PREVenting infection using Antimicrobial Impregnated Long lines

Protocol

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Trial Sponsor(s):
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CTRC
Clinical Trials Research Centre

NHS
National Institute for Health Research

Protocol Approval

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General Information

This document describes the PREVAIL trial and provides information about procedures for entering participants into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but sites entering participants for the first time are advised to contact the coordinating centre Medicines for Children Clinical Trials Unit (MC CTU) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator via the MC CTU.

This protocol defines the participant characteristics required for trial entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements and waivers to authorise non-compliance are not permitted. Incidence of protocol non-compliance, whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

Statement of Compliance

This trial will be 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, CTRC Standard Operating Procedures 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 as amended.

Relationship Statements

The UK Clinical Research Collaboration (UKCRC; www.ukcrc.org) is a partnership organisation working to establish the UK as a world leader in clinical research. Following a review by an international panel, the Clinical Trials Research Centre (CTRC) at the University of Liverpool has been assessed as reaching the highest quality standard required by the UKCRC and achieved full UKCRC registration.

The CTRC encompasses clinical trials activity in areas including MC CTU), cancer (The Liverpool Cancer Trials Unit; LCTU), epilepsy, oral health and obstetrics and gynecology (http://www.ctrc.org.uk/). All CTRC activities are underpinned by methodological rigour, a modern data management system, similar technical requirements and a common set of standard operating procedures.

The NIHR Clinical Research Network Children and National Cancer Research Network is part of the National Institute for Health Research Clinical Research Network.

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The contact details of other individuals involved in the trial are detailed in the Trial Oversight Committee Membership document.

Table of Contents

Glossary

AM-PICC	Antimicrobial Impregnated coated Peripherally Inserted Central Catheter
AE	Adverse Event
AI	Adverse Incident
AIC	Adverse Incident Centre
CCS	Continuing Care Site
CE	French phrase "Conformité Européene" which literally means "European Conformity". The symbol CE is used by manufacturers to show that a medical device meets the relevant requirements of the regulations and that it is fit for its intended purpose.
CFU	Colony Forming Units
CHE	Centre for Health Economics - University of York
CI	Chief Investigator
CPA	Clinical Pathology Accreditation
CRF	Case Report Form
CTRC	Clinical Trials Research Centre
FR	French Gauge
GP	General Practitioner
HES	Hospital Episodes Statistics
HTA	Health Technology Assessment
ICH GCP	International Conference on Harmonisation Good Clinical Practice
IDSMC	Independent Data and Safety and Monitoring Committee
IMP	Investigational Medicinal Product
Kg	Kilograms
MHRA	Medicines and Healthcare products Regulatory Agency
NEC	Necrotising Enterocolitis
NRES	National Research Ethics Service
ONS	Office of National Statistics
PI	Principal Investigator
PICC	Peripherally Inserted Central Catheter
PREVAIL	Trial Title: PREVenting infection using Antimicrobial Impregnated Long lines – long lines will be referred to as PICCs throughout the protocol
MC CTU	Medicines for Children Clinical Trials Unit
MHRA	Medicines and Healthcare products Regulatory Agency
NNU	Neonatal Unit
NNRD	National Neonatal Research Database
R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RN	Research Nurse – although the protocol refers to a RN it may be anyone who has been delegated the relevant duties on the delegation log.
S-PICC	Standard Peripherally Inserted Central Catheter
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee

1 PROTOCOL SUMMARY

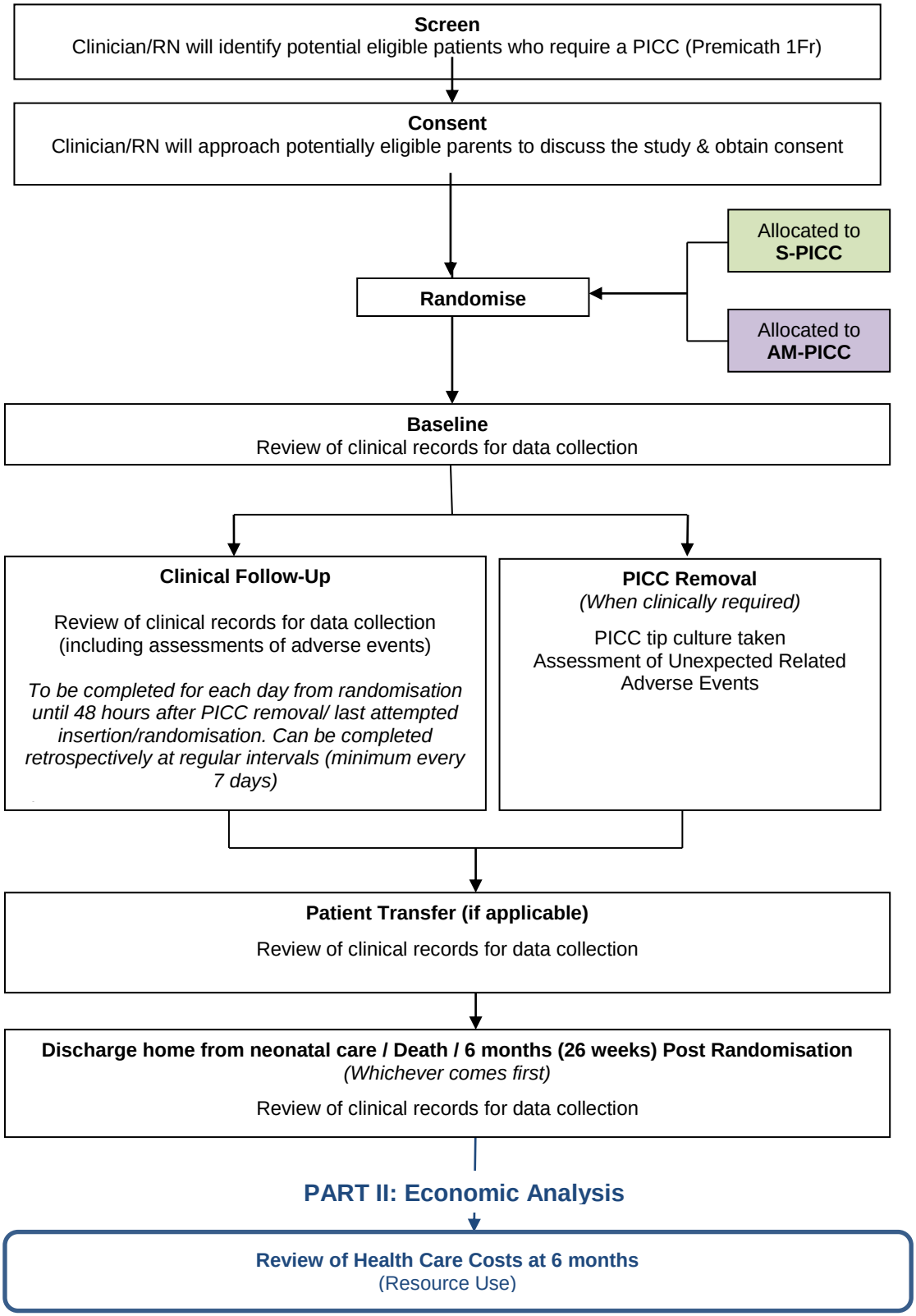
Title:	**PREVAIL: PREVenting infection using Antimicrobial Impregnated Long lines**
Full Title:	An unblinded, 2-arm randomised controlled trial to determine the effectiveness and cost effectiveness of antimicrobial impregnated (with rifampicin and miconazole) long lines (termed peripherally inserted central venous catheters, or AM- PICC (AM-PICC)) compared with standard PICC (S-PICC) for reducing blood stream infection (BSI).
Part I:	**Randomised controlled trial**
Phase:	III
Population:	The trial population aims to include 858 babies who require the narrowest PICC (Premicath 1 French gauge (Fr)). Premicaths are designed for babies <1kg and most participants will be very preterm (born at <32 weeks of gestation). A PICC is usually inserted after the first 2 days of age to administer fluids, medicines and nutrition.
Trial Sites and Distribution:	The trial will take place in 18 Neonatal Units (NNUs) in England.
Trial Duration **Recruitment:** **Follow up:**	2 years. Participant follow-up to ascertain the primary outcome (BSI): • 48 hours after removal of the randomised PICC or; • 48 hours after attempted insertion of randomised PICC Participant follow-up to ascertain secondary outcomes: • Until discharge from NNU or; • Death or; • 6 months (26 weeks) post randomisation (whichever is sooner). Data will be based on routinely recorded clinical data collated by the Research Nurse (RN). For long-term participant follow-up please refer to part II.

Description of Agent/ Intervention:	We will use a web-based interface to randomly allocate new born babies to S-PICC or AM-PICC). All PICCs used in the trial are CE marked medical devices used for their intended purpose. AM-PICCs can be distinguished from S-PICCs as rifampicin causes brown staining on the tubing. Hence, this is an unblinded trial.
Primary Outcomes:	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.
Secondary Outcomes:	Secondary outcomes include: i) outcomes recorded during randomised PICC insertion: type of organisms isolated from BSI; evidence of rifampicin resistance in isolates from blood or PICC tips; other measures of BSI (rate of BSI per 1000 PICC days, rate of PICC related BSI per 1000 PICC days, occurrence of 1 or more BSI); rate of blood/CSF culture sampling per 1000 PICC days, duration of antimicrobial exposure; time to PICC removal ii) clinical outcomes recorded at discharge home from neonatal care: necrotising enterocolitis, chronic lung disease, retinopathy of prematurity, cranial ultrasound abnormalities, duration of parenteral nutrition, time to full milk feeds, death before discharge and within 6 months (26 weeks) of randomisation, time to death.
Part II	**Economic analysis**
Aim	To determine the cost-effectiveness of AM-PICC vs S-PICC to the NHS.
Objectives	To evaluate: i) The direct hospital costs of using AM-PICC compared with S-PICC up to 6 months from randomisation. ii) The cost-effectiveness of AM-PICC compared with S-PICC over the participants' expected lifetime from the perspective of the NHS. iii) The potential value of additional research to reduce any uncertainty observed in the cost-effectiveness model. This will be used to inform decisions about long-term follow up of the trial cohort. iv) The value of implementing the cost-effective intervention (AM-PICC vs S-PICC) throughout the NHS in England and Wales.

v) The costs of a BSI to the NHS.

Trial Duration: Long term follow-up of participants from part I will be until 6 months after randomisation and will be ascertained from linked electronic records.

1.1 Schematic of Trial Design



2 BACKGROUND INFORMATION

2.1 Introduction

Review of the literature and rationale for the trial:

Preterm delivery is a major public health problem with around 8% of babies born prematurely, and 1.4% born very preterm (less than 32 weeks gestation) (1). Infant mortality is reported to be 144/1000 live births for infants born very preterm, compared to 1.8/1000 for those born at 38 to 41 weeks (1). Long term neurological, cognitive and attentional impairments are common and occur more frequently for very preterm births (2). These infants also face a high risk of serious neurological impairment, for example, 25% of babies born at less than 27 weeks in 2006 in England had detectable severe or moderate impairment at 3 years of age (3). Nationwide, 10% of all babies are admitted to NNU (68,000 per year in England) and around 6% of these develop one or more BSI (4). Compared with babies born at 37 weeks or more of gestation, babies born before 28 weeks have 1.6 to 2.7 times the rate of BSI, reflecting their greater immune immaturity, included immature skin and their need for more intensive care with invasive devices and intravenous feeding using parenteral nutrition (5). Very preterm babies account for a minority of admissions to NNU (10%-15% are <32 weeks of gestation) but around half of NNU care days (53%) and babies experiencing any BSI (58%) (6-8).

Based on an unpublished audit of 5 NNUs for this trial, we estimate that 8.4% of babies admitted to NNU would be born at less than 32 weeks of gestation and will require a Premicath PICC. 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. These lines can stay in place for several weeks, avoiding the need for repeated procedures, which can be harmful and distressing for small babies.

The disadvantage of a PICC is the increased risk of BSI. Bacteria or fungi stick onto the inside or around the tube and multiply. In babies with immature immunity, infection spreads via the blood stream, causing sepsis and infecting other organs. Treatment requires intravenous antibiotics for at least 5 days and sometimes antifungals are required. BSIs occur in 5-20% of babies born before 32 weeks of gestation (unpublished data from audit of 5 NNUs), mostly in association with central venous catheters. The consequences can be serious and include death, increased duration of intensive care, and in the longer term, permanent neurological impairment, even when BSI is due to less pathogenic skin organisms (9). Although intensive antibiotic treatment for BSI may be lifesaving, it also carries risks. Intensive antibiotic treatment alters the microbial ecology of the gut, which may increase the risk of necrotising enterocolitis (NEC) (10-12). NEC involves severe inflammation of the intestine and can result in necrosis of large sections of the bowel. Strategies to prevent BSI are therefore important to help babies who need a PICC avoid these serious and costly consequences (13).

There are 45 published randomised controlled trials (RCTs) of central venous catheters that have been impregnated with antiseptics or antimicrobial substances to prevent BSI, but none have been conducted in very preterm babies (14). Antibiotic impregnation was investigated in 7 RCTs and was one of the most effective interventions with an average 80% reduction in catheter-related BSI (odds ratio 0.18; 95%CI 0.08-0.34). The 7 RCTs were all confined to

adults. All used catheter-related BSI as the primary outcome, which could overestimate the effect of impregnation due to contamination of culture media with antibiotic from impregnated catheter tips. A further RCT has recently been completed of children in UK paediatric intensive care units comparing minocycline-rifampicin impregnated central venous catheters (Fr 4 or 5) with standard catheters. Heparin-bonded catheters are included as a third arm in this trial. The median duration of catheters was 2.5 days and the median age was 6 months (personal communication from trial investigators).

There is limited evidence for the effectiveness of antimicrobial impregnation in catheters inserted for weeks rather than days, or in patients receiving parenteral nutrition (15-18). Two RCTs, both in adults had median catheter durations of 44-63 days, mainly for chemotherapy (19, 20). A few patients receiving parenteral nutrition were included in these studies.

Several cost-effectiveness analyses have been published, but all focus on adult patients (21-24). A UK analysis showed that even very small reductions in absolute BSI rates would be cost-effective (as low as 0.2%) and based on results from the most relevant meta-analysis, we expect the effect size to be much larger than this (14, 21).

There are several reasons why these results in adults and children cannot be generalised to very preterm neonates. Please see section 2.2 for further details.

2.2 Rationale

Antibiotic impregnated central venous catheters are used widely in paediatric and adult intensive care. However, no NNUs in the UK use AM-PICCs (despite the AM-PICCs being licensed). To address this gap, the Neonatology Clinical Studies Group of the MCRN prioritised evaluation of impregnated lines for use in preterm babies in 2012.

Reasons given by neonatologists for the lack of adoption of impregnated lines in the UK focused on the lack of RCT evidence in preterm babies and the limited availability of licensed products (AM-PICCs that are licensed and manufactured by Vygon will be used in this trial). Other reasons included concerns about antibiotic resistance and the additional costs of AM-PICCs.

A further reason for lack of uptake of AM-PICCs may be declining rates of hospital acquired BSI. In paediatric intensive care units, rates have fallen over the last decade, due in part to implementation of catheter care ‘bundles’ that aim to improve sterile procedures during catheter insertion and maintenance of the line (25-28). There is a paucity of evidence on trends in rates of BSI in NNU. There is therefore a clear need to take into account changing background rates of hospital acquired BSI in NNUs, through generalisability and economics analyses.

There are a large number of RCTs demonstrating benefits of impregnated lines in adults and children but no studies in very preterm neonates. However here are several reasons why results cannot be directly applied to very preterm neonates.

i) Effects of antimicrobial impregnation may be attenuated because very preterm babies have immature immunity and skin defences, which could allow skin organisms to track internally and externally along the catheter from the insertion site (29).

ii) Most very preterm babies with a PICC in-situ receive infusions of parenteral nutrition (a protein solution co-infused with lipid) which increase organism adherence and the development of BSI (15, 30).

iii) The lumens of PICC used in very preterm babies are far narrower (1 Fr compared to 4 or 5 Fr used for children in the CATCH trial and 7 to 10 Fr used for adults). Narrower lumens increase bacterial adherence, potentially reducing the benefits of impregnation. Thrombosis causing obstruction of the lumen is also more common with narrower lumens.

iv) The combination of rifampicin and an antifungal – miconazole - has not previously been evaluated in a RCT for its effect on BSI. Candidaemia is an infrequent, but well-recognised problem in very preterm neonates, and is associated with a high mortality rate (31). Use of miconazole may therefore be appropriate for this population.

v) Emergence of resistant organisms is a major problem for NNUs. Rifampicin is known to cause emergence of resistant organisms, particularly when used as the sole antibiotic in therapeutic levels (32). However this may or may not occur with the very small dose in the AM-PICC. Rifampicin resistance may attenuate any reduction in BSI risk due to antibiotic impregnation over time. This has not been evaluated previously. Rifampicin resistance does not impact on NNU treatment regimens as this drug is not used routinely in NNUs.

vi) Unlike more mature children, very preterm survivors of BSI are at increased risk of long-term neurological impairment, even when BSI is due to skin organisms (33). It is not known whether the reduction in BSI associated with antibiotic impregnated catheters is associated with a commensurate reduction in the risk of neurological impairment.

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 effects of AM-PICC on BSI, the safety of AM-PICC, and on cost-effectiveness, before neonatologists will be willing or able to change purchasing decisions to adopt these devices in NNUs.

2.3 Objectives

The overall objective of the PREVAIL trial is to determine whether AM-PICCs should be introduced across the NHS for very preterm babies. To achieve this objective, we are conducting two separate but integrated analyses: Part 1: Randomised Controlled Trial and Part 2: Economic analyses.

2.3.1 Part I: Randomised Controlled Trial

2.3.1.1 Primary Objective

To determine the effectiveness of antimicrobial impregnated (with rifampicin and miconazole) long lines (AM-PICC) compared with S-PICC for reducing BSI.

2.3.1.2 Secondary Objectives

To determine the effect of AM-PICC vs S-PICC on:

1. Rifampicin resistance in isolates from blood/CSF cultures.
2. Rifampicin resistance in isolates from PICC tips.
3. Type of organism isolated from BSI.
4. Measures of BSI (rate of BSI per 1000 PICC-days (including recurrent BSI), occurrence of 1 or more BSI, rate of catheter-related BSI per 1000 PICC days).
5. Rate of blood/CSF culture sampling per 1000 PICC days.
6. Duration of antimicrobial exposure from randomisation up to 48 hours after line removal.
7. Time to PICC removal.
8. Occurrence of Chronic Lung Disease.
9. Occurrence of necrotizing enterocolitis (NEC): Bell's stage II or III.
10. Occurrence of cranial ultrasound abnormality.
11. Requirement for treatment for retinopathy of prematurity.
12. Time to full milk feeds.
13. Duration of parenteral nutrition from randomisation until discharge home from neonatal care/death/6 months post randomisation.
14. Death:
    a) Within six months (26 weeks) of randomisation;
    b) Before discharge home from neonatal care.
    c) Time to death

2.3.2 Part II: Economic Analyses

2.3.2.1 Primary Objective

To evaluate the cost-effectiveness of AM-PICC vs S-PICC.

2.3.2.2 Secondary Objectives

To evaluate:

1. The direct hospital costs of using AM-PICC compared with S-PICC over 6 months from randomisation.
2. The cost-effectiveness of AM-PICC compared with S-PICC over the participants' expected lifetime from the perspective of the NHS.
3. The potential value of additional research to reduce any uncertainty observed in the cost-effectiveness model. This will be used to inform decisions about long-term follow up of the trial cohort.
4. The value of implementing the cost-effective intervention (AM-PICC vs S-PICC) throughout the NHS in England and Wales.

5. The costs of a BSI to the NHS.

2.4 Potential Risks and Benefits

2.4.1 Potential Risks

As the control and intervention arms of the trial are similar in so many respects, the risks of intervention are confined to those attributable to the antimicrobial coating of the AM-PICC. The actual dose of antimicrobials and the slow release which is believed to occur mean that even if total systemic bioavailability were to occur, the foreseeable disadvantage to a baby would be less than receiving a single systemic dose of either active ingredient. Thus adverse drug reactions are likely to be rare and unlikely to be serious and should not prevent the trial from proceeding.

A second possible risk of participation could be the emergence of resistant organisms (34). However, rifampicin resistance is unlikely to be clinically significant as rifampicin is only very rarely used in neonatal practice and rifampicin resistance does not confer resistance against other classes of antibiotics (35).

Colonisation with rifampicin resistant organisms may be confined to the device as the serum level of rifampicin remote from the indwelling device will be very low. It is possible that bacteria at the entry site might become resistant to rifampicin, and similarly that fungal species with resistance to miconazole might emerge. If colonisation with resistant organisms does occur, there is no reason to believe that such resistant organisms should have higher virulence than other skin commensal organisms which might colonise the line site. If resistant organisms do colonise the line and, if these organisms give rise to BSI, antibiotics commonly prescribed for presumed line infections would be expected to be efficacious.

2.4.2 Known Potential Benefits

Ten percent of all babies are admitted to NNU (68,000 per year in England) and around 6% of these develop one or more BSI. Very preterm babies (<32 weeks gestation) account for 10-15% of admissions to NNU but 53% of NNU care days and (58%) of total BSI in NNU (6-8). BSI occurs in 5-20% of very preterm babies, mostly in association with PICC or other central venous catheters (CVCs). The consequences of BSI include death, increased duration of intensive care and permanent neurological impairment. Hence, strategies to prevent BSI could have enduring health benefits and reduce long-term health and welfare costs.

Based on evidence in older children and adults, antimicrobial impregnation of PICC appears promising for very preterm babies, but specific evidence is needed for this population. Several cost-effectiveness analyses of impregnated lines have been published, but all focus on adult patients (21-24). A UK analysis showed that even very small reductions in absolute BSI rates would be cost-effective (as low as 0.2%) (14, 21).

PART I: RANDOMISED CONTROLLED TRIAL

3 SELECTION OF SITES/CLINICIANS

Trial sites will be initiated once all governance (e.g. local R&D approval) and trial-specific conditions (e.g. training requirements) have been met, and all necessary documents have been returned to MC CTU. Initiation meetings will cover the requirements outlined in CTRC SOPs TM017 and TM018.

It will be expected that all sites selected will follow good clinical standards with particular attention to aseptic practise and infection monitoring. For example, use nationally recommended asepsis procedures (0.5% chlorhexidine and will take a minimum of 0.5ml of blood for any blood culture).

3.1 Site/Clinician Inclusion Criteria

The trial will take place in NNUs in England. Any NNU can participate providing they obtain approval as a Recruiting Site or Continuing Care Site (CCS).

3.1.1 Recruiting Sites

Prioritisation for site inclusion will be given to the 5-6 largest NNU's providing level 2 and 3 care within 3 neonatal networks (Yorkshire and Humber, North East North Central London and Trent). Other sites will be invited to participate through the Children's Clinical Research Network.

Training in the protocol requirements and the requirements outlined in CTRC SOPs TM017 and TM018 will be disseminated to personnel at a trial launch meeting and continually on site for all relevant new staff who may be involved in the trial.

Adherence to the protocol procedures will be monitored throughout the trial by the Trial Coordinator/Data Manager. Participating sites will be expected to maintain a file of essential trial documentation (Investigator Site File), which will be provided by the MC CTU, and keep copies of all completed CRFs for the trial.

3.1.2 Continuing Care Sites (CCS)

CCS will be required to gain R&D approval in order to follow-up the participant.

3.2 Site/Clinician Exclusion Criteria

Not meeting the inclusion criteria listed above.

4 TRIAL DESIGN

4.1 Primary Endpoint

The primary endpoint will be time to first BSI based on a 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 removal.

As part of the primary endpoint there will be two sensitivity analyses:

1. A sensitivity analysis confined to clinically serious BSI defined by positive culture and the baby is treated for more than 72 hours with intravenous antibiotics or dies during treatment.
2. Time to first BSI based on a positive blood culture (including fungal BSI) taken between 24 hours after PICC insertion until 48 hours after removal.

4.2 Secondary Endpoint(s)

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 line 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

For health economics outcomes, please refer to Part II: Economic Analysis.

4.3 Internal pilot

There will be an internal pilot to assess recruitment. The pilot will last for 8 months so that the initial sites open will have 6 months of recruitment at full capacity. Recruitment will be demonstrated as being feasible if at least 130 patients have been recruited at the end of the pilot study.

5 TRIAL POPULATION

The trial will be open to all new-born babies who require the narrowest PICC (Premicath 1 Fr).

5.1 Inclusion Criteria

Participants with the following characteristics will be eligible for inclusion in the trial:

1. Babies who require a PICC (Premicath 1 Fr).
2. Parent/legal representative of the baby gives informed written consent for the trial.

Note: Babies with the following can be included in the trial:

- Congenital malformations
- Gastrointestinal surgical conditions
- Previous PICC (non-trial PICC)
- Previously treated BSI which has resolved in the opinion of the Investigator.

5.2 Exclusion Criteria

1. Baby has been previously entered into this trial.
2. Baby has a known allergy or hypersensitivity to rifampicin or miconazole.

5.3 Participant Transfer

Participating NNUs will be defined as either:

1. A **recruiting site:** Where parent/legal representative consent is obtained and babies may be recruited, randomised, and trial PICC inserted.
2. A **continuing care site (CCS):** Where babies may be transferred from the recruiting site with trial PICC still in situ. Follow up data will be collected from the routine clinical records until 48 hours after the PICC is removed or the appropriate follow-up time.

5.3.1 Transfer: Recruiting site to another recruiting site

If a baby is transferred from one recruiting site to another recruiting site, it is the responsibility of the original site to provide copies of all completed trial documentation for that participant thus far as part of a transfer pack. This will include a copy of the completed consent form and copies of CRFs completed to date.

Once the baby is received by the new recruiting site they:

a. Should confirm that transfer has been successful to the MC CTU by completing and submitting Form 7b: Transfer Acknowledgement to the MC CTU.

b. Will then be responsible for all further data collection and will act as the main contact for the parent/legal representative.

5.3.2 Transfer: Recruiting site to a CCS

If a baby is transferred from a recruiting site to a CCS:

a. It is the responsibility of the recruiting site to provide copies of all completed trial documentation for that participant thus far as part of a transfer pack. This will include a copy of the completed consent form. The transfer pack will also include blank copies of CRFs for completion by the CCS, a protocol and training materials.

b. CCS should confirm that transfer has been successful to the MC CTU by completing and submitting Form 7b: Transfer Acknowledgement to the MC CTU.

c. Although it will be the responsibility of the CCS to complete data collection until 48 hours after the PICC is removed or the appropriate follow-up time (discharge home from neonatal care/death/26 weeks after randomisation, whichever occurs first) and provide medical care, the recruiting site will maintain responsibility of ensuring all data collection is complete and accurate.

5.3.3 Transfer: CCS to CCS

If the baby transfers from one CCS to another CCS:

a. It will remain the responsibility of the original recruiting site to provide the transfer pack with all essential documents included to the new CCS.

b. Once a baby is transferred to a CCS, the CCS will be responsible for all clinical care. The new CCS should confirm that transfer has been successful to the MC CTU by completing and submitting Form 7b: Transfer Acknowledgment to the MC CTU.

c. If the parent/legal representative has questions regarding the trial, the CCS/parent/legal representative will be able to contact the recruiting site for further information.

5.3.4 Transfer: Recruiting site/CCS to a Non-Participating Site

All attempts will be made to ensure that all sites where babies may be transferred to have the appropriate approvals to allow follow up to continue. However, if the baby is transferred to a site that is not participating, the RN from the last recruiting site will endeavour to collect as much study information as possible. At a minimum the RN should try to obtain data for the primary endpoint.

Guidance sheets will be provided to both the transferring and receiving sites with all details required for the transfer and continuation of responsibilities (as required).

5.4 Participant Withdrawal

In consenting to the trial, participants are consented to the trial intervention, follow-up and data collection.

The Parent/legal representative is free to withdraw consent from the entire trial (including the intervention) at any time prior to PICC insertion without providing a reason.

Once the PICC has been inserted it will only be removed when clinically indicated. Clinically indicated removal includes but is not limited to: PICC no longer needed or expected adverse outcomes such as thrombosis, infection, or PICC displacement. Once the PICC is removed for whatever reason – this should be recorded on Form 6:Removal.

The Parent/legal representative is free to withdraw consent for follow-up and data collection at any time without providing a reason.

Sites should explain the value of remaining in trial follow-up, or failing this, of allowing routine follow-up data to be used for trial purposes. It should therefore, if possible, be clarified with the Parent/legal representative the level of follow-up and data collection they would like to withdraw from.

A withdrawal CRF will then be completed and any further data will be collected for the trial as per the parent/legal representative's wishes.

Data up to the time of withdrawal will be included in the analyses unless the participant explicitly states that this is not their wish. If this occurs, contact should be made with the MC CTU to discuss and an additional withdrawal CRF (for withdrawal of data) will be provided for completion.

If a parent/legal representative decides to withdraw consent, regardless of the level of withdrawal, data for Health Episode Statistics and Data linkage will not be sought.
When withdrawn, the participant will receive appropriate care under medical supervision until the symptoms of any adverse events resolve or the participant's condition becomes stable. Blood/CSF cultures and PICC tip culture will still be undertaken if clinically indicated and deemed necessary as part of routine clinical care. In line with usual clinical care, decisions as to the clinical management of the baby will be made by the attending clinical team in conjunction with parent/legal representative.

6 ENROLMENT, RANDOMISATION AND FOLLOW-UP

6.1 Screening

A screening log will be maintained by clinical staff or the designated RN at each trial site, recording all patients who are approached about the trial. Reasons will be documented where consent is declined and where consent is provided but the baby is not randomised and this information will be used for monitoring purposes.

Additionally, a log to record patients who had a PICC (Premicath 1Fr) inserted but weren't approached for the trial will be kept. This will include reasons why patients weren't approached along with the birth weights and gestational ages.

Both logs should be maintained by the RN or designated other (recorded on delegation log) and should be faxed to the MC CTU monthly.

6.2 Enrolment

For patients who are likely to require a PICC (Premicath1Fr), the clinician or RN will provide written information and will meet with the parents or legal representative at the earliest time that can be arranged to discuss participation in the trial. The RN will allow the parent or legal representative sufficient time to discuss the trial and decide whether to consent to trial entry (see section for consent procedures).

If written consent (see section 11.3) is provided by the parent or legal representative and the patient meets all the inclusion/exclusion criteria, the patient will be eligible to be randomised to the trial. The RN will inform the inserting clinician of the patient's participation. Eligibility needs to be confirmed by the PI or designated other (on the delegation log) prior to the patient being randomised. Eligibility for the trial can be confirmed by a Research Nurse (on Form 1) if they are delegated this duty by the PI or co-PI on the delegation of responsibilities log and have provided their signed CV and GCP certificate to the CTRC. **All medical decisions within neonatal care, such as the decision to place a PICC, are the responsibility of qualified physicians even when they are carried out by non-medical staff who are delegated to do so**. In trial context, the decision for trial delegated staff to consider a patient eligible to participate in PREVAIL is under the wider supervision of a medical practitioner.

Once written consent has been provided by the parent or legal representative it is valid for 14 days. If the patient has not been randomised within the 14 days the RN or clinician will need to reconsent the patient.

6.2.1 Enrolment of twins

Twins should be treated as individuals and if both babies require a PICC (Premicath 1Fr), they should be randomised separately. Separate consent forms should be completed for each baby.

6.3 Randomisation

Randomisation should be carried out as close as possible to the time of PICC insertion. PICC insertion should occur within 48 hours of randomisation by a designated staff member (as specified on the training log). See section 7.3 for administration. Participants will be issued with a unique randomisation number and PICC allocation at randomisation. Confirmation of trial entry, randomisation number and treatment allocation should be in the patient's medical notes.

Participants will be randomised using a secure (24-hour) web based randomisation programme controlled centrally by the MC CTU to ensure allocation concealment.

The treatment allocation for the participant will be displayed on a secure webpage and an automated email confirmation sent to the authorised randomiser, the PI and any other member of the team as requested by site.

In the event of an internet connection failure between the site and the randomisation system, the site should contact the MC CTU immediately to try to resolve the problem. If the problem can't be resolved the MC CTU will inform site to open a randomisation back-up envelope. These envelopes will be sequentially numbered, opaque, envelopes similar to those used for pay slips, which cannot be viewed without fully opening and their construction is resistant to accidental damage or tampering. Once opened the first page of the envelope should be returned to the MC CTU and pages 2 and 3 should be placed in the patient's medical notes.

Randomisation: web access https://ctrc.liv.ac.uk/Randomisation/Prevail

If there are any problems with web randomisation, please contact the MC CTU
Monday to Friday: 0151 795 8757
Or via email on prevail@liv.ac.uk

(Note that the MC CTU is open for randomisation support from 0900 – 1700, Monday – Friday, excluding public holidays)

For any out of hours randomisation problems back-up randomisation envelopes will be provided.

Research staff will be trained to use the web randomisation system during the initiation process. After research staff are trained they will be issued with login and password details.

6.4 Baseline (Form 3: Baby Characteristics CRF)

The following information will be recorded on Form 3: Baby Characteristics CRF :

- Baby details:
  - Gender

  - Date and time of birth
  - Birth weight
  - Final estimated delivery date
  - Location of birth and transfer date (if applicable)
  - Mode of delivery
  - Membranes ruptured >24 hours before delivery?
  - Condition at birth
- Maternal medication
- Surgical procedures in 14 days prior to randomisation
- Samples taken within 72 hours prior to randomisation
- Antimicrobial medication (including therapeutic antibiotics) used within 72 hours prior to randomisation.
- Respiratory support within 72 hours prior to randomisation.
- Devices in situ at randomisation.
- PICC placement details

6.5 Clinical Follow-up – starting at Randomisation

The following information will be captured on Form 4: Daily Follow-up which should be completed for each day from randomisation until 48 hours after randomised PICC removal / attempted insertion / randomisation if not attempted as per table 1 section 8.2. It may be completed retrospectively but it must be completed regularly (at a minimum of every 7 days). It should be completed as at 23.59 on the specified dates.

- Randomised PICC status (in situ/removed/etc)
- PICC tip culture taken (if applicable) – Form 5: Microbiology also needs updating
- Blood/CSF cultures samples taken – Form 5: Microbiology also needs updating
- Antibiotics/Antifungals
- Related adverse events – Form 8: Related AEs also needs updating

6.6 Discharge home from neonatal care/Transfer/ /Death/26 weeks after randomisation

Retrospective review of the following key events will be completed where applicable when a participant is transferred, discharged from NNU or has died. This will be recorded on Form 7a: Clinical Outcomes

If a participant is not discharged from NNU or dies within 6 months (26 weeks) of randomisation, the last collection of the following information should be at 6 months (26 weeks) post randomisation.

- Details of Transfer/Discharge/Death.
- Details of receiving hospital
- Milk intake
- Level of care
- Necrotising enterocolitis (NEC)

- Periventricular leukomalacia
- Retinopathy of prematurity
- Bronchopulmonary dysplasia
- Intracranial haemorrhage
- Duration of parenteral nutrition

6.7 Co-enrolment with other trials

All centres will complete a log after trial follow-up has finished. This will allow the trial team to review any co-enrolment of participants to other trials whilst participating in PREVAIL.

7 TRIAL INTERVENTIONS

7.1 Introduction

Participants will be randomised to S-PICC or AM-PICC in a ratio of 1:1. This ratio reflects uncertainty about which of these two types is best in terms of reducing BSI and cost effectiveness.

7.2 Packaging, Labelling, Storage and Stability

The PICCs used in the trial will be sourced from Vygon (www.**vygon**.co.uk) according to Vygon's standard business procedures. Only the following devices will be supplied for trial use see section 15.1.2 for pricing:

- Premicath with stylet (1261.203), premicath without stylet (1261.21)
- Premistar 20 cm with stylet+ 24G breakaway needle (6261.203), premistar with stylet, premistar without stylet (6261.20).

Both PICCs allowed in the trial design are CE-marked medical devices used in accordance with the manufacturer's instructions for their intended purpose

PICCs should be stored in accordance with local policy clearly marked for PREVAIL trial use, where they are readily accessible to the clinician responsible for randomisation and insertion. Vygon recommends that PICCs should be stored in a dark, dry, cool place. All PICCs have a 36-month expiry date from the date of manufacture.

All stock is shipped from the UK and has a minimum lead time of 3-5 days. It will be the responsibility of the site in liaison with the local procurement department to ensure the disposal of those supplies when the shelf life expires and arrange resupply where appropriate. The RN will monitor that trial allocated PICCs are being used within their shelf life.

7.3 Administration of Trial Intervention

It is the responsibility of the PI or delegated research staff to ensure there is enough supply of the PICC lines.

To administer the randomly allocated PICC:

a. **The randomising/inserting clinician** will select the allocated PICC which will be inserted by a member of the clinical team.

b. If the initial attempt at insertion is unsuccessful (see section 7.3.1), and the same size PICC is appropriate, the allocated PICC will be used for the subsequent attempt on the same patient. The clinical team will have up to 48 hours after randomisation to insert the allocated PICC. After 48 hours the default PICC line used at the site should be inserted.

c. If insertion is not successful as it is discovered that the participant requires a different size PICC, then the default PICC (appropriate size) at the site should be inserted.

d. If a participant is randomised and the allocated PICC not used this will be recorded on the Form 3: Baby characteristics. Each participant should be randomised separately. Allocation cannot be transferred to the next eligible participant.

The PICC will be removed when clinically indicated. The time, date and reasons for removal will be recorded on Form 6: Removal by the RN from the participant's medical records (see section 8).

7.3.1 Defining Successful PICC Insertion

The PREVAIL trial consider a PICC insertion to be "successful" if the site of line insertion is dressed in preparation for a radiograph (X-ray) to confirm PICC tip position.

If a PICC is completely withdrawn at any time following X-ray, removal should be documented on the line removal form, and daily follow up should continue until 48 hours after removal of this PICC. If a PICC placement is simply adjusted following an X-ray, and the line redressed, daily follow up should continue until 48 hours after line removal.

For all successfully inserted PICCs (irrespective of whether they are removed after X-ray), follow-up for clinical outcomes should also be completed at discharge home from neonatal care/death/6 months (26 weeks) post randomisation, whichever occurs first.

Note: If a trial participant requires an additional PICC(s) at the same time as the trial PICC (i.e. in parallel), the default PICC for that site will be used.

If a trial participant requires a subsequent PICC(s) after the trial PICC has been removed (i.e. in series), the subsequent PICC(s) will not be randomised and the default PICC used at that site will be used.

7.4 Accountability Procedures for Trial Interventions

As the PICCs used in the trial will be sourced from Vygon, the RN will liaise with the local procurement department to ensure that the site has the following procedures in place as per their local policy:

- A record of deliveries of device/s;
- A record of administration of device/s in medical records as a minimum;
- A system in place that allows for the retrieval of defective products;
- Ensure that there are enough devices within their shelf life assigned to be used in the trial;
- Ensure devices are used in compliance with the protocol requirements and accountability records are maintained as per local policy;
- Ensure that the PICCs are stored where they are readily accessible to the clinician responsible for randomisation and line insertion.

If the site has any ongoing issues they will liaise with the MC CTU to resolve them.

Once the trial has closed at a site, Vygon will be informed indicating the end of the Vygon pricing structure detailed in section 15.1.2. All PICCs supplies already procured will remain the property of the procuring institution.

7.5 Concomitant Medications

Use of antibiotic and antifungal medications will be recorded at from 72 hours before randomisation and documented throughout trial participation until the baby has reached the end of the clinical follow up for primary outcome (see section 8.2).

7.6 Co-enrolment Guidelines

Co-enrolment into other trials is encouraged as this trial involves minimal burden on the parents or baby. To avoid potential confounding issues, participants should not be recruited into other trials using PICCs as the trial intervention. Where recruitment into another trial is considered to be appropriate and without having any detrimental effect on the PREVAIL trial this must first be discussed with the MC CTU who will contact the Chief Investigators.
Co-enrolment will be captured retrospectively at the end of trial follow-up (see section 6.7).

8 ASSESSMENTS AND PROCEDURES

All paper CRFs should be completed as described in section 13.

8.1 Schedule of Assessments

Procedures	Screening	Consent	Randomisation	Baby Characteristics	Daily follow-up[1]	PICC Removal[2]	Discharge from NNU/Transfer/Death/6 months post randomisation[3]
Screening of NNU inpatients to identify patients who potentially require a Premicath	X						
Signed consent form		X					
Assessment of eligibility criteria	X	X	X				
Trial intervention (allocation & insertion of PICC)			X				
Birth details				X			
Review surgical procedures				X[4]			X
Review of results of blood/CSF cultures				X[5]	X		
Review of concomitant antimicrobials				X[5]	X		
Review of respiratory support required				X[5]			
Details of other devices in-situ				X[6]			
PICC placement details				X			
PICC tip culture taken						X	
Randomised PICC status					X		
Review of PICC tip culture[7]					X		
Assessment of related adverse events					X		
Review of parental nutrition					X		
Clinically indicated blood/CSF cultures taken					X		
Medical record review for clinical outcomes as detailed in section 6.6							X
Details of NNU transfer / discharge / death							X

Procedures/assessments where parent/legal representative contact time is required over and above clinical practice is highlighted by shading.

[1] Completed from randomisation and then at regular intervals (at a minimum of every 7 days) until clinical follow-up for primary outcome as defined in table 1.
[2] Only applicable if a PICC is inserted within 48 hours from randomisation.
[2]
[3] If a participant is not discharged home from neonatal care or dies within 6 months (26 weeks) of randomisation, the last collection of the following information should be at 6 months post randomisation.
[4] Within 14 days prior to randomisation.
[5] Within 72 hours prior to randomisation.
[6] At randomisation.
[7] 48 hours after PICC removed.

8.2 Clinical Follow-up for Primary Outcome

Table 1: Definitions of Clinical Follow-up for Primary Outcome

Situation:		**Clinical follow-up for primary outcome will continue until *48 hours after*:**
Type of PICC used for attempted insertion *within 48 hours from randomisation*	**Type of PICC inserted *within 48 hours from randomisation***	
Allocated PICC	Allocated PICC	Allocated PICC removed
Allocated PICC	Non-allocated PICC	Non-allocated PICC removed
Allocated PICC and non-allocated PICC	None	Last attempted insertion of allocated PICC
Allocated PICC	None	Last attempted insertion of allocated PICC
Non-allocated PICC	Non-allocated PICC	Non-allocated PICC removed
Non-allocated PICC	None	Last attempted insertion of non-allocated PICC
None	None	Randomisation

Note: 'Allocated PICC' refers to the type of PICC allocated to the participant during the randomisation process. Whether the allocated PICC or a non-allocated PICC was inserted within 48 hours of randomisation, the inserted PICC will be referred to hereafter as the 'Randomised PICC'.

8.3 Procedures for Assessing Efficacy

For all participants from the time of randomisation until the clinical follow up for primary outcome (see table 1 in section 8.2).

When clinically indicated, blood/CSF culture samples will be taken. It will be the responsibility of the clinician to decide when blood/CSF culture samples need to be taken. The RN will monitor blood/CSF culture sampling and ensure that the PICC tip is sent for culture at removal. The RN will be responsible for recording the culture results and resistance profiles on Form 5: Microbiology.

Blood for blood cultures is best taken prior to commencing antibiotics. However, it is still worth taking blood cultures even if already on antibiotics if there is a clinical indication.

A minimum of 0.5ml should be taken from a new peripheral site (e.g. new peripheral line or closed blood culture system).

The primary outcome will be based on any clinically indicated positive blood culture taken between 24 hours after randomisation to 48 hours after PICC removal. Information on factors contributing to death should be considered a clinical indication for blood/CSF culture sampling, when factors leading to death are uncertain. Blood/CSF cultures should be taken

before death in babies who are deteriorating as blood/CSF cultures taken after death may be a consequence rather that a cause of death and will not be included in the primary outcome.

For all participants who have a PICC inserted within 48 hours from randomisation:
At PICC removal, the attending clinical staff/RN will routinely take a PICC tip culture according to standard clinical practice.
A detailed SOP version 1.0 dated 05/03/2015 on handling and culturing premicath line tips will be disseminated to site's microbiology laboratories.

8.4 Procedures for Assessing Safety

Adverse events whose causal relationship to the trial intervention (PICC) is assessed and judged by the investigator to be possibly, probably, or almost certainly related to the intervention that occur at the time from the first attempt of PICC insertion within 48 of randomisation hours until the clinical follow up for primary outcome (see table 1 in section 8.2) should be reported (see section 10.1).

These will be reported as they arise as described in section 10. An independent Data and Safety Monitoring Committee (IDSMC) will be convened to monitor safety data (see section 16.3 for further details).

Note: Although this is an unblinded trial all sites are expected to adhere to good practice in terms of treating babies similarly, regardless of the allocated PICC.

8.5 Loss to Follow-up

Trial follow-up is by the trial RN until discharge home from neonatal care, death or 6 months (26 weeks) after randomisation (whichever occurs first). Refer to section 5.3 for further details relating to the process of transferring participants and the prevention of loss to follow-up.

If a participant is lost to follow-up prior to discharge home from neonatal care, all participants will still be followed up at 6 months (26 weeks) post randomisation as detailed in section 17.

8.6 Trial Closure

The end of the trial is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the trial database. However, the trial may be closed prematurely by the Trial Steering Committee (TSC), on the recommendation of the Independent Data and Safety Monitoring Committee (ISDMC).

9 STATISTICAL CONSIDERATIONS

9.1 Introduction

A separate and full Statistical Analysis Plan (SAP) will be developed prior to the final analysis of the trial. The SAP will be agreed by the Trial Steering Committee (TSC). The main features of these planned statistical analyses are included here in the main protocol.

9.2 Method of Randomisation

Participants will be randomised to S-PICC or AM-PICC in a ratio of 1:1. Randomisation lists will be generated using blocks of random length and stratified by NNU. The lists will be produced by an independent statistician (who is not involved with the PREVAIL trial) at the MC CTU.

9.3 Outcome Measures

The primary and secondary outcomes are provided in section 4.

9.4 Sample Size

When the sample size in each group is 408, with a total number of blood stream infections required of 79, a 0.050 level two-sided log-rank test for equality of survival curves will have 90% power to detect the difference between a proportion of 0.14 and a proportion of 0.07 (a constant hazard ratio of 2.078). Assuming 5% loss to follow up due to transfers, we estimate that 858 babies would need to be randomised (429 to each arm).

The basis of this calculation is as follows:

i) Baseline event rate: The incidence of BSI in babies less than 32 weeks gestation with PICC was assumed to be 14/1000 CVC days, based on unpublished audits of BSI event rates at 3 hospitals (Table 2). Hospital A shows a recent reduction in BSI which follows a series of hospital infection control initiatives. As other units have not seen major reductions in rates, and recent rates from one unit are as high as 20/1000 CVC days, we have used 14/1000 CVC days for the sample size estimate. In addition, the rates in Table 2 are considered conservative as the denominators include a minority of babies with umbilical venous catheters and surgically inserted venous catheters for which the rate of BSI is lower than for PICC. In addition, the rates of BSI measured in the units reflects all kinds of CVC, and babies for whom Premicath insertion is appropriate may be expected to experience BSI more frequently than typical NNU inpatients.

ii) Duration of PICC insertion. This was estimated as a median of 10 days, based on an audit of 5 NNUs (with mean duration ranging from 10 to 29 days). Hence the proportion of babies with a BSI in the standard arm is estimated to be 14%.

iii) A 50% absolute reduction in the event rate. This is conservative when viewed against results of a network meta-analysis by Wang et al (mean odds ratio 0.18 and upper

limit of a 95% confidence interval of 0.34) because of the factors that may attenuate the treatment effect in very preterm babies (see section 2.2).

iv) A 5% loss to follow is realistic as follow up should be complete for babies remaining on the NNU, but a very small number may be transferred with their PICC in-situ. Efforts will be made to capture primary outcome data for babies transferred to non-participating NNUs.

Table 3 demonstrates the impact on statistical power of the control group event rate variation maintaining the sample size of 408 in each group (prior to adjusting for loss to follow up).

Table 2: BSI rate (any positive culture) for babies born at <32 weeks of gestation per central venous catheter days

Site	Audit period	BSI/1000 CVC days
Hospital A	2007-2010	14.3 (160/11166)
Hospital A	2011	7.2 (21/2898)
Hospital A	2012	4.8 (13/2713)
Hospital B	Jan-June 2013	10.8 (9/833)
Hospital C	July 2012-July 2013	20.0 (28/1398)

Table 3: Power to detect an effect given different control group rates of BSI

Control group rate (%)	Impregnated line group rate (%)	Power (%)	Number of events
5	2.5	46	28
10	5	77	56
15	7.5	90	79
20	10	97	112

9.5 Interim Monitoring and Analyses

The trial will be monitored by an Independent Data and Safety Monitoring Committee (IDSMC) who will assess the trial data and take into account the current world-wide evidence. The IDSMC members will comply with a trial-specific IDSMC charter according to International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines.

The trial statistician at the MC CTU will prepare the report for the IDSMC, the contents of which will be agreed by the IDSMC. The IDSMC will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community. If a decision is made to continue, the IDSMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The IDSMC will make recommendations to the Trial Steering Committee (TSC, see section 16) as to the continuation of the trial.

There will be an interim analysis of the primary outcome half-way through the trial (when approximately half of the participants have been randomised), using Peto-Haybittle stopping rules. A full statistical analysis plan will be written prior to any comparison of the treatment groups. At this point the Independent Data and Safety Monitoring Committee (IDSMC) will make a recommendation to the 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 participants 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.

9.6 Analysis Plan

The trial will be analysed using the International Conference on Harmonisation E9 guidelines and reported using the 'Consolidation Standard of Reporting Trials' (CONSORT) guidelines. A full and detailed statistical analysis plan will be developed prior to the final analysis of the trial. The main features of the statistical analysis plan are included here.

The analysis of primary and secondary outcomes will use the principle of intention to treat, based on all the randomised participants, as far as is practically possible. Per protocol sensitivity analyses will also be carried out on a number of outcomes, these will be specified in the statistical analysis plan. A p-value of 0.05 or less will be used to declare statistical significance for all analyses and results will be presented with 95% confidence intervals. Baseline characteristics will be presented but no comparisons will be undertaken, rather the clinical importance of any imbalance will be noted.

Kaplan-Meier survival curves and log rank tests will be used for time to event outcomes including the primary outcome 'time to first BSI'. Continuous data will be presented as means and standard deviations and analysed using two-sample tests (if data is skewed, medians and ranges will be presented and analysis will be by Mann Whitney U tests). Binary data will be reported in terms of relative risk and analysed using chi-squared or Fisher's exact tests as appropriate.

All related adverse events (AEs) and related serious adverse events (SAEs) reported by the clinical investigator will be presented, identified by treatment group, but no formal comparisons will be made across the treatment groups.

Missing data will be monitored and strategies developed to minimise its occurrence, however as much data as possible will be collected about the reasons for missing data and this will be used to inform the handling of missing data.

10 SAFETY REPORTING

10.1 Reporting of Adverse Events

The table below (table 4) provides an overview of the reporting requirements for any adverse events occurring between the first attempt of PICC insertion following randomisation until the clinical follow up for primary outcome (see table 1 section 8.2).

The definitions detailed later in section 10 should be utilised to confirm that correct reporting is achieved.

Table 4: Reporting of Adverse Events

Event	Relatedness *For definition see section 10.2.4*	Expectedness *For definition see section 10.2.6*	Seriousness *For definition see section 10.2.2*	Reporting to MC CTU required within	Forms to complete
	Related	Not-expected	Serious[1]	24 hours	Form 9a: Serious Unexpected Related Adverse Events Form 9b: Medical Device Adverse Incident Report[2]
	Related	Expected	Serious[1]	7 days	Form 8: Related Adverse events
	Related	Not-expected	Not Serious	7 days	Form 8: Related Adverse events Form 9b: Medical Device Adverse Incident Report[2]
	Related	Expected	Not Serious	7 days	Form 8: Related Adverse events
	Not related	N/A	N/A[1]	None	None

[1] If outcome of event is death, this should also be recorded on Form 7a: Clinical Outcomes, independent of relatedness or expectedness.

[2] Once Form 9b: Medical Device Adverse Incident Reports is submitted to the MC CTU, it is the responsibility of the MC CTU to report the event to the Medicines and Healthcare products Regulatory Agency Adverse Incident Centre (MHRA AIC) via the online reporting system.

Flowchart Section 10.3 can also be used to determine the reporting requirements of adverse events).

10.2 Terms and Definitions

10.2.1 Adverse Event (AE)

An **Adverse Event (AE)** is defined as any untoward medical occurrence in a participant to whom a research procedure has been administered, including occurrences which are not necessarily caused by or related to that procedure.

10.2.2 Serious Adverse Event (SAE)

Serious Adverse Event (SAE) is an untoward occurrence that:

- Results in death;
- Is life-threatening*;
- Requires in-patient hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability or incapacity, or;
- Consists of a congenital anomaly or birth defect;
- Other important medical events***.

*'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.
***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Note: It is the responsibility of the PI or designated to grade an event as 'not serious' (AE) or 'serious' (SAE).

10.2.3 Adverse Incident (AI)

An **Adverse Incident (AI)** is defined as an event that causes, or has the potential to cause, unexpected or unwanted effects involving the safety of device users (including patients) or other persons.

By the above definition, AIs are the same as:

- Related and unexpected AEs and;
- Related and unexpected SAEs.

Causes of AIs involving devices may include:

- Design or manufacturing problems;
- Inappropriate local modifications;
- Unsuitable storage and use conditions;
- Selection of the incorrect device for the purpose;
- Inappropriate management procedures;
- Poor user instructions or training (which may result in incorrect user practice).

Conditions of use e.g. environmental conditions or location may also give rise to adverse incidents.

10.2.4 Relatedness

Table 5 provides definitions of causality of an AE (relatedness to PICC insertion).

Table 5: Definitions of Relatedness

Relationship	Description
Unrelated	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given.
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after insertion of the PICC). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly*	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after insertion of the PICC). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably*	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly*	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

*Those which are highlighted in green are referred to throughout the protocol as **'related'** and need to be reported as part of the trial (refer to table 4 for reporting requirements).

It is the responsibility of the investigator responsible for the care of the participant to assess each AE and assign the causality/relatedness using the definitions in Table 5.

If any doubt about the causality/relatedness exists the local investigator should inform the trial coordination centre who will notify the Chief Investigators. In the case of discrepant views on causality between the investigator and others, HRA and the MHRA AIC will be informed of both points of view.

10.2.5 Severity

The assignment of the severity should be made by the investigator responsible for the care of the participant using the definitions below for all related AEs:

Table 6: Definitions of Severity

Severity	Description
Mild	Does not interfere with routine activities
Moderate	Interferes with routine activities.
Severe	Impossible to perform routine activities.

Note: There is a distinction between a SAE and a severe AE. Severity is a measure of intensity (as above) whereas seriousness is defined using the criteria in section 10.2.2, hence, a severe AE need not necessarily be a SAE.

10.2.6 Expectedness

Table 7 provides a list of the AEs which are **expected** as part of the trial and could be **related** to the insertion of the PICC and need to be recorded on Form 8: Related Adverse Events.

Table 7: Expected AEs Associated with PICC Insertion that DO need to be recorded on Form 8: Related Adverse Events

Adverse Event Description
Cardiac tamponade
Catheter damage
Difficulty in successfully flushing catheter or other evidence of catheter blockage
Difficulty in removing catheter
Difficulty in removing stylet
Extravasation
Hypersensitive reaction to PICC (rifampicin or miconazole)
Perforation in line
Skin damage associated with line dressing
Swelling at line site / haematoma at line site

If an event is considered **related** and is **included** in table 7 it should be reported as an **expected** AE/SAE (as applicable).

If an event is considered **related** and is **not included** in the table 7 it should be reported as an **unexpected** AE/SAE (as applicable).

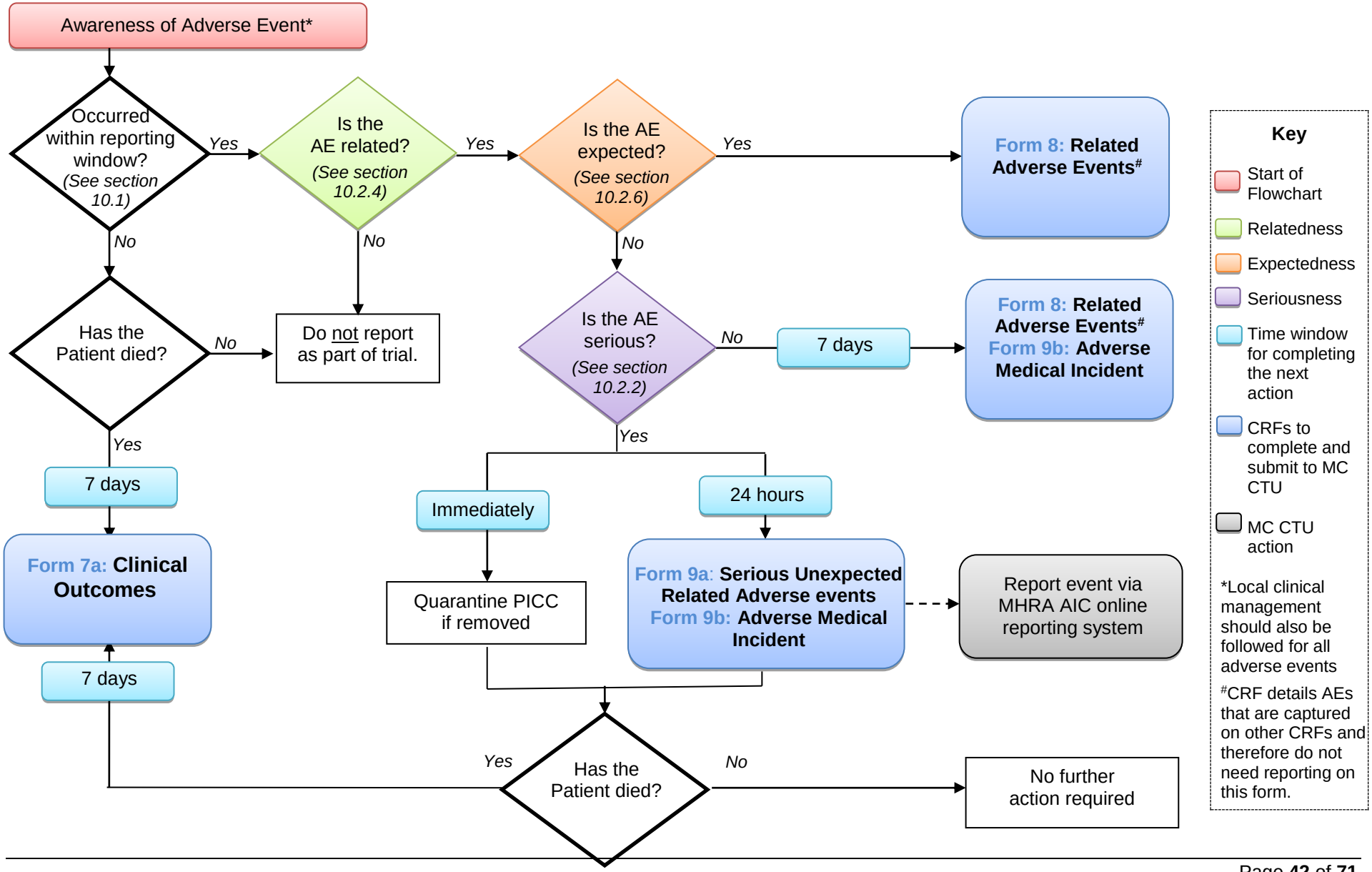
Table 8 provides a list of the AEs which are expected as part of the trial and could be related to the insertion of the PICC but do not need to be recorded on Form 8: Related Adverse Events as they are captured elsewhere.

Table 8: Expected AEs Associated with PICC Insertion that DO NOT need to be recorded on Form 8: Related Adverse Events

Adverse Event Description	Captured on
Emergence of rifampicin resistant bacteria	Form 5: Microbiology
Suspected BSI or confirmed BSI	Form 5: Microbiology Form 6: Removal
Thrombophlebitis in vein of insertion	Form 6: Removal
Thrombosis	Form 6: Removal

Please refer to table 4 for reporting requirements.

10.3 Flowchart for Reporting Requirements of Adverse Events



10.4 Follow-up after Adverse Events

All adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the participant to be stable.

Follow-up information is noted on another AE/SAE form by ticking the box marked 'follow-up' and faxing to the MC CTU as information becomes available. Extra, annotated information and/or copies of test results may be provided separately.

When reporting SAEs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at final follow-up; fatal or unknown.

10.5 Quarantine, Labelling & Storage of Devices Involved in an Adverse Incident (i.e. Related Unexpected AE/SAE)

Medical devices that have been involved in an adverse incident (i.e. related and unexpected AE), whether serious or not, should be quarantined as per your local trust policy. Except for serious unexpected adverse incidents which should follow the MHRA guidelines below.

Until the MHRA has been given the opportunity to carry out an investigation for the related unexpected SAE, they should not be discarded, repaired or returned to the manufacturer. All material evidence, i.e. devices/parts removed, replaced or withdrawn from use following an incident, instructions for use, records of use, repair and maintenance records, packaging materials, or other means of batch identification must be:

- Clearly identified and labelled;
- Stored securely.

Evidence should not be interfered with in any way except for safety reasons or to prevent its loss. Where appropriate, a record should be made of all readings, settings and positions, together with any photographic evidence and eyewitness reports.

If it is thought that an urgent examination of the device (and/or related items) may be required, upon notification of the incident an MHRA device specialist will decide whether to inspect the item urgently on site (or at other appropriate facilities), or may request that the device is sent to the MHRA. If required, the MHRA will contact the manufacturer (Vygon) and, if accompanied by an appropriate person, they may be allowed to inspect the items. To facilitate an investigation, it may be possible to provide the manufacturer with a sample of unused stock from a large batch. However, until advised to the contrary by the MHRA, the manufacturer must not be allowed to exchange, interfere with, or remove any part of the product implicated in the incident as this might prejudice MHRA investigations, or those of other official bodies.

10.6 Responsibilities – Investigator

The Investigator is responsible for reporting all related AEs/SAEs that are observed or reported during the trial.

All related Unexpected SAEs must be reported immediately by the investigator to the MC CTU on a RUSAE form, Form 9a..

Minimum information required for reporting:

- Trial identifier
- Trial site
- Participant number
- A description of the event
- Date of onset
- Current status
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and trial intervention

i. The Investigator is responsible for reporting all AEs that are observed as possibly, probably, or almost certainly related to the intervention using Form 8 Related Adverse Events.

ii. The RUSAEs forms (form 9a) should be completed by a designated investigator, a physician named on the 'signature list and delegation of responsibilities log' as responsible for reporting RUSAEs and making trial related medical decisions, and submitted to the MC CTU within the timelines specified in section10.3. The investigator should assess the SAE for the likelihood that it is a response to the intervention. In the absence of the designated investigator, the form should be completed and signed by an alternative member of the research site trial team and submitted to the MC CTU. As soon as possible thereafter the responsible investigator should check the RUSAE form (form 9a), make amendments as appropriate, sign and re-send to the MC CTU. The initial report shall be followed by detailed reports as appropriate.

iii. When submitting a RUSAE to the MC CTU research sites should also telephone the appropriate trial co-ordinator on telephone number **0151 795 8757** to advise that an RUSAE report has been submitted.

iv. Send the RUSAE form (form 9a) by fax (within 24 hours) to the MC CTU:

Fax Number: 0151 795 8770

v. For all RUSAEs, follow-up the participant as described in section 10.4.
The participant **must** be identified by trial number, date of birth and initials only. The participant's name **should not** be used on any correspondence

vi. For medical devices that have been involved in an adverse incident (related unexpected AE), whether classed as serious or not, ensure that they have been quarantined if local policy dictates this and fax Form 9b, Medical Device Adverse Incident Report, to the MC CTU.

vii. The responsible investigator must **notify** their R&D department and medical device liaison officer of the event as per standard local governance procedures.

viii. Participant safety incidents that take place in the course of research should be reported to the National Patient Safety Agency (NPSA) by each participating NHS Trust in accordance with local reporting procedures.

10.7 Responsibilities – MC CTU

The MC CTU is undertaking duties delegated by the trial sponsor and is responsible for the reporting of AEs to the main REC and MHRA AIC as follows:

- Related unexpected SAEs must be reported to the main REC within 15 days of the MC CTU first becoming aware of the event;
- All investigators will be informed, in a timely manner, of all related unexpected SAEs occurring throughout the trial;
- All related unexpected SAEs will also be reported to the Sponsor.
- A list of all SAEs (expected and unexpected) will be reported annually to the main REC.
- All device-related unexpected SAEs and AEs (Adverse Incidents) will be reported to the MHRA AIC as part of user device vigilance reporting.
- Copies of the reports will be sent to the Principal Investigator at all institutions participating in the trial.

It is recommended that the following safety issues should also be reported to the main REC in an expedited fashion:

- New events related to the conduct of the trial or the development of the devices and likely to affect the safety of the subjects. For example, a SAE which could be associated with the trial procedures and which could modify the conduct of the trial.
- Recommendations of the Data Monitoring Committee, if any, where relevant for the safety of the subjects.

Staff at the MC CTU will liaise with the Chief Investigator (or designated other specified in the protocol) who will evaluate all SAEs received for seriousness, expectedness and causality. The causality assessment given by the Local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report.

10.7.1 Safety reports

Safety reports will be generated during the course of the trial which allows for monitoring of AE reporting rates across sites. The MC CTU will send annual safety reports containing a list of all SAEs to the Main REC. Any concerns raised by the IDSMC or inconsistencies noted at a given site may prompt additional training at sites, with the potential for the MC CTU to carry out site visits if there is suspicion of unreported AEs in participant case notes. Additional training will also be provided if unacceptable delay in safety reporting timelines.

11 ETHICAL CONSIDERATIONS

11.1 Ethical Considerations

The trial will abide by the principles of the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996). The specific ethical issue is:

Informed consent in a neonatal population

Admission to a NNU is a time of enormous anxiety for children and their family. To minimise additional stress due to enrolment in the trial, recruiting investigators (such as consultant neonatologists and RNs) will be experienced at imparting information to families with sick children. Parents or a legal representative of the baby will be made aware that both PICCs under investigation licenced for use. They will be informed of the potential risks and benefits associated with trial participation and their right to withdraw the baby from the trial at any time without the baby or family being subject to any resulting detriment. They will be provided with written information and contact details of the trial personnel, who will also be readily available in the NNU, from whom further information about the trial may be obtained.

11.2 Ethical Approval

The trial protocol, including Parent Information Sheet and Consent form and all other relevant trial documentation that is submitted to the Yorkshire and the Humber – Sheffield National Research Ethics Service (NRES) Committee must also undergo independent review at the R&D offices at recruiting sites. For recruiting sites the local R&D office should also be sent the appropriate site specific information form complete with the necessary authorisation signatures, plus any other documentation requested for review. A copy of local Research & Development (R&D) approval should be forwarded to MC CTU before the site is initiated and participants recruited. For CCSs, one site specific information form will be disseminated to all CCSs complete with the necessary authorisation signatures, plus any other documentation requested for review. A copy of local Research & Development (R&D) approval should be forwarded to MC CTU before the site can commence data collection.

Proxy consent from the parent or legal representative should be obtained prior to each participant participating in the trial, after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment. The right of the parent/ legal representative to refuse consent for the baby to participate in the trial without giving reasons must be respected. For cases where the father has provided consent for the participant to be entered into the trial, the mother should be approached to complete a second consent form to provide consent for her information to be collected. The maternal date of birth and NHS number should therefore not be included on consent forms where the father of the participant has given consent for trial participation. Note that this does not disqualify fathers (married to the mother and/or named on the birth certificate) from providing consent for their child to participate in the trial.

After consent has been obtained for the participant to be entered into the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage

prior to PICC insertion, if he/she feels it to be in the best interest of the participant. However, the reason for doing so should be recorded and the participant will remain within the trial for the purpose of follow-up and data analysis. Once the PICC has been inserted, it is the clinician's judgement as to when the PICC should be removed (when he/she feels it to be in the best interest of the participant).

Similarly, the parent/legal representative of the participant remains free to withdraw the participant from:

- Protocol treatment prior to PICC insertion
- Trial follow-up at any time.

Parent/legal representative can withdraw without giving reasons and without prejudicing the further treatment of the baby (see section 5.4).

11.3 Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to the parent/legal representative by staff with experience in obtaining informed consent with reference to the patient information leaflet, the investigator will explain the research trial to the parent/legal representative. This information will emphasise that participation in the trial is voluntary and that the parent/legal representative may withdraw from the trial at any time and for any reason. The parent/legal representative will be given opportunity to ask any questions that may arise, the opportunity to discuss the trial with family members, friend or an independent healthcare professional outside of the research team and time to consider the information prior to agreeing to participate. Time to consider the trial will be dependent on how quickly a PICC is required. Typically once a decision has been made that a PICC is required, the PICC will be inserted within a few days. A contact point where further information about the trial may be obtained will also be provided.

Written consent is the only method of consent for PREVAIL; verbal or telephone consent are **not** to be taken as full informed consent. Written consent is valid if the current version of the informed consent form is used; other forms or procedures are not acceptable. If a patient is randomised into the trial prior to informed written consent being taken on the current consent form this will be treated as a potential serious breach and reported to the sponsor and, where appropriate, the REC and MHRA Adverse Incidents Centre.

The consent form will request permission for personnel involved in the research (Responsible individuals from the sites research team, MC CTU, Regulatory Authorities, Sponsor and the applicable NHS trust) to have access to the individual's medical records. Both the person taking consent and the parent or legal representative must personally sign and date the form. The original copy will be filed in the participant's medical notes and a copy of the signed informed consent will be given to the parent or legal representative for

their records. One further copy will be filed in the investigator site file and one final copy of the consent form should be sent to the MC CTU.

The parent/legal representative may, without being subject to any resulting detriment, withdraw from the trial at any time by revoking the informed consent. The rights and welfare of the participants will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this trial (see section 5.4).

11.4 Trial Discontinuation

In the event that the trial is discontinued, babies will be reverted to default care usually provided by the NNU (NNU policy).

12 REGULATORY APPROVAL

This trial involves the use of CE-marked devices employed for their intended purpose, therefore this trial is not considered to be a clinical investigation under the Medical Devices Regulations 2002.

13 TRIAL MONITORING

Trial monitoring is carried out to ensure that the rights and well-being of human participants are protected during the course of a clinical trial. A risk assessment is performed for each trial coordinated by the MC CTU to determine the level and type of monitoring required for specific hazards. The nature and extent of monitoring will be specific to the individual trial.

Trial Oversight Committees related to the monitoring of the trial are detailed in section 16.

13.1 Risk Assessment

The PREVAL trial is anticipated to be categorised as ***Type A*** *'no higher than that of standard medical care'*. The categorisation will be based on the risk assessment yielding a score ≤33% which is indicative of a low risk'.

13.2 Source Documents

Each participating site should maintain appropriate medical and research records for this trial, in compliance with International Conference on Harmonisation – E6- Good Clinical Practice guidelines Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of participants.
Additional source documents for the PREVAIL trial are:

- Screening log
- Missing Patient log

13.3 Data Capture Methods

13.3.1 Case Report Forms

The trial case report form (CRF) is the primary data collection instrument for the trial. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". Or if the data item is un-known, write "NK". If a data item has not been recorded on source data then write 'NR'. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialled and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

CRFs must be returned within 28 days following assessment unless otherwise specified on individual forms.

13.3.2 Data from electronic routine administrative databases

Please refer to section 17 for details.

13.4 Central Monitoring

MC CTU Data stored at MC CTU will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at the MC CTU from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation log). Sites will respond the queries providing an explanation/resolution to the discrepancies and return the data query forms to MC CTU. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database. There are a number of monitoring features in place at the MC CTU to ensure reliability and validity of the trial data, to be detailed in the trial monitoring plan.

13.5 Clinical Site Monitoring

In order to perform their role effectively, the trial coordinator (or monitor) and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. participant records, laboratory reports, appointment books, etc. Since this affects the participant's confidentiality, this fact is included on the Parent Information Sheet and Informed Consent Form.

13.5.1 Confidentiality

All Individual participant medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below.
Case report forms will be labelled with the participant's initials and unique trial screening and/or randomisation number. Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

The MC CTU will be undertaking activities requiring the transfer of identifiable data:
Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent/assent forms being supplied to the MC CTU by recruiting sites, which requires that name data will be transferred to the MC CTU. This will also enable future follow-up of participants to occur.

This transfer of identifiable data is disclosed in the PISC. The MC CTU will preserve the confidentiality of participants taking part in the trial and The University of Liverpool is registered as a Data Controller with the Information Commissioners Office.

13.5.2 Quality Assurance and Control

QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented/recorded and reported in compliance with applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled e.g. state what clinical site monitoring (and audit) is planned, if any.

- Data will be evaluated for compliance with protocol and accuracy in relation to source documents

- The trial will be conducted in accordance with procedures identified in the protocol.
- The Principal Investigator and RN from each site will attend the trial launch meeting, coordinated by MC CTU in conjunction with the Co-Chief investigators, Dr Sam Oddie and Professor Ruth Gilbert, which will incorporate elements of trial specific training necessary to fulfil the requirements of the protocol;
- The Trial Coordinator is to verify appropriate approvals are in place prior to initiation of a site and the relevant personnel have attended trial specific training;
- The Trial Coordinator is to check safety reporting rates between sites;
- The Trial Coordinator is to monitor screening, recruitment and drop-out rates between sites;
- The Trial Coordinator is to conduct data entry consistency checks and follow-up data queries;
- Independent oversight of the trial will be provided by the Data and Safety Monitoring Committee and independent members of the Trial Steering Committee.

13.6 Records Retention

The investigator at each investigational site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Site File until the Clinical Trials Unit informs the investigator that the documents are no longer to be retained, or for a maximum period of 15 years (whichever is soonest).

In addition, the investigator is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities).

The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The MC CTU undertakes to store originally completed CRFs for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator only. The MC CTU will archive the documents in compliance with ICH GCP utilising the Records Management Service of the University of Liverpool. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to specially renovated, secure, premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

14 INDEMNITY

PREVAIL is sponsored by UCL-Institute of Child Health and co-ordinated by the MC CTU in the University of Liverpool. The UCL-Institute of Child Health insurance policy covers for non-negligent harm to trial participants, that is, compensation to participants where negligence cannot be, or is not, proved.

However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees.

Clinical negligence is defined as:
"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

15 FINANCIAL ARRANGEMENTS

This trial is funded by the Health Technology Assessment programme (HTA) of the Department of Health. Contractual agreements will be in place between sponsor and collaborating sites that will incorporate financial arrangements.

Trial participants will not be paid to participate in the trial. The schedule of the trial will be in line with routine standard care.

As the trial is funded by the NIHR HTA, it will automatically be adopted onto the NIHR portfolio, which will allow trusts to apply to their comprehensive local research network for service support costs if required.

15.1 Financial Support to Collaborating Sites

15.1.1 Staffing

0.33 FTE RNs will be employed at each of the confirmed participating trial sites to support the identification, recruitment and management of participants for the PREVAIL trial.

15.1.2 PICCs supplied by Vygon

The devices S-PICC and AM-PICC will be supplied by Vygon to the recruiting sites for use in the trial as per the following pricing structure, for the duration of the individual recruiting sites participation in PREVAIL.

The Trial Coordinator will be responsible for informing Vygon of a Recruiting sites participation and closure to PREVAIL. Recruiting sites will only be able to source the PICCs at the discounted price once all required approvals are in place and the sites have been initiated into the trial.

- S-PICCs at list price
- AM-PICCs same price as S-PICCs list price.

15.1.3 Other payments

Funding for culture and antibiotic resistance testing

16 TRIAL COMMITTEES

16.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the Co-Chief Investigators, other lead investigators (clinical and non-clinical) and members of the MCRN Clinical Trials Unit. The TMG will be responsible for the day-to-day running and management of the trial and will meet approximately 3 times a year. Refer to the TMG terms of reference and trial oversight committee membership document for further details.

16.2 Trial Steering Committee (TSC)

The Trial Steering Committee will consist of an independent chairperson, an independent expert in the field of neonatology, a biostatistician and a lay member. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC. Refer to the TSC terms of reference and trial oversight committee membership document for further details.

16.3 Independent Data and Safety Monitoring Committee (IDSMC)

The independent Data and Safety Monitoring Committee (IDSMC) consists of an independent chairperson, plus 2 independent members. Members include an expert in the field of microbiology and an expert in medical statistics.

The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC will first convene prior to the start of recruitment and will then define frequency of subsequent meetings (at least annually). Details of the interim analysis and monitoring are provided in section 9.

The IDSMC will provide a recommendation to the Trial Steering Committee concerning the continuation of the trial. Refer to the IDSMC charter and trial oversight committee membership document for further details.

PART II: ECONOMIC ANALYSES

17 ECONOMIC ANALYSES

The economic analysis will estimate:

a) The direct hospital costs of using AM-PICC compared with S-PICC over 6 months from randomisation.
b) The cost-effectiveness of AM-PICC compared with S-PICC over the participants' expected lifetime from the perspective of the NHS
c) The potential value of additional research to reduce any uncertainty observed in the cost-effectiveness model. This will be used to inform decisions about long-term follow up of the trial cohort.
d) The value of implementing the cost-effective intervention (AM-PICC vs S-PICC) throughout the NHS in England and Wales
e) The costs of a BSI to the NHS.

The evaluation of the hospital costs (a) of using AM-PICC compared with S-PICC over the time horizon of the trial (6-months) will use routinely collected data from the National Neonatal Research Database (NNRD), Paediatric Intensive Care Audit Network (PICANet), and Hospital Episode Statistics (HES) inpatient and outpatient and Accident and Emergency (A&E), complemented as needed with hospital administrative data, over the six months of follow-up. Hospital administrative data will be used when NNRD does not hold the complete data on the baby's admission, this is the case for several of the participating hospitals that do not contribute towards NNRD. For the remaining hospitals the NNRD will provide data on the NNU stay.

PICANet will provide data on any stay in a paediatric intensive care unit. HES inpatient, outpatient and A&E will provide data on hospitalisations, outpatient appointments and A&E attendance respectively, including transfers out of the neonatal unit during the initial admission. Parent or guardian consent will be sought to obtain data on morbidity, mortality and resource use from PICANet, HES, hospital administrative data and NNRD. Participant identifiers (NHS number, date of birth, gender, name and postcode) of the babies recruited for the trial will be used to request health and social care data from the Health & Social Care Information Centre (H&SC IC) for HES, from the Neonatal Data Analysis Unit (NDAU) for NNRD, from the PICANet administrators for PICANet, from the relevant hospital finance departments for hospital administrative data and ONS for deaths. The health economics team (at the Centre for Health Economics - University of York [CHE]), with the assistance of the chief investigator, will request the data from HES, PICANet, NNRD and ONS, which will held be at CHE.

Data on resource use is held in PICANet, HES and NNRD as Healthcare Resource Group (HRG) Version 3.5. However, NHS reference costs are provided for HRG Version 4. Therefore, the data on resource use in HES and NNRD will be converted to HRG Version 4 for costing. The relevant HRG Version 4 codes are: XA01Z for intensive care, XA02Z for high dependency care, XA03Z for special care, XA04Z for special care with primary carer resident or transitional care, XA05Z for normal care and XA06Z for transportation Hospital

administrative data will be collected as number of days in each HRG code if the hospital has such records available. Alternatively, relevant resource use data will be collect to inform the costing procedure (grouping according the HRG). The HRG codes may be updated over time following the UK Department of Health guidance for the use of HRGs. The costs of AM-PICC and of S-PICC will be based on the purchasing costs by the participating sites.

The cost-effectiveness analysis (b) will estimate the difference in NHS costs and health outcomes over the participants' lifetime of using AM-PICC vs S-PICC. This will involve the development of a new decision-analytic model, following the principles established in the reference case by the National Institute of Health and Care Excellence (NICE) (36). The decision-analytic model will link the evidence on short term outcomes collected in the trial (BSI, necrotising enterocolitis, antibiotic exposure, sepsis, etc.) to external evidence on the risk of adverse neurodevelopmental outcomes in early childhood (e.g. cerebral palsy, vision impairment, hearing impairment, motor impairment, etc.). Studies on the relationship between different outcomes (e.g. odds ratio for cerebral palsy associated with necrotising enterocolitis) will be obtained from an informal literature review, advised by the clinical team. Adverse neurodevelopmental outcomes in early childhood will be linked to estimates of the loss of health and additional costs in early adolescence obtained from external evidence (37). Final health outcomes will be expressed as quality-adjusted life years (QALYs). The model will be probabilistic and Monte Carlo simulation will be used to propagate the uncertainty in the input parameters. Cost-effectiveness acceptability curves (CEACs) will be used to represent the probability that an intervention (AM-PICC or S-PICC) is a cost-effective use of NHS resources over a range of cost-effectiveness threshold values (38). In addition, the structure of the decision-analytic model will be informed by a systematic review of published cost-effectiveness models in interventions that reduce the risk of BSI in neonates.

The value of information analysis (c) will be conducted to assess the value of potential additional research, to identify which research is most valuable to the NHS and estimate the maximum investment that should be allocated to such research. The value of information analysis will estimate the expected value of perfect information and, if appropriate, the expected value of perfect information for parameters (39).

The value of implementation analysis (d) will estimate the value of implementing the cost-effective technology (AM-PICC or S-PICC) throughout the NHS in England and Wales. It will combine the information on the baseline risk of BSI and the number of PICC required all NHS NNUs, estimated in the Generalisability analysis (see Section 18) with the additional value of the cost-effective technology.

The evaluation of the costs of a BSI to the NHS (e) will take two stages. This first stage involves the evaluation of the costs of a BSI to the hospital over the time horizon of the trial by regressing hospital costs on and the number of BSI and other adjusting variables as appropriate. The first stage will be performed if there are differences in hospital costs and in the BSI rate between the groups allocated to AM-PICC and S-PICC. On a second stage, decision model built for b) will be used to estimate the lifetime costs of a BSI to the NHS.

18 PUBLICATION

The results from different sites will be analysed together and published as soon as possible. Individual Clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group. Publications must also acknowledge the PREVAIL trial.

The Trial Management Group will form the basis of the Writing Committee and will have the opportunity to advise and comment on the nature of all publications arising from patients included in the study. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants, and if there are named authors, consideration should be given to including the trial's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved and other members of the study team where relevant. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial and acknowledgement of the funding source should be attached to any publications resulting from patients included in this trial.

The members of the TSC and IDSMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

19 PROTOCOL AMENDMENTS

19.1 Version 1 (18/09/2014)

Original Approved version.

19.2 First substantial amendment Version 2.0 05/05/2015

Summary of Amendments from Protocol V1.0 to Protocol V2.0		
Page Number	**Section**	**Amendment**
Throughout		Updated version and date.
Throughout		MC CTU phone number.
Throughout		PICC 'Percutaneously Inserted Central venous Catheter' changed to 'Peripherally Inserted Central Catheter'.
Throughout		PICC Line specified as 'Premicath 1 French gauge'
Throughout		6 months specified as 26 weeks.
Throughout		BSI specified as 'BSI per 1000 PICC days)'.
Throughout		Blood culture changed to blood/CSF culture.
Throughout		Miconazole resistance testing deleted.
Throughout		Form 7b: Transfer Acknowledgement Form added to the Transfer Pack on all the transfers that will take place for the recruited baby.
Page 1		ISRCTN number: 81931394 added.
Page 11		Primary Outcome: 'CSF culture' to be collected for test and 'fungal isolates' removed from testing.
Page 11		Secondary Outcomes: Inclusion of, 'outcomes recorded during randomised PICC insertion', occurrence of 1 or more BSI, rate of blood/CSF culture sampling per 1000 PICC days BSI rated as BSI per 1000 PICC days, duration of antimicrobial exposure, time to PICC removal, clinical outcomes recorded at discharge to home from neonatal care 'Culture Negative BSI', Miconazole resistance testing removed, duration of PICC Insertion and duration of antibiotic exposure. 'rate of death' changed to 'death'
Page 11		Objectives: 'over 6 months' changed to up to '6 months'
Page 12	1.1	Clinical Follow Up: Review of clinical records specified to include, 'assessments of adverse events'. Follow up time points changed, 'To be completed for each day from randomisation until 48 hours after PICC removal/ last attempted insertion/randomisation. Can be completed retrospectively at regular intervals (minimum every 7 days). Patient Transfer to specify' if applicable'. 'Discharge from NNU' changed to 'discharge home from neonatal care'

Page 17	2.3.1.2	Secondary Objectives The following has been deleted; Rifampicin or miconazole resistance in isolates from blood cultures. Rifampicin or miconazole resistance in isolates from PICC tips. The rate of death: a)Within six months of randomisation; Before discharge from neonatal care. Requirement for treatment for retinopathy of prematurity 'before discharge' has been deleted. Time to PICC removal. The following has been added; Rifampicin resistance in isolates from blood/CSF cultures. Rifampicin resistance in isolates from PICC tips. Type of organism isolated from BSI. Time to PICC removal Death: Within six months (26 weeks) of randomisation; Before discharge home from neonatal care. Rate of CSF culture sampling per 1000 PICC days. Duration of parenteral nutrition specified that is; 'from randomisation until discharge home from neonatal care/death/6 months post randomisation' Measures of BSI, clarified to 'occurrence of 1 or more BSI'.
Page 21	4.1	Primary Endpoint Time to first BSI edited to include blood/ CSF positive culture, any positive bacterial or fungal BSI blood/CSF culture.
	4.2	Secondary Endpoints Time point for secondary endpoints stipulated 'Outcomes captured up until 48 hours after PICC removal' The following has been added to endpoints; Type of organism isolated from BSI. Time to PICC removal. The following has been deleted; Death within 6 months of randomisation. Death before discharge Time to a composite measure of BSI including culture negative BSI (based on reason for antibiotic treatment beyond 72 hours after a negative blood culture sample). 'Rate' has been deleted and replaced by 'occurrence'. Outcomes specified as; Outcomes captured up until discharge home from neonatal care/death/6 months post randomisation 'Rate of' deleted for clarity on the outcomes. Breast milk intake at discharge from NNU and Time to PICC removal have been deleted. Death has been included ;

		within 6 months (26 weeks) of randomisation before discharge home from neonatal care.
Page 22	4.3	Internal pilot included The pilot study procedure explained.
Page 23	5.1	Inclusion Criteria 'Admitted to a NNU that is recruiting for this trial' deleted.
	5.1.3	'copies of CRFs completed to date' added to the transfer pack used for transfer. Transfer Forrm Number added used for submission to MC CTU when baby is transferred.
Page 24	5.3.2	Transfer Pack for CCS, a protocol and training materials added to the pack. Follow up time for data collection for specified as; 'discharge home from neonatal care/death/26 weeks after randomisation, whichever occurs first'.
	5.3.3	Transfer: Recruiting site/CCS to a Non-Participating Site has been revised so that 'each' has been replaced by 'all' to explain that all sites to have required approvals to be able to follow up the baby upon transfer.
	5.3.4	The statement has been reworded so that the following words have been replaced; 'each' by 'all', 'which a baby is/could' by 'where babies may',' has' by 'have',' this is considered not possible' by 'the baby is transferred to a site that is not participating' and 'once the baby has been transferred has been' deleted.
Page 25	5.4	Withdrawal of consent has been rephrased so that it implicitly states the option to withdraw from the intervention before insertion without giving reason. The form to be filled in once PICC is removed is specified that is Form 6. Further clarification has been given when participant does not want their data up to withdrawal to be included in analyses. The process has been clarified and the form to be filled in stated.
Page 26	6.1	The screening process has been revised to clarify what information to be captured on the screening log to identify participants where consent is declined and where consent is provided but the baby is not randomised, the information required for monitoring purposes. Additional PICC log to be maintained, to record patients who had a PICC (Premicath 1Fr) inserted but weren't approached. The log to include reasons why patients weren't approached along with the birth weights and gestational ages.

	6.2	Eligibility confirmation clarified, to be done by the PI or designated other (on the delegation log) prior to the patient being randomised. 'Representation' replaced by representative and 'need to' added to the statement on reconsenting when patient is not randomised within 14 days.
	6.2.1	Randomisation of twins procedure has been added and clarified that twins will be treated as individuals.
Page 27	6.3	PICC insertion was specified to be, 'within 48 hours prior to PICC insertion' and trial records on randomisation changed from 'recorded' in patients notes to 'should be in patient's notes'. Randomisation Envelope procedure more information added to include the statement, 'Once opened the first page of the envelope should be returned to the MC CTU and pages 2 and 3 should be placed in the patient's medical notes'. Randomisation website details confirmed and randomisation envelopes provision word 'used' changed to 'provided'
	6.4	Form 3: Baby Characteristic Form added. Baseline consent details have been deleted to be replaced with Form 3 details. The following details have been added; age, Final estimated delivery date, Membranes ruptured >24 hours before delivery?, Maternal medication, Surgical procedures in 14 days prior to randomisation, Samples taken within 72 hours prior to randomisation and PICC placement details. The following details have been removed; Apgar score at 5, 10 minutes and Gestational age, Antifungal medication (including antifungal prophylaxis) taken within 72 hours prior to randomisation, Ruptured membranes for >24 hours pre delivery, Antenatal steroid exposure and Details of abdominal and thoracic surgical procedures within 7 days prior to randomisation The statement on respiratory support 'required at' replaced with 'within 72 hours prior to'
Page 28	6.5	Clinical follow-up time has been changed to 'at randomisation' from 'starting at 48hours after randomisation'. Form 4 has been added with the details to be captured on the Follow-up form that is; Daily Follow-up which should be completed for each day from randomisation and the statement 'randomisation if not attempted' has been added to the statement. The following statement has been included in completing the follow-up form, 'It may be completed retrospectively but it must be completed regularly (at a minimum of every 7 days).

		It should be completed as at 23.59 on the specified dates'. The following information has been deleted; Parental nutrition and whether lipid included, Level of care required (intensive care, high dependency care or special care), Randomised PICC status Clinical outcomes (related expected adverse events), PICC tip culture taken (if applicable) and 'Unexepected related Adverse Events' have been changed to 'Rrelated adverse events – Form 8: Related AEs also needs updating'. The following information to be collected added; Randomised PICC status (in situ/removed/ etc) and 'Form 5: Microbiology also needs updating' statement added to collection of PICC tip culture and blood/ CSF culture samples.
Page 29	6.6	'NNU/ Transfer/ Discharge/Death' event has been changed to, 'Discharge home from neonatal care/Transfer/ /Death/26 weeks after randomisation' The statement 'This will be recorded on Form 7a: Clinical Outcomes' has been added to the retrospective review aspect. The following key events have been added; Details of receiving hospital, Breast milk intake, Level of care, Necrotising enterocolitis (NEC), Periventricular leukomalacia, Retinopathy of prematurity, Bronchopulmonary dysplasia, Intracranial haemorrhage and Duration of parenteral nutrition. The following has been removed' Development of NEC (Bell stage II criteria or greater), Details of any cranial ultrasound abnormalities, Development of chronic lung disease at 36 weeks gestation age, Development of retinopathy of prematurity and grade, Date first reached full milk feeds, Details of breast milk intake at discharge, Details of abdominal and thoracic surgical procedures and Details of Transfer/Discharge/Death.
Page 30	7.3	Administering of the PICC the allocated PICC not used will be recorded Form 3: Baby characteristics changed from 'Randomisation CRF' 'Form 6: Removal' added to where to record PICC removal details.
	7.4	Typing error 'in' transposed to read 'procedures in'
	7.5	'type of treatment' replaced with 'medication' and 'route of administration' is deleted.
		The following statement 'Co-enrolment into other trials is encouraged as this trial involves minimal burden on the parents or baby' is added for clarity.
Page 33	8.1	The following schedule of assessments revised to fit in with the trial procedures and timelines.
Page 34	8.3	Microbiology Form 5 added for clarification on data collection.

		Blood and blood culture collection clarified and the procedure explained for accuracy. SOP on PICC culture included for easy reference on culturing the PICCs.
Page 35	8.3	Clinical outcomes not to be collected as not required.
	8.5	Loss of follow up procedure further clarified to make it easy to follow procedure.
Page 40		Table 4: Reporting adverse Events revised to match with the type of forms to be used.
Page 43	10.2.6	Table 7: Expected AEs related to PICC Insertion revised on AE description for clarity.
Page 44		Table 8 included to spell out the Related Adverse Events associated with PICC insertion and on which form adverse event description to be captured.
Page 45	10.3	Flow chart for reporting requirements of AEs revised to accommodate the changes of the forms used to capture AEs.
Page 52	13.2	Source documents specified for clarity.
	13.3.1	CRF retention timelines specified and location of timelines for submission indicated on the forms.
Page 56	15.1.3	Other payments revised to remove payment of archiving costs. The resistance cost added.
Page 57	16.2	Lay member added to the TSC group.
Page 54 -55		Health Economics analyses revised to clarify procedures on how data will be collected and the databases where information will be collected from and timelines of data collection.

19.3 Second substantial Amendment Version 3.0 12/10/2015

Summary of Amendments from Protocol V2.0 to Protocol V3.0		
Page Number	**Section**	**Amendment**
Throughout		Updated version and date.
2		Added protocol authorisation by Lead Statistician
23	5.4	Clarification added regarding data linkage in the case of participant withdrawal
26	6.6	Breast milk intake amended to milk intake
27	7.2	Reference added to section 7.3.1
28	7.3.1	Added definition of successful line placement
28	7.4	Procurement of lines updated to reflect changes in ordering lines from Vygon
29	7.5	Description of how concomitant medications will be captured amended for clarity
31	8.2	Table 1 updated to include length of follow-up in situations where non-allocated PICC inserted

36	10.1	Table 4 corrected to include completion of Form 9b (Medical Device Adverse Incident Report) for related, unexpected adverse not-serious events
39	10.2.6	Table 7 updated to include difficulty in removing stylet as an expected Adverse Event
43	10.6	Safety Reporting updated to clarify that only related AE/SAEs are reported. SAE Reporting updated to reflect that only Related Unexpected SAEs need to be reported on Form 9a. Updated acronyms to consistent use of RUSAE throughout.
45	11.2	Clarification on circumstances under which fathers of potential participants can/cannot provide consent.

19.4 Third Substantial Amendment, Version 4.0 date 19/08/2016

Summary of Amendments from Protocol V3.0 to Protocol V4.0		
Page Number	**Section**	**Amendment**
Throughout		Updated version and date.
26	6.2	Added confirmation of who can confirm eligibility and sign Form 1. Clarified trial team and sponsor opinion on physician supervision of all neonatal care.
29	6.7	Addition of co-enrolment log to be completed at the end of trial follow-up.
32	7.6	Addition of co-enrolment log to be completed at the end of trial follow-up.
49	11.3	Additional clarification of what constitutes informed consent added along with statement regarding consequences of not following informed consent procedures (potential serious breach).

19.5 Fourth Substantial Amendment, Version 5.0 date 26/04/2017

Summary of Amendments from Protocol V4.0 to Protocol V5.0		
Page Number	**Section**	**Amendment**
Throughout		Updated version and date.
Throughout		Updated contact telephone number for CTRC from 0151 282 4716 to 0151 795 8757
Throughout		Updated contact fax number for CTRC from 0151 282 4721 to 0151 795 8770
2, 3, 4		Updated contact email address for Sponsor from R&Dgovernance@gosh.nhs.uk to research.governance@gosh.nhs.uk
11	1	Time to death added as a secondary outcome

16	2.3.1.	Time to death added as a secondary outcome
19	4.2	Time to death added as a secondary outcome
45	10.6	“or next working day” removed from time frame for returning RUSAE reports (in line with Clinical Trials Regulations, CT3)

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21 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

- Parent/Legal Guardian information sheets and consent form
- Recruiting / Care Continuing Sites
- Guidance sheets for hospital transfers
- Oversight committee membership.

22 APPENDICES

Appendix 1: Case Definition of Necrotising Enterocolitis

NEC may be diagnosed at surgery, at post-mortem examination or clinically and radiologically using the following criteria:

At least one of the following clinical signs present:
• Bilious gastric aspirate or emesis
• Abdominal distension
• Occult or gross blood in stool (no fissure)

and at least one of the following radiological features:
• Pneumatosis intestinalis
• Hepato-biliary gas
• Pneumoperitoneum

Infants who satisfy the definition of NEC above but are found at surgery or post-mortem examination for that episode to have a “Focal Gastrointestinal Perforation” should be coded as having “Focal Gastrointestinal Perforation”, not as having NEC.