Research Protocol

The effect of surfactant dose on outcomes in preterm infants with Respiratory Distress Syndrome

Study name	The effect of surfactant dose on outcomes in preterm infants with RDS
Sponsor	Chiesi Limited
Chief Investigator	Dr Kevin Goss
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Protocol Approval

Signatures

By signing this document I am confirming that I have read, understood and approve the protocol for this research.

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Contents

List of Abbreviations

BPD	Bronchopulmonary dysplasia
CPAP	Continuous positive airway pressure
ETT	Endotracheal tube
IVH	Intraventricular haemorrhage
LISA	Less invasive surfactant administration
MIST	Minimally invasive surfactant administration
NDAU	Neonatal Data Analysis Unit
NHS	National Health Service
NNRD	Neonatal Network Research Database
R&D	Research and Development
RDS	Respiratory Distress Syndrome
REC	Research Ethics Committee
ROP	Retinopathy of prematurity
SAE	Serious Adverse Events
SUSAR	Suspected Unexpected Serious Adverse Reaction

1. Summary

Title: The effect of surfactant dose on outcomes in preterm infants with Respiratory Distress Syndrome

Chief Investigator: Dr Kevin Goss

Objective: To assess whether the dose and method of administration of surfactant given to preterm infants with respiratory distress syndrome (RDS) affects neonatal outcomes.

Research Design: Prospective observational study using de-identified data from the Neonatal Network Research Database (NNRD) supplemented by additional information on dose, method of surfactant administration and dosing frequency.

Participant Numbers: 1300

Inclusion Criteria:

- Gestational age of 36^{+6} weeks $^{+days}$ or less
- Treated with surfactant
- Record of birth-weight available
- Infants born after the initiation date of the study
- Parental opt-out consent

Exclusion Criteria:

- Gestational age of 37^{+0} weeks $^{+days}$ and above

2. Introduction

a. Background

Respiratory Distress Syndrome

Respiratory distress syndrome (RDS) is a condition that commences shortly after birth and increases in severity during the first 12 to 24 hours[1]. RDS is due, at least in part, to insufficiency of pulmonary surfactant and is mainly confined to preterm infants[1-3]. Its incidence decreases with increasing gestational age[4]. The aim of RDS management is to minimise lung damage using the least invasive treatment, avoiding unnecessary intubation and mechanical ventilation, enabling normal lung development, preventing bronchopulmonary dysplasia (BDP) and providing respiratory support[5].

Management of RDS

The European Consensus Guidelines for the management of RDS recommend stabilisation of the infant using non-invasive respiratory support such as high flow and continuous positive airway pressure (CPAP)[5]. The infant's oxygen requirements are monitored and should the fraction of inspired oxygen (FiO_2) required increase above 30% in infants under 26 weeks gestational age or 40% in infants over 26 weeks gestational age, then surfactant administration is recommended. Surfactant is normally administered by endotracheal tube whilst the infant is sedated, but the European Consensus Guidelines recommend the Intubate-SURfactant-Extubate (INSURE) method (where the endotracheal tube is extubated within 1 hour) or by less/minimally invasive surfactant administration using a thin catheter to deliver surfactant whilst the infant is spontaneously breathing[5].

CPAP failure

The successful management of infants on CPAP means that intubation, surfactant administration and mechanical ventilation can be avoided and a suggestion of lower risk of BDP has been observed[6-8.] However, between 21%-68% of infants initially managed on CPAP will require mechanical ventilation, termed 'CPAP failure', and defined as "intubation within the first 48-72 hours of starting CPAP" [6-12]. Furthermore, infants who fail on CPAP have similar outcomes to those who are mechanically ventilated in terms of rates of BDP, mortality, pneumothorax, periventricular haemorrhage and discharge on oxygen [9-10,12].

Surfactant dose

The licensed dose of surfactant for preterm infants with RDS is 100 to 200mg/kg[13]. A dose of 200mg/kg reduces FiO_2 requirements and the need for redosing[14-15] as well as indicating possibility of reduced mortality and oxygen requirement at 36 weeks post menstrual age[16]. A pharmacokinetic study has also demonstrated that a dose of 200mg/kg results in a higher half-life of surfactant compared to the 100mg/kg[16].

Administration techniques

The drive towards minimally invasive treatments for premature infants as well as the difficulties associated with intubation for surfactant delivery has led to innovations in surfactant administration. Minimally invasive surfactant administration (MIST) or less invasive surfactant administration (LISA) are techniques that use a thin catheter (Angiocath or nasogastric tube) to deliver surfactant whilst the infant is spontaneously breathing[17-18] and this method is gaining popularity across Europe[19]. A recent meta-analysis[20] found that the use of LISA/MIST has reduced the composite outcome of death or bronchopulmonary dysplasia (BDP) at 36 weeks, need for mechanical ventilation within 72 hours of birth, or need for mechanical ventilation anytime during the neonatal intensive care stay.

Use of the LISA/MIST techniques of surfactant administration also supports the drive towards non-invasive methods of ventilatory support, as no intubation is required to instil the surfactant, in contrast to the intubate-surfactant-extubate (INSURE) method.

b. Rationale for study

The rationale for this study is the clinical relevance of understanding whether surfactant dose affects neonatal outcomes in infants with RDS who are treated in the immediate postnatal period.

In a research environment, the dose of surfactant is rigorously controlled, usually administered at a dose of 100mg/kg or 200mg/kg. In clinical practice, clinicians more frequently follow the 'whole vial dosing' approach, where a full vial is given aiming to get as close as possible to the desired dose. Reasons for whole vial use include reduction of waste and administration of surfactant shortly after birth where an infant's weight is unknown. It is unclear whether whole vial dosing leads to under-dosing or over-dosing and whether either situation affects outcomes.

Information regarding the dose of surfactant delivered, and the method of administration, are not currently routinely recorded in the UK.

The aim of this study is to investigate the following objectives:

Primary objective

- To determine whether the first dose of surfactant (100-130 mg/kg compared to 170-200 mg/kg) has an effect on the requirement for mechanical ventilation within four days of birth

Secondary objectives

- To measure the association between first dose of surfactant and:
    - Respiratory support at day 28 post birth (for babies born ≤ 32 weeks)
    - Surfactant re-dosing within the first four days of birth
    - Respiratory support at 36^{+0} weeks gestational age (for babies born ≤ 32 weeks)
    - Duration of respiratory support
    - O_2 at discharge home
    - Respiratory support at 2 years

Exploratory objectives

- Association between method of surfactant administration and:
    - Mechanical ventilation within four days of birth
    - Respiratory support at day 28 post birth (for babies born ≤ 32 weeks)
    - Surfactant re-dosing within the first four days of birth
    - Respiratory support at 36^{+0} weeks gestational age (for babies born ≤ 32 weeks)
    - Duration of respiratory support
    - O_2 at discharge home
    - Respiratory support at 2 years
    - Incidence of complications such as retinopathy of prematurity, and intraventricular haemorrhage
    - Development at 2 years
    - Bayley III score at 2 years
- Association between dose of surfactant and:
    - Respiratory support at 2 years
    - Incidence of complications such as retinopathy of prematurity and intraventricular haemorrhage
    - Development at 2 years
    - Bayley III score at 2 years
- Association between FiO_2 (at point of decision to administer surfactant) and:
    - Mechanical ventilation within four days of birth
    - Respiratory support at day 28 post birth (for babies born ≤ 32 weeks)
    - Respiratory support at 36^{+0} weeks gestational age (for babies born ≤ 32 weeks)
    - Duration of respiratory support
    - O_2 at discharge home

- Association between method of respiratory support in the first two days of life and:
    - Mechanical ventilation within four days of birth
    - Respiratory support at day 28 post birth (for babies born ≤ 32 weeks)
    - Respiratory support at 36^{+0} weeks gestational age (for babies born ≤ 32 weeks)
    - Duration of respiratory support
    - O_2 at discharge home
- Association between use of analgesia and/or sedation at time of surfactant administration and:
    - Mechanical ventilation within four days of birth
    - Respiratory support at day 28 post birth (for babies born ≤ 32 weeks)
    - Respiratory support at 36^{+0} weeks gestational age (for babies born ≤ 32 weeks)
    - Duration of respiratory support
    - O_2 at discharge home
- Association between dose of analgesia and/or sedation at time of surfactant administration and:
    - Mechanical ventilation within four days of birth
    - Respiratory support at day 28 post birth (for babies born ≤ 32 weeks)
    - Respiratory support at 36^{+0} weeks gestational age (for babies born ≤ 32 weeks)
    - Duration of respiratory support
    - O_2 at discharge home

The endpoints for this study are as follows:

Primary endpoint

- Mechanical ventilation within four days of birth

Secondary endpoints

- Number of doses of surfactant
- Respiratory support at day 28 post birth
- Respiratory support at 36^{+0} weeks gestational age
- Duration of respiratory support
- Requirement for O_2 at discharge home
- Respiratory support at 2 years

Exploratory endpoints

- Incidence of complications such as retinopathy of prematurity, and periventricular haemorrhage
- Development at 2 years
- Bayley III score at 2 years

3. Research Design

It is proposed to minimise data collection requirements for this study through incorporation into routine clinical care. The data items required all form part of what would normally be recorded in a patient's case records. Hence it is proposed to obtain these from the Neonatal Network Research Database (NNRD).

The Neonatal Network Research Database (NNRD) is an electronic platform where neonatal patient data on all admissions to a National Health Service (NHS) neonatal unit in England, Scotland or Wales are recorded. Clinical data on all admissions to NHS neonatal units are entered by healthcare professionals, as part of routine clinical practice, onto electronic patient record systems at the point of care; from these data, approximately 450 data items (the Neonatal Data Set, an NHS Information Standard) are extracted quarterly to form the NNRD. Data held in the NNRD are used for audits, research, service evaluations and quality improvement projects.

A small number of additional data items not currently held in the NNRD, are required for this study. They are however all items that would normally be recorded in the patient's case notes; hence it is proposed to incorporate these into the electronic data capture system. Specific Research Ethics Approval will be sought for this study.

Multiple centres across the UK will be selected to participate. The parents of eligible babies will be approached for op-out consent for their child's data to be included in the study.

The study will continue recruiting until 1300 babies have been consented, and will remain open until 2 year follow up data has been obtained for those babies born < 30 weeks gestation. There will be no further follow up in those babies that have no data available at the 2 year follow-up.

NNRD Fields

Surfactant can be administered prophylactically (usually within the delivery room) or as rescue (usually within the neonatal ward). If surfactant is given prophylactically, it is assumed that this is the first administration.

If administered prophylactically, it is proposed that the following data items are added under the 'NNUEpisodes-Labour & Delivery' category within the electronic record:

	Question	Answer
1	Volume of surfactant administered in millilitres (mL)	[free text box]
2	Method of surfactant administration	• Endotracheal tube • INSURE (endotracheal tube in place for 15 minutes or less) • Thin catheter for minimally invasive/less invasive surfactant administration • Other
3	Time of initial surfactant administration	[free text]
4	Specify any analgesics and/or sedatives used for surfactant administration (drug and dose)	[free text]

Surfactant can also be administered in a rescue setting, usually within the neonatal unit. In this setting, the frequency of administration is captured (i.e. whether this is the infant's first, second or third dose). The following fields are proposed under the 'Respiratory-Daily' category:

	Question	Answer
1	Volume of surfactant administered in first dose, millilitres (mL)	[free text box]
2	Specify the method of surfactant administration	• Endotracheal tube • INSURE (endotracheal tube in place for 15 minutes or less) • Thin catheter for minimally invasive/less invasive surfactant administration • Other
3	How many doses of surfactant were administered today?	[Free text box]
4	Time of initial surfactant administration	[free text]
5	Specify any analgesics and/or sedatives used for surfactant administration (drug and dose)	[free text]
6	FiO_2 at point of decision to administer surfactant	• < 30 % • 30- 39 % • 40 - 49 % • 50 - 59 % • ≥ 60 %

a. Comparative fields

In order to investigate whether surfactant dose affects neonatal outcomes, the following data will be obtained from the NNRDs:

	NNRD field	Purpose of using this field for this study
1	Demographics > Birth weight	Using this field alongside the volume of surfactant used, the dose of surfactant will be calculated.
2	Demographics > Sex of the baby (phenotypic)	Characterisation of cohort
3	Demographics > Gestation weeks and day	Inclusion/exclusion criteria
4	Antenatal > Were steroids given during pregnancy?	Characterisation of cohort
5	Antenatal > Number of antenatal steroid courses given	Characterisation of cohort
6	Labour & delivery > Methods of resuscitation	Characterisation of cohort
7	Labour & delivery > Drugs used during resuscitation	Characterisation of cohort
8	Labour & delivery > Was surfactant given during resuscitation?	Characterisation of cohort
9	Respiratory > Respiration: Surfactant given today	Inclusion/exclusion criteria
10	Discharge details > Discharge time and date (anonymised)	Duration of hospitalisation, age at discharge
11	Discharge details > Date of death and time - anonymised	Calculation of mortality
12	Discharge details > cause of death	Determination of outcomes
13	Discharge details > Discharge oxygen	To investigate whether the dose of surfactants can affect whether infants are discharged on oxygen.
14	Respiratory > Respiratory support device and support mode (daily)	To investigate whether using there is a correlation between surfactant dose and respiratory device
16	Discharge details > Clinical diagnoses at discharge	To correlate the dose of surfactant, and/or method of surfactant administration is related to clinical diagnoses at discharge
17	Retinopathy of prematurity > ROP stage*	To determine whether the dose of surfactant is related to the severity of retinopathy of prematurity
18	Cranial ultrasound scan > IVH**	To determine whether the dose of surfactant is related to the severity of periventricular haemorrhage

19	Medication > Drugs given on this day	To identify infants who have received surfactant during their hospitalisation period, and which surfactant To identify which infants received analgesics or sedatives on the same day as surfactant, and which babies were given postnatal steroids
20	Two year follow up > Respiratory & CVS system – On supplemental oxygen or any respiratory support?	To determine whether the dose of surfactant is related to whether the infants requires supplemental oxygen at 2 years
21	Two year follow up > Development – at 24 month corrected age***	To determine whether the dose of surfactant is related to infant development (normal or mild, moderate or severe delay).
22	Two year follow up > Bayley III cognitive, total raw score	To determine whether the dose of surfactant is related to the infant's cognitive ability

*There are two NNRD fields for this outcome (right and left eye)
**There are two NNRD fields for this outcome (right and left side)
***There are four NNRD fields for this outcome (normal and mild, moderate or severe delay)

The full list of NNRD fields can be found in Appendix A.

4. Study Population

a. Number of Participants

Proposed sample size: 1300

The study is powered based on assumed proportions requiring mechanical ventilation within 72 hours of 60% and 45% in the dosing groups 100-130 mg/kg and 170-200 mg/kg respectively. The required power is 80% with the treatment comparison being undertaken at the two-sided 5% level of significance. At the planning stage the proportions of patients falling into the two dosing groups is not known. The sample size for the propensity score matched analysis is determined by the smaller of the two dosing groups and also the ability to find a match for each infant in that group. The table below provides total sample sizes required based on the assumptions set down according to various splits for the proportions of infants in the two dosing groups. Note also that the assumption has also been made that 10% of infants will receive a dose that falls between the upper limit of the lower dose group and the lower limit of the higher dose group. We will also assume that for 25% of infants in the smaller dosing group a match cannot be found. Sample sizes for 90% power are provided for completeness.

The proposed initial sample size of 1300 covers a range of possible assumptions regarding the split across the dosing groups including 45%/45%, 40%/50% and 35%/55%. An interim evaluation of the proportions of infants who fall into the two dosing groups will be undertaken on the first 400 infants recruited into the study to provide a check of the assumed breakdown and a sample size change considered if these assumptions are not correct.

Table: Sample Sizes under Various Assumptions

Proportion of infants in each dosing group	45%/45%	45%/45%	40%/50%	40%/50%	35%/55%	35%/55%
Event rates	80% power	90% power	80% power	90% power	80% power	90% power
60% vs 45%	1014	1352	1140	1520	1303	1738
60% vs 40%	563	753	634	847	724	968

b. Inclusion/Exclusion Criteria

Inclusion Criteria:

- Gestational age of 36^{+6} weeks or less
- Treated with surfactant
- Record of birth-weight available
- Infants born after the initiation date of the study
- Parental opt-out consent

Exclusion Criteria:

- Gestational age of 37^{+0} weeks and above

5. Data and Research Management

Selected study sites for participation will be approached to allow healthcare professional the opportunity to discuss the study and its aims. Data champions will be appointed at each study site; their responsibility will be to ensure data are fully recorded on all eligible infants who have provided opt-out consent.

Confirmation of quality assurance will be obtained from the NNRD every 3 months. No patient identifiers, or individual Trust identifiers, will be included in this study file.

Interim anonymised data will be analysed by an independent statistician within 3 months of the last patient recruited reaching 28 days post birth. All data will be anonymised and shall include no individual patient data.

The final anonymised data will be analysed by an independent statistician within 3 months of completion of the study (when the last patient has reached the 2 year time point). All data will be anonymised and shall include no individual patient data.

Once the final analysis of the data has been carried out, the original data will be destroyed. The analysed data will be kept by Chiesi for a minimum period of 5 years to allow dissemination.

This is an observational study, and the NNRD hold the relevant permissions for the data to be provided in anonymised form for the purposes of research by parties other than the NNRD upon specific Research Ethics Committee approval. Opt-out consent will be gained from the parents of babies eligible for inclusion in the study to confirm that they are happy for their baby's data to be utilised for this study.

6. Data Analysis

The primary objective of the study is to compare the two dosing groups (100-130 mg/kg and 170-200 mg/kg) in terms of the proportions of infants who require mechanical ventilation within four days of birth. This comparison will be undertaken primarily through propensity score matching with the key sensitivity analysis comparing the unmatched dosing groups.

The propensity score model will be a logistic regression model with binary 'outcome' corresponding to dosing group and with the following baseline factors included in the model; birth weight, gestational age, sex, antenatal steroids, inborn, age at first dose, and baseline FiO_2. This analysis will be based on the modified Intention-to-Treat population (mITT) defined as all patients who satisfy the inclusion/exclusion criteria, who provide complete data on each of the baseline factors considered for inclusion in the propensity model and who are evaluable for the primary endpoint.

Following 1 to 1 matching between the dosing groups 100-130 mg/kg and 170-200 mg/kg using a caliper of 0.025, an analysis of the matched cohorts will be based on a logistic regression model with the primary endpoint, requiring mechanical ventilation within 4 days of birth, as the response and dosing group plus each of the covariates listed used in the propensity score model included as terms in this analysis model. The key sensitivity analysis will compare the dosing groups in the full mITT population using the same modelling structure.

ROC Analysis

The amount of surfactant dose received (1st dose only) is potentially a key determinant of whether or not an infant requires mechanical ventilation within 4 days of birth. A ROC analysis will be undertaken to explore the ability of dose received to discriminate between those infants who do and those infants who do not require mechanical ventilation over this time period. The ROC analysis plots sensitivity against 1-specificity with points on the ROC curve (AUC) determined by varying the cut-off for dose received. Providing the AUC is greater than 0.7 an optimal cut-off for discrimination purposes will be chosen using Youden's J statistic. A one-sided p-value assessing whether the AUC is significantly greater than 0.5 will also be calculated.

The FiO_2 level at the point of decision to administer surfactant is potentially a key determinant of CPAP failure resulting in the requirement for mechanical ventilation within 72 hours of birth. A ROC analysis will be undertaken to explore the ability of FiO_2 level to discriminate between those infants who fail on non-invasive methods of ventilation and those infants who do not require mechanical ventilation over this time period. The ROC analysis plots sensitivity against 1-specificity with points on the ROC curve (AUC) determined by varying the cut-off for dose received. Providing the AUC is greater than 0.7 an optimal cut-off for discrimination purposes will be chosen using Youden's J statistic. A one-sided p-value assessing whether the AUC is significantly greater than 0.5 will also be calculated.

Analysis of secondary and exploratory objectives

Statistical analysis will also be carried out on secondary and exploratory endpoints.

7. MHRA reporting

Chiesi Limited is legally obliged to all report off-license use of any of its products to the MHRA. Any off-license use of Curosurf which is identified as part of the analysis of the raw data will be collated by the Chiesi pharmacovigilance team and reported to the MHRA. This includes the following:

- Dose of Curosurf used outside the licensed dose (100 – 200 mg/kg)
- Curosurf administered to treat RDS in a baby < 700g
- Curosurf administered prophylactically in a baby < 24 weeks or > 31 weeks gestational age

As only anonymised data will be analysed as part of this study, only aggregate data will be reported, and there will be no further follow-up to identify further information.

8. Good Clinical Practice

The research will be conducted in accordance with Good Clinical Practice, the Association of the British Pharmaceutical Industry (ABPI) Code of Practice, and the Data Protection Act.

Data extracted from the NNRD for the purposes of this protocol is anonymised. No patient identifiable data will be shared with any party, including the sponsoring pharmaceutical company, Chiesi Limited.

9. Research Conduct Responsibilities

a. Protocol Amendments

The Chief Investigator will seek approval from Chiesi Limited for any amendments to the protocol or other associated documentation, and vice versa. Amendments to the protocol or other associated documentation will not be implemented without approval from Chiesi Limited and if necessary from the REC and NHS Trust R&D Office.

b. End of Research

The end of the research is defined as the extraction of the two year data for the final patient recruited. Chiesi Limited has the right to terminate the research for any reason.

10. Reporting and Publication of Results

The study will be registered on the ISRCTN registry.

An independent statistician will analyse the NNRD data set against the pre-agreed analysis plan.

The results of the research will be made publicly available either in the form of a conference abstract/poster presentation, or submitted as a publication in a peer-reviewed journal within one year of study closure.

The decision to publish will be jointly taken between Chiesi and all the Investigators. The authors on any publication(s) will be based on the ICMJE authorship guidelines.

The final data set will be available to other researchers within three years of study end.

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12. Appendix A

Category	Category Detail	Item Name	Field ID	NHS data Dictionary Item Name	Format/ Length	Coding/allowed values	Description	Purpose
NNUEpisodes	Demographics and Birth Information (Baby)	Birth weight (g)	Birthweight	BIRTHWEIGHT	N4	Accepted range is between 001-9998g…9999 Unknown	Birth weight at the time of delivery in grams	Used to identify risk factors on admission to neonatal care
NNUEpisodes	Demographics and Birth Information (Baby)	Sex of the baby (phenotypic)	SexPhenotype	PERSON PHENOTYPIC SEX	N1	1 Male 2 Female 9 Indeterminate/ Intersex	The sex of the baby. 'Not known' is an option if information is missing or not recorded. 'Not specified' is an option for instances where the sex cannot be determined at birth.	Used to aggregate data by sex
NNUEpisodes	Demographics and Birth Information (Baby)	Gestation age in weeks	GestationsWeeks	GESTATION LENGTH (AT DELIVERY)	N2	10-49	The best obstetric estimate at the time of delivery in weeks. This will normally be based on the postmenstrual age but, if appropriate, may be modified on the basis of antenatal ultrasound. Where gestation at delivery is not known, this is based on the postnatal estimate of maturity	Used to identify risk factors on admission to neonatal care

NNUEpisodes	Antenatal (Pregnancy details)	Were steroids given during pregnancy?	Steroids AntenatalGiven	STEROIDS GIVEN DURING PREGNANCY TO MATURE FETAL LUNGS INDICATOR	an 1	Derived N No Y Yes 9 Unknown	Administration of any dose of steroid to mother (dexamethasone or betamathasone), at any time during pregnancy, with the intention of maturing foetal lungs.	Used to compare outcomes for babies
NNUEpisodes	Antenatal (Pregnancy details)	Number of antenatal steroid courses given	Steroids AntenatalCourses	ANTENATAL STEROID COURSE COMPLETION STATUS CODE	n1	1 - Complete: A full course of steroids at any time during pregnancy 2 - Incomplete: At least one injection of steroids given at any time during pregnancy 3 - Not Given 9 - Unknown	A complete course of steroids is defined by the RCOG guideline as two 12mg doses of betamethasone, given intramuscularly, 24 hours apart. Some units may use another regimen, including a different steroid. A complete course is one which complies with the local protocol.	Used to compare outcomes for babies
NNUEpisodes	Labour & delivery	Methods of resuscitation	MethodsOfResuscitation	NEONATAL RESUSCITATION METHOD (NATIONAL NEONATAL DATA SET)	an 3	00 None 10 Stimulation 11 Positioning managing airways 12 Oxygen 13 Suction 14 Bag and face mask IPPV 15 Intubation 16 Cardiac massage	Interventions used during resuscitation or stabilisation immediately after delivery of the baby.	Used to monitor neonatal outcomes

NNUEpisodes	Labour & delivery	Drugs used during resuscitation	DrugsFroResuscitation	NEONATAL RESUSCITATION DRUG (SNOMED CT DM+D)	n18	dm+d code for any drug	If medication was administered at resuscitation please select relevant medications.	Used to monitor neonatal outcomes
NNUEpisodes	Labour & delivery	Was surfactant given during resuscitation?	SurfactantGivenResuscitation	SURFACTANT GIVEN INDICATOR (DURING RESUSCITATION)	an1	N No Y Yes 9 Unknown	Surfactant given during resuscitation	Used to monitor neonatal outcomes
NNUEpisodes	Discharge details	Discharge date and time	DischDateTime	CRITICAL CARE DISCHARGE DATE AND TIME	an19	DateTime coding (e.g. 1997-07-16T19:20:30) Date (an10 CCYY-MM-DD) Time (an8 HH:MM:SS)	The date and time, Coordinated Universal Time (UTC), on which an inpatient completes this episode of care, either because of death, transfer to another ward or hospital, or because of discharge home.	Used to measure length of stay and to calculate the anonymised version of this field
NNUEpisodes	Discharge details	Date of death and time	DateofDeath	PERSON DEATH DATE AND TIME (DURING NEONATAL CRITICAL CARE PERIOD	an19	DateTime coding (e.g. 1997-07-16T19:20:30) Date (an10 CCYY-MM-DD) Time (an8 HH:MM:SS)	The date and time, Coordinated Universal Time (UTC), on which an inpatient had died in this episode of care as stated on the death certificate. If the discharge destination indicates the infant died this item is required	Used in survival analyses and calculate anonymised dates

NNUEpisodes	Discharge details	Cause of death	Causeof death	DEATH CAUSE ICD CODE (DURING NEONATAL CRITICAL CARE PERIOD)	an 6	ICD-10	Specify the major reasons for death of the baby from the list of International Classification of Diseases (ICD) as corresponding with death certificate.	Used to compare outcomes for babies
NNUEpisodes	Discharge details	Discharge:: Oxygen	Discharge Oxygen	RECEIVING OXYGEN THERAPY ON DISCHARGE INDICATOR	N	Delivered from Daily Data Item N No Y Yes	Item specifies if the baby is receiving and is dependant on oxygen therapy on discharge home.	Used to compare outcomes for babies.
NNUEpisodes	Discharge details	Clinical diagnoses at discharge	DiagnosesAtDischarge	DIAGNOSIS (ICD RECORDED ON DISCHARGE FROM NEONATAL CRITICAL CARE) and/or DIAGNOSIS (SNOMED CT ON DISCHARGE FROM NEONATAL CRITICAL CARE)	an 16/ n18	ICD-10 and/or SNOMED CT Can be derived from daily records	Specify all the applicable diagnoses for this baby if not already recorded in the daily diagnoses	Used to monitor infant care, evaluate health status and outcomes
Daily	Respiratory	Respiration: Respiratory support device	Respiratory support	RESPIRATORY SUPPORT MODE (NATIONAL NEONATAL DATA SET)	N1	1 Endotracheal tube2 Tracheostomy 3 Nasal cannula4 Nasopharyngeal cannula5 Face mask	Type of respiratory support device any time during the 24 hour period (00.00-23.59)	Used to determine level of care
Daily	Respiratory	Respiration: Surfactant given today	DaySurfactantGiven	SURFACTANT GIVEN INDICATOR (ON NEONATAL CRITICAL CARE DAILY CARE DATE)	an 1	N No Y Yes	Records if baby received any dose of surfactant in this day while in the neonatal unit.Surfactant given at delivery/resuscitation is a data	Used to determine health status of infant

							item collected separately	
Daily	Respiratory	Respiration: Respiratory support mode	ModeofRespiratorySupport	RESPIRATORY SUPPORT MODE (NATIONAL NEONATAL DATA SET)	N1	1 Positive pressure ventilation 2 High Frequency Oscillatory Ventilation (HFOV)3 High frequency jet ventilation (HFJV)4 CPAP5 BiPAP/ SiPAP 6 High flow	Mode of respiratory support via endotracheal tube. Conventional ventilation includes intermittent mandatory ventilation, synchronised intermittent mandatory ventilation, assist/control ventilation, pressure support ventilation, pressure targeted, volume targeted, hybrid.	Used to determine level of care
Daily	Medication	Drug given: Medication given o this day	DailyDrugs	MEDICATIONG GIVEN DYRING NEONATAL CRITICAL CARE DAILY CARE DATE (SOMED CT + DM+D)	N18	Dm+d code for any drug	Specify the exact medication the baby has received on this day of care	Used for multiple purposes including National Neonatal Audit Programme, monitor outcomes, and derive items for level of care where necessary.
NNUAdhoc	Retinopathy of prematurity screening	ROP stage - left eye	ROPStageLeft	RETINOPATHY OF PREMATURITY STAGE (LEFT EYE)	an1	0 No ROP1 Stage 1 ROP2 Stage 2 ROP3 Stage 3 ROP4 Stage 4 ROP5 Stage 5 ROPA Aggressive posterior ROP	The ROP stage for the left eye at the relevant ROP screening.	Used in the National Neonatal Audit Programme
NNUAdhoc	Retinopathy of prematurity screening	ROP stage - right eye	ROPStageRight	RETINOPATHY OF PREMATURITY STAGE (LEFT EYE)	an1	0 No ROP1 Stage 1 ROP2 Stage 2 ROP3 Stage 3 ROP4 Stage 4 ROP5 Stage 5 ROPA Aggressive posterior ROP	The ROP stage for the left eye at the relevant ROP screening.	Used in the National Neonatal Audit Programme

NNUAdhoc	Cranial ultrasound scan	Cranial scan findings (left): IVH	LeftIVH	INTRAVENTRICULAR HAEMORRHAGE GRADE (LEFT SIDE)	N2	0 No IVH seen1 Grade 1 (germinal matrix) IVH2 Grade 2 IVH3 Grade 3 IVH4 Grade 4 IVH	Most severe grade of intraventricular haemorrhage seen on left side	Used to monitor health status and outcomes
NNUAdhoc	Cranial ultrasound scan	Cranial scan findings (right): IVH	RightIVH	INTRAVENTRICULAR HAEMORRHAGE GRADE (RIGHT SIDE)	N1	0 No IVH seen1 Grade 1 (germinal matrix) IVH2 Grade 2 IVH3 Grade 3 IVH4 Grade 4 IVH	Most severe grade of intraventricular haemorrhage seen on left side	Used to monitor health status and outcomes
NNUAdhoc	Two Year Follow-up	Respiratory & CVS system – On supplemental oxygen or any respiratory support ?	MalformationImpairActivities	TPRG-SEND TWO YEAR CORRECTED AGE OUTCOME ASSESSMENT SCORE (RESPIRATORY AND CARDIOVASCULAR SYSTEM QUESTION B)	N	0 No1 Yes9 Unknown	Specify if the child is on supplemental oxygen or any respiratory support.	Use in assessing two year health outcomes following discharge from neonatal care
NNUAdhoc	Two Year Follow-up	Development – at 24 month corrected age. Is development normal (<3months delay)?	DevelopmentNormal	TPRG-SEND TWO YEAR CORRECTED AGE OUTCOME ASSESSMENT SCORE (DEVELOPMENT ADDITIONAL QUESTION FOR NATIONAL NEONATAL DATA SET)	An 1	N NoY YesU Unknown	Specify if the development at 24 months is normal with less than 3 months delay.	Additional item for two year follow up
NNUAdhoc	Two Year Follow-up	Development – at 24 month corrected age. Is there mild delay (3-6 months delay)?	DevelopmentMildDelay	TPRG-SEND TWO YEAR CORRECTED AGE OUTCOME ASSESSMENT SCORE (DEVELOPMENT QUESTION A)	N	0 No1 Yes9 Unknown	Specify the child development is correct at 24 months or is mild delay (3-6 months delay?)	Use in assessing two year health outcomes following discharge from neonatal care
NNUAdhoc	Two Year Follow-up	Development – at 24 month corrected age. Is there moderate delay (6-12	DevelopmentModerateDelay	TPRG-SEND TWO YEAR CORRECTED AGE OUTCOME ASSESSMENT SCORE (DEVELOPMENT	n	0 No1 Yes9 Unknown	Specify the child developments are correct at 24 months or are moderate delay (6-	Use in assessing two year health outcomes following discharge from neonatal care

		month delay)?		QUESTION B)			12 months delay?)	
NNUAd hoc	Two Year Follow-up	Develo pment – at 24 month correcte d age. Is there severe delay (>12 month delay)?	Develop mentSe vereDel ay	TPRG-SEND TWO YEAR CORRECTE D AGE OUTCOME ASSESSME NT SCORE (DEVELOP MENT QUESTION C	n	0 No1 Yes9 Unknown	Specify if the child's developme nt is correct at 24 months or if there is severe delay (>12 months delay).	Use in assessing two year health outcomes following discharge from neonatal care
NNUAd hoc	Two Year Follow-up	Bayley III – cognitiv e, total raw score	Cognitiv eTRS	BAYLEY III COGNITIVE TOTAL SCORE	N3	0-200	Specify the total raw score as assessed using Bayley III. (The Cognitive Scale (Cog) looks at how your child thinks, reacts, and learns about the world around him or her.(2008, Pearsons))	Use in assessing two year health outcomes following discharge from neonatal care