

The efficacy and safety of two topical antiseptic solutions for skin disinfection prior to percutaneous central venous catheter insertion in preterm neonates: a feasibility study

PROTOCOL

This protocol has regard for the HRA guidance

Chief Investigator: Dr Paul Clarke
Consultant Neonatologist
Neonatal Intensive Care Unit
Norfolk and Norwich University Hospitals NHS Foundation Trust,
Colney Lane, Norwich,
Norfolk, NR4 7UY
Tel. 01603 286337

Clinical Trials Unit: National Perinatal Epidemiology Unit Clinical Trials Unit
Nuffield Department of Population Health, University of Oxford
Old Road Campus, Oxford, OX3 7LF
Tel: 01865 289700

Sponsor: Norfolk and Norwich University Hospitals NHS Foundation Trust

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:/...../.....

Name (please print):

Position: Research Services Manager

Trial Statistician:

Signature: Date:/...../.....

Name: (please print):

LOUISE LINSELL

Chief Investigator:

Signature: Date:/...../.....

Name: (please print):

DR PAUL CLARKE

KEY TRIAL CONTACTS

Chief Investigator	<p>Dr Paul Clarke Consultant Neonatologist Neonatal Intensive Care Unit Norfolk and Norwich University Hospitals NHS Foundation Trust, Colney Lane, Norwich, Norfolk, NR4 7UY Tel. 01603 286337 Fax. 01603 289800 Email: paul.clarke@nnuh.nhs.uk</p>
Sponsor	<p>The Research Service Manager Research and Development Office Level 3 East Block, Norfolk and Norwich University Hospitals NHS Foundation Trust, Colney Lane, Norwich, Norfolk, NR4 7UY Tel. 01603 288437 Fax. 01603 289800 Email: rdoffice@nnuh.nhs.uk</p>
Funder	<p>National Institute of Health Research – Research for Patient Benefit Programme (project ref. PB-PG-1013-32076) National Institute for Health Research Central Commissioning Facility Grange House 15 Church Street Twickenham TW1 3NL Tel. 0208 843 8057 Fax. 0208 843 8001</p>
Clinical Trials Unit	<p>National Perinatal Epidemiology Unit Clinical Trials Unit Nuffield Department of Population Health University of Oxford Old Road Campus Oxford OX3 7LF Tel: 01865 289728 Fax. 01865 289740 Email: ctu@npeu.ox.ac.uk</p>

INDEX OF CONTENTS

Title Page	1
Research Reference Numbers	2
Signature Page	3
Key Trial Contacts	4
Index of Contents	5
SECTION:	
1. Trial Summary	8
2. Trial Flow Chart	11
3. List of Abbreviations	12
4. Introduction	14
4.1 Background.....	14
4.2 Rationale.....	15
4.3 Assessment and Management of Risk.....	17
5. Trial Definitions, Objectives, and Outcome Measures/Endpoints	18
5.1 Case definitions.....	18
5.1.1 Definite Catheter-Related Sepsis.....	18
5.1.2 Catheter colonisation.....	18
5.1.3 Catheter-Associated Sepsis.....	18
5.2 Primary Objective.....	18
5.3 Secondary Objectives.....	18
5.4 Primary Endpoint/Outcome.....	19
5.5 Secondary Endpoints/Outcomes.....	19
5.5.1 Efficacy Measures.....	19
5.5.2 Safety Measures.....	19
5.5.3 Process Outcomes.....	19
6. Trial Design	20
6.1 Summary.....	20
6.2 Study Setting.....	20
6.3 Eligibility Criteria.....	20
6.3.1 Inclusion Criteria.....	20
6.3.2 Exclusion Criteria.....	20
7. Trial Procedures	21
7.1 Recruitment.....	22
7.1.1 Duration of Recruitment.....	22
7.1.2 Screening and Eligibility Assessment.....	22
7.1.3 Informed Consent.....	22
7.1.4 Enrolment.....	22
7.1.5 Remuneration.....	22
7.2 Randomisation.....	22
7.3 Trial Interventions.....	23
7.3.1 Catheters.....	23
7.3.2 Protocol for Catheter Insertion.....	23
7.3.3 Study Packs.....	24

7.3.4 Skin Disinfection at Catheter Insertion.....	24
7.3.5 Assessment of Skin Condition.....	24
7.3.6 Study Samples to be Obtained at Catheter Removal.....	25
7.3.7 Protocol for Catheter Removal and Obtainment of Study Samples at Removal...	25
7.3.8 Microbiology.....	26
7.3.9 Arrangements for Transport, Storage and Custodianship of Study Samples.....	27
7.3.10 Unsuccessful Catheterisation Attempts.....	27
7.4 Data Collection.....	27
7.5 Supportive Care of Enrolled Babies.....	28
7.6 Discontinuation of trial intervention.....	28
7.7 End of Trial.....	28
7.8 Early Trial Cessation.....	29
8. Investigational Medicinal Product (IMP).....	30
8.1 Legal Status of the Antiseptic Investigational Medicinal Products.....	30
8.2 Summary of Product Characteristics.....	30
8.3 Preparation and Labelling of Investigational Medicinal Products.....	30
8.4 Distribution.....	30
8.5 Storage.....	30
8.6 Accountability.....	30
8.7 Blinding of Trial Medication.....	31
8.8 Procedure for Unblinding.....	31
8.9 Known Drug Reactions and Interaction with Other Therapies.....	31
8.10 Concomitant Medications.....	32
9. Pharmacovigilance.....	33
9.1 Definitions	33
9.1.1 Adverse Event (AE)	33
9.1.2 Adverse Reaction (AR)	33
9.1.3 Serious Adverse Event (SAE)	33
9.1.4 Serious Adverse Reaction (SAR)	33
9.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)	33
9.1.6 Foreseeable Serious Adverse Events.....	34
9.1.7 Unforeseeable Serious Adverse Events.....	34
9.2 Causality.....	34
9.3 Assessment of Safety.....	34
9.4 Reporting Procedures.....	35
9.4.1 AE/SAE Reporting.....	35
9.4.2 SAR Reporting.....	36
9.4.3 SUSAR Reporting.....	37
9.4.4 Yellow Card Scheme Reporting.....	37
9.4.5 Development Safety Update Reports.....	37
10. Statistics and Data Analysis.....	38
10.1 Sample Size Calculation and Expected Recruitment Rate.....	38
10.2 Data Analysis and Assessment of Feasibility Criteria.....	38
10.3 Economic Evaluation.....	38
11. Source Data/Documents.....	39

12. Quality Control and Assurance	40
12.1. Risk Assessment.....	40
12.2 National Registration Systems.....	40
12.3 Site Initiation and Training.....	40
12.4 Site Monitoring and Auditing.....	40
12.5 Archiving.....	40
13. Regulatory Considerations	42
13.1 Serious Breach of Good Clinical Practice or of the Trial Protocol.....	42
13.2 Regulatory Compliance.....	42
14. Ethics	43
14.1 Declaration of Helsinki.....	43
14.2 ICH Guidelines for Good Clinical Practice.....	43
14.3 Approvals.....	43
14.4 Participant Confidentiality, Data Handling and Record Keeping.....	43
14.5 Retention of Personal Data.....	44
15. Funding	45
16. Insurance	45
17. Trial Governance	45
17.1 Site Research and Development Approval.....	45
17.2 Trial Sponsor.....	45
17.3 Trial Co-ordinating Centre.....	45
17.4 Trial Management Group (TMG)	45
17.5 Trial Steering Committee (TSC)	46
17.6 Data Monitoring Committee (DMC)	46
18. Public and Patient Involvement	47
19. Communication	48
19.1 Study Findings.....	48
19.2 Dissemination Plan.....	48
19.3 Publication Policy/Acknowledgement of Contribution.....	48
20. Expected Output of Research/Plans for Future Large-Scale Study	49
21. References	50

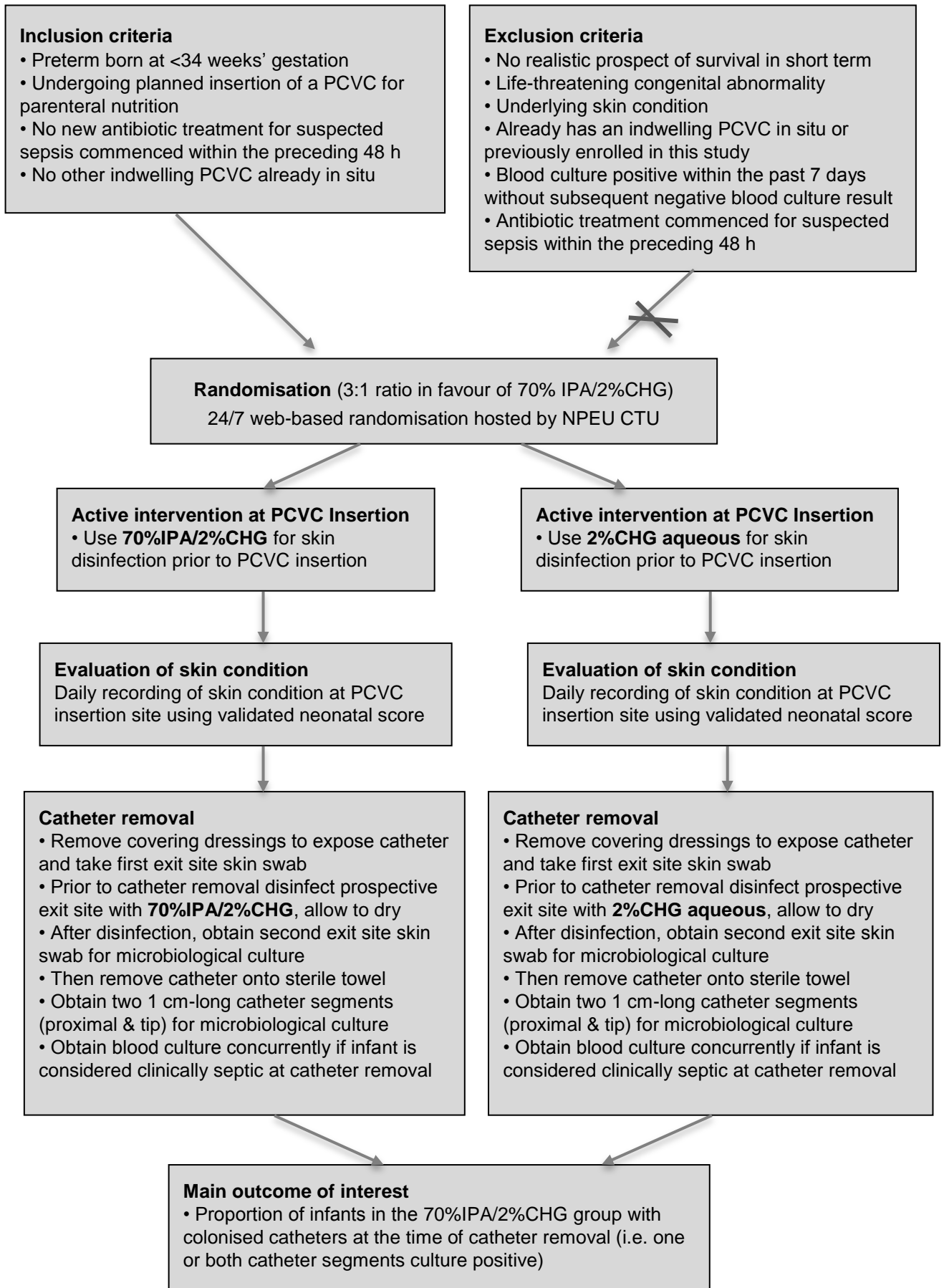
1. TRIAL SUMMARY

Full Trial Title	The efficacy and safety of two topical antiseptic solutions for skin disinfection prior to percutaneous central venous catheter insertion in preterm neonates: a feasibility study
Short Title	ARCTIC - Antiseptic Randomised Controlled Trial for Insertion of Catheters
Clinical Phase	III
Trial Design	Feasibility Study (masked randomised controlled trial)
Trial Participants	<p>Preterm infants who are undergoing planned insertion of a percutaneous central venous catheter (PCVC) will be randomised to receive one of two commonly used topical disinfection agents for skin antisepsis</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Preterm infants born at <34 weeks' gestation • Requiring routine insertion of a PCVC for parenteral nutrition • No new suspected sepsis with commencement of antibiotics occurring within the 48 hours preceding planned catheter insertion • No other indwelling PCVC already in situ <p>Exclusion criteria</p> <ul style="list-style-type: none"> • No realistic prospect of survival in the short term • Life-threatening congenital abnormality • Underlying skin condition • Already has another indwelling PCVC in situ or was previously enrolled into the study in respect of an earlier PCVC episode • Positive blood culture (BC) within the past 7 days without a subsequent negative blood culture result • Antibiotic treatment commenced for suspected sepsis within the preceding 48 hours
Trial Sites	Two Neonatal Intensive Care Units (level 3)
Planned Sample Size	Approximately 93 infants who successfully undergo PCVC insertion
Follow up duration	Participants will be studied from the time of catheter insertion until 48 hours after catheter removal. When catheterisation proves unsuccessful, participants will be monitored until 48 hours after antiseptic application.
Planned Trial Period	24 months
Primary Objective	To estimate the prevalence of babies in the 70%IPA/2%CHG arm with central venous catheter bacterial colonisation at the time of catheter removal in order to inform the sample size calculation for the large-scale trial

Primary Outcome Measure	Proportion of babies in the 70%IPA/2%CHG arm with catheter colonisation as determined by positive bacterial culture from one or both of the catheter segments taken at catheter removal
Secondary Objectives	<ol style="list-style-type: none"> I. To gauge parents' and clinicians' willingness for babies to be randomised to 2%CHG or 70%IPA/2%CHG skin antiseptics and to determine views on factors that may affect recruitment II. To determine whether taking a skin swab after skin disinfection at catheter removal needs to be incorporated into the future large-scale trial III. To examine whether culture of paired rather than single segments of removed catheters should be incorporated into the future large-scale trial, to increase the sensitivity of detection of catheter colonisation IV. To determine whether molecular typing of skin and catheter isolates to a species level will be essential for the future large-scale trial V. To estimate numbers of enrolled infants who have definite catheter-related sepsis VI. To estimate numbers of enrolled infants who have catheter-associated sepsis VII. To determine suitability and completeness of data collection methods VIII. To describe any skin morbidity occurring in trial participants related to use of the two study antiseptics in this population
Secondary Outcome Measures	<p>Efficacy measures:</p> <ol style="list-style-type: none"> I. Rates of recruitment and retention to the study, and the collection of views of parents and clinicians on factors affecting recruitment and retention II. Proportion of infants with positive exit-site skin swabs (ESSS) at catheter removal III. Number and type of catheter segments culture positive at removal IV. Bacterial species (typed via molecular methods) of isolates identified on positive BC, ESSS, and catheter segment V. Proportion of infants undergoing an infection screen in the period between catheter insertion and 48 hours post-catheter removal that meets case definition for definite catheter-related sepsis VI. Proportion of infants with positive blood culture from any infection screen in the period between catheter insertion and 48 hours post-catheter removal that meets definition for catheter-associated sepsis VII. Rate of catheter-related sepsis per 1000 PCVC days VIII. Rate of catheter-associated sepsis per 1000 PCVC days IX. Proportion of infants completing study with complete data for the primary outcome and proportions of infants with missing data collection forms

	<p>Safety measure:</p> <p>VIII. Daily skin morbidity scores in the period between catheter insertion and 48 hours post-catheter removal, and in the period between antiseptic application and 48 hours post antiseptic application where catheterisation was unsuccessful.</p>
<p>Investigational Medicinal Products</p>	<p>The two antiseptics that will be used in this study are:</p> <ul style="list-style-type: none"> • Aqueous-based 2% chlorhexidine gluconate (2%CHG) • Alcohol-based (70% isopropyl alcohol) 2% chlorhexidine gluconate (70%IPA/2%CHG) <p>Each study pack will contain two high-density polyethylene bottles with polypropylene caps each containing 20 mL of coloured Investigational Medicinal Product (IMP) antiseptic solution in ready-to-use form. Each pair of bottles will be assigned a unique randomisation number present on the label to ensure concealment of allocation. The bottles are for single patient use at the time of catheter insertion and removal. The antiseptic will be applied sparingly and will be allowed to dry completely on the skin for at least 30 seconds after application.</p>

2. TRIAL FLOW CHART



3. LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BC	Blood Culture
CHG	Chlorhexidine Gluconate
CI	Chief Investigator
CRS	Catheter-Related Sepsis
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DCF	Data Collection Form
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
ESSS	Exit Site Skin Swab
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HRA	Health Research Authority
IB	Investigator Brochure
IPA	Isopropyl Alcohol
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
ICMJE	International Committee of Medical Journal Editors
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IRAS	Integrated Research Application System
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
MHRA	Medicines and Healthcare products Regulatory Agency
NHS R&D	National Health Service Research & Development
NICU	Neonatal Intensive Care Unit
NIHR	National Institute for Health Research
NPEU CTU	National Perinatal Epidemiology Unit Clinical Trials Unit
PCVC	Percutaneous Central Venous Catheter
PI	Principal Investigator
PICF	Parental Informed Consent Form
PPI	Patient and Public Involvement
QA	Quality Assurance

QC	Quality Control
RCT	Randomised Controlled Trial
RCPCH	Royal College of Paediatrics and Child Health
REC	Research Ethics Committee
RfPB	Research for Patient Benefit
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SIMPD	Simplified Investigational Medicinal Product Dossier
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File

STUDY PROTOCOL

The efficacy and safety of two topical antiseptic solutions for skin disinfection prior to percutaneous central venous catheter insertion in preterm neonates: a feasibility study

4. INTRODUCTION

4.1 Background

Percutaneous central venous catheters (PCVCs) are inserted daily in neonatal intensive care for intravenous feeding of sick premature neonates. The presence of indwelling PCVCs is a significant risk factor for catheter-related sepsis (CRS), a dangerous healthcare complication associated with considerable morbidity and mortality. Colonisation of the catheter with bacteria is strongly associated with definite CRS; in a previous study, a colonised catheter tip was associated with a 10-fold increased risk of CRS[1].

Adequate skin antisepsis at catheter insertion is an important component of catheter-care bundles to prevent CRS. Despite many advances in neonatal care in the past few decades we still do not know the best antiseptic to use for preterm babies. There are very few studies in neonates and their vulnerability to skin damage is greater. Consequently there is no national recommendation regarding the preferred antiseptic for neonates and a wide variety of them are currently used. Alcohol-based antiseptics are considered superior in adults, but there are no controlled studies of alcohol-based antiseptics for PCVC insertion in neonates. Topical alcohol use increases the risk of neonatal skin damage and systemic chemical absorption[2,3], yet still there is no evidence in babies that alcohol is an essential component of antiseptics for preventing CRS.

Antibiotic/antiseptic-impregnated PCVCs are recommended in older children and adults *only* after failure of comprehensive measures to reduce CRS that include '*a >0.5% chlorhexidine preparation with alcohol*'. [4] Clearly optimising skin antisepsis in babies must be prioritised. Studies are needed to find out whether alcohol-based antiseptics are indicated for PCVC insertion.

This study aims to obtain information essential for the design of a large future multicentre, randomised controlled non-inferiority trial that will compare the efficacy and safety of two topical antiseptics for skin disinfection prior to neonatal PCVC insertion. This feasibility study will test study procedures and, in particular, will estimate the prevalence of extraluminal catheter colonisation at the time of catheter removal to allow accurate estimation of the requisite sample size for the large-scale study.

This feasibility study will be a multicentre, randomised controlled trial of two antiseptics for neonatal skin disinfection. We aim to recruit at least 93 preterm infants who successfully undergo planned insertion of a PCVC in two centres over a 14-month period. Infants will be randomised to either aqueous-based 2% chlorhexidine gluconate (2%CHG) or 70% isopropyl alcohol-based 2% chlorhexidine gluconate (70%IPA/2%CHG) for skin disinfection prior to PCVC insertion. Both these antiseptics are commonly used in neonates in the UK, Europe, and United States[5-7]. Neonatal skin burns have been reported with alcohol-based antiseptics[3,8-12], but we have identified only a single report with 2% CHG aqueous[13]. Thus there is good reason to prefer the CHG solution, should it provide at least equivalent efficacy against infection as the alcohol-based solution. The

2%CHG aqueous solution will allow direct comparison of neonatal skin sterilisation versus the alcohol-containing preparation. Two PCVC segments and an insertion-site skin swab will be collected for microbiological culture at catheter removal. Isolates from culture-positive skin swabs, catheter segments, and blood will undergo molecular typing to verify that skin-colonising and blood-cultured organisms match catheter-colonising organisms to a species level. Detection of mainly extraluminal catheter colonisation provides a valid marker of antiseptic efficacy, and is thus a reasonable surrogate for the incidence of CRS. Safety will be determined by daily skin monitoring using a validated neonatal skin assessment tool.

This feasibility study will directly inform the design of a large-scale trial. The large trial will test whether 2% CHG aqueous is not inferior in terms of antiseptic efficacy to 70%IPA/2%CHG for skin disinfection prior to PCVC insertion in preterm neonates. This will provide sound evidence for the preferred antiseptic in neonates. If the aqueous-based antiseptic is found to be non inferior, then aqueous rather than alcohol-based chlorhexidine can be widely promoted for use in neonates. This would remove risks and costs of morbidity from neonatal skin damage and the potential harm of systemic absorption from alcohol-based chlorhexidine use.

4.2 Rationale

Insertion of PCVCs is an everyday procedure in neonatal intensive care units (NICUs). Many thousands are inserted in neonates each year in the UK. In 2012, 921 babies in our region alone had PCVCs inserted; these remained in situ for a collective total of 10,590 days (East of England 2012 Annual Report). PCVCs are essential for intravenous feeding of sick premature neonates but their presence is a significant risk factor for infection. In neonates, catheter infection is one of the most dangerous healthcare complications and is associated with considerable morbidity and mortality[14-18]. A recent prospective study by our collaborative group showed that almost 8% of PCVCs inserted are associated with definite catheter infection, and around a quarter of catheters removed from well infants are colonised with potentially-pathogenic bacteria[19]. Neonatal sepsis prolongs the duration of intensive care and overall hospitalisation, increases the need for antibiotics, and increases the risks of adverse neurodevelopmental outcome[17,20-23]. The main mechanism by which catheters become infected is via extraluminal colonisation, i.e. skin bacteria traversing the insertion site onto the catheter's external surface thereby colonising it while in situ, and eventually acting as the focus for development of catheter infection[19,24- 26]. The density of skin bacteria at the catheter insertion site is a major risk factor for catheter-related sepsis (CRS)[4]. An optimal skin disinfectant will safely eradicate or significantly reduce numbers of residual skin organisms present before a PCVC is inserted, with a sufficient duration of action, to limit the risk of extraluminal PCVC colonisation and subsequent systemic infection. Use of antibiotic/antiseptic-impregnated PCVCs in older children and adults is recommended as a last resort, *only* after failure of comprehensive measures to reduce CRS that include 'a >0.5% chlorhexidine preparation with alcohol'[4]. Clearly optimising skin antisepsis in babies is the priority.

Adequate skin disinfection before PCVC insertion is a crucial factor in reducing the risk of CRS. However very few randomised studies of antiseptics have been conducted in neonates. The lack of consensus is highlighted by national surveys of antiseptic use in neonates[5-7]. Seven different antiseptic formulations are currently used for PCVC insertion in UK NICUs[7] (**Table 1**). Many clinicians hold strong preferences for and against the use of concentrated alcohol-based CHG solutions[7].

Table 1 *Antiseptics used in the 57 tertiary-level UK neonatal units in 2013*

Name of product used for PCVC insertion*	Antiseptic/s	Number of NICUs
ChloraPrep	2% chlorhexidine gluconate + 70% isopropyl alcohol	23
Clinell	2% chlorhexidine gluconate + 70% isopropyl alcohol	3
Hydrex	0.5% chlorhexidine gluconate + 70% isopropyl alcohol	8
Hibitane	1% chlorhexidine gluconate (aqueous)	2
Sterexidine 200	0.5% chlorhexidine gluconate (aqueous)	7
Unisept	0.05% Chlorhexidine gluconate (aqueous)	19
Tisept	0.015% chlorhexidine gluconate + 0.15% cetrimide (aqueous)	7
Videne	7.5% Aqueous povidone iodine	1

*twelve units used more than one antiseptic according to gestational age group
Data are from Heron et al.[7].

Chlorhexidine gluconate (CHG) is a broad-spectrum bactericidal agent with a long duration of action. It is the most commonly used antiseptic in adults, and the antiseptic currently used in one form or another in almost all UK NICUs[7]. Studies in adults showed that a 2%CHG concentration is more effective than weaker CHG preparations, and approximately half of UK NICUs now use 2%CHG (**Table 1**). However a major question about CHG use in neonates remains unanswered: is alcohol needed to accompany CHG for adequate skin disinfection? A single comparative study in adults showed that use of an alcohol-based CHG solution resulted in significantly fewer skin bacteria after 24h, implying short-term superiority for topical antiseptics over aqueous CHG[27].

UK national evidence-based guidelines recommend use of 2% chlorhexidine in 70% isopropyl alcohol (70%IPA/2%CHG) for skin antiseptics in adults and older children, but give no specific guidance for preferred antiseptic in infants (<1 year of age) due to a lack of evidence in this population[28,29]. A recent review of good practice guidelines for reducing catheter infections in neonates recommends 70%IPA/2%CHG as the preferred skin antiseptic[30], yet the only supporting data come from adult studies. Even the manufacturers of the CHG/alcohol solutions specifically advise against their use in infants.

There are risks associated with use of concentrated and alcohol-containing antiseptics in premature infants. Their thin skin is particularly vulnerable to chemical injury and absorption. Chemical skin burns have been described with all the currently-used topical antiseptics, including both aqueous and alcohol-containing CHG formulations and iodine solutions[8-13,31,32], though alcohol-based formulations account for most reports. Skin burns cause significant morbidity[9-12], including scarring and need for plastic surgery[10], and can be life threatening by predisposing to bacterial invasion and sepsis[9,12]. Alcohol may also increase the risk for systemic CHG absorption[2].

Alcohol itself can also be absorbed through the skin of neonates with local and systemic toxic effects[3]. While alcohol is teratogenic to developing humans, no studies have yet been done in preterm neonates to assess blood levels from isopropyl alcohol absorption after topical antiseptics, and any possible effect on neurodevelopment is unknown.

Since 2010, the adoption by NICUs of catheter-care bundles essentially formulated for use in adult patients has led to increasing use of alcohol-based CHG solutions in babies[7]. 53% of tertiary UK NICUs now use alcohol-based CHG preparations[7](**Table 1**). Yet still there is no trial evidence in premature infants to show that alcohol-based CHG antiseptics are more effective, necessary, or safe. Their increasingly widespread adoption in preterm babies without good supporting evidence may be exposing neonates to adverse morbidity without any corresponding increase in efficacy at preventing CRS.

No published RCTs have so far examined the need for alcohol-based CHG in neonatal antiseptics. A Canadian RCT is comparing 70%IPA/2%CHG versus 2%CHG aqueous in preterm infants for skin disinfection prior to peripheral venepuncture. Notably, interim analysis showed identical short-term efficacy of these antiseptics (www.tinyurl.com/pa756j4). Importantly, this finding supports this present study's rationale that alcohol may be superfluous beyond 2%CHG alone for skin disinfection in preterm neonates. Only a large well-conducted RCT can provide data of sufficient quality to indicate what antiseptic should be used for the longer-term skin disinfection needed prior to *central* venous cannulation, to minimise risks of both CRS and iatrogenic harm.

This will be the first trial performed in the neonatal population to address this question. This feasibility study is needed to design the large-scale trial that will examine whether 2%CHG aqueous is non-inferior in antiseptic efficacy when compared to 70%IPA/2%CHG for skin disinfection prior to PCVC insertion in preterm neonates.

4.3 Assessment and Management of Risk

According to the MRC/DH/MHRA Joint Project on Risk-adapted Approaches to the Management of Clinical Trials of IMPs (October 2011),[33] this feasibility study will be classified as Type A (risk no higher than that of standard medical care).

A risk assessment has also been undertaken by the Sponsor.

The study will be NIHR registered and conducted in accordance with the principles of ICH-GCP.

5. TRIAL DEFINITIONS, OBJECTIVES, AND OUTCOME MEASURES/ENDPOINTS

5.1 Case definitions

5.1.1 Definite Catheter-Related Sepsis:

This feasibility study will use a strict definition of 'definite CRS' as follows:

“A peripheral blood culture plus any catheter segment positive with the same organism, based on bacterial culture, antibiotic sensitivity and molecular typing, from a neonate with an indwelling PCVC and clinical signs of sepsis but no other focus of sepsis.”

The study will therefore assess a more stringent definition of 'definite CRS' than is commonly applied in clinical practice. Namely, it additionally requires identical bacterial species to be present in paired blood and catheter-positive isolates. If such detailed characterisation proves feasible and improves/refines diagnostic determination of CRS beyond the currently used clinical definition (which does not demand typing to species level), we will consider incorporating this addition into the future large-scale trial also.

5.1.2 Catheter Colonisation:

“A catheter that at the time of removal has either one or both segments that are culture positive.”

This encompasses catheters removed from well infants as well as those removed from infants with suspected sepsis.

5.1.2 Catheter-Associated Sepsis:

“A baby with clinical signs of sepsis and an accompanying positive blood culture in the period between catheter insertion and 48 hours post removal but who has no other focus of sepsis and in whom both catheter segment cultures are negative for the blood-cultured organism.”

5.2 Primary Objective

The primary objective of this feasibility study is:

- To estimate the prevalence of babies in the 70%IPA/2%CHG arm with central venous catheter bacterial colonisation at the time of catheter removal in order to inform the sample size calculation for the large-scale trial.

5.3 Secondary Objectives

The secondary objectives are:

- I. To gauge parents' and clinicians' willingness for babies to be randomised to 2%CHG or 70%IPA/2%CHG skin antiseptics and to determine views on factors that may affect recruitment
- II. To determine whether taking a skin swab after skin disinfection at catheter removal needs to be incorporated into the future large-scale trial.
- III. To examine whether culture of paired rather than single segments of removed catheters should be incorporated into the future large-scale trial, to increase the sensitivity of detection of catheter colonisation.
- IV. To determine whether molecular typing of skin and catheter isolates to a species level will be essential for the future large-scale trial.
- V. To estimate numbers of enrolled infants who have definite catheter-related sepsis
- VI. To estimate numbers of enrolled infants who have catheter-associated sepsis

- VII. To determine suitability and completeness of data collection methods.
- VIII. To describe any skin morbidity occurring in trial participants related to use of the two study antiseptics in this population

5.4 Primary Endpoint/Outcome

The primary outcome measure will be the proportion of babies in the 70%IPA/2%CHG arm with catheter colonisation as determined by culture of catheter segment/s taken at catheter removal.

Rationale: Previous work by our group has shown that extraluminal catheter colonisation is strongly associated with definite CRS (see Sec. 5.1 for case definitions): a colonised catheter tip was associated with a 10-fold increased risk[1]. Catheter colonisation in well babies is a preface to the development of CRS. While the incidence of CRS is the main factor of overriding clinical interest, the incidence of definite CRS in our previous study was only 8% of all catheters inserted[19]. In the context of this feasibility study, which utilises standardised good practices for catheter-care and more concentrated/ alcohol-based CHG solutions, the incidence of CRS may be lower. However the prevalence of catheter colonisation at catheter removal in our previous study was 32%[19]. Detection of mainly extraluminal catheter colonisation provides a valid marker of antiseptic efficacy, and is therefore a reasonable surrogate for CRS.

5.5 Secondary Endpoints/Outcomes

5.5.1 Efficacy Measures:

- I. Rates of recruitment and retention to the study, and the collection of views of parents and clinicians on factors affecting recruitment and retention.
- II. Proportion of infants with positive exit-site skin swabs (ESSS) at catheter removal
- III. Number and type of catheter segments culture positive at removal
- IV. Bacterial species (typed via molecular methods) of isolates identified on positive blood culture (BC), ESSS, and catheter segment
- V. Proportion of infants undergoing an infection screen in the period between catheter insertion and 48 hours post-catheter removal that meets case definition for definite catheter-related sepsis
- VI. Proportion of infants with positive BC from any infection screen in the period between catheter insertion and 48 hours post-catheter removal that meets definition for catheter-associated sepsis
- VII. Rate of catheter-related sepsis per 1000 PCVC days
- VIII. Rate of catheter-associated sepsis per 1000 PCVC days.
- IX. Proportion of infants completing the study with complete data for the primary outcome and proportions of infants with missing data collection forms

5.5.2 Safety Measures:

- VIII. Daily skin morbidity scores in the period between catheter insertion and 48 hours post-catheter removal, and in the period between antiseptic application and 48 hours post antiseptic application where catheterisation was unsuccessful.

5.5.3 Process Outcomes

- Number of attempted and failed PCVC insertions for included participants
- Adherence to study protocol
- Study withdrawals

6. TRIAL DESIGN

6.1 Summary

This feasibility study is a two-centre, masked randomised controlled trial of two topical antiseptics for neonatal skin disinfection prior to insertion of a percutaneous central venous catheter in the neonatal intensive care unit. Preterm infants born at <34 weeks' gestation who are undergoing planned insertion of a PCVC will be randomised to receive one of two commonly used topical disinfection agents for skin antiseptics: aqueous-based 2% chlorhexidine gluconate (2%CHG), or 70% isopropyl alcohol-based 2% chlorhexidine gluconate (70%IPA/2%CHG). The primary efficacy outcome of catheter colonisation (i.e. mainly extraluminal colonisation, a surrogate of catheter-related sepsis), the safety outcome of skin condition, and other process outcomes will be monitored in each group. It is planned to recruit at least 93 infants from two tertiary-level neonatal units over a 14-month period.

6.2 Study Setting

This feasibility study will be conducted in two level 3 neonatal units in the UK (Norfolk and Norwich University Hospital, Norwich, and Medway Maritime Hospital, Gillingham).

6.3 Eligibility Criteria

6.3.1 Inclusion Criteria

- Preterm infants born at <34 weeks' gestation
- Requiring routine insertion of a PCVC for parenteral nutrition
- No new suspected sepsis with commencement of antibiotics occurring within the 48 hours preceding planned catheter insertion
- No other indwelling PCVC already in situ

6.3.2 Exclusion Criteria

- No realistic prospect of survival in the short term
- Life-threatening congenital abnormality
- Underlying skin condition
- Already has another indwelling PCVC in situ or was previously enrolled into the study in respect of an earlier PCVC episode
- Positive blood culture within the past 7 days without a subsequent negative BC result
- Antibiotic treatment commenced for suspected sepsis within the preceding 48 hours

7. TRIAL PROCEDURES

Procedure	Screening	Trial entry/ PCVC insertion	Daily until 48 hours post-PCVC removal	PCVC removal
Confirm Eligibility	√			
Demographics		√		
Consent		√		
Randomisation		√		
Open Study Pack/ PCVC insertion		√		
Skin Assessment ^a		√	√	√
Sepsis evaluation		√	√	√
Obtain blood culture if sepsis suspected ^b			√	√
Obtain two exit site skin swabs				√
Obtain proximal and tip PCVC segments				√
SAE reporting ^c		√	√	√
Concomitant Medications (Antibiotics/antifungals only)		√	√	√

- a. Skin status to be recorded at baseline (prior to application of skin antiseptic), 10-30 minutes after catheter insertion, at 24 h (+/- 12 h), then daily until 48 h (+/- 12 h) after catheter removal using the modified neonatal contact dermatitis scoring system. Where catheter insertion is not achieved after IMP use, skin assessment for each anatomical region that was subject to IMP application will be recorded within 30 minutes following washing of the region with sterile water (to remove residual dried antiseptic compound), and then daily for a further 48 hours (see Sec 7.3.10).
- b. Peripheral blood culture obtained using standard aseptic technique.
- c. Only adverse events which are serious will be recorded from the time of catheter insertion until 48 hours after catheter removal (or until 48 hours after antiseptic removal where catheterisation unsuccessful). Only unforeseeable SAEs will be reported. Note that skin reactions to IMP use classed as moderate or severe should also be notified to MHRA via the yellow card scheme in line with the specific current MHRA request for clinicians to report chlorhexidine-related skin burns in neonates (see Sec 9.4.4).

7.1 Recruitment

7.1.1. Duration of Recruitment

It is expected that recruitment to this study will be completed within 14 months of randomisation of the first participant.

7.1.2 Screening and Eligibility Assessment

Preterm babies potentially suitable for the trial will be identified by the healthcare team within the neonatal unit. A baby considered eligible for potential enrolment into the trial will be any preterm infant <34 weeks' gestation who requires a PCVC to be inserted for delivery of parenteral nutrition. The parents of such infants will be approached for consent by the research team or delegated clinical members of the healthcare team who have been trained in study procedures. A study poster will also be displayed in the participating neonatal units to inform parents about the study.

7.1.3 Informed Consent

Written informed consent will be sought from parents of potentially eligible babies. Parents of eligible babies will be approached by the study team and invited to consider having their infant participate in the study. Most PCVC insertions are done within the first week after birth[19], usually towards the end of the first week when the umbilical venous catheter is removed. Therefore most parents will be approached for consent regarding this study within the first few days after birth. In some cases there may be the opportunity to first approach parents in the days leading up to delivery. A written parent information sheet that forms part of the Parental Informed Consent Form (PICF) will be provided that gives an explanation of the study. Parents who do not speak English will only be approached if an independent adult interpreter is available.

Written informed parental consent will be obtained by means of a dated maternal signature on the PICF. The PICF will also be countersigned by the person who obtained informed consent; this will be the Principal Investigator (PI) or appropriately qualified healthcare professional who has delegated authority. The original signed copy of the PICF will be retained in the baby's medical notes. A copy of the signed PICF will be given to the parents and a copy will be retained by the PI in the site study file. A further copy will be transferred to the Trial co-ordinating centre,

7.1.4. Enrolment

After informed consent has been given, the study Entry Form should be completed. Information recorded on the Entry Form will be entered onto the randomisation website. Infants will be considered to have been enrolled once they have been allocated a study number and also a treatment Study Pack number by the randomisation facility.

7.1.5. Remuneration

No financial or material incentive or other form of compensation will be given to babies or their parents as a result of taking part in this trial.

7.2. Randomisation

Following consent, recruited babies will be randomised as close as possible to the time of planned catheter insertion. Randomisation will be to one of two skin antiseptic preparations: either

70%IPA/2%CHG or 2%CHG. Separate bottles containing the same allocated antiseptic (each with the same unique study pack ID on the label) will be used at both the catheter insertion and removal for individual enrolled babies.

Randomisation will be managed via a secure web-based randomisation facility hosted by the NPEU CTU with telephone back-up available at all times (24/7, 365 days a year). The randomisation will use a stratified block randomisation to stratify groups by birth gestation (<28 weeks; 28⁺⁰ to 33⁺⁶ weeks) and within neonatal centre. Randomisation will provide a 3:1 allocation ratio in favour of the alcohol-based antiseptic (70%IPA/2%CHG). The randomisation is designed in this feasibility study to be unbalanced because 70%IPA/2%CHG is the most commonly-used antiseptic in the UK (Table 1) and will be the reference antiseptic for the large-scale study; hence a main objective of this feasibility study is to obtain an accurate estimate of the prevalence of (mainly extraluminal) catheter colonisation in infants treated with 70%IPA/2%CHG in order to determine the sample size needed for the large-scale study.

On successful randomisation the research team will be provided with a unique study pack identification number and will also be allocated an individual patient study number. The study pack chosen locally by the research site for use at catheter insertion will match the unique study pack ID number generated at randomisation. Treatment allocation of antiseptic will be masked such that the allocation will not be known by clinicians, the baby's family, the laboratory staff or the trial outcome assessors.

At the NPEU CTU, a Senior Trials Statistician will generate the randomisation schedule and a Senior Trials Programmer will generate the pack allocation codes and develop and manage the secure web-based randomisation system. If necessary, the code may be broken for a single baby at the emergency request of the site PI or clinician in charge of the baby. See Section 8.8 for the procedure for unblinding treatment allocation.

7.3 Trial Interventions

There are no interventions over and above normal clinical care, with the exception of the topical antiseptic medication used and the procedures for catheter insertion, maintenance, and removal. All other aspects of care will be as per local policy, practice, and discretion.

Throughout the trial, participating infants may be prescribed any concomitant medications deemed necessary to provide appropriate supportive care.

7.3.1 Catheters

The PCVC catheter types that will be used are Premicath 1Fr/28G and Epicutaneo-Cava catheter 2Fr/24G (both Vygon UK Ltd, Cirencester, UK). These are the percutaneous central venous catheters most frequently inserted in neonates in the UK and the ones routinely used in both participating NICUs. The decision to insert a PCVC in any infant will be made by the attending clinical team and will not be influenced by the study. Catheter selection is a decision of the operator. Catheter type used will be recorded in the study documentation.

7.3.2 Protocol for Catheter Insertion

Catheter insertion will be standardised, using a protocol common to both participating centres that encompasses established good clinical practices for PCVC insertion and care adopted from

catheter-care bundles[30,34,35,36]. The guideline for the procedure is described in a separate Working Document “Standardised guideline for catheter insertion utilising good catheter insertion and care practices”). All personnel involved will be educated in the catheter insertion and maintenance protocol. The insertion procedure will be recorded using a checklist which forms part of the patient data collection record and will be completed at the time of insertion by the person accompanying the operator who directly observes the catheter insertion procedure (a trained neonatal nurse or member of the research team).

7.3.3 Study Packs

A study pack containing two labelled bottles of the antiseptic IMP will be opened at the time of catheter insertion. The unique study pack to be selected will be obtained using web-based randomisation (see Sec. 7.2). The unique study pack identification code will be recorded in the patient’s Trial Entry Form.

7.3.4 Skin Disinfection at Catheter Insertion

The operator will:

- apply the allocated antiseptic solution to the skin over the area selected for catheter insertion for a minimum of 10 seconds and maximum of 20 seconds
- take great care to use only the minimal volume of antiseptic necessary for skin coverage, avoid any pooling of antiseptic, and ensure that any excess solution and any soaked materials, drapes, or gowns are removed to avoid any prolonged contact with the skin
- allow the disinfected area to air dry completely (for ≥ 30 seconds) before proceeding with catheter insertion
- **not** use saline or water to wipe off the disinfected skin area at any time after application of antiseptic solution before catheterisation, because this practice potentially negates the efficacy of the antiseptic, will therefore potentially confound the study findings, and will constitute a violation of the protocol. The only exception to this is in case of failed catheterisation, as described in Sec. 7.3.10)
- insert the PCVC aseptically according to catheter insertion protocol

7.3.5 Assessment of Skin Condition

- Skin status will be recorded on a scoring sheet using the validated neonatal contact dermatitis scoring system, the Neonatal Skin Condition Score[37] (with minor modification)
- Assessments to record skin condition will be undertaken by an attendant neonatal nurse/research nurse trained in use of the scoring system.
- Assessments will be recorded at the following time-points:
 - ❖ baseline (prior to application of skin antiseptic)
 - ❖ within 10-30 minutes after catheter insertion
 - ❖ daily post-insertion until 48 hours (+/- 12 h) following catheter removal
- Immediate or late skin reactions to the topical antiseptics (presence/ absence /severity/ morbidity) will be recorded
- Moderate or severe skin reactions will be notified to the MHRA (see safety reporting section 9.4) in line with its current advice (Available at: <https://www.gov.uk/drug-safety-update/chlorhexidine-solutions-reminder-of-the-risk-of-chemical-burns-in-premature-infants>)
- Where an enrolled study subject receives topical IMP application but catheterisation proves to be unsuccessful, a limited assessment of skin condition will be undertaken (for a 48-hour period) for each anatomical region to which IMP has been applied (see sec. 7.3.10)

7.3.6 Study Samples to be Obtained at Catheter Removal

The following will be collected at the time of catheter removal:

i) Before catheter removal:

- Two exit site skin swabs (the first to be taken after removing the transparent covering dressings *but prior to* skin disinfection; the second to be taken *post* disinfection but still pre-catheter removal)

ii) After catheter removal:

- Proximal and tip catheter segments (~1 cm long)

Because the proximal in vivo catheter segments (i.e. the segments of indwelling catheter located just distal to the skin insertion site) have higher colonisation rates than tips[19], two catheter segments will be collected for microbiological analysis (rather than solely catheter tip as is routine in many units) to assess if diagnostic yield of catheter colonisation is improved.

7.3.7 Protocol for Catheter Removal and Obtainment of Study Samples at Removal

Catheters are removed as part of routine clinical care, usually because they are no longer required but sometimes because of complications including suspected sepsis. If the catheter is being removed from a baby with suspected sepsis a peripheral blood culture (BC) must be obtained at the time of catheter removal as per usual practice. The decision for catheter removal for babies enrolled in this study will not be influenced by study participation.

Catheter removal requires two persons. Great care must be taken to avoid cross-contamination between segments while cutting the catheter into segments for microbiological culture. Two separate sets of sterile forceps, two pairs of sterile scissors, and two sterile pre-labelled universal containers are required to obtain and submit to microbiology the individual catheter segments. Full instructions regarding the list of equipment needed, detailed method of catheter removal, and specimens to be taken are provided in the working study document 'Guideline for Catheter Removal'.

The procedure is summarised as follows:

i) Obtain First Skin Swab *before exit site disinfection and before PCVC removal*

Remove all external covering dressings of the PCVC (e.g. Tegaderm/ Steristrips/ cotton gauze). Inspect and record the skin condition on the skin record form. Take the first skin swab for microbiological culture *before* disinfection of the prospective catheter exit site and *before PCVC removal*. Obtain by rolling the swab tip several times across the skin of the catheter insertion site, over an area confined to within <0.5 cm radius of the insertion site, but also including the actual insertion site.

ii) Exit Site Disinfection *before PCVC removal*

After obtaining first skin swab, carefully disinfect the prospective catheter exit site *prior to* catheter removal. Cleansing for this purpose will use the same skin disinfectant agent that the infant was allocated for catheter insertion. The antiseptic bottle used will therefore usually be the second bottle from the pack that was first allocated at randomisation, although may be from a subsequent pack specifically allocated by the web-based randomisation website in the case where a further pack allocation became necessary (e.g. difficult catheter insertion where the initial attempts at catheter insertion proved unsuccessful and the second bottle of the pack had already been used for a

subsequent catheterisation attempts on a subsequent day). The pack number on the label of the allocated antiseptic bottle used at catheter removal must be recorded on the DCF. Clean for minimum 10 s and maximum 20 s, and be careful to avoid any pooling of antiseptic. The actual site skin puncture site itself must be included. Allow to dry for minimum 30 seconds, and wait until the site is completely dry before obtaining the second skin swab. *This disinfection procedure aims to minimise the risk of catheter contamination by skin organisms at the exit site during the removal process, to assure validity of the Maki-roll catheter culture technique which detects mainly extraluminal colonisation.*

iii) Obtain Second Skin Swab *after antiseptic application but before PCVC removal*

Take the skin swab for microbiological culture *after* disinfection of the prospective catheter exit site but *before PCVC removal*. The skin must be completely dry from antiseptic before obtaining the second microbiological swab. Obtain by rolling the swab tip several times across the skin of the catheter insertion site, over an area confined to within <0.5 cm radius of the insertion site. Previous studies in neonates[38] and adults[27] indicate excellent short-term clearance with both the antiseptics being used in this study, so it may be anticipated that very few skin swabs will be positive after skin disinfection. *A negative post-disinfection swab in the presence of a culture-positive catheter segment will help assure that identified cases of catheter colonisation are true positives, i.e. that contamination of a sterile catheter by skin bacteria has not arisen during catheter removal, particularly if its paired pre-disinfection swab was culture positive..*

iv) Obtain Catheter segments

Before removing the catheter the subcutaneous PCVC insertion length should be noted from the external catheter markings. Remove the catheter onto a sterile paper towel field then cut it using the sterile scissors provided in the following order to obtain two ~1 cm-long formerly subcutaneous catheter segments: i) tip, and ii) a proximal segment, taken approximately 1-2 cm distal to the point of skin entry. Separate pairs of sterile scissors and forceps must be used when sectioning the catheter to avoid cross contamination between segments. Each individual segment should be placed in turn into a separate appropriately-labelled sterile universal container using a separate pair of sterile forceps.

7.3.8 Microbiology

The two catheter segments and the two skin swabs will be sent to the local microbiology laboratory for routine culture and antibiotic sensitivities. BCs sent (as part of standard clinical care) from babies with suspected sepsis at the time of catheter removal will undergo standard culture methods. Bacterial growths from skin swab cultures will be assessed using a semi-quantitative method. All laboratory staff will be blinded to antiseptic allocation. Isolates from all culture-positive skin swabs, blood, and catheter segmental cultures will be retained for molecular typing. Initial identification of organisms will be done by Mass Spectrometry. Those giving similar patterns will be analysed using Next Generation sequencing using a multiplexed approach on the Illumina MiSeq. Molecular typing of paired blood and catheter isolates from the same baby will allow confirmation that isolates are identical, proving definitive diagnosis of definite CRS. While few post-disinfection skin swabs are expected to be positive, molecular typing of skin swab isolates will be done for any babies with colonised catheters: isolation of paired identical species could indicate possible catheter contamination by skin organisms during catheter removal. Babies with positive BCs will be managed according to local clinical guidelines; involvement in this trial will not dictate or influence clinical antibiotic prescriptions.

7.3.9 Arrangements for Transport, Storage and Custodianship of Study Samples

Isolates from all culture-positive skin swabs, blood, and catheter segmental cultures will be retained for molecular typing. Initial storage of positive isolates will be in the NHS microbiology laboratories of the participating centres. Positive isolates will be transferred for further analysis according to the relevant 'Working Guideline for the Safe Transfer of Clinical Isolates' between each participating NHS site and the microbiology laboratory of Dr Mark Webber at Quadram Institute Bioscience, Norwich Research Park, Norwich. Any isolates forwarded from the NHS sites will be identified only by study number and patient initials and will not contain any other patient identifiers. Responsibility for the safe and secure-keeping of the study samples for molecular typing will rest with the Quadram Institute Bioscience. Positive isolates will be retained for a period of 2 years after completion of the study.

7.3.10 Unsuccessful Catheterisation Attempts

It is recognised that in some babies PCVC insertion is very difficult. Sometimes multiple cannulation attempts are required before a catheter is successfully inserted; sometimes successful cannulation proves to be impossible despite multiple attempts. It is therefore to be expected that some babies in this trial will undergo multiple applications of skin antiseptic IMP during repeated catheterisation attempts involving different anatomical sites. Where a cannulation attempt involving a particular region (eg a limb or the scalp) is abandoned because it proves unsuccessful, that region should be washed promptly with sterile water. This aims to remove any redundant antiseptic residue and so minimise the risk of any dermatitis or skin reaction.

In cases where catheter insertion is unsuccessful, assessment of skin condition for each anatomical region subject to IMP application will be recorded within 30 minutes after washing the region, and then daily for 48 hours, using the 'Unsuccessful Catheterisation Episode Form'. A separate form should be completed for each main anatomical region subject to IMP application (e.g. left upper limb, right side of scalp etc.).

7.4 Data Collection

Outcome data for this trial include items routinely recorded clinically that can be obtained from the clinical case notes or from the local microbiological laboratory records that form part of the patient's medical record. The primary outcome data relating to catheter colonisation as verified by molecular typing will be collected after analysis of positive isolates in the laboratory of Dr Mark Webber at Quadram Institute Bioscience, Norwich Research Park, Norwich.

Information will be collected using the following study-specific data collection forms:

- Trial Entry and Randomisation Form
- Outcome Data Collection Forms (comprising Main Outcome Data Form, Catheter Removal Form, Microbiology Data Form, and Unsuccessful Catheterisation Episode Form)
- Discontinuation of Intervention Form
- Withdrawal Form
-
- Foreseeable Serious Adverse Event Form

In addition, information will be collected and reported to the Sponsor using the Sponsor's reporting forms, as follows:

- Serious Adverse Event (SAE/SUSAR) report Form
- Incident Form* (Form for Protocol Deviation, Violation, Breach or Serious Breach of Protocol or GCP)

* To report any deviation from the protocol, trial-specific procedures or good clinical practice.

The trial co-ordinating centre (Norwich) will hold the main administrative database for the trial. The clinical database will be administered by the NPEU and access to this database will be via a web browser and restricted to authorised users only. The data acquired by the enrolling units will initially be recorded onto paper DCFs, which will be returned to the trial co-ordinating centre for data entry. During the data entry process, data queries, validation, and cleaning will be undertaken by the CI with assistance from the trial administrator and study research nurse.

7.5 Supportive Care of Enrolled Babies

The clinical management of babies enrolled in the study will follow standard local practices. It is recognised that practices may vary between and within centres with regards to management of central venous catheters in babies for whom sepsis is suspected: some practitioners prefer to retain the catheter and attempt catheter sterilisation by giving antibiotics while retaining the catheter, while others prefer to remove the catheter in such babies so that the potential source of infection is also controlled. For the purposes of this feasibility study, the ideal will be catheter removal at the time that catheter-related sepsis is first suspected. However this protocol recognises that a pragmatic approach is sometimes needed, especially for very premature babies in whom catheter replacement may be difficult and challenging. All efforts will be made to minimise differences in treatment practices between sites through training.

7.6 Discontinuation of Trial Intervention

The trial intervention will have to be stopped if the baby develops serious adverse skin damage that, in the opinion of the responsible PI, was caused by the IMP. For example, if any baby had clinically significant chemical skin burn to the IMP applied at catheter insertion then this should be reported (as per safety section) and the allocated antiseptic should be withheld from use for site disinfection at catheter removal. In this instance the reason for the protocol deviation will be recorded in the DCF but the skin swab and catheter sections should be obtained as per protocol.

At all stages it will be made clear to the parents that they remain free to withdraw their baby from the trial at any time without the need to provide any reason or explanation. Parents will be made aware that a decision to withdraw their baby will have no impact on any aspect of their baby's continuing care. If parents choose to withdraw their baby from trial participation, permission will be sought to complete data collection and use data up to the point of withdrawal from the trial. A baby may also be withdrawn from the trial by the PI, if deemed to be in the baby's best interests.

7.7 End of Trial

The end of trial for an individual infant is defined as being on completion of their final skin and sepsis assessment done at 48 hours post-catheter removal. The end of trial for an infant in whom catheter placement remains unsuccessful despite repeated insertion attempts is defined as being on completion of their final skin assessment done at 48 hours post the final IMP application. The end of trial overall will be defined as the time of final database lock. An end of trial declaration will

be made to the Medicines and Healthcare products Regulatory Agency (MHRA) and to the approving Research Ethics Committee (REC) within 3 months of this date. The responsibility for submitting the Clinical Study Report will lie with the Chief Investigator and Sponsor.

7.8 Early Trial Cessation

A decision may be made by the Trial Steering Committee (TSC) to stop the trial early following a recommendation from the Data Monitoring Committee (DMC), on review of interim trial data, or evidence from other relevant studies becoming available. Guidelines for the early cessation of the trial will be agreed with the DMC and documented in the DMC Charter.

8. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

The two antiseptic Investigational Medical Products (IMPs) used in this study will be:

- Chlorhexidine Gluconate 2% aqueous solution (“2%CHG”)
- Chlorhexidine Gluconate 2% in isopropyl alcohol 70% solution (“70%IPA/2%CHG”).

8.1 Legal Status of the Antiseptic Investigational Medicinal Products

The trial is being carried out under a Clinical Trial Authorisation (CTA). The antiseptics supplied for use in this study are therefore only to be used by the named investigators, for the patients specified in this protocol, within this trial only, and strictly in accordance with this protocol.

8.2 Summary of Product Characteristics (SmPC)

A simplified Investigational Medicinal Product Dossier (sIMPD) is provided for the antiseptics used in this study. The sIMPD contains SmPCs with Reference Safety Information (RSI) applicable for both the antiseptic IMPs. The Reference Safety Information will be reviewed annually.

8.3 Preparation and Labelling of Investigational Medicinal Products

Both these products will be manufactured by Guy's and St Thomas' NHS Foundation Trust specialist Pharmacy Manufacturing Unit, under Manufacturer's and Importer's License MIA(IMP) 11387. The manufactured products will be ready-for-use solutions presented in high-density polyethylene (HDPE) bottles with polypropylene child-resistant caps. Each bottle will contain 20 mL of IMP antiseptic solution. Both IMP solutions will be coloured pink and visually indistinguishable. Packs containing two single-use bottles will be provided. Each pack will be assigned a unique identification pack number, and each pair of bottles in the pack will be labelled with this same code. The production and labelling will be in compliance with the guidance given in Annexe 13 of the European Commission's guidelines for Good Manufacturing Practice.

8.4. Distribution

Manufacture of IMP will be done in two batches. Sufficient supplies of IMP will be provided to each site direct from the specialist Manufacturing Unit.

8.5. Storage

The IMPs/antiseptic solutions should be stored at room temperature. Product shelf-life and stability information will be provided in the sIMPD. The paired bottles are for single-patient use only and once the bottle is opened the antiseptic should be used within 24 hours.

8.6. Accountability

Study packs will be dispensed by pharmacy and stocked in a secure location on the participating neonatal units at room temperature. The dispensing of the study packs from pharmacy will require a completed prescription form. Detailed accountability records will be maintained to document which unique study pack is used for which baby. Site staff will be required to write the baby's trial number and initials on the study pack allocated. Part used packs will be kept separate from unused packs. Pharmacy will maintain an overall inventory of stock received and dispensed. Any unused

IMP at the end of the study will be destroyed by the local pharmacy in accordance with the local Standard Operating Protocol (SOP) for secure IMP destruction.

8.7. Blinding of Trial Medication

The two antiseptic IMPs will be supplied in bottles. The products will each be coloured pink (using carmoisine) and so will be visually indistinguishable from each other. To maintain blinding, each baby will be issued a unique allocation number that will correspond to the study pack number.

8.8. Procedure for Unblinding

The study code should only be broken for valid medical or safety reasons e.g. in the case of a severe adverse event where it is necessary for the investigator or treating health care professional to know which treatment the patient is receiving before the participant can be treated. Subject always to clinical need, where possible, members of the research team should remain blinded.

Clinicians requesting emergency unblinding must be satisfied that it is a genuine emergency and that knowledge of the antiseptic treatment allocation is needed to guide the appropriate clinical management of the participant.

In the event of an emergency, the PI can unblind the allocation for a participant by logging in to the randomisation website using a single-use access code provided in a sealed envelope from the Investigator Site File. Details of the person requesting the unblinding, and the reason for that request, will be recorded. In any situation where an investigator considers that emergency unblinding is necessary, prior discussion with or approval from the CI or their designee is not required in order to request unblinding. In cases where an investigator is uncertain as to whether emergency unblinding is necessary, the CI or their designee should ideally be consulted to discuss and approve the unblinding.

- On receipt of the treatment allocation details the CI/PI or treating health care professional will continue to deal with the participant's medical emergency as appropriate
- The CI/PI documents the breaking of the code and the reasons for doing so on the DCF/data collection tool, in the site file and medical notes. It will also be documented at the end of the study in any final study report and/or statistical report
- The CI/Investigating team will notify the Sponsor in writing as soon as possible following the code break, detailing the necessity of the code break
- The written information will be disseminated to the Data Monitoring Committee (DMC) for review in accordance with the DMC Charter

As it is best practice to not unblind participants until all follow up is completed, all other requests for unblinding must be made in writing to the NPEU CTU.

8.9 Known Drug Reactions and Interaction with Other Therapies

Neither of the antiseptic IMPs used in this study has any known interactions with any other drugs or therapies (see sIMPD).

8.10 Concomitant Medications

There are no prohibited concomitant medications or therapies. The only concomitant medications that will be recorded routinely for all enrolled babies are antibiotics and antifungals. The indications, type, and start and stop dates of antimicrobials given any time between birth and 48 hours post-catheter removal will be recorded. In the event that an unforeseeable serious adverse event is reported for any enrolled baby, data concerning any other concomitant medications given during the study period (enrolment until 48 hours post-catheter removal) will be obtained and recorded on the SAE form provided for the trial.

9. PHARMACOVIGILANCE

9.1 Definitions

	Term	Definition
9.1.1	Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
9.1.2	Adverse Reaction (AR)	<p>An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.</p> <p>The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.</p> <p>All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.</p>
9.1.3	Serious Adverse Event (SAE)	<p>A serious adverse event is any untoward medical occurrence that:</p> <ul style="list-style-type: none"> • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect <p>Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.</p> <p>NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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.</p>
9.1.4	Serious Adverse Reaction (SAR)	<p>An adverse event that is both serious and, in the opinion of the reporting Investigator (CI, PI, or safety delegate), is believed with reasonable probability to be due to one of the trial treatments, based on the information provided.</p> <p>In this study a serious adverse reaction is a SAE which is considered to have been caused by the administration of trial antiseptic. For a SAE to be considered as a reaction there must be a reasonable probability that it was related to the administration of IMP.</p>
9.1.5	Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the known safety profile of either trial antiseptic as detailed in the simplified Investigational Medicinal Product Brochure.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

9.1.6 Foreseeable Serious Adverse Events

Foreseeable SAEs are those events which are foreseen in the patient population or as a result of the routine care/treatment of a patient. The following serious adverse events are a foreseeable occurrence in this population of preterm babies and as such **do not** require reporting as SAEs, unless considered that they may be causally related to the IMP or trial procedures:

- Death (unless unforeseeable in this population)
- Respiratory failure
- Pulmonary haemorrhage
- Necrotising enterocolitis
- Clinically significant intracranial abnormality on cranial ultrasound scan (intracranial haemorrhage or white matter injury)
- Retinopathy of prematurity
- Hypotension
- Hyperbilirubinemia necessitating exchange transfusion
- Pulmonary hypertension requiring treatment with pulmonary vasodilator
- Spontaneous intestinal perforation
- Impaired renal function (urine output <0.5 mL/kg/hour, and or serum creatinine >100 µmol/L)
- Anaemia requiring transfusion
- Hypoglycaemia
- Hyperglycaemia
- Haemothorax
- Culture proven sepsis
- Coagulopathy requiring treatment
- Sepsis / ventilator associated pneumonia
- Pneumothorax or air leaks
- Seizures not related to an intracranial event
- Gastrointestinal haemorrhage

Only if these events are thought to be causally related to the IMP (or trial procedures) would they require urgent reporting to the trial coordinating centre (as SUSARs), as outlined in section 9.4.

9.1.7 Unforeseeable Serious Adverse Events

An unforeseeable SAE is any event that meets the definition of a SAE and is not detailed in the list above as foreseeable. These events should be reported on the trial SAE form provided following the procedures detailed in Section 9.4.

9.2 Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Unrelated: where an event is not considered to be related to the IMP;

Possibly: although a relationship to the IMP cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible;

Probably: the temporal relationship and absence of a more likely explanation suggest the event could be related to the IMP;

Definitely: the known effects of the IMP, its therapeutic class or based on challenge testing suggest that the IMP is the most likely cause.

All SAEs as discussed in Section 9.4.1 labelled possibly, probably, or definitely will be considered as related to the IMP.

9.3 Assessment of Safety

During the course of the trial, safety data will be reviewed by the Data Monitoring Committee (DMC). This will include safety data for SAEs as stated in Section 9.1.3 as well as Sections 9.1.4 and 9.1.5. The DMC will, if appropriate, make recommendations regarding continuation of the trial or modification of the trial protocol. The TSC will have ultimate responsibility for deciding whether the trial should be stopped on safety grounds.

9.4 Reporting Procedures

9.4.1. AE/SAE Reporting

A high incidence of adverse events is foreseeable due to the nature of the patient population and their routine care/ treatment. Consequently, only those adverse events identified as serious will be recorded for the trial.

Safety reporting as described in this section will be monitored from the time of the first application of IMP antiseptic until 2 days after the final application of trial antiseptic during PCVC removal, and for 2 days after application of trial antiseptic in cases of unsuccessful PCVC insertion.

In order to prevent a breach of patient confidentiality, SAE reports and any accompanying information should contain only anonymised or pseudo-anonymised patient data.

Where not all information is available while the SAE Form is being completed, the initial report must contain the following as a minimum:

- Identifiable Event
- Identifiable Patient
- Identifiable IMP (i.e. by providing batch number)
- Identifiable Reporter

If the information available is less than the specified minimum or if the SAE Form is not available for completion and reporting to meet the 24-hours deadline an initial report can be made verbally but must be followed within 48 hours by a detailed, written report.

All unforeseeable SAEs including SUSARs must be followed up by the PI/CI until satisfactory resolution and this should be recorded as a Follow Up report on the SAE form, and on the SAE log. At each stage of follow up the PI/CI should sign and date the form.

Unforeseeable Serious Adverse Events will be reported to the Sponsor and to the CI by emailing to rdoffice@nnuh.nhs.uk and paul.clarke@nnuh.nhs.uk within 24 hours of a research team member at the site becoming aware of the event using the Study SAE form (filed in the Investigator Site File).

The initial SAE report should be completed by the PI or a member of the research team with this delegated responsibility on the delegation log. At the earliest opportunity, the PI must review and amend as necessary the initial report, and then email a copy of the signed reviewed form to the Sponsor and CI via e-mail addresses rdoffice@nnuh.nhs.uk and paul.clarke@nnuh.nhs.uk. Patients must be followed up until satisfactory resolution of the SAE. As follow-up information becomes available it should be reported on a new SAE form, clearly marked as follow-up information and forwarded to the Sponsor and CI by email.

The CI and/or safety delegate will review the report, request any additional information and sign the report form. The Sponsor and CI will ensure that review of SAEs are timely, taking into account the reporting time for a potential SUSAR. SAEs will be reviewed by the study DMC. The CI will inform the PIs at any other sites of relevant information that could adversely affect the safety of the participants. The SAE will be recorded in the SAE log and the form will be stored in the Trial Master File.

All SAEs assigned by the PI or delegate (or following Sponsor/CI review) as both suspected to be related to IMP-treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA). The Sponsor will inform the MHRA and the REC of SUSARs within the required expedited reporting timescales.

9.4.2. SAR Reporting

The CI will decide if he/she agrees with the PI on the classification or whether the status of the event should be upgraded to SUSAR. The assessment of causality must be carried out by a medically qualified doctor who is part of the research team. The CI may not downgrade an event graded by a PI as a SUSAR.

If an adverse event involving the neonate's skin occurs during the study that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial antiseptic treatments, this will be reported to the MHRA.

Skin burns are a relatively rare but recognised potential complication of both the antiseptic formulations used in the study. In the event of a serious skin burn (one adjudged by the PI or delegate to be severe or moderately severe) associated with an antiseptic IMP used in this study, this requires additional notification to the MHRA via the 'Yellow Card Scheme' (see Sec 9.4.4 below). Providing that the local PI or delegate considers that there is no immediate safety need to unmask the allocated antiseptic to the local clinical or research team, the 'Yellow Card' notification to MHRA will be done by either the clinical or research staff and will quote the unique study pack ID reference number. Preservation of the blind in this way will minimise the risk of compromising the integrity of the trial. Breaking the blind will only be permitted where information about the participant's trial treatment is clearly necessary for the appropriate ongoing medical management of the participant.

9.4.3. SUSAR Reporting

The trial team will notify the CI and Sponsor of SUSARs. The Sponsor will inform the MHRA, the approving Research Ethics Committee (REC) and the authorised manufacturer/ supplier of IMP within 7 days of being informed if the event resulted in death or was life-threatening and within 15 days for all other SUSARs. The Sponsor will complete an eSUSAR report via the MHRA eSUSAR system. Any additional information will be reported within 8 days of the initial report. In addition, a copy of the SAE form corresponding to the event will be forwarded to the Chair of the DMC. The Chair will also be provided with details of the baby's treatment allocation (unblinded) if requested.

Expectedness: Expectedness will be determined by reference to the SmPCs applicable to the IMPs. Copies of the applicable SmPCs will be found in the sIMPD within the Investigator Site File. The current approved UK versions of the applicable SmPCs are also available on the MHRA website <http://www.mhra.gov.uk> (see '*Chloraprep with tint 2% w/v / 70% v/v cutaneous solution*', and '*Chlorhexidine Gluconate 2% w/v Impregnated Pad*').

The only undesirable adverse reactions expected with isopropyl alcohol and/or chlorhexidine are allergic dermatitis, irritation skin reactions, or – in severe cases - chemical burns. Additional undesirable effects are not expected. With topical IMP application as directed in this protocol the risk of a skin reaction in the study population is expected to be low (<3%). Skin reactions must be reported in accordance with section 9.4 of this protocol.

9.4.4 Yellow Card Scheme Reporting

In 2014 the MHRA issued advice reminding practitioners to be aware of the risk of chlorhexidine-related skin burns in preterm neonates (Available at: <https://www.gov.uk/drug-safety-update/chlorhexidine-solutions-reminder-of-the-risk-of-chemical-burns-in-premature-infants>). The MHRA requests that practitioners report cases of chlorhexidine-related skin injury in neonates via its Yellow Card scheme. In line with this advice, any case of skin injury to a neonate enrolled in this study which is judged by the responsible PI to be a moderate or severe skin reaction will be notified to the MHRA. The notification will provide the details of the infant's unique study number so that once the trial has completed, the randomisation code can be broken and the nature of the exact IMP responsible can be provided to the MHRA in a follow up report. Note well that this notification under the Yellow Card scheme is *in addition to* all study-specific Safety Reporting requirements stated elsewhere in this Section of the study protocol.

9.4.5. Development Safety Update Reports

In addition to the expedited reporting above, the CI will submit once a year throughout the clinical trial, or on request, Development Safety Update Reports to the Competent Authority (MHRA), approving REC, Host NHS Trust, and Sponsor.

The CI will send a line listing of all logged SAEs quarterly (from the date of R&D approval) to R&D for review by the Joint Research Governance Committee. If there is nothing to report in a particular quarter, an email must be sent to R&D, to confirm this. All logged events will be reported to the REC and MHRA annually as a Safety report.

10. STATISTICS AND DATA ANALYSIS

10.1 Sample Size Calculation

Our previous study[19] found that 32% of PCVCs were colonised at removal after using much weaker concentration (0.015%- 0.05%) CHG solutions and the definite CRS rate was 6.8 per 1000 catheter days. In comparison, the NICU of John Radcliffe Hospital, Oxford, routinely use 70%IPA/2%CHG for all PCVC insertions and reported a 34% lower CRS rate (4.5 per 1000 catheter days)[34]. Presuming that alcohol-based 2%CHG is the major factor of benefit in catheter care, by extrapolation we might reasonably expect to see a 34% reduction in extraluminal catheter colonisation rates by using 70%IPA/2%CHG solution. Thus we estimate a baseline catheter colonisation rate of approximately 20% ($0.66 \times 32\% = 21\%$) with 70%IPA/2%CHG solution. With a 3:1 allocation ratio in favour of the reference 70%IPA/2%CHG group: a target sample size of approximately 93 babies with successfully inserted catheters (approximately $n=70$ in the reference group) will be necessary to estimate the critical parameters for a future, large-scale trial with an adequate degree of precision. If this target sample size is achieved in the feasibility study, the anticipated incidence of the primary outcome (catheter colonisation) in the reference group of 20% will be estimated with a 95% Confidence Interval (CI) of 11% to 31%. With a sample size of 93 babies with successfully inserted catheters, the anticipated recruitment/uptake rate of 75%[35] will be estimated with a 95% CI of 0.65 to 0.83. To obtain a sample size in the region of 93 babies having catheters inserted will require parents of at least 124 eligible babies to be approached. Based on our previous collaborative observational study of PCVCs that recruited 127 preterm infants between two tertiary centres in a 14-month study period[19], we would expect to complete recruitment within 14 months.

10.2 Data Analysis and Assessment of Feasibility Criteria

Demographic factors, clinical characteristics, and microbiological species isolated will be summarised with counts (percentages) for categorical variables, mean (standard deviation) for Normally distributed continuous variables, and median (ranges) for other continuous variables. Summary statistics and 95% CIs will be estimated for recruitment, completeness of data, and the prevalence of catheter colonisation. These data, reasons for declining participation, and any skin morbidity, will be carefully considered by the TMG and TSC to decide on the feasibility of the future large-scale trial, and any adaptations required. Estimated prevalence of babies with PCVC colonisation will allow calculation of sample size for the large-scale study. If the prevalence of babies with identical bacterial species on post-disinfection skin swabs and catheter segmental isolates is zero or very low, then post-disinfection skin swabbing and need for molecular typing of skin organisms can be dispensed with for the large trial, which will save costs. If we find no difference in colonisation rates between tips and proximal segments or by using aggregate paired analysis, then tips alone will be collected in the large-scale study, with cost savings.

10.3 Economic Evaluation

No formal health economics evaluation is included in this feasibility study. Data associated with costs of the intervention and other NHS costs (including those of adverse events such as infection, sepsis, skin injury) are routinely recorded. These data may therefore readily be extracted from patient notes post-hoc as required to permit consideration whether a health economics evaluation should be included in the future large-scale study.

11. SOURCE DATA/DOCUMENTS

Direct access to source data/documents (including hospital records/notes, clinical charts, laboratory reports, pharmacy records and test reports) will be granted to authorised representatives from the Sponsor, the NPEU CTU, the MHRA, and the host organisation to permit trial-related monitoring, audits and inspections.

12. QUALITY CONTROL AND ASSURANCE

12.1. Risk Assessment

The Sponsor has performed a risk assessment of the trial prior to commencement that will be reviewed at regular intervals during the course of the trial.

12.2. National Registration Systems

This clinical trial of IMPs falls under the Medicines for Human Use (Clinical Trials) Regulations 2004, and so has been registered on the European Clinical Trials (EudraCT) database (URL: <https://eudract.ema.europa.eu/>). The trial has also been registered on a global trial register, namely the International Standard Randomised Controlled Trial registry (URL: <http://www.isrctn.com/ISRCTN82571474>).

12.3. Site Initiation and Training

Each recruiting centre will be staffed by a local Research Nurse dedicated to support this study. Initiation visits at each participating neonatal unit will be performed by the Chief Investigator or his delegate and a local Research Nurse, and will be attended by a representative of the Sponsor. The trial will only commence recruitment with the permission of the Sponsor and once all appropriate approvals are in place, IMP has been shipped to the site, and site staff have been trained on trial procedures. The local Research Nurses and PIs/co-investigators will ensure adherence to the protocol and deal with any specific site issues.

12.4. Site Monitoring and Auditing

The CI, PI, and local co-investigators will, along with the dedicated local Research Nurse, facilitate the day-to-day smooth running of the trial at the site. They will encourage recruitment, provide ongoing staff education and training, and will monitor safety of patients, data completeness, and quality, and respond to queries promptly.

The Sponsor's nominated representatives will undertake monitoring visits during the course of the study at each recruiting site to check for completeness and quality of data collection and adherence to the study protocol and reporting requirements.

12.5 Archiving

The PI 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, Good Clinical Practice) including the Investigator Site File until the Sponsor informs the investigators that the documents no longer need to be retained, or for a maximum period of 25 years (whichever occurs sooner). This duration may be subject to future revision, for example if there are any changes in statutory requirements pertaining to retention of records.

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 by regulatory authorities).

The CI will take overall responsibility for ensuring that each participant's information is kept confidential. All paper documents will be stored securely and kept in strict confidence in compliance

with the Data Protection Act (1998).

The Sponsor undertakes to store originally completed DCFs for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator / investigator's NHS Trust only. The Sponsor will archive documents in compliance with its Records Management Standard Operating Procedure (SOP). Hard copies of trial data and essential trial documents will be boxed and transferred to secure premises with unique reference numbers applied to enable confidentiality, tracking and retrieval.

SOPs are in place for the collection and handling of data received at the NPEU CTU. All eCRFs uploaded into OpenClinica will be archived by NPEU CTU onto appropriate media for long-term accessible storage once the trial has been completed and the reports published. The data will be archived in a secure physical or electronic location with controlled access. Storage will be on a restricted area of a file server. The server is in a secure location and access is restricted to a few named individuals. Access to the building in which the NPEU CTU is situated is via an electronic tag and individual rooms are kept locked when unoccupied. Authorisation to access restricted areas of the NPEU network is as described in the NPEU security policy.

Data collected onto the DCFs which is then transferred onto an electronic database for sending to NPEU will be transmitted and stored without personal participant identifiers and will therefore only be identifiable by a trial-specific number. The infant's name and any other identifying personal details will be stored in a separate database held only by the CI/PI/authorised delegate (Clinical Trial Administrator) which links with the trial number. Personal identifying information will be collected and retained with parents' consent to enable follow-up contact to be undertaken to provide the results of the study. If parents opt out of further contact then no relevant identifying information will be retained electronically.

13. REGULATORY CONSIDERATIONS

13.1 Serious Breach of Good Clinical Practice or of the Trial Protocol

The MHRA require that they be informed of all serious breaches in good clinical practice (GCP) or the trial protocol within 7 days of the Sponsor becoming aware of the breach. A serious breach is defined as a breach of GCP or of the trial protocol which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the patient on the trial or
- The scientific value of the trial

In the event that a serious breach is suspected the Trial Co-ordinating Centre (Norwich) should be contacted as soon as possible so that the Sponsor can be made aware of the serious breach immediately.

The CI or their delegate will also notify any protocol violations to the Sponsor and will notify the REC of these in accordance with trial procedures.

13.2 Regulatory Compliance

A Clinical Trial Authorisation (CTA) for this trial has been obtained from the MHRA . The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

14. ETHICS

14.1 Declaration of Helsinki

The Investigators will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

14.2 Guidelines for Good Clinical Practice

The Investigators will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

14.3 Approvals

The trial will only start after gaining the requisite approvals from the MHRA, a UK national REC, and the NHS Trust Research and Development Offices at the individual trial sites.

Applications will be submitted through the Integrated Research Application System (IRAS). A copy of the protocol and the Parental Informed Consent Form will be submitted to the REC for approval. The CI or their delegate will submit and, where necessary, obtain approval from the MHRA and REC for any substantial amendments. Substantial amendments are defined as those that affect:

- the safety or physical or mental integrity of the participants of the trial
- the scientific value of the trial
- the conduct or management of the trial
- the quality or safety of any IMP used in the trial

All correspondence with the REC will be retained in the Trial Master File/Investigator Site File. Responsibility for maintenance of the Trial Master File has been delegated by the Sponsor to the CI.

An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

It is the CI's responsibility to produce the annual reports as required. The CI will also notify the REC of the End of the Study. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within 1 year after the End of the Study, the CI will submit to the REC, the MHRA, and to the Funder a final Clinical Trial Report with the results of the study, including details of any presentations or publications arising or in preparation.

14.4 Participant Confidentiality, Data Handling and Record Keeping

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. Overall responsibility for ensuring that each participant's information is kept confidential will lie with the trial Sponsor. All trial data will be collected using bespoke data collection forms. Data will be processed in line with the Sponsor's Data Management SOP, using validated data management systems to ensure consistency, viability, and quality of the data. It is then stored in line with the Data Protection Act (1998). All paper documents will be stored securely and kept in strict confidence in compliance with the Data Protection Act (1998). Data collected on the Data Collection Forms (DCFs) will be transferred for storage in an electronic database held by the Trial Co-ordinating Centre in which the participant will be identified only by a trial-specific number.

Data Collection 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 Trial Co-ordinating Centre 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 participants' signed PICFs being supplied to the Trial Co-ordinating Centre by recruiting sites, which requires that name data be transferred to the Trial Co-ordinating Centre. Transfer of contact details will also enable the future follow-up contact with parents of participants to occur.

This collection of identifiable data is disclosed in the PICF. The Trial Co-ordinating Centre will preserve the confidentiality of participants taking part in the trial. Contact details of the baby's parents, as well as the baby's name and any other identifying details will be stored in a separate database also held at the The Trial Co-ordinating Centre. This database will be linked to the database containing trial data only by the baby's trial number.

Electronic data submitted to NPEU CTU for data analysis will be anonymised and participants will be identifiable only by their trial-specific number.

After the trial has been completed and the reports published, the data will be archived in a secure physical and/or electronic location with controlled access.

14.5 Retention of Personal Data

Personal data will be retained to enable contact with parents who consented to receive the results of the study so that the trial results may be disseminated to them. With consent, personal data will be kept for a period of no less than 10 years in case there is peer query regarding the study findings within this period following peer-reviewed publication, and in case any longer-term issue related to either of the IMPs became apparent which necessitated further contact with the family. In such instance it will be important to know exact details of patients recruited so that casenotes can be retrieved as necessary for further source verification and/ or analysis of relevant patient-specific data. Full research records for this study will be retained for 25 years (see Sec. 12.5).

Once study analyses and the Clinical Trial Report are completed, parents will be routinely informed of the results of the study (unless they opted out from further contact). Thus they will be contacted when the results are available to disseminate the study findings and personal data will need to be retained for this specific purpose.

Only the Chief Investigator, local Principal Investigator, and Trial Study Co-ordinator will store any personal data (with consent) for >12 months. At all times personal data will be held securely and will not be used for any other purpose.

15. FUNDING

The National Institute for Health Research (NIHR) Research for Patient Benefit (RfPB) programme is funding this trial.

16. INSURANCE

The NHS indemnity scheme will apply to the potential liability of the sponsor for harm to participants arising from the management and conduct of the research. NHS indemnity operates in respect of the clinical treatment provided during the course of the study.

17. TRIAL GOVERNANCE

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA.

The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

17.1 Site Research and Development Approval

Individual sites will only commence recruiting participants once they receive approval from NHS Trust Research and Development (R&D) Offices. The R&D Departments will issue Capacity and Capability approvals following receipt of the relevant approval documents from the Health Research Authority.

17.2 Trial Sponsor

The Norfolk and Norwich University Hospitals NHS Foundation Trust is the nominated Sponsor for this trial. The Sponsor assumes overall responsibility for the initiation and management of the trial.

17.3 Trial Co-ordinating Centre

The trial co-ordinating centre will be at the Norfolk and Norwich University Hospitals NHS Foundation Trust, where the Trial Administrator will be based. The NPEU CTU will be responsible for all trial programming, including construction, validation, testing, release and support of the web-based randomisation facility; generation of the randomisation sequence and pack numbers plus all statistical analysis. In addition the NPEU CTU will service both the TSC and the DMC.

17.4 Trial Management Group (TMG)

The trial will be supervised on a day-to-day basis by the Trial Management Group. This group reports to the Trial Steering Committee (TSC) which is responsible to the trial Sponsor. At each participating centre, the local PI will report to the TMG via the CI and trial administrator based at the trial co-ordinating centre.

The core TMG will be comprised of the CI and key clinical co-applicants/ CTU members. There will be teleconferences at least bi-monthly and at least one face-to-face meeting annually. PPI representatives will be invited to attend all face-to-face meetings.

17.5 Trial Steering Committee (TSC)

The trial will be overseen by a TSC consisting of an independent chair, an independent vice-chair, and at least five other independent members. The majority of the membership of the TSC will be independent of the trial. Committee members will be deemed to be independent if they are not involved in trial recruitment and are not employed by any organisation directly involved in the trial conduct.

Representatives from relevant Patient/Public Involvement groups, the CI, and other Investigators/co-applicants will be joined by observers from the NPEU CTU. The NIHR RfPB programme manager will also be invited to attend all TSC meetings.

The TSC will provide the overall supervision of the trial. The TSC will monitor the progress of the trial and will conduct and advise on its scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the DMC and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy. The TSC will review trial progress and report on progress to the funder.

17.6 Data Monitoring Committee (DMC)

A DMC, independent of the applicants and of the TSC, will review the progress of the trial at least annually and provide advice on the conduct of the trial to the TSC and (via the TSC) to the RfPB programme manager. The committee will periodically review trial progress and outcomes. A meeting of the DMC will be scheduled after 50 infants have been recruited to the study so that an interim safety analysis can be carried out. The content and timings of other DMC reviews will be detailed in a DMC Charter, which will be agreed at its first meeting.

18. PUBLIC AND PATIENT INVOLVEMENT

The aims of Public and Patient Involvement (PPI) in this research are:

1. To incorporate a diversity of views from relevant parties in the design and management of the project.
2. To ensure that the parent information leaflet is developed in consultation with those who will receive it, and to receive advice on best recruitment strategy
3. To ensure that findings of the research are disseminated to relevant parties in an appropriate manner.

This study proposal has already benefitted from extensive PPI during its development, including advice regarding Parental Informed Consent Form content, aspects of the protocol, and reassurance regarding acceptability to parents of the proposed antiseptics. Input into these relevant aspects therefore assisted our ethics submission.

Formal PPI input was given during study development by:

- i) Bliss baby charity (www.bliss.org.uk)
- ii) PPIRes (<http://nspccro.nihr.ac.uk/ppires>), a local initiative with ~70 lay members from Norfolk and Suffolk who collaborate with researchers in local Trusts and Universities
- iii) the Neonatal Clinical Specialty Group of the Medicines for Children Research Network, which has consumer member representation.

Informal but nevertheless valuable PPI was also obtained from a local parent support group of ex-premature babies, and from parents of babies who suffered catheter-related infections with whom we consulted and outlined our proposed study.

Plans for ongoing PPI involvement in this study include roles in study management and in dissemination of findings:

Management: We have invited two independent lay members to join the TSC (in a shared role). Both are parents with recent experience of having a premature baby on a neonatal unit. The lay members will be supported in their role by our local PPI panel (PPIRes), which will also offer them training. The lay members will be included in all aspects of study management, including recruitment strategy and advising how/when is best to approach parents. Their input will ensure that parents' perspective is readily available and given due prominence throughout the study.

Dissemination: Participants and support groups will be invited to a local dissemination event. We will seek the assistance of Bliss to support dissemination of the findings to parents and professionals (via their website, study days, and e-bulletin). We will send parents whose babies participate a short summary of the findings if they wish to receive this. This report will be prepared in collaboration with the lay representatives.

19. COMMUNICATION

19.1 Study Findings

The CI will co-ordinate dissemination of the results from this study. All publications using data from this study will be submitted to the TSC for review before release. To safeguard the scientific integrity of the trial, data from this study will not be presented publically before the main results are published, without the prior consent of the TSC.

19.2 Dissemination plan

The findings of this feasibility study will be shared with colleagues regionally and nationally to help recruit centres which may be interested to join the future large-scale trial. We will achieve this by presenting of our findings regionally and at, for example, the annual scientific meetings of the RCPCH and the British Association for Perinatal Medicine. The NIHR Clinical Research Network will assist recruitment of sites by calling for expressions of interest via their e-mail contacts with UK NICUs. We will share our findings with Bliss for dissemination to parents and professionals via the Bliss e-newsletter and website. Parents who allowed their baby's participation in the study and members of the Public & Patient Involvement in Research (PPIRes) panel will be given a summary study report. We will also aim to publish our feasibility study methodology and findings in a suitable Open Access peer-reviewed journal. The funding body (NIHR RfPB) will be properly acknowledged in any publication and presentations arising.

19.3 Publication Policy/Acknowledgement of Contribution

Publication of any reports or articles arising from this trial will comply with the NIHR terms and conditions on report publication policy as specified in the funding contract. In submitting any paper, article or report for publication, appropriate due acknowledgment will be given to the NIHR in order to maximise awareness of the impact of the research it funds, nationally and internationally.

The success of the trial will depend upon a large number of neonatologists, neonatal nurses and parents. Credit for the trial findings will be given to all who have collaborated and participated in the trial. The Authorship of the primary results paper arising will comprise all who have made a substantial intellectual contribution to the study (including the research question, design, analysis, interpretation), and so is expected to include all main applicants on this study who fulfil all four criteria of the ICMJE recommendations for authorship (www.icmje.org). The initial drafting of the paper will be the responsibility of the CI. All contributors to the trial will be listed at the end of the manuscript, with their contribution identified.

20. EXPECTED OUTPUT OF RESEARCH/PLANS FOR FUTURE LARGE-SCALE STUDY

It is hoped that the findings of this feasibility study will pave the way for the definitive large-scale efficacy/safety study. The large-scale study will be a multi-centre non-inferiority RCT of the same two antiseptics for skin disinfection prior to PCVC insertion in preterm neonates. Primary outcome measure will be catheter colonisation as determined by culture of catheter segment/s taken at catheter removal.

This research ultimately promises to provide, for the first time, evidence-based guidance regarding suitable antiseptic to use on the skin of premature babies.

National evidence-based guidelines for preventing healthcare-associated infections in the NHS were commissioned by the Department of Health. Versions of these guidelines ('epic3') have been published in 2001, 2007, and 2014 to incorporate new research evidence[29]. None has included advice or recommendations on antiseptics specific for preterm neonates. We expect that our research findings should be incorporated into a future version.

This research will directly benefit the care of the many thousands of premature neonates in the UK who need central venous catheters each year. The findings can also be applied to many preterm infants who require peripheral venous cannulas, because if non inferiority of 2%CHG is shown for central catheters, then logically alcohol-based CHG can also be avoided for the much shorter-term peripheral catheters. This research therefore has the potential to save large numbers of babies each year from the risks of skin injury and chemical absorption of isopropyl alcohol, and the concomitant pain and distress caused to infants and their families. Associated costs arising from scarring, need for dressings to chemical burns, plastic surgery, and later legal claims because of iatrogenic skin injury can all be avoided.

This study may provide economic benefits to the NHS if a cheaper 2%CHG aqueous solution was found not to be inferior to a more expensive 2%CHG alcohol-based solution. Evidence for a preferred antiseptic for use in the neonatal population will allow units to standardise practices and move towards adoption of a single recommended agent. This would also likely have economic benefits to the NHS.

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Contact Details:
NPEU Clinical Trials Unit
National Perinatal Epidemiology Unit
Nuffield Department of Population Health
University of Oxford
Old Road Campus
Oxford
OX3 7LF
T: 01865 289 728
F: 01865 289 740
E: arctic@npeu.ox.ac.uk

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