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

Summary

EudraCT number	2019-003764-45
Trial protocol	GB
Global end of trial date	27 May 2025

Results information

Result version number	v1 (current)
This version publication date	13 June 2026
First version publication date	13 June 2026

Trial information

Trial identification

Sponsor protocol code	UOL0727

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Leicester
Sponsor organisation address	Research Governance Office, Research & Enterprise Division, University of Leicester, University Road, Leicester, United Kingdom, LE1 7RH
Public contact	Professor Elaine M Boyle, University of Leicester, 0116 252 5447, eb124@leicester.ac.uk
Scientific contact	Professor Elaine M Boyle, University of Leicester, 0116 252 5447, eb124@leicester.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 May 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 May 2025
Global end of trial reached?	Yes
Global end of trial date	27 May 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives for the SurfON trial are:

(i) To compare duration of neonatal hospital stay in infants randomised to receive early surfactant versus those who received expectant management (standard hospital care)

(ii) To compare incidence of severe respiratory failure in infants randomised to receive early surfactant therapy versus those who received expectant management

(iii) To investigate the effects of early surfactant therapy versus expectant management on perinatal secondary outcomes, and

(iv) To investigate the cost-effectiveness of early surfactant therapy versus expectant management.

Protection of trial subjects:

Surfactant is routinely used in babies and there are no extra risks involved from taking part in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 September 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 1515
Worldwide total number of subjects	1515
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	877
Newborns (0-27 days)	638
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment ran from September 2020 to April 2025, with a five-month pause from February to July 2022. Across 50 participating centres (NICUs, LNUs and Special Care Units), 1515 infants were enrolled out of a target of 1522.

Pre-assignment

Screening details:

Infants with respiratory distress admitted to NNU were screened; parents approached for consent, sometimes antenatally. Eligibility confirmed at randomisation. Inclusion: 34+0–38+6 wks, ≤24 h, respiratory distress, need for NIV, consent. Exclusion: major anomalies, no survival, prior intubation/surfactant, HIE, airway or neuromuscular disorder

Period 1

Period 1 title	Trial Entry
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Early Surfactant

Arm description:

Single dose of surfactant, administered as soon as possible after the infant has been randomised.

Arm type	Experimental
Investigational medicinal product name	CUROSURF (R)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Endotracheopulmonary instillation
Routes of administration	Endotracheopulmonary use

Dosage and administration details:

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 Respiratory Distress Syndrome. 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.

Arm title	Expectant Management

Arm description:

Standard non-invasive respiratory support such as nasal continuous positive airway pressure (nCPAP), biphasic positive airway pressure (BiPAP) or high flow therapy (HFT).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Early Surfactant	Expectant Management
Started	758	757
Completed	758	757

Period 2

Period 2 title	Trial Analysis
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Early Surfactant

Arm description:

Single dose of surfactant, administered as soon as possible after the infant has been randomised.

Arm type	Experimental
Investigational medicinal product name	CUROSURF (R)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Endotracheopulmonary instillation
Routes of administration	Endotracheopulmonary use

Dosage and administration details:

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 Respiratory Distress Syndrome. 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.

Arm title	Expectant Management

Arm description:

Standard non-invasive respiratory support such as nasal continuous positive airway pressure (nCPAP), biphasic positive airway pressure (BiPAP) or high flow therapy (HFT).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Early Surfactant	Expectant Management
Started	758	757
Completed	758	757

Baseline characteristics

Reporting groups	
Reporting group title	Early Surfactant
Reporting group description:	
Single dose of surfactant, administered as soon as possible after the infant has been randomised.	
Reporting group title	Expectant Management
Reporting group description:	
Standard non-invasive respiratory support such as nasal continuous positive airway pressure (nCPAP), biphasic positive airway pressure (BiPAP) or high flow therapy (HFT).	

Reporting group values	Early Surfactant	Expectant Management	Total
Number of subjects	758	757	1515
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Late preterm (34+0-36+6 weeks)	439	438	877
Early term (37+0-38+6 weeks)	318	319	637
Term (39+0–40+6 weeks)	1	0	1
Age continuous Units: weeks			
arithmetic mean	36.3	36.3	
standard deviation	± 1.4	± 1.4	-
Gender categorical Units: Subjects			
Female	271	281	552
Male	486	475	961
Indeterminate	1	1	2
One of Multiple Pregnancy Units: Subjects			
Yes	92	93	185
No	666	664	1330

End points

End points reporting groups

Reporting group title	Early Surfactant
Reporting group description:	
Single dose of surfactant, administered as soon as possible after the infant has been randomised.	
Reporting group title	Expectant Management
Reporting group description:	
Standard non-invasive respiratory support such as nasal continuous positive airway pressure (nCPAP), biphasic positive airway pressure (BiPAP) or high flow therapy (HFT).	
Reporting group title	Early Surfactant
Reporting group description:	
Single dose of surfactant, administered as soon as possible after the infant has been randomised.	
Reporting group title	Expectant Management
Reporting group description:	
Standard non-invasive respiratory support such as nasal continuous positive airway pressure (nCPAP), biphasic positive airway pressure (BiPAP) or high flow therapy (HFT).	

Primary: Length of infant's hospital stay after birth

End point title	Length of infant's hospital stay after birth
End point description:	
End point type	Primary
End point timeframe:	
Number of days from birth to discharge home.	

End point values	Early Surfactant	Expectant Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	748[1]	752[2]		
Units: days				
arithmetic mean (standard deviation)	10.0 (± 6.2)	10.3 (± 6.8)		

Notes:

[1] - Outcome data missing (n = 9)
Infant died (n = 1)
[2] - Outcome data missing (n = 3)
Infant died (n = 2)

Statistical analyses

Statistical analysis title	Length of Hospital Stay (HR)
Statistical analysis description:	
Stratified Cox proportional hazards regression of length of hospital stay, deaths excluded (not censored)	
Comparison groups	Early Surfactant v Expectant Management

Number of subjects included in analysis	1500
Analysis specification	Pre-specified
Analysis type	superiority[3]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.22

Notes:

[3] - Stratified Cox proportional hazards regression of length of hospital stay, adjusted for week of gestation at birth as a fixed effect with multiple births and centre included in the model as random effects.

Primary: Incidence of severe respiratory failure

End point title	Incidence of severe respiratory failure

End point description:

End point type	Primary

End point timeframe:

From randomisation to discharge home.

End point values	Early Surfactant	Expectant Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	756[4]	755[5]		
Units: Number of infants				
Yes	127	138		
No	629	617		

Notes:

[4] - Outcome data missing (n = 2)

[5] - Outcome data missing (n = 2)

Statistical analyses

Statistical analysis title	Incidence of Severe Respiratory Failure (RR)

Statistical analysis description:

Risk ratio for severe respiratory failure, analysed using Poisson regression with a robust variance estimator.

Comparison groups	Early Surfactant v Expectant Management
Number of subjects included in analysis	1511
Analysis specification	Pre-specified
Analysis type	superiority[6]
Parameter estimate	Risk ratio (RR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.14

Notes:

[6] - Poisson regression with a robust variance estimator, adjusted for week of gestation at birth as a fixed effect with multiple births and centre included as random effects.

Statistical analysis title	Incidence of Severe Respiratory Failure (RD)

Statistical analysis description:

Risk difference for severe respiratory failure, analysed using Poisson regression with a robust variance estimator.

Comparison groups	Early Surfactant v Expectant Management
Number of subjects included in analysis	1511
Analysis specification	Pre-specified
Analysis type	superiority[7]
Parameter estimate	Risk difference (RD)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.02

Notes:

[7] - Poisson regression with a robust variance estimator, adjusted for week of gestation at birth as a fixed effect with multiple births and centre included as random effects.

Secondary: Total duration of neonatal unit stay (days)

End point title	Total duration of neonatal unit stay (days)

End point description:

End point type	Secondary

End point timeframe:

From randomisation to discharge home

End point values	Early Surfactant	Expectant Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	751[8]	754[9]		
Units: days				
median (inter-quartile range (Q1-Q3))	8.0 (5.0 to 12.0)	8.0 (5.0 to 12.0)		

Notes:

[8] - Outcome data missing (n = 7)

[9] - Outcome data missing (n = 3)

Statistical analyses

Statistical analysis title	Total duration of NNU stay (days)

Statistical analysis description:

Quantile regression on the median total duration of neonatal (NNU) stay in days.

Comparison groups	Expectant Management v Early Surfactant

Number of subjects included in analysis	1505
Analysis specification	Pre-specified
Analysis type	superiority[10]
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	0.58

Notes:

[10] - Quantile model adjusted for week of gestation at birth, multiple birth and centre. All covariates treated as fixed effects.

Secondary: Duration of mechanical ventilation via an endotracheal tube (days)

End point title	Duration of mechanical ventilation via an endotracheal tube (days)

End point description:

End point type	Secondary

End point timeframe:

From randomisation to discharge home

End point values	Early Surfactant	Expectant Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	756[11]	755[12]		
Units: Number of infants with a positive value				
Yes	150	102		
No	606	653		

Notes:

[11] - Outcome data missing (n = 2)

[12] - Outcome data missing (n = 2)

Statistical analyses

Statistical analysis title	Duration of mechanical ventilation via an ET tube

Statistical analysis description:

Negative binomial regression on the duration of mechanical ventilation via an endotracheal (ET) tube, in days.

Comparison groups	Early Surfactant v Expectant Management
Number of subjects included in analysis	1511
Analysis specification	Pre-specified
Analysis type	superiority[13]
Parameter estimate	Rate ratio
Point estimate	1.29

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.78

Notes:

[13] - Negative binomial regression on the duration of mechanical ventilation via an endotracheal due to zero inflated data. Negative binomial regression model adjusted for week of gestation at birth, multiple birth and centre. Week of gestation and centre were treated as fixed effects, and multiple births was treated as a random effect.

Secondary: Duration of non-invasive respiratory support

End point title	Duration of non-invasive respiratory support

End point description:

End point type	Secondary

End point timeframe:

From randomisation to discharge home

End point values	Early Surfactant	Expectant Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	756[14]	755[15]		
Units: days				
median (inter-quartile range (Q1-Q3))	2.0 (2.0 to 4.0)	3.0 (2.0 to 4.0)		

Notes:

[14] - Outcome data missing (n = 2)

[15] - Outcome data missing (n = 2)

Statistical analyses

Statistical analysis title	Duration of non-invasive respiratory support

Statistical analysis description:

Quantile regression on the median duration of non-invasive respiratory support, using positive airway pressure or high flow, in days.

Comparison groups	Early Surfactant v Expectant Management
Number of subjects included in analysis	1511
Analysis specification	Pre-specified
Analysis type	superiority[16]
Parameter estimate	Median difference (final values)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.93
upper limit	-0.07

Notes:

[16] - Quantile regression model adjusted for week of gestation at birth, multiple birth and centre. All covariates treated as fixed effects.

Secondary: Pulmonary air leaks requiring insertion of a chest drain

End point title	Pulmonary air leaks requiring insertion of a chest drain

End point description:

End point type	Secondary

End point timeframe:

From randomisation to discharge home

End point values	Early Surfactant	Expectant Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	751[17]	754[18]		
Units: Number of infants				
Yes	7	17		
No	744	737		

Notes:

[17] - Outcome data missing (n = 7)

[18] - Outcome data missing (n = 3)

Statistical analyses

Statistical analysis title	Pulmonary air leaks requiring insertion of a drain

Statistical analysis description:

Risk ratio for pulmonary air leaks requiring insertion of a chest drain, analysed using Poisson regression.

Comparison groups	Early Surfactant v Expectant Management
Number of subjects included in analysis	1505
Analysis specification	Pre-specified
Analysis type	superiority[19]
Parameter estimate	Risk ratio (RR)
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	1.13

Notes:

[19] - Poisson regression model adjusted for week of gestation at birth, multiple birth and centre. Week of gestation was treated as a fixed effect, and centre and multiple births were treated as random effects.

Statistical analysis title	Pulmonary air leaks requiring insertion of a drain

Statistical analysis description:

Risk difference for pulmonary air leaks requiring insertion of a chest drain, analysed using Poisson regression.

Comparison groups	Early Surfactant v Expectant Management
Number of subjects included in analysis	1505
Analysis specification	Pre-specified
Analysis type	superiority[20]
Parameter estimate	Risk difference (RD)
Point estimate	-0.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0

Notes:

[20] - Poisson regression model adjusted for week of gestation at birth, multiple birth and centre. Week of gestation was treated as a fixed effect, and centre and multiple births were treated as random effects.

Secondary: Days of mother-infant separation

End point title	Days of mother-infant separation

End point description:

End point type	Secondary

End point timeframe:

From randomisation to discharge home

End point values	Early Surfactant	Expectant Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	751[21]	754[22]		
Units: days				
median (inter-quartile range (Q1-Q3))	7.0 (4.0 to 11.0)	7.5 (5.0 to 12.0)		

Notes:

[21] - Outcome data missing (n = 7)

[22] - Outcome data missing (n = 3)

Statistical analyses

Statistical analysis title	Days of mother-infant separation

Statistical analysis description:

Quantile regression on the median days of mother-infant separation.

Comparison groups	Early Surfactant v Expectant Management
Number of subjects included in analysis	1505
Analysis specification	Pre-specified
Analysis type	superiority[23]
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	0.58

Notes:

[23] - Quantile regression model adjusted for week of gestation at birth, multiple birth and centre. All covariates treated as fixed effects.

Secondary: Breast milk feeding

End point title	Breast milk feeding

End point description:

End point type	Secondary

End point timeframe:

From randomisation to discharge home

End point values	Early Surfactant	Expectant Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	615[24]	625[25]		
Units: Number of infants				
Yes	481	479		
No	134	146		

Notes:

[24] - Outcome data missing (n = 143)

[25] - Outcome data missing (n = 132)

Statistical analyses

Statistical analysis title	Breast milk feeding (RR)

Statistical analysis description:

Risk ratio for any breast milk feeding, analysed using Poisson regression. Breast milk feeding is 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.

Comparison groups	Early Surfactant v Expectant Management
Number of subjects included in analysis	1240
Analysis specification	Pre-specified
Analysis type	superiority[26]
Parameter estimate	Risk ratio (RR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.08

Notes:

[26] - Poisson regression with a robust variance estimator, adjusted for week of gestation at birth as a fixed effect with multiple births and centre included as random effects.

Statistical analysis title	Breast milk feeding (RD)

Statistical analysis description:

Risk difference for any breast milk feeding, analysed using Poisson regression. Breast milk feeding is 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.

Comparison groups	Early Surfactant v Expectant Management

Number of subjects included in analysis	1240
Analysis specification	Pre-specified
Analysis type	superiority[27]
Parameter estimate	Risk difference (RD)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.06

Notes:

[27] - Poisson regression with a robust variance estimator, adjusted for week of gestation at birth as a fixed effect with multiple births and centre included as random effects.

Secondary: Late-onset sepsis

End point title	Late-onset sepsis

End point description:

End point type	Secondary

End point timeframe:

From randomisation to discharge home

End point values	Early Surfactant	Expectant Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	751[28]	754[29]		
Units: Number of infants				
Yes	15	12		
No	736	742		

Notes:

[28] - Outcome data missing (n = 7)

[29] - Outcome data missing (n = 3)

Statistical analyses

Statistical analysis title	Late-onset sepsis (RR)

Statistical analysis description:

Risk ratio for late-onset sepsis, analysed using Poisson regression.

Comparison groups	Early Surfactant v Expectant Management
Number of subjects included in analysis	1505
Analysis specification	Pre-specified
Analysis type	superiority[30]
Parameter estimate	Risk ratio (RR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	2.63

Notes:

[30] - Poisson regression model adjusted for week of gestation at birth, multiple birth and centre. Week of gestation was treated as a fixed effect, and centre and multiple births were treated as random effects.

Statistical analysis title	Late-onset sepsis (RD)

Statistical analysis description:

Risk difference for late-onset sepsis, analysed using Poisson regression.

Comparison groups	Early Surfactant v Expectant Management
Number of subjects included in analysis	1505
Analysis specification	Pre-specified
Analysis type	superiority[31]
Parameter estimate	Risk difference (RD)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.02

Notes:

[31] - Poisson regression model adjusted for week of gestation at birth, multiple birth and centre. Week of gestation was treated as a fixed effect, and centre and multiple births were treated as random effects.

Secondary: Need for inhaled nitric oxide therapy

End point title	Need for inhaled nitric oxide therapy

End point description:

End point type	Secondary

End point timeframe:

From randomisation to discharge home

End point values	Early Surfactant	Expectant Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	751[32]	754[33]		
Units: Number of infants				
Yes	8	5		
No	743	749		

Notes:

[32] - Outcome data missing (n = 7)

[33] - Outcome data missing (n = 3)

Statistical analyses

Statistical analysis title	Need for inhaled nitric oxide therapy (RR)

Statistical analysis description:

Risk ratio for need for inhaled nitric oxide therapy, analysed using Poisson regression.

Comparison groups	Early Surfactant v Expectant Management

Number of subjects included in analysis	1505
Analysis specification	Pre-specified
Analysis type	superiority[34]
Parameter estimate	Risk ratio (RR)
Point estimate	1.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	4.4

Notes:

[34] - Poisson regression model adjusted for week of gestation at birth, multiple birth and centre. Week of gestation was treated as a fixed effect, and centre and multiple births were treated as random effects.

Statistical analysis title	Need for inhaled nitric oxide therapy (RD)

Statistical analysis description:

Risk difference for need for inhaled nitric oxide therapy, analysed using Poisson regression.

Comparison groups	Early Surfactant v Expectant Management
Number of subjects included in analysis	1505
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.01

Secondary: Medical respiratory diagnoses

End point title	Medical respiratory diagnoses

End point description:

End point type	Secondary

End point timeframe:

From randomisation to discharge home

End point values	Early Surfactant	Expectant Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	758	757		
Units: Number of infants				
Yes	751	754		
No	7	3		

Statistical analyses

Statistical analysis title	Medical respiratory diagnoses (RR)

Statistical analysis description:

Risk ratio for any medical respiratory diagnoses, analysed using Poisson regression. An infant had a medical respiratory diagnosis if, at any time post-randomisation, they were diagnosed with at least on pre-defined respiratory condition.

Comparison groups	Early Surfactant v Expectant Management
Number of subjects included in analysis	1515
Analysis specification	Pre-specified
Analysis type	superiority[35]
Parameter estimate	Risk ratio (RR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1

Notes:

[35] - Poisson regression model adjusted for week of gestation at birth, multiple birth and centre. Week of gestation was treated as a fixed effect, and centre and multiple births were treated as random effects.

Statistical analysis title	Medical respiratory diagnoses (RD)

Statistical analysis description:

Risk difference for any medical respiratory diagnoses, analysed using Poisson regression. An infant had a medical respiratory diagnosis if, at any time post-randomisation, they were diagnosed with at least on pre-defined respiratory condition.

Comparison groups	Early Surfactant v Expectant Management
Number of subjects included in analysis	1515
Analysis specification	Pre-specified
Analysis type	superiority[36]
Parameter estimate	Risk difference (RD)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0

Notes:

[36] - Poisson regression model adjusted for week of gestation at birth, multiple birth and centre. Week of gestation was treated as a fixed effect, and centre and multiple births were treated as random effects.

Secondary: Surfactant administration

End point title	Surfactant administration

End point description:

End point type	Secondary

End point timeframe:

From randomisation to discharge home

End point values	Early Surfactant	Expectant Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	758	757		
Units: Number of infants				
Yes	91	212		
No	667	545		

Statistical analyses

Statistical analysis title	Surfactant administration (RR)

Statistical analysis description:

Risk ratio for need for surfactant administration, analysed using Poisson regression. Surfactant administration is defined as (a) administration of any non-trial doses of surfactant in infants randomised to receive early surfactant (including infants who did not receive trial intervention but went on to receive rescue surfactant) or (b) administration of any surfactant in infants receiving expectant management.

Comparison groups	Early Surfactant v Expectant Management
Number of subjects included in analysis	1515
Analysis specification	Pre-specified
Analysis type	superiority[37]
Parameter estimate	Risk ratio (RR)
Point estimate	0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	0.65

Notes:

[37] - Poisson regression model adjusted for week of gestation at birth, multiple birth and centre. Week of gestation was treated as a fixed effect, and centre and multiple births were treated as random effects.

Statistical analysis title	Surfactant administration (RD)

Statistical analysis description:

Risk difference for need for surfactant administration, analysed using Poisson regression. Surfactant administration is defined as (a) administration of any non-trial doses of surfactant in infants randomised to receive early surfactant (including infants who did not receive trial intervention but went on to receive rescue surfactant) or (b) administration of any surfactant in infants receiving expectant management.

Comparison groups	Early Surfactant v Expectant Management

Number of subjects included in analysis	1515
Analysis specification	Pre-specified
Analysis type	superiority[38]
Parameter estimate	Risk difference (RD)
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	-0.11

Notes:

[38] - Poisson regression model adjusted for week of gestation at birth, multiple birth and centre. Week of gestation was treated as a fixed effect, and centre and multiple births were treated as random effects.

Secondary: Need for extra-corporeal membrane oxygenation (descriptive)

End point title	Need for extra-corporeal membrane oxygenation (descriptive)
End point description:	
Descriptive analysis only.	
End point type	Secondary
End point timeframe:	
From randomisation to discharge home	

End point values	Early Surfactant	Expectant Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	751[39]	754[40]		
Units: Number of infants				
Yes	1	0		
No	750	754		

Notes:

[39] - Outcome data missing (n = 7)

[40] - Outcome data missing (n = 3)

Statistical analyses

No statistical analyses for this end point

Secondary: Maternal length of hospitalisation

End point title	Maternal length of hospitalisation
End point description:	
End point type	Secondary
End point timeframe:	
From randomisation to maternal discharge home	

End point values	Early Surfactant	Expectant Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	750[41]	751[42]		
Units: days				
median (inter-quartile range (Q1-Q3))	5.0 (4.0 to 8.0)	6.0 (4.0 to 8.0)		

Notes:

[41] - Outcome data missing (n = 8)

[42] - Outcome data missing (n = 6)

Statistical analyses

Statistical analysis title	Maternal length of hospitalisation

Statistical analysis description:

Quantile regression on the length of maternal hospitalisation, in days.

Comparison groups	Early Surfactant v Expectant Management
Number of subjects included in analysis	1501
Analysis specification	Pre-specified
Analysis type	superiority[43]
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	0.53

Notes:

[43] - Quantile regression model adjusted for week of gestation at birth, multiple birth and centre. All covariates treated as fixed effects.

Secondary: Discharged home on oxygen (descriptive)

End point title	Discharged home on oxygen (descriptive)

End point description:

Descriptive analysis only.

End point type	Secondary

End point timeframe:

From randomisation to discharge home

End point values	Early Surfactant	Expectant Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	748[44]	752[45]		
Units: Number of infants				
Yes	4	10		
No	744	742		

Notes:

[44] - Outcome data missing (n = 10)

[45] - Outcome data missing (n = 5)

Statistical analyses

No statistical analyses for this end point

Secondary: Neonatal death (descriptive)

End point title	Neonatal death (descriptive)
End point description:	
Descriptive analysis only.	
End point type	Secondary
End point timeframe:	
Up to 28 days of age.	

End point values	Early Surfactant	Expectant Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	758	757		
Units: Number of infants				
Early (< 7 days)	1	0		
Late (7 - 28 days)	0	1		
N/A - infant did not die within 28 days from birth	757	756		

Statistical analyses

No statistical analyses for this end point

Secondary: Mother has confirmed COVID-19 (descriptive)

End point title	Mother has confirmed COVID-19 (descriptive)
End point description:	
Descriptive analysis only. Question was introduced during the trial, so question will not have been asked for all participating mothers.	
End point type	Secondary
End point timeframe:	
From randomisation to discharge home	

End point values	Early Surfactant	Expectant Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	758	757		
Units: Number of mothers				
Yes	4	2		
No	52	53		
N/A - mother not tested	693	698		
N/A - question not asked	9	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Infant has confirmed COVID-19 (descriptive)

End point title	Infant has confirmed COVID-19 (descriptive)

End point description:

Descriptive analysis only. Question was introduced during the trial, so question will not have been asked for all infants.

End point type	Secondary

End point timeframe:

From randomisation to discharge home

End point values	Early Surfactant	Expectant Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	758	757		
Units: Number of infants				
Yes	0	0		
No	48	54		
N/A - infant not tested	703	699		
N/A - question not asked	7	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Total duration of neonatal intensive care (days)

End point title	Total duration of neonatal intensive care (days)

End point description:

End point type	Secondary

End point timeframe:

From randomisation to discharge home

End point values	Early Surfactant	Expectant Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	751	754		
Units: Days				
median (inter-quartile range (Q1-Q3))	3.0 (2.0 to 5.0)	3.0 (2.0 to 5.0)		

Statistical analyses

Statistical analysis title	Total duration of neonatal intensive care (days)
Statistical analysis description:	
Quantile regression on the median total duration of neonatal intensive care days.	
Comparison groups	Early Surfactant v Expectant Management
Number of subjects included in analysis	1505
Analysis specification	Pre-specified
Analysis type	superiority[46]
Parameter estimate	Median difference (final values)
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	-0.13

Notes:

[46] - Quantile model adjusted for week of gestation at birth, multiple birth and centre. All covariates treated as fixed effects.

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From randomization to infant’s discharge home

Adverse event reporting additional description:

In this population day-to-day fluctuations of pre-existing conditions were anticipated. As a result, many adverse events were foreseeable due to the nature of the participant population and their routine care/treatment. Consequently, only those adverse events identified as serious were reported for the trial.

Assessment type	Non-systematic

Dictionary used

Dictionary name	No dictionary
Dictionary version	0

Reporting groups

Reporting group title	Early Surfactant

Reporting group description:

Serious Adverse Events reported for infants allocated to the Early Surfactant (intervention) arm.

Reporting group title	Expectant Management

Reporting group description:

Serious Adverse Events reported for infants allocated to the Expectant Management (control) arm.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: In this population day-to-day fluctuations of pre-existing conditions were anticipated. As a result, many adverse events were foreseeable due to the nature of the participant population and their routine care/treatment. Consequently, only those adverse events identified as serious were reported for the trial.

Serious adverse events	Early Surfactant	Expectant Management	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 758 (2.51%)	23 / 757 (3.04%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	0	0	
Congenital, familial and genetic disorders			
Death neonatal			
subjects affected / exposed	1 / 758 (0.13%)	2 / 757 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Congenital anomaly			
subjects affected / exposed	1 / 758 (0.13%)	5 / 757 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Transfer for escalation of care			
subjects affected / exposed	8 / 758 (1.06%)	15 / 757 (1.98%)	
occurrences causally related to treatment / all	0 / 8	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Obstruction gastric			
subjects affected / exposed	1 / 758 (0.13%)	0 / 757 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus	Additional description: Malrotation & volvulus of the gut		
subjects affected / exposed	1 / 758 (0.13%)	0 / 757 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Apnoea	Additional description: Significant apnoeas requiring stimulation		
subjects affected / exposed	1 / 758 (0.13%)	0 / 757 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endotracheal intubation complication			
subjects affected / exposed	2 / 758 (0.26%)	0 / 757 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 758 (0.26%)	0 / 757 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress	Additional description: Respiratory distress (cyanosis neonatal and apnoea)		
subjects affected / exposed	1 / 758 (0.13%)	0 / 757 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypoglycaemia neonatal	Additional description: Severe hypoglycaemia		

subjects affected / exposed	0 / 758 (0.00%)	1 / 757 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Meningitis			
subjects affected / exposed	1 / 758 (0.13%)	0 / 757 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Early Surfactant	Expectant Management	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 758 (0.00%)	0 / 757 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 May 2020	Substantial Amendment 1 i) Addition of a Secondary Outcome: The health economic outcomes have been amended to include survival at one year of age, corrected for prematurity; ii) Local Translation Services: Following feedback from sites, regarding the importance of not excluding those that do not have a good understanding of-English, detail has been included in the Protocol to allow the use of routinely used translation services in obtaining consent; iii) Surfactant being Animal Derived: In the REC's initial application review, it was requested that the PIL include detail that surfactant is an animal derived product. This has now been included in both the PIL and Protocol; iv) Personal Identifiers to be Shared with National Databases: As requested by NHS Digital, details have been included in the Consent Form and PIL, regarding the personal identifiers that will be shared with National Databases, when collecting follow-up data; v) Additional Detail on Safety Reporting: Further detail is provided on serious adverse events that are foreseeable in the patient population and do not require reporting as SAEs. Amends have also been made to the review and reporting of SAEs. Replaces the first Protocol, PIL and Consent Form V2.0 5th Feb 2020 on the study.
21 July 2020	Substantial Amendment 2 i) Addition of 8x Recruiting Sites; ii) Change of Principal Investigator (PI) at Royal Devon and Exeter NHS Foundation Trust; iii) Addition of 150x Continuing Care Sites. During their postnatal stay, infants on SurfON study could be transferred from their Recruiting Site to another hospital. By gaining approval pre-emptively for as many Continuing Care Sites as possible, we hope to allow transferred infants to continue to participate in SurfON without disruption and to allow Recruiting Sites to complete data collection using Case Report Forms by liaising with the Continuing Care Sites.
02 September 2020	Substantial Amendment 3 i) Addition of 1x Recruiting Site; ii) Change of PI at Northern Lincolnshire & Goole NHS Foundation Trust.

11 December 2020	Substantial Amendment 4 i) Protocol updated to include: change of Trial Manager; addition of use of Laryngeal Mask for method of administration of IMP; clarification of SAE reporting in relation to category level of infant transfers; removal of reference to SAE reporting method via Fax; removal of 'Once reported online, forms will be printed by the local PI to perform a causality review'; ii) Change of Trust Name to previously approved sites: Luton & Dunstable University Hospital NHS Foundation Trust changed to Bedfordshire Hospitals NHS Foundation Trust; Poole Hospital NHS Foundation Trust changed to University Hospitals Dorset NHS Foundation Trust: iii) Addition of new recruiting site: Birmingham Women's & Children's NHS Foundation Trust.
15 March 2021	Substantial Amendment 5 i) Addition of OID for Continuing Care Sites; ii) Addition of new recruiting site - North Bristol NHS Trust; iii) Change of PI - at Countess of Chester Hospital NHS Foundation Trust and University Hospitals Coventry and Warwickshire NHS Trust.
10 June 2021	Substantial Amendment 6 i) Protocol updated to include: Clarification regarding counter-signature by mother on consent form; change of place of data entry for Mothers Trial Entry and Trial Discharge questionnaires; ii) Addition of 11x Continuing Care Sites.
31 March 2022	Substantial Amendment 7 i) Protocol Changes: Rationale & inclusion of ANNPs to confirm eligibility; Minor formatting errors corrected and contact details updated; Recently published systematic review included; Inclusion of Special Care Units as participating centres; Clarification on optional participation for mother when they have provided consent to complete questionnaire; Clarification on hospital transfers only related to early respiratory management will need to be reported to the trial team as a SAE and further explanation; ii) Consent Form Changes: Minor formatting and guidance provided to indicate that the mother's countersignature must be obtained as soon as possible if other parent has provided original consent; Guidance provided to indicate that the mother can complete questionnaires only if consent has been provided in the mother's section which will also require signature from health professional obtaining consent; iii) Trial Questionnaire Changes: Donor breast milk added as an option in the question pertaining to how the baby has fed since delivery in both questionnaires; iv) Changes to Trial Timeline: Extension approved by funder for a further period of 7 months taking the overall trial end date to June 2023. No change in research activities or recruitment numbers.

25 April 2024	Substantial Amendment 8 Protocol changes: 1) Addition of a reference to the 'Background and rationale' section 2) Clarification for inclusion criteria #3: Definition of 'respiratory distress' has been refined 3) Sentence about providing women having a planned caesarean section at 37-38 weeks with study information antenatally reworded for clarity 4) The timeframe for completing the Discharge Questionnaire has been updated to reflect that it occurs around the time of discharge. 5) Sentance about withdrawal of participants reworded for clarity. 6) Section defining events that need to be reported as SAEs reworded for clarity. 7) Development Safety Update Reports' section updated to reflect that the trial is now approved under the notification scheme rather than expected to be. 8) Edit to reflect that the HTA Programme Manager will not be invited to attend all TSC meetings. Minor changes to study documents 1) New document - SurfON Parent Card - QR card to scan to access SurfON Introduction Podcast 2) Amendments to SurfON General Data Protection Regulation (GDPR) for Patients - to reflect changes to the HRA Patient Data and Research leaflet. Study Design Extension approved by funder for a further period of 26 months taking the overall trial end date to 31st August 2025. No change in research activities or recruitment numbers.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 June 2019	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 start of the trial was delayed to 02.09.2020 and the trial was extended, with an anticipated duration of 75 months.	02 September 2020
08 February 2022	Formal pause in recruitment from February to July 2022 during the COVID-19 pandemic.	04 July 2022

Notes:

Limitations and caveats

None reported