CTRC
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PREVAIL

PREVenting infection using Antimicrobial Impregnated Long lines

Trial registration: ISRCTN 81931394

Statistical Analysis Plan for final analysis version 3.0 28/03/2018

	ORIGINATED BY	QC PERFORMED BY	APPROVED BY
Name	Naomi Bacon	TBC	Michaela Brown
Title	Trial Statistician	TBC	Lead Statistician
Date	28/03/2018		
Protocol Version and Date	Protocol version 5.0 26/04/2017		

1. Change Control

Protocol version	Updated SAP version no.	Section number changed	Description of change	Date changed
5.0	2.0	9.2	Secondary outcome of "Time to death" added	08/02/2018
5.0	2.0	12	Details regarding decimal places added	09/02/2018
5.0	2.0	14.1	Clarification to section on CONSORT flow diagram	09/02/2018
5.0	2.0	17.2	Categories added to birth weight, age at randomisation, apgar score and respiratory support	06/03/2018
5.0	2.0	17.3	Number of mixed growth cultures removed as covered in section 17.5.3 "Type of organism isolated from BSI"	09/02/2018
5.0	2.0	17.4.1.1	Clarification of wording throughout. Multiple cultures changed from 48 hours to 24 hours. Justification includes giving less weight to contaminants and difference episodes of BSI can occur in relatively quick succession in preterm babies	08/02/2018
5.0	2.0	17.4.1.2	Removal of "total number of days PICC is in situ for" and "event rate of BSI per 1000 PICC days" as this is presented within other secondary outcomes.	08/02/2018
5.0	2.0	17.4.2	Clarification of definitions	08/02/2018
5.0	2.0	17.5.1.1	Clarification of definitions. Detail added regarding clinical input for "other" sample types. Definitions regarding Gram –ve/+ve organisms added.	08/02/2018
5.0	2.0	17.5.1.2 17.5.2.2	Clarification of definitions. Frequency tables by Gram –ve/+ve added. Line listings of Rifampicin resistant isolates added	08/02/2018
5.0	2.0	17.5.2.1	Clarification of definitions. Definitions regarding Gram –ve/+ve organisms added.	08/02/2018
5.0	2.0	17.5.3.1	Definitions for multiple cultures within the POTW added	08/02/2018
5.0	2.0	17.5.4.1 17.5.6.1 17.5.7.1	Clarification added for the time from of during the POTW.	08/02/2018
5.0	2.0	17.5.5.1	Clarification of wording added.	08/02/2018
5.0	2.0	17.5.15.1	Removal of wording around using NNRD data to supplement the outcome.	14/02/2018
5.0	2.0	17.5.16.1.1	"ONS" changed to "PDS"	08/02/2018
5.0	2.0	17.5.16.1.2 17.5.16.3.2	Clarification of presentation of results using PDS data added.	14/02/2018
5.0	2.0	17.5.16.3	Secondary outcome of "Time to death" added	08/02/2018
5.0	2.0	18	Clarification to wording regarding lost to follow up and reporting of missing data. Time imputations added.	08/02/2018
5.0	2.0	19.1.4	Clarification of definitions added. Fourth sensitivity of the primary outcome added.	08/02/2018
5.0	2.0	19.2	Six sensitivity analyses of the secondary outcomes added.	08/02/2018
5.0	2.0	19.3	Additional secondary analysis added	28/02/2018
5.0	2.0	22.2	Appendix II added	08/02/2018
5.0	3.0	17.5.6.1	Samples amended to include CSF samples	28/03/2018
5.0	3.0	19.1.1	Definition of clinically serious BSI added	28/03/2018

2. Approval and agreement

At a minimum two versions of the SAP should be approved and stored within the statistics trial file.

1. SAP version 1.0 should be created after it has been reviewed and signed-off to ensure all are in agreement with the planned analysis and no further changes are foreseen.

2. The final SAP version should be converted to PDF and signed following the blinded review for protocol deviations and immediately prior to database lock as evidence of the analysis planned prior to unblinding of the study.

SAP Version Number being approved: 3.0

Trial Statistician

Name NAOMI BACON

Signed N Bacon Date 28/3/18

Senior Statistician

Name MICHAELA BROWN

Signed MBrown Date 28/03/18

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Signed Date 28/3/18

3. Roles and responsibilities

Trail Statistician: N Bacon (Department of Biostatistics, University of Liverpool), Senior Statistician: M Brown (Department of Biostatistics, University of Liverpool), Co-chief Investigator: R Gilbert (UCL Institute of Child Health), Co-chief Investigator: S Oddie (Bradford Teaching Hospitals NHS Foundation Trust).

Author's contributions

N Bacon and M Brown proposed the statistical analysis plan. N Bacon drafted the manuscript. M Brown, R Gilbert and S Oddie read, amended and approved the statistical analysis plan.

4. List of abbreviations and definitions of terms

AE	Adverse event
AFT	Accelerated failure time
AM-PICC	Antimicrobial Impregnated coated Peripherally Inserted Central Catheter
AR	Adverse reaction
BSI	Blood stream infection
CONSORT	Consolidated Standards Of Reporting Trials
CRF	Case report form
CSF	Cerebrospinal fluid
CTRC	Clinical Trials Research Centre
CTU	Clinical Trials Unit
IDSMC	Independent Data and Safety and Monitoring Committee
IQR	Interquartile range
ITT	Intention to treat
NEC	Necrotizing enterocolitis
NNU	Neonatal unit
PREVAIL	Trial Title: PREVenting infection using Antimicrobial Impregnated Long lines
RCT	Randomised controlled trial
RN	Research nurse
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOP	Standard operating procedure
S-PICC	Standard Peripherally Inserted Central Catheter
TSC	Trial Steering Committee

Contents

5. Statement of Compliance

This Statistical Analysis Plan (SAP) provides a detailed and comprehensive description of the pre-planned final analyses for the study "PREVenting infection using Antimicrobial Impregnated Long lines (PREVAIL)". The planned statistical analyses described within this document are compliant with those specified in brief within the PREVAIL protocol version 5.0.

This study is carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996) amendments and will be conducted in compliance with the protocol, Clinical Trials Research Centre (CTRC) Clinical Trials Unit (CTU) Standard Operating Procedures (SOPs) and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004.

These planned analyses will be performed by the trial statistician. The results of the final analysis described within this statistical analysis plan will be contained within a statistical analysis report. This report will be used as the basis of the primary research publications according to the study publication plan.

All analyses are performed with standard statistical software (SAS version 9.3 or later). The finalised analysis datasets, programs and outputs will be archived following Good Clinical Practice guidelines and SOP TM021 Archiving procedure in CTRC. The testing and validation of the statistical analysis programs will be performed following SOP ST001.

6. Background and Rationale

The rationale for the trial is outlined in the protocol. To summarise, currently antibiotic impregnated central venous catheters are used in paediatric and adult intensive care. However, no neonatal units (NNUs) in the UK use antimicrobial impregnated coated peripherally inserted central catheters (AM-PICCs) (despite the AM-PICCs being CE marked). When surveyed, neonatologists cite the lack of randomised controlled trial (RCT) evidence in preterm babies as an important reason for the lack of adoption of impregnated lines in the UK (unpublished). The trial is needed now because potential health gains are unlikely to be realised without robust evidence from a RCT. Clear evidence is needed of the effectiveness of AM-PICC on blood stream infection (BSI), the safety of AM-PICC, particularly on antibiotic resistance, and the cost-effectiveness, to enable neonatologists to decide about whether or not to adopt these devices in NNUs.

7. PREVAIL Study Objectives

The primary objective of this trial is to determine the effectiveness of antimicrobial impregnated (with rifampicin and miconazole) peripherally inserted central catheter (AM-PICC) compared with standard peripherally inserted central catheter (S-PICC) for reducing BSI.

The null hypothesis is that there is no difference in time to BSI based on any positive blood culture (including fungal isolates) taken between 24 hours after randomisation until 48 hours after PICC removal between the intervention (AM-PICC) group and the control (S-PICC) group. The alternative hypothesis is that there is a difference between the two groups.

The secondary objectives of this trial are to determine the effect of AM-PICC vs S-PICC on the secondary outcomes listed in section 9.2

8. Investigational Plan and Study Design

8.1. Overall study design and plan- description

This trial is an open label, 2-arm randomised controlled trial to determine the effectiveness and cost effectiveness of antimicrobial impregnated (with rifampicin and miconazole) long lines (AM-PICC) compared with standard long lines (S-PICC) for reducing blood stream infection (BSI).

8.2. Treatments studied

A PICC is a very narrow tube placed through the skin and into a central vein to allow medicines, fluids or parenteral nutrition to be given into one of the large veins near to the heart. The control treatment in PREVAIL is an S-PICC, which is an un-impregnated PICC. The intervention treatment is an AM-PICC, which is an antimicrobial impregnated PICC. Further details on the trial treatments can be found in sections 2.1 and 7.2 of the study protocol.

8.3. Description of treatment adherence

If a baby has their PICC removed less than 24 hours after insertion then this is classed as non-adherence to treatment. Babies who receive a PICC other than the randomised PICC will be reported in the CONSORT flow diagram (see section 14).

8.4. Patient population studied

The trial population aims to include 858 babies who require the narrowest PICC (Premicath 1 French gauge (Fr)).

8.4.1. Inclusion criteria

The inclusion criteria can be found in section 5.1 of the protocol.

8.4.2. Exclusion criteria

The exclusion criteria can be found in section 5.2 of the protocol.

8.4.3. Removal of patients from therapy or assessment

All babies will have their PICC removed at some point. Case report form (CRF) "Form 6: Removal" records the reason for PICC removal. These include:

- PICC no longer needed
- Removed because of confirmed infection
- Removed because of suspected infection
- Damaged
- Unintended removal
- PICC blocked
- Thrombosis

- Clinically evident thrombophlebitis
- Pre-specified duration of use reached
- Malposition identified during x-ray

Babies will be observed for clinical follow-up for 48 hours after the PICC removal and a retrospective review of key events will take place when the baby is discharged home/dies/reached 26 weeks post randomisation, unless the parent/legal representative instructs otherwise.

8.5. Consent process

Consent is sought from the parent or legal representative for those babies who are likely to require a PICC.

Once written consent has been provided by the parent or legal representative it is valid for 14 days. If the baby has not been randomised within the 14 days the research nurse (RN) or clinician will need to reconsent the parent/legal representative of the baby. Further details can be found in sections 6.2 and 11.3 of the protocol.

8.6. Blinding

This is an open-label trial because AM-PICCs can be distinguished from S-PICCs as rifampicin causes brown staining on the tubing. No details on blinding will be presented.

8.7. Method of assignment to treatment

Full details of the randomisation procedure can be found in sections 6.3 and 9.2 of the protocol. The randomisation list will be generated by a statistician (who is not involved with the PREVAIL trial) at the CTU. Babies will be randomised to AM-PICC or S-PICC in a ratio of 1:1. Randomisation will be stratified by centre. Babies will be randomised using a secure (24-hour) web based randomisation programme controlled centrally by the CTU to ensure allocation concealment. Details of block sizes can be found in the Statistics Trial File under section 4.

8.8. Sequence and duration of all study periods

A schematic of the study design can be found in section 1 of the study protocol. A table of trial assessments can be found in section 8.1 of the protocol.

To summarise this information, the researcher (clinician or research nurse) will approach parents of eligible babies to discuss PREVAIL and to obtain consent. Once consent is obtained, the baby will then be randomised to either AM-PICC or S-PICC. Consent is valid for 14 days. If the baby has not been randomised within 14 days, the parents will need to reconsent. Babies are followed up clinically and for safety until 48 hours after removal or attempted insertion (if attempted but not inserted) or randomisation (if randomised but not inserted). There is a retrospective review of key events at discharge home from neonatal care, death or 26 weeks post randomisation, whichever occurs first and at all transfers to other hospitals.

8.9. Schedule of assessments

A full schedule of trial assessments and timeline of data collection can be found in section 8.1 of the protocol.

9. Listing of Outcomes

9.1. Primary outcome

The primary outcome is time to BSI based on any positive blood/CSF culture (any positive bacterial or fungal blood/CSF culture will be included) taken between 24 hours after randomisation until 48 hours after PICC removal.

9.2. Secondary outcomes

Outcomes captured up until 48 hours after PICC removal:

1. Rifampicin resistance in any isolate from blood/CSF culture.
2. Rifampicin resistance in any isolate from PICC tips.
3. Type of organism isolated from BSI.
4. Rate of BSI per 1000 PICC-days (including recurrent BSI).
5. Occurrence of 1 or more BSI.
6. Rate of catheter-related BSI per 1000 PICC days.

7. Rate of blood/CSF culture sampling per 1000 PICC days.
8. Duration of antimicrobial exposure from randomisation up to 48 hours after PICC removal.
9. Time to PICC removal.

Outcomes captured up until discharge home from neonatal care/death/6 months post randomisation:

10. Chronic lung disease 36 weeks postmenstrual age.
11. Necrotizing enterocolitis (NEC): Bell's stage II or III.
12. Treatment for retinopathy of prematurity.
13. Abnormalities on cranial ultrasound.
14. Time to full milk feeds after randomisation.
15. Total duration of parenteral nutrition from randomisation until discharge from NNU.
16. Death:
    a) within 6 months (26 weeks) of randomisation
    b) before discharge home from neonatal care
    c) time to death

10. Determination of Sample Size

The sample size calculation can be found in section 9.4 of the protocol.

11. Study Framework

The overall objective for each of the study outcomes (primary and secondary) is to test the superiority of AM-PICCs compared with S-PICCs.

12. Confidence Intervals, p-values and Multiplicity

All applicable statistical tests will be two-sided and will be performed using a 5% significance level; confidence intervals presented will be 95%. No adjustment will be made for multiplicity for the secondary outcomes. Percentages will be presented as 1 decimal place. Test statistics, p-values, confidence intervals and measures of spread will be presented as 2 decimal places.

13. Timing and Objectives of Interim and Final Analyses

13.1. Interim monitoring and analyses

Details on interim analyses are compatible with those found in the protocol in section 9.5. The IDSMC will meet annually unless members have specific concerns that would require the meetings to be held more frequently as stated within section 5.3 of the IDSMC Charter.

There will be a formal interim analysis of the primary outcome half-way through the trial (when approximately half of the participants have been randomised), using Peto-Heybittle stopping rules. At this point the IDSMC will make a recommendation to the Trial Steering Committee (TSC) for the trial to continue or stop. Statistical significance alone will not stop the trial; a decision to discontinue recruitment will be made only if the result is likely to convince a broad range of clinicians including parents of babies in the trial and the general clinical community or if there are safety issues. The IDSMC will also review the parameters used within the sample size calculation at this time. See "Statistical Analysis Plan for IDSMC reports" for details on the information presented to the IDSMC.

13.2. Final analysis

The final analysis for all outcomes will be analysed after the end of the trial, which is defined in section 8.6 of the protocol as "the date on which data for all participants is frozen and data entry privileges are withdrawn from the trial database."

14. Disposition of Participants

14.1. Screening, eligibility and recruitment

If the parents/legal representative has been approached for consent, the baby will be recorded on "Log A: Screening Log" and details of whether they went on to be randomised will also be recorded here.

If a baby's parent/legal guardian was not approached for consent but later went on to receive a PICC, they will be recorded on "Log B: Missed patient log".

Screening logs will be summarised by site in a table detailing:

i) the number of babies whose parents/legal representatives were approached for consent,
ii) the number of babies whose parents/legal representatives were not approached for consent (missed babies),
iii) those who provided consent, (expressed as a frequency and a % with the denominator being i),
iv) those who were randomised (expressed as a frequency and a % with the denominator being iii),

Reasons for not being approached will be summarised in a table with the following categories:

- Parents not available to consent
- Parents lack of understanding
- Parents don't understand English/Urdu
- Consultant preference
- Missed by clinical team
- Baby previously entered into PREVAIL
- Not approached for other reason

Frequencies will be presented along with percentages using the denominator as ii).

Reasons for consent declined will be summarised in a table with the following categories:

- No reason provided.
- Parent doesn't want to take part in research.
- Parent doesn't wish baby to be randomly assigned to treatment.
- Parent doesn't wish baby to have antimicrobial PICC.
- Other reason.

Frequencies will be presented along with percentages using the denominator as iii).

Reasons for consent provided but not randomised will be summarised in a table with the following categories:

- Baby requires different size PICC
- Baby no longer requires a PICC
- Baby died
- Trial trained staff not available
- Unable to access randomisation system
- PICC (Premicath 1Fr) not available

- Other reason

Frequencies will be presented along with percentages using the denominator as iv).

A recruitment summary table will be presented showing the following for each centre: centre code, hospital name, dates site opened/closed to recruitment, dates of first/last randomisation and total number randomised.

The following details will be summarised in a CONSORT flow diagram (appendix A):

- the number of babies whose parents were approached for consent
- the number of babies whose parents were not approached for consent
- the number of babies whose parents were approached but didn't go on to be randomised
- those babies who were randomised
- those who received the randomised allocation
- those who did not receive the randomised allocation
- those who withdrew from the study after randomisation
- those who were lost to follow-up
- the number of babies included in primary analysis

14.2. Post randomisation discontinuations

Information on participant withdrawal can be found in section 5.4 of the protocol. Before the PICC has been inserted, parents are free to withdraw from any aspect of the trial, however once the PICC has been inserted, it will only be removed for clinical reasons only.

Withdrawals from follow-up and data collection will be recorded and presented descriptively along with any reasons given.

15. Protocol Deviations

Possible protocol deviations will be specified as minor or major in the Trial Monitoring Plan.

Protocol deviations are classified prior to requesting the treatment allocations and any analysis being performed. The number (and percentage) of babies with at least one protocol deviation will be summarised overall and by treatment group. Details will also be presented on the

number of babies with at least one major/minor protocol deviation. The babies that are included in the intention to treat (ITT) analysis data set will be used as the denominator to calculate the percentages. No formal statistical testing will be undertaken.

Babies to be excluded from analysis populations need to be defined in template ST001TEM04: Protocol deviations and data set definitions template agreed and approved prior to any release of randomisation code.

16. Unblinding

N/A as PREVAIL is an open label study. No details on unblinding will be presented.

17. Efficacy Evaluations

17.1. Data Sets Analysed

The principle of intention-to-treat, as far as practically possible, will be the main strategy of the analysis adopted for all efficacy outcomes. These analyses will be conducted on all randomised participants, in the group to which they were allocated, and for whom the outcome(s) of interest have been observed/measured.

The membership of the analysis set for the efficacy outcomes will be determined and documented and any reason for participant exclusion will be given prior to the blind being broken and the randomisation lists being requested. Reasons may include missing data, loss to follow up.

The numbers included in the ITT and safety populations (described in section 20.1) will be presented in a table.

17.2. Demographic and Other Baseline Characteristics

The comparability of the two randomised groups with respect to the baseline clinical factors of the following will be presented

- Gender
- Birth weight in grams (categories of <750, 750 – <1000, 1000 - <1250, 1250 – <1500, 1500 - <1750, 1750 - < 2000 and ≥2000)

- Gestational age in weeks (categories of <26, 26 - <28, 28 - <30, 30 - <32, 32 - <34, 34 - <36, 36 - <38, ≥38). Note: This will be estimated by calculating the difference in weeks between the baby's date of birth and final estimated date of delivery. It will be assumed that the final estimated date of delivery will be 40 weeks. Weeks are complete weeks, for example "36 weeks" would mean 36 weeks plus anything up to and including 6 days.
- Major congenital anomaly
- Age at randomisation in days (categories of <2, 2 - <7, 7 - <14,, 14 - < 21, 21 - < 28 ≥28). Note: "<2 days" = "<48 hours".
- Location of birth (categories of 'inborn' and 'Baby transferred to the study hospital after birth)
- Mode of delivery (categories of 'vaginal' and 'caesarean')
- Membranes ruptured more than 24 hours before delivery (Yes/No)
- Apgar score at 5 minutes (categories of 0 – 3, 4 – 7, 8 - 10)
- Maternal antenatal corticosteroids (Yes/No)
- Maternal antibiotics within 12 hours prior to delivery (Yes/No)
- Surgery before randomisation (categories of 'longer than 6 days ago', 'within the last 6 days' and 'no surgery'
- Positive blood culture within 72 hours prior to randomisation (Yes/No) – taken from microbiology form
- Antibiotics or antifungals within 72 hours prior to randomisation excluding Prophylaxis (Yes/No). Note: See table below for details on classifying this from information in section 5 of CRF "Form 3: Baby Characteristics"

Questions on Form 3: Baby characteristics			Baby classified as having "Antibiotics or antifungals within 72 hours prior to randomisation"
1: IV antibiotics within 72 hours prior to randomisation?	2: IV and/or enteral antifungal medication within 72 hours prior to randomisation?	2a: If yes, was the antifungal for prophylaxis only?	
Yes	Yes	No	Yes
Yes	Yes	Yes	Yes
Yes	No	N/A	Yes
No	Yes	No	Yes
No	Yes	Yes	No
No	No	N/A	No

- Number of devices in situ at randomisation (<4, ≥4)
- Respiratory support (categories of ' None', 'ET Tube', 'Non-invasive ventilation', and 'Oxygen')
- PICC insertion site (categories of 'No line inserted', 'Lower limb', 'Upper limb', 'Scalp', 'Other').

All comparisons between the groups will be descriptive in nature and no formal hypothesis testing will be performed. Categorical variables in each group will be summarised by counts (percentages) while continuous variables will be summarised by measures of central tendency (mean, standard deviation (SD), range, median, interquartile range (IQR)).

17.3. Presentation of data for treatment adherence

Tables mentioned within this section will be presented overall and split by treatment.

Frequency tables (with percentages) will be presented for:

- Reasons for PICC removal
- The number of babies whose PICC was removed less than 24 hours after randomisation
- The number of babies receiving the allocated PICC
- The number of babies receiving a non-allocated PICC
- The number of babies randomised but did not receive any PICC
- The type of sample and whether an e-test was performed for positive cultures
- Length of time PICC is in situ for (from insertion to removal).

17.4. Analysis of outcomes

17.4.1. Primary Outcome

The primary efficacy outcome is time to BSI based on any positive blood/CSF culture (including fungal isolates) taken between 24 hours after randomisation until 48 hours after PICC removal.

17.4.1.1. Derivation

The date and time that a sample was taken is recorded on CRF "Form 5: Microbiology". The samples included for the primary outcome are those taken between 24 hours after randomisation until 48 hours after PICC removal. The date and time of randomisation can be

found on CRF "Form 2: Randomisation". The date and time of PICC removal can be found on CRF "Form 6: Removal". The unit of measurement will be hours.

BSI is defined as any positive culture recorded on CRF "Form 5: Microbiology" for the field "organism cultured" (any culture except an entry of 'none') from blood or CSF samples. Any 'other' recorded organism will be referred to the clinical team for confirmation of whether this is a positive culture. Organisms grown from 'other' sample types will also be referred to the clinical team for confirmation of whether this constitutes the primary outcome.
All decisions made by the clinical team, will be made blinded to treatment allocation.

If there is a positive culture prior to the primary outcome time window and a positive culture in the primary outcome time window:

- If the second positive culture is from the same isolate as the first and:
    - there were less than 14 days between the two samples they should be classified as the same episode of BSI and the positive culture within the primary outcome time window will not be counted.
    - there were 14 days of more between the two samples they should be classified as two independent episodes of BSI and the positive culture within the primary outcome time window will be counted.
- If the second positive culture is from a different isolate to the first and:
    - there were less than 24 hours between the two samples they should be classified as the same episode of BSI and the positive culture within the primary outcome time window will not be counted.
    - there were 24 hours or more between the two samples they should be classified as two independent episodes of BSI and the positive culture within the primary outcome time window will be counted.

If there are multiple positive cultures within the primary outcome time window, each positive culture will be assessed using the criteria above and the first one that meets the definition will be counted.

Survival times will be measured from the date and time of randomisation to the date and time of the first sample, that meets the definition of independent episode of BSI outlined above. For those not experiencing the primary outcome, they will be censored at death (date and time found on Form 7a: Clinical Outcomes under section 1 question 3), 48 hours after PICC removal or for those with no PICC inserted, 48 hours after randomisation. All censoring will be assumed to be non-informative.

17.4.1.2. Analysis

The following will be reported overall and split by sample type and treatment:

- Number of babies with sample taken in primary outcome time window (24 hours after randomisation and up to 48 hours after PICC removal)
- Number of samples taken in primary outcome time window
- Number of babies with BSI in the POTW

This is a time to event outcome and will be analysed using the log-rank test and Kaplan-Meier curves presented with the numbers at risk for each treatment group. The median and interquartile range for time to BSI will be presented.

Cox proportional hazard regression models will be used if appropriate. However, since the hazard of infection may not be constant post CVC insertion, non-proportional hazards survival models will also be investigated. Results will be presented using Hazard Ratios and 95% confidence intervals, along with the log-rank p-value.

Differences between date and time of randomisation and date and time of insertion will be summarised using medians and IQR.

17.4.2. Secondary Outcomes

For outcomes which require samples to be taken, events are only considered on samples taken between 24 hours after randomisation until 48 hours after PICC removal. This time period is referred to as the "primary outcome time window".

17.5.1. Rifampicin resistance in any isolate from blood/CSF culture

17.5.1.1. Derivation

This is a binary outcome of 'Yes/No' for each baby. Rifampicin resistance can be found on CRF "Form 5: Microbiology". Isolates from blood/CSF culture can be found under "Sample Type" as any sample type except 'PICC tip'. Isolates from 'other' sample types will be referred to the clinical team for confirmation of whether they should be included in analysis of this outcome.

For rifampicin resistance to be tested, "organism cultured" must be anything except zero, and the E-test must be selected as being performed. If the Rifampicin minimum inhibitory concentration value is >0.5 mg/L then the sample is classed as being resistant to rifampicin. If a baby has any sample which is rifampicin resistant, then this will be classed as "yes" for that baby.

UK Standards for Microbiology Investigations[7] details which organisms are classed as Gram-negative and Gram-positive. The organisms cultured will be classified based on this.

17.5.1.2. Analysis

The analysis will use the method of Fisher's exact test to compare proportions of babies with rifampicin resistance in the standard group compared to the impregnated group and relative risks will be presented with 95% confidence intervals.

Frequency tables will be presented overall and split by treatment and gram negative/gram positive samples.

Line listings of Rifampicin resistant isolates will be presented showing treatment and organism cultured.

17.5.2. Rifampicin resistance in any isolate from PICC tips

17.5.2.1. Derivation

This is a binary outcome of 'Yes/No'. The definition of rifampicin resistance can be found in section 17.5.1.1. Isolates from PICC tips can be found under "Sample Type" as type 3 (PICC tip). If a baby has a PICC tip sample which is rifampicin resistant, then this will be classed as "yes" for that baby.

UK Standards for Microbiology Investigations[7] details which organisms are classed as Gram-negative and Gram-positive. The organisms cultured will be classified based on this.

17.5.2.2. Analysis

The analysis will use the method of Fisher's exact test to compare proportions of babies with rifampicin resistant PICC tips in the standard group compared to the impregnated group and relative risks will be presented with 95% confidence intervals.

Frequency tables will be presented overall and split by treatment and gram negative/gram positive samples.

Line listings of Rifampicin resistant isolates will be presented showing treatment and organism cultured.

17.5.3. Type of organism isolated from BSI

17.5.3.1. Derivation

BSI is defined as in section 17.4.1.1. If there are multiple positive cultures within the primary outcome time window, each positive culture will be assessed using the criteria in section 17.4.1.1 and the following (comparing positive cultures within the POTW as well as comparing to positive cultures prior to POTW):

- If the second positive culture is from the same isolate as the first and
    - there were less than 14 days between the two samples they should be classified as the same episode of BSI.
    - there were 14 days of more between the two samples they should be classified as two independent episodes of BSI.
- If the second positive culture is from a different isolate to the first and
    - there were less than 24 hours between the two samples they should be classified as the same episode of BSI.
    - there were 24 hours or more between the two samples they should be classified as two independent episodes of BSI.

The type of organism can be found on CRF "Form 5: Microbiology" under "Organism cultured". Where a sample grows 3 or more different organisms, it is recorded as mixed growth rather than as the individual organisms.

17.5.3.2. Analysis

This data will be presented descriptively with frequency tables split by treatment arm. No formal statistical analysis will be undertaken.

17.5.4. Rate of BSI per 1000 PICC-days (including recurrent BSI)

17.5.4.1. Derivation

BSI is as defined in section 17.4.1.1. Where there are multiple positive cultures in the POTW, independent episodes of BSI will be classified as in section 17.5.3.1. The total number of independent episodes of BSI that occur when the line is in situ during the POTW should be calculated for each baby and then summed to find the total number of BSI in each treatment arm.

The number of days that the PICC is in situ for during the POTW can be calculated by subtracting the date and time of the start of the POTW (Date and time of randomisation + 24 hours) from the date and time of PICC removal (or date and time of death if the baby died with the line in situ). The date and time of PICC removal can be found on CRF "Form 6: Removal" under section 1. The number of days should be summed to find the total number of days that the PICC is in situ for during the POTW in each arm. For babies that did not have a line inserted, this will be zero.

The rate of BSI per 1000 PICC-days is calculated as:

$$\frac{Total\ number\ of\ independent\ episodes\ of\ BSI\ that\ occur\ when\ line\ is\ in\ situ\ during\ POTW, across\ treatment\ arm}{Total\ number\ of\ days\ PICC\ is\ in\ situ\ for\ during\ the\ POTW\ (across\ treatment\ arm)} \times 1000$$

17.5.4.2. Analysis

For this outcome the rate ratio and 95% confidence intervals will be presented based on Poisson regression.

17.5.5. Occurrence of 1 or more BSI

17.5.5.1. Derivation

BSI is as defined in section 17.4.1.1. Where there are multiple positive cultures in the POTW, independent episodes of BSI will be classified as in section 17.5.3.1. If a baby has one or more independent episodes of BSI within the POTW then this is classed as 'Yes'.

17.5.5.2. Analysis

The analysis will use the method of Fisher's exact test to compare proportions in the standard group compared to the impregnated group and relative risks will be presented with 95% confidence intervals.

17.5.6. Rate of catheter-related BSI per 1000 PICC days

17.5.6.1. Derivation

Catheter-related BSI is defined as "Yes" if the same organism is grown on the PICC-tip and blood/CSF sample. This information can found on CRF "Form 5: Microbiology" under "organism cultured". The total number of independent episodes of catheter-related BSI that occur when the line is in situ during the POTW should be calculated for each baby and then summed to find the total number of catheter-related BSI in each treatment arm. Where a baby has multiple positive cultures within the primary outcome time window they will be classified as single/multiple episodes of independent catheter-related BSI as in section 17.5.3.1.

The total number of days the PICC is in situ for during the POTW will be calculated using the derivation in section 17.5.4.1.
The rate of BSI per 1000 PICC-days is calculated as:

$$\frac{Total\ number\ of\ independent\ episodes\ of\ CR\ BSI\ that\ occur\ when\ line\ is\ in\ situ\ during\ POTW, across\ treatment\ arm}{Total\ number\ of\ days\ PICC\ is\ in\ situ\ for\ during\ the\ POTW\ across\ treatment\ arm} \times 1000$$

17.5.6.2. Analysis

For this outcome the rate ratio and 95% confidence intervals will be presented based on Poisson regression.

17.5.7. Rate of blood/CSF culture sampling per 1000 PICC days

17.5.7.1. Derivation

Each blood/CSF culture sample can be found on CRF "Form 5: Microbiology". The total number of these samples taken when the line is in situ during the primary outcome time window should be summed across each treatment arm.

Details on calculating the total number of days PICC is in situ for during the primary outcome time window can be found in section 17.5.4.1.

The rate of BSI per 1000 PICC-days is calculated as:

$$\frac{Total\ number\ of blood\ or\ CSF\ samples\ taken\ when\ the\ line\ is\ \ in\ situ\ during\ the\ POTW, across\ treatment\ arm}{Total\ number\ of\ days\ PICC\ is\ in\ situ\ for\ during\ the\ POTW\ across\ treatment\ arm} \times 1000$$

17.5.7.2. Analysis

For this outcome the rate ratio and 95% confidence intervals will be presented based on Poisson regression.

17.5.8. Duration of antimicrobial exposure from randomisation up to 48 hours after line removal

17.5.8.1. Derivation

This can be found on CRF "Form 4: Daily follow-up". If "Yes" is selected for either "Were IV antibiotics given?" or "Were IV or enteral antifungals given?" **and** "Prophylaxis" was **not** selected for "If yes, were antifungals used for the following?", then the baby has antimicrobial exposure for that day. The total number of days should be summed for each baby.

17.5.8.2. Analysis

The analysis will use the method of the two sample t test or Mann Whitney U test depending on the distribution of the data. Means will be presented with 95% confidence intervals or medians and interquartile range as appropriate.

17.5.9. Time to PICC removal

17.5.9.1. Derivation

The date of PICC removal is captured on CRF "Form 6: Removal". The date of randomisation is recorded on CRF "Form 2: Randomisation". The amount of days between randomisation and PICC removal can be calculated from this. Babies whose parents have withdrawn consent for the baby to continue in the trial will be censored at the date of last observation if the PICC is still in situ. Babies who die with the PICC in situ will be censored at date of death.

17.5.9.2. Analysis

The survival analysis will use the method of the Log rank test and Cox proportional hazard regression models if appropriate. Results will be presented using Hazard Ratios and 95% confidence intervals. Kaplan-Meier curves stratified by treatment will be presented. Survival times will be measured from the date of randomisation to the date of PICC removal.

17.5.10. Chronic lung disease 36 weeks postmenstrual age

17.5.10.1. Derivation

This is a binary outcome with a "Yes/No" response and can be found on CRF "Form 7a: Clinical Outcomes" under section 6 for the question "Bronchopulmonary dysplasia". It should be noted that Form 7a is completed each time a baby is transferred and so there may be more than one "Form 7a" for each baby. If "Yes" is selected on any completed 'Form 7a' then the outcome is "Yes" for that baby, if "No" is selected on all forms then the outcome is "No".

17.5.10.2. Analysis

The analysis will use the method of Fisher's exact test to compare proportions in the standard group compared to the impregnated group and relative risks will be presented with 95% confidence intervals.

17.5.11. Necrotizing enterocolitis (NEC): Bell's stage II or III

17.5.11.1. Derivation

This is a binary outcome with a "Yes/No" response and can be found on CRF "Form 7a: Clinical Outcomes" under Section 5. It should be noted that Form 7a is completed each time a baby is transferred and so there may be more than one "Form 7a" for each baby. If "Yes" is selected on any completed 'Form 7a' then the outcome is "Yes" for that baby, if "No" is selected on all forms then the outcome is "No".

17.5.11.2. Analysis

The analysis will use the method of Fisher's exact test to compare proportions in the standard group compared to the impregnated group and relative risks will be presented with 95% confidence intervals.

17.5.12. Treatment for retinopathy of prematurity

17.5.12.1. Any treatment given

17.5.12.1.1 Derivation

This is a binary outcome with a "Yes/No" response and can be found on CRF "Form 7a: Clinical Outcomes" under section 6. It should be noted that Form 7a is completed each time a baby is transferred and so there may be more than one "Form 7a" for each baby. If "Yes" is selected

on any completed 'Form 7a' then the outcome is "Yes" for that baby, if "No" is selected on all forms then the outcome is "No".

17.5.12.1.2 Analysis

The analysis will use the method of Fisher's exact test to compare proportions in the standard group compared to the impregnated group and relative risks will be presented with 95% confidence intervals.

17.5.12.2. Type of treatment given

17.5.12.2.1 Derivation

If "Yes" is selected for the question "Retinopathy of prematurity treatment medically or surgically" then the type of treatment is given as either "Laser", "Cryotherapy" or "Injection".

17.5.12.2.2 Analysis

This data will be presented descriptively with frequency tables split by treatment arm. No formal statistical analysis will be undertaken.

17.5.13. Abnormalities on cranial ultrasound

17.5.13.1. Derivation

This is a binary outcome with a "Yes/No" response based on the following two clinical outcomes:

- Periventricular leukomalacia
- Intracranial haemorrhage detected on head ultrasound

Each of these can be answered with a "Yes/No" response and can be found on CRF "Form 7a: Clinical Outcomes" under section 6 for the questions 3/4/4a. It should be noted that Form 7a is completed each time a baby is transferred and so there may be more than one "Form 7a" for each baby. If "Yes" is selected on any completed 'Form 7a' then the outcome is "Yes" for that baby, if "No" is selected on all forms then the outcome is "No". Where babies experience intracranial haemorrhage, the worst grade that is observed will also be reported.

17.5.13.2. Analysis

The analysis will use the method of Fisher's exact test to compare proportions in the standard group compared to the impregnated group and relative risks will be presented with 95%

confidence intervals. No testing will be conducted in relation to the grade of IVH that was experienced.

17.5.14. Time to full milk feeds after randomisation

17.5.14.1. Derivation

Whether a baby reached full milk feeds is captured on CRF "Form 7a: Clinical Outcomes". The date that the baby first reached full milk feed is recorded alongside this. The date of randomisation is recorded on CRF "Form 2: Randomisation". The amount of days between randomisation and full milk feeds can be calculated from this. It should be noted that Form 7a is completed each time a baby is transferred and so there may be more than one "Form 7a" for each baby. If there are multiple dates for the baby reaching full milk feeds on the different forms, the first date will be used.

17.5.14.2. Analysis

The survival analysis will use the method of the Log rank test and Cox proportional hazard regression models if appropriate. Results will be presented using Hazard Ratios and 95% confidence intervals. Kaplan-Meier curves stratified by treatment will be presented. Survival times will be measured from the date of randomisation to the date of full milk feeds.

If a baby has already reached full milk feeds at randomisation then they will be excluded from this outcome. If a baby does not reach full milk feeds then they will be censored at the last observation recorded.

17.5.15. Total duration of parenteral nutrition from randomisation until discharge from NNU

17.5.15.1. Derivation

The total number of calendar days of parenteral nutrition can be found on CRF "Form 7a: Clinical Outcomes" under section 7. As each baby may have more than one 'Form 7a' completed, the overall total number of days should be summed across all 'Form 7a's returned. Sites should only be recording the amount of days on full milk feeds **at that hospital**. A check will be performed to ensure that the number of days on full milk feeds does not exceed the number of days spent at that hospital.

17.5.15.2. Analysis

The analysis will use the method of the two sample t test or Mann Whitney U test depending on the distribution of the data. Means will be presented with 95% confidence intervals or medians and interquartile range as appropriate.

The proportion of days in the primary outcome time window spent on parenteral nutrition will be reported.

17.5.16. Death

17.5.16.1. Within 6 months (26 weeks) of randomisation

17.5.16.1.1 Derivation

If a baby has died within 26 weeks of randomisation and before discharge, see section 17.5.16.2.1 for details on where this information is captured. For the babies who are alive at discharge home from neonatal care, PDS data will be used to determine the baby's status at 26 weeks.

17.5.16.1.2 Analysis

The analysis will use the method of Fisher's exact test to compare proportions in the standard group compared to the impregnated group and relative risks will be presented with 95% confidence intervals. This will be presented in two ways:

- Using CRF data only
- Using CRF and PDS data combined once available.

17.5.16.2. Before discharge home from neonatal care

17.5.16.2.1 Derivation

This is a binary outcome with a "Yes/No" response. Whether a baby has died can be found on CRF "Form 7a: Clinical Outcomes" under section 1. It should be noted that Form 7a is completed each time a baby is transferred and so there may be more than one "Form 7a" for each baby. If "Yes" is selected on any completed 'Form 7a' then the outcome is "Yes" for that baby, if "No" is selected on all forms then the outcome is "No".

17.5.16.2.2 Analysis

The analysis will use the method of Fisher's exact test to compare proportions in the standard group compared to the impregnated group and relative risks will be presented with 95% confidence intervals.

17.5.16.3. Time to death

17.5.16.3.1 Derivation

If a baby has died within 26 weeks of randomisation and before discharge, see section 17.5.16.2.1 for details on where this information is captured. There will be an initial analysis performed on this dataset. For the babies who are alive at discharge home from neonatal care, PDS data will be used to determine the baby's status at 26 weeks and the initial analysis will be updated to take into account this information.

17.5.16.3.2 Analysis

The survival analysis will use the method of the Log rank test and Cox proportional hazard regression models if appropriate. Results will be presented using Hazard Ratios and 95% confidence intervals. Kaplan-Meier curves stratified by treatment will be presented. Survival times will be measured from the date of randomisation to the date of death. This will be presented in two ways:

- Using CRF data only
- Using CRF and PDS data combined once available.

18. Missing data and withdrawals

The numbers (with reasons) of losses to follow-up and withdrawals over the course of the trial will be summarised by treatment arm. This will be presented in a CONSORT diagram alongside a table detailing numbers and reasons for withdrawal and/or exclusion from analysis.

The primary outcome is time to event so even if babies are withdrawn or lost to follow up, they will still contribute to the primary analysis up to the point of withdrawal or lost to follow up provided that parents do not remove consent to use data that has been collected up to that point. Where dates are known but times are missing, times will be imputed as 12:00. The number of babies where imputation is used will be reported.

19. Additional analyses

19.1 Sensitivity analyses: Primary outcome

Four sensitivity analyses will be undertaken on the primary outcome.

19.1.1. Time to first clinically serious BSI

Time to first clinically serious BSI where clinically serious BSI is defined by a BSI as defined in section 17.4.1.1 and the baby is treated for more than 72 hours or more of antimicrobials (found on Form 5: Microbiology) or dies during treatment (determined from date and time of death captured on Form 7a: Clinical Outcomes). The analysis will be the same as in section 17.4.1.2.

Note: it was identified during blind review that the definition of this sensitivity analysis in the protocol and previous versions of this SAP did not capture all cases of clinically serious BSI as antibiotics are only used to treat bacterial infections, whereas BSI includes bacterial and fungal infections.

19.1.2. Time to first BSI from insertion

Time to first BSI where BSI is defined as in section 17.4.1.1 but survival times will be calculated from date and time of insertion rather than date and time of randomisation. The analysis will be the same as in section 17.4.1.2. Babies with no line inserted will be excluded.

19.1.3. Time to first BSI excluding arterial or CVC samples

Time to first BSI where BSI is defined as in section 17.4.1.1 but excluding arterial or CVC samples. The analysis will be the same as in section 17.4.1.2.

19.1.4. Time to first BSI only including "clearly pathogenic organisms"

Time to first BSI where BSI is defined as in section 17.4.1.1 but only including "clearly pathogenic organisms" (as defined in Section 23.2 Appendix II) as positive cultures.

19.2 Sensitivity analyses: Secondary outcomes

Sensitivity analyses will be undertaken to complement some of the secondary outcomes to test the robustness of the results drawn from the main analyses.

19.2.1. Rate of BSI per 1000 PICC-days over total time that the line is in situ

Rate of BSI per 1000 PICC-days (including recurrent BSI) using the total number of independent episodes of BSI that occur when the line is in situ and the total number of days that the line is in situ. The analysis will be the same as in section 17.5.4.2. A table will be presented showing the timings of BSIs.

19.2.2. Rate of catheter-related BSI per 1000 PICC-days over total time that the line is in situ

Rate of catheter-related BSI per 1000 PICC using the total number of independent episodes of catheter related BSI that occur when the line is in situ and the total number of days that the line is in situ. The analysis will be the same as in section 17.5.6.2.

19.2.3. Rate of blood/CSF culture sampling per 1000 PICC-days over total time that the line is in situ

Rate of blood/CSF culture sampling per 1000 PICC days using the total number of blood/CSF samples taken when the line is in situ and the total number of days that the line is in situ. The analysis will be the same as in section 17.5.7.2.

19.2.4. Type of organism grown (clinically serious BSI)

The definition of clinically serious BSI can be found in section 19.1.1. The analysis will be the same as in section 17.5.3.2.

19.2.5. Type of organism grown (from BSI excluding arterial or CVC samples)

The definition of BSI excluding arterial or CVC samples can be found in section 19.1.3. The analysis will be the same as in section 17.5.3.2.

19.2.6. Type of organism grown (from BSI only including "clearly pathogenic organisms")

The definition of BSI only including "clearly pathogenic organisms" can be found in section 19.1.4. The analysis will be the same as in section 17.5.3.2.

19.3 Additional secondary analyses

In addition to the secondary outcomes for Rifampicin resistance listed in sections 17.5.1 and 17.5.2, Rifampicin resistance in any isolate from blood/CSF cultures or PICC tips will be presented. This outcome is not pre-specified within the protocol but has been requested by the chief investigators prior to them seeing any unblinded data.

This is a binary outcome of 'Yes/No' for each baby. Rifampicin resistance can be found on CRF "Form 5: Microbiology". For rifampicin resistance to be tested, "organism cultured" must be anything except zero, and the E-test must be selected as being performed. If the Rifampicin minimum inhibitory concentration value is >0.5 mg/L then the sample is classed as being resistant to rifampicin. If a baby has any blood/CSF or PICC tip sample which is rifampicin resistant, then this will be classed as "yes" for that baby.

The analysis will use the method of Fisher's exact test to compare proportions of babies with rifampicin resistant samples in the standard group compared to the impregnated group and relative risks will be presented with 95% confidence intervals.

20. Safety Evaluations

20.1. Data sets analysed

Adverse events will be summarised descriptively with babies analysed according to the treatment they received.

All babies who either had a PICC inserted or had an attempted insertion will be included within the safety analysis population. Babies that had a PICC inserted will be analysed according to the treatment they received. If a baby had an attempted insertion but did not have a PICC successfully inserted then as it is not captured which PICC was attempted, the baby will be analysed according to the treatment group they were randomised to.

20.2. Presentation of the data

Adverse events (AEs) and serious adverse events (SAEs) reported by the clinical investigator and are classified as "possibly", "probably" or "almost certainly" related to the study treatment will be presented by treatment group. The number (and percentage) of babies experiencing

each AE/SAE will be presented for each treatment arm categorised by severity. For each baby, only the maximum severity experienced of each type of AE will be displayed. The number (and percentage) of occurrences of each AE/SAE will also be presented for each treatment arm. No formal statistical testing will be undertaken.

Adverse events will be categorised according to severity as "Mild", "Moderate", or "Severe". They will also be classified in relation to the causality with the treatment as "Possibly", "Probably", or "Almost certainly". Full details on the definition and classification of these adverse events are presented in section 10 of the protocol.

21. Quality Control

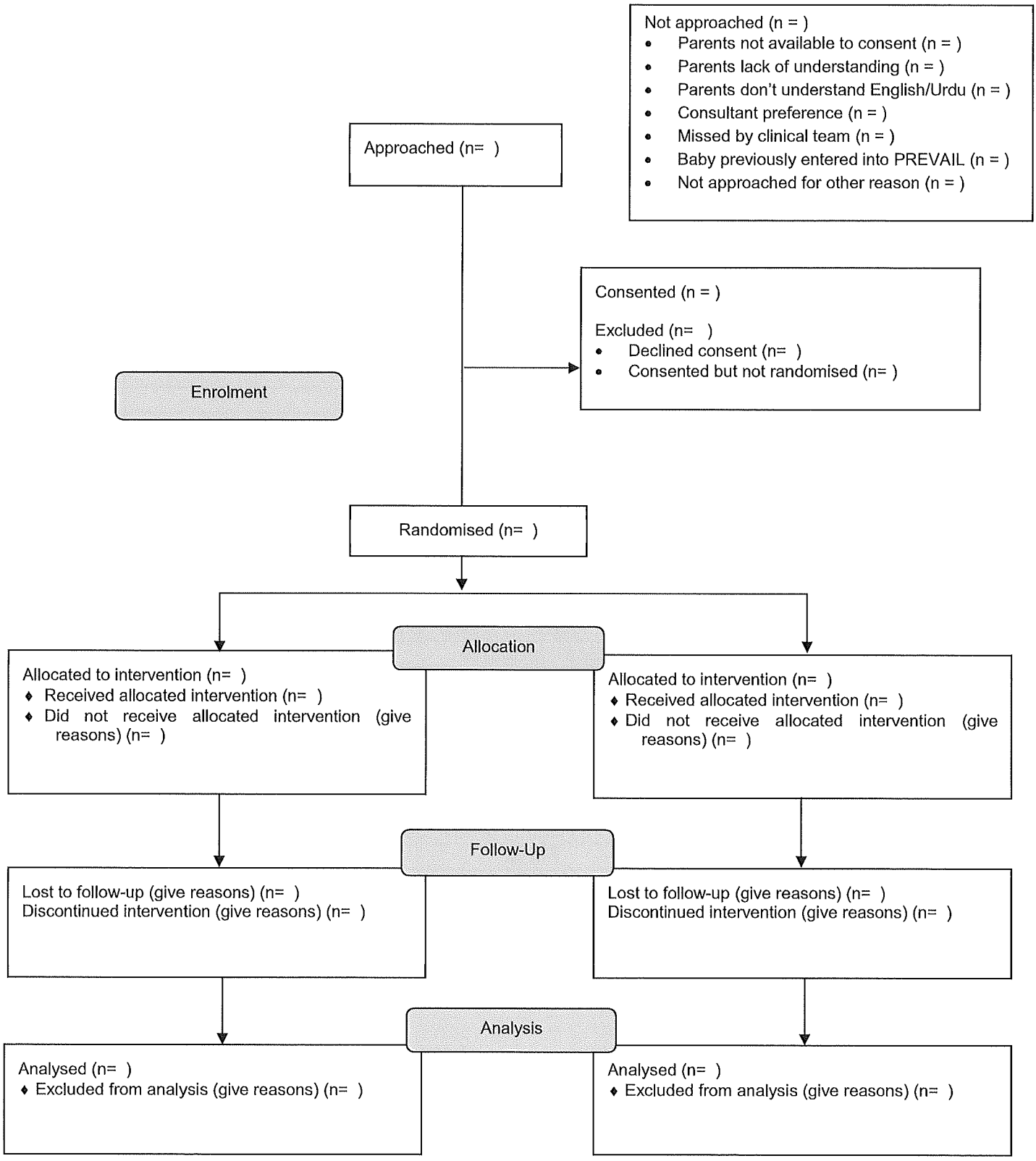
To ensure quality control, an independent statistician will follow this SAP to independently program the primary analysis from the raw data. Any discrepancies found will be discussed with the trial statistician to resolve. No programming will be shared or shown between the statisticians. The independent statistician will also check the report against their output obtained from the statistical software.

22. References

1. International Conference on Harmonisation. Topic E9 Statistical Principles for Clinical Trials (CPMP/ICH/363/96). 1998.
2. Guidance on Statistical Analysis Plans.
3. Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332..
4. *Shuster JJ: Diagnostics for assumptions in moderate to large simple clinical trials: do they really help? Stat Med 2005, 24(16):2431–2438.*
5. *Campbell H, Dean CB. The consequences of proportional hazards based model selection. Statistics in Medicine. 2013*
6. *Raab GM, Day S, Sales J: How to select covariates to include in the analysis of a clinical trial. Control Clin Trials 2000, 21(4):330–342.*
7. *UK Standard for Microbiology Investigations: Introduction to the Preliminary Identification of Medically Important Bacteria. Bacteriology – Identification, ID 1, Issue no: 1.6, Issue date: 12.03.2014, p14-17*

23. Appendices

23.1. Appendix I



23.2. Appendix II

Organisms coded on Form 5: Microbiology will be classified as follows:

Organism	Pathogen group
Coagulase-negative staphylococcus	Potential pathogen or likely contaminant
Staph aureus	Clearly pathogenic organism
Klebsiella spp.	Clearly pathogenic organism
Enterobacter spp.	Clearly pathogenic organism
Pseudomonas aeruginosa	Clearly pathogenic organism
Acinetobacter spp.	Clearly pathogenic organism
E.coli	Clearly pathogenic organism
Enterococcus spp.	Clearly pathogenic organism
Candida Albicans	Clearly pathogenic organism
Non candida albicans species	Clearly pathogenic organism

Organisms coded as 'Other' will be referred to the clinical team for confirmation. Classifications will be made as follows but as the 'Other' organisms will be written in free text clinical interpretation is required.

Organism	Pathogen group
Gram Positive	
Group B Streptococci	Clearly pathogenic organism
Streptococcus (other)	Potential pathogen or likely contaminant
Micrococcus sp.	Potential pathogen or likely contaminant
Bacillus sp.	Clearly pathogenic organism
Diphtheroids	Potential pathogen or likely contaminant
Streptococcus pneumoniae	Clearly pathogenic organism
Propionibacterium acnes	Potential pathogen or likely contaminant
Listeria monocytogenes	Clearly pathogenic organism
Other Gram Positive	Need to review name of isolated species
Gram Negative	
Pseudomonas sp.	Clearly pathogenic organism
Serratia sp.	Clearly pathogenic organism
Coliform	Clearly pathogenic organism
Citrobacter sp.	Clearly pathogenic organism
Burkholderia sp.	Clearly pathogenic organism
Haemophilus sp.	Clearly pathogenic organism
Other Gram negative	Need to review name of isolated species
Fungi	
Candida (other)	Clearly pathogenic organism
Other Fungi	Clearly pathogenic organism
Other fungal organism	Clearly pathogenic organism