Trial Title: Multicentre, open-label, randomised controlled trial of early surfactant therapy versus expectant management in late preterm and early term infants with respiratory distress.

Short title: SurfON – Surfactant **O**r **N**ot

Ethics Ref: 20/EM/0003

IRAS Project ID: 269023

Sponsor Ref: UOL 0727

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Chief Investigator:

Professor Elaine M Boyle
Professor in Neonatal Medicine
College of Life Sciences
University of Leicester
eb124@leicester.ac.uk;
0116 252 5447

Sponsor:

University of Leicester

Research Governance Office
Research & Enterprise Division
Leicester General Hospital
Gwendolen Road
Leicester
LE5 4PW
RGOsponsor@leicester.ac.uk;
0116 258 4099/4867

Funder:

National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (17/89/07)

Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor: Signature:  Name (please print): Kyla Harrington Position: Clinical Trials Governance M	Date: 23/05/24
Chief Investigator: Signature: E M Boyle E M Boyle (May 23, 2024 12:43 GMT+1) Name (please print): Elaine M Boyle Position: Chief Investigator	Date: 23/05/24
Statistician: Signature:  Name (please print): Pollyanna Hardy Position: Statistician	Date: 23/05/24

There are no conflicts of interest to declare.

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1. Key trial contacts

Chief Investigator	Professor Elaine M Boyle Professor of Neonatal Medicine Department of Health Sciences College of Life Sciences George Davies Centre University of Leicester University Road Leicester LE1 7RH Email: eb124@leicester.ac.uk Phone: 0116 252 5447
Sponsor	University of Leicester Research Governance Office Research & Enterprise Division Leicester General Hospital Gwendolen Road Leicester LE5 4PW Email: RGOsponsor@leicester.ac.uk Phone: 0116 258 4099/4867
Funder	NIHR HTA Programme National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre University of Southampton Alpha House Enterprise Road Southampton SO16 7NS Phone: 023 8059 7366
Clinical Trials Unit	National Perinatal Epidemiology Unit (NPEU) Clinical Trials Unit (CTU) SurfON Trial Team Nuffield Department of Population Health University of Oxford Old Road Campus Headington Oxford OX3 7LF Email: surfon@npeu.ox.ac.uk Phone: 01865 289 437/738

Statistician	Ms Pollyanna Hardy NPEU CTU, University of Oxford Email: pollyanna.hardy@npeu.ox.ac.uk Phone: 01865 289 743
Co-Investigators	Professor Ben Stenson Neonatal Unit Simpson Centre for Reproductive Health Royal Infirmary of Edinburgh Edinburgh EH16 4SA Email: Ben.Stenson@nhslothian.scot.nhs.uk Phone: 0131 536 1000 Dr David Sweet Royal Jubilee Maternity Hospital Grosvenor Road Belfast BT12 6BA Email: david.sweet@belfasttrust.hscni.net Phone: 0289 024 0503 Bliss Fourth Floor, Maya House 134-138 Borough High Street London SE1 1LB Email: research@bliss.org.uk Phone: 020 737 84765 Ms Marie Hubbard Neonatal Unit Second Floor Kensington Building Leicester Royal Infirmary Leicester LE1 5WW Email: marie.hubbard@uhl-tr.nhs.uk Phone: 0116 258 6464 Professor Ed Juszczak Professor of Clinical Trials and Statistics in Medicine University of Nottingham Email: ed.juszczak@nottingham.ac.uk Phone: 0115 823 1600

	Associate Professor Oliver Rivero-Arias NPEU CTU, University of Oxford Email: oliver.rivero@npeu.ox.ac.uk Phone: 01865 617 908
NPEU CTU Project Management	Ms Christina Cole NPEU CTU, University of Oxford Email: christina.cole@npeu.ox.ac.uk Tel: 01865 617 923 Ms Kayleigh Stanbury NPEU CTU, University of Oxford Email: kayleigh.stanbury@npeu.ox.ac.uk Tel: 01865 289 749
NPEU CTU Trials Programming	Mr Andrew King NPEU CTU, University of Oxford Email: andy.king@npeu.ox.ac.uk Tel: 01865 289 708 Mr David Murray NPEU CTU, University of Oxford Email: david.murray@npeu.ox.ac.uk Tel: 01865 289 709

2. Synopsis

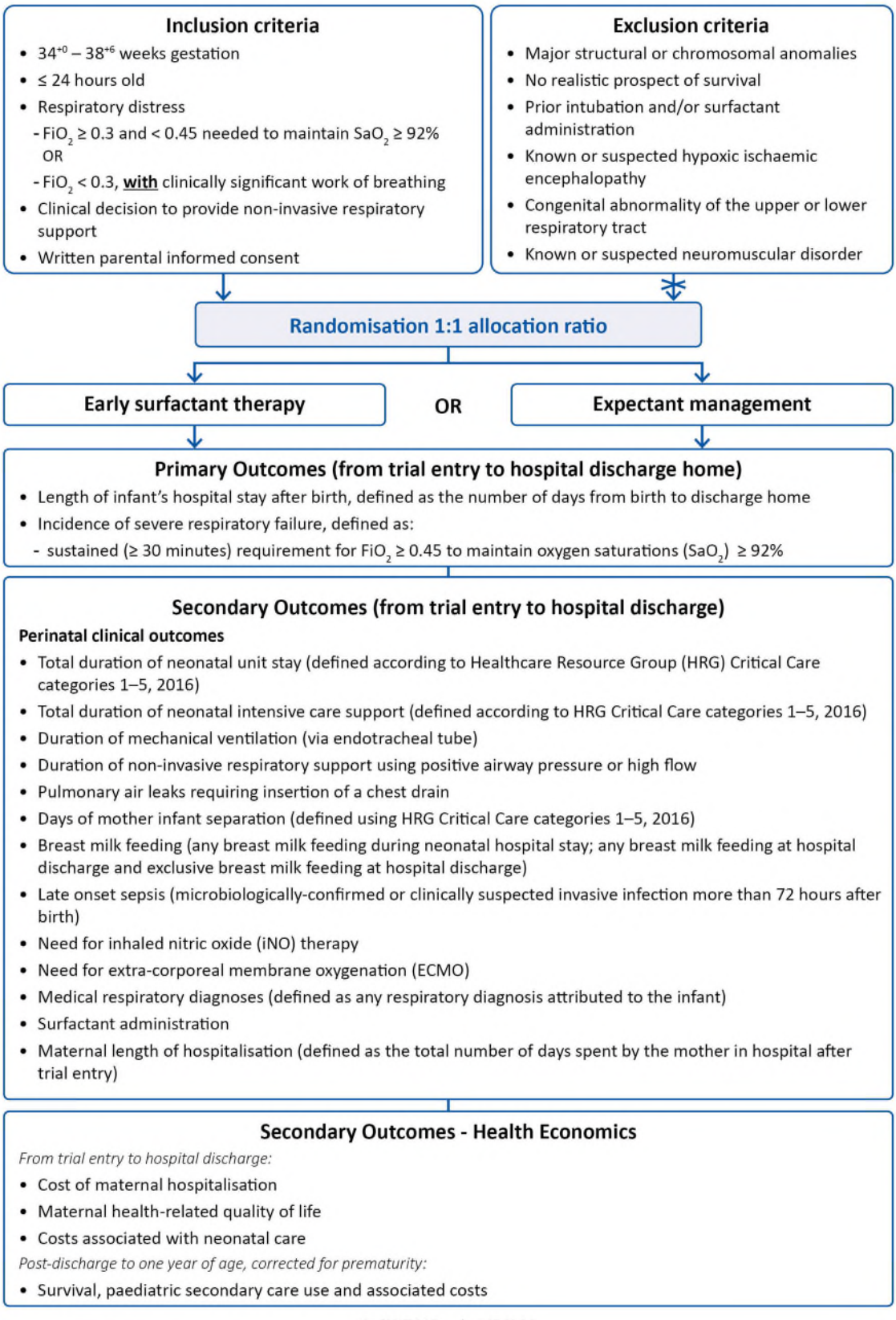
Trial Title	Multicentre, open-label, randomised controlled trial of early surfactant therapy versus expectant management in late preterm and early term infants with respiratory distress.
Internal ref. no. (or short title)	SurfON – **Surf**actant **O**r **N**ot
Trial registration	ISRCTN15915394
Sponsor	University of Leicester
Funder	NIHR HTA Programme
Clinical Phase	III

*This excludes the period the trial was paused to recruitment between 11/02/2022-04/07/2022.

Trial Design	Multicentre, open-label, two-arm, parallel-group, pragmatic randomised controlled trial.
Trial Participants	Infants born between 34^{+0} and 38^{+6} weeks of gestation admitted to a Neonatal Unit (NNU) with respiratory distress and for whom a clinical decision has been made to provide non-invasive respiratory support.
Sample Size	1,522
Treatment duration	Single dose
Planned Trial Period	The planned trial duration was for 42 months with a start date of 01.06.2019. Following the impact of the COVID-19 pandemic, the trial was extended - the overall trial end date is expected to be 31.08.2025, with a total expected duration of 75 months.
Planned Recruitment period	Active recruitment was initially planned for 30 months. Following the extension to the trial, this was increased to approximately 49 months*.
Trial Aim	To investigate whether, in late preterm and early term infants with respiratory distress, the early use of surfactant versus expectant management, results in a shorter duration of hospital stay and fewer infants who fail to respond to treatment.
Objectives	To compare duration of neonatal hospital stay in infants randomised to receive early surfactant versus those randomised to expectant management. To compare incidence of severe respiratory failure in infants randomised to receive early surfactant therapy versus those randomised to expectant management. To investigate the effects of early surfactant therapy versus expectant management on perinatal secondary outcomes. To investigate the cost-effectiveness of early surfactant therapy versus expectant management.
Intervention	Single dose of surfactant.
Investigational Medicinal Product (IMP)	Surfactant is available under the brand name of CUROSURF®.
Formulation	CUROSURF® 120 mg / vial Endotracheopulmonary Instillation Suspension. CUROSURF® 240 mg / vial Endotracheopulmonary Instillation Suspension.
Dose	CUROSURF® 100–200 mg/kg birth weight (1.25–2.5 ml/kg).

*This excludes the period that the trial was paused between 11.02.2022 – 04.07.202

3. Trial Flowchart



4. Abbreviations

AE	Adverse Event
ANNP	Advanced Neonatal Nurse Practitioners
APR	Annual Progress Report
AR	Adverse Reaction
BiPAP	Biphasic Positive Airway Pressure
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
ECMO	Extra-Corporeal Membrane Oxygenation
eDRIS	Electronic Data Research and Innovation Service
ETT	Endotracheal Tube
EudraCT	European Union Drug Regulating Authorities Clinical Trials
GCP	Good Clinical Practice
HES	Hospital Episode Statistics
HFT	High Flow Therapy
HRA	Health Research Authority
HRG	Healthcare Resource Group
HTA	Health Technology Assessment
IMP	Investigational Medicinal Product
iNO	Inhaled Nitric Oxide
LMA	Laryngeal Mask Airway
MHRA	Medicines and Healthcare products Regulatory Agency
nCPAP	Nasal Continuous Positive Airway Pressure
NHS	National Health Service
NIHR	National Institute for Health Research
NNU	Neonatal Unit
NPEU CTU	National Perinatal Epidemiology Unit Clinical Trials Unit
ONS	Office for National Statistics
PEDW	Patient Episode Database for Wales
PI	Principal Investigator
PIL	Parent Information Leaflet
PMG	Project Management Group

PPI	Public and Patient Involvement
RA	Risk Assessment
RDS	Respiratory Distress Syndrome
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SmPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee

5. Background and rationale

There are around 35,000 late preterm (34–36 weeks of gestation) and 130,000 early term (37–38 weeks of gestation) live births per year in the UK. Outcomes for these infants, both in the neonatal period and in the long term, were historically thought to be no different from those of infants born at full term (39–41 weeks of gestation). Only in the last decade has it been recognised that outcomes are worse in this group, particularly with respect to respiratory problems [1-9]. Rates of serious neonatal morbidity in late preterm and early term infants are low in comparison with the much smaller population of very preterm infants (< 32 weeks of gestation), but the impact of even modest rates of illness in such a large population of more mature infants is significant.

For the majority of late preterm and early term infants, neonatal care can be managed alongside their mother on a normal postnatal ward, but up to 30–40% require admission to a Neonatal Unit (NNU). Respiratory disease is the commonest reason for late preterm and early term infants to need NNU admission [10-12] . Respiratory distress syndrome (RDS) is due to lung immaturity and the associated deficiency of surfactant. Surfactant is a phospholipid and protein substance, which is produced in the lungs to reduce alveolar surface tension and improve lung compliance. The treatment for RDS is exogenous surfactant, administered either post-intubation via the endotracheal tube (ETT) or via a small catheter into the lungs (less invasive surfactant administration; LISA) or via a laryngeal mask (LMA). Usually, a single dose of surfactant is sufficient, but occasionally a second or third dose may be required in infants with very significant respiratory disease. The risk of RDS increases with increasing prematurity, and it is most prominent in very preterm infants, but it also occurs in late preterm and early term infants [13,14]. Other respiratory conditions, such as respiratory infection are also common in these infants and are characterised by secondary inactivation of surfactant [14,15]. Surfactant is most effective if given early in the course of respiratory disease [16]. Very preterm infants with significant RDS are routinely treated with surfactant early in their neonatal course to reduce respiratory complications and the need for prolonged mechanical ventilation [17]. In contrast, respiratory maturity is often assumed for late preterm and early term infants; it is expected that they will not need surfactant and few receive it, even when a diagnosis of RDS is made and confirmed on chest x-ray [18]. Studies of long-term outcomes have shown that both late preterm and early term infants experience more respiratory problems in childhood and have impaired lung function, when compared with infants born at full term [5-8,19] . Long-term respiratory morbidity is an ongoing burden for both families and health care providers during childhood [7,8,20,21]. Evidence is emerging suggesting that respiratory morbidity persists into adolescence and adulthood [3,9]. We do not know whether long-term respiratory deficits occur as a result of immaturity *per se* or whether the presence of and/or the approach to management of early respiratory disease, plays a part in long-term adverse outcomes.

Many late preterm and early term infants with respiratory disease do not require urgent intubation and mechanical ventilation at birth, yet have some degree of respiratory compromise. The effects of surfactant deficiency resolve, with or without surfactant treatment, as infants begin to produce their own endogenous surfactant in the lungs within the first postnatal week. Larger, more mature infants are more likely to manage through this period of transition without mechanical ventilation than their more immature counterparts. These infants are therefore generally managed expectantly, without surfactant administration, during the first hours and days of life with non-invasive respiratory support such as nasal continuous positive airway pressure (nCPAP), biphasic positive airway pressure (BiPAP) or high flow therapy (HFT). All are commonly used, and have been shown to be equivalent [22], so the choice of initial respiratory support is clinician dependent. In a small but significant proportion of these infants,

respiratory status deteriorates, oxygen requirements rise, blood gases worsen and mechanical ventilation is required. However, it is difficult to predict which infants will deteriorate and which will recover spontaneously and, in the early stages of the disease the specific cause of the respiratory distress is often not known with certainty. Chest x-ray changes are often non-specific and clinical signs are similar in all common neonatal respiratory conditions. It is likely, however, that either primary or secondary surfactant deficiency is present in many of these infants. Surfactant administration in this population is at the attending clinician's discretion, and no universally accepted criteria or guidance for this group have been defined. Some neonatologists choose to treat respiratory illness early in its course to prevent respiratory deterioration or pneumothorax, which is a recognised complication of nCPAP. However, others delay surfactant administration in the hope that intubation, surfactant administration and mechanical ventilation will be avoided. In some cases, the high cost of surfactant therapy might be an influencing factor in this decision-making. Delay in treatment can potentially result in increased severity of illness, requiring mechanical ventilation, prolonged intensive care and longer hospital stay. A recently published systematic review[23] confirmed a paucity of high quality evidence for management of respiratory distress in late preterm and term infants, and widely differing thresholds for intervention with surfactant, and recommended further trials in this area.

The impact of their infant's illness on mothers and families in this population should not be underestimated. Most mothers delivering at 34–38 weeks of gestation, knowing that they are delivering close to term, do not anticipate that their infant will have problems in the neonatal period. Clinicians do not expect problems, and therefore potential neonatal morbidities are not necessarily discussed with families antenatally. Unexpected prolonged neonatal hospitalisation of these more mature infants and separation of mothers and infants therefore causes significant psychological distress for families. Even late preterm and early term neonates who are not overtly unwell are generally sleepier and less eager to breastfeed than their full term counterparts. Respiratory illness and separation make this even more challenging and many mothers who intend to exclusively breastfeed their infant either stop, or decide not to start breastfeeding. Breastfeeding rates are low in both late preterm and early term infants, compared with full term infants [18,24], and have been reported as lower, even when compared with very preterm infants [25]. For mothers who plan and look forward to breastfeeding their infant, being unable to do so successfully is often interpreted as a personal failure and may affect maternal well-being [26].

Large numbers of late preterm and early term infants can contribute substantially to the intensive care workload of NNUs and generate high costs for the NHS. "Blocking" of intensive care cots is a common problem if the neonatal stay is prolonged and this can lead to lack of capacity for sicker or more preterm infants needing tertiary level care. Neonatal specialist care for these more mature infants is spread across all levels of NNUs. Infants with significant respiratory disease who become very sick in a Local Neonatal Unit (LNU) often need to be transferred to a Neonatal Intensive Care Unit (NICU) for ongoing management. This has inherent risks for the infant associated with transport, disrupts the family unit and is costly for the NHS. Such transfers might be avoided with more timely intervention to avert respiratory deterioration.

Although evidence exists for high risk very preterm neonates, there have been no clinical trials to date in this much lower risk population. Therefore, no evidence-based guidance exists, and there is no consensus among clinicians about optimum strategies for the early care of late preterm and early term infants with respiratory distress and consequently, management varies considerably [18]. In some NNUs, clinicians prefer to give early surfactant therapy to avoid possible deterioration. It is likely that in these units, some infants are routinely treated 'unnecessarily' and exposed to the invasive procedure of airway

manipulation and/or intubation for administration of surfactant. However, maybe more commonly clinicians adopt the 'wait and see' approach of expectant management, rather than to intervene early for an infant that may get better on their own. This can potentially result in increased severity of illness, requiring mechanical ventilation, prolonged intensive care and longer hospital stay. Given that both approaches have both positive and negative aspects, opinion is divided; either approach is currently considered acceptable and both are commonly used and therefore considered as Standard of Care in NNUs within the United Kingdom and other developed countries. There is a need to define the most clinically effective and cost effective approach to early respiratory management in this population.

6. Objectives and outcome measures

Primary objectives	**Outcome measures**	**Time point(s) of evaluation of this outcome measure**
To compare duration of neonatal hospital stay in infants randomised to receive early surfactant versus those who received expectant management. To compare incidence of severe respiratory failure in infants randomised to receive early surfactant therapy versus those who received expectant management.	• **Length of infant's hospital stay** after birth, defined as the number of days from birth to discharge home from hospital	Between birth and discharge home from hospital.
	• **Incidence of severe respiratory failure**, defined as, sustained (≥ 30 minutes) requirement for FiO_2 ≥ 0.45 to maintain oxygen saturations (SaO_2) ≥ 92%	Between trial entry and discharge home from hospital.
Secondary objectives	**Perinatal clinical outcomes measures**	**Time point(s) of evaluation of this outcome measure**
To investigate the effects of early surfactant therapy versus expectant management on perinatal secondary outcomes.	• **Total duration of NNU stay**, defined as total number of days of inpatient care in a neonatal unit (defined according to Healthcare Resource Group (HRG) Critical Care categories 1–5, 2016)	Between trial entry and infant discharge home from hospital.
	• **Total duration of neonatal intensive care**, defined as number of days of neonatal intensive care (defined according to HRG Critical Care categories 1–5, 2016)	

.	• **Duration of mechanical ventilation**, defined as days of ventilation via an ETT	
	• **Duration of non-invasive respiratory support**, using positive airway pressure or high flow	
	• **Pulmonary air leaks**, requiring insertion of a chest drain	
	• **Days of mother-infant separation**, defined using HRG Critical Care categories 1–5, 2016	
	• **Breast milk feeding**, defined as (a) any breast milk feeding during neonatal hospital stay, (b) any breast milk feeding at hospital discharge and (c) exclusive breast milk feeding at hospital discharge	
	• **Late onset sepsis**, defined as the incidence of microbiologically-confirmed or clinically suspected invasive infection more than 72 hours after birth	
	• **Need for inhaled nitric oxide (iNO) therapy**	
	• **Need for Extra-corporeal membrane oxygenation (ECMO)**	
	• **Medical respiratory diagnoses**, defined as any respiratory diagnosis attributed to the infant	
	• **Surfactant administration**, defined as (a) administration of any additional surfactant in infants randomised to receive early surfactant or (b) administration of any surfactant in infants receiving expectant	

	management, including number of doses and dose given	
	• **Maternal length of hospitalisation**, defined as the total number of days spent by the mother in hospital after trial entry	Between trial entry and maternal discharge home from hospital.
Secondary objectives	**Health economics outcomes measures**	**Time point(s) of evaluation of this outcome measure**
To investigate the cost-effectiveness of early surfactant therapy versus expectant management.	• **Cost of maternal hospitalisation**	Between trial entry and infant discharge home from hospital.
	• **Self-reported maternal health-related quality of life**	
	• **Costs associated with neonatal care**	
	• **Survival, paediatric secondary care use and associated costs** using routine national databases such as Hospital Episode Statistics (HES) data	Between infant discharge home and one year of age, corrected for prematurity.

7. Trial design

We will conduct a pragmatic, multicentre, open-label, two-arm parallel-group, randomised controlled trial along with an economic evaluation of early surfactant therapy in late preterm and early term infants with respiratory distress, where a clinical decision has been made to provide non-invasive respiratory support.

This research will take place within NHS neonatal services in hospitals within the UK. There will be a 12-month internal pilot phase, after which "stop-go" criteria will be used to evaluate feasibility of recruitment and other trial processes. We aim to recruit 1,522 infants who will be randomised to receive expectant management or early surfactant therapy.

The trial data collection will be from trial entry until one year of age corrected for prematurity and will include screening, consent, treatment and follow-up. Outcome information will be collected by case report forms (CRFs), with clinical data collection from medical records at the hospital. Questionnaires will be given to the mother at trial entry and around the time the infant is discharged from hospital. Survival, paediatric secondary care use and associated costs from discharge up to one year of age, corrected for prematurity, will be collected from routine national database e.g HES, with no direct contact with the parent(s).

The trial flowchart and schedules of events are summarised in sections 3 and 9 respectively.

7.1. Internal pilot

The 12-month internal pilot will assess recruitment and retention of infants, delivery of interventions, assess protocol adherence, monitor safety and evaluate completeness of data collection.

Funder pre-defined stop-go criteria after 12 months, with 359 recruits predicted, will be:

- Recruitment is 75% or more (N ≥ 269) – continue seamlessly into the main trial;
- Recruitment is 50–75% (179 ≤ N < 269) – recruit more centres if considered necessary and review in 6 months;
- Recruitment is < 50% (N < 179) – undertake an urgent detailed review of options with the Trial Steering Committee (TSC) and make subsequent recommendations to the funder.

8. Participant identification

8.1. Trial participants

The trial population is late preterm infants (born at 34^{+0}–36^{+6} weeks of gestation) and early term infants (born at 37^{+0}–38^{+6} weeks of gestation) with respiratory distress, where a clinical decision has been made to provide non-invasive respiratory support.

8.2. Inclusion criteria

1. Born at 34^{+0}–38^{+6} weeks of gestation
2. ≤ 24 hours old
3. Respiratory distress defined as:
    - FiO_2 ≥ 0.3 and < 0.45 needed to maintain SaO_2 ≥ 92%, or
    - FiO_2 <0.3 with clinically significant work of breathing
4. Clinical decision to provide non-invasive respiratory support
5. Written parental informed consent

8.3. Exclusion criteria

1. Major structural or chromosomal abnormality
2. No realistic prospect of survival
3. Prior intubation and/or surfactant administration
4. Known or suspected hypoxic ischaemic encephalopathy
5. Congenital abnormality of the upper or lower respiratory tract
6. Known or suspected neuromuscular disorder

9. Trial procedures

9.1. Schedule of trial procedures

PROCEDURES	BEFORE TRIAL ENTRY	AFTER TRIAL ENTRY				
	Screening	Baseline	Randomisation	Intervention	Data collection	
	Within 24 hours of birth			Post-randomisation	At hospital discharge	At one year of age[#]
Eligibility assessment	X					
Informed consent		X				
Randomisation			X			
Surfactant administration				X*		
Questionnaires		X[+]			X[+]	
Perinatal clinical data collection		X	X	X	X	
Follow-up data collection using routine national database						X
Adverse events assessments (SAEs, SUSARs etc)			X	X	X	

[#] Corrected for prematurity.

* Surfactant for infants randomised to early surfactant therapy will be administered as soon as possible after randomisation.

+Provide questionnaire for completion only if mother has provided consent to participate.

9.2. Recruitment

The trial will be conducted in at least 35 NNUs in the UK. We aim to recruit 1,522 infants. Participating centres will be NICUs and LNUs, and Special Care Units (SCUs). Information about the trial will be widely available using posters and banners throughout the NNUs. Eligible infants will be identified and screened by the clinical care team and recruited by appropriately trained, delegated individuals.

9.3. Screening and eligibility assessment

Infants with respiratory distress admitted to the NNU will be screened for eligibility by the clinical care team. Parents with legal responsibility will be approached to discuss the trial. Women for whom delivery between 34 and 36 weeks of gestation is anticipated, may be made aware of the trial prior to delivery, at the clinical team's discretion. Women having planned caesarean delivery at 37-38 weeks may also be provided with information about the study antenatally, as delivery by caesarean section that is not

preceded by labour is a known risk factor for early respiratory distress. Eligibility will be reconfirmed at the point of randomisation. Clinicians involved in independent decision-making about patient management in neonatology include both medically qualified doctors and advanced neonatal nurse practitioners (ANNPs). In many centres, ANNPs work in a middle-grade role as part of the medical rota, providing identical care to that given by paediatric registrar grade doctors. As such, an ANNP may be the most senior neonatal clinician on site, particularly outside normal working hours. It is therefore important that, in the SurfON Study, eligibility may be confirmed by either a doctor or ANNP, to maximise the opportunity for eligible infants to participate in this research.

9.4. Informed consent

Parents with legal parental responsibility for infants identified as being potentially eligible will be approached to discuss the trial further and to request consent. Parents will be given the opportunity to consider the information, and to ask questions of the research team or other independent parties to decide whether they will participate in the trial. Where parents do not have a good understanding of English, sites may use the translation and interpreting services, which they routinely use in clinical practice to communicate the trial. A delegated individual must obtain written informed consent from the parent prior to any trial related procedures being undertaken.

A parent must sign and date the latest approved consent form and the delegated individual will also sign and date the form. If the father or other parent provides consent, the mother must counter-sign the top section of the consent form as soon as practically possible. There will be a separate optional section for the mother's consent to take part in trial questionnaires. The original consent form will be stored in the site file. A copy of the signed informed consent form will be given to the parent, a copy will be stored in the infant's medical notes and a copy will be sent to the NPEU CTU.

9.5. Randomisation

Randomisation will occur as soon as possible after consent is obtained and eligibility is confirmed, using a 1:1 allocation ratio, with twins (or higher order multiple births) randomised to the same arm, to either:

- Early surfactant therapy
  or
- Expectant management

For infants in the "early surfactant therapy" group, surfactant administration should occur as soon as possible after the infant has been randomised.

Randomisation of infants will be managed via a secure web-based randomisation facility hosted by the National Perinatal Epidemiology Unit Clinical Trials Unit (University of Oxford) with telephone backup available at all times (365 days per year). The randomisation program will use a minimisation algorithm to ensure balance between the groups with respect to week of gestation at birth, multiple birth, and centre. A senior trials programmer will write the web-based randomisation program and hold the treatment allocation codes. The senior trials programmer and senior statistician will monitor implementation of the randomisation procedure throughout the trial. Reports will be provided to the Data Monitoring Committee (DMC).

9.6. Study data collection

Most outcome data for the trial are routinely collected clinical data that will be collected from hospital records and the BadgerNet or equivalent electronic data collection systems, from trial entry to hospital discharge home. All data will be entered on trial specific paper or electronic CRFs.

The outcome CRF will be completed at the time of discharge from the hospital. Where the mother has consented to questionnaire completion, they will also be asked to assess quality of life and breast milk feeding at trial entry and when the infant is discharged home, participation in this part of the trial is optional. The questionnaires should be entered at site on to the OpenClinica database and the hard copies filed in the site Data Collection File.

If the infant is transferred to another hospital, the recruiting site will be responsible for data collection.

Paediatric secondary care use and survival data will be obtained from the available electronic national databases in each of the four nations in the UK. This will include databases such as HES in England, the electronic Data Research and Innovation Service (eDRIS) in Scotland, the Patient Episode Database for Wales (PEDW) and the Hospital Activity Statistics in Northern Ireland or equivalent. We will access the equivalent datasets to hospital inpatient admissions, outpatient visits and paediatric critical care in each nation. Mortality data will be extracted from the HES-Office for National Statistics (ONS) linked database in England or equivalent in the other nations. Our data extract will cover the period from hospital discharge home, up to one year of age, corrected for prematurity. Parental consent will be obtained at trial entry requesting permission to follow up infants using routine national databases.

9.7. Additional respiratory intervention

Infants in the "expectant management" group should, where possible, be maintained on non-invasive respiratory support alone, at least until a more severe disease threshold is reached, defined as:

- sustained (≥ 30 minutes) requirement for $FiO_2 \geq 0.45$ to maintain oxygen saturations (SaO_2) ≥ 92%

In either study group, if intubation is required for another reason, surfactant may be given if the attending clinician deems this necessary. Information on the reasons for additional respiratory intervention and surfactant administration will be collected.

9.8. Withdrawal of participants

Parents will have the right to withdraw their infant from the trial at any time. Withdrawal from the trial will not affect their infant's ongoing clinical care. Data collected up to the point of withdrawal will be used in the trial.

Parents who do not wish to continue with the trial will be asked for permission for the trial team to complete data collection using medical records and indirect long-term follow-up using routine national databases when the infant reaches one year of age, corrected for prematurity. Parents who have consented to their infant's participation will be able to withdraw consent. The same applies to the mother who has consented to participate. In addition, the treating clinician may discontinue a participant from the trial intervention at any time if they consider it to be in the best interests of the infant's health and wellbeing. Withdrawals will be recorded on a CRF.

The need for additional respiratory intervention for infants randomised to either of the study arms does not constitute as withdrawal and and all data will be collected as part of routine trial outcome data collection.

9.9. Definition of end of trial

The end of trial will be defined as the point when the trial database is locked. An End of Trial Declaration will be made to the Medicines and Healthcare products Regulatory Agency (MHRA) and approving Research Ethics Committee (REC) within 90 days of end of trial. HES data or equivalent will be requested from routine national databases six months prior to the end of recruitment, and the timeframe and provision of these data will be dependent on the national database provider's response.

10. Trial interventions

10.1. Investigational Medicinal Product(s) (IMP) description

The IMP is CUROSURF®, a natural animal-derived surfactant manufactured and supplied by Chiesi Farmaceutici S.p.A. at 96, Via San Leonardo, 43122 Parma, Italy. The Reference Safety Information (RSI) will be the latest approved Summary of Product Characteristics (SmPC) for the surfactant used.

10.1.1. Blinding of IMPs

This is not a blinded trial. The IMP will be dispensed from the hospital stock through routine prescription.

10.1.2. Dosage

The recommended starting dose for the IMP is 100–200 mg/kg (1.25–2.5 ml/kg), administered in a single dose as soon as possible after diagnosing RDS. The administration of the IMP will be as per local site policy and procedure and may be completed by an ANNP, once eligibility is confirmed by a clinician or ANNP.

As part of the intervention in this trial, surfactant will be given to infant **as soon as possible after randomisation.**

10.1.3. IMP side-effects

The IMP is a commonly used drug in NNUs and is being used in line with standard care. Side effects are uncommon and usually transient during administration.

10.1.4. Compliance with trial treatment

The timing and dosage of IMP administration will be collected.

10.1.5. Accountability of the trial treatment

Surfactant is a stock drug for all NNUs and will be administered and accounted for as per local practice.

10.1.6. Contraindications

No specific contraindications are known.

11. Safety reporting

11.1. Adverse Event definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the RSI for the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the approved investigator's brochure (IB) relating to the trial in question.

NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

11.2. Assessment of causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

- **Unrelated** – where an event is not considered to be related to the IMP
- **Possibly** – although a relationship to the IMP cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible
- **Probably** – the temporal relationship and absence of a more likely explanation suggest the event could be related to the IMP
- **Definitely** – the known effects of the IMP, its therapeutic class or based on challenge testing suggest that the IMP is the most likely cause

All AEs (SAEs) labelled possibly, probably or definitely will be considered as related to the IMP.

11.3. Procedures for reporting Adverse Events

The safety reporting window for this trial will be from randomisation to infant’s discharge home. All trials run by the NPEU Clinical Trials Unit (NPEU CTU) follow the unit’s safety reporting Standard Operating Procedure (Safety Reporting in Trials using IMPs).

In this population we anticipate day-to-day fluctuations of pre-existing conditions. As a result, many adverse events are foreseeable due to the nature of the participant population and their routine care/ treatment.

Consequently, only those adverse events identified as serious will be reported for the trial.

11.4. Procedures for reporting Serious Adverse Events

11.4.1. Events exempt from immediate reporting as SAEs

The following expected SAEs are pre-defined trial outcomes and as such will only be recorded on the CRFs but not expeditiously reported:

- Pulmonary air leaks (pneumothoraces or pneumomediastinum)
- Late onset sepsis
- Need for mechanical ventilation via an ETT
- ECMO
- iNO

The following serious adverse events are a foreseeable occurrence in this population of infants and as such do not require reporting as SAEs:

- Common minor deviations from normal haematological values, including anaemia and thrombocytopenia
- Common minor deviations from normal biochemical values including hyponatraemia, hyperbilirubinaemia, and hypoglycaemia
- Patent ductus arteriosus

11.4.2. Events that need to be reported as SAEs

All events meeting the definition of an SAE (table in Section 11.1) other than those listed in the above section (11.4.1), will be reported (as described in section 11.4.3).

Events of particular interest (which must also be reported as SAEs) are:

- Death
- Transfer to another hospital related to early respiratory management
    - for escalation of care
    - for neonatal intensive care because of lack of intensive care cot capacity in the NICU or LNU of birth

  (Please note that transfers for a lower level of care (SCU) or for reasons unrelated to respiratory management do *not* need to be reported as an SAE.)
- Serious complication of ETT intubation such as hypoxia resulting in encephalopathy
- Severe pulmonary haemorrhage
- Severe intracranial haemorrhage

11.4.3. Procedure for immediate reporting of SAEs

All SAEs, other than those defined in this protocol as not requiring reporting, must be reported on the SAE Reporting Form to NPEU CTU trial team immediately or within 24 hours of the site becoming aware of the event being defined as serious.

Sites may use one of the following methods:

- Paper forms, with instructions, will be provided with the trial documentation to enable anyone to report an SAE. The completed SAE form must be emailed to NPEU CTU
- Staff with access to the trial electronic database should complete the SAE form online. An automatic email notification to the NPEU CTU staff will be triggered for SAEs reported electronically.
- Where the above routes are not possible, then the SAE may be reported to NPEU CTU by telephone and the SAE form will be completed by NPEU CTU staff

Follow-up SAE information should be reported as necessary by the site staff and sent back to the NPEU CTU electronically or by email.

11.4.4. Review and reporting of SAEs

The NPEU CTU will forward a copy of the SAE form to the CI / safety delegate as soon as possible on receipt. The CI will assess whether the SAE was related to the trial IMP (is it an SAE or an SAR?). If assessed to be related, the CI / safety delegate will proceed to assess expectedness (see Section 11.4.5).

All reported SAEs will be reviewed by the DMC at regular intervals throughout the trial. The CI will inform all the co-investigators concerned of relevant information that could adversely affect the safety of participants.

11.5. Expectedness

If the event is considered to be a SAR, it is assessed for expectedness against the known adverse reaction profile of the IMP. Expectedness will be determined according to the RSI in section 4.8 of the latest SmPC for the surfactant approved by the MHRA, for use in this study.

11.6. SUSAR reporting

All SUSARs will be reported by the Sponsor or NPEU CTU to the MHRA and by NPEU CTU to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be **done no later than seven calendar days** after NPEU CTU is first aware of the reaction. Any additional relevant information will be reported **within eight calendar days** of the initial report. All other SUSARs will be reported **within 15 calendar days**. NPEU CTU will ensure Sponsor are sent copies of all reports at the time of submission to REC.

SUSARs will be reported to the MHRA using the eSUSAR reporting system, https://esusar.mhra.gov.uk/ and will be submitted to the REC with a completed Report of Serious Adverse Event, which can be accessed via HRA website.

11.7. Development Safety Update Reports

.The CI will submit (in addition to the expedited reporting above) a Development Safety Update Report (DSUR) once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee, HRA (where required), Host NHS Trust and Sponsor.

As SurfON is approved under the notification scheme, the HRA Annual Progress Report (APR) form will be used as a template for the DSUR, and will include a list of all SARs in Section 6. The cover letter will state that this is an APR in lieu of a full DSUR, and include the EudraCT number and CTA reference number.

For assessment of SARs in the DSUR, the RSI that was approved at **the start of the safety reporting period** will be used. When there has been approved changes to the RSI by substantial amendment during the reporting period, the RSI used for the DSUR will differ to the RSI used to assess expectedness at the time of SAR occurrence for SARs which require expedited reporting.

12. Statistics & economic evaluation

12.1. Sample size determination

One of the primary outcomes is length of hospital stay from trial entry to discharge home. Reported length of stay for late preterm infants with respiratory distress is estimated to be between 10 and 15 days from the literature [4,10,18] . Calculations are based on the reduction in median length of stay in NNU from 12 days to 10 days in the early surfactant versus expectant management group. To detect a two-day reduction in length of stay (equivalent to a hazard ratio of 1.2) with 90% power and a two-sided 5% significance level, a total sample size of 1,280 is required. We estimate the prevalence of multiple births in our patient population to be 25% [17] with an intra-class correlation coefficient of 0.9, based on previous perinatal trials. Allowing for an inflation factor of 1.13 for this and a 5% attrition rate, the required recruitment target is 1,522 (761 per group). Based on data from NNUs, around 40–50 late preterm and early term infants per year require respiratory support. We aim to recruit an average of two infants per month over 30 months in approximately 35 NNUs to reach the target sample size of 1,522, allowing for a staggered start.

The other primary outcome is the proportion of infants who reach a pre-defined higher threshold of disease severity, at which clinicians may choose to give 'rescue' surfactant. A recent study [27] reported an event rate of 45% in a cohort of late preterm infants admitted to neonatal intensive care for respiratory failure. This is likely to be lower in the trial population, which also includes early term infants. With a sample size of 1,522, a treatment difference of 9% could be detected with 90% power and a two-sided 5% significance level, if the expectant management group event rate was 45%. A smaller treatment difference could be detected if the expectant management group event rate (CER) was lower than this (e.g. 8% difference for a CER of 35%, 7% difference for a CER of 25%).

12.2. Description of statistical methods

Analysis will be undertaken according to a pre-specified statistical analysis plan.
Demographic and clinical data will be summarised with counts and percentages for categorical variables, means (standard deviations) for normally distributed continuous variables and medians (with interquartile or simple ranges) for other continuous variables.

Infants will be analysed in the groups to which they were randomly assigned, comparing the outcome of all infants allocated to intervention with all those allocated to the comparator group, regardless of deviation from the protocol or treatment received (referred to as the Intention to Treat (ITT) population).

The primary analysis will be adjusted for minimisation factors (week of gestation at birth, multiple birth and centre). The correlation in outcomes between multiples will also be adjusted for.

For the primary outcome length of hospital stay, a hazard ratio and 95% confidence interval (CI) will be calculated using a time-to-event analysis, and a Kaplan-Meier plot will be presented. Each arm will be summarised with median length of stay with interquartile ranges. A very low death rate is expected in this population (< 1% [1]), and any deaths will be excluded (not censored) from this time to event analysis and reported separately.

Risk ratios will be presented for severe respiratory failure and other binary outcomes, and mean or median differences for continuous outcomes, as appropriate. 95% CIs will be presented for analyses of the primary and secondary outcomes.

There will be no adjustment made to the type I error when testing the two primary outcomes as they are both key outcomes of a focussed scientific research question addressing clinical and cost-effectiveness, and will be interpreted accordingly.

Pre-specified subgroup analyses will use the statistical test of interaction to examine the effect of the intervention on the primary outcomes across gestational age group at delivery (late preterm 34^{+0}–36^{+6} weeks vs. early term 37^{+0}–38^{+6} weeks), and first type of non-invasive respiratory support given after randomisation (high flow vs. positive airways pressure).

12.3. Data monitoring

Accumulating data from the trial will be reviewed by an independent Data Monitoring Committee (DMC) at least annually during their recruitment period of the trial, or as requested (see 14.3.2).

12.4. Early trial cessation

A recommendation may be made by the DMC to the Trial Steering Committee (TSC) to stop the trial early following review of accumulating data, or evidence from other relevant studies becoming available. Guidelines for the early cessation of the trial will be agreed with the DMC and documented in the DMC Charter.

12.5. Level of statistical significance

Two-sided statistical testing will be performed throughout. A 5% level of statistical significance will be used for analyses of all outcomes.

12.6. Procedures for reporting any deviations from the statistical analysis plan

All deviations from the original statistical analysis plan will be reported in the final report, as appropriate.

12.7. Economic evaluation

An economic evaluation using a cost-consequence analysis will be conducted alongside this trial. The aim of the cost-consequence analysis will be to determine whether the additional costs incurred by the use of early surfactant are justified by its additional benefits when compared to a policy of expectant management. An NHS perspective will be used in the analysis. The main outcome measures of the cost-consequence analysis will be a thorough and comprehensive cost-analysis from the mothers' and infant perspective and maternal health-related quality of life. Maternal health-related quality of life will be captured using the preference-based EQ-5D-5L instrument at trial entry and at hospital discharge.

We will collect health care resource use for infants and mothers during their original hospital stay from trial entry to discharge home. Paediatric secondary care use including hospital admissions and outpatients visits up to one-year follow-up, corrected for prematurity will be extracted from the Hospital Episode Statistics. Unit costs will be taken primarily from national sources.

The different components (costs and outcomes) of the cost-consequence analysis will be presented in a disaggregated and tabulated manner and presented separately up to hospital discharge and at one-year follow up.

Main outcomes for the cost-consequence analysis will be presented as mean estimates with associated 95% CI for each group in the trial. Mean differences and associated 95% CIs between the two arms of the trial for the different components of the cost-consequence analysis will be estimated using regression analysis to adjust (if necessary) for potential imbalances at baseline.

13. Data management

The data management aspects of the trial will be fully described in the Data Management Plan to ensure that high quality data are produced for statistical analysis.

13.1. Source data

Source documents (hospital records) are where data are first recorded, and from which infants' CRF data are obtained. CRF entries will be considered source data if the CRF is the site of the original recording (i.e. there is no other written or electronic record of data). Quality of life and infant feeding data will be provided by the mother using the trial questionnaire.

13.2. Access to data

Direct access will be granted to authorised representatives from the Sponsor, funder, research team, host institution (NHS trust) and the regulatory authorities to permit trial-related monitoring, audits and inspections.

Site staff will have authenticated and restricted access to the Clinical Database Management System (OpenClinica), ensuring they are only able to see data on participants recruited at their Trust. Access to the electronic data is strictly controlled using individual passwords for all staff accessing the electronic databases.

13.3. Data recording and record keeping

All clinical data will be entered directly into the clinical database by the site staff. As per ICH GCP (section 5.5), the clinical database will be validated and maintained in accordance with NPEU CTU Standard Operating Procedures (SOPs). Data will be entered and at the point of entry and will undergo a number of validation checks to verify the validity and completeness of the data captured. A separate administrative database application will be used to store the participant's name and any other identifiable details. Trial participants will be identified by a unique trial number, which is used to link the clinical and administrative database applications.

Consent forms containing the infant and parent's names will be sent securely. All data will be processed in line with the NPEU CTU Data Management SOPs. It is the responsibility of all parties involved (Sponsor, NPEU CTU, and the NHS organisations) to ensure confidentiality of participant information is maintained.

Electronic files will be stored on a restricted access (named individuals) server held in a secure location. The data are backed up daily. In line with the NDPH Information and Security Policies, authorised access

to the NPEU CTU is via an electronic tag entry system and individual rooms are kept locked when unoccupied. Authorised staff will process data via a secure network, which requires individual login name and password (changed regularly). No data are stored on individual workstations.

Archiving will follow the completion of the trial and publication of results as detailed in NPEU SOPs and in line with NHS guidelines for a minimum of 25 years. At this point, the requirements to continue to archive these data will be reviewed in line with the applicable data protection guidelines.

All paper and electronic data will be stored securely in strict compliance with data protection regulations.

14. Quality assurance procedures

14.1. Risk assessment

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and SOPs. A risk assessment (RA) and monitoring plan (MP) will be prepared before the trial opens and will be reviewed as necessary over the course of the trial to reflect significant changes to the protocol or outcomes of monitoring activities.

14.2. Monitoring

The Principal Investigator (PI) will be responsible for the running of the trial at their site. This will include ensuring successful recruitment, staff education and training, and trial data completeness and quality.

The NPEU CTU will develop an appropriate central monitoring plan for the trial, based on the RA. Recruitment patterns at sites and within the data will be monitored. Any unexpected patterns, issues, or outlier data will be investigated and may trigger 'for cause' site monitoring. No other routine monitoring or auditing will be conducted unless the central monitoring triggers cause to do so.

14.3. Trial committees

14.3.1. Trial Steering Committee (TSC)

The trial will be overseen by a TSC consisting of an independent chair and other members to include clinicians, statisticians and Patient and Public Involvement (PPI) representatives. Committee members will be deemed independent if they are not involved in trial recruitment. The chair and members of the TSC will be nominated as per the guidance outlined by the NIHR HTA for their approval. The TSC will aim to meet in person at least annually.

The TSC will monitor the progress of the trial and its conduct, and advise on its scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the DMC and ultimately carry the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy.

14.3.2. Data Monitoring Committee (DMC)

The DMC members will be independent of the trial team and the TSC, and will include a chair, clinician and statistician. During the recruitment phase, the committee will annually or more often as appropriate, review trial conduct, progress and accumulating data, and make recommendations to the TSC. Details

about the roles, responsibilities and conduct of the committee with be set out in a DMC Charter, which will be agreed at the first meeting.

15. Protocol deviations

A trial related deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g. consent process or IMP administration) or from GCP or any applicable regulatory requirements. Any deviations from the protocol will be documented in incident forms and where applicable the relevant corrective and preventative action completed.

16. Serious breaches

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the written notification of "serious breaches" to the MHRA within seven days of the Sponsor becoming aware of the breach.

A serious breach is defined as “A breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial”.

In the event that a serious breach is suspected this must be reported to Sponsor within 24 hours. In collaboration with the CI, the serious breach will be reviewed by the Sponsor and if appropriate, the Sponsor will report it in writing to the REC committee, Regulatory authority and the relevant NHS host organisation within seven calendar days.

17. Ethical and regulatory considerations

17.1. Declaration of Helsinki

The Investigators will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

17.2. Guidelines for Good Clinical Practice

The Investigators will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

17.3. Other ethical considerations

There are no other ethical considerations associated with the trial.

17.4. Approvals

Following Sponsor approval, the protocol, informed consent form, participant information sheet and any other participant facing material will be submitted to an appropriate Research Ethics Committee (REC), HRA and MHRA for written approval.

NPEU CTU will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

17.5. Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an APR to the REC, HRA (where required), funder (where required) and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, and Sponsor.

17.6. Participant confidentiality

The trial will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018. All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial staff will safeguard the privacy of participants' personal data.

All personal identifiers details will be stored in a separate database also held at the NPEU CTU. These databases will only be linked by the infant's trial number.

After the trial has been completed and the reports published, the data will be archived in a secure physical or electronic location with controlled access.

17.7. Expenses and benefits

No financial or material incentive or compensation will be provided to parents for enrolling their infant(s) in this trial.

18. Finance and insurance

18.1. Funding

This trial is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) [Project: 17/89/07]. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

18.2. Insurance

University of Leicester is the sponsor for the trial. They have a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research. NHS indemnity operates in respect of the clinical treatment which is provided.

19. Publication policy

The success of the trial depends on a large number of neonatal nurses, neonatologists, and parents. Credit for the trial findings will be given to all who have collaborated and participated in the trial

including all local co-ordinators and collaborators, members of the trial committees, the SurfON Co-ordinating Centre and trial staff. Authorship at the head of the primary results paper will take the form "[name], [name] and [name] on behalf of the 'The SurfON Collaborative Group'". The drafting of the paper will be the responsibility of a writing committee. All contributors to the trial will be listed at the end of the main paper, with their contribution identified. It is the intention of the SurfON Collaborative Group to publish the protocol and peer-reviewed articles including the analysis of key outcomes. All published material will contain an acknowledgement of funding, as required by the NIHR HTA.

20. Development of a new product/process or the generation of intellectual property

It is not anticipated the research will lead to the generation of intellectual property (IP), however this will be reviewed as the trial progresses in line with the funder's requirements.

21. Archiving

Archiving will follow the completion of the trial and publication of results as detailed in NPEU Standard Operating Procedures (SOPs) and in line with Sponsor's guidelines for a minimum of 25 years. At this point, the requirements to continue to archive these data will be reviewed in line with the applicable data protection guidelines.

22. References

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SurfON Protocol V7.0_250424_

Final Audit Report 2024-05-23

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