A systematic review identifying common data items in neonatal trials and assessing their completeness in routinely recorded United Kingdom national neonatal data

Sena Jawad
Imperial College London
Neena Modi
Imperial College London
A Toby Prevost
Imperial College London
Chris Gale (christopher.gale@imperial.ac.uk)
Imperial College London https://orcid.org/0000-0003-0707-876X

Review

Keywords: common data items, data quality, NNRD, efficient trials, Electronic Patient Records, Electronic Health Records, neonatal clinical trials

Posted Date: October 3rd, 2019

DOI: https://doi.org/10.21203/rs.2.9763/v2

Version of Record: A version of this preprint was published on December 16th, 2019. See the published version at https://doi.org/10.1186/s13063-019-3849-7.

Abstract

Background We aimed to test whether a common set of key data items reported across high impact neonatal clinical trials could be identified, and to quantify their completeness in routinely recorded United Kingdom neonatal data held in the National Neonatal Research Database (NNRD). Methods We systematically reviewed neonatal clinical trials published in four high impact medical journals over 10 years (2006-2015) and extracted baseline characteristics, stratification items, and potential confounders used to adjust primary outcomes. Completeness was examined using data held in the NNRD for identified data items, for infants admitted to neonatal units in 2015. The NNRD is a repository of routinely recorded data extracted from neonatal Electronic Patient Records (EPR) of all admissions to National Health Service (NHS) Neonatal Units in England, Wales and Scotland. We defined missing data as an empty field or an implausible value. We reported common data items as frequencies and percentages alongside percentages of completeness. Results We identified 44 studies involving 32,095 infants and 126 data items. Fourteen data items were reported by more than 20% of studies. Gestational age (95%), sex (93%) and birth weight (91%) were the most common baseline data items. The completeness of data in the NNRD was high for these data with greater than 90% completeness found for 9 of the 14 most common items. Conclusion High impact neonatal clinical trials share common data items. In the United Kingdom, these items can be obtained at a high level of completeness from routinely recorded data held in the NNRD. The feasibility and efficiency using routinely recorded EPR data, such as that held in the NNRD, for clinical trials, rather than collecting these items anew, should be examined. Registration PROSPERO registration number CRD42016046138, registered prospectively 17 th August 2016

Introduction

High quality randomised controlled trials are considered the gold standard research approach to identify causality or demonstrate treatment efficacy. There are many treatment uncertainties in neonatal practice (1) that would benefit from being subjected to high quality randomised clinical trials (2). However, the high cost of undertaking large and methodologically robust trials (3) means that only a small number are undertaken each year: the median cost of phase III trials of therapeutic agents in 2015-2016 was $19 million (4) and publicly funded pragmatic neonatal trials cost £1.5-2 million (5). A key driver of cost in clinical trials is data collection; the mean costs of trial data collection using conventional Case Record Forms have been estimated to be €1,135 per participant (6) . More efficient collection, for example using electronic case record forms (6) and routinely available clinical data (7), provide opportunities to reduce costs and facilitate neonatal trials to improve the limited evidence base upon which much of neonatal care currently relies.

Methods to increase the efficiency of clinical trial data collection have been described by organisations such as the Institute of Medicine (8) and the Clinical Trials Transformation Initiative (9); these include targeted collection of common core data items, and extraction of trial data from existing sources, such as Electronic Patient Record (EPR) systems or disease registries; these approaches are most likely to be applicable to pragmatic trials (10). The use of existing "real-world" data sources such as these provides additional advantages: they can provide up-to-date incidence estimates for baseline and outcome event rates to better inform sample size calculations, and the accuracy and completeness of key data items can be estimated in advance from historical data to inform trial feasibility at the planning stage, and address widely held concerns about poor quality of data from existing sources (11). However, because not all data items held within a routinely recorded database or registry will be relevant to clinical trials, the data items that are "core" (9) for clinical trials in a particular clinical area need to be established. Established approaches exist for the definition of Core Outcome Sets (12), but none for core *non-outcome* data for clinical trials, for example baseline or background data, and items used in randomisation.

An increasing proportion of neonatal Cochrane reviews are inconclusive because of insufficient high-quality data from randomised trials (2). Neonatal care in the United Kingdom is well placed to develop large, efficient trials that use existing data: all infants admitted for National Health Service (NHS) neonatal care in England, Scotland and Wales have clinical data recorded in a summary EPR system as part of routine clinical care, and predefined data (13) are extracted to form the National Neonatal Research Database (NNRD). The effectiveness and efficiency of using routinely recorded clinical data held in the NNRD for data-enabled neonatal trials, are currently being investigated (14). We hypothesised that a set of common data items have been reported across neonatal trials that impact clinical practice; the aim of this study was to identify common neonatal data items. As there is no established approach for the identification of common baseline data items we undertook a systematic review to identify baseline data items reported in neonatal trials. A secondary aim was to quantify the completeness of these commonly reported items in the NNRD to inform whether this could be used as the sole or principal data source for clinical trials.

Methods

Systematic review

To identify data commonly reported in neonatal trials we conducted a systematic review of neonatal clinical trials published in high impact journals. We developed a protocol with explicitly defined objectives, information to be extracted, and statistical methods. We prospectively registered the protocol with PROSPERO International Prospective Register of Systematic Reviews, registration number CRD42016046138 (https://www.crd.york.ac.uk/prospero), registered on 17th August 2016.

We searched the four most highly cited general medical journals that publish neonatal trials (15) (New England Journal of Medicine, Lancet, British Medical Journal, and Journal of the American Medical Association) over a 10 year period from January 1st 2006 to December 31st 2015, using the PubMed database. The PubMed search strategy is described in supplemental item 1. We extracted randomised clinical trials written in English that tested an intervention delivered to newborn infants in a neonatal unit setting, with no restriction on the disease area or treatment type. Prior to data extraction we changed the inclusion criteria for studies to include trials of infants born at more than 34 gestational weeks, so that the results would be more generalisable to neonatal trials. We did not include trials where an intervention was applied to a pregnant mother and infant outcomes were reported. Two authors (SJ and CG) independently performed the screening of each potentially relevant record and reviewed full text where necessary to assess eligibility. Discrepancies between the authors were resolved through discussion.

Two authors (SJ, CG) independently extracted the following items from included clinical trials: baseline items, items used in stratification or minimisation, and items used to adjust primary outcomes. Other study characteristics that we extracted included whether the trial was multi-centre and whether it involved preterm or term infants. Outcome data were not extracted as these are the subject of other parallel work (16). A comprehensive list of reported data items and frequencies was extracted. Items were combined where appropriate, for example administration of different medications was combined into the item "medications". Preterm studies were defined as studies involving babies with a gestational age of less than 37 weeks or weighing less than 1,500 grams and term studies as studies on babies born at or above 37 weeks gestation. A formal risk of bias assessment was not conducted as the interest of this study was limited to the data collected, not the interventions or the measure of efficacy.

Data completeness

Data completeness in the NNRD was examined for infants born in England, Scotland and Wales during the period January 1st 2015 to December 31st 2015 for the first 7 postnatal days. The NNRD contains over 400 different data per each baby; data held in the NNRD are extracted from individual infants' EPR data routinely recorded by healthcare professionals as part of clinical care. Details of the Neonatal Dataset are searchable at the following webpage (13) and descriptive data for infants within the NNRD are available here (17). We calculated the completeness in the NNRD of each data item reported by at least 20% of clinical trials included in the systematic review.

We defined incompleteness as an empty field or an implausible value. Where an item identified through the systematic review (for example *birth weight*) directly matched a corresponding NNRD field, the completeness of these items was directly calculated. Where an item identified in the systematic review mapped to several fields in the NNRD (for example *respiratory support*, identified in the systematic review, maps to several NNRD fields, including respiratory support, mode of ventilation, non-invasive respiratory support, nitric oxide, tracheostomy, surfactant (13)), completeness was determined by at least one value that was not missing or implausible (according to the neonatal data set data dictionary definition) over the multiple possible NNRD fields.

Results

Systematic review

We identified 161 articles in the literature search. We excluded 117 articles leaving 44 eligible to be included in the review (figure 1). Twenty-nine studies included only preterm babies, 6 only term babies and 9 studies included both terms and preterm babies (table 1). The majority of studies (91%) were multicentre trials and overall included 30,968 participants (table 1).

The median number of baseline data items reported in the 44 included trials was 12. Gestational age, sex and birth weight were collected as baseline items for 42 of 44 studies (table 2). Fourteen data items were reported by at least 20% of studies; 66 baseline data items were reported by 1 study alone (supplementary table 1). No study reported all 14 of the most common data items.

Sixteen stratification items were reported by 35 trials. Neonatal unit identifier (57%) and gestational age (39%) were the most common items used for stratification during randomisation. Two (13%) of these stratification items were reported by more than 20% of trials and 9 (56%) were reported by 1 study only (supplementary tables). Twenty-four items were reported by 33 trials to adjust the primary outcome. Of these, 3 (13%) were reported by more than 20% of all trials and 12 (50%) were reported by 1 study only (supplementary tables). Eight (50%) stratification and 9 (38%) adjustment items were in the top 14 background data items. A full list of all common items can be found in the supplementary tables.

Data completeness

In 2015, 96,699 infants were admitted to 180 neonatal units in England, Wales and Scotland. Admitted infants received 472,187 days of neonatal care during the first 7 days following birth (data not shown).

The completeness of common data items in the NNRD are summarised by age groups in table 4. Data completeness in the NNRD is 99.9% for gestational age at birth, 99.9% for sex, 100% for birth weight, 99.7% for multiple birth and 100% for respiratory support on day 1 (table 2). The majority of data items were more than 90% complete, exceptions include maternal ethnicity (70.2%), mode of delivery (81.4%) and Apgar score at 5 minutes (79.1%). Completeness was higher for all data items for preterm (mean completeness 94.4%) compared to term babies (mean completeness 89.2%) (table 3).

Discussion

We have identified a common set of non-outcome data items reported in high impact neonatal trials. We find that these 14 data items can be obtained from the NNRD with high completeness for most items. The common data items identified here have previously been validated against independently collected trial data (17) where they were shown to be highly accurate and complete in the NNRD. This supports the assertion that non-outcome data held in the NNRD can be used to support large, efficient neonatal trials. We recognise that the trials included in the systematic review also reported a wide range of additional non-outcome data items that were not included in the common set identified here. In planning future pragmatic neonatal trials, the completeness and accuracy of additional data items critical to the integrity of a planned trial can be evaluated using approaches similar to those applied here. However, the finding that reported data items were variable even between similar trials (supplemental table 2) suggests that some reported data items may not have been critical to trial integrity, and that harmonisation of non-outcome data items may improve the consistency and efficiency of future neonatal trials. The common non-outcome

data items we identify here, and their completeness and accuracy (17) in the NNRD, can be used to assess the suitability and feasibility of using the NNRD and other similar routinely recorded data sources for neonatal trials.

Data completeness of the NNRD has previously been calculated by Battersby et al (17) in relation to a single clinical trial between 2008 and 2015. In this study percentage completeness was very similar to that found in the present study where common data items examined multiple births, gestational age, sex and birth weight, indicating that data completeness within the NNRD for these items is consistent over time. The present study builds upon this work by examining completeness for a wider range of empirically identified non-outcome data items, therefore extending the relevance of these results to a wider range of potential clinical trials. For large neonatal trials in the United Kingdom, we demonstrate that the core non-outcome data items identified here are held in the NNRD to a high degree of completeness. For some core non-outcome data items, such as gestational age at birth, we show that the likelihood of missing data in clinical trials utilising the NNRD is small. These results can be used to develop and apply approaches to improve the recording of critical data items with lower completeness in a targeted way, for example mode of delivery.

Common data sets in other clinical and research areas have been identified using a variety of methods. Doods et al. (18) identified common data groups and elements for feasibility analysis in cardiovascular, diabetes, inflammatory, oncology and neurology through the use of an expert panel, but did not review the literature or include expertise from outside the field. This study identified a wide range of laboratory tests for feasibility studies. Diagnostic test data were not identified in our systematic review of large neonatal trials as commonly reported non-outcome data items, indicating that such data items are not as relevant to the pragmatic neonatal trials that are the focus of this work. Sheehan at al. (19) outline previously developed common data element sets, and some of the challenges inherent in adopting and using such set. Chari et al. (20) conducted a systematic review of included trials and observational studies to identify common data elements in chronic subdural hematoma studies and, in keeping with our results, identified a core set of commonly reported non-outcome items. The approach that we used was a more limited systematic review of trials published in high impact journals. This approach was chosen *a-priori* to focus on data-items reported in trials that influence neonatal practice. This was a pragmatic decision and there are limitations to this approach: by limiting our review to general medical journals we may have missed influential trials published in specialty journals, and have not sampled the range of outcomes reported in smaller trials. Furthermore, no approach to date has sought parent or patient views on the importance of different non-outcome data items; this may be important given the different priorities identified by these groups compared to health professionals and researchers (21). The examples cited here demonstrate the interest in, and potential value of, common sets of non-outcome data items, across different specialties. The development of an established methodological approach, analogous to that developed by the COMET initiative (12) would increase the consistency, robustness and comparability of such endeavours in future.

Our study has focused on defining the data items usually recorded at baseline or used as explanatory data items in clinical trials. To our best knowledge there have been no previous attempts to identify core non-outcome trial data items such as these. We included the most common data items used in randomisation, which are often selected to conduct pre-specified subgroup analyses, and to adjust for the primary outcome. These items are often overlooked when exploring the impact of data quality in trials, despite the importance of completeness of these items for preserving statistical power and avoiding misinterpretation of results. We did not focus on outcome data items because the methodology to identify these data is well developed and such work is underway in neonatal medicine (16). A limitation of our study is that data may have been selectively reported thus introducing bias, however this is lessened as the included journals review protocols are designed to ensure those items listed in the protocol are presented in the main trial outcomes publication. A further limitation of our study was that some items identified were dichotomous, for example presence or absence of infection prior to trial enrolment and it was not possible to calculate completeness for such items as absence of the condition is not always actively recorded. An additional limitation stems from the fact that some data items collected in clinical trials did not directly align with data items in the NNRD, therefore there may be a loss of information from aggregating several data items into a common data item held by the NNRD to assess data quality. Furthermore, included trials used different approaches to ascertain commonly reported data items, for example the most commonly reported data item – gestational age – may be derived from maternal reported data, ultrasound measurement or clinical evaluation. Data held within the NNRD are extracted from routine clinical information used to inform clinical care, these clinically relevant data may be more appropriate for pragmatic trials than more granular data items reported in trials. Differences between trials and routinely recorded data sources in how data items are ascertained and synthesised have the potential to introduce biases into clinical trials seeking to use such routinely recorded data. Where such differences are randomly distributed between trial arms, the impact may be limited to lower precision, rather than systematic bias in favour of one trial arm. Further exploration is needed to understand how to accurately assess and synthesise similar data items and to quantify the direction and magnitude of potential biases.

It is important to note that some NNRD data items had between 10 and 30% missing data. The implications of such degrees of missingness depend on the role of the data item in the trial, but are likely to lead to a loss of precision (22). Baseline variables have a role in pre-specified statistical analyses of outcomes in order that treatment effects can be estimated more precisely. Where the baseline is missing, there are methods which do allow incomplete baseline variables to be included without removing the patients with missing baselines, and to achieve some increase in precision. This is relevant to individually randomised trials, whereas incomplete baseline may have a greater impact in trials randomising centre clusters when baseline completeness varies by centre. Baseline variables are also used to describe the trial population, for example to allow readers to judge generalisability, and a high level of baseline completeness may be important for this purpose. Finally, baseline variables are important for subgroup analyses and missing data may limit such analyses. The results presented here will allow the impact that different degrees of missingness have in neonatal trials to be further explored and modelled to better understand which trials are most suitable to use routinely recorded data. The more widespread use of routinely collected data for clinical trials also has the potential to improve the recording of such data (23). Another limitation is that we did not evaluate the accuracy of common non-outcome data-items in the NNRD in this study, although this has recently been undertaken (17). Completeness and accuracy are key factors in determining the suitability of using routinely recorded clinical data for clinical trials and should be evaluated for all data items deemed critical to any trial seeking to use such data.

The clinical and economic efficiency of using routinely recorded common data items has been demonstrated by trials that have used common registries such as SWEDEHEART (24, 25). Common data items, as identified here and in core outcome sets (26), can be used to ensure existing primary data capture systems

such as EPR systems and registries capture appropriate data for trials, and in planning such trials. High accuracy and completeness of data are critical for trials; it may however, not be feasible to evaluate such metrics for all data items within a database or registry – common data items and core outcome sets can be used to target quality assessment of data items most critical to a range of clinical trials. Ongoing data-enabled pilot trials that use routinely recorded data held in the NNRD (14) will provide prospective data regarding the feasibility of such an approach in the neonatal field.

Conclusion

Neonatal trials in high impact journals report a common set of non-outcome data items in their primary publications. In the UK, our study indicates that these core non-outcome data can be obtained from the NNRD; the feasibility and efficiency using routinely recorded EPR data such as that held in the NNRD for neonatal clinical trials, rather than collecting these items anew, should be examined. We suggest that when planning primary data collection systems such as EPR systems, registries or clinical databases, consideration is given to fostering a culture of completeness and ensuring that important items are accurately and completely captured.

List Of Abbreviations

caDSR: Cancer Data Standards Registry

EPR: Electronic Patient Record

NHS: National Health Service

NDAU: Neonatal Data Analysis Unit

NNRD: National Neonatal Research Database

PROMIS: Patient Reported Outcomes Measurement Information System

Declarations

Ethics approval and consent to participate

The National Neonatal Research Database has Research Ethics Approval (London Queen Square Research Ethics Committee Reference number 16/LO/1930).

Consent for publication

Not applicable.

Availability of data and materials

The datasets analysed during the current study are available in the National Neonatal Research Database https://www.imperial.ac.uk/neonatal-data-analysis-unit/neonatal-data/utilising-the-nnrd/

Competing interests

NM is Director of the Neonatal Data Analysis Unit that created and manages the NNRD. CG and NM are voluntary, unremunerated members of the Neonatal Data Analysis Unit (NDAU) Steering Board which oversees the NNRD.

Funding

This study is part of a PhD funded by a tuition fees grant from the Westminster Medical School Research Trust awarded to Sena Jawad. Sena Jawad and Chris Gale are supported by a Medical Research Council Clinician Scientist Fellowship awarded to Chris Gale.

Authors contributions

CG and SJ conceived this project, CG and SJ undertook data extraction, SJ analysed data and drafted the first draft of this manuscript, all authors contributed to and revised the manuscript. All authors read and approved the final manuscript.

Acknowledgments

Daniel Gray (data analyst and reporting specialist, Clevermed Ltd) provided data support.

References

1. Sinclair JC, Haughton DE, Bracken MB, Horbar JD, Soll RF. Cochrane neonatal systematic reviews: a survey of the evidence for neonatal therapies. Clinics in perinatology. 2003;30(2):285-304.
2. Willhelm C, Girisch W, Gottschling S, Graber S, Wahl H, Meyer S. Systematic Cochrane reviews in neonatology: a critical appraisal. Pediatr Neonatol. 2013;54(4):261-6.

3. Collier R. Rapidly rising clinical trial costs worry researchers. CMAJ : Canadian Medical Association Journal. 2009;180(3):277-8.
4. Moore TJ, Zhang H, Anderson G, Alexander GC. Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015-2016. JAMA Intern Med. 2018;178(11):1451-7.
5. NIHR. NIHR Journals Library 2019 [Available from: https://www.journalslibrary.nihr.ac.uk.
6. Le Jeannic A, Quelen C, Alberti C, Durand-Zaleski I, CompaRec I. Comparison of two data collection processes in clinical studies: electronic and paper case report forms. BMC medical research methodology. 2014;14:7.
7. Lauer MS, D'Agostino RB, Sr. The randomized registry trial--the next disruptive technology in clinical research? N Engl J Med. 2013;369(17):1579-81.
8. Grossmann C, Sanders J, English RA. Large simple trials and knowledge generation in a learning healthcare system. In: Medicine Io, editor. Washington D.C.: The National Academies Press; 2013.
9. Eapen ZJ, Lauer MS, Temple RJ. The imperative of overcoming barriers to the conduct of large, simple trials. JAMA. 2014;311(14):1397-8.
10. Ford I, Norrie J. Pragmatic Trials. N Engl J Med. 2016;375(5):454-63.
11. Kopcke F, Trinczek B, Majeed RW, Schreiweis B, Wenk J, Leusch T, et al. Evaluation of data completeness in the electronic health record for the purpose of patient recruitment into clinical trials: a retrospective analysis of element presence. BMC medical informatics and decision making. 2013;13:37.
12. Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, et al. The COMET Handbook: version 1.0. Trials. 2017;18(Suppl 3):280.
13. Digital N. National Neonatal Data Set NHS Data Dictionary; [Available from: https://www.datadictionary.nhs.uk/data_dictionary/messages/clinical_data_sets/overviews/national_neonatal_data_set_overviews/national_neonatal_da shownav=1?query=%22national+neonatal%22&rank=100&shownav=1.
14. Gale C, Modi N, Jawad S, Culshaw L, Dorling J, Bowler U, et al. The WHEAT pilot trial-WithHolding Enteral feeds Around packed red cell Transfusion to prevent necrotising enterocolitis in preterm neonates: a multicentre, electronic patient record (EPR), randomised controlled point-of-care pilot trial. BMJ open. 2019;9(9):e033543.
15. Reuters T. InCites Journal Citation Reports [Available from: https://jcr.incites.thomsonreuters.com.
16. Webbe J, Brunton G, Ali S, Duffy JMN, Modi N, Gale C. Developing, implementing and disseminating a core outcome set for neonatal medicine. BMJ Paediatrics Open. 2017;1(e000048).
17. Battersby C, Statnikov Y, Santhakumaran S, Gray D, Modi N, Costeloe K, et al. The United Kingdom National Neonatal Research Database: A validation study. PLoS One. 2018;13(8):e0201815.
18. Doods J, Botteri F, Dugas M, Fritz F, Ehr4Cr WP. A European inventory of common electronic health record data elements for clinical trial feasibility. Trials. 2014;15:10.
19. Sheehan J, Hirschfeld S, Foster E, Ghitza U, Goetz K, Karpinski J, et al. Improving the value of clinical research through the use of Common Data Elements. Clin Trials. 2016;13(6):671-6.
20. Chari A, Hocking KC, Edlmann E, Turner C, Santarius T, Hutchinson PJ, et al. Core Outcomes and Common Data Elements in Chronic Subdural Hematoma: A Systematic Review of the Literature Focusing on Baseline and Peri-Operative Care Data Elements. J Neurotrauma. 2016;33(17):1569-75.
21. Webbe J, Brunton G, Ali S, Longford N, Modi N, Gale C, et al. Parent, patient and clinician perceptions of outcomes during and following neonatal care: a systematic review of qualitative research. BMJ Paediatr Open. 2018;2(1):e000343.
22. White IR, Thompson SG. Adjusting for partially missing baseline measurements in randomized trials. Statistics in medicine. 2005;24(7):993-1007.
23. Gale C, Modi N, group Wtd. Neonatal randomised point-of-care trials are feasible and acceptable in the UK: results from two national surveys. Arch Dis Child Fetal Neonatal Ed. 2015.
24. Frobert O, Lagerqvist B, Olivecrona GK, Omerovic E, Gudnason T, Maeng M, et al. Thrombus aspiration during ST-segment elevation myocardial infarction. N Engl J Med. 2013;369(17):1587-97.
25. Hofmann R, James SK, Jernberg T, Lindahl B, Erlinge D, Witt N, et al. Oxygen Therapy in Suspected Acute Myocardial Infarction. N Engl J Med. 2017;377(13):1240-9.
26. Webbe J, Sinha I, Gale C. Core Outcome Sets. Archives of disease in childhood Education and practice edition. 2018;103(3):163-6.
27. Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med. 2009;361(14):1349-58.
28. Azzopardi D, Strohm B, Marlow N, Brocklehurst P, Deierl A, Eddama O, et al. Effects of hypothermia for perinatal asphyxia on childhood outcomes. N Engl J Med. 2014;371(2):140-9.
29. Ballard RA, Truog WE, Cnaan A, Martin RJ, Ballard PL, Merrill JD, et al. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. N Engl J Med. 2006;355(4):343-53.
30. Bassler D, Plavka R, Shinwell ES, Hallman M, Jarreau PH, Carnielli V, et al. Early Inhaled Budesonide for the Prevention of Bronchopulmonary Dysplasia. N Engl J Med. 2015;373(16):1497-506.
31. Baud O, Maury L, Lebail F, Ramful D, El Moussawi F, Nicaise C, et al. Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMILOC): a double-blind, placebo-controlled, multicentre, randomised trial. Lancet. 2016;387(10030):1827-36.
32. Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart AL, Vanhole C, Palmer CR, van Weissenbruch M, et al. Early insulin therapy in very-low-birth-weight infants. N Engl J Med. 2008;359(18):1873-84.
33. Benjamin DK, Jr., Hudak ML, Duara S, Randolph DA, Bidegain M, Mundakel GT, et al. Effect of fluconazole prophylaxis on candidiasis and mortality in premature infants: a randomized clinical trial. JAMA. 2014;311(17):1742-9.

34. Brocklehurst P, Farrell B, King A, Juszczak E, Darlow B, Haque K, et al. Treatment of Neonatal Sepsis with Intravenous Immune Globulin. New England Journal of Medicine. 2011;365(13):1201-11.
35. Carlo WA, Finer NN, Walsh MC, Rich W, Gantz MG, Laptook AR, et al. Target Ranges of Oxygen Saturation in Extremely Preterm Infants. New England Journal of Medicine. 2010;362(21):1959-69.
36. Carr R, Brocklehurst P, Dore CJ, Modi N. Granulocyte-macrophage colony stimulating factor administered as prophylaxis for reduction of sepsis in extremely preterm, small for gestational age neonates (the PROGRAMS trial): a single-blind, multicentre, randomised controlled trial. Lancet. 2009;373(9659):226-33.
37. Ceelie I, de Wildt SN, van Dijk M, van den Berg MM, van den Bosch GE, Duivenvoorden HJ, et al. Effect of intravenous paracetamol on postoperative morphine requirements in neonates and infants undergoing major noncardiac surgery: a randomized controlled trial. JAMA. 2013;309(2):149-54.
38. Costeloe K, Hardy P, Juszczak E, Wilks M, Millar MR, Study PPI. Bifidobacterium breve BBG-001 in very preterm infants: a randomised controlled phase 3 trial. Lancet. 2016;387(10019):649-60.
39. Davidson AJ, Disma N, de Graaff JC, Withington DE, Dorris L, Bell G, et al. Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. Lancet. 2016;387(10015):239-50.
40. Fergusson DA, Hebert P, Hogan DL, LeBel L, Rouvinez-Bouali N, Smyth JA, et al. Effect of Fresh Red Blood Cell Transfusions on Clinical Outcomes in Premature, Very Low-Birth-Weight Infants The ARIPI Randomized Trial. Jama-J Am Med Assoc. 2012;308(14):1443-51.
41. Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, Laptook AR, et al. Early CPAP versus Surfactant in Extremely Preterm Infants. New England Journal of Medicine. 2010;362(21):1970-9.
42. Fivez T, Kerklaan D, Mesotten D, Verbruggen S, Wouters PJ, Vanhorebeek I, et al. Early versus Late Parenteral Nutrition in Critically Ill Children. New England Journal of Medicine. 2016;374(12):1111-22.
43. Gopel W, Kribs A, Ziegler A, Laux R, Hoehn T, Wieg C, et al. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. Lancet. 2011;378(9803):1627-34.
44. Harris DL, Weston PJ, Signal M, Chase JG, Harding JE. Dextrose gel for neonatal hypoglycaemia (the Sugar Babies Study): a randomised, double-blind, placebo-controlled trial. Lancet. 2013;382(9910):2077-83.
45. Hyttel-Sorensen S, Pellicer A, Alderliesten T, Austin T, van Bel F, Benders M, et al. Cerebral near infrared spectroscopy oximetry in extremely preterm infants: phase II randomised clinical trial. Bmj-Brit Med J. 2015;350.
46. Kelleher J, Bhat R, Salas AA, Addis D, Mills EC, Mallick H, et al. Oronasopharyngeal suction versus wiping of the mouth and nose at birth: a randomised equivalency trial. Lancet. 2013;382(9889):326-30.
47. Kimberlin DW, Whitley RJ, Wan W, Powell DA, Storch G, Ahmed A, et al. Oral acyclovir suppression and neurodevelopment after neonatal herpes. N Engl J Med. 2011;365(14):1284-92.
48. Kimberlin DW, Jester PM, Sanchez PJ, Ahmed A, Arav-Boger R, Michaels MG, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. N Engl J Med. 2015;372(10):933-43.
49. Kirpalani H, Millar D, Lemyre B, Yoder BA, Chiu A, Roberts RS, et al. A trial comparing noninvasive ventilation strategies in preterm infants. N Engl J Med. 2013;369(7):611-20.
50. Leuchter RHV, Gui L, Poncet A, Hagmann C, Lodygensky GA, Martin E, et al. Association Between Early Administration of High-Dose Erythropoietin in Preterm Infants and Brain MRI Abnormality at Term-Equivalent Age. Jama-J Am Med Assoc. 2014;312(8):817-24.
51. Makrides M, Gibson RA, McPhee AJ, Collins CT, Davis PG, Doyle LW, et al. Neurodevelopmental Outcomes of Preterm Infants Fed High-Dose Docosahexaenoic Acid A Randomized Controlled Trial. Jama-J Am Med Assoc. 2009;301(2):175-82.
52. Manley BJ, Owen LS, Doyle LW, Andersen CC, Cartwright DW, Pritchard MA, et al. High-Flow Nasal Cannulae in Very Preterm Infants after Extubation. New England Journal of Medicine. 2013;369(15):1425-33.
53. Manzoni P, Stolfi I, Pugni L, Decembrino L, Magnani C, Vetrano G, et al. A multicenter, randomized trial of prophylactic fluconazole in preterm neonates. N Engl J Med. 2007;356(24):2483-95.
54. Manzoni P, Rinaldi M, Cattani S, Pugni L, Romeo MG, Messner H, et al. Bovine lactoferrin supplementation for prevention of late-onset sepsis in very low-birth-weight neonates: a randomized trial. JAMA. 2009;302(13):1421-8.
55. Mercier JC, Hummler H, Durrmeyer X, Sanchez-Luna M, Carnielli V, Field D, et al. Inhaled nitric oxide for prevention of bronchopulmonary dysplasia in premature babies (EUNO): a randomised controlled trial. Lancet. 2010;376(9738):346-54.
56. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB, et al. Nasal CPAP or intubation at birth for very preterm infants. New England Journal of Medicine. 2008;358(7):700-8.
57. Morris BH, Oh W, Tyson JE, Stevenson DK, Phelps DL, O'Shea TM, et al. Aggressive vs. conservative phototherapy for infants with extremely low birth weight. New England Journal of Medicine. 2008;359(18):1885-96.
58. Morris RK, Malin GL, Quinlan-Jones E, Middleton LJ, Hemming K, Burke D, et al. Percutaneous vesicoamniotic shunting versus conservative management for fetal lower urinary tract obstruction (PLUTO): a randomised trial. Lancet. 2013;382(9903):1496-506.
59. Moss RL, Dimmitt RA, Barnhart DC, Sylvester KG, Brown RL, Powell DM, et al. Laparotomy versus peritoneal drainage for necrotizing enterocolitis and perforation. N Engl J Med. 2006;354(21):2225-34.
60. Natalucci G, Latal B, Koller B, Rugger C, Sick B, Held L, et al. Effect of Early Prophylactic High-Dose Recombinant Human Erythropoietin in Very Preterm Infants on Neurodevelopmental Outcome at 2 Years A Randomized Clinical Trial. Jama-J Am Med Assoc. 2016;315(19):2079-85.

61. Schmidt B, Anderson PJ, Doyle LW, Dewey D, Grunau RE, Asztalos EV, et al. Survival Without Disability to Age 5 Years After Neonatal Caffeine Therapy for Apnea of Prematurity. Jama-J Am Med Assoc. 2012;307(3):275-82.
62. Schmidt B, Whyte RK, Asztalos EV, Moddemann D, Poets C, Rabi Y, et al. Effects of targeting higher vs lower arterial oxygen saturations on death or disability in extremely preterm infants: a randomized clinical trial. JAMA. 2013;309(20):2111-20.
63. Shankaran S, Pappas A, McDonald SA, Vohr BR, Hintz SR, Yolton K, et al. Childhood outcomes after hypothermia for neonatal encephalopathy. N Engl J Med. 2012;366(22):2085-92.
64. Shankaran S, Laptook AR, Pappas A, McDonald SA, Das A, Tyson JE, et al. Effect of Depth and Duration of Cooling on Deaths in the NICU Among Neonates With Hypoxic Ischemic Encephalopathy A Randomized Clinical Trial. Jama-J Am Med Assoc. 2014;312(24):2629-39.
65. Slater R, Cornelissen L, Fabrizi L, Patten D, Yoxen J, Worley A, et al. Oral sucrose as an analgesic drug for procedural pain in newborn infants: a randomised controlled trial. Lancet. 2010;376(9748):1225-32.
66. Stenson BJ, Tarnow-Mordi WO, Darlow BA, Simes J, Juszczak E, Askie L, et al. Oxygen Saturation and Outcomes in Preterm Infants. New England Journal of Medicine. 2013;368(22):2094-104.
67. Taddio A, Lee C, Yip A, Parvez B, McNamara PJ, Shah V. Intravenous morphine and topical tetracaine for treatment of pain in preterm neonates undergoing central line placement. Jama-J Am Med Assoc. 2006;295(7):793-800.
68. Tarnow-Mordi W, Stenson B, Kirby A, Juszczak E, Donoghoe M, Deshpande S, et al. Outcomes of Two Trials of Oxygen-Saturation Targets in Preterm Infants. New England Journal of Medicine. 2016;374(8):749-60.
69. Vaucher YE, Peralta-Carcelen M, Finer NN, Carlo WA, Gantz MG, Walsh MC, et al. Neurodevelopmental Outcomes in the Early CPAP and Pulse Oximetry Trial. New England Journal of Medicine. 2012;367(26):2495-504.
70. Zivanovic S, Peacock J, Alcazar-Paris M, Lo JW, Lunt A, Marlow N, et al. Late Outcomes of a Randomized Trial of High-Frequency Oscillation in Neonates. New England Journal of Medicine. 2014;370(12):1121-30.

Tables

Table 1 The identified studies and their characteristics

r and	Title	N	Intervention Arm	Comparator Arm	Single/ Multiple Centre Trial	Age/ Weight Inclusion Criteria of Participants	Infant Age Group	Disease Area
ardi (27)	Moderate hypothermia to treat perinatal asphyxial encephalopathy	325	Total body cooling and intensive care	Intensive care	Multiple	≥36 weeks gestation	Term	Neurological
ardi (28)	Effects of hypothermia for perinatal asphyxia on childhood outcomes	325	Standard care with hypothermia	Standard care	Multiple	≥36 weeks	Term	Neurological
d (29)	Inhaled Nitric Oxide in Preterm Infants Undergoing Mechanical Ventilation	582	Nitric Oxide	Placebo	Multiple	<32 weeks	Preterm	Respiratory
er (30)	Early inhaled Budesonide for the prevention of bronchopulmonary dysplasia	856	Early inhaled budesonide	Placebo	Multiple	23^{+0} to 27^{+6} weeks^{+days}	Preterm	Respiratory
(31)	Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMILOC): a double-blind, placebo-controlled, multicentre randomised trial	521	Hydrocortisone	Placebo	Multiple	24^{+0} to 27^{+6} weeks^{+days}	Term	Respiratory
lsall (32)	Early insulin therapy in very-low-birth-weight infants	386	Early insulin	Standard neonatal care	Multiple	<1500g	Preterm	Other- Metabolic/ endocrine
min (33)	Effect of fluconazole prophylaxis on candidiasis and mortality in premature infants, a randomized clinical trial	361	Fluconazole	Placebo	Multiple	<750g	Preterm	Infection
lehurst (34)	Treatment of neonatal sepsis with intravenous immune globulin	3493	Polyvalent IgG immune globulin	Placebo	Multiple	<1500g	Preterm	Infection
(35)	Target ranges of oxygen saturation in extremely preterm infants	1316	Oxygen saturation 85-89%	Oxygen saturation 91-95%	Multiple	24^{+0} to 27^{+6} weeks^{+days}	Preterm	Respiratory
(36)	Granulocyte-macrophage colony stimulating factor administered as prophylaxis for reduction of sepsis in extremely preterm, small for gestational age neonates (PROGRAMS): a single-blind, multicentre randomised controlled trial	280	Granulocyte-macrophage colony stimulating factor	Standard care	Multiple	≤31 weeks	Preterm	Infection
(37)	Effect of intravenous paracetamol on postoperative morphine requirements in neonates and infants undergoing major noncardiac surgery	71	Continuous morphine	Intermittent intravenous paracetamol	Single	>36^{+1} week^{+days} to 1 year	Term	Other- Pain
loe (38)	Bifidobacterium breve BBG-001 in very preterm infants: a randomised controlled phase 3 trial	1310	Probiotic B breve BBG-001	Placebo	Multiple	23^{+0} to 30^{+6} weeks^{+days}	Preterm	Infection
lson (39)	Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial	719	Awake-regional anaesthesia	General anaesthesia	Multiple	≥26 weeks to 60 weeks	Both	Other- Sedation/ Anaesthesia
sson (40)	Effect of fresh red blood cell transfusions on clinical outcomes in premature, very low-birth weight infants	377	Fresh red blood cell transfusions	Standard red blood cell transfusions	Multiple	<1250g	Preterm	Other- Haematological
(41)	Early CPAP versus surfactant in extremely preterm infants	1316	Intubation and surfactant	Continuous positive airway pressure	Multiple	24^{+0} to 27^{+6} weeks^{+days}	Preterm	Respiratory
(42)	Early versus late parenteral nutrition in critically ill children	1440	Late parenteral nutrition	Early parenteral nutrition	Multiple	Term newborns to 17 years	Term	Other- Nutrition
(43)	Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants: an open-label randomised, controlled trial	220	Surfactant without ventilation	Standard care	Multiple	26 to 28^{+6} weeks^{+days}	Preterm	Respiratory
(44)	Dextrose gel for neonatal hypoglycaemia (the Sugar Babies study): a randomised, double-blind, placebo-controlled trial	237	Dextrose gel	Placebo	Single	35 to 42 weeks	Both	Other- Metabolic/ endocrine
son (45)	Cerebral near infrared spectroscopy oximetry in extremely preterm infants: phase II randomised clinical trial	166	Cerebral near infrared spectroscopy monitoring	Blinded near infrared spectroscopy monitoring	Multiple	<27^{+6} weeks^{+days}	Preterm	Neurological
ner (46)	Oronasopharyngeal suction versus wiping of the mouth and nose at birth: a randomised equivalency trial	488	Gentle wiping of the face, mouth and nose with a towel	Suction with a bulb syringe of the mouth and nostrils	Single	≥35 weeks	Both	Respiratory
erlin (47)	Oral acyclovir suppression and neurodevelopment after neonatal herpes	74	Oral acyclovir	Placebo	Multiple	>800g	Both	Infection
erlin (48)	Valganciclovir for symptomatic congenital cytomegalovirus disease	96	Valganciclovir therapy	Placebo	Multiple	≥32 weeks	Both	Infection

lani (49)	A trial comparing noninvasive ventilation strategies in preterm infants	1007	Nasal intermittent positive-pressure ventilation	Nasal continuous positive airway pressure	Multiple	<30 weeks and <1000g	Preterm	Respiratory
ıter (50)	Association between early administration of high-dose erythropoietin in preterm infants and brain MRI abnormality at term-equivalent age	165	Recombinant human erythropoietin	Placebo	Multiple	26 weeks to 31^{+6} $weeks^{+days}$	Preterm	Neurological
des (51)	Neurodevelopmental outcomes of preterm infants fed high-dose docosahexaenoic acid	657	High docosahexaenoic acid diet	Standard docosahexaenoic acid diet	Multiple	<33 weeks	Preterm	Other- Nutrition
ey (52)	High-flow nasal cannulae in very preterm infants after extubation	303	High-flow nasal cannulae	Nasal continuous positive airway pressure	Multiple	<32 weeks	Preterm	Respiratory
oni (53)	A multicentre, randomized trial of prophylactic fluconazole in preterm neonates	322	Fluconazole	Placebo	Multiple	<1500g	Preterm	Infection
oni (54)	Bovine lactoferrin supplementation for prevention of late-onset sepsis in very low birth weight neonates	472	Lactoferrin	Lactoferrin + Lactobacill-us rhamnosus GG Placebo	Multiple	<1500g	Preterm	Infection
er (55)	Inhaled nitric oxide for prevention of bronchopulmonary dysplasia in premature babies (EUNO): a randomised controlled trial	800	Inhaled nitric oxide	Placebo	Multiple	24^{+0} to 28^{+6} $weeks^{+days}$	Preterm	Respiratory
y (56)	Nasal CPAP or intubation at birth for very preterm infants	610	CPAP	Intubation and ventilation at 5 minutes	Multiple	25^{+0} to 28^{+6} $weeks^{+days}$	Preterm	Respiratory
s (57)	Aggressive vs conservative phototherapy for infants with extremely low birth weight	1974	Aggressive phototherapy	Conservative phototherapy	Multiple	501 to 1000g	Preterm	Other- Hepatic
s (58)	Percutaneous vesicoamniotic shunting versus conservative management for fetal lower urinary tract obstruction (PLUTO): a randomised trial	31	Percutaneous vesicoamniotic shunting	Conservative management	Multiple	No age or weight criteria	Both	Genitourinary
(59)	Laparotomy versus peritoneal drainage for NEC and perforation	117	Primary peritoneal drainage	Laparotomy with bowel resection	Multiple	<34 weeks, <1500g	Preterm	Gastrointestinal
ucci (60)	Effect of early prophylactic high-dose recombinant human erythropoietin in very preterm infants on neurodevelopmental outcome at 2 years	365	Prophylactic early high-dose recombinant human erythropoietin (rhEPO)	Placebo	Multiple	26^{+0} to 31^{+6} $weeks^{+days}$	Preterm	Neurological
ıidt (61)	Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity	1640	Caffeine therapy	Placebo	Multiple	500g to 1250g	Preterm	Respiratory
ıidt (62)	Effects of targeting higher vs lower arterial oxygen saturations on death or disability in extremely preterm infants	1201	Oxygen saturation 85% -89%	Oxygen saturation 91% - 95%	Multiple	23^{+0} to 27^{+6} $weeks^{+days}$	Preterm	Respiratory
karan (63)	Childhood outcomes after hypothermia for neonatal encephalopathy	190	Hypothermia	Usual care	Multiple	≥36 weeks	Both	Neurological
karan (64)	Effect of depth and duration of cooling on deaths in the NICU among neonates with hypoxic ischemic encephalopathy, a randomised clinical trial	364	32deg for 72h 33.5deg for 120h 32deg for 120h	33.5degrees for 72h	Multiple	≥36 weeks	Both	Neurological
· (65)	Oral sucrose as an analgesic drug for procedural pain in newborn infants: a randomised controlled trial	44	Sucrose solution	Sterile water	Single	37 to 43 weeks	Term	Other- Pain
on (66)	Oxygen saturation and outcomes in preterm infants	2448	Oxygen saturation of 85-89%	Oxygen saturation of 91-95%	Multiple	<28 weeks	Preterm	Respiratory
o (67)	Intravenous Morphine and topical tetracaine for treatment of pain in preterm neonates undergoing central line placement	132	Tetracaine or Morphine or Both	Neither Tetracaine nor Morphine	Multiple	No age or weight criteria	Both	Other- Pain
w- (68)	Outcomes of two trials of oxygen-saturation targets in preterm infants	1858	Lower oxygen-saturation range	Higher oxygen-saturation range	Multiple	<28 weeks	Preterm	Respiratory
ner (69)	Neurodevelopmental outcomes in the early CPAP and pulse oximetry trial	990	Early CPAP with a limited ventilation strategy	Early surfactant administration (2x2 factorial) Also to: 85-89% oxygen saturation or 91-95% oxygen saturation	Multiple	24^{+0} to 27^{+6} $weeks^{+days}$	Preterm	Respiratory

ovic (70)	Late outcomes of a randomized trial of high-frequency oscillation in neonates	319	High-frequency oscillatory ventilation	Conventional ventilation	Multiple	<29 weeks	Preterm	Respiratory

Number of infants presenting baseline characteristics

Table 2 Data items reported in more than 20% of studies and stratified by the age of the study participants

	Infant Age							
	Preterm Studies (n=29)		Term Studies (n=6)		Mixed Ages Studies (n=9)		All studies (n=44)	
Baseline Characteristics								
Gestational age	29	(100%)	4	(67%)	9	(100%)	42	(96%)
Sex	29	(100%)	6	(100%)	6	(67%)	41	(93%)
Birth weight	29	(100%)	5	(83%)	6	(67%)	40	(91%)
Antenatal steroids	25	(86%)	1	(17%)	1	(11%)	27	(61%)
Multiple births	21	(72%)	1	(17%)	2	(22%)	24	(55%)
Respiratory support	17	(59%)	3	(50%)	3	(33%)	23	(52%)
Mode of delivery	14	(48%)	2	(33%)	5	(56%)	21	(48%)
Infection	15	(52%)	3	(50%)	3	(33%)	21	(48%)
Drug treatment	15	(52%)	0	(0%)	5	(56%)	20	(45%)
Maternal ethnicity	15	(52%)	1	(17%)	3	(33%)	19	(43%)
Apgar score 5 minutes	14	(48%)	0	(0%)	5	(56%)	19	(43%)
Age	11	(38%)	6	(100%)	2	(22%)	19	(43%)
Inborn	13	(45%)	0	(0%)	2	(22%)	15	(34%)
Maternal age	6	(21%)	1	(17%)	6	(67%)	13	(30%)
Stratification Items								
Neonatal Unit Identifier	22	(76%)	1	(17%)	2	(22%)	25	(57%)
Gestational age	14	(48%)	1	(17%)	3	(33%)	17	(39%)
Primary Outcome Adjusting Items								
Gestational Age	17	(59%)	1	(8%)	1	(11%)	19	(43%)
Neonatal Unit Identifier	10	(34%)	1	(8%)	2	(22%)	13	(28%)
Birth weight	9	(31%)	0	(0%)	1	(11%)	10	(22%)

Table 3 Data completeness in the NNRD for the data items reported in 20% of studies or more

	Age			
	Preterm (n=37,424) (%)	Term (n=59,130) (%)	Unknown (n=145) (%)	All (n= 96,699) (%)
Gestational Age	100.0	100.0	0	99.9
Sex	99.9	99.9	99.3	99.9
Birth Weight	100.0	100.0	91.7	100.0
Antenatal Steroids	94.5	89.7	4.8	91.4
Maternal Ethnicity	75.6	66.9	1.4	70.2
Multiple Births	100.0	99.8	11.7	99.7
Mode of Delivery	90.7	75.7	2.8	81.4
Apgar Score at 5 minutes	87.6	73.9	0.7	79.1
Maternal Age	96.6	89.2	3.4	92.0
Inborn†	98.8	96.6	6.2	97.3
Drug Treatment in the first 1 day‡*				91.9
Respiratory support in the first 1 day*				100.0

† Corresponding NNRD data item: place of birth

‡ Corresponding NNRD data item: any medication recorded on day 1 of admission

* For babies less than 28 weeks gestational age (n=1,967)

Supplemental Tables

Supplemental Table 1- All baseline data items reported by the studies stratified by whether the study recruited preterm or term infants. Data items refer to infant chanracteristics unless otherwise stated.

	Preterm Studies (n=29)		Term Studies (n=6)		Mixed Ages Studies (n=9)		All Studies (n=44)	
Gestational age	29	100%	4	67%	9	100%	42	95%
Sex	29	100%	6	100%	6	67%	41	93%
Birth weight	29	100%	5	83%	6	67%	40	91%
Antenatal steroids	25	86%	1	17%	1	11%	27	61%
Multiple birth	21	72%	1	17%	2	22%	24	55%
Respiratory Support	17	59%	3	50%	3	33%	23	52%
Mode of delivery	14	48%	2	33%	5	56%	21	48%
Infection	15	52%	3	50%	3	33%	21	48%
Drug treatment	15	52%	0	0%	5	56%	20	45%
Mother's Ethnicity	15	52%	1	17%	3	33%	19	43%
Apgar 5 min	14	48%	0	0%	5	56%	19	43%
Age at randomisation	11	38%	6	100%	2	22%	19	43%
Born at study hospital	13	45%	0	0%	2	22%	15	34%
Mother age	6	21%	1	17%	6	67%	13	30%
SES	5	17%	0	0%	2	22%	7	16%
Blood test on the neonatal unit	3	10%	0	0%	3	33%	6	14%
Head Circumference	3	10%	1	17%	1	11%	5	11%
Apgar Score at 1 Minute	2	7%	1	17%	2	22%	5	11%
Family Setup	3	10%	0	0%	2	22%	5	11%
Temperature	3	10%	2	33%	0	0%	5	11%
Mother Parity	1	3%	0	0%	3	33%	4	9%
Apgar Score at 10 Minutes	0	0%	2	33%	2	22%	4	9%
Early Feeding Characteristics	4	14%	0	0%	0	0%	4	9%
pH	2	7%	0	0%	2	22%	4	9%
Intraventricular Haemorrhage	3	10%	0	0%	1	11%	4	9%
Umbilical cord blood tests	3	10%	0	0%	1	11%	4	9%
Birth Length	2	7%	0	0%	1	11%	3	7%
Pre-eclampsia	2	7%	0	0%	1	11%	3	7%
Retinopathy	2	7%	0	0%	1	11%	3	7%
Smoking during pregnancy	2	7%	0	0%	1	11%	3	7%
Patent Ductus Arteriosus	2	7%	0	0%	1	11%	3	7%
Umbilical Arterial pH	2	7%	0	0%	1	11%	3	7%
Weight	1	3%	1	17%	1	11%	3	7%
Necrotising Enterocolitis	3	10%	0	0%	0	0%	3	7%
Mother BMI	0	0%	0	0%	2	22%	2	5%
Amplitude Integrated Electroencephalography	0	0%	2	33%	0	0%	2	5%
Delivery Complications	0	0%	2	33%	0	0%	2	5%
Clinical Seizures	0	0%	2	33%	0	0%	2	5%
Clinical Risk Index for Babies Score	2	7%	0	0%	0	0%	2	5%
Neutropenia	2	7%	0	0%	0	0%	2	5%
Hypertension	1	3%	0	0%	1	11%	2	5%
Blood glucose	0	0%	0	0%	2	22%	2	5%
Score for Neonatal Acute Physiology II Score	2	7%	0	0%	0	0%	2	5%

Diabetic Mother	0	0%	0	0%	2	22%	2	5%
White cell count	1	3%	0	0%	1	11%	2	5%
Bronchopulmonary Dysplasia	2	7%	0	0%	0	0%	2	5%
Base Deficit	0	0%	0	0%	2	22%	2	5%
Seizure	0	0%	0	0%	2	22%	2	5%
Encephalopathy	0	0%	0	0%	2	22%	2	5%
Complications in pregnancy	0	0%	0	0%	2	22%	2	5%
Intrapartum complications	0	0%	0	0%	2	22%	2	5%
Mother in Labour	1	3%	0	0%	1	11%	2	5%
Duration of surgery	0	0%	1	17%	1	11%	2	5%
Haemoglobin level at NICU	1	3%	0	0%	1	11%	2	5%
Partial pressure of carbon dioxide before extubation	2	7%	0	0%	0	0%	2	5%
FiO2	2	7%	0	0%	0	0%	2	5%
Periventricular Leukomalacia	2	7%	0	0%	0	0%	2	5%
Umbilical cord packed cell volume	0	0%	1	17%	0	0%	1	2%
Mother weight	0	0%	1	17%	0	0%	1	2%
Mother haemoglobin	0	0%	1	17%	0	0%	1	2%
Umbilical Cord Haemoglobin	1	3%	0	0%	0	0%	1	2%
Blood Group	1	3%	0	0%	0	0%	1	2%
Amniotic Fluid Volume	0	0%	0	0%	1	11%	1	2%
Renal Pelvis Dilatation	0	0%	0	0%	1	11%	1	2%
Renal Pelvis Severe Hydronephrosis	0	0%	0	0%	1	11%	1	2%
Macrocystic Renal Appearance	0	0%	0	0%	1	11%	1	2%
Respiratory support through endotracheal tube	1	3%	0	0%	0	0%	1	2%
Vitamin A	1	3%	0	0%	0	0%	1	2%
Respiratory severity score	1	3%	0	0%	0	0%	1	2%
Clinical complications	1	3%	0	0%	0	0%	1	2%
Epidural	0	0%	1	17%	0	0%	1	2%
Neutrophil count	1	3%	0	0%	0	0%	1	2%
Cranial ultrasound abnormality	1	3%	0	0%	0	0%	1	2%
Proteinuria	1	3%	0	0%	0	0%	1	2%
Surgical procedure	0	0%	1	17%	0	0%	1	2%
Surgical stress	0	0%	1	17%	0	0%	1	2%
PRISM3	0	0%	1	17%	0	0%	1	2%
PIM2	0	0%	1	17%	0	0%	1	2%
hearing defects	0	0%	0	0%	1	11%	1	2%
Language Spoken	0	0%	0	0%	1	11%	1	2%
STRONGkids risk	0	0%	1	17%	0	0%	1	2%
PELOD score	0	0%	1	17%	0	0%	1	2%
Emergency admission	0	0%	1	17%	0	0%	1	2%
Diagnostic group	0	0%	1	17%	0	0%	1	2%
Condition on admission	0	0%	1	17%	0	0%	1	2%
Risk factors for neonatal hypoglycaemia	0	0%	0	0%	1	11%	1	2%

Weight change during pregnancy	0	0%	0	0%	1	11%	1	2%
Intended method of feeding	0	0%	0	0%	1	11%	1	2%
Cause of infection	1	3%	0	0%	0	0%	1	2%
Bowel perforation or definite NEC	1	3%	0	0%	0	0%	1	2%
Surgery in previous 7 days	1	3%	0	0%	0	0%	1	2%
Risk of death	1	3%	0	0%	0	0%	1	2%
C-reactive protein	1	3%	0	0%	0	0%	1	2%
Duration of membrane rupture	1	3%	0	0%	0	0%	1	2%
Source of intravenous immune globulin or placebo	1	3%	0	0%	0	0%	1	2%
No prenatal care	0	0%	0	0%	1	11%	1	2%
Medical insurance	0	0%	0	0%	1	11%	1	2%
Magnesium given during Labour	0	0%	0	0%	1	11%	1	2%
Meconium-stained amniotic fluid	0	0%	0	0%	1	11%	1	2%
HSV type	0	0%	0	0%	1	11%	1	2%
HSV DNA	0	0%	0	0%	1	11%	1	2%
Evidence of HSV disease on MRI	0	0%	0	0%	1	11%	1	2%
CMV disease	0	0%	0	0%	1	11%	1	2%
Microcephaly	0	0%	0	0%	1	11%	1	2%
Chorioretinitis	0	0%	0	0%	1	11%	1	2%
Neuroimaging results	0	0%	0	0%	1	11%	1	2%
BSER of best ear	0	0%	0	0%	1	11%	1	2%
Previous preterm births	1	3%	0	0%	0	0%	1	2%
Total Parenteral Nutrition	1	3%	0	0%	0	0%	1	2%
Umbilical cathether positioned	1	3%	0	0%	0	0%	1	2%
Duration of stay in NICU	1	3%	0	0%	0	0%	1	2%
Central venous catheter positioned	1	3%	0	0%	0	0%	1	2%
Hematocrit	1	3%	0	0%	0	0%	1	2%
Positive result on Coombs test	1	3%	0	0%	0	0%	1	2%
Bilirubin	1	3%	0	0%	0	0%	1	2%
Renal echogenicity	0	0%	0	0%	1	11%	1	2%
Bladder wall thickness	0	0%	0	0%	1	11%	1	2%
Platelet count	1	3%	0	0%	0	0%	1	2%
Retinopathy of Prematurity	1	3%	0	0%	0	0%	1	2%
Right heel lanced	0	0%	1	17%	0	0%	1	2%
Death of infant in delivery room	1	3%	0	0%	0	0%	1	2%
Epinephrine in the delivery room	1	3%	0	0%	0	0%	1	2%
Fluid or normally sterile body fluid	1	3%	0	0%	0	0%	1	2%

Supplemental Table 2- The most common baseline data items by each identified study. Black indicates the study presented the data item at baseline

Author and Year	Most common baseline data items												
	Gestational Age	Sex	Birth Weight	Antenatal Steroids	Multiple Births	Mode of Delivery	Respiratory*	Maternal Ethnicity	Infection	Apgar Score at 5 Minutes	Infant Age	Drug Treatment	Mate Ag
Respiratory													
Ballard 2006													
Bassler 2015													
Baud 2016													
Carlo 2010													
Finer 2010													
Gopel 2011													
Kelleher 2013													
Kirpalani 2013													
Manley 2013													
Mercier 2010													
Morley 2008													
Schmidt 2012													
Schmidt 2013													
Stensen 2013													
Tarnow-Mordi 2016													
Vaucher 2012													
Zivanovic 2014													
Infection													
Benjamin 2014													
Brocklehurst 2011													
Carr 2009													
Costeloe 2016													
Kimberlin 2011													
Kimberlin 2015													
Manzoni 2007													
Manzoni 2009													
Neurological													
Azzopardi 2009													
Azzopardi 2014													
Hyttel-Sorenson 2015													
Leuchter 2014													
Natalucci 2016													
Shankaran 2012													
Shankaran 2014													
Gastrointestinal													
Moss 2006													
Genitourinary													
Morris 2013													
Other													
Beardsall 2008													
Ceelie 2013													
Davidson 2016													
Fergusson 2012													
Fivez 2016													
Harris 2013													

Makrides 2009												
Morris 2008												
Slater 2010												
Taddio 2006												

***** Respiratory refers to respiratory support required prior to trial entry

Supplemental Table 3- All data items used as stratifying items during randomisation reported by the studies and by the age of infants included in the studies

Stratification Items	Preterm Studies (n=29)	Term Studies (n=6)	Mixed Ages Studies (n=9)	All Studies (n=44)
Centre	22 (76%)	1 (17%)	2 (22%)	25 (57%)
Gestational age	13 (45%)	1 (17%)	3 (33%)	17 (39%)
Birth weight	7 (24%)	0 (0%)	1 (11%)	8 (18%)
Sex	4 (14%)	0 (0%)	0 (0%)	4 (9%)
Multiple birth	3 (10%)	0 (0%)	0 (0%)	3 (7%)
Inborn	2 (7%)	0 (0%)	0 (0%)	2 (5%)
Infant Age	0 (0%)	2 (33%)	0 (0%)	2 (5%)
Abnormality on amplitude-integrated electroencephalography	0 (0%)	1 (17%)	0 (0%)	1 (2%)
Sibling Enrolment Status	1 (3%)	0 (0%)	0 (0%)	1 (2%)
Randomisation Time from Birth	1 (3%)	0 (0%)	0 (0%)	1 (2%)
Diagnosis on Admission	0 (0%)	1 (17%)	0 (0%)	1 (2%)
Maternal Diabetes	0 (0%)	0 (0%)	1 (11%)	1 (2%)
Prior-Intubation Status	1 (3%)	0 (0%)	0 (0%)	1 (2%)
Age of Mother	0 (0%)	0 (0%)	1 (11%)	1 (2%)
Volume of Amniotic Fluid	0 (0%)	0 (0%)	1 (11%)	1 (2%)
Encephalopathy	0 (0%)	0 (0%)	1 (11%)	1 (2%)

Supplemental Table 4 - All data items used as confounders to adjust the primary outcome reported by the studies and by the age of infants included in the studies

Primary Outcome Confounders	Preterm Studies (n=29)	Term Studies (n=6)	Mixed Ages Studies (n=9)	All Studies (n=44)
Gestational Age	17 (59%)	1 (17%)	1 (11%)	19 (43%)
Centre	10 (34%)	1 (17%)	2 (22%)	13 (30%)
Birth Weight	9 (31%)	0 (0%)	1 (11%)	10 (23%)
Sex	7 (24%)	1 (17%)	0 (0%)	8 (18%)
Multiple Births	7 (24%)	0 (0%)	0 (0%)	7 (16%)
Ventilation	5 (17%)	0 (0%)	0 (0%)	5 (11%)
Steroids	5 (17%)	0 (0%)	0 (0%)	5 (11%)
Maternal Education	3 (10%)	1 (17%)	0 (0%)	4 (9%)
Abnormality on Amplitude-Integrated Electroencephalography	0 (0%)	1 (17%)	2 (22%)	3 (7%)
Severity of Illness	1 (3%)	1 (17%)	0 (0%)	2 (5%)
Nutrition	1 (3%)	1 (17%)	0 (0%)	2 (5%)
Infant Age	0 (0%)	2 (33%)	0 (0%)	2 (5%)
Caffeine Use	1 (3%)	0 (0%)	0 (0%)	1 (2%)
Time of Randomisation	1 (3%)	0 (0%)	0 (0%)	1 (2%)
Diagnostic Group	0 (0%)	1 (17%)	0 (0%)	1 (2%)
Maternal Diabetes	0 (0%)	0 (0%)	1 (11%)	1 (2%)
Central Nervous System Involvement	0 (0%)	0 (0%)	1 (11%)	1 (2%)
Risk Factors Possibly Associated with Invasive Fungal Infection	1 (3%)	0 (0%)	0 (0%)	1 (2%)
Use of H2 Blockers	1 (3%)	0 (0%)	0 (0%)	1 (2%)
Daily Milk Intake	1 (3%)	0 (0%)	0 (0%)	1 (2%)
Pneumatosis	1 (3%)	0 (0%)	0 (0%)	1 (2%)
Platelet Count	1 (3%)	0 (0%)	0 (0%)	1 (2%)
Familial Clustering	1 (3%)	0 (0%)	0 (0%)	1 (2%)
Mode of Delivery	1 (3%)	0 (0%)	0 (0%)	1 (2%)

Supplemental File

Supplemental item 1

NeoCODE Pubmed search strategy

(((neonat*) OR preterm)) AND ((((BMJ.[Journal]) OR JAMA.[Journal]) OR N Engl J Med.[Journal]) OR Lancet.[Journal])

- Limited to Humans
- Limited to Clinical Trials
- Between 2006/01/01 to 2015/12/31

Figures

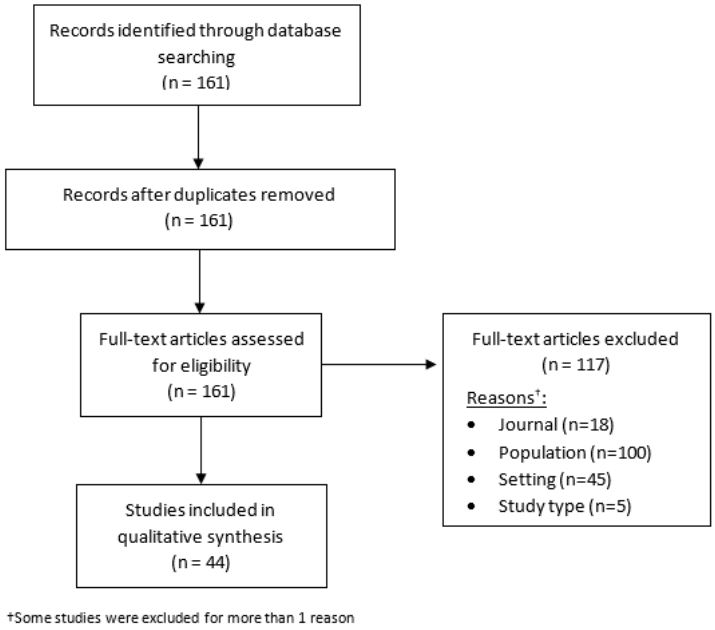

Figure 1

Flow of studies through the systematic review

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- NeoCODEPRISMA140419.docx