1. TITLE

The National Neonatal Collaborative Necrotising Enterocolitis Study: using operational clinical data captured electronically at the point of care for surveillance and research.

2. SHORT STUDY TITLE

NNC-NEC Study

3. MEDICINES FOR NEONATES

This work forms a component of a 4 year National Institute of Health Research (NIHR) programme "Medicines for Neonates" led by Professor N Modi. Co-applicants are Mrs Jane Abbott, Professor Deborah Ashby, Professor Peter Brocklehurst, Professor Kate Costeloe, Professor Elizabeth Draper, Mrs Jacquie Kemp, Professor Azeem Majeed, Professor Stavros Petrou and Professor Alys Young. The purpose of the programme is to utilise operational electronic clinical data captured at the point of care to support health services and facilitate research.

4. THE NEONATAL DATA ANALYSIS UNIT AND NATIONAL NEONATAL RESEARCH DATABASE

Patient records for babies admitted to neonatal units in England are captured on the Badger.net NHS web-based platform. Operational data is collected as part of NHS clinical care and used for patient management, including discharge summaries, administration and commissioning. Neonatal unit staff enter data at the point of care onto the Badger.net platform using password protected access. These data are managed by the authorised NHS hosting company Clevermed. The Neonatal Data Analysis Unit (NDAU), based at Chelsea & Westminster Campus of Imperial College London is led by Professor Modi and was established in 2007 to oversee analyses of national neonatal data. The NDAU holds Caldicott Guardian approval from NHS Trusts to receive Badger.net electronic data and Research Ethics Committee approval to create a National Neonatal Research Database from these records. In accordance with the terms of the approval governing the National Neonatal Research Database (Ref 10/H0803/151), a separate and specific Research Ethics approval is being sought for this study.

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8. BACKGROUND AND AIMS

8.1 Necrotising enterocolitis (NEC)

NEC is a serious neonatal condition that primarily but not exclusively, affects preterm babies. Most incidence data have come from a few multi-centre studies though these report by birth weight categories rather than gestational age, have been limited to very low birth weight infants (VLBW), born weighing between 401 and 1500g (1-3), and have used variable case-definitions. Approximate estimates are that NEC affects up to 5% of infants admitted to neonatal units and overall affects 0.5–5/1000 live births (7% of VLBW infants) (4, 5). There have been 2 multi-centres studies reporting by gestational age categories. The Pediatrix Medical Group reported a NEC rate of 2.6% in 15,072 preterm infants born between 23-34 weeks gestation from 1998-2000 in 98 neonatal units across 24 states in the United States (6). The Neonatal Intensive Care Study reported a NEC rate of 3.8% of 4649 infants born between 24-31 weeks gestation (6.6% born between 24-27 weeks, 2.6% born between 28-31 weeks gestation) in New South Wales, Australia (7). Surgical intervention is required for 30-50%, mortality is high at 15-30% (5, 7) as are short and long-term morbidities. Both incidence and mortality rates of NEC increase in inverse proportion to birth weight and gestational age.

There has been an increase in NEC-related mortality in England and Wales between 1999-2005, believed to be attributable to the increasing numbers of extremely preterm and low birth weight infants who survive (8). There is poor understanding of the epidemiology, multi-factorial aetiology and pathophysiology of NEC, and strategies for prevention remain elusive, making this an issue of prime importance for neonatal care.

8.2 STUDY AIMS

These are 1) to establish an objective case-definition for NEC suitable for national and international surveillance, 2) determine the population incidence and geographical variation of NEC in England, and 3) identify enteral-feed related factors that precede onset, in order to inform the design of future interventional randomised controlled trials.

9. STUDY RATIONALE/PREVIOUS RESEARCH

9.1 Case definition for NEC surveillance

For surveillance an objective case-definition for NEC needs to be developed and used consistently. The lack of an accepted case-definition has hindered surveillance of NEC worldwide. Previous epidemiological studies have used different case-definitions for NEC and variability invalidates any comparative analyses. Rees et al (United Kingdom survey) reported NEC using Bell's staging 1-3 (9). Guillet et al (US NICHD study) (1), Llanos et al (New York state) (5), and Sankaran et al (Canadian study) (3) defined NEC as Bell's stage 2 or above. The Vermont Oxford Network (VON) defines NEC using findings at surgery, at post mortem or by using key clinical and radiographic criteria (at least one clinical finding (bilious gastric aspirate/emesis, abdominal distension, or occult/gross blood in the stool in the absence of anal fissures) and at least one radiographic finding (pneumatosis intestinalis, hepatobiliary gas, or pneumoperitoneum)). Any infant with an operative diagnosis of isolated intestinal perforation is excluded (10). The VON definition is not evidence-based and has been adopted in only a few studies (6, 11). The VON requirement for only 1 clinical and 1 radiological finding may be too loose a definition for NEC and is likely to result in over-reporting. A case-definition for NEC surveillance needs to be distinguished from criteria used for clinical diagnosis and management. For diagnostic purposes, sensitivity (identifying true positives) is the prime consideration, but for surveillance, identification of true positives and true negatives are equally important to avoid over or under reporting (i.e. the sum of sensitivity and specificity should be maximal).

9.2 Population incidence

The design of high quality randomised controlled trials and evaluation of quality improvement initiatives are hindered by scant baseline incidence data. Most incidence data come from retrospective studies using varying case-definitions, and reporting by birth weight categories rather than gestational age. As the incidence of NEC is low in individual neonatal units, large population-based surveillance studies are required to assess baseline rates and temporal trends.

9.3 Enteral feed related antecedents of NEC

9.3.1 Aetiology

NEC is a disease with a multi-factorial aetiology. Enteral feeding regimens are widely believed to influence susceptibility to NEC and are a key potential area for preventative stratagems. The major modifiable risk factors for NEC in preterm babies relate to enteral feeding practices but the optimal strategies have yet to be elucidated. The time of initial enteral feeding, rate of advancement, and type of feed are likely to be important factors in determining the risk of NEC. Much research in this area is conflicting and no consensus has been reached regarding the optimal neonatal enteral feeding regimen. Most studies have had insufficient power and have not used a consistent case-definition.

9.3.2 Type of milk

Data on short and long-term advantages of maternal breast milk are extensive. It is widely accepted that maternal breast milk is the milk of choice for preterm babies. However, if not available, the best alternative is unclear. Pasteurised human donor milk has been increasingly available in England although it is unknown whether it is as beneficial as maternal breast milk or whether it is more beneficial than formula (12). A major benefit of maternal breast milk is the delivery of immunoprotective and growth factors to the immature gut mucosa. A review of studies conducted in the 1980s, comparing donor human milk and formula, suggested

that donor milk was associated with a significantly lower incidence of NEC [5]. Those studies, however, mainly involved relatively mature infants, and the now widely used human milk fortifiers and contemporary preterm formulae have not been evaluated in relation to NEC. A meta-analysis and systematic review of donor breast milk versus infant formula for preterm infants concluded that donor milk given as a sole diet is associated with a lower risk of NEC but slower growth in the early postnatal period (12). These trials were not powered to address NEC as a primary outcome. Since this review, a further small randomised controlled study involving only 19 cases of NEC concluded that an exclusively human milk-based diet is associated with a lower rate of NEC than a diet of human milk and bovine milk-based products (13). However, the primary outcome for this study was parenteral nutrition use. The low incidence of NEC necessitates large multi-centre collaborative studies.

9.3.3 Alternatives to human milk

There is concern that human breast milk alone does not meet nutrient needs of most very preterm infants (<30 weeks) (14). These deficiencies may have adverse consequences for growth and development. The alternatives are to fortify human breast milk or introduce formula (full protein, hydrolysed or elemental). A meta-analysis suggests that human milk reduces the risk of NEC by almost 80% compared to formula feeding (15). Furthermore, a Cochrane review did not suggest NEC is increased by use of bovine origin human milk fortification (16). However, sample sizes were small, one of the studies started more than 20 years ago, and the methodological quality was considered no more than fair (17). Due to the ethical constraints around recruitment of infants to a randomised trial of human or formula milk, few trial data are available to support this (18). In addition, there are currently no data suggesting any differences in the occurrence of NEC for currently available commercial milk formulas.

9.3.4 Timing and rate of advancement of feeds

Feeds are commonly delayed in high-risk infants but there is little evidence that this approach is beneficial. Benefits have been shown following early enteral feeding, known as trophic feeding , with breast milk (19). Although studies have examined the relationship between age at starting feeds, or rate of increase, few are well controlled and sufficiently powered with adequate sample sizes. A recent Cochrane review concludes that current data do not provide evidence that slow advancement of enteral feed volumes reduces the risk of NEC in infants and the long term clinical significance of these effects is uncertain (20). A prospective observational study found that an absence of enteral feeding is an independent risk factor for severe disease, which has not been described previously (21).

10. PARTICIPATING CENTRES

Neonatal units in England contributing data to the National Neonatal Research Database will be informed of this study and asked if they wish their data to be included in the analysis for this study. Although the data used will be from the National Neonatal Research Database, and hence Site Specific Approval is not required, neonatal staff should be informed about this study so that they have opportunity to maximise quality and completeness of data entered into the electronic record. It is hoped that participation will enhance engagement of clinicians and improve overall data quality and completeness. In managed clinical networks preterm neonates are often transferred between neonatal units in a network according to the level of care they require. Therefore the ideal would be for all neonatal units within a network to participate.

11. DATA

11.1 Data source

Data from the National Neonatal Research Database will be utilised. No patient contact/recruitment is required. The following data required for this study will be analysed.

11.2 Exposures (enteral-feed related antecedents):

- Days (from birth) to first feed

- Type of first feed (Maternal Expressed Breast Milk, Human Donor Milk, Formula)
- Days to reach 120ml/kg/day of enteral feed
- Summary measure of type of feed up to development of NEC (1) exclusive maternal breast milk; 2) maternal breast milk with breast milk fortifier; 3) exclusive human donor milk; 4) human donor milk with breast milk fortifier; 5) exclusive formula; 6) mixed human (maternal or donor) milk and formula; 7) nil by mouth.)

11.3 Outcomes ("NEC" or "no NEC" using the working case-definition):

Data from the "Abdominal x-ray performed" ad-hoc form (completed for every abdominal x-ray performed to investigate abdominal signs):

- X-ray appearances (pneumatosis/ air in the liver/pneumoperitoneum/none of these)
- Clinical findings (abdominal distension/abdominal tenderness/Increased gastric aspirate/bilious aspirate/abdominal discolouration/abdominal mass/bloody stools/mucous stools/none of these)
- Was laparotomy for acute NEC required? (yes and done/no/yes, but too sick to be done)
- If yes and done was there visually confirmed NEC? (yes/no)
- Did histology confirm NEC? (yes/no/not done)
- Was peritoneal drain inserted? (yes/no)

11.4 Confounding factors:

Birth weight (g), gestational age (weeks and days), sex (male/female), mother's race (NHS category), gastrointestinal anomalies (gastroschisis, exomphalos, intestinal/colonic atresias, tracheo-oesophageal fistula, oesophageal atresias, congenital diaphragmatic hernia) (yes/no), antenatal steroids (yes/no), antibiotic use (days), COX inhibitors (yes/no), inotropes (yes/no), umbilical arterial line (days), red cell transfusion (yes/no)

12. ANALYSIS PLAN

12.1 Establishing an objective case-definition for NEC

Working case-definition of NEC:

X-ray finding of gas in liver

OR

X-ray finding of pneumatosis AND one or more clinical sign(s) of a) bloody stools b) abdominal discolouration c) abdominal mass

OR

X-ray finding of pneumoperitoneum AND bloody stools

The analysis has 2 components:

1. To establish an objective case-definition suitable for surveillance purposes.
2. To test the ability of the working case-definition to predict NEC as defined by the "gold-standard" definition (NEC on histology of resected bowel OR visual inspection at laparotomy OR visual inspection at post mortem examination).

For each clinical and radiological feature, the specificity, sensitivity, positive predictive values will be calculated and area under the Receiver Operating Characteristic (ROC) curve analysis performed. This will be used to select the candidate clinical and radiological features for the case-definition which maximises the area under the ROC curve. The sensitivity and specificity using sequential numbers of clinical signs as a cut-off to define NEC using the "gold-standard" definition will be calculated. Multivariable logistic regression will be used with clinical and radiological features as covariates in order to determine which features are the strongest predictors of NEC defined using the "gold-standard" definition. Features which are strongly predictive of NEC will be mandatory elements of the definition. The model will be validated using bootstrapping which is a re-sampling technique which can be used to obtain estimates of future model performance (22). The predictive properties of the working case-definition to discriminate patients with "NEC" (as defined by the "gold-standard" definition) from patients with "No NEC" will be evaluated using Receiver Operating Characteristic

(ROC) curve analysis. The area under the ROC curves for both the working case-definition and the established case-definition will be compared.

A minimum of 10 events per variable is required for multivariable logistic regression (23). There are 6 potential clinical and radiological findings for the case definition, therefore 60 cases which fulfil the "gold-standard" definition for NEC will be required (23). From 2010 Neonatal Data Analysis Unit data (from 165/171 neonatal units in England), 8135 babies were born at or less than 32+6 weeks gestation in England. If approximately 7% develop NEC, this would be 569 babies a year. Of these, 170 (30%) babies will require surgery for NEC (fulfils "gold-standard" definition for NEC) in England. Therefore, it should be feasible to obtain an adequate sample of at least 60 cases over a period of 18 months.

12.2 Incidence of NEC

This will be determined for all participating neonatal units/networks. A high participation rate is anticipated and hence ability to provide incidence by geographically defined area.

12.3 Enteral-feed related antecedents of NEC

The hypothesis "There is an association between enteral-feed related factors and NEC" will be tested. A cohort study design using data from the National Neonatal Research Database will be used to test the hypothesis, comparing the outcome (NEC or no NEC) between groups of patients with different enteral-feed antecedents (exposures). Some statistical methods may be theoretically superior to others by taking into account the range of potential confounding factors, but may not be the most pragmatic solution as data quality may not be adequate to enable such analyses. A selection of statistical methods including the use of propensity scores to adjust for confounding will be explored. The final analysis plan which provides the most efficacious method of using the data will be developed as part of this PhD.

13. FEASIBILITY

This study is intended to be a national multi- network population-based study in England. A study of such a large-scale clearly has practical challenges. Engagement of clinicians at each unit is paramount for the success of this study. Regular network and national meetings, communication and newsletters are required to make it a truly collaborative study. Each participating neonatal unit will be asked to identify a lead investigator to drive the completeness and quality of data entry.

14. PARENT CONSENT

Anonymised data from an existing database will be utilised and therefore it is not intended to seek parent consent.

15. STUDY TIMELINE

The time frame for completion of this study is 3 years. It is anticipated that an adequate period will be 18 months but this will depend on the quality of data. An interim analysis will be performed and if necessary, the data collection period may be extended.

16. FUNDER

Dr Cheryl Battersby is funded by the National Institute for Health Research as part of the NIHR Medicines for Neonates Programme held by Professor Modi.

17. INTENDED OUTPUTS

A series of publications and other outputs are intended, including peer-reviewed publications, publications for the professional and lay press, information for parents, conference presentations

18. PUBLICATION POLICY

All publications will be authored "on behalf of the "NNC-NEC Study Group" that will include all named participating doctors and nurses. In other respects the Publication Policy for the Medicines for Neonates Programme will be followed.

19. SPONSOR AND INDEMNITY

The sponsor is Imperial College London; insurance policies are held that apply to this study.

20. USER INVOLVEMENT

One of the 6 components of the Medicines for Neonates programme involves user engagement and the national charity and parent advocacy organisation, Bliss, is a member of the co-investigator team.

21. REFERENCES

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