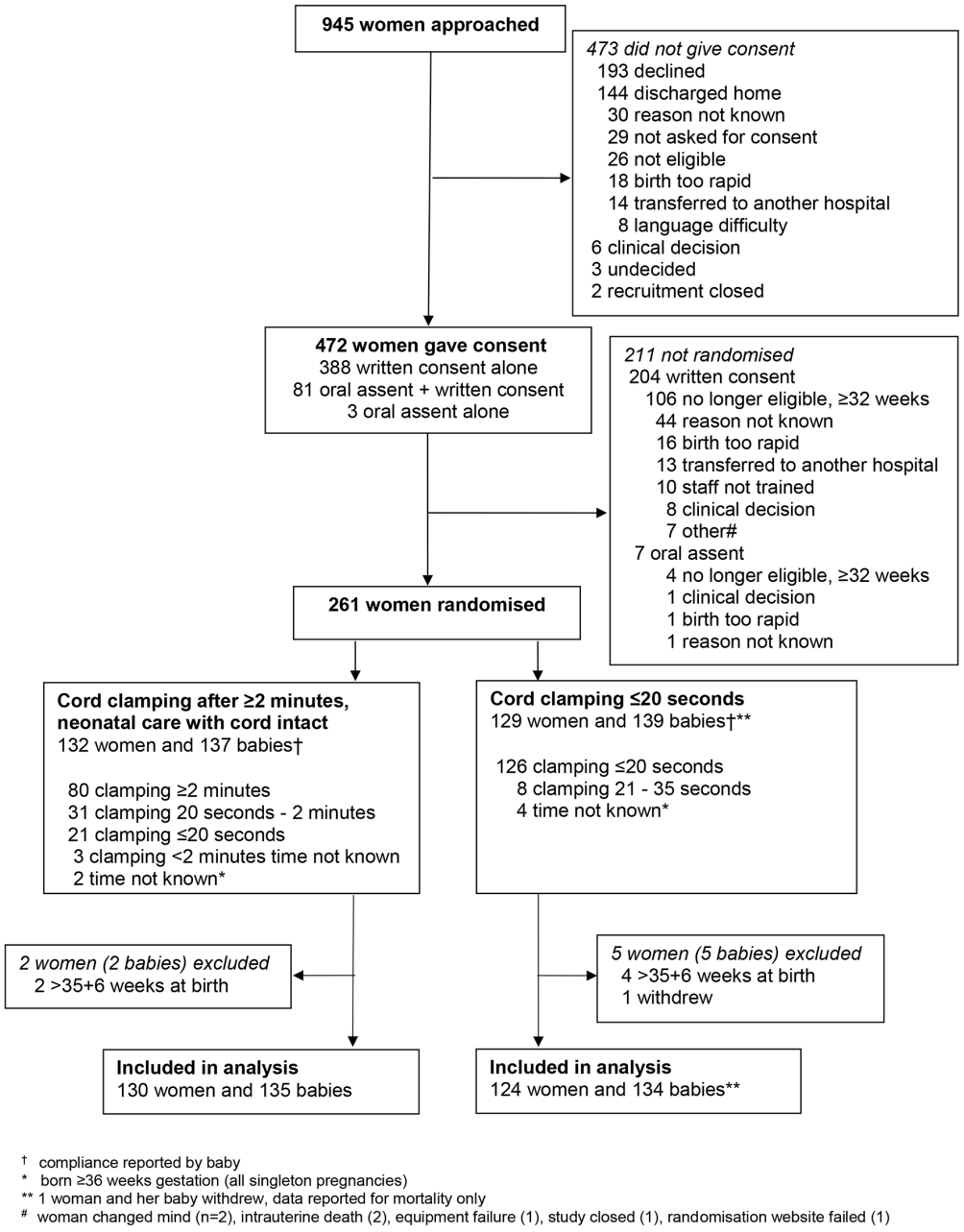



**Figure 1** Participant flow.

the women. Having developed strategies for providing stabilisation and resuscitation with the cord intact,[18 19] we conducted a randomised trial.

## METHODS

### Trial design and changes since trial registration

This pragmatic randomised parallel group trial was conducted at eight UK tertiary maternity units with a neonatal intensive care unit. The protocol is published[20] along with an update,[21] and these are summarised here. Initially, the study aimed to assess the feasibility of a large multicentre trial and planned to recruit for 1 year. Feasibility was demonstrated and, on the advice of the independent Trial Steering Committee, recruitment continued while funding was sought for the main trial. Recruitment closed in February 2015 when the funding application was unsuccessful. The sponsor is Nottingham University Hospitals NHS Trust. Trial coordination was at the Nottingham Clinical Trials Unit (NCTU).

As the original protocol was for a pilot trial, outcomes were measures of feasibility and analysis by allocated group was not planned. The statistical analysis plan (SAP) for the extended study was agreed before data were unblinded. For the planned main trial, main outcomes were death before discharge and intraventricular haemorrhage (all grades), hence these were the main outcomes in this SAP. Data presented here are for outcomes at discharge. Follow-up for women at 1 year, and for children at age 2 years (corrected for gestation) will be reported separately.

### Parent and parent representative involvement

Three parent representatives were coinvestigators, involved in identifying the research question, securing funding and designing

Downloaded from http://fn.bmj.com/ on September 27, 2017 - Published by group.bmj.com



and conducting the study. They advised on plans for recruitment; contributed to developing the oral assent pathway; advised on study implementation and conduct; participated in investigator meetings, including training in explaining the study to women and offering consent and contributed to interpretation and writing up of results. Two parents were independent members of the Trial Steering Committee. Participants in the trial have been thanked for participation, asked for their views of participation and updated on progress. When results are published they will be summarised in lay language.

## Participants

Women were eligible if they were expected to have a live birth before 32 weeks gestation, regardless of mode of birth or fetal presentation. Exclusion criteria were monochorionic twins; triplets or higher-order multiple pregnancy and known major congenital malformation.

## Interventions

Umbilical cord clamping after at least 2 min and, if needed, immediate neonatal stabilisation and resuscitation with cord intact was compared with clamping within 20 s and, if needed, immediate neonatal stabilisation and resuscitation after clamping. Waiting at least 2 min before clamping was based on a balance between waiting until umbilical flow ceased (which may take 3–5 min, or longer),[2 3 8 22] and what was acceptable to clinicians. For the intervention group, with cord intact babies were placed onto a firm surface with easy access to resuscitation equipment; either the usual equipment[19] or a smaller trolley designed for this purpose[23] moved alongside the mother's bed. For caesarean births, the neonatal resuscitation equipment was covered with sterile drapes, and the neonatologist scrubbed and gowned. For both groups, after cord clamping neonatal care was either beside the mother or at the usual location (side of the room or separate room), at the discretion of the local clinicians. Six sites used their usual resuscitation equipment (153 women recruited) and two the trolley (108). Until cord clamping, the baby was kept at the level of placenta (introitus or mothers' abdomen, or if a caesarean birth the anterior thigh). Clamping within 20 s with stabilisation and resuscitation after cord clamping was based on the current UK practice,[24] and previous trials.[11]

For both groups, all other aspects of care including intubation and respiratory support 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.[14 25] Standard equipment was used according to local practice, including plastic sheets or bags, towels and hats, warming mattresses or overhead heaters and saturation monitors.

## Outcome measures

Main outcomes were death before hospital discharge and intraventricular haemorrhage (all grades using the Papile classification[26]). A single assessor reviewed the cranial ultrasound scan reports for intraventricular haemorrhage, blind to the allocated group. Then eight trained clinicians (neonatologists or radiologists) independently adjudicated each scan, blind to allocation.[27] If the adjudication disagreed with the scan report review, a second independent adjudicator assessed the scan images. Remaining discrepancies were resolved by discussion.

Other outcomes for the baby were: severe intraventricular haemorrhage,[26] periventricular leukomalacia, blood transfusion, hypothermia (<36°C, <35°C), chronic lung disease (supplemental oxygen or ventilator support at 36 weeks postmenstrual age), ventilation, necrotising enterocolitis (grade 2 or higher), clinical sepsis, treatment for jaundice, treatment for patent ductus arteriosus, treatment for retinopathy of prematurity and duration of hospital stay.

Outcomes for women were: postpartum haemorrhage (≥500 or ≥1000 mL), postpartum infection, breast feeding and for vaginal births manual removal of placenta and third stage of labour longer than 30 min. Data were collected up to discharge by research staff at site.

## Recruitment and randomisation

Study information was available in antenatal clinics and wards. Women at risk of very preterm birth were offered participation, and if they accepted gave written consent. Eligibility and consent were checked before randomisation, which was during labour or before caesarean section. If birth was imminent and the attending clinician considered it appropriate, women were offered a brief explanation of the study and offered participation (oral assent). Those who gave oral assent were then randomised. After the birth, these women had an opportunity to discuss the study and were invited to give written consent for participation in follow-up.

Randomisation was by attending clinicians, who took the next sealed consecutively numbered opaque envelope from a ringbinder folder. Sequence generation (1:1) was by computer, stratified by centre with balanced blocks of randomly varying size, created by NCTU. On the envelope was a label to record the date, time, woman's initials, her date of birth and gestation. Once this label was completed she was 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) to record information about the third stage of labour and neonatal care at birth. This was completed by clinical staff, and filed in the baby's medical notes. Used envelopes and yellow cards were placed in a locked mailbox, which was emptied regularly. Details from each envelope were entered into the online randomisation log maintained by NCTU. If an envelope was taken but not used, it was returned unopened to NCTU.

During the last few months of recruitment, a secure web-based randomisation system, using the same randomisation sequence, was introduced in three sites to assess its feasibility.

## Sample size

Based on a total of 43 600 live births per year at the eight maternity units, we expected 610 (1.4%)[28] live births to be before 32 weeks; as target accrual was 16%–18% of eligible births we anticipated 100–110 women randomised per year. This was planned as a pilot trial so there was no formal power calculation.

## Statistical analysis

All analyses are based on the groups as randomly allocated (intention to treat). For twin pregnancies, outcome is reported for both babies. Where appropriate, results are presented as relative risk (RR) or risk difference (RD) with 95% CIs. Women who were randomised but gave birth after $35^{+6}$ weeks are excluded, as outcomes for these babies are different from those born very preterm. For secondary outcomes, missing data for individual items are only reported if they exceeded 1% of total data available. No formal interim analysis was planned. Data were monitored in

Downloaded from http://fn.bmj.com/ on September 27, 2017 - Published by group.bmj.com



confidence by an independent Data Monitoring Committee, which met four times.

## RESULTS

Of 945 women approached, 472 (50%) gave consent (figure 1). Oral assent was offered to 93 women, of whom 84 (90%) assented and of these 77 were randomised. For eight of the 77 women randomised following oral assent birth was not imminent as anticipated, and written consent was given before birth, hence 69 were randomised with oral assent only (33 cord clamping ≥2 min, 36 clamping ≤20 s). For 66 of these women written consent was given after the birth; written consent was not obtained for three, for two their baby died and they did not return for their counselling appointment at which written consent would have been sought and one was transferred to another unit.

Recruitment was from March 2013 to February 2015, and 261 women were randomised (132 cord clamping after at least 2 min, 129 within 20 s). Six women were excluded as they gave birth after $35^{+6}$ weeks and one withdrew (outcome data reported only for death before discharge), leaving 254 women for analysis (figure 1). In 2 of the 17 twin pregnancies, one fetus died in utero before randomisation, so 269 babies are included in analysis. Time between randomisation and birth was within 30 min for 81 women (32%), within 1 hour for 128 (50%) and within 2 hours for 178 (70%); 20 (8%) gave birth 24 hours or more after randomisation.

### Baseline characteristics

The groups were balanced at trial entry (table 1). A third of women were randomised before 28 weeks, and two-thirds before 30 weeks. One hundred forty-four (57%) were in their first pregnancy and just over half had a caesarean birth. Of the babies, 143 (53%) were males (71/135 clamping after ≥2 min vs 72/134 clamping ≤20 s).

### Compliance with the allocated intervention

Median time to cord clamping was 120 s (IQR 36–134), for those allocated clamping after at least 2 min and neonatal care with cord intact, and 11 s for those allocated clamping within 20 s and neonatal care after clamping (IQR 10–20). In the intervention group, cord clamping was after at least 2 min for 80 (59%) babies and after 20 s for 111 (82%) (figure 2). Baseline characteristics were similar for babies with cord clamping after at least 2 min and those clamped before 2 min; for example, gestation at birth $28^{+0}$ to $31^{+6}$ weeks 64% vs 63%, respectively; antenatal corticosteroids 87% vs 94% and caesarean birth 61% vs 67%. For the 55 babies for whom clamping was before 2 min, reasons were: cord too short (21, 38%), an issue that improved with experience; clinical decision (12, 22%); baby born either membranes intact or with the placenta (8, 15%); placental abruption (5, 9%); neonatal team not there in time (4, 7%); staff error (4, 7%) and cord snapped (1, 2%). In the control group, cord clamping was within 20 s for 126 (94%). There were no clear differences in compliance based on whether the site used usual resuscitation equipment or the trolley (data not shown). Neonatal care was comparable between the two allocated groups (table 2). For live-born babies, median birth weight was 1108 g (IQR 880–1360) in the intervention group and 1180 g (IQR 900–1418 g) in the control group (figure 2).

A prophylactic uterotonic drug was given to 127 women (98%) allocated clamping after at least 2 min, and 120 (97%) allocated clamping within 20 s. Administration was before cord clamping for 40 (31%) and 15 (12%), respectively; however, timing was unknown for 47 (37%) and 34 (28%).

**Table 1** Baseline characteristics for the women

| | Clamp ≥2 min+neonatal care with cord intact | Clamp ≤20 s+neonatal care after clamping |
|---|---|---|
| | (n=130) | (n=124) |
| Gestation at randomisation (weeks) ≥32 | 1 (1%) | 1 (1%) |
| 30 to $31^{+6}$ | 44 (34%) | 46 (37%) |
| 28 to $29^{+6}$ | 38 (29%) | 42 (34%) |
| 26 to $27^{+6}$ | 25 (19%) | 21 (17%) |
| <26 | 22 (17%) | 14 (11%) |
| Gestation at birth (weeks) ≥32 | 2 (2%) | 2 (2%) |
| 30 to $31^{+6}$ | 47 (36%) | 44 (35%) |
| 28 to $29^{+6}$ | 35 (27%) | 43 (35%) |
| 26 to $27^{+6}$ | 25 (19%) | 21 (17%) |
| <26 | 21 (16%) | 14 (11%) |
| Age (years), mean (SD) | 30.3 (6.1) | 29.2 (6.6) |
| Primiparous | 69 (53%) | 75 (60%) |
| Twin pregnancy | *7 (5%) | 10 (8%) |
| Pregnancy complications | | |
| Prelabour rupture of membranes | 43 (33%) | 40 (32%) |
| Spontaneous onset of labour | 31 (24%) | 33 (27%) |
| CTG abnormalities/fetal distress | 21 (16%) | 23 (19%) |
| Pre-eclampsia/PIH | 33 (25%) | 24 (19%) |
| Antepartum haemorrhage/placenta previa | 14 (11%) | 18 (15%) |
| Chorioamnionitis | 15 (12%) | 14 (11%) |
| Fetal growth restriction/small for gestational age | 13 (10%) | 13 (10%) |
| Other† | 5 (4%) | 6 (5%) |
| In last week received | | |
| Magnesium sulfate | 67 (52%) | 49 (40%) |
| Not known | 4 (3%) | – |
| Corticosteroids | 117 (90%) | 111 (90%) |
| Caesarean section | 82 (63%) | 67 (54%) |
| Before labour | 69 | 57 |
| During labour | 13 | 10 |
| Vaginal birth | 48 (37%) | 57 (46%) |
| Breech presentation | 9 | 8 |

*For two, one twin known intrauterine death before randomisation.
†Clamp ≤20 s: abdominal pain (n=2), severe asthma (1), pyelonephritis (1), antiphosphate lipid syndrome (1) and not known (1). Clamp ≥2 min: renal failure and diabetes (1), previous cervical surgery (1), coagulopathy (1), Crohn's disease (1) and hypotension (1).
CTG, cardiotocograph; PIH, pregnancy-induced hypertension.

### Outcome for babies

Overall, 7/135 (5.2%) babies allocated clamping after at least 2 min and neonatal care with cord intact died compared with 15/135 (11.1%) allocated clamping within 20 s and neonatal care after clamping (table 3), RR 0.47 (95% CI 0.20 to 1.11); RD −5.9% (−12.4% to 0.6%). The only death of an infant born after 30 weeks gestation was due to congenital anomaly that was not known before randomisation (if it had been the woman would not have been eligible). Excluding this death gives RR 0.50 (0.21 to 1.20), and RD −5.2% (-11.5% to 1.2%). The three stillbirths were born before 28 weeks, and were resuscitated at birth; cause of death was intrapartum asphyxia for two, and antepartum infection for one.

Downloaded from http://fn.bmj.com/ on September 27, 2017 - Published by group.bmj.com



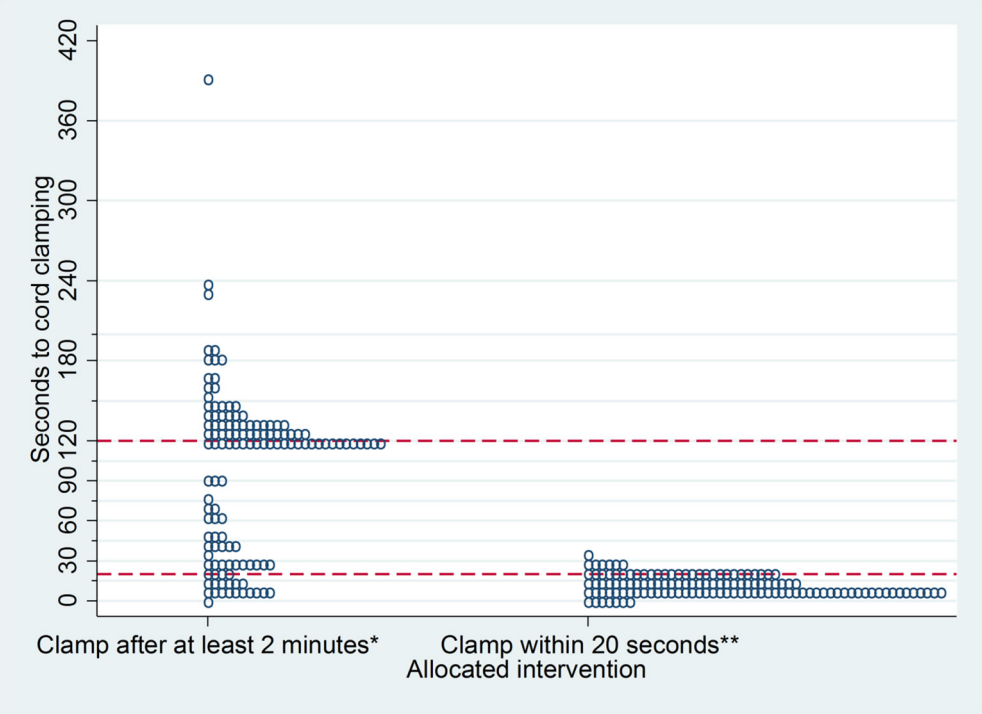



**Figure 2** Actual timing of cord clamping for each baby in the two allocated groups. *n=135 babies, seconds to cord clamping not known for 9. **n=134 babies, seconds to cord clamping not known for 9.

Of live births allocated to the intervention, 43/134 (32%) had an IVH versus 47/132 (36%) allocated to the control group (RR 0.90 95% CI 0.64 to 1.26; RD −3.5% (95% CI −14.9% to 7.8%)) (table 4). Overall, 251 babies (94%) had a cranial ultrasound scan (127 vs 124, respectively), and both adjudicated scan and review of the original clinical scan report were available for 224/266 (84%). Diagnosis of IVH was based on adjudication for 81 infants, scan report only for 8 and site data only for 1. There were no clear differences between the allocated groups for any other outcome (table 4).

### Outcome for women

There was no clear difference between the groups in blood loss at birth (≥500 mL 58/130 vs 59/124, RR 0.97, 0.71 to 1.35; ≥1000 mL 11/130 vs 13/124; RR 0.81, 0.38 to 1.73), or in any other outcomes for the women (table 5).

## DISCUSSION

This trial suggests that cord clamping after at least 2 min and providing neonatal care with cord intact may improve outcome at discharge for the infants compared with early clamping and neonatal care after clamping, but the CIs are wide and include harm. We achieved a substantial difference of 109 s between the two groups in median time to clamping, and neonatal care at birth was equivalent in the two groups. For 82% of infants allocated clamping after at least 2 min umbilical flow continued for longer than in the

**Table 2** Neonatal care and newborn life support at birth

| | Clamp ≥2 min+neonatal care with cord intact (n=135) | | | Clamp ≤20 s+neonatal care after clamping (n=134) | | |
|---|---|---|---|---|---|---|
| | Beside mother | Away from mother | Total | Beside mother | Away from mother | Total |
| Baby in plastic bag/sheet | 100* | 15 | 115 (85%) | 41* | 67 | 108 (81%) |
| Mask ventilation | 68 | 32 | 100 (74%) | 14 | 89 | 105† (78%) |
| Supplemental oxygen | 46 | 38 | 84 (62%) | 9 | 79 | 89‡ (66%) |
| Airway suction | 39 | 36 | 75 (56%) | 10 | 76 | 87‡ (65%) |
| Successful intubation | 38 | 40 | 78 (58%) | 10 | 77 | 87 (65%) |
| Surfactant | 28 | 39 | 67 (50%) | 9 | 66 | 75 (56%) |
| Attempted, unsuccessful intubation | 20 | 15 | 35 (26%) | 5 | 33 | 38 (28%) |
| Continuous positive airway pressure | 27 | 17 | 44 (33%) | – | 34 | 34 (25%) |
| Cardiac massage | 3 | 3 | 6 (4%) | 3 | 7 | 10 (7%) |
| Umbilical venous catheterisation | 1 | 2 | 3 (2%) | – | 6 | 6 (4%) |
| Other | – | 1§ | 1 (1%) | – | – | – |

*Placed in plastic bag beside mother, received all other care at roomside; n=14 clamp ≥2 min, n=26 clamp ≤20 s.
†Location not known for two.
‡Location not known for one.
§Packed cell transfusion.

Downloaded from http://fn.bmj.com/ on September 27, 2017 - Published by group.bmj.com



**Table 3** Mortality for the baby before discharge from hospital

| | Clamp ≥2 min+neonatal care with cord intact | Clamp ≤20 s+neonatal care after clamping |
|---|---|---|
| | (n=135) | (n=135)* |
| Death | 7 (5%) | 15 (11%) |
| Stillbirth | 1 | 2 |
| Early neonatal death | 3 | 7 |
| Late neonatal death | 2 | 5 |
| Postneonatal death | 1 | 1 |
| Gestation at birth (weeks) | | |
| $30–31^{+6}$ | – | 1 |
| $28–29^{+6}$ | 1 | 3 |
| $26–27^{+6}$ | – | 4 |
| <26 | 6 | 7 |
| Cause of death: | | |
| Congenital anomaly† | – | 1 |
| Severe pulmonary immaturity | 3 | 3 |
| Intrapartum asphyxia | 1 | 1 |
| IVH | 1 | 2 |
| Infection | | |
| Antepartum | – | 1 |
| Early onset | 1 | 1 |
| Late onset | – | 2 |
| Necrotising enterocolitis | – | 2 |
| Other‡ | 1 | 2 |

*Includes the baby of one woman who withdrew.
Clamp ≥2 min: prolonged oligohydramnios (n=1); clamp ≤20 s: myocardial ischaemia (1), prolonged oligohydramnios (1).
†Not known before randomisation.

**Table 4** Neonatal morbidity for liveborn babies

| | Clamp ≥2 min+neonatal care with cord intact | Clamp ≤20 s+neonatal care after clamping |
|---|---|---|
| | (n=134) | (n=132) |
| Any IVH (grade1–4) | 43 (32%) | 47 (36%) |
| Alive at discharge from hospital | 38 | 42 |
| Severe IVH (grade 3 or 4) | 6 (4%) | 7 (5%) |
| Periventricular leukomalacia | 7 (5%) | 8 (6%) |
| Other brain injury | 5 (4%) | 10 (8%) |
| Porencephalic cysts | – | 1 |
| Ventriculomegaly | – | 3 |
| Other* | 5 | 7 |
| Heart rate <100 at 1 min | 46† (34%) | 49 (37%) |
| Temperature, admission to NICU (°C) mean (SD) | 36.7 (0.6)‡ | 36.9 (0.8) |
| ≤36°C | 17 (13%) | 14 (11%) |
| ≤35°C | 2 (1%) | 3 (2%) |
| Blood transfusion (any) | 63 (47%) | 68 (52%) |
| For anaemia | 58 | 66 |
| For hypotension | – | 6 |
| Other indication | 4 | 7 |
| Jaundice requiring treatment | 123 (92%) | 120 (91%) |
| Phototherapy | 123 | 120 |
| Exchange transfusion | – | – |
| Polycythaemia requiring intravenous fluids | – | 1 (1%) |
| Chronic lung disease§ | 40 (31%) | 39 (33%) |
| Ventilation | 100 (75%) | 103 (78%) |
| Duration (days), median (IQR) | 3 (1, 9) | 2 (1, 9) |
| Necrotising enterocolitis | 8 (6%) | 5 (4%) |
| X-ray with perforation or pneumatosis | 7 | 3 |
| Laparotomy | 6 | 3 |
| Suspected necrotising enterocolitis¶ | 15 (11%) | 13 (10%) |
| Sepsis | 72 (53%) | 80 (61%) |
| Positive culture+antibiotics ≥5 days | 30 | 33 |
| Negative culture+antibiotics ≥5 days | 42 | 47 |
| Treatment for: | | |
| Patent ductus arteriosus | 20 (15%) | 20 (15%) |
| Retinopathy of prematurity§ | 5 (4%) | 5 (4%) |
| Duration of hospital stay** (days) median (IQR) | 57 (39, 85) | 57 (38, 75) |
| Mother's breast milk at discharge**†† | 71 (55%) | 68 (57%) |

*Clamp ≥2 min: prominent subarachnoid spaces suggestive of atropy (n=2), periventricular cyst (1), absent cavum septum pellucidum (1), occipital cyst (1). Clamp ≤20 s: prominent subarachnoid spaces suggestive of atropy (n=2), periventricular echodensities (1), increased echogenicity of deep white matter (1), mega cysterna (1), ventriculitis (1) and marked ventricular asymmetry (1).
†Not known n=2.
‡Temperature not recorded for two babies.
§Babies who survived to 36 weeks postmenstrual age: n=129 clamping ≥2 min, n=120 clamping ≤20 s. Data collected at 36 weeks postmenstrual age, or discharge whichever happened first.
¶Defined as bowel rest+antibiotics ≥5 days.
**Admitted to neonatal unit and alive at discharge: n=128 clamping ≥2 min; n=120 clamping ≤20 s
††Not known n=3 clamping ≥2 min; n=1 clamping ≤20 s.

control group, as the cord was clamped after 20 s. Providing neonatal care with cord intact required a multidisciplinary team approach, planning and training. For the neonatal teams, training was consistent with newborn life support recommendations,[14 15] and included communication with the woman, her partner and other clinical staff. The decision to intubate was based on local hospital policy; the risk of intubation was similar in the two allocated groups, and consistent with the UK practice.[29] Our study demonstrates that neonatal care with the cord intact is feasible using a range of procedures, and can be done with existing resuscitation equipment[19] or with a trolley designed for this purpose.[18 23] This is a more practical and potentially more widely generalisable strategy for supporting continued umbilical flow at birth than in other trials to date.

This study was not powered to detect differences between the allocated interventions. Nevertheless, the most striking result is the difference in death before discharge, this is based on a small number of events however with a wide CI that cannot rule out any difference. Also, there are no clear differences between the groups in IVH or any other serious morbidity that would potentially explain a difference in mortality. Hence, this difference probably reflects the play of chance.

Bringing neonatal care to the mother's bedside allows her and her partner to share the first moments of their child's life. Family presence during resuscitation is standard for other areas of healthcare, where it is preferred by families and appears to be beneficial.[30–33] Our preliminary work suggests neonatal care beside the mother is acceptable to women and their partners,[34] and to clinicians.[18 35] Nevertheless, some women reported negative emotions,[34] and clinicians, particularly those with less experience, were

Downloaded from http://fn.bmj.com/ on September 27, 2017 - Published by group.bmj.com



**Table 5** Outcome for the women

| | Clamp ≥2 min+neonatal care with cord intact | Clamp ≤20 s+neonatal care after clamping |
|---|---|---|
| | n=130 | n=124 |
| Blood loss at birth | | |
| ≥500 mL | 58 (45%) | 59 (48%) |
| ≥1000 mL | 11 (8%) | 13 (10%) |
| For vaginal births* | | |
| manual removal of placenta | 5 (10%) | 6 (11%) |
| Third stage>30 min | 4 (8%) | 6 (11%) |
| Blood transfusion | 5 (4%) | 3 (2%) |
| Postpartum infection+parenteral antibiotics | 34 (26%) | 29 (23%) |
| Fever >38°C | 8 (6%) | 5 (4%) |
| Duration of hospital stay (days) median (IQR) | 4 (2, 6) | 4 (2, 6) |
| Expressing/breast feeding at discharge† | 121 (96%) | 111 (93%) |

*n=48 clamping ≥2 min; n=57 clamping ≤20 s.
†For women whose babies were alive at time of their discharge, n=126 clamping ≥2 min; n=120 clamping ≤20 s.

concerned about 'performing' in front of the parents.[35] Few babies in these studies required resuscitation, however, and further evaluation is required.

In our study, median birth weight was lower, rather than higher, for infants allocated deferred clamping; suggesting that net change in neonatal blood volume may not be relevant for very preterm births and supporting our hypothesis that continued umbilical flow has a role in the expanding pulmonary circulation during transition to the neonatal circulation.

## Strengths and limitations of this study

Previous trials have largely excluded infants needing immediate resuscitation at birth.[15] We developed two strategies that enabled us to recruit these high-risk births. First, providing resuscitation with cord intact as needed allowed infants requiring immediate resuscitation at birth to be included. Second, if birth was imminent leaving insufficient time for the usual consent process, women were offered the opportunity to participate through a two-stage oral assent pathway; a quarter of recruitment used this pathway. The two-stage approach seems acceptable to women and to clinicians.[36] Other strengths are that the study was multicentre and conducted within existing clinical services, hence widely generalisable to similar settings, and that independent adjudication of cranial ultrasound scans improved reliability in ascertainment of IVH.[37]

Although the largest preterm cord clamping trial published to date, this trial was not powered to demonstrate clinically important differences in outcome between the two policies, therefore the key limitation is sample size.

## Comparison with other studies

One previous trial comparing alternative policies for timing of cord clamping (46 babies) has described providing neonatal care with the cord intact,[38] but the only outcome reported was neonatal blood volume. Other trials comparing alternative policies for cord clamping do not report providing immediate neonatal care with cord intact. One recent trial (150 babies) has evaluated ventilation with cord intact for infants born before 32 weeks gestation, but in this study cord clamping was at 60 s in both intervention arms.[39]

The Cochrane review includes 15 trials (738 babies) before 37 weeks gestation.[11] Restricting this to trials largely recruiting before 32 weeks and excluding those evaluating cord milking leaves 12 trials (552 babies) with deferred clamping between 30 and 120 s. In these trials, 8/236 (3.4%) babies allocated deferred clamping died compared with 14/250 (5.6%) allocated immediate clamping, and IVH was 31/195 (16%) vs 50/199 (25%), respectively. These event rates are substantially lower than in our trial, as high-risk infants requiring resuscitation at birth were not recruited. In our study, the overall mortality at discharge from hospital (8.1%) is comparable to that reported for infants of a similar gestation admitted to the 37 UK neonatal units participating in the Vermont Oxford Network (for 1116 inborn infants born between 24 and 31 weeks gestation during 2015, mortality at discharge was 10.8%).[40] This provides reassurance that we successfully recruited a generalisable group of babies. Diagnosis of any IVH (34%) is higher than reported in the UK for similar babies (27%),[40] but reassuringly severe IVH is similar (5% and 6%, respectively). Hence, the difference in any IVH diagnosis is likely to be due to variation in the grade 1 and 2 IVH, with another potential factor being differences between hospitals in the proportions of infants born before 32 weeks gestation who have a cranial ultrasound scan. Although some previous studies reported that cranial ultrasound scans were conducted blind to the allocation, none have reported independent adjudication of the scan diagnosis.

Other issues with the trials included in the Cochrane Review are that only two appear to have been registered. This may be relevant since most studies reported mortality, the definition (eg, including or excluding major congenital abnormality and/or stillbirth) varied, and of 11 other outcomes none were reported by more than 6 out of the 15 trials: therefore, selective outcome reporting must be at least a possibility. The apparently high compliance noted in some previous trials seems rather implausible and raises the possibility of unreported postrandomisation exclusions, and hence further potential for bias.

Resuscitation guidelines state 'there is insufficient evidence to recommend an appropriate time for clamping the cord in infants who are severely compromised at birth, and that for infants requiring resuscitation, resuscitative intervention remains the immediate priority'.[15] Clearly, uncertainty remains about when to clamp the cord for infants requiring resuscitative interventions. For preterm infants who are stable at birth and do not require resuscitation, recommendations are to wait at least 30 s and no longer than 3 min.[15 41]

Cord milking is advocated to increase neonatal blood volume without needing to defer cord clamping.[42] This technique disrupts umbilical blood flow, however, over-riding autoregulation of blood volume and blood pressure. As a different intervention to cord clamping, with greater potential to do harm, it requires rigorous evaluation.[43–45]

## CONCLUSIONS

A large multicentre trial is urgently needed to confirm whether a long delay (2 min or more) in cord clamping combined with stabilisation and/or resuscitation with cord intact, rather than standard care, really does improve outcome for very preterm births. This study demonstrates that such a trial is feasible.

**Acknowledgements** The authors thank all the women who participated in this trial, and their families, and to the clinical and research staff at the sites. The authors

Downloaded from http://fn.bmj.com/ on September 27, 2017 - Published by group.bmj.com



also thank Diane Whitham and Gill Bumphrey for preparation of the randomisation envelopes; to Alec Whitham for making the mail boxes and to Dushyant Batra, Louise Hattingh, Shoaib Khan and Kiran Yajamanyam for their assistance with the cranial ultrasound scan adjudication.

**Collaborators** Cord Pilot Trial Collaborative Group: Nottingham Clinical Trials Unit: Lelia Duley (chief investigator). Lindsay Armstrong-Buisseret (trial manager from November 2015). Brian Barnes (data coordinator). Lucy Bradshaw (statistician). Natalie Hutchings (trial administrator). Eleanor Mitchell (senior trial manager). Angela Pushpa-Rajah (trial manager May 2013-July 2015). Keith Whittaker (database programmer). Trial Management group: Lucy Bradshaw, Jon Dorling, Lelia Duley, Eleanor Mitchell, Angela Pushpa-Rajah (chair). Trial Steering Committee: Lucy Bradshaw (statistician), Kate Branchett, Mike Clarke (chair), Richard Cooke, Jon Dorling (neonatologist), Lelia Duley (chief investigator), Liz Goddard, Sara Kenyon, Angela Pushpa-Rajah (trial manager), Philip Steer. Data Monitoring Committee: Douglas Altman (chair), Declan Devane, Andrew Shennan, Ben Stenson. Patient and public involvement: Jane Abbott (Bliss, the special care baby unit charity) (until June 2014), Zoe Chivers (Bliss), Gill Gyte (NCT, National Childbirth Trust). Cranial ultrasound adjudication: Lindsay Armstrong-Buisseret, Lucy Bradshaw, Robert Dineen, Jon Dorling, Lelia Duley, Eleanor Mitchell. Clinical advisors: David Field, Jim Thornton, William Tarnow-Mordi. Writing committee: Lucy Bradshaw, Rob Dineen, Jon Dorling, Lelia Duley (chair) and Eleanor Mitchell. Collaborators by site (total number of women recruited). Aberdeen Maternity Hospital (13): Medhat Ezzat, Nikolaus Kau, Vijender Kistareddy, Annie Robertson: Bradford Royal Infirmary (43): Amal Mighell, Sam Oddie, Kelly Young City Hospital (39): Dushyant Batra, Bernard Schoonakker, Carys Smith, Kumar Swamy Homerton University Hospital (18): Narendra Aladangady, Amit Kandhari, Elaine van der. Pool: Leicester Royal Infirmary (39): Ros Astles, Joe Fawke, Marie Hubbard, Penny McParland Liverpool Women's Hospital (69): Margaret Thomas, Andrew Weeks, Charles William Yoxall New Cross Hospital (14): Kate Cheshire, David Churchill, Tilly Pilley, Melanie Sutcliffe Queen's Medical Centre (26): George Bugg, Jon Dorling, Yvonne Hooton, Gill Kirkwood.

**Contributors** The study was conceived by LD and GG. The protocol, trial procedures and strategies for recruitment and consent were developed in consultation with a board range of stakeholders including parent representatives, clinicians, researchers, the NIHR programme grant steering group and the Nottingham Clinical Trials Unit. The paper was drafted by LD, with comments from other authors. All authors have read and agreed the final paper.

**Funding** Funding: This trial is independent research funded by the National Institute for HealthResearch (NIHR) under its Programme Grants for Applied Research funding scheme (RPPG-0609-10107). The views expressed are those of the authors and not necessarily thoseof the NHS, the NIHR or the Department of Health. The funder had no role in study design,conduct, analysis or reporting.

**Competing interests** All authors declare no support from any organisation for the submitted work other than the NIHR programme grant; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; the grant funded research included development of a neonatal resuscitation trolley now marketed as 'LifeStart' and purchased by two sites for use in this trial, several authors were involved in development of the trolley but have no further relationship with the manufacturer; no other relationships or activities that could appear to have influenced the submitted work.

**Patient consent** Obtained.

**Ethics approval** Nottingham REC 2 (NRES reference 12/EM/0283).

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** Patient level data and the dataset presented here are available from the corresponding author. Participant consent for data sharing was not obtained but the presented data are anonymised and risk of identification is low.

**Open Access** 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/

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

## REFERENCES

1 Dawes GS. *Foetal and neonatal physiology; a comparative study of the changes at birth [by] Geoffrey S Dawes*. Chicago: Year Book Medical Publishers, 1968. *Chapter 13*.
2 Boere I, Roest AA, Wallace E, *et al*. Umbilical blood flow patterns directly after birth before delayed cord clamping. *Arch Dis Child Fetal Neonatal Ed* 2015;100:F12 1–F125.
3 Farrar D, Airey R, Law GR, *et al*. Measuring placental transfusion for term births: weighing babies with cord intact. *BJOG* 2011;118:70–5.
4 Gunther M. The transfer of blood between baby and placenta in the minutes after birth. *Lancet* 1957;272:1277–80.
5 Ersdal HL, Linde J, Mduma E, *et al*. Neonatal outcome following cord clamping after onset of spontaneous respiration. *Pediatrics* 2014;134:265–72.
6 Committee on Obstetric Practice, American College of Obstetricians and Gynecologists. Committee Opinion No.543: Timing of umbilical cord clamping after birth. *Obstet Gynecol* 2012;120:1522–6.
7 Bhatt S, Alison BJ, Wallace EM, *et al*. Delaying cord clamping until ventilation onset improves cardiovascular function at birth in preterm lambs. *J Physiol* 2013;591(8):2113–26.
8 Vijayaselvi R, Abraham A, Kumar M, *et al*. *Measuring umbilical flow and placental transfusion for preterm births: weighing babies at 33-36 weeks gestation with cord intact*: 1st congress of joint European Neonatal Societies, 2015.
9 Hofmeyr GJ, Bolton KD, Bowen DC, *et al*. Periventricular/intraventricular haemorrhage and umbilical cord clamping. Findings and hypothesis. *S Afr Med J* 1988;73:104–6.
10 Hofmeyr GJ, Bex PJ, Skapinker R, *et al*. Hasty clamping of the umbilical cord may initiate neonatal intraventricular hemorrhage. *Med Hypotheses* 1989;29:5–6.
11 Rabe H, Diaz-Rossello JL, Duley L, *et al*. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. *Cochrane Database Syst Rev* 2012;8:CD003248.
12 RCOG Scientific Advisory Committee. *Clamping of the umbilical cord and placental transfusion*. London: Royal College of Obstetricians and Gynaecologists, 2015.
13 National Institute for Health and Care Excellence. Preterm labour and birth. *NICE Guideline. London* 2015.
14 Richmond S, Wyllie J. European Resuscitation Council Guidelines for Resuscitation 2010 Section 7. Resuscitation of babies at birth. *Resuscitation* 2010;81:1389–99.
15 Wyllie J, Bruinenberg J, Roehr CC, *et al*. European Resuscitation Council Guidelines for Resuscitation 2015: Section 7. Resuscitation and support of transition of babies at birth. *Resuscitation* 2015;95:249–63.
16 Tarnow-Mordi WO, Duley L, Field D, *et al*. Timing of cord clamping in very preterm infants: more evidence is needed. *Am J Obstet Gynecol* 2014;211:118–23.
17 Duley L, Uhm S, Oliver S, *et al*. Top 15 UK research priorities for preterm birth. *Lancet* 2014;383:2041–2.
18 Thomas MR, Yoxall CW, Weeks AD, *et al*. Providing newborn resuscitation at the mother's bedside: assessing the safety, usability and acceptability of a mobile trolley. *BMC Pediatr* 2014;14:135.
19 Schoonakker B, Dorling J, Oddie S, *et al*. *Bedside resuscitation of preterm infants with cord intact is achievable using standard resuscitaire. European Society for Pediatric Research*: Oporto, Portugual, 2013. http://www.espr.info/templates/espr/images/pdf/9349_abstract_book_-_25sett13-it-it.pdf
20 Pushpa-Rajah A, Bradshaw L, Dorling J, *et al*. Cord pilot trial - immediate versus deferred cord clamping for very preterm birth (before 32 weeks gestation): study protocol for a randomized controlled trial. *Trials* 2014;15:258.
21 Bradshaw LE, Pushpa-Rajah A, Dorling J, *et al*. Cord pilot trial: update to randomised trial protocol. *Trials* 2015;16:407.
22 Batey N, Dorling J, Oddie S, *et al*. Placental transfusion in preterm infants: how long does the transfusion last? European Society for Pediatric Research. *Oporto, Portugual* 2013.
23 Weeks AD, Watt P, Yoxall CW, *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.
24 Farrar D, Tuffnell D, Airey R, *et al*. Care during the third stage of labour: a postal survey of UK midwives and obstetricians. *BMC Pregnancy Childbirth* 2010;10:23.
25 Perlman JM, Wyllie J, Kattwinkel J, *et al*. Part 11: Neonatal resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation* 2010;122(16 Suppl 2):S516–S538.
26 Papile LA, Burstein J, Burstein R, *et al*. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr* 1978;92:529–34.
27 Bradshaw LE, Pushpa-Rajah A, Dorling J, *et al*. Cord pilot trial: update to randomised trial protocol. *Trials* 2015;16:407.
28 Moser K, Macfarlane A, Chow YH, *et al*. Introducing new data on gestation-specific infant mortality among babies born in 2005 in England and Wales. *Health Stat Q* 2007;35:13–27.
29 Singh Y, Oddie S. Marked variation in delivery room management in very preterm infants. *Resuscitation* 2013;84:1558–61.
30 Critchell CD, Marik PE. Should Family Members Be Present During Cardiopulmonary Resuscitation? A Review of the Literature. *American Journal of Hospice and Palliative Medicine* 2007;24:311–7.
31 Boie ET, Moore GP, Brummett C, *et al*. Do parents want to be present during invasive procedures performed on their children in the emergency department? A survey of 400 parents. *Ann Emerg Med* 1999;34:70–4.
32 Moons P, Norekvål TM. European nursing organizations stand up for family presence during cardiopulmonary resuscitation: a joint position statement. *Prog Cardiovasc Nurs* 2008;23:136–9.
33 Resuscitation Council. *Should relatives witness resuscitation?: Resuscitation Council (UK)*, 1996.

Downloaded from http://fn.bmj.com/ on September 27, 2017 - Published by group.bmj.com




34 Sawyer A, Ayers S, Bertullies S, *et al*. Providing immediate neonatal care and resuscitation at birth beside the mother: parents' views, a qualitative study. *BMJ Open* 2015;5:e008495.
35 Yoxall CW, Ayers S, Sawyer A, *et al*. Providing immediate neonatal care and resuscitation at birth beside the mother: clinicians' views, a qualitative study. *BMJ Open* 2015;5:e008494.
36 Ayers S, Sawyer A, Chhoa C, *et al*. Clinicians' and womens' experiences of two consent pathways in a trial of timing of clamping at very preterm birth: a qualitative study. *Trials* 2015;16:1.
37 Dorling J, Duley L, Bradshaw L, *et al*. Impact of independent Adjudication of Neonatal Cranial Ultrasound Scans in a Randomised Trial. *European Academy of Paediatric Societies Geneva* 2016.
38 Aladangady N, McHugh S, Aitchison TC, *et al*. Infants' blood volume in a controlled trial of placental transfusion at preterm delivery. *Pediatrics* 2006;117:93–8.
39 Katheria A, Poeltler D, Durham J, *et al*. Neonatal Resuscitation with an Intact Cord: A Randomized Clinical Trial. *J Pediatr* 2016;178:75–80.
40 Boyle E, Manktelow B, Field D, *et al*. *The neonatal survey report 2014*: The Infant Mortality and Morbidity Studies, 2014. http://www2leacuk/departments/health-sciences/research/timms/reports
41 *Preterm Labour and Birth. National Institute for Health and Care Excellence: Clinical Guidelines*. London, 2015.
42 Hosono S, Mugishima H, Fujita H, *et al*. Umbilical cord milking reduces the need for red cell transfusions and improves neonatal adaptation in infants born at less than 29 weeks' gestation: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2008;93:F14–F19.
43 Nolan JP, Hazinski MF, Aickin R, *et al*. Part 1: Executive summary. *Resuscitation* 2015;95:e1–e31.
44 Rabe H, Jewison A, Alvarez RF, *et al*. Milking compared with delayed cord clamping to increase placental transfusion in preterm neonates: a randomized controlled trial. *Obstet Gynecol* 2011;117(2 Pt 1):205–11.
45 Katheria AC, Truong G, Cousins L, *et al*. Umbilical Cord Milking Versus Delayed Cord Clamping in Preterm Infants. *Pediatrics* 2015;136:61–9.

Downloaded from http://fn.bmj.com/ on September 27, 2017 - Published by group.bmj.com



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

Lelia Duley, Jon Dorling, Angela Pushpa-Rajah, Sam J Oddie, Charles William Yoxall, Bernard Schoonakker, Lucy Bradshaw, Eleanor J Mitchell and Joe Anthony Fawke

*Arch Dis Child Fetal Neonatal Ed* published online September 18, 2017

Updated information and services can be found at:
**http://fn.bmj.com/content/early/2017/09/17/archdischild-2016-312567**

*These include:*

**References** This article cites 35 articles, 8 of which you can access for free at:
**http://fn.bmj.com/content/early/2017/09/17/archdischild-2016-312567**
#BIBL

**Open Access** 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/

**Email alerting service** Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections** Articles on similar topics can be found in the following collections

Open access (63)

**Notes**

To request permissions go to:
**http://group.bmj.com/group/rights-licensing/permissions**

To order reprints go to:
**http://journals.bmj.com/cgi/reprintform**

To subscribe to BMJ go to:
**http://group.bmj.com/subscribe/**

OPEN ACCESS

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

APPENDIX 3: Cord Pilot Trial: results at 2 years publication

Lindsay Armstrong-Buisseret [1], Katie Powers,[1] Jon Dorling,[2] Lucy Bradshaw,[1] Samantha Johnson,[3] Eleanor Mitchell,[1] Lelia Duley [1]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/archdischild-2019-316912).

[1]Nottingham Clinical Trials Unit, University of Nottingham, Nottingham, UK
[2]Division of Neonatal-Perinatal Medicine, Dalhousie University, Halifax, Canada
[3]Department of Health Sciences, University of Leicester, Leicester, UK

**Correspondence to**
Professor Lelia Duley, Nottingham Clinical Trials Unit, University of Nottingham, Nottingham NG7 2RD, UK; Lelia.Duley@nottingham.ac.uk

Received 24 January 2019
Revised 15 July 2019
Accepted 17 July 2019
Published Online First 1 August 2019

Check for updates

© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY. Published by BMJ.

**To cite:** Armstrong-Buisseret L, Powers K, Dorling J, *et al*. *Arch Dis Child Fetal Neonatal Ed* 2020;**105**:F292–F298.

## ABSTRACT

**Objective** To report outcomes at 2 years corrected age for children of women recruited to a trial comparing alternative policies for timing of cord clamping and immediate neonatal care at very preterm birth.

**Design** Parallel group randomised (1:1) trial.

**Setting** Eight UK tertiary maternity units.

**Participants** Two hundred and seventy-six babies born to 261 women expected to have a live birth before $32^{+0}$ weeks' gestation.

**Interventions** Deferred cord clamping (≥2 min) and immediate neonatal care with cord intact or immediate (≤20 s) clamping and immediate neonatal care after clamping.

**Main outcome measure** Composite of death or adverse neurodevelopmental outcome at 2 years corrected age.

**Results** Six babies born after $35^{+6}$ weeks were excluded. At 2 years corrected age, outcome data were not available for a further 52 children, leaving 218 for analysis (115 deferred clamping, 103 immediate clamping). Overall, 24/115 (21%) children allocated deferred clamping died or had an adverse neurodevelopmental outcome compared with 35/103 (34%) allocated immediate clamping; risk ratio (RR) 0.61 (95% CI 0.39 to 0.96); risk difference (RD) −13% (95% CI −25% to −1%). Multiple imputation for missing data gave an RR 0.69 (95% CI 0.44 to 1.09) and RD −9% (95% CI −21% to 2%).

**Conclusions** Deferred clamping and immediate neonatal care with cord intact may reduce the risk of death or adverse neurodevelopmental outcome at 2 years of age for children born very premature. Confirmation in larger studies is needed to determine the real benefits and harms.

**Trial registration number** ISRCTN21456601.

## What is already known on this topic?

- A short delay in umbilical code clamping may reduce the risk of death before hospital discharge at very preterm birth.
- Immediate neonatal care can be provided with the cord intact, allowing cord clamping to be deferred for longer in babies requiring resuscitation at birth.
- Previous trials have been small, and few have reported outcomes beyond discharge from hospital.

## What this study adds?

- Neurodevelopmental assessment at 2 years corrected age is feasible using a range of strategies, including routine clinical data.
- Deferred clamping with immediate neonatal care, if needed, may reduce the risk of death or adverse neurodevelopmental outcome at 2 years of age.
- Large high-quality trials and meta-analysis of individual participant data from these trials are needed to confirm the true benefits and harms.

## INTRODUCTION

Although just 1.1% of live births in the UK are very preterm (before 32 weeks' gestation), these infants account for 43% of neonatal deaths.[1] Those who survive are at increased risk for a range of neurodevelopmental sequelae including cerebral palsy, neurosensory and cognitive impairment, and attention, social and emotional problems.[2 3] Such difficulties can have a major impact on a child's health, well-being and academic attainment and may persist into adulthood.[4 5] Interventions that could provide even a modest improvement in long-term outcomes would be of substantial benefit to these children and their families.

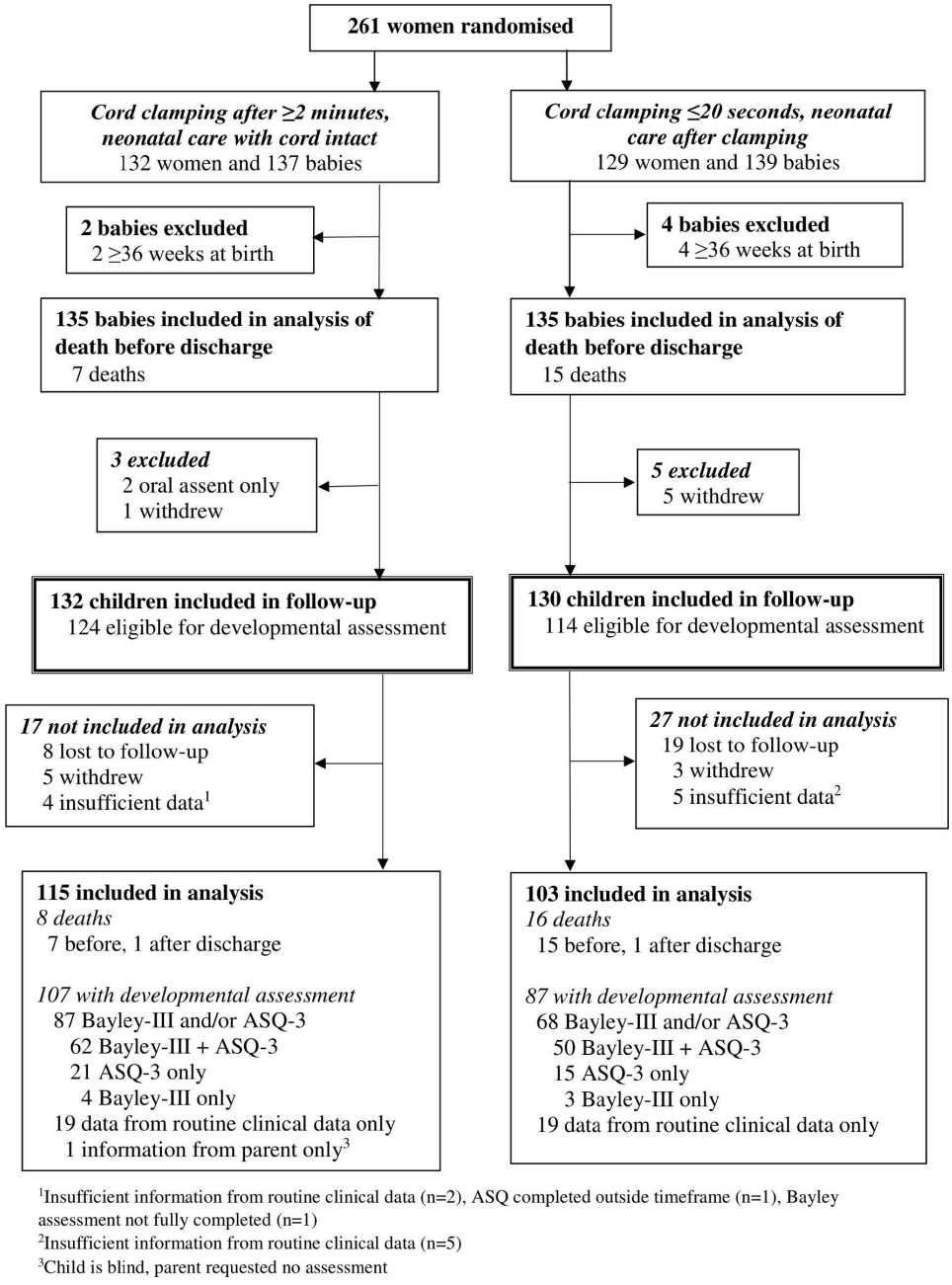
Systematic reviews have suggested that deferring clamping of the umbilical cord at preterm birth may reduce the risk of intraventricular haemorrhage (IVH)[6] and death before hospital discharge.[6 7] However, the trials largely excluded infants requiring immediate resuscitation at birth, and for very preterm births, most trials deferred clamping for 60 s or less. Also, data on long-term safety are sparse. The Cord Pilot Trial compared alternative policies for cord clamping and immediate neonatal care for very preterm births and results to discharge have been reported.[8] This paper presents follow-up of the children after discharge and the results of neurodevelopmental assessments at 2 years corrected age.

## METHODS

The Cord Pilot Trial was conducted at eight UK hospitals, and the protocol is published.[9 10] Women expected to have a live birth before $32^{+0}$ weeks' gestation (very preterm) were randomised 1:1 either to deferred cord clamping after at least 2 min and, if needed, immediate neonatal care with cord intact or to immediate clamping within



Arch Dis Child Fetal Neonatal Ed: first published as 10.1136/archdischild-2019-316912 on 1 August 2019. Downloaded from http://fn.bmj.com/ on September 21, 2021 by guest. Protected by copyright.




[1]Insufficient information from routine clinical data (n=2), ASQ completed outside timeframe (n=1), Bayley assessment not fully completed (n=1)
[2]Insufficient information from routine clinical data (n=5)
[3]Child is blind, parent requested no assessment

**Figure 1** Flow for follow-up of children at 2 years (corrected age). ASQ-3, Ages and Stages Questionnaire-3.

20 s and neonatal care after clamping. To ensure women could be recruited when birth was imminent, we included a two-stage consent pathway, with oral assent for recruitment followed by written consent after the birth, alongside the usual one stage pathway (described in detail elsewhere[8 9]). Between March 2013 and February 2015, 261 women were randomised with six excluded as birth was after $35^{+6}$ weeks.[8] Of the remaining 255 women, 17 had a twin pregnancy, for two of which one fetus died in utero before randomisation, leaving 270 children for the analysis of outcomes at hospital discharge.[8] Of these, 22 babies died before discharge (including three stillbirths), and a further two died after discharge, giving a total of 24 deaths. Eight children were excluded from follow-up either because the mother had already withdrawn consent (n=6) or she gave oral assent for recruitment,[8] and subsequent consent for follow-up was not available (n=2). Therefore, 238 children were eligible for assessment (figure 1).

## Parent and parent representative involvement

Parent and parent representative involvement has been reported.[8] For the follow-up, parent representatives contributed to study design and materials, including the process for contacting families.

## Neurodevelopmental assessment of children

Children were assessed using the parent-completed Ages and Stages Questionnaire-3 (ASQ-3)[11] and the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III).[12] If neither assessment was conducted, routine clinical data for 2-year outcomes were obtained if available.



Arch Dis Child Fetal Neonatal Ed: first published as 10.1136/archdischild-2019-316912 on 1 August 2019. Downloaded from http://fn.bmj.com/ on September 21, 2021 by guest. Protected by copyright.

**Table 1** For children included in analysis of outcomes to discharge and outcome at 2 years, characteristics at entry and outcomes to discharge

| | Included in analysis of outcomes to discharge | | Included in analysis of outcomes at 2 years | |
|---|---|---|---|---|
| | Clamp ≥2 min | Clamp ≤20 s | Clamp ≥2 min | Clamp ≤20 s |
| | n=135 (%) | n=134 (%)* | n=115 (%) | n=102 (%)* |
| Women's age (years) mean (SD) | 30.5 (6.3) | 29.4 (6.7) | 30.1 (5.8) | 29.8 (6.6) |
| Gestation at birth (weeks) | | | | |
| Median (25th, 75th centile) | 29 (27.1, 30.7) | 29.1 (27.6, 30.4) | 29 (27.1, 30.7) | 29 (27.0, 30.3) |
| Two-stage consent pathway | 36 (27) | 37 (28) | 30 (26) | 31 (30) |
| Twin pregnancy | 12 (9) | 20 (15) | 10 (9) | 14 (14) |
| Caesarean delivery | 86 (64) | 73 (54) | 74 (64) | 56 (55) |
| Baby sex | | | | |
| Male | 71 (53) | 72 (54) | 58 (50) | 60 (59) |
| **For live births** | **n=134** | **n=132** | **n=114** | **n=100** |
| Any IVH (grade 1–4) | 43 (32) | 47 (36) | 36 (32) | 35 (35) |
| Severe IVH (grade 3 or 4) | 6 (4) | 7 (5) | 4 (4) | 5 (5) |
| Periventricular leucomalacia | 7 (5) | 8 (6) | 6 (5) | 5 (5) |
| Blood transfusion | 63 (47) | 68 (52) | 53 (46) | 58 (58) |
| Jaundice requiring treatment | 123 (92) | 120 (91) | 105 (92) | 89 (89) |
| Chronic lung disease† | 40 (31) | 39 (33) | 31 (28) | 31 (35) |
| Ventilation | 100 (75) | 103 (78) | 84 (74) | 80 (80) |
| Necrotising enterocolitis | 8 (6) | 5 (4) | 7 (6) | 4 (4) |
| Sepsis‡ | 72 (54) | 80 (61) | 59 (52) | 63 (63) |
| Treatment for patent ductus arteriosis | 20 (15) | 20 (15) | 15 (13) | 19 (19) |
| Duration of hospital stay (nights)§ | | | | |
| Median (25th, 75th centile) | 57 (39, 85) | 57 (37, 75) | 57 (38, 80) | 60 (40, 83) |
| Receiving mother's breast milk at discharge§¶ | 71 (55) | 68 (57) | 61 (56) | 55 (63) |

*One woman withdrew (outcome data reported only for death before discharge).
†For babies surviving to 36 weeks postmenstrual age. n=129 clamping ≥2 min, n=120 clamping ≤20 s for all children and n=109, n=88 respectively for children included in analysis at 2 years.
‡Clinical sepsis defined as positive culture and ≥5 days antibiotics or negative culture and ≥5 days antibiotics.
§For babies alive at discharge n=128 clamping ≥2 min, n=120 clamping ≤20 s for all children and n=108, n=88 respectively for children included in analysis at 2 years.
¶Receiving breast milk at discharge not known for three babies in the clamp cord ≥2 min group (two included in analysis at 2 years) and one baby in clamp cord ≤20 s group (not included in analysis at 2 years).
IVH, intraventricular haemorrhage.

Shortly before children reached 2 years corrected age, the ASQ-3 was posted to the mother along with an invitation for a Bayley-III assessment. If a completed ASQ-3 was not returned, the family was contacted with up to two reminder letters and a phone call. If no ASQ-3 was returned, parents were asked to complete the appropriate version (24, 27 or 30 months) during the home visit prior to the Bayley-III assessment or during a hospital visit. If >1 ASQ-3 was returned, the one completed closest to the date the child was 2 years corrected age was used for analysis.

The ASQ-3 includes 30 questions covering five domains: communication, fine motor skills, gross motor skills, problem solving and personal-social skills. The response to each question is 'not yet', 'sometimes' or 'yes' (scored 0, 5 and 10, respectively). For each domain, scores are summed to produce a total. The domain score is not calculated if ≥3 responses are missing. If one or two responses are missing, the domain score is calculated using the mean of the completed items to impute the missing items. Four further questions to assess hearing, vision and gross motor function were added to the ASQ-3 questions.[13]

The Bayley-III comprises three scales to assess cognitive, language and motor development.[12] Children were assessed during a home visit by a trained researcher (KP) blind to intervention allocation. Three assessments were video recorded and scored by an independent observer (SJ) to assess inter-rater reliability.

## Outcome measures

The main outcome was a composite of death or adverse neurodevelopmental outcome at 2 years corrected age. Secondary outcomes included the individual components of the composite.

## Classification of adverse neurodevelopmental outcome

Neurodevelopmental outcomes were classified using the Bayley-III scores if available.[14 15] If the child did not have a Bayley-III assessment, or individual scales could not be completed, ASQ-3 data plus our additional questions on hearing, vision and gross motor function were used. To account for underestimation of developmental delay using the Bayley-III, moderate or severe impairment was based on scores >1SD below the normative mean (scores <85).[14 15] For each ASQ-3 domain, developmental delay was based on a total score >2 SDs below the mean using published norms.[11]

Children were classified as having an adverse neurodevelopmental outcome if they met the criteria for a moderate/severe impairment in any one of five functions: motor, cognitive, speech/language, hearing or vision (see online supplementary appendix 1).[16] For motor, this was defined as a Bayley-III gross motor scale score <7. If this scale had not been completed, assessment was based on our additional gross motor function questions from the ASQ-3, that is, if the child was unable to walk without assistance or sit without support. For cognitive and speech/language functions, this was defined as having a composite score <85



Arch Dis Child Fetal Neonatal Ed: first published as 10.1136/archdischild-2019-316912 on 1 August 2019. Downloaded from http://fn.bmj.com/ on September 21, 2021 by guest. Protected by copyright.

**Table 2** For children included in follow-up and eligible for neurodevelopmental assessment (at 2 years corrected age), information about the assessment

| | Clamp ≥2 min+neonatal care with cord intact | Clamp ≤20 s +neonatal care after clamping |
|---|---|---|
| | n=124 (%) | n=114 (%) |
| Any neurodevelopment data | 107 (86) | 87 (76) |
| Bayley-III and/or ASQ-3 | 87 (70) | 68 (60) |
| Bayley-III+ASQ-3 | 62 | 50 |
| Bayley-III only | 4 | 3 |
| ASQ-3 only | 21 | 15 |
| Clinical data only | 20 (16)* | 19 (17) |
| Age (corrected) at Bayley-III (months) | | |
| <24 | 2 | 7 |
| ≥24 to <27 | 53 | 37 |
| ≥27 to <30 | 9 | 9 |
| ≥30 | 2 | - |
| ASQ-3 version (months) | | |
| 24 | 78 | 60 |
| 27 | 3 | 3 |
| 30 | 2 | 2 |
| No neurodevelopmental data | 17 (14) | 27 (24) |

*Information from parent only for one child.
ASQ-3, Ages and Stages Questionnaire-3.

on the relevant Bayley-III scale. If these scales had not been completed, assessment was based on a score below the relevant domain cut-off on the ASQ-3 (problem solving for cognition and communication for language). Hearing and vision were assessed, respectively, as moderate/severely impaired if the child required hearing aids or was deaf, or had difficulty seeing with glasses, could only see light or was blind.

### Blinded review of neurodevelopmental outcome

A blinded review of outcome data was undertaken if: clinical follow-up data only were available, the Bayley-III was not fully completed, the ASQ-3 was not completed within the correct timeframe or the additional questions included on the ASQ-3 about hearing and vision were not completed. For each child, data were assessed independently by two reviewers blind to the allocated group. Discrepancies were resolved by discussion or if needed by a third independent reviewer.

### Statistical analyses

As this was planned as a pilot trial, there was no formal power calculation.[9 10] All analyses are based on the groups as randomly allocated (intention to treat) and were carried out using Stata SE 15.1. The main outcome (death or adverse neurodevelopmental outcome) is summarised by allocated group and presented with a risk ratio (RR), risk difference (RD) and 95% CIs. Each component of the main outcome is also summarised by group.

Multiple imputation using chained equations[17] was used as a sensitivity analysis to include children with missing outcome data in order to explore their potential impact on the estimate of RR and RD. Variables included in the imputation model were maternal age, gestation at birth, mode of delivery, sex, receiving breast milk at discharge, necrotising enterocolitis, grade of IVH, bronchopulmonary dysplasia, treatment for retinopathy of prematurity and country specific decile of Index Multiple Deprivation.[18] Thirty datasets were imputed, and estimates were combined using Rubin's rules.[17] This sensitivity analysis assumed that missing outcomes were missing at random,[19] that is, conditional on the observed variables the distribution of the observed and missing outcomes are assumed to be the same.

## RESULTS

Of the 238 children eligible for assessment, 27 were lost to follow-up, consent was withdrawn for a further 8 and for 9, there were insufficient data for analysis (figure 1). Therefore,

**Table 3** For children alive at 2 years (corrected age) outcomes at discharge according to availability of developmental outcome data and allocated group

| | Clamp ≥2 min+neonatal care with cord intact | | Clamp ≤20 s +neonatal care after clamping | |
|---|---|---|---|---|
| | Neurodevelopmental data not available n=20 (%) | Neurodevelopmental data available n=107 (%) | Neurodevelopmental data not available n=32 (%) | Neurodevelopmental data available n=87 (%) |
| Any IVH (grade 1–4) | 7 (35) | 30 (28) | 12 (38) | 30 (34) |
| Severe IVH (grade 3 or 4) | 2 (10) | – | 2 (6) | 3 (3) |
| Periventricular leucomalacia | 1 (5) | 5 (5) | 3 (9) | 3 (3) |
| Blood transfusion | 10 (50) | 46 (43) | 10 (31) | 45 (52) |
| Jaundice requiring treatment | 18 (90) | 98 (92) | 31 (97) | 80 (92) |
| Chronic lung disease | 9 (45) | 29 (27) | 8 (25) | 31 (36) |
| Ventilation | 16 (80) | 77 (72) | 23 (72) | 68 (78) |
| Necrotising enterocolitis | 1 (5) | 6 (6) | 1 (3) | 2 (2) |
| Sepsis* | 13 (65) | 55 (51) | 17 (53) | 54 (62) |
| Treatment for patent ductus arteriosis | 5 (25) | 15 (14) | 1 (3) | 16 (18) |
| Duration of hospital stay (nights) | | | | |
| Median (25th, 75th centile) | 64 (48, 105.5) | 57 (38, 80) | 46 (36, 63.5) | 60 (40, 83) |
| Receiving mother's breast milk at discharge† | 10 (50) | 61 (57) | 13 (41) | 54 (62) |

*Clinical sepsis defined as positive culture and ≥5 days antibiotics or negative culture and ≥5 days antibiotics.
†Receiving breast milk at discharge not known for two babies in the clamp cord ≥2 min group with main outcome data available and one baby in both groups with no main outcome data available.
IVH, intraventricular haemorrhage.



Arch Dis Child Fetal Neonatal Ed: first published as 10.1136/archdischild-2019-316912 on 1 August 2019. Downloaded from http://fn.bmj.com/ on September 21, 2021 by guest. Protected by copyright.

**Table 4** Death or adverse neurodevelopmental outcome at age 2 years (corrected)

| | Clamp ≥2 min+neonatal care with cord intact n=115 (%) | Clamp ≤20 s+neonatal care after clamping n=103 (%) | Risk difference (95% CI) | Risk ratio (95% CI) |
|---|---|---|---|---|
| Death or adverse neurodevelopmental outcome | 24 (21) | 35 (34) | −13% (−25% to −1%) | 0.61 (0.39 to 0.96) |
| Death | 8 (7) | 16 (16) | −9% (−17% to 0%) | 0.45 (0.20 to 1.00) |
| Adverse neurodevelopmental outcome | 16 (14) | 19 (18) | −5% (−14% to 5%) | 0.75 (0.41 to 1.39) |
| For children alive at 2 years, type of adverse neurodevelopment outcome* | | | | |
| Motor | 2 (2) | 5 (6) | | |
| Cognitive | 11 (10) | 6 (7) | | |
| Hearing | 2 (2) | 2 (2) | | |
| Speech/language | 9 (8) | 14 (16) | | |
| Vision | 2 (2) | 2 (2) | | |

*For: clamp ≥2 min+neonatal care with cord intact n=107; clamp ≤20 s+neonatal care after clamping n=87.

194 children were assessed at 2 years corrected age. As there were 24 deaths, 218 children were included in the analysis of the main outcome (115 allocated deferred clamping (≥2 min); 103 allocated immediate clamping (≤20 s)) (figure 1).

### Baseline characteristics and outcomes to discharge

Baseline characteristics and outcomes at discharge were similar for children included in the analysis of outcomes to discharge (n=270) and those included in the analysis of outcomes at 2 years (n=218) (table 1). For children included in analysis of outcomes at 2 years, baseline characteristics remained balanced between the allocated groups, with a median gestation at birth of 29 weeks (table 1).

### Neurodevelopmental assessment

Data were available for 194/238 (82%) children alive at 2 years corrected age (table 2). Bayley-III data were available for 119/238 (50%) children, with a higher percentage allocated deferred clamping (66/124, 53%) than immediate clamping (53/114, 46%; table 2) being assessed. Corrected age at assessment was similar between groups. For 24 children with Bayley-III data, one or more scales were incomplete (13 deferred clamping, 11 immediate clamping); for 18, this was the motor scale. Inter-rater reliability of Bayley-III assessments was excellent with 97% agreement for the cognitive scale, 97% for language and 100% for motor (data not shown).

ASQ-3 data were available for 148/238 (62%) children, again with a higher response for those allocated deferred clamping (83/124, 67%) than immediate clamping (65/114, 57%) (table 2). For most children (138), the 24-month ASQ-3 was completed. The main reason for having neither Bayley-III nor ASQ-3 data was no response to the invitation to participate (72 children).

Routine clinical data were obtained for 39/238 (16%) children with neither ASQ-3 nor Bayley-III data (20 deferred clamping, 19 immediate clamping; table 2).

For children allocated deferred clamping, there was some evidence that those lost to follow-up had poorer outcomes at discharge than those who were assessed (table 3). In this group, a greater percentage of children with no neurodevelopmental data had IVH, blood transfusion or chronic lung disease compared with those with data. This was not observed for children allocated immediate clamping where there was some evidence of the opposite trend (table 3).

### Death and adverse neurodevelopmental outcomes

Of children allocated deferred clamping, 24/115 (21%) died or had an adverse neurodevelopmental outcome compared with 35/103 (34%) allocated immediate clamping (table 4); RR 0.61 (95% CI 0.39 to 0.96); RD −13% (95% CI −25% to −1%). Using multiple imputation to account for loss to follow-up gave RR 0.69 (95% CI 0.44 to 1.09) and RD −9% (95% CI −21% to 2%).

In the deferred clamping group, 8/115 (7%) children died compared with 16/103 (16%) in the immediate clamping group (table 4). Of these, 3 were stillborn (1 deferred clamping, 2 immediate clamping), 19 died before discharge from hospital (6 deferred clamping, 13 immediate clamping) and 2 died after discharge (one in each group). Of children alive at 2 years, 16/107 (15%) allocated deferred clamping had an adverse neurodevelopmental outcome compared with 19/87 (22%) allocated immediate clamping.

Of children with a neurodevelopmental assessment, the most common type of adverse outcomes were in speech/language and cognitive impairment (table 4). Summary statistics for the 24-month ASQ-3 and Bayley-III are available in online supplementary appendix 2.

## DISCUSSION

Follow-up of children in the Cord Pilot Trial at 2 years corrected age suggests that deferring cord clamping for at least 2 min and providing immediate neonatal care, if needed, with cord intact may reduce the risk of death or adverse neurodevelopmental outcome compared with immediate clamping (≤20 s) and neonatal care after clamping. However, these results were sensitive to imputation to account for missing data. More children allocated deferred clamping had neurodevelopmental assessment data available; however, these children appeared to have fared slightly better at hospital discharge than those with missing follow-up data. In the immediate clamping group, there was evidence of the opposite trend when outcomes at discharge were compared according to availability of neurodevelopmental assessment data. Since the trial was not powered to demonstrate clinically important differences in outcome, confirmation is required in large high-quality randomised trials.

Strengths of our trial were that clamping was deferred for longer than in other trials at very preterm birth and that immediate neonatal care (including stabilisation and resuscitation), if needed, was provided with the cord intact.[20] Providing neonatal care with the cord intact allowed high-risk babies needing immediate resuscitation at birth to be randomised, a group largely excluded from previous trials.[21]

A composite of death and adverse neurodevelopment was chosen as the main outcome, a decision supported by our parent representatives as being relevant to parents. Despite the problems of composite outcomes, this is considered acceptable for perinatal and neonatal trials provided it is likely that the direction of effect is the same for all components of the composite[22]



Arch Dis Child Fetal Neonatal Ed: first published as 10.1136/archdischild-2019-316912 on 1 August 2019. Downloaded from http://fn.bmj.com/ on September 21, 2021 by guest. Protected by copyright.

as is the case for alternative policies for cord clamping. In our trial, the overall reduction in death or adverse neurodevelopment in the deferred clamping group was primarily due to the reduction in death before discharge. There was no clear evidence of a difference between groups in adverse neurodevelopmental outcome or death after discharge.

Achieving high response rates for long-term follow-up is necessary to ensure sample representation; however, this is challenging. In order to achieve our 82% response rate, this necessitated employing multiple approaches and combining results obtained from different assessment tools, including diagnostic tests (Bayley-III), parent questionnaires (ASQ-3) and data obtained from routine clinical assessments. As screening tests may have poor diagnostic accuracy compared with gold standard tests[23] and routine clinical assessments have poor sensitivity for evaluating cognitive outcomes in this population,[24] this approach represents a limitation of our study. Future trials should attempt to attain long-term follow-up rates in excess of 90% and use a single standardised test to assess neurodevelopmental outcomes. Lower follow-up for children allocated immediate clamping may have been due to the women feeling they were not part of the trial as they received usual care or being disappointed they did not receive the 'intervention' of deferred clamping.[25]

Using routine data for developmental assessment in perinatal trials merits further evaluation as it is less intrusive for parents and less costly in terms of resources. In the UK, the National Institute for Health and Care Excellence has recently introduced guidance that high-risk children, such as those born before 30 weeks' gestation, are eligible for enhanced developmental surveillance. This includes a developmental assessment at 2 years corrected age.[26] Provided they are of sufficient quality, these data could be used to determine neurodevelopmental outcomes for children in future trials.

The most recent systematic review, which includes the Cord Pilot Trial, concluded that delayed clamping reduces hospital mortality compared with immediate clamping, with no clear effect on serious neonatal morbidity.[7] This review emphasises the importance of follow-up for children recruited to both existing and future trials. The latter should be large enough to provide adequate power to detect clinically important differences in outcomes and will also need to achieve high follow-up rates to enable reliable comparisons of neurodevelopmental outcomes. Since providing robust evidence is likely to require multiple trials, a systematic review and individual participant data meta-analysis of cord management at preterm birth is underway.[27]

## CONCLUSIONS

Follow-up of children in the Cord Pilot Trial suggests deferred clamping with immediate neonatal care, if needed, beside the mother may reduce the risk of death or adverse neurodevelopmental outcome at 2 years corrected age compared with immediate clamping and neonatal care after clamping. Large high-quality trials are needed to confirm the true benefits and harms.

**Acknowledgements** The authors would like to thank all children and women who participated in this trial along with their families and the clinical and research staff at the sites. The authors would also like to thank Bernard Schoonakker for participating in the Blinded Endpoint Review Committee along with Gill Gyte (National Childbirth Trust) and Zoe Chivers (Bliss) for their advice and input.

**Contributors** The trial was conceived by LD and Gill Gyte. The protocol, trial procedures and strategies for recruitment and consent were developed in consultation with a broad range of stakeholders including parent representatives, clinicians, researchers, National Institute for Health Research (NIHR) preterm birth programme grant steering group, independent Trial Steering Committee, Data Monitoring Committee and the Nottingham Clinical Trials Unit. The paper was drafted by LA-B with input and comments from other authors. All authors have read and agreed the final paper.

**Funding** This trial is independent research funded by the NIHR under its Programme Grants for Applied Research funding scheme (RPPG0609-10107).

**Disclaimer** The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. The funder had no role in study design, conduct, analysis or reporting.

**Competing interests** JD reports grants from NIHR during the conduct of the trial; LD reports memberships to CTUs funded by NIHR. All other authors have nothing to disclose.

**Patient consent for publication** Not required.

**Ethics approval** Nottingham REC 2 (NRES reference 12/EM/0283).

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: https://creativecommons.org/licenses/by/4.0/.

**ORCID iDs**
Lindsay Armstrong-Buisseret http://orcid.org/0000-0002-8045-5464
Lelia Duley http://orcid.org/0000-0001-6721-5178

## REFERENCES

1 Manktelow BN, Smith LK, Prunet C, *et al*. *MBRACE-UK Perinatal Mortality Surveillance Report, UK Perinatal Deaths for Births from January to December 2015*. Leicester: The Infant Mortality and Morbidty Studies, Department of Health Sciences, University of Leicester, 2017.
2 Johnson S, Marlow N. Early and long-term outcome of infants born extremely preterm. *Arch Dis Child* 2017;102:97–102.
3 Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet* 2008;371:261–9.
4 Linsell L, Johnson S, Wolke D, *et al*. Cognitive trajectories from infancy to early adulthood following birth before 26 weeks of gestation: a prospective, population-based cohort study. *Arch Dis Child* 2018;103:363–70.
5 Eryigit Madzwamuse S, Baumann N, Jaekel J, *et al*. Neuro-cognitive performance of very preterm or very low birth weight adults at 26 years. *J Child Psychol Psychiatry* 2015;56:857–64.
6 Rabe H, Diaz-Rossello JL, Duley L, *et al*. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. *Cochrane Database Syst Rev* 2012;8:Cd003248.
7 Fogarty M, Osborn DA, Askie L, *et al*. Delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis. *Am J Obstet Gynecol* 2018;218:1–18.
8 Duley L, Dorling J, Pushpa-Rajah A, *et al*. Randomised trial of cord clamping and initial stabilisation at very preterm birth. *Arch Dis Child Fetal Neonatal Ed* 2018;103:F6–14.
9 Pushpa-Rajah A, Bradshaw L, Dorling J, *et al*. Cord pilot trial - immediate versus deferred cord clamping for very preterm birth (before 32 weeks gestation): study protocol for a randomized controlled trial. *Trials* 2014;15:258.
10 Bradshaw LE, Pushpa-Rajah A, Dorling J, *et al*. Cord pilot trial: update to randomised trial protocol. *Trials* 2015;16:407.
11 Squires J, Twombly E, Bricker D, *et al*. *Ages & Stages Questionnaires, Third Edition (ASQ-3) User's Guide*. Baltimore, MD: Brookes Publishing, 2009.
12 Bayley N. *Bayley Scales of Infant and Toddler Development*. 3rd edn. San Antonio, Texas: Pearson, 2005.
13 Johnson S, Evans TA, Draper ES, *et al*. Neurodevelopmental outcomes following late and moderate prematurity: a population-based cohort study. *Arch Dis Child Fetal Neonatal Ed* 2015;100:F301–8.
14 Anderson PJ, De Luca CR, Hutchinson E, *et al*. Underestimation of developmental delay by the new Bayley-III Scale. *Arch Pediatr Adolesc Med* 2010;164:352–6.
15 Johnson S, Moore T, Marlow N. Using the Bayley-III to assess neurodevelopmental delay: which cut-off should be used? *Pediatr Res* 2014;75:670–4.
16 British Association of Perinatal Medicine. *Report of a BAPM/RCPCH Working Group. Classification of Health Status at 2 years as a perinatal outcome*. London: BAPM, 2008.
17 White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* 2011;30:377–99.
18 Gill B. The English Indices of Deprivation London: Department for Communities and Local Government. 2015. Available: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015 [Accessed 19 Nov 2018].
19 Carpenter JR, Kenward MG. *Missing data in randomised controlled trials: a practical guide*. London: London School of Hygiene & Tropical Medicine, 2007.
20 Batey N, Yoxall CW, Fawke JA, *et al*. Fifteen-minute consultation: stabilisation of the high-risk newborn infant beside the mother. *Arch Dis Child Educ Pract Ed* 2017;102:235–8.



Arch Dis Child Fetal Neonatal Ed: first published as 10.1136/archdischild-2019-316912 on 1 August 2019. Downloaded from http://fn.bmj.com/ on September 21, 2021 by guest. Protected by copyright.

21 Wyllie J, Bruinenberg J, Roehr CC, *et al*. European Resuscitation Council Guidelines for Resuscitation 2015: Section 7. Resuscitation and support of transition of babies at birth. *Resuscitation* 2015;95:249–63.
22 Marlow N. Is survival and neurodevelopmental impairment at 2 years of age the gold standard outcome for neonatal studies? *Arch Dis Child Fetal Neonatal Ed* 2015;100:F82–F84.
23 Johnson S, Marlow N. Developmental screen or developmental testing? *Early Hum Dev* 2006;82:173–83.
24 Wong HS, Cowan FM, Modi N. Medicines for Neonates Investigator Group. Validity of neurodevelopmental outcomes of children born very preterm assessed during routine clinical follow-up in England. *Arch Dis Child Fetal Neonatal Ed* 2018;103:F479–84.
25 Sawyer A, Chhoa C, Ayers S, *et al*. Women's views and experiences of two alternative consent pathways for participation in a preterm intrapartum trial: a qualitative study. *Trials* 2017;18:422.
26 National Institute for Health and Care Excellence. *Developmental follow-up of children and young people born preterm*: NICE Quality Standard London, 2018. Available: https://www.nice.org.uk/guidance/qs169 [Accessed 13 Nov 2018].
27 Duley L, Askie L, Yang M. Cord clamping and placental transfusion at preterm birth prospective meta-analysis. *PROSPERO* 2013:CRD42013004405. Available: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42013004405 [Accessed 13 Nov 2018].




Arch Dis Child Fetal Neonatal Ed: first published as 10.1136/archdischild-2019-316912 on 1 August 2019. Downloaded from http://fn.bmj.com/ on September 21, 2021 by guest. Protected by copyright.

APPENDIX 4: FEED1 oral assent baseline survey questions

# FEED1 Trial - Oral Assent Survey Final Version 1.0 04 February 2020

## Page 1: FEED1 Trial - Oral Assent Survey

We have a two-stage consent pathway in the FEED1 Trial. This enables women to give full written informed consent antenatally or oral assent antenatally (when delivery may be imminent) or postnatally. We are currently developing a range of resources to help clinicians in taking oral assent. We are interested in hearing your opinions on this process and would be grateful if you complete a short, anonymous online survey. Your responses will help us create a more streamlined consent pathway and training materials that are suited to your needs.

We anticipate this taking you no more than 5 minutes of your time. Many thanks.

1. **Prior** to the FEED1 Trial have you taken oral assent/verbal consent from a parent for another **clinical trial**?

- Yes
- No
- Can't remember

2. How many times have you taken oral assent from a woman in the FEED1 Trial?

- 0
- 1-3
- 4-6
- 6-9
- 10+

2.a. *If you have taken oral assent:* On a scale of 0-10 (0 being not confident at all, 10 being extremely confident), how confident did you feel about taking oral assent from a woman in the FEED1 Trial?

Please don't select more than 1 answer(s) per row.

| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Not confident at all | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | Extremely confident |

2.a.i. Having now had an oral assent conversation, do you feel more confident than previously?

- Yes
- No
- Unsure

2.b. *If you have not taken oral assent before:* On a scale of 0-10 (0 being not confident at all, 10 being extremely confident), how confident do you feel about taking oral assent from a woman in the FEED1 Trial when the opportunity presents itself?

Please don't select more than 1 answer(s) per row.

| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Not confident at all | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | Extremely confident |

3. What **do you like** about the oral assent process? – select all that apply

- ☐ It reduces the time it takes to obtain full written informed consent
- ☐ It allows us to approach women for participation in a trial during a stressful and sensitive period when full informed consent might not be practicable
- ☐ It helps with recruitment in a trial where there is limited time to enter the participant in to the trial.
- ☐ It is an ethically approved process within the trial
- ☐ Having a witness signature to confirm that oral assent was taken
- ☐ Other

3.a. If you selected Other, please specify:

4. What **don't you like** about the oral assent process? – select all that apply

- ☐ Unsure of how much information to give in an assent conversation
- ☐ Lack of a signed consent form confirming participation
- ☐ It is unfamiliar – I am more familiar in taking written informed consent
- ☐ It does not feel appropriate to approach women at this stressful time
- ☐ Other

4.a. If you selected Other, please specify:

5. What support would help you with the oral assent process? – select all that apply

- ☐ Online training materials from the FEED1 team
- ☐ Sharing experiences between sites
- ☐ Peer support within the team at my site
- ☐ Seeing other people have an oral assent conversation
- ☐ Other

5.a. If you selected Other, please specify:

6. Do you have any other comments you would like to share on the oral assent process?

*7.* What is your role within the FEED1 Trial?

- Principal Investigator at site
- Co-investigator
- Research Nurse / midwife
- ANNP
- Neonatal Nurse
- Other

*7.a.* If you selected Other, please specify:

*8.* If you are a clinician, outside of the immediate research team at your hospital, please indicate your level:

- Consultant
- Neonatal Specialist trainee (GRID or equivalent)
- Second tier trainee (eg “registrar” or ANNP acting in this role)
- First tier trainee (formerly known as “SHO”)
- Other

*8.a.* If you selected Other, please specify:

## Page 5: Final page

Thank you for taking the time to answer these questions. Your feedback is crucial to the ongoing development of the FEED1 trial.

Are you aware that we have another questionnaire in circulation at present? We would like to hear your feedback on the recruitment process in the FEED1 trial. It would be appreciated if you could complete this questionnaire too. It should take you no more than 2-3 minutes to complete. Follow the link below to access this questionnaire:

Click here to access the FEED1 Trial Recruitment Feedback Questionnaire.

Thank you for all of your hard work so far. Remember that the trial management team are always available to answer any questions you have.

You can reach us at feed1@nottingham.ac.uk or by phone on 0115 82 31592.

The FEED1 team

---

**APPENDIX 5**

# Oral Assent in the FEED 1 Trial

The FEED1 Trial has an ethically approved two-stage consent process for women. This process was developed in a previous neonatal trial the team led and was found acceptable to women and clinicians. The process is now recommended by the Royal College of Obstetricians and Gynaecologists (RCOG) in their *"Obtaining Valid Consent to Participate in Perinatal Research Where Consent is Time Critical"* guidance. If you want to find out more, there are some references at the bottom of this sheet. We have included a two-stage process since we are keen to recruit women both **antenatally** and **postnatally**. This is to ensure we recruit a broad range of women and babies. The oral assent pathway should be chosen when time is scarce and the provision of full written information to women, at a sensitive and emotional time, might be difficult. Further there is reason to believe that "consent" obtained without sufficient time for discussion and reflection doesn't represent informed consent with its typically understood attributes. The guidance below will help you obtain oral assent (followed by written consent at a later date) for women where this is preferable.

**The principles of obtaining oral assent are given below.**

- If a woman is not judged able to participate in a full informed consent conversation, but is able to join a conversation (as evidenced by verbal or nonverbal communication) then undertaking the assent process may be applicable.
- Under many or most circumstances postnatal participation without prior discussion will only be via the assent process.
- Under the assent process, the clinician recording assent takes responsibility for randomisation because full explanation and comprehension of the trial is not feasible.
- Assent conversations must be followed by efforts to secure fully informed consent, as per the protocol within 72 hours where appropriate.
- Assent participation may follow a wider or more focused discussion – some conversations may be as inclusive, or nearly as inclusive, as consent conversations

**At its most limited, oral assent conversations MUST include:**

- **"You do not have to take part":** It is a choice to participate; parents can decline a non-standard approach to management
- **Feeding strategy:** That the proposed study involves non-standard management. The variation from standard management is in the domain of feeding baby – whether to feed milk only, or to incrementally introduce milk in combination with intravenous fluids.
- **"The computer decides":** In order for it to be a fair test, the computer decides, at random, the feeding strategy
- **Research:** Having explained the above, this is called "research"
- **Documentation:** We must still do some paperwork, but can do this later and this is "allowed"

For guidance on the documentation of the oral assent process please refer to protocol
***Turn overleaf for an example oral assent conversation***
**An example oral assent conversation, to be used postnatally:**

*Your baby is doing well and is ready to have milk. With babies like yours we usually start with a little milk and increase it over a few days. While we increase the milk, we give fluids in the vein to ensure baby has enough fluid.*

*An alternative is to give all the fluids as milk and fully feed your baby from today. This may help your baby and be more comfortable. We think that as your baby is doing well, it would be safe to give all milk.*

*For babies like yours, we do not know which of these two approaches is better. We are comparing them – we let the computer decide which way to feed baby, and see which is best. We want to propose that your baby joins our comparison of treatments – is that OK with you?*

*If baby does join in our comparison of treatments ('research'), we can sort out all the paperwork in the next few days (the "committee" says that's OK). If you don't want baby to join in, that's fine.*

Of course, these words are not intended to be read out verbatim. The intention is to illustrate the kind of content that might be appropriate.

If you have any queries or concerns about the two-stage consent pathway you should contact the FEED1 team in the first instance; feed1@nottingham.ac.uk.

**References:**

Chhoa, C.Y., Sawyer, A., Ayers, S. *et al.* Clinicians' views and experiences of offering two alternative consent pathways for participation in a preterm intrapartum trial: a qualitative study. *Trials* **18,** 196 (2017) doi:10.1186/s13063-017-1940-5

Sawyer, A., Chhoa, C., Ayers, S. *et al.* Women's views and experiences of two alternative consent pathways for participation in a preterm intrapartum trial: a qualitative study. *Trials* **18,** 422 (2017) doi:10.1186/s13063-017-2149-3

**APPENDIX 6**

**QUESTIONNAIRES TO EVALUATE THE ENHANCED TRAINING PACKAGE**
*n.b. the informed consent and ICH-GCP questionnaires are publicly available at The Global Health Network Training Centre: https://globalhealthtrainingcentre.tghn.org*

Site Name:_____ Study ID Number: | | | | | |

## Born Too Soon – Optimising Nutrition

## Study 4 – Baseline characteristics

Before you are involved in the training session for this study, we would like to find out a little bit about your research experience. We would be grateful if you could therefore take a few minutes to answer the following questions. Once completed, please hand back to your local study coordinator who will then send onto the coordinating team in Nottingham, UK.

**Many thanks for your time**

---

**Section 1 – Demographics**

**Gender** Male ☐ Female ☐ Prefer not to say ☐

**Age**
16-25 years ☐
26-34 years ☐
35-44 years ☐
45-54 years ☐
55+ years ☐

**Job title** _____

**Clinical area:**
Obstetrics
Neonatology
Midwifery
General nursing

**Section 2 - Research experience**

**Have you worked on a research study before?** Yes ☐ No ☐

*If no, there are no further questions. Thank you for your time.*

## The following questions should only be answered if you have worked on a research study before.

**How many research studies have you worked on previously? (Please tick one box)**

**1-3 ☐ 4-6 ☐ 7-10 ☐ 10+ ☐ Don't remember ☐**

**When was the last time you worked on a research study?**

**Working on one now ☐ In the last year ☐ More than 1+ year ago ☐**

**What types of research studies have you worked on?**
***(Please complete the table below)***

| ***Study type*** | ***Have you ever worked on this type of study?*** | ***If yes, approximately how many studies of this type have you worked on? (if none, state 0. If you don't remember, state DK)*** |
|---|---|---|
| Observational (no intervention) | Yes ☐ No ☐ | |
| Clinical trial | Yes ☐ No ☐ | |
| Questionnaire-based study | Yes ☐ No ☐ | |
| Other – please state _____ | Yes ☐ No ☐ | |

**Have you previously received any research specific training?** Yes ☐ No ☐
If yes, please give a brief description of the training…

**What tasks have you undertaken in previous research studies? (Please tick all that apply)**

| | |
|---|---|
| Overall responsibility of the study as Principal Investigator | ☐ |
| Study coordination/management | ☐ |
| Obtaining consent from participants | ☐ |
| Recruiting participants | ☐ |
| Data collection | ☐ |
| Data entry | ☐ |
| Data analysis | ☐ |
| Reporting | ☐ |

**Thank you for completing this form, please hand back to your local study coordinator.**

Site Name:_____ Study ID Number:

Job Title:_____

**Born Too Soon Protocol questions:**

| | | |
|---|---|---|
| 1) A baby is born who weighs 1700g. You ask the parent whether they would be happy for their baby to take part in the randomised controlled trial of feeding methods? They say they do not want to. What do you do? (Please select all that apply) | a. Try and change their mind, informing them of how important the study is for us to understand how to best feed premature babies<br>b. Thank them for their time and take no further action<br>c. Thank them for their time and record their details on the study database<br>d. Thank them for their time and ask if they would be willing to take part in a focus group<br>e. Thank them for their time and enrol them in the observational study<br>f. Nothing | ☐<br>☐<br>☐<br>☐<br>☐ |
| 2) A baby is born who meets the eligibility criteria for taking part in the randomised controlled trial of feeding methods. The parent is happy for their baby to take part. They have expressed that they would like their baby to be fed according to the "full milk" feeding method.<br>Is this acceptable? | a. Yes<br>b. No | ☐<br>☐ |
| 3) A baby is born who weighs 1900g. Which study should you enrol them into? | a. The observational study<br>b. The randomised controlled trial<br>c. Both<br>d. Neither | ☐<br>☐<br>☐<br>☐ |
| 4) Whilst taking part in the randomised controlled trial, a baby develops late onset sepsis, which has been confirmed by a positive culture. Should you report this as a Serious Adverse Event? | a. Yes<br>b. No<br>c. Not sure | ☐<br>☐<br>☐ |

| | | |
|---|---|---|
| 5) A family don't have access to a telephone and therefore aren't able to be contacted for their 6-week telephone call. What should you do? | a. Don't include them in the observational study<br>b. Don't include them in the randomised controlled trial<br>c. Include them in either the observational study or randomised controlled trial but accept you won't collect this follow-up data | ☐<br>☐<br>☐ |
| 6) A baby weighing 1500g is born but is very unwell and unlikely to survive. Should you approach the parents about participating in the randomised controlled trial? | a. Yes, the data from the infant will still be helpful<br>b. Yes, participating in the study may help the infant<br>c. No, it is inappropriate to approach a family about participating in a research study when their infant is so ill<br>d. No, this baby does not meet the inclusion criteria for the study | ☐<br>☐<br>☐<br>☐ |
| 7) You are considering entering a 1000 gram birth weight baby into the randomised controlled trial, but aren't happy in feeding infants of this gestation/birthweight with full milk feeds from birth because you think they may go onto develop necrotising entercolitis or other complications of prematurity. What should you do? | a. Baby's birth weight is 1000-1800 gm so the baby must be entered into the trial. The baby fulfils the entry criteria and all such babies should be in the trial unless parents refuse consent.<br>b. Baby can be entered into the trial only if they go into the "gradual milk" arm of the trial. I will randomise and if the baby goes into the "full milk" arm they can be withdrawn from the trial.<br>c. Baby should not be entered into the trial because it would not be safe for the baby to receive "full milk" from day 1. Babies should be entered into trials only if there is clinical equipoise about the two arms of the trial. | ☐<br>☐<br>☐ |
| 8) You have appropriately recruited and randomised a 1300g birth weight baby in to the trial. Baby is randomised to the "full milk" arm and has been started on full milk feeds on day 1. On day 2 the baby becomes unwell, is vomiting repeatedly, has a distended and tender abdomen, and looks septic. What will you do? | a. Do sepsis investigations, treat the sepsis but continue full milk feeds as the baby is in the "full milk" arm.<br>b. Do sepsis investigations, treat the sepsis, stop feeding and give IV fluids as the baby is unwell and irrespective of which arm of the trial the baby is in, we have to do what is best for the baby's wellbeing first. | ☐<br>☐ |