EFFECT OF MINIMALLY INVASIVE SURFACTANT THERAPY VERSUS SHAM TREATMENT ON DEATH OR NEURODEVELOPMENTAL DISABILITY AT 2 YEARS POST-MENSTRUAL AGE IN PRETERM INFANTS WITH RESPIRATORY DISTRESS SYNDROME

THE OPTIMIST-A2 STUDY

Statistical Analysis Plan
Version 1, 23-Nov-2022

Document Version History

Version Date	Version	Author	Signature	Change Description	Reason/Comment
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LIST OF ABBREVIATIONS

BPD	Bronchopulmonary Dysplasia
BSID III	Bayley Scales of Infant Development: Third Edition
CI	Confidence Interval
CP	Cerebral palsy
CPAP	Continuous Positive Airway Pressure
FiO_2	Fraction of Inspired Oxygen
GLM	Generalised Linear Model
GMFCS	Gross Motor Function Classification System
IQR	Interquartile Range
MIST	Minimally Invasive Surfactant Therapy
PARCA-R	Parent Report of Children's Abilities – Revised
RD	Risk Difference
RR	Relative Risk
SD	Standard Deviation

1. STUDY OBJECTIVES

1.1. OVERVIEW

The overarching aim of the OPTIMIST-A trial was to evaluate in a randomised controlled trial the efficacy of minimally invasive surfactant therapy in preterm infants 25-28 weeks gestation with respiratory distress syndrome treated with continuous positive airway pressure (CPAP).

The primary outcome of the OPTIMIST-A trial was the composite of death or physiological bronchopulmonary dysplasia (BPD) assessed at 36 weeks' postmenstrual age (PMA). The primary outcome and its components (death prior to 36 weeks' PMA and BPD at 36 weeks' PMA) as well as key clinical and safety outcomes and secondary outcomes in relation to early respiratory management and in-hospital care were analysed and results published in December 2021.[1]

The current document describes the Statistical Analysis Plan (SAP) for the outcomes ascertained in the OPTIMIST-A two year follow up study (OPTIMIST-A2).

1.2. PRIMARY OBJECTIVE

To evaluate in a randomised controlled trial the effect of minimally invasive surfactant therapy versus sham treatment on death or neurodevelopmental disability at 2 years PMA in preterm infants 25-28 weeks gestation with respiratory distress syndrome.

2. BACKGROUND/INTRODUCTION

2.1. STUDY DESIGN

Multicentre, blinded, parallel group randomised controlled trial.

2.2. TREATMENT GROUPS

After assessment of eligibility and with parental consent, infants were randomised in a 1:1 allocation ratio to receive minimally invasive surfactant therapy (MIST) followed by return to support with CPAP, or to remain on CPAP with no surfactant administration (control group). The intervention (MIST or control) was blinded from clinical staff. Parents and outcome assessors were also blinded to the group allocation. The parental consent encompassed participation in the in-hospital and follow up components of the study.

2.3. STUDY POPULATION

Preterm infants of gestation 25 weeks 0 days to 28 weeks 6 days who were inborn and admitted to the NICU of a participating study centre, and who fulfilled inclusion and exclusion criteria as detailed in the OPTIMIST-A Statistical Analysis Plan, version 1, 30th October 2020.

2.4. INTERVENTION

Once randomised, infants randomised to MIST received surfactant (Curosurf™, Chiesi Farmaceutici, Parma, Italy) administered via the Hobart method[2] at a dosage of 200 mg/kg. Infants randomised to the control group with no surfactant administration remained on CPAP, receiving a sham treatment with no intervention other than a change to body position.

2.5. SAMPLE SIZE

As described in the OPTIMIST-A Trial SAP, sample size for the study was determined in relation to the composite outcome of death or BPD and its projected incidence.[3] The calculated sample size of 606

infants (303 per group) afforded 90% power to detect an absolute risk reduction of 13% from an assumed baseline risk of 38% for this outcome in the control group ($\alpha = 0.05$).[4]

Recruitment for the trial commenced in December 2011, and proceeded slowly, reaching 100 infants/yr during the calendar years 2016-2018. Recruitment was ceased on the advice of the Trial Steering Committee in March 2020 as research activities were put in abeyance in many participating Units in the wake of the COVID-19 pandemic, at which stage 486 infants were correctly randomised.

2.6. STUDY PROCEDURE – OPTIMIST-A2 STUDY

Pre-specified outcomes for the OPTIMIST-A2 study were: death or major disability at 2 years (and its components and sub-components); number of hospitalisations in the first 2 years (respiratory illness, non-respiratory illness and all admissions); parent-reported wheezing or breathing difficulty with and without a viral infection; parent-reported use of bronchodilator therapies in the first 2 years; parent report of a physician diagnosis of asthma in the first two years; and requirement for feeding via nasogastric or gastrostomy tube beyond 1 year PMA.

Collection of outcome data for the OPTIMIST-A2 study commenced in 2014. A face-to-face follow up assessment at 2 years PMA was opted for initially, including i) history-taking of events in the first 2 years, ii) a clinical examination including an assessment for cerebral palsy (CP) and categorisation of motor performance using the Gross Motor Function Classification System (GMFCS)[5] and iii) a Bayley Scales of Infant Development III (BSID III) psychometric assessment performed by a trained assessor.[6] The inclusion of international sites, along with the lack of large-scale funding for the follow up component of the trial, led to the development and implementation of an online questionnaire for assessment of outcomes in the first two years, completed by parents and submitted electronically. This questionnaire included collection of some baseline post-hospital data (duration of home oxygen therapy, immunisations, family history of asthma), a report of outcomes during the first two years of life (hospitalisations, bronchodilator use, diagnosis of asthma, requirement for tube feeding), and a detailed description of neurodevelopmental outcomes at two years PMA, incorporating the Parent Report of Children's Abilities – Revised (PARCA-R).[7;8] The PARCA-R is a norm-referenced standardised neurodevelopmental assessment tool that has been validated against the BSID III[9] and used previously in RCTs in preterm infants.[10;11]

For the OPTIMIST-A2 study, the questionnaire including the PARCA-R tool was uploaded to an online survey platform and administered in 8 languages. After a careful investigation of whether the infant had survived to 2 years, an electronic link to the questionnaire was sent to the parents of participating infants by the Site Investigator or Trial Coordinator. Up to 3 reminders were sent at intervals by phone, text message or email if the results of the questionnaire were not received by the Trial Management Centre. In the event of no data being collected by either face-to-face assessment or the online questionnaire, site personnel were asked to gather data from parents using an abbreviated questionnaire consisting of 6 questions related to neurodevelopmental disability and respiratory hospitalisations, which allowed the primary outcome to be assessed. In all cases, data collected for the OPTIMIST-A2 study were collected by blinded data collectors (site trial or follow up personnel, parents).

3. ANALYSIS POPULATION

Participants will be compared according to the group to which they were randomly allocated in the OPTIMIST-A trial, regardless of compliance, crossover to other treatments or withdrawal from the study. This approach preserves the prognostic balance in the study groups achieved by randomisation. This population will EXCLUDE:

- Infants randomised and immediately recognised to be ineligible
- Infants in whom the randomisation failed and the treatment allocation was not revealed to the Treatment Team at the site
- Infants whose parents/guardian withdrew their consent to be in the study and the use of all the data collected

4. OUTCOME VARIABLES

4.1. PRIMARY OUTCOME

Table 1 – Primary outcome and its components

#	Outcome	Description
1	Composite of death by 2 years PMA or moderate-severe neurodevelopmental disability*, defined as any of: i. moderate-severe cognitive or language impairment ii. CP equivalent to GMFCS ≥2 iii. visual impairment iv. hearing impairment	Binary outcome 1= Death or moderate-severe neurodevelopmental disability at 2 years PMA 0= No death and no neurodevelopmental disability
Components of the primary outcome:		
1a	**Death** prior to 2 years PMA (all causes)	Binary outcome 1= Death by 2 years PMA 0= No death by 2 years PMA
1b	**Moderate-severe neurodevelopmental disability*** in survivors to 2 years PMA	Binary outcome, in those who survived to 2 years PMA 1= Moderate-severe neurodevelopmental disability 0= Mild or no disability

* The identification of each of the components of disability in the forms of follow-up data available is shown in Table 2. Participants identified as meeting criteria for one component of the disability definition will be classified as being disabled, with data on all components required in order to allow a classification of no disability.

CP = cerebral palsy

GMFCS = Gross Motor Function Classification System

PMA = post-menstrual age

Table 2: Definitions of moderate-severe disability by components and form of data capture

Component	Form of data capture at 2 years PMA		
	A. Face-to-face assessment and BSID III	B. Parent questionnaire including PARCA-R assessment	C. Abbreviated questionnaire
i. Cognitive or language impairment	BSID III* standard score <80 for either cognitive composite scale or language composite scale	PARCA-R† standard score <70 for either non-verbal cognition or language development	<5 words
ii. Cerebral palsy	GMFCS ≥2 on clinical assessment	"Walks only with help", or "doesn't walk" (± diagnosis of CP)	"Walks only with help", or "doesn't walk" (± diagnosis of CP)
iii. Visual impairment	Sees close-up objects at best, even with glasses	Sees close-up objects at best, even with glasses	Sees close-up objects at best, even with glasses
iv. Hearing impairment	No useful hearing without amplification, or deaf	No useful hearing without amplification, or deaf	No useful hearing without amplification, or deaf

*BSID III data will be included if the assessment was performed between 12 and 36 months PMA.
†All PARCA-R data received in the age range 24-30 months PMA will be included. Normative data for the PARCA-R cognitive and language scales are reported from 24-27 months PMA.[8] For questionnaires received between 28 and 30 months PMA, the raw score thresholds used for standard score determination in males and females at 27 months will be applied. For PARCA-R questionnaires received beyond 30 months PMA, if the raw cognitive or language score is below the 27 month threshold for impairment, the data will be included; otherwise the data will be treated as missing and handled as per 5.1.3 below.
BSID III: Bayley Scales of Infant Development: Third Edition
CP = cerebral palsy
GMFCS = Gross Motor Function Classification System
PARCA-R = Parent Report of Children's Abilities – Revised

4.2. SECONDARY OUTCOMES

Table 3: SECONDARY OUTCOMES – INDICES OF DISABILITY AT 2 YEARS PMA

#	Outcome	Description
2	Cognitive or language impairment (Table 2, row i.)	Binary outcome 1=Yes if: - BSID III* cognitive composite standard score < 80 (A. Table 2) **or** - BSID III* language composite standard score < 80 (A. Table 2) **or** - PARCA-R† non-verbal cognitive scale standard score < 70 (B. Table 2) **or** - PARCA-R† language scale standard score < 70 (B. Table 2) **or** - less than 5 words (C. Table 2) 0=No if: - BSID III* cognitive composite standard score >= 80 (A. Table 2) **and** - BSID III* language composite standard score >= 80 (A. Table 2) **or** - PARCA-R† non-verbal cognitive scale standard score >= 70 (B. Table 2) **and** - PARCA-R† language scale standard score >= 70 (B. Table 2) **or** - more than or equal to 5 words (C. Table 2)

#	Outcome	Description
3	Cognitive impairment (Table 2, row i.)	Binary outcome 1=Yes if: - BSID III* cognitive composite standard score < 80 (A. Table 2) or - PARCA-R† non-verbal cognitive scale standard score < 70 (B. Table 2) 0=No if: - BSID III* cognitive composite standard score >= 80 (A. Table 2) or - PARCA-R† non-verbal cognitive scale standard score >= 70 (B. Table 2)
3a	Cognitive development - BSID III cognitive composite standard score (Table 2, row i, column A)	Continuous outcome (data received from 12-36 months PMA)
3b	Cognitive development - PARCA-R non-verbal cognitive scale standard score (Table 2, row i, column B)	Continuous outcome (data received from 24-30 months PMA)
4	Language impairment (Table 2, row i)	Binary outcome 1=Yes if: - BSID III* language composite standard score < 80 (A. Table 2) or - PARCA-R† language scale standard score < 70 (B. Table 2) 0=No if: - BSID III* language composite standard score >= 80 (A. Table 2) or - PARCA-R† language scale standard score >= 70 (B. Table 2)
4a	Language development - BSID III language development composite standard score (Table 2, row i, column A)	Continuous outcome (data received from 12-36 months PMA)
4b	Language development - PARCA-R language scale standard score (Table 2, row i, column B)	Continuous outcome (data received from 24-30 months PMA)
5	Cerebral palsy (Table 2, row ii)	Binary outcome 1=Yes if - GMFCS ≥2 (A. Table 2) or - “Walks only with help”, or “doesn’t walk” (B. and C. Table 2) 0=No if: - GMFCS <2 (A. Table 2) or - NOT “Walks only with help”, or “doesn’t walk” (B. and C. Table 2)

#	Outcome	Description
6	Visual impairment (parent reported) (Table 2, row iii)	Binary outcome 1=Yes if Sees close-up objects at best, even with glasses 0=No, otherwise
7	Hearing impairment (parent reported) (Table 2, row iv)	Binary outcome 1=Yes if No useful hearing without amplification, or deaf 0=No, otherwise

*BSID III data will be included if the assessment was performed between 12 and 36 months PMA.
†All PARCA-R data received in the age range 24-30 months PMA will be included. Normative data for the PARCA-R cognitive and language scales are reported from 24-27 months PMA.[8] For questionnaires received between 28 and 30 months PMA, the raw score thresholds used for standard score determination in males and females at 27 months will be applied. For PARCA-R questionnaires received beyond 30 months, if the raw cognitive or language score is below the 27 month threshold for impairment, the data will be included; otherwise the data will be treated as missing and handled as per 5.1.3 below.
BSID III: Bayley Scales of Infant Development: Third Edition
GMFCS = Gross Motor Function Classification System
PARCA-R = Parent Report of Children's Abilities – Revised
PMA = post-menstrual age

Table 4: SECONDARY OUTCOMES – OTHER

#	Outcome	Description
8a	One or more overnight hospitalisation with <u>any</u> illness in first 2 years	Binary outcome 1=Yes 0=No
8b	Three or more overnight hospitalisations with <u>any</u> illness in first 2 years	Binary outcome 1=Yes 0=No
8c	Number of overnight hospitalisations with <u>any</u> illness in first 2 years	Categorical outcome 0 1 2 3 4 5 >5
8d	Age at hospitalisation with <u>any</u> illness in first 2 years (months)	Continuous outcome
9a	One or more 1 overnight hospitalisation with <u>respiratory</u> illness in first 2 years	Binary outcome 1=Yes 0=No
9b	Three or more overnight hospitalisations with <u>respiratory</u> illness in first 2 years	Binary outcome 1=Yes 0=No
9c	Number of overnight hospitalisations with <u>respiratory</u> illness in first 2 years	Categorical outcome 0 1

#	Outcome	Description
		2 3 4 5 >5
9d	Age at hospitalisation with respiratory illness in first 2 years (months)	Continuous outcome
9e	Respiratory diagnosis leading to hospitalisation	Categorical outcome Bronchiolitis/respiratory syncytial virus infection Other respiratory problem (e.g. croup, pneumonia)
10	Parent-reported wheezing or breathing difficulty (with or without a cold/viral infection	Binary outcome 1=Yes 0=No
10a	Frequency of parent-reported wheezing or breathing difficulty (with or without a cold/viral infection)	Categorical outcome (mutually exclusive) No episodes < once a month 1-4 times per month 1-6 times per week Daily
11	Use of any bronchodilator therapy in first 2 years	Binary outcome 1=Yes 0=No
11a	Form of bronchodilator therapy used	Categorical outcome, may be multiple forms of therapy used No bronchodilator therapy used Relievers, inhaled Preventers, inhaled Preventers, oral Other medication
12	Physician diagnosis of asthma in first 2 years (as reported by parent)	Binary outcome 1=Yes 0=No
13	Requirement for feeding via nasogastric or gastrostomy tube beyond 1 year PMA	Binary outcome 1=Yes 0=No

PMA = post-menstrual age

4.3. OTHER PARAMETERS

Demographic characteristics

- Gestation (weeks and days)
- Age at randomisation (hrs)
- Birth weight (g)
- Infant sex
- Plurality, birth order (singleton; first of multiples; second or subsequent multiple)

Peripartum details

- Exposure to antenatal glucocorticoids (complete; incomplete; none)
- Delivery mode (vaginal delivery; Caesarean delivery with labour; Caesarean delivery; no labour)
- Apgar score at 5 min

Clinical state at randomisation

- CPAP level at randomisation (cm H_2O)
- Fraction of inspired oxygen (FiO_2) at randomisation
    - FiO_2 30-35%
    - FiO_2 >35%

Post-discharge characteristics

- Oxygen therapy at home (Y/N)
- Duration of oxygen therapy at home (months from time of discharge, only in those receiving oxygen therapy at home)
- Immunisation against influenza (Y/N)
- Immunisation against respiratory syncytial virus (Y/N)
- Family history of asthma (parents / siblings) (Y/N)

Characteristics of participants completing assessment at 2 years

- Age at 2 year assessment (years and months PMA)

5. STATISTICAL METHODOLOGY

5.1. GENERAL METHODOLOGY

Data analysis for this study will be performed within the Clinical Epidemiology and Biostatistics Unit at the Murdoch Children's Research Institute.

The demographic characteristics, peripartum details, clinical state at randomisation of the infants and post-discharge characteristics will be presented for each treatment group using the mean and standard deviation (SD) or median and interquartile range (IQR) for continuous data and using proportions for categorical data in those participants who are not lost to follow up at the 2 years PMA timepoint. The same baseline characteristics will also be summarised by treatment group in those in participants who are lost to follow up at the 2 years PMA timepoint, to be able to assess potential loss to follow up bias.

Multiple outcomes will be considered in evaluating the effectiveness of the trial intervention. The magnitude of potential treatment effect, with 95% confidence interval (CI) and p-value, will be

estimated for each outcome, but these results will not be interpreted dichotomously against any specific statistical threshold. Instead, findings concerning multiple secondary outcomes will be interpreted cautiously and in context with one another rather than in isolation. Patterns and consistency in the responsiveness of outcomes, and the overall balance of the evidence, will be examined rather than isolated findings that may well be due to chance.

5.1.1 MEASURES OF TREATMENT EFFECT

Relative Risk (RR) between active and control groups will be the main measure of treatment effect for binary outcomes. Risk Difference (RD) between treatment groups will also be measured.

No measure of treatment effect will be estimated for categorical and continuous outcomes, which will only be descriptively analysed.

5.1.2 ESTIMATION OF TREATMENT EFFECTS

Treatment effects will be estimated for all binary outcomes described in Section 4.1 and 4.2. using regression methods (generalised linear models, GLMs) to adjust for the stratification factor of gestation. In a secondary analysis in relation to the primary outcome, the GLM will include additional covariates expected to be associated with the primary outcome.

The following two estimates will be obtained.

Primary analysis: adjusted only for gestational age stratum

The treatment effect will be estimated using GLMs for RR and RD, with adjustment for the gestational age stratum (25-26 weeks; 27-28 weeks) used during randomisation as a covariate. The method will incorporate a cluster-robust standard error calculation to account for clustering by study site.

Secondary analysis: adjusted

For the primary outcome and its components only, the GLM specification above will be extended to include further adjustment for the following covariates, which are expected to be associated with the primary outcome:

- birth weight <10^{th} percentile
- sex
- mode of delivery
- plurality
- antenatal glucocorticoid exposure
- 5-minute Apgar score

5.1.3 HANDLING OF MISSING DATA

It is expected that the proportion of missing data will be less than 10%, therefore the available case analysis will be the primary one. However, if the proportion of missing outcome data is greater than 10% in the primary outcome, missing data will be handled using multiple imputation, which will be regarded as the primary analysis. Multiple imputation will be conducted using chained equations, also known as fully conditional specification. Within the chained equations algorithm, ordinal variables will be imputed using ordinal regression and binary variables using logistic regression. Baseline variables will be included as auxiliary variables in the imputation model. Imputation will be carried out separately by treatment group, to ensure that any treatment effects are maintained, using 50 imputed datasets.

5.1.4 SENSITIVITY ANALYSES

Sensitivity 1 –Parent questionnaire including PARCA-R assessment completers

In this sensitivity analysis the primary outcome and its second component of moderate-severe neurodevelopmental disability will be derived only using information collected in the parent questionnaire including PARCA-R assessment (Table 2, column B), this being the most common mode of receiving follow up data for the study. For this analysis, data will be included if the questionnaire is completed between 24 and 27 months PMA, matching the age range of published normative data.[8] Data in relation to those participants who did not complete the parent questionnaire, or completed the PARCA-R questionnaire outside the time frame of 24-27 months PMA, will be handled using multiple imputation, adopting the same approach as described in section 5.1.3.

5.1.5 SUB-GROUP ANALYSES

Sub-Group analysis 1 – Gestational age at birth

Baseline information and all the outcomes (primary and its components and sub-components, all secondary outcomes) will be presented in supplementary tables by gestation strata (25-26 weeks; 27-28 weeks). Further, for binary outcomes, this sub-group analysis will examine the evidence for differences in the effect of the intervention between the gestational age sub-groups. The specific sub-group estimates, and CIs will be presented, together with the p-value for interaction, as a guide to how strongly the effects seem to be differentiated. As we have not powered the trial to consider sub-groups, this analysis is considered exploratory.

5.2. PRIMARY DATA ANALYSES

*Primary outcome: composite outcome of **death before 2 years PMA** or **moderate-severe disability at 2 years PMA***

Results will be summarised as the number and proportion of infants who either died before 2 years PMA or have moderate-severe disability at 2 years PMA in the two treatment groups.

Given that the data for the 2 year PMA assessment were collected in three different ways (A. face-to-face assessment using the BSID III psychometric assessment; B. parent reported questionnaire which incorporates the PARCA-R; C. abbreviated questionnaire consisting of 6 questions related to neurodevelopmental disability and respiratory hospitalisations), absolute and relative frequency will be also reported for each data collection modality, by treatment group.

The primary analysis of the primary composite outcome:

The RR with 95% CI will be estimated using a GLM (the "modified Poisson" approach of Zou)[12] to adjust for the gestational age stratum (25-26 weeks; 27-28 weeks) used during randomisation as a covariate. The GLM approach will use the Poisson family and employ a log link function. The method will incorporate a cluster-robust standard error calculation to account for clustering by study site. The RD with 95% CI will also be estimated, using a GLM approach with Gaussian error distribution (to avert convergence difficulties with low-prevalence outcomes) and linear link function.

Secondary analyses of the primary composite outcome:

The RR with 95% CI will be estimated using a GLM (the "modified Poisson" approach of Zou) to adjust for the gestational age stratum (25-26 weeks; 27-28 weeks) as well as a number of covariates known to have influence on death, BPD as well as disabilities at 2 years (birth weight <10th percentile, sex, mode of delivery, plurality, antenatal glucocorticoid exposure, and 5-minute Apgar score). The method will incorporate a cluster-robust standard error calculation to account for clustering by study site. With

analogous covariate adjustments, the RD with 95% CI will be estimated using a GLM (Gaussian error distribution and linear link function).

Sensitivity analysis, Parent questionnaire/PARCA-R data:
In another secondary analysis the primary composite outcome will be derived using only information collected with the parent questionnaire including PARCA-R assessment between 24 and 27 months PMA (Table 2, column B), handling missing data using multiple imputation techniques. The RR and RD with 95% CI will be estimated in the same way as the main analysis of the primary outcome, adjusting by gestational age only.

Sub-Group analysis, by gestation strata (25-26 weeks; 27-28 weeks):
The RR and RD with their 95% CI will be estimated using the GLM models mentioned in the sections above within each subgroup 25-26 weeks and 27-28 weeks. Particularly, in both the adjusted models, gestational age will be included as a binary covariate, i.e. 25 vs 26 weeks for sub-group 25-26 weeks; and 27 vs 28 weeks for sub-group 27-28 weeks.

Primary outcome components: Death by 2 years PMA (all causes) and moderate-severe disability in survivors to 2 years PMA

Analogously to the primary composite outcome, absolute and relative frequencies of infants meeting the definition of outcome 1a and 1b will be calculated and presented by treatment group.

RR and RD with 95% CIs will be estimated using the appropriate GLM (refer to analysis on primary outcome 1) and a cluster-robust standard error calculation to account for clustering by study site. The following analyses will be run:

- adjusted only for randomisation strata
- fully adjusted
- sensitivity analysis, using parent questionnaire/PARCA-R data (only for outcome 1b)
- sub-group analysis, by gestation strata (25-26 weeks; 27-28 weeks)

5.3. SECONDARY DATA ANALYSES

Binary secondary outcomes

Analogously to the primary outcome and its components, absolute and relative frequencies of infants meeting the definition of the outcome will be calculated and presented by treatment group.

RR and RD with 95% CIs will be estimated using the appropriate GLM (refer to analysis on primary outcome 1) and a cluster-robust standard error calculation to account for clustering by study site. The following analyses will be run:

- adjusted only for randomisation strata
- sub-group analysis, by gestation strata (25-26 weeks; 27-28 weeks)

Continuous secondary outcomes

Continuous outcomes will only be descriptively reported, in graphical form (histograms) and by presenting mean and SD (or median and IQR range if their distribution is severely skewed) by treatment group.

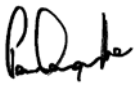
Categorical outcomes with more than 2 categories

Categorical outcomes with more than 2 categories will only be descriptively reported, by presenting absolute and relative frequencies of infants in each category of the outcome by treatment group.

5.4. SUMMARY OF THE ANALYSES

Outcomes	Measures of effect and Models	Additional analyses
Primary outcome and components	RR (GLM, Poisson family, log link function) RD (GLM, Gaussian family, linear link function) Adjusted only for randomisation strata	- Subgroup by gestation strata - Sensitivity Parent questionnaire/PARCA-R (outcomes 1 and 1b)
	RR (GLM, Poisson family, log link function) RD (GLM, Gaussian family, linear link function) Fully Adjusted*	
Binary secondary outcomes	RR (GLM, Poisson family, log link function) RD (GLM, Gaussian family, linear link function) Adjusted only for randomisation strata	- Subgroup by gestation strata
Continuous secondary outcomes	Only descriptive	- Subgroup by gestation strata
Categorical secondary outcomes with >2 categories	Only descriptive	- Subgroup by gestation strata

**adjusted for gestational age stratum, birth weight <10th percentile, sex, mode of delivery, plurality, antenatal glucocorticoid exposure, 5-minute Apgar score.*

Signature of Principal Investigator:  Date 22-11-2022

Print Name Prof Peter Dargaville

Signature of Trial Statistician:  Date 22-11-2022

Print Name Prof John Carlin

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