**ABSTRACT**

**Introduction** Necrotising enterocolitis (NEC) is a potentially devastating neonatal disease. A temporal association between red cell transfusion and NEC is well described. Observational data suggest that withholding enteral feeds around red cell transfusions may reduce the risk of NEC but this has not been tested in randomised trials; current UK practice varies. Prevention of NEC is a research priority but no appropriately powered trials have addressed this question. The use of a simplified opt-out consent model and embedding trial processes within existing electronic patient record (EPR) systems provide opportunities to increase trial efficiency and recruitment.

**Methods and analysis** We will undertake a randomised, controlled, multicentre, unblinded, pilot trial comparing two care pathways: continuing milk feeds (before, during and after red cell transfusions) and withholding milk feeds (for 4 hours before, during and for 4 hours after red cell transfusions), with infants randomly assigned with equal probability. We will use opt-out consent. A nested qualitative study will explore parent and health professional views of this approach in a nested qualitative study.

**Ethics and dissemination** This study holds Research Ethics Committee approval to use an opt-out approach to consent. Results will inform future EPR-embedded and data-enabled neonatal trials and will be disseminated through conferences, publications and parent-centred information.

**Strengths and limitations of this study**

- **Necrotising enterocolitis (NEC)** is a rare but potentially devastating neonatal disease, occurring predominantly in the most preterm infants. Neonatal trials to-date have not been adequately powered to detect realistic reductions in NEC.
- In this prospective, randomised pilot trial we will evaluate the feasibility of a data-enabled neonatal trial with processes embedded within an existing electronic patient record (EPR) system; accuracy and completeness of trial data will be validated at source.
- In this individually randomised, comparative effectiveness trial we will pilot opt-out consent and explore parent and health professional views of this approach in a nested qualitative study.
- We will evaluate the feasibility of EPR-embedded randomised comparative-effectiveness trials using a simplified opt-out consent for efficient, quicker and less resource burdensome neonatal trials at scale.

**BACKGROUND**

Necrotising enterocolitis (NEC) is among the most potentially devastating neonatal diseases and has a mortality of up to 33%, the most severe form (requiring surgery or resulting in death) affects about 5% of infants born at...
<30 gestational weeks; survivors are at high risk of long-term health and developmental problems. Prevention of NEC has been identified as one of the most important research uncertainties in the field of preterm birth. The pathogenesis of NEC is incompletely understood, however a temporal association between red cell transfusion and the subsequent development of the disease is well described. This ‘transfusion associated NEC’ may be more severe with higher mortality. The mechanism thought to underpin this relationship links milk feeds and red cell transfusion to NEC through altered mesenteric blood flow and intestinal barrier function; this is supported by animal and human studies. Understanding the link between NEC and blood transfusion is of particular importance given that almost all very preterm babies will have a red cell transfusion and many will receive multiple transfusions.

Stopping milk feeds around the time of packed red cell transfusion is currently practised in some neonatal settings to reduce the risk of NEC, putatively by maintaining more physiological intestinal blood flow. This practice has not, however, been tested in an adequately powered randomised trial, and there are physiological reasons why stopping milk feeds in preterm infants may lead to harm. Interrupting enteral feeding prolongs the time taken to reach full milk feeds, which is associated with invasive infection, and may paradoxically be associated with an increased risk of NEC. One small, single-centre randomised pilot trial has assessed withholding enteral feeds around red cell transfusion but was underpowered to detect a difference in NEC. A systematic review of observational studies identified seven historical control studies including 7492 preterm infants; these studies were at high risk of bias including regression to the mean and ascertainment bias. Pooled results found an association between withholding feeds in the peritransfusion period and a reduced risk of NEC. The authors concluded that adequately powered randomised controlled trials are needed to confirm these findings.

There is considerable variation in current UK practice in relation to withholding enteral feeds during packed red cell transfusion in preterm infants: a 2011 survey of UK neonatal units (68% response rate) demonstrated that 35% of UK units routinely withheld enteral feeds during packed red cell transfusion.

If withholding enteral feeds around the time of packed red cell transfusion reduces the risk of NEC, then implementing this simple practice will reduce the mortality and long-term complications of NEC. Conversely, if the safety of continued feeding can be demonstrated, this will facilitate increased and consistent feeding with breast-milk, which has well described short-term and long-term benefits.

NEC is rare and occurs at a higher incidence in the most preterm infants and so trials targeting NEC need a large number of very preterm infants, who are themselves rare. As a result, no previous trial has been powered to look at NEC and there is no intervention to prevent NEC supported by high-quality randomised evidence. Methodologies that have been proposed to improve efficiency and recruitment into randomised trials include the use of simplified opt-out approaches to consent, and embedding trial processes into existing electronic patient record (EPR) systems.

The objectives of this pilot trial are:
1. To determine whether a large multicentre trial addressing the following question is feasible: among preterm infants (patient), does the practice of withholding enteral feeds around the time of blood transfusion (intervention), compared with continued enteral feeding around the time of blood transfusion (comparator), lead to a reduction in severe necrotising enterocolitis (outcome)?
2. To determine whether clinical trial processes (identifying participants, randomisation and data collection) can be successfully integrated into existing neonatal EPR systems, and whether trial data can be extracted from routinely recorded clinical data held in the National Neonatal Research Database (NNRD).
3. To determine whether using a simplified opt-out consent process is feasible and acceptable to parents and health professionals.

METHODS
Design
The WHEAT trial is a randomised controlled, unblinded, multicentre, pilot trial comparing two care pathways.

Eligibility criteria
Inclusion criteria:
1. Preterm birth at <30+0 gestational weeks+days.
2. Packaged red cell transfusion with concurrent enteral feeds prior to enrolment.

Exclusion criteria:
1. Parent(s) opted out of trial participation.
2. Parent(s) opted out of trial participation.
3. Infants where enteral feeding is contraindicated in the first 7 days after birth (eg, congenital abnormality).

**Interventions**

Both comparator pathways of care are standard in the UK; the WHEAT trial is a pilot comparative effectiveness trial. The two care pathways that will be compared are:

1. Withholding feeds around transfusion: all enteral feeds will be discontinued (the infant will be placed nil by mouth) for a period of 4 hours prior to packed red cell transfusion, during the packed red cell transfusion and until 4 hours post packed red cell transfusion. During this period (~12 hours), hydration and blood glucose will be maintained according to local practice, commonly by provision of parenteral nutrition or intravenous dextrose. Four hours after the red cell transfusion has finished, feeds will be restarted in the manner in which they were being received prior to the decision to transfuse. This duration of withholding feeds will follow the approach used in other trials and observational studies, and identified to be the most acceptable in a survey of UK neonatal units.

2. Continuing feeds around transfusion: enteral feeds will continue to be given prior, during and after the packed red cell transfusion, in the manner in which they were being given prior to the decision to transfuse. Infants will remain allocated to the same care pathway until 34+6 weeks+days gestational age.

In order to ensure that this pragmatic trial is as generalisable as possible to current practice, blood transfusions will be administered when clinically indicated according to local packed red cell transfusion guidelines. Data will be collected about pretransfusion haemoglobin level for packed red cell transfusion, in the manner in which they were being received prior to the decision to transfuse. This duration of withholding feeds will follow the approach used in other trials and observational studies, and identified to be the most acceptable in a survey of UK neonatal units.

**Outcomes**

Feasibility outcomes:

1. Recruitment: proportion of infants <30 weeks of gestation admitted whose parents agree to trial involvement and the infant is randomised in the WHEAT trial.

2. Retention: proportion of recruited infants where outcome data are available up to the end of the follow-up period.

3. Compliance: proportion of recruited infants who correctly received their allocated care pathway around all packed red cell transfusions between randomisation and 34+6 gestational weeks+days.

4. Data completeness: proportion of missing data for each data item reported as a baseline characteristic or an outcome.

5. Data accuracy: proportion of cases where the following data items are correctly recorded when compared with source data (clinical notes or EPR data).

a. Severe NEC: all infants who had a diagnosis of non-severe NEC and a random sample of 25% of infants who did not have a diagnosis of NEC will have their source data verified to ensure that they do not meet the criteria for severe NEC; 25% was selected for pragmatic reasons.

b. Spontaneous intestinal perforation.

c. All-cause mortality.

d. Central line associated blood stream infection.

Clinical outcomes:

All clinical outcomes will be assessed from randomisation to 40+0 weeks of gestation or neonatal unit discharge, whichever occurs first.

1. Severe NEC: histologically or surgically confirmed, or recorded in part 1 the death certificate. These infants will be identified as described in Battersby et al, which include infants recorded as being transferred for surgery.

2. Spontaneous intestinal perforation: histologically or surgically confirmed, or recorded in part 1 the death certificate.

3. All-cause mortality.

4. Total duration of neonatal care in days: including all levels of care (intensive care, high dependency care, special care and ordinary care).

5. Duration of any parenteral nutrition in days.

6. Number of days with a central venous line in situ.

7. Number of central line associated blood stream infections defined according to National Neonatal Audit Programme 2017 definition.

8. Growth: change in birth weight and head circumference for gestational age SD score.

**Sample size**

There is no predefined sample size for this pilot trial. Recruitment (absolute numbers and the rate) will be a primary outcome for the pilot trial. The estimated recruitment target for the pilot trial is up to 250, based on predicted infant throughput at participating neonatal units and assuming 65%-70% recruitment of eligible infants.

**Data collection**

Potential participants will be identified through the existing neonatal EPR systems that are widely used across England, Scotland and Wales; BadgerNet (a clinical summary system) or BadgerEPR (a complete EPR system). Baseline data for all infants admitted to neonatal units in the UK are routinely entered into the EPR admission summary as part of normal clinical care. These data are updated in real-time and held securely on BadgerNet and BadgerEPR servers. In participating units, data entered electronically into the admission summary will be interrogated by the EPR platform in real time to identify and flag infants meeting the WHEAT trial inclusion criteria. When an infant in a participating unit meets the inclusion criteria, this will result in an electronic reminder appearing on the EPR platform at the participating...
unit. This 'flag' will inform the health professional that the infant is eligible for the WHEAT trial and link to the parent information leaflet. The EPR system will use data (neonatal unit, gestational age and sex) entered as part of the admission summary to stratify infants.

Baseline characteristics and clinical outcomes will be extracted from routinely recorded clinical data held in the NNKD. The NNKD holds data from all infants admitted to National Health Service (NHS) neonatal units in England, Scotland and Wales (~90,000 infants annually). Contributing neonatal units are known as the UK Neonatal Collaborative. Data are extracted from point-of-care neonatal electronic health records completed by health professionals during routine clinical care. A defined data extract, the Neonatal Dataset of ~450 data items, is transmitted quarterly to the Neonatal Data Analysis Unit at Imperial College London and Chelsea and Westminster NHS Foundation Trust where patient episodes across different hospitals are linked and data are cleaned (queries about discrepancies and implausible data configurations are fed back to health professionals and rectified).

**Randomisation**
Infants will be randomly assigned to either pathway of care in a 1:1 allocation ratio as per a computer-generated randomisation sequence using permuted blocks of various sizes with stratification as described below. The block sizes will not be disclosed to ensure allocation concealment.

Stratification will be by neonatal unit of enrolment and using the following categories:
1. Gestational age at birth.
   - <28+0 weeks+days
   - 28+0 to 29+6 weeks+days.
2. Infant sex.
   
   Infants who are part of a multiple birth set (twins, triplets or higher order multiples) will be randomised as a set to the same pathway of care following feedback from parent representatives, parent organisations including Bliss and TAMBA (Twins and Multiple Births Association) and research involving parents and adult ex-preterm twins.

**Allocation concealment**
Infants will be randomised using an online secure central randomisation system which will be embedded into the existing neonatal EPR systems (BadgerNet and BadgerEPR). Randomisation will occur within the EPR to ensure allocation concealment.

**Blinding**
The WHEAT trial will be unblinded as it is not possible to mask the different care pathways.

**Statistical methods**
The planned main WHEAT trial will be based on a superiority hypothesis; however, the pilot trial is not powered to detect any differences between the intervention arm (withholding feeds) and the comparator arm (continuing feeds).

Therefore, no formal statistical hypothesis testing will be conducted.

Continuous variables will be summarised using means and SD unless their distributions are skewed, in which case medians, 25th quartiles, 75th quartiles and the range (lowest and highest values) will be presented. Dichotomous variables will be presented as frequencies and percentages. In addition, 95% CIs will be presented for the feasibility outcomes. The recruitment rate will be reported for both arms combined, and retention and compliance rates will be reported separately by treatment arm in addition to both arms combined.

**Changes to the statistical analysis described in the original protocol**
The original protocol is available as supplementary data. The following changes to the statistical analysis plan were made prior to completion of data collection:
1. The pilot trial will not be performing any comparative analysis of outcomes between trial arms, or conducting any formal statistical hypothesis testing.
2. The denominator for the recruitment rate will be infants ≤30 weeks of gestation admitted to recruiting sites; the planned denominator (infants who fulfil all of the eligibility criteria and whose parents have been approached) cannot be used as regulatory approval to use these data was not granted.
3. The opt-out rate of parents whose infants are eligible for the trial will not be reported as regulatory approval to use these data was not granted.
4. Data completeness will be reported for each individual data item and not the proportion of eligible infants for which trial items are complete.
5. A random sample of 25% of infants who did not have a diagnosis of NEC recorded in the EPR system had their source data verified to ensure that they did not meet the criteria for severe NEC.
6. All outcome events, including duration of hospital stay and growth scores, were be measured until neonatal unit discharge or 40+0 weeks of gestation, whichever occurs first.

**Steering committee**
An independent Trial Steering Committee (TSC) appointed by the study sponsor and approved by the funder (MRC) will oversee the project. The TSC will consist of an independent chair and at least two other independent members. The Chief Investigator and Clinical Trials Unit Director will also sit on the TSC.

**Data monitoring**
A Data Monitoring Committee (DMC) independent of the applicants and of the TSC will review the progress of the trial as agreed and provide advice on the conduct of the trial to the TSC and, via the TSC, to the sponsor. The DMC will act according to its charter, which will be agreed at its first meeting.
Adverse events
Due to the nature of the patient population, neonates in intensive care, a high incidence of adverse events is foreseeable during their routine care and treatment. Consequently, only those adverse events identified as serious adverse events (SAEs) will be recorded for the trial. Unforeseen SAEs and the SAEs associated with the allocated pathway of care must be reported to the Clinical Trials Unit by a member of site staff within 24 hours of becoming aware of the event. Reporting of SAEs will not use existing EPR systems but will use telephone, fax and email systems.

Registration
This study is registered in ISRCTN.

Parent, patient and public involvement
The WHEAT pilot trial addresses one of the most important research uncertainties in preterm birth, as identified by over 500 parents, patients, health professionals and researchers. The WHEAT trial has been developed in partnership with parents; protocol author HR is a parent with experience of preterm birth and protocol author LC represents Bliss, the charity for babies born premature or sick; both HR and Bliss have contributed to trial development from inception. Over 400 parents and patients have contributed to the selection of trial outcomes through the COIN project. Parents and Bliss have been involved in developing the opt-out consent process, how this is communicated, in designing information leaflets and posters. The WHEAT trial has parent representatives on oversight committees to ensure that the trial be undertaken with both parents that consented to the trial and health professionals from the recruiting sites.

Due to the common nature of packed red cell transfusion in the trial population (infants born at <30+0 gestational weeks+days), health professionals will explain the WHEAT trial and opt-out process shortly after birth (in most cases within the first 24 hours). A minority of infants will not receive a packed red cell transfusion during their neonatal unit stay. These will not be included in the main analysis population of clinical outcomes.

Results will be presented at national and international academic conferences and published in peer-reviewed scientific publications. Protocol author HR will work with the neonatal charity Bliss to produce parent-centred information for dissemination through social media, online and to be distributed on neonatal units.

DISCUSSION
Preventing NEC is a recognised research priority in preterm birth; however, there are no preventative interventions supported by high quality evidence. One key reason is because NEC is a rare condition, therefore any trial seeking to detect a realistic reduction in NEC will require recruitment and randomisation of more preterm infants than ever previously achieved. For example, a trial seeking to detect a 25% relative risk reduction in NEC from a background rate of 6% would need to randomise over 9000 infants to have 90% power to detect such a difference with a two-sided 5% significance level. The largest previous individually randomised trial that included preterm infants was the INIS trial which enrolled 3493 infants. Undertaking neonatal trials on this scale will be challenging; for such large trials to be funded and sustainable, they will need to be more efficient, less burdensome and international in scope. There are successful examples of large simple trials in other specialties that can inform neonatal practice: the TASTE trial demonstrated high efficiency and low burden by integrating trial processes within an existing data capture system, and the TRANSFUSE trial demonstrated very high recruitment rates (>75%) through the use of opt-out models of consent. The WHEAT pilot trial will apply these approaches and measure their feasibility and acceptability in neonatal care. If these methodologies can be successfully applied, they will facilitate efficient, large, simple trials suitable to address the many clinical uncertainties the plague neonatal care.

The WHEAT pilot trial will determine the feasibility of addressing an important clinical question regarding the optimal approach to feeding preterm infants around the time of red cell transfusions, in preparation for a future definitive trial. Currently, there is insufficient evidence to recommend withholding or continuing milk feeds around red cell transfusion in preterm infants because available physiological and observational data are inconclusive.

Gale C, et al. BMJ Open 2019;9:e033543. doi:10.1136/bmjopen-2019-033543
Strength and limitations

The proposed trial has a number of strengths. The robustness of core NNRD data (birth weight, sex, length of stay and death) have been previously demonstrated for research purposes.1 3 36 this pilot trial will prospectively evaluate their accuracy and completeness for clinical trials. The trial will evaluate the feasibility of recruiting infants across two neonatal networks, including smaller neonatal units that do not traditionally recruit into neonatal randomised trials. Limitations include the unblinded nature of the trial and the use of a potentially subjective primary outcome, NEC. We endeavoured to mitigate against these through use of a previously validated, objective definition for NEC.1

CONCLUSION

Neonatal trials to date have been unable to robustly evaluate strategies to prevent major preterm morbidities, such as optimal feeding around transfusion to prevent NEC, because of the large sample sizes required. This protocol describes a prospective, randomised controlled pilot trial to evaluate trial methodologies aiming to efficiently address such neonatal uncertainties.

Author affiliations

1 Neonatal Medicine, School of Public Health, Chelsea and Westminster campus, Imperial College London, London, UK
2 Division of Neonatal-Perinatal Medicine, Faculty of Medicine, Dalhousie University, IWK Health Centre, Halifax, Nova Scotia, Canada
3 Clinical Trials Unit, Nuffield Department of Population Health, University of Oxford, National Perinatal Epidemiology Unit, Oxford, UK
4 Neonatal Unit, James Cook University Hospital, Middlesbrough, UK
5 Nuffield Department of Population Health, University of Oxford, National Perinatal Epidemiology Unit, Oxford, UK
6 Women’s and Children’s Health, Institute of Translational Medicine, University of Liverpool, Liverpool, UK
7 Parent of Preterm Twins, Bliss – The National Charity for the Newborn, London, UK
8 Centre for Health Informatics, Division of Informatics, Imaging and Data Science, School of Health Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK

Acknowledgements We are grateful to all the families who agreed to the inclusion of their baby’s data in the NNRD, the health professionals who recorded data and the NDAU team, the members of the study steering group and the members of the NU Neonatal Collaborative representing neonatal units that contribute data to the NNRD.

Contributors CG, NM, JD, AF, MAT, HR, TVS and EJ conceived the study. CG, NM, SJ, LC, JD, UB, AF, AK, JM, LL, MAT, HR, KS, TVS and EJ contributed to the planning, conduct and reporting of the study, and writing this manuscript. All authors read and approved the final manuscript. HR is a parent of a preterm twins and LC is a representative of Bliss the charity for babies born premature or sick.

Funding The trial is funded through a United Kingdom Medical Research Council (MRC) Clinician Scientist Fellowship awarded to CG.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Research Ethics Committee approval was granted on 6 July 2018 by London—Bloomsbury Research Ethics Ethics Committee (18/LO/0900).

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/.

REFERENCES

1. Battersby C, Longford N, Mandalisa S, et al. Incidence and enteral feed antecedents of severe neonatal necrotising enterocolitis across neonatal networks in England, 2012–13: a whole-population surveillance study. Lancet Gastroenterol Hepatol 2017;2:43–51.
2. Duro D, Kallah LA, Johnston P, et al. Risk factors for intestinal failure in infants with necrotizing enterocolitis: a Glaser pediatric research network study. J Pediatr 2010;157:203–8.
3. Hintz SR et al. Neurodevelopmental and growth outcomes of extremely low birth weight infants after necrotizing enterocolitis. Pediatrics 2005;115:696–703.
4. Rees CM, Pierno A, Eaton S. Neurodevelopmental outcomes of neonates with medically and surgically treated necrotising enterocolitis. Arch Dis Child Fetal Neonatal Ed 2007;92:F193–8.
5. Halfon N, Uhm S, Oliver S, Preterm neonatal mortality setting partnership steering G: top 15 UK research priorities for preterm birth. Lancet 2014;383:2041–2.
6. Seges RA, Kenny A, Bird GW, et al. Pediatric surgical patients with severe anaerobic infection: report of 16 T-antigen positive cases and polycythemia hazards of blood transfusion. Journal of pediatric surgery 1981;16:905–10.
7. Stritzke AI, Smyth J, Synnes A, et al. Transfusion-associated necrotising enterocolitis in neonates. Arch Dis Child Fetal Neonatal Ed 2013;98:F10–F1.
8. Blau J, Caio JM, Dozor D, et al. Transfusion-related acute gut injury: necrotizing enterocolitis in very low birth weight neonates after packed red blood cell transfusion. J Pediatr 2011;158:403–9.
9. Mally P, Golombok S, Mishra R, et al. Association of necrotizing enterocolitis with elective packed red blood cell transfusions in stable, growing, premature neonates. Am J Perinatol 2006;23:451–8.
10. Cunningham KE, Okolo FC, Baker R, et al. Red blood cell transfusion in premature infants leads to worse necrotizing enterocolitis outcomes. J Surg Surgical Research 2017;213:158–65.
11. Nair J, Gugino SF, Nielsen LC, et al. Packed red cell transfusions alterations mesenteric arterial reactivity and nitric oxide pathway in preterm lambs. Pediatr Res 2013;74:652–7.
12. Szabo JS, Mayfield SR, Oh W, et al. Postprandial gastrointestinal blood flow and oxygen consumption: effects of hypoxemia in neonatal piglets. Pediatr Res 1987;21:93–8.
13. Krimmel GA, Baker R, Yanowitz TD. Blood transfusion alters the superior mesenteric artery blood flow velocity response to feeding in premature infants. Am J Perinatol 2009;26:99–105.
14. Kempley ST, Gamsu HR. Superior mesenteric artery blood flow velocity in necrotising enterocolitis. Arch Dis Child 1992;67:793–6.
9c499f48-9ff9-4000-9b0d-b3119df8e2fa. Marin T, Josephson CD, Kosmetatos N, et al. Feeding preterm infants during red blood cell transfusions is associated with a decline in postprandial mesenteric oxygenation. J Pediatr 2014;165:464–71.
15. Kirpalani H, Whyte RK, Anderssen C, et al. The premature infants in need of transfusion (pint) study: a randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. J Pediatr 2006;149:301–7.
16. El-Dib M, Narang S, Lee E, et al. Red blood cell transfusion, feeding and necrotizing enterocolitis in preterm infants. J Perinatol 2011;31:183–7.
17. 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:CD002141.
18. Kritsmann M, Yoon EW, Ojaj C, et al. Nip-per-os days and necrotizing enterocolitis in extremely preterm infants. Am J Perinatol 2015;32:785–94.
19. Sahin S, Gozde Kamanz Kutman H, Bozkurt O, et al. Effect of withholding feeds on transfusion-related acute gut injury in preterm infants: a pilot randomized controlled trial. J Matern Fetal Neonatal Med 2019;4:1–6.
20. Jasani B, Rao S, Patole S. Withholding feeds and transfusion-associated necrotizing enterocolitis in preterm infants: a systematic review. Adv Nutr 2017;8:784–9.
21. Parige R, Turner C, Sundaram S, et al. Enteral feeding during packed red blood cell transfusion in English neonatal units. Arch Dis Child Fetal Neonatal Ed 2014;99:F173.
22. Gale C, Hyde MJ, Modl N. Research ethics Committee decision-making in relation to an efficient neonatal trial. Arch Dis Child Fetal Neonatal Ed 2016.
24. van Staa T-P, Dyson L, McCann G, et al. The opportunities and challenges of pragmatic point-of-care randomised trials using routinely collected electronic records: evaluations of two exemplar trials. *Health Technol Assess* 2014;18:1–146.

25. Battersby C, Longford N, Costeloe K, et al. Development of a gestational Age–Specific case definition for neonatal necrotizing enterocolitis. *JAMA Pediatr* 2017;171:256.

26. RCPCH. *National neonatal audit programme (NNAP) 2018 annual report on 2017 data*. London: Royal College of Paediatrics and Child Health (RCPCH), 2018.

27. NHS Digital. National neonatal data set. in. edited by dictionary Nd, 3 EDN., 2016. Available: http://www.datadictionary.nhs.uk/web_site_content/navigation/national_neonatal_data_sets_menu.asp

28. Spencer A, Modi N. National neonatal data to support specialist care and improve infant outcomes. *Arch Dis Child Fetal Neonatal Ed* 2013;98:F175–F180.

29. Bernardo J, Nowacki A, Martin R, et al. Multiples and parents of multiples prefer same arm randomization of siblings in neonatal trials. *J Perinatol* 2015;35:205–13.

30. Webbe J, Brunton G, Ali S, et al. Developing, implementing and disseminating a core outcome set for neonatal medicine. *BMJ Paediatrics Open* 2017;1:e000048.

31. Brocklehurst P, Farrell B, King A, et al. Treatment of neonatal sepsis with intravenous immune globulin. *N Engl J Med* 2011;365:1201–11.

32. Fröbert O, Lagerqvist B, Olivecrona GK, et al. Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med* 2013;369:1587–97.

33. Cooper DJ, McQuilten ZK, Nichol A, et al. Age of red cells for transfusion and outcomes in critically ill adults. *N Engl J Med* 2017;377:1858–67.

34. Wilhelm C, Girisch W, Gottschling S, et al. Systematic Cochrane reviews in neonatology: a critical appraisal. *Pediatr Neonatol* 2013;54:261–6.

35. Gale C, Santhakumaran S, Nagarajan S, et al. Impact of managed clinical networks on NHS specialist neonatal services in England: population based study. *BMJ* 2012;344:e2105.

36. Battersby C, Statnikov Y, Santhakumaran S, et al. The United Kingdom national neonatal research database: a validation study. *PLoS One* 2018;13:e0201816.