Outcome after Selective Early Treatment for Closure of Patent Ductus ARteriosus in Preterm Babies

Statistical Analysis Plan for Long Term Outcomes

Version 1.0

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Contents

List of abbreviations:

BERC	Blinded End-point Review Committee
BPD	Bronchopulmonary dysplasia
CI	Confidence interval
CONSORT	Consolidated standards of reporting trials
COX	Cyclo-oxygenase
CPAP	Continuous Positive Airway Pressure
CRIB II	Clinical risk index for babies score II
CRF	Case report form
CTU	Clinical trials unit
DMC	Data monitoring committee
ECHO	Echocardiography
GP	General practitioner
HTA	Health technology assessment
IMP	Investigational Medicinal Product
IVH	Intraventricular haemorrhage
ITT	Intention to treat
Kg	Kilograms
L	Litre
mg	Milligram
min	Minute
ml	Millilitre
mm	Millimetre
NEC	Necrotising enterocolitis
NIHR	National Institute for Health Research
NNU	Neonatal unit
NPEU	National Perinatal Epidemiology Unit
PARCA-R	Parent Report of Children's Abilities – Revised
PDA	Patent ductus arteriosus
PVL	Periventricular leukomalacia
RCT	Randomised controlled trial
ROP	Retinopathy of prematurity
UK	United Kingdom

1. Introduction

This document details the proposed presentation and analyses for the long-term outcomes of the Baby-OSCAR trial, a multi-centre, masked, randomised controlled trial (RCT) funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme. The analysis strategy for short-term outcomes at hospital discharge are documented in a separate analysis plan.

The analysis plan will be available upon request when the principal manuscripts are submitted for publication. Suggestions for subsequent analyses by journal editors or referees will be considered carefully and carried out, as far as possible, in line with the principles of this analysis plan. If reported, the source of the suggestion will be acknowledged. The health economic outcomes and analysis will be outlined in a separate analysis plan.

Any deviations from the statistical analysis plan will be described along with the rationale given in the final report of the trial. The analysis will be carried out by an identified, appropriately qualified and experienced statistician, who will ensure the integrity of the data during processing. This document and the final analysis will be produced in line with NPEU Standard Operating Procedures ST105 Statistical Analysis Plan and ST107 Statistical Analysis and Reporting.

2. Background

The Baby-OSCAR trial is a masked, multi-centre, randomised, placebo-controlled, parallel group trial to determine short- and long-term health and economic outcomes of the treatment of a large Patent Ductus Arteriosus (PDA) in extremely preterm babies with ibuprofen within 72 hours of birth.

The trial followed an internal pilot phase, which was run to assess the suitability of trial procedures and likelihood of recruitment targets being achieved. A total of 653 out of a target of 730 infants were recruited (including those recruited during the internal pilot phase) between 12 July 2015 and 31 Dec 2020 from 35 UK tertiary neonatal units (NNUs).

3. Interventions

3.1 Intervention (ibuprofen) group

The intervention was given as an initial loading dose of 10 mg/kg (2 ml/kg) of ibuprofen, followed by two 5 mg/ml (1 ml/kg) doses at 24 and 48 hours after the initial dose. Doses were calculated on the birth weight of the baby. If required, the investigational medicinal product (IMP) was diluted to appropriate volume with 5% glucose or 0.9% Sodium Chloride. Each dose was given as a short dose intravenous infusion over 15 minutes. All 3 doses were given unless there were adverse effects necessitating stoppage, as referenced in the trial protocol, section 7.9.

3.2 Control (placebo) group

The placebo was given as a clear sterile solution of 0.9% Sodium Chloride for injection. Cartons identical to those for ibuprofen, each containing four identical single use ampoules, were provided. The volume to be withdrawn from the ampoule was calculated following the same methods for ibuprofen dosing.

4. Description of two-year outcomes

All outcomes at 24 months of age corrected for prematurity.

4.1 Main long-term outcome

Survival without moderate or severe neurodevelopmental impairment (defined as any one or more of moderate or severe non-verbal cognitive, language, gross motor, hearing or visual impairment, each of which will additionally be presented descriptively only):

- Moderate or severe cognitive impairment; PARCA-R non-verbal cognitive scale score <70, or moderate or severe impairment classified by the Blinded End-point Review Committee (BERC).
- Moderate or severe language impairment; PARCA-R language scale score <70, or moderate or severe impairment classified by the BERC.
- Moderate or severe gross motor impairment; unable to walk and/ or sit independently, as reported by parents or classified by the BERC.

- Moderate or severe hearing impairment; hearing loss corrected with aids, or some hearing loss, not corrected by aids, or deaf, as reported by parents or classified by the BERC.
- Moderate or severe visual impairment; reduced vision, uncorrected with aids, or blind in one eye, or blind/ can perceive light only, as reported by parents or classified by the BERC.

4.2 Other long-term outcomes

4.2.1 Individual components of the main long-term outcome

- Death (up to 24 months of age corrected for prematurity).
- Moderate or severe neurodevelopmental impairment (defined as above), in survivors.

4.2.2 Respiratory morbidity

- Survival without respiratory morbidity (defined as any 2 or more of need for oxygen or respiratory support; presence of a persistent cough and/ or wheeze; need for regular treatment for respiratory illness; 4 or more unscheduled attendances at hospital/ GP for respiratory problems; 1 or more readmission to hospital for respiratory problems).
- Respiratory morbidity (defined as above), in survivors.
- Individual components of respiratory morbidity, in survivors, as follows (presented descriptively only):
    - Need for oxygen or respiratory support.
    - Presence of a persistent cough and/ or wheeze.
    - Need for regular treatment for respiratory illness.
    - 4 or more unscheduled attendances at hospital/ GP for respiratory problems.
    - 1 or more readmission to hospital for respiratory problems.
- Duration of oxygen supplementation from randomisation.

5. Sample size and power

The sample size for the Baby-OSCAR trial was based on clinical evidence suggesting the risk of death or bronchopulmonary dysplasia (BPD) in babies with a large PDA to be approximately 60%, and for those receiving the intervention risk of death or BPD to be approximately 48%. Assuming 1% were lost to follow-up, a sample size of 730 babies was required to detect this 12% reduction in absolute risk with 90% power and a 2-sided significance level of 5%.

The proportion of infants surviving to 24 months corrected age without moderate or severe neurodevelopmental impairment in the control group is expected to be 55%. If outcome data are available on a total sample size of 600 (including deaths), the trial will have an 80% power to detect an increase in survival without moderate or severe neurodevelopmental

impairment of 11% from 55% to 66%, and a 90% power to detect an increase of 13% from 55% to 68%.

A total number of 653 infants were recruited, of which 646 were included in the short-term outcomes analysis.

6. Random allocation

Randomisation was managed via a secure web-based randomisation facility hosted by the NPEU CTU with telephone back-up available at all times. The allocation ratio of intervention (ibuprofen) to control (placebo) was 1:1. A minimisation algorithm was used to ensure balance between the two groups with respect to the size of the PDA, gestational age at birth, age at randomisation, sex, trial site, multiple births, mode of respiratory support at randomisation; (1) invasive ventilation (by an endotracheal tube); or (2) non-invasive respiratory support through, nasal CPAP, nasal ventilation, humidified high flow nasal cannula therapy or, low flow oxygen ≥ 1.1 L/min; or (3) receiving no mechanical ventilation, or pressure support (in room air, or low flow oxygen < 1.1 L/min or ambient oxygen) and receiving inotropes or not at the time of randomisation. Babies of multiple births were randomised individually.

7. Protocol and data non-compliances

All protocol non-compliances were listed in the final report of short-term outcomes, and there are no further changes anticipated since this analysis. Protocol non-compliances are defined as below.

7.1 Major protocol non-compliers

Data considered to be fraudulent is defined as a major protocol non-compliance.

7.2 Minor protocol non-compliers

The following were defined as minor protocol non-compliances:

Participants randomised in error

These include infants:

- Who are < 23 weeks or ≥ 29 weeks of gestation.
- Who are ≥ 72 hours old.
- With a PDA < 1.5 mm in diameter OR who does not have unrestrictive pulsatile left to right flow or, growing pattern with right to left flow of 30% or more.
- Who have clinical or echocardiography evidence of pulmonary hypertension.
- Where written informed consent has not been obtained from the parent(s).
- With a severe congenital anomaly.
- With contraindications to the use of ibuprofen.
- Who have had indomethacin, ibuprofen, or paracetamol administered after birth.

Treatment non-compliances

These include infants who:

- Do not receive allocated intervention. These include infants who were allocated ibuprofen, who instead received placebo, and vice versa.
- Do not receive the correct number of doses. These include infants who received less than 3 doses of the trial medication.
- Do not receive medication at the correct time. These include infants who received their first dose later than 72 hours after birth, or received their 2nd or 3rd dose outside the specified dosing window (< 18 hours or > 72 hours between doses 1 and 2, or doses 2 and 3, or dose 3 completed > 7 days after first dose administered).
- Received open-label treatment without meeting the criteria. These include infants who received open-label treatment but did not meet the defined criteria for doing so:
    1. Inability to wean on ventilator (ventilated for at least 7 days continuously) and any of: inability to wean oxygen; persistent hypotension; pulmonary haemorrhage; signs of cardiac failure,
        AND
    2. Echocardiographic findings of a large PDA (PDA ≥ 2.0 mm with pulsatile flow)
        AND
    3. Echocardiographic findings of hyper-dynamic circulation or ductal steal.

Trial procedure non-compliances

- ECHO not done around 3 weeks (18-24 days) of age.
- Oxygen reduction test will be reported in a process outcomes table.

7.3 Data non-compliers

The following were defined as data non-compliers:

Non-verbal cognitive and language sections of the two-year follow-up parent report questionnaire completed outside of the time window for deriving PARCA-R standard scores

These include infants:

- Who were aged less than 23.5 months or more than 27.5 months corrected age when the 24 month follow-up questionnaire was completed.

8. Interim analyses

An independent Data Monitoring Committee (DMC) was established, whose remit was to review the progress and conduct of the trial. The DMC are independent of the trial organisers and the terms of reference are documented in the DMC charter. The DMC does not plan to review any interim analyses of the two-year follow-up data.

9. Data collection

Data for the two-year outcomes were collected by questionnaire using the following CRF(s) sent to parents when the child was 24 months corrected age:

- Baby-OSCAR 2 Year Form – V2.0 July 2018; your child's health and development at 2 years.

This included the PARCA-R to assess cognitive and language impairment, and validated parent report items to assess gross motor, vision, and hearing impairment.

10. Derivation of variables

10.1 Corrected age

The expected date of delivery for each child will be used to calculate their age at 24 months corrected for prematurity:

- (Date 2-year follow-up parent report questionnaire was completed minus expected date of delivery)/ (365 divided by 12)

10.2 Survival at 24 months corrected age

Deaths before hospital discharge are recorded in CRF Form 6: Baby Outcomes. Section D of this form will determine whether the infant died before discharge. Deaths after discharge and up to 24 months of age are recorded on the Baby-OSCAR administrative database. All deaths after discharge were checked directly with the recruiting hospital.

10.3 Infant neurodevelopment

Non-verbal cognitive and language development

The PARCA-R is a parent completed questionnaire that is used to assess children's non-verbal cognitive and language development at 23.5 to 27.5 months of age. It is comprised of a non-verbal cognitive scale and a language scale. The first subscale comprises 34 items to assess non-verbal cognition. For each item, the parent is asked to respond 'yes', 'no', or 'don't know' to whether their child has exhibited a specific ability. The number of 'yes' responses are summed to produce a non-verbal cognition subscale raw score with a range from 0 to 34. The language subscale score comprises a 100-word vocabulary checklist, from which the number of words the child can say is summed to produce a score with a range from 0 to 100, along with 18 forced-choice items to obtain information regarding the child's use of sentences to produce a score with a range of 0 to 24. These are summed together to produce the language subscale raw score with a range of 0 to 124 [1]. On both the non-verbal cognitive scale and the language scale, raw scores are converted to age-standardised scores with a normative mean of 100 (SD 15).

Children with non-verbal and language assessments completed outside of the corrected age range of 23.5 to 27.5 months with no classification from the BERC will be treated as missing data and a multiple imputation analysis performed to estimate these infants' PARCA-R standardised scores (see section 13.1). Scores for missing questions on the non-verbal

cognitive scale will be substituted with the average of the score of each individual child for completed questions if 4 or fewer questions are missing. If more than 4 questions are missing, a non-verbal cognition standardised score cannot be derived. These will therefore be treated as missing data and a multiple imputation analysis will be performed to estimate the PARCA-R standardised scores of infants with 4 or more missing non-verbal cognitive questions. Reasons for missing data will be reported and described by type, based on whether the assessments were completed outside of the corrected age range, or whether there were 4 or more data points missing in the non-verbal cognitive subscale.

PARCA-R standardised scores will then be used to classify non-verbal cognitive and language impairment for which two binary outcomes (non-verbal and language) will be derived. On each scale, children with scores < -2 SD (standard score <70) will be classified with moderate or severe impairment.

Gross motor, vision and hearing impairment

Gross motor, vision and hearing impairment were assessed using parent report items with impairment classified into binary outcomes as follows:

- Moderate or severe gross motor impairment: the child is unable to sit on the floor independently (Q4 = can sit with support or with help from an adult, or unable to sit), and/ or the child is unable to walk independently (Q5 = can only walk if helped by an adult or a walking aid, or unable to walk, even with help).
- Moderate or severe hearing impairment: the child has some hearing loss corrected with aids (Q3 = has a cochlear implant or hearing aid, but hears well with it), or the child has some hearing loss, not corrected by aids (Q3 = has difficulty hearing, even with a cochlear implant or hearing aid), or the child is deaf (Q3 = my child is deaf).
- Moderate or severe visual impairment: the child has reduced vision, uncorrected with aids (Q2 = has difficulty seeing, even when wearing glasses), or the child is blind in one eye (Q2 = is blind in one eye, but has good vision in the other eye), or the child is blind or can perceive light only (Q2 = is able to see light only or is blind).

Blinded Endpoint Review Committee

The BERC reviewed and classified impairment using clinical data relating to the child's two year neurodevelopmental assessment where available for children who survived to 24 months corrected age for whom: a 2-year study questionnaire was not completed by a parent or carer; a 2-year study questionnaire was completed outside of the timeframe of 23.5 to 27.5 months corrected age; or, there are missing data on questionnaire items precluding classification of one of more of the individual components of the main 2-year outcome. The purpose of the BERC is to make a final determination on whether these children have moderate or severe neurodevelopmental impairment (for each domain and overall). For further details see the Baby-OSCAR Follow-up BERC Charter (see section 26).

10.4 Survival without moderate or severe neurodevelopmental impairment

The main long term outcome of survival without moderate or severe neurodevelopmental impairment is a binary outcome defined as surviving to 24 months corrected age without

moderate or severe neurodevelopmental impairment in non-verbal cognitive, language, gross motor, hearing or visual function.

10.5 Respiratory morbidity

Respiratory morbidity will be assessed by the need for oxygen or respiratory support which, using section A: Your Child's Health and Development of the Baby-OSCAR 2 Year Form, will be defined as having two or more of the following:

- Need for oxygen or respiratory support; the child was discharged home on oxygen using a nasal cannula (Q6=Yes), or the child received oxygen using a nasal cannula at any other time since discharge (Q6ii=Yes) or the child has received any other breathing support since being discharged home after birth (Q7=Yes).
- Presence of a persistent cough and/ or wheeze; the child has suffered from a persistent wheeze (Q8=Yes), or persistent cough (Q9=Yes and Q9i=cough affects at least one of feeding, sleeping, or physical activity), since being discharged home after birth.
- Need for regular treatment for respiratory illness; the child has required at least one of the following regular treatments since being discharged home after birth (Q10=Yes, and at least one treatment ticked): inhaler – relievers, e.g. Ventolin or Bricanyl (blue); inhaler – preventers, e.g. Pulmicort (brown), or Flixotide (yellow); steroids, e.g. Prednisolone; other (to be specified).
- Unscheduled attendances at hospital/ GP for respiratory problems; the child has been taken to a GP or Accident and Emergency department for any respiratory illness more than 3 times since being discharged home after birth (Q11=Yes and Q11i=4-12 times, or more than 12 times).
- Readmission to hospital for respiratory problems; the child has been admitted to hospital for any respiratory illness since being discharged home after birth at least once (Q12=Yes).

10.6 Survival without respiratory morbidity

Survival without respiratory morbidity is therefore a binary outcome defined as surviving to 24 months corrected age with fewer than two of the following: a need for oxygen or respiratory support, presence of a persistent cough and/ or wheeze, need for regular treatment for respiratory illness, unscheduled attendances at the hospital/ GP for respiratory problems, or readmission to hospital for respiratory problems (see section 10.5).

10.7 Duration of oxygen supplementation from randomisation

Duration of oxygen supplementation from randomisation will be determined by the sum of the total number of days up to 24 months corrected age the child was receiving invasive ventilation by ET tube, the number of days the child was receiving non-invasive respiratory support by nasal ventilation, CPAP, or high flow oxygen therapy, and the number of days the child was receiving ambient or low-flow oxygen. If the child was still receiving oxygen supplementation at 24 months corrected age this will be calculated as the number of days between their date of birth and the date the 2-year parent report questionnaire was completed.

11. **Participant groups for analysis**

11.1 Primary analysis strategies

For the two-year outcomes, the primary inference will be based on an intention-to-treat (ITT) analysis, i.e. infants will be analysed in the groups to which they were randomised, regardless of treatment they received.

11.2 Post-randomisation exclusions

Exclusions to the analysis population post-randomisation consist of the following:

- Infants for whom a written consent form from the parent(s) was not received
- Infants for whom consent to use their data was withdrawn by the parent(s)
- Infants for whom an entire record of fraudulent data was detected (should fraudulent data be detected, consideration will be given to excluding all data for the site where such data were found)

11.3 Descriptive analysis population

Baseline demographic and clinical characteristics will be reported for all infants and their mothers in the ITT population by randomised group for whom main long-term outcome data are available (including deaths).

11.4 Comparative analysis population

All infants randomised with available outcome data at two years, minus post-randomisation exclusions (see section 11.2).

11.5 Interim analysis population

The DMC does not plan to review any interim analyses of the two-year follow-up data.

12. **Descriptive analyses**

12.1 Representativeness of trial population and participant throughput

The flow of participants through each stage of the trial will be summarised by randomised group using a CONSORT diagram. This will described the following numbers of infants:

- Assessed for eligibility
- Eligible
- Randomised
- Allocated to ibuprofen
- Allocated to placebo
- Withdrawn consent
- Included in analysis of short-term primary outcome
- Deaths
- Lost to follow-up following discharge home
    - Non-response at two years with no classification by the BERC

    - Response at two years but with too much missing data and no classification by the BERC
- Included in analysis population for the main long-term outcome

12.2 Baseline comparability of randomised groups

The following demographic and clinical characteristics collected at baseline and two years, and important short-term outcomes, will be described by randomised group for infants who had available data on the main long-outcome data at two years.

Mother's baseline characteristics:

- Ethnicity
- Age (years)
- Deprivation index
- Antenatal steroid use (any)
    - < 24 hours before birth
    - ≥ 24 hours before birth
    - Antenatal COX inhibitor use
    - Antenatal magnesium sulphate use for neuroprotection

Infant's characteristics at trial entry:

- Enrolling centre
- Born in enrolling centre
- Postnatal age at randomisation (hours)
- Gestational age at birth (weeks)
- Mode of delivery
- Forceps or Ventouse used in delivery
- Main cause of preterm birth
- Birth weight (g)
- Birth weight z score
- Head circumference (cm)
- Head circumference z score
- Sex
- Baby is one of a multiple pregnancy
- Sibling enrolled in the study (in multiple pregnancies)
- APGAR score 5 minutes after birth
- Baby's worst base excess at first hour after birth
- CRIB II (without temperature)
- Size of PDA
- Mode of respiratory support at randomisation
- Receiving inotropes at randomisation

Data collected at two years:

- Family history of asthma or wheezing

- Environmental factors

Short-term outcomes:

- **Primary outcome:** composite outcome of death by 36 weeks' postmenstrual age, or moderate or severe BPD at 36 weeks' postmenstrual age.
- Moderate or severe BPD at 36 weeks' postmenstrual age.
- Severe intraventricular haemorrhage (IVH) (grade III/ IV with ventricular dilation or intraparenchymal abnormality).
- Cystic periventricular leukomalacia (PVL).
- Babies treated for retinopathy of prematurity (ROP).
- Necrotising enterocolitis (NEC) definitive and/ or complicated (Bell stage II and above) confirmed by radiology and/ or histopathology.
- PDA ≥ 1.5 mm at around 3 weeks (range of 18-24 days), not treated medically or by surgical closure.
- Discharge home on oxygen.
- Postnatal steroid use for chronic lung disease.

The number and percentage will be presented for binary and categorical variables. The mean and standard deviation or the median and interquartile range - where data are skewed - will be presented for continuous variables, or the range if appropriate.

12.4 Loss to follow-up

The number and percentage of infants for whom there is no two-year outcome data will be reported for the two trial arms, and the reasons will be recorded. All deaths will be reported separately. Demographic and clinical characteristics at baseline and collected at two years, and important short-term outcomes, will also be described for infants for whom main long-term outcome data were and were not obtained at two years, within each trial arm.

13. **Comparative analyses**

All models will be adjusted for minimisation factors where possible (see section 6). Size of PDA, gestational age at birth, and age at randomisation will be treated as continuous variables. Sex, multiple births, and whether the infant received inotropes at the time of randomisation will be treated as binary variables. Trial site and mode of respiratory support at randomisation will be treated as categorical variables. Centre and multiple births will be treated as random effects and all other factors will be treated as fixed effects. Correlations between siblings from multiple births will be accounted for in the adjusted model by nesting "multiple" cluster as a random effect within centre. If a quantile regression is necessary, all factors will be treated as fixed effects, as random effects cannot be modelled using these methods of analysis.

Both crude and adjusted effect estimates will be presented, but the primary inference will be based on the adjusted estimates.

13.1 Main long-term outcome

A mixed-effect log binomial regression model will be fit to estimate the risk ratio (RR) and 95% confidence interval (CI) and p-value for survival without moderate or severe neurodevelopmental impairment at two-years corrected age between the control group and the intervention group. Children with PARCA-R questionnaires completed outside of the 23.5 to 27.5 months of age who did not have cognitive and language impairment classified by the BERC will be regarded as having missing standardised PARCA-R scores and will be treated as missing at random.

A multiple imputation analysis will be performed for the non-verbal cognitive and language PARCA-R standardised scores for children with PARCA-R questionnaires completed outside of the 23.5 to 27.5 months corrected age range or for those with 4 or more missing non-verbal cognitive scale questions, and without classification of cognitive and language impairment by the BERC. The continuous value of the standardised PARCA-R score will be imputed and this will then be converted to the binary outcome. The multiple imputation model will include raw PARCA-R score, corrected age, sex and any other baseline characteristics and short-term outcomes associated with the missing status of the PARCA-R score. If there is evidence that the variables used to inform the imputation are not strongly associated with the primary outcome, or if there are non-significant concerns around the specification of the imputation model, Predictive Mean Matching will be used, with the 10 closest observations (donors) informing the imputation. The estimates from this multiple imputation analysis will be presented as the primary inference [2, 3].

If the model fails to converge, a Poisson regression model with a robust variance estimator will be used. If the Poisson model fails to converge, centre will be removed as a random effect.

13.2 Other long-term outcomes

For continuous outcomes, a mixed-effect linear regression model will be fitted to estimate the mean difference and 95% CIs for the outcome variables between the control group and intervention group, assuming model assumptions are satisfied (i.e. independence and normality of residuals). If model assumptions are not satisfied, a quantile regression model will be employed, with median differences and 95% CIs presented.

For binary outcomes, log-binomial regression models will be used to calculate risk ratios and 95% CIs. Details of procedures in place for the log-binomial regression failing to converge are outlined in section 13.1.

Analysis of the main long-term outcome will be clearly delineated from the other long-term outcomes in any statistical reports produced.

14. **Secondary analysis**

There are no planned secondary analyses.

15. **Pre-specified subgroup analysis**

Pre-specified subgroup analyses will use the statistical test of interaction and where appropriate, results will be presented as risk ratios with 95% CIs.

Pre-specified subgroups on the main long-term outcome will be based on:

- Gestational age at birth (< 26 weeks; ≥ 26 weeks).
- Size of the PDA (1.5 mm to < 2.0 mm; 2.0 mm to < 3.0 mm; ≥ 3.0 mm).
- Mode of respiratory support at randomisation invasive ventilation (defined as ventilation via an endotracheal tube); or, non-invasive or no respiratory support (defined as ventilation via nasal CPAP, nasal ventilation, humidified high flow nasal cannula therapy, or low flow oxygen ≥ 1.1 L/min, or receiving no mechanical ventilation, or pressure support (in room air, or low flow oxygen < 1.1 L/min, or ambient oxygen)).

16. **Sensitivity analysis**

PARCA-R questionnaires completed outside of the range of 23.5 to 27.5 months of age with no classification of cognitive and language impairment by the BERC, and PARCA-R questionnaires with >4 missing items on the non-verbal cognition scale, will be treated as missing data with results from the multiple imputation analysis treated as the primary inference. A further sensitivity analysis will be conducted on the primary outcome, excluding those infants whose PARCA-R scores were imputed.

17. **Safety data analysis**

No further safety data was collected post hospital discharge home

18. **Statistical significance**

95% CIs will be used along with two-sided 5% statistical tests of superiority for all pre-specified outcome comparisons including subgroup analyses.

19. **Procedure for accounting for missing data**

Missing data will be described, by presenting the number of individuals in the missing category.

Standardised PARCA-R scores for non-verbal cognitive and language impairment cannot be calculated for infants whose questionnaires were completed outside of the age range 23.5 to 27.5 months, although raw scores may be available. Standardised PARCA-R scores for non-verbal cognitive impairment cannot be calculated for infants with 4 or more missing

questions. It is assumed that these standardised scores are missing at random, with a multiple imputation analysis to be performed on the PARCA-R assessment scores, imputing standardised scores for these infants (see section 13.1).

The other components of neurodevelopment impairment assessed using PARCA-R, including motor, hearing and visual function, are not restricted by age in the same way. Therefore, imputation for these scores will not be performed.

20. **Deviation from the protocol**

Minor changes to definitions and additions of variables absent from the protocol appeared in this SAP. The secondary long term outcome named in the protocol as survival is defined here as death, to aid interpretation of the individual components of the main long-term outcome. This will not impact the outcome of the statistical test. Moderate or severe neurodevelopmental impairment in survivors, and moderate or severe respiratory morbidity in survivors were additional variables defined in this SAP not included in the protocol.

The pre-specified subgroup analyses outlined in the protocol were only identified as part of the short-term outcomes analysis. These same sub-group analyses will be performed on the main long-term outcome as well.

Imputing missing data for those children with 4 or more missing questions in the non-verbal cognitive subscale was not specified in the protocol, however this is a standard approach recommended for the use of PARCA-R.

21. **Statistical software employed**

The statistical software Stata version 17 (or later) for Windows will be used for all analyses and R version 4.2.3 (or later) will be used for figures.

22. **Additional exploratory analysis**

Any additional analyses not specified in the analysis protocol will be exploratory in nature and will be documented in a separate statistical analysis plan. Any post-hoc analysis requested by a steering committee, investigator, journal editor or referees will be clearly labelled as such.

23. **Dummy tables**

Dummy tables are provided in a separate document.

24. **Health economic analysis**

The health economic analysis is described in a separate analysis plan.

25. **References**

1. Johnson S, Bountziouka V, Linsell L, Brocklehurst P, Marlow N, Wolke D, Manktelow B. Parent Report of Children's Abilities – Revised (PARCA-R). Technical and Interpretive Manual. University of Leicester, Leicester, 2019
2. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. Statistics in medicine. 2011 Feb 20;30(4):377-99.
3. Morris TP, White IR, Royston P. Tuning multiple imputation by predictive mean matching and local residual draws. BMC medical research methodology. 2014 Dec;14:1-3.

26. **Additional documents**

Charter for Blinded Endpoint Review Committee follow up data_Final_v1.0.

27. **Approval**

Senior Statistician	Name: Heather O'Connor	
	Signature H OConnor 20/04/2023 16:42:22 Heather OConnor	Date 20/04/2023
Chief Investigator	Name: Samir Gupta	
	Signature S Gupta 20/04/2023 18:57:42 Samir Gupta	Date 20/04/2023
Chair of Trial Steering Committee (or delegate)	Name: Michael Weindling	
	Signature M Weindling 26/04/2023 14:24:24 Michael Weindling	Date 26/04/2023

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