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2% chlorhexidine gluconate aqueous versus 2% chlorhexidine gluconate in 70% isopropyl alcohol for skin disinfection prior to percutaneous central venous catheterisation: the ARCTIC randomised controlled feasibility trial

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ABSTRACT

Objective Catheter-related sepsis (CRS) is a major complication with significant morbidity and mortality. Evidence is lacking regarding the most appropriate antiseptic for skin disinfection before percutaneous central venous catheter (PCVC) insertion in preterm neonates. To inform the feasibility and design of a definitive randomised controlled trial (RCT) of two antiseptic formulations, we conducted the Antiseptic Randomised Controlled Trial for Insertion of Catheters (ARCTIC) feasibility study to assess catheter colonisation, sepsis, and skin morbidity.

Design Feasibility RCT.

Setting Two UK tertiary-level neonatal intensive care units.

Patients Preterm infants born <34 weeks' gestation scheduled to undergo PCVC insertion.

Interventions Skin disinfection with either 2% chlorhexidine gluconate (CHG)-aqueous or 2% CHG-70% isopropyl alcohol (IPA) before PCVC insertion and at removal.

Primary outcome Proportion in the 2% CHG-70% IPA arm with a colonised catheter at removal.

Main feasibility outcomes Rates of: (1) CRS, catheter-associated sepsis (CAS), and CRS/CAS per 1,000 PCVC days; (2) recruitment and retention; (3) data completeness.

Safety outcomes Daily skin morbidity scores recorded from catheter insertion until 48 hours post-removal.

Results 116 babies were randomised. Primary outcome incidence was 4.1% (95% confidence interval: 0.9% to 11.5%). Overall catheter colonisation rate was 5.2% (5/97); CRS 2.3/1000 catheter days; CAS 14.8/1000 catheter days. Recruitment, retention and data completeness were good. No major antiseptic-related skin injury was reported.

Conclusions A definitive comparative efficacy trial is feasible, but the very low catheter colonisation rate would make a large-scale RCT challenging due to the very large sample size required. ARCTIC provides preliminary reassurance supporting potential safe use of 2% CHG-70% IPA and 2% CHG-aqueous in preterm neonates.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Good skin disinfection is vital prior to central venous catheterisation to minimise risk of catheter colonisation and subsequent sepsis.
⇒ The skin of preterm neonates is particularly vulnerable to antiseptic chemical burn injury.
⇒ The most effective antiseptic for reducing risks of both catheter sepsis and skin harms in preterm neonates is unknown due to lacking clinical trial evidence.

WHAT THIS STUDY ADDS

⇒ The ARCTIC study provides contemporary evidence for rates of catheter-related infections associated with pre-procedural skin disinfection using topical 2% CHG-70% IPA and 2% CHG-aqueous solutions.
⇒ Use of 2% CHG-70% IPA for central venous catheterisation in preterm neonates is associated with a very low rate of catheter colonisation at catheter removal.
⇒ The robust safety data obtained would support the use of these agents in a large comparative trial, with skin application adhering to strict guidelines.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

The ARCTIC study results provide an accurate indication of the very large sample size that would be needed for a definitive comparative non-inferiority antiseptic trial.

TRIAL REGISTRATION NUMBER

ISRCTN82571474.

INTRODUCTION

Percutaneous central venous catheters (PCVCs) are essential, but pose a significant risk for bloodstream infection.[1–3] Catheter-related and catheter-associated sepsis (CRS and CAS) are dangerous

complications that carry significant neonatal morbidity. Sepsis increases intensive care days, antibiotic usage, and risk of adverse neurodevelopmental outcomes and death.[4–7]

Reducing CRS remains a major goal of the NHS.[8] Adoption of catheter care 'bundles' helps reduce CRS rates,[9 10] but with a multifactorial aetiology the goal of zero CRS still proves elusive.[11 12] Individual components of bundles have rarely been rigorously studied through randomised controlled trials (RCTs) in neonates.[3 10 12] One crucial component in preventing catheter infection is optimal antiseptic choice for pre-procedural skin disinfection of the catheter insertion site.[2 13] Studies in adults, including meta-analysis, show that alcohol-based antiseptics are superior for topical antisepsis.[14 15] UK evidence-based guidelines in adults and older children recommend 2% chlorhexidine gluconate (CHG) in 70% isopropyl alcohol (2% CHG-70% IPA),[16 17] but they lack guidance on preferred antiseptic in preterm infants, reflecting the paucity of evidence and safety concerns specific to this population.[3 13 18] Consequently, multiple different antiseptics, concentrations and combinations are in use in UK neonatal intensive care units (NICUs).[19 20]

No published RCT has so far examined the safety and efficacy of alcohol-based versus aqueous CHG formulations for skin antisepsis prior to PCVC insertion in preterm neonates. We therefore undertook the Antiseptic Randomised Controlled Trial for Insertion of Catheters (ARCTIC) feasibility study to inform the safety, design and scale of a potential large-scale multicentre RCT to determine whether 2% CHG-aqueous is non-inferior in antiseptic efficacy compared with 2% CHG-70% IPA for skin disinfection prior to PCVC insertion.

METHODS

Study design and setting

A blinded parallel group feasibility RCT conducted in two UK tertiary-level NICUs: Norfolk and Norwich University Hospital, and Medway Maritime Hospital.

Participants

Preterm infants born at <34 weeks' gestation were eligible if they required PCVC insertion for parenteral nutrition. We excluded infants: unlikely to survive; with a life-threatening congenital abnormality or an underlying skin condition; who already had an indwelling PCVC or were previously enrolled; with a new episode of suspected sepsis with commencement of antibiotics within the previous 48 hours; with a positive blood culture (BC) within the previous 7 days without a subsequent negative culture.[3]

Antiseptic products and blinding

The two topical Investigational Medicinal Product (IMP) antiseptic agents used, 2% CHG-aqueous and 2% CHG-70% IPA, were specially manufactured under licence for this trial. Production, labelling and blinding of study packs containing paired bottles each containing 20 mL of IMP was as described.[3]

Randomisation

Secure internet-based randomisation was performed as close to catheter insertion as possible by a research team member or trained clinician.[3] The randomisation system used stratified block randomisation with allocation sequence generated by the senior trials statistician (LL). Blocks of size 4 and 8 were generated using Stata (V.13/SE for Windows). Stratification was by centre and gestational age at birth (<28 weeks and 28^{+0} to 33^{+6} weeks). Allocation was weighted 3:1 in favour of the 2% CHG-70% IPA IMP group to inform the primary objective of sample size calculation for a phase-III trial.[3]

Interventions

The trial procedures have been published in detail.[3] Trained clinical staff inserted and removed PCVCs according to the trial's protocol and working good clinical practice guidelines for catheter insertion and removal (online supplemental files 1 and 2). Specimens collected on catheter removal were: (1) two exit site skin swabs (ESSSs), one before and one after skin disinfection of insertion site using the same allocated IMP as at catheter insertion; (2) two ~1 cm long catheter segments, namely the tip plus a proximal segment taken approximately 1-2 cm distal to the former skin entry point; and (3) a peripheral BC (only if catheter removal was for suspected sepsis).[3]

Catheter-related sepsis, catheter colonisation and catheter-associated sepsis

Our study had strict definitions for definite CRS, catheter colonisation and CAS (table 1, footnotes).

Microbiological and molecular analysis

Catheter segments, skin swabs, and BCs underwent routine culture and antibiotic sensitivities in our hospital microbiology laboratories. Bacterial growths from ESSS cultures were assessed semi-quantitatively.[21] Culture-positive isolates were retained for whole genome sequencing, allowing for unequivocal diagnosis of CRS.[3]

Outcome measures and assessments

Primary outcome

Proportion of babies in the 2% CHG-70% IPA group with catheter colonisation, determined by at least one of the two catheter segments taken at catheter removal being bacterial culture positive.

Secondary outcomes

Efficacy outcomes

(1) Proportion of infants with positive ESSSs (pre disinfection and post disinfection) at catheter removal; (2) number and type of culture-positive catheter segments at removal; (3) bacterial species identified on positive BC, ESSSs and catheter segments as typed by molecular methods (undertaken to prove concordance of paired blood and catheter isolates to a species level for definitive diagnosis of definite CRS); (4) proportion of infants with definite CRS in the period between catheter insertion and 48 hours post catheter removal; (5) proportion of infants with CAS in the period between catheter insertion and 48 hours post catheter removal; (6) rate of CRS per 1000 PCVC days; (7) rate of CAS per 1000 PCVC days; (8) rates of recruitment and retention; (9) views of parents and clinicians on factors affecting recruitment and retention; (10) proportion of infants completing the study with complete data for the primary outcome; and (11) proportions of infants with missing data collection forms.

Safety outcomes

Skin condition and morbidity, assessed at catheter insertion and daily until 48 hours post catheter removal. A validated neonatal contact dermatitis scoring system was used,[22] with minor modification.[3]

Table 1 Summary efficacy outcomes for bacteriology and sepsis including primary outcome

	2% CHG-70% IPA (n=79)	2% CHG-aqueous (n=27)	All (n=106)
Positive exit site skin swab at catheter removal before disinfection, n (%)	11 (15.1)	4 (16.7)	15 (15.5)
Missing	6	3	9
Positive exit site skin swab at catheter removal after disinfection, n (%)	1 (1.4)	1 (4.3)	2 (2.1)
Missing	7	4	11
Culture-positive catheter segment at removal†, n (%)	3 (4.1)*	2 (8.3)	5 (5.2)
Positive tip alone	1 (1.3)	1 (3.7)	2 (1.9)
Positive proximal segment alone	2 (2.5)	0	2 (1.9)
Both tip and proximal segment positive	0	1 (4.2)	1 (1.0)
Missing	6	3	9
Definite catheter-related sepsis‡, n (%)	1 (1.5)	1 (4.5)	2 (2.3)
Missing	13	5	18
Catheter-associated sepsis§, n (%)	10 (13.7)	3 (12.5)	13 (13.4)
Missing	6	3	9
Total number of PCVC days	653	223	876
Definite catheter-related sepsis, n (rate per 1000 PCVC days)	1 (1.5)	1 (4.5)	2 (2.3)
Catheter-associated sepsis, n (rate per 1000 PCVC days)	10 (15.3)	3 (13.5)	13 (14.8)

*Primary outcome: 3/73 (4.1%) with 95% confidence interval of 0.9% to 11.5%.
†Catheter colonisation: a catheter that at the time of removal has either one or both segments culture positive.
‡Definite catheter-related sepsis: a peripheral BC plus any catheter segment (i.e. proximal and/or tip) positive with the same organism, based on bacterial culture, antibiotic sensitivity and molecular typing, from a neonate who had an indwelling PCVC and clinical signs of sepsis but no other focus of sepsis.
§Catheter-associated sepsis: clinical signs of sepsis and an accompanying positive BC in the period between catheter insertion and 48 hours post removal but with no other focus of sepsis and with both catheter segment cultures negative.
BC, blood culture; CHG, chlorhexidine gluconate; PCVC, percutaneous central venous catheter.

Process outcomes

(1) Adherence to study protocol; (2) numbers of attempted and failed catheterisations; and (3) withdrawals.

Sample size and statistical analysis

A target sample size comprising ~93 babies having successfully inserted catheters would suffice to estimate the anticipated incidence of the primary outcome (20%) in the reference 2% CHG-70% IPA group with a 95% CI of 11% to 31%.[3] A statistical analysis plan was developed and approved by the Trial Steering Committee (TSC) chair by the end of enrolment (online supplemental file 3). This feasibility study is reported in accordance with the Consolidated Standards of Reporting Trials extension guidelines for randomised pilot and feasibility trials.[23]

Data management

Outcome data were collected as described,[3] using study-specific forms. Data were transferred and stored in compliance with Good Clinical Practice (GCP) and Data Protection legislation.[3]

Monitoring

The Sponsor's nominated representatives undertook regular monitoring visits during the course of the trial, according to a monitoring plan.[3]

Pharmacovigilance, data and safety monitoring

Pharmacovigilance was conducted as described.[3] The trial had a Data Monitoring Committee (DMC) and TSC with respective charters signed off by their independent chairs prior to first enrolment. The DMC met regularly before, during and at the end of the trial to review the protocol, compliance, safety and outcome data, including after the first 50 babies were enrolled.[3]

Patient and public involvement

The study was developed with extensive parent and public input.[3] Two lay TSC parent members assisted dissemination of a final summary report to parents of all participants.

Ethics and regulatory approvals

A clinical trial authorisation was granted by the responsible authority on 23rd October 2015 (MHRA reference: 13630/0009/001-0001).

RESULTS

Between March 2017 and July 2018, 207 infants were assessed for eligibility. 116 were randomised of whom 88 were allocated 2% CHG-70% IPA and 28 were allocated 2% CHG-aqueous (figure 1). Table 2 presents baseline characteristics of all 114 babies who underwent attempted catheterisation. Additional details relating to catheterisation are provided (online supplemental table S1).

Efficacy outcomes

Clinical and microbiological outcomes including primary outcome

One hundred and six babies were assessed for clinical and microbiological outcomes (figure 1). Table 3 shows individual results for the 31 babies who had at least one positive culture result isolated from culture of blood, ESSSs and catheter segments. Paired catheter segment culture results were available for 97 babies, losses mainly being due to repatriation of neonates to non-participating hospitals before catheter removal. The overall catheter colonisation rate was 5.2% (5/97). Of 79 babies allocated the 2% CHG-70% IPA antiseptic and successfully catheterised, 73 had paired catheter segments available and 3 babies had a colonised catheter at the time of removal, an incidence for the primary outcome of 4.1% (95% CI 0.9% to 11.5%). One baby in each group had definite CRS (2% CHG-70% IPA 1.5% (1/66) vs 2% CHG-aqueous

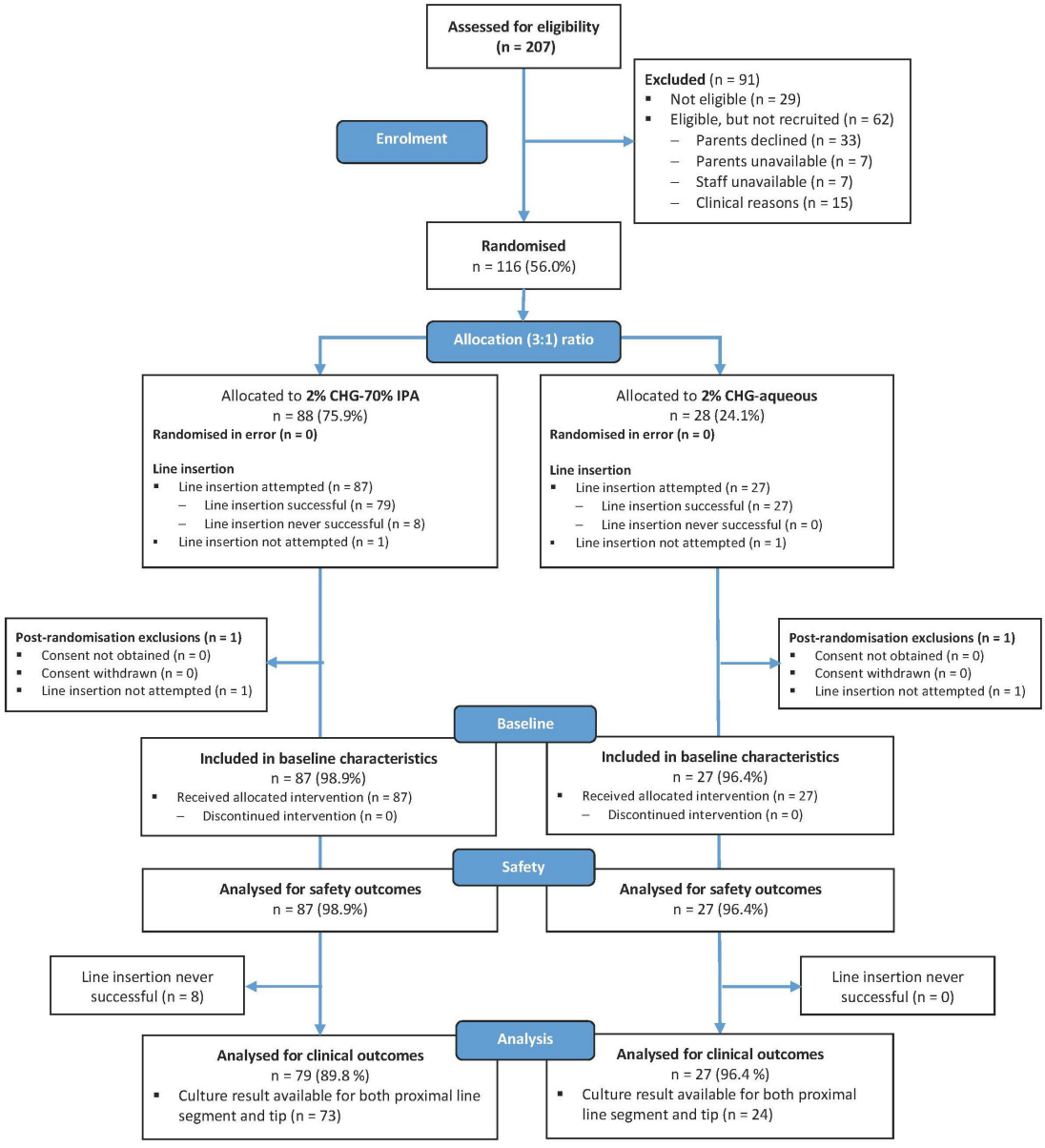

Figure 1 Study flow diagram.

4.5% (1/22)), and rates of CAS were similar (2% CHG-70% IPA 13.7% vs 2% CHG-aqueous 12.5%). The bacteriology and sepsis-related secondary outcomes are summarised by allocation in table 1. At catheter removal, 15 babies (15.5%) overall had a culture-positive ESSS pre-disinfection, with proportions similar between groups, and only one baby in each group had a positive ESSS post-disinfection (tables 1 and 3).

Paired bacterial isolates from relevant babies underwent whole genome sequencing for definitive speciation. Specimens of particular interest were blood and catheter isolates in the two CRS cases (ID numbers 15 and 26, table 3), and the blood and ESSS isolates in the two CAS cases (ID numbers 14 and 16, table 3). Genome sequencing confirmed identity and exact match of the CoNS species in both the CRS cases. Unfortunately, the paired BC isolates were not retained for the two CAS cases, so their typing and matching was not possible.

Recruitment, retention and factors affecting

Of 178 eligible infants, we approached the parents of 149 and 116 (77.9%) gave consent. The overall retention rate was 83.6% (online supplemental table S2). Voluntary feedback collected from parents who declined participation and clinicians' views on factors affecting recruitment are summarised (online supplemental table S3).

Study completion and completeness of data collection

The proportion of randomised infants with complete data for the proposed primary outcome of catheter colonisation was 97/116 (83.6%) (online supplemental table S2). Completeness of data collection forms was excellent, with only two forms missing (from babies who did not complete the study) (online supplemental table S4).

Safety outcomes

One hundred and fourteen babies who received IMP underwent a total of 274 separate skin applications with allocated IMP (2% CHG-70% IPA, n=197; 2% CHG-aqueous n=77), comprising insertion and removal disinfections and applications that preceded failed catheterisation attempts (figure 1; online

Table 2 Infant and maternal baseline characteristics

	2% CHG-70% IPA (n=87)	2% CHG-aqueous (n=27)
Centre*, n (%)		
Norfolk and Norwich	56 (64.4)	17 (63.0)
Medway	31 (35.6)	10 (37.0)
Male sex, n (%)	46 (52.9)	13 (48.1)
Infant's birth weight (g)		
Mean (SD)	1089 (340.5)	1075 (366.3)
Range	(508–2150)	(575–1900)
<500 g	0	0
500 to 999 g	39 (44.8)	15 (55.6)
1000 to 1499 g	37 (42.5)	8 (29.6)
≥1500 g	11 (12.6)	4 (14.8)
Gestational age at birth* (completed weeks)		
Median (IQR)	28 (26–30)	28 (26–30)
Range	(23–32)	(23–33)
$<26^{+0}$	20 (23.0)	5 (18.5)
26^{+0} to 27^{+6}	19 (21.8)	7 (25.9)
28^{+0} to 33^{+6}	48 (55.2)	15 (55.6)
One of a multiple pregnancy, n (%)	16 (18.4)	9 (33.3)
Mode of delivery, n (%)		
Vaginal	29 (33.3)	7 (25.9)
Caesarean	58 (66.7)	20 (74.1)
Membranes ruptured prior to labour, n (%)	35 (41.7)	9 (36.0)
>24 hours before delivery	20 (57.1)	6 (66.7)
≤24 hours before delivery	15 (42.9)	3 (33.3)
Unknown	0	0
Apgar score at 5 minutes		
Median (IQR)	8 (7–9)	8 (6–9)
<4	2 (2.4)	2 (7.7)
First recorded temperature on admission to NICU after birth, mean (SD) °C	36.8 (0.7)	36.8 (0.9)
Infant ventilated via an endotracheal tube at the time of randomisation, n (%)	34 (39.1)	13 (50.0)
Infant born in recruiting hospital, n (%)	68 (78.2)	19 (70.4)
Any surgical procedure prior to randomisation, n (%)	6 (6.9)	1 (3.7)
Prophylactic antifungal medication at the time of randomisation, n (%)	27 (31.0)	9 (33.3)
Received antibiotics prior to randomisation†, n (%)	78 (98.7)	26 (96.3)
Devices in situ at time of PCVC insertion†, n (%)		
Chest drain	1 (1.3)	0 (0.0)
Endotracheal tube	28 (35.4)	12 (44.4)
Peripheral arterial line	2 (2.5)	2 (7.4)
Peripheral venous cannula	70 (88.6)	18 (66.7)
Umbilical arterial catheter	24 (30.4)	11 (40.7)
Uumbilical venous catheter	43 (54.4)	14 (51.9)
Other	2 (2.5)	0 (0.0)
Mother's age (years), mean (SD)	29.7 (6.0)	29.4 (5.7)
Received any antenatal corticosteroids, n (%)	80 (92.0)	24 (88.9)
Received antibiotics within the week before delivery, n (%)	27 (31.0)	8 (29.6)
Feverish in labour (temperature>38.0°C)‡, n (%)	4 (4.8)	0 (0.0)
Chorioamnionitis suspected clinically before delivery, n (%)	7 (8.0)	1 (3.7)

Unless otherwise stated, data are n (%). SD, standard deviation; IQR, interquartile range.
*Stratification factors.
†Data missing for eight cases in the 2% CHG-70% IPA group.
‡Data missing for three cases in the 2% CHG-70% IPA group.
CHG, chlorhexidine gluconate; IPA, isopropyl alcohol; NICU, neonatal intensive care unit; PCVC, percutaneous central venous catheter.

supplemental tables S2 and S5). Safety data were obtained for all 114 babies (100%) who received allocated antiseptic, including for babies transferred before catheter removal. Table 4 summarises daily skin morbidity scores in the period between catheter insertion and 48 hours post catheter removal (or post antiseptic application when catheterisation unsuccessful). No baby had any serious or major chemical burn injury or moderate/severe skin reaction recorded or requiring reporting after antiseptic application. A minority showed limited erythema (20/114; 17.5%); this appeared more common if catheterised in the first postnatal days and/or extremely preterm. Seven (6.1%) had limited skin breakdown/excoriation recorded (table 4). All skin morbidity was minor, self-limiting and resolved fully. None required special dressing or plastic surgical referral.

Table 3 Bacterial species isolated via standard microbiology laboratory culture for infants with at least one positive culture result

		Blood culture(s)				Exit site skin swab		Catheter segment	
		Closest to PCVC removal (days)	Blood culture results						
ID no	IMP allocation		#1	#2	#3	Before disinfection	After disinfection	Proximal	Tip
1	2% CHG-70% IPA	6.2 pre	No growth	No growth	–	CoNS: *S. capitis*	No growth	No growth	No growth
2	2% CHG-70% IPA	–	N/A	N/A	N/A	No growth	No growth	CoNS: *S. capitis*	No growth
3	2% CHG-70% IPA	0.3 pre	Mixed CoNS (not specified)	No growth	–	No growth	No growth	No growth	No growth
4	2% CHG-70% IPA	–	N/A	N/A	N/A	CoNS: *S. haemolyticus*	No growth	No growth	No growth
5	2% CHG-70% IPA	0.0 post	CoNS: *S. epidermidis*	CoNS: *S. capitis*	–	No growth	No growth	No growth	No growth
6	2% CHG-70% IPA	1.8 post	No growth	–	–	CoNS: *S. capitis*	No growth	No growth	No growth
7	2% CHG-70% IPA	0.9 post	No growth	–	–	No growth	CoNS: *S. capitis*	No growth	No growth
8	2% CHG-70% IPA	–	N/A	N/A	N/A	CoNS: *S. epidermidis*	No growth	No growth	No growth
9	2% CHG-70% IPA	–	N/A	N/A	N/A	Mixed CoNS (not specified)	No growth	No growth	No growth
10	2% CHG-70% IPA	1.3 post	CoNS: (not specified)	–	–	No growth	No growth	No growth	No growth
11	2% CHG-70% IPA	0.0 post	No growth	CoNS: *S. capitis*	–	No growth	No growth	No growth	No growth
12	2% CHG-70% IPA	–	N/A	N/A	N/A	CoNS: *S. capitis*	No growth	No growth	CoNS: *S. capitis*
13	2% CHG-70% IPA	1.4 post	No growth	CoNS: *S. haemolyticus*	–	No growth	No growth	No growth	No growth
14*	2% CHG-70% IPA	0.0 post	CoNS: 1. *S. haemolyticus*; 2. *S. epidermidis*	No growth	–	CoNS: *S. capitis*	No growth	No growth	No growth
15†	2% CHG-70% IPA	1.7 post	CoNS: *S. capitis*	CoNS: *S. capitis*	No growth	No growth	No growth	CoNS: *S. capitis*	No growth
16*	2% CHG-70% IPA	6.1 pre	No growth	CoNS: *S. capitis*	–	CoNS: *S. capitis*	No growth	No growth	No growth
17	2% CHG-70% IPA	0.2 pre	CoNS: *S. haemolyticus*	No growth	CoNS: *S. capitis*	No growth	No growth	No growth	No growth
18	2% CHG-70% IPA	5.8 pre	CoNS: *S. haemolyticus*	*CoNS: S. epidermidis*	No growth	No growth	No growth	No growth	No growth
19	2% CHG-70% IPA	–	N/A	N/A	N/A	CoNS: *S. warneri*	No growth	No growth	No growth
20	2% CHG-70% IPA	0.2 pre	No growth	CoNS: *S. capitis*	No growth	No growth	No growth	No growth	No growth
21	2% CHG-70% IPA	–	N/A	N/A	N/A	1. CoNS: *S. capitis*; 2. *S. aureus*	No growth	No growth	No growth
22	2% CHG-70% IPA	–	CoNS: not specified	–	–	Missing‡	Missing‡	Missing‡	No growth
23	2% CHG-70% IPA	–	N/A	N/A	N/A	CoNS: *S. haemolyticus*	No growth	No growth	No growth
24	2% CHG-aqueous	1.7 post	No growth	–	–	CoNS: *S. haemolyticus*	No growth	No growth	No growth
25	2% CHG-aqueous	0.0 post	CoNS: *S. warneri*	No growth	–	No growth	No growth	No growth	No growth
26†	2% CHG-aqueous	0.3 pre	No growth	CoNS: *S. warneri*	–	No growth	No growth	No growth	CoNS: *S. warneri*
27	2% CHG-aqueous	–	N/A	N/A	N/A	CoNS: *S. haemolyticus*§	No growth	No growth	No growth
28	2% CHG-aqueous	–	N/A	N/A	N/A	CoNS: *S. capitis*	CoNS: *S. capitis*	No growth	No growth
29	2% CHG-aqueous	4.0 pre	CoNS: *S. capitis*	No growth	–	No growth	No growth	No growth	No growth
30	2% CHG-aqueous	0.5 post	CoNS: 1. *S. epidermidis*; 2. *S. capitis*	No growth	–	No growth	Missing¶	No growth	No growth
31	2% CHG-aqueous	–	N/A	N/A	N/A	CoNS: *S. epidermidis*	No growth	CoNS: *S. epidermidis*	CoNS: *S. epidermidis*

*One of two cases of catheter-associated sepsis.
†One of two cases of definite catheter-related sepsis, both paired isolates confirmed via whole genome sequencing.
‡Infant was transferred to a non-participating site where their line was removed.
§Detail of species was not captured in database, but was found post data lock.
¶Sample not obtained.
CoNS, coagulase-negative staphylococcus; ID, identifier; IMP, Investigational Medicinal Product; N/A, not applicable because no blood culture taken between catheter insertion and 48 hours post removal; PCVC, percutaneous central venous catheter; *S. aureus*, *Staphylococcus aureus*; *S. capitas*, *Staphylococcus capitis*; *S. epidermidis*, *Staphylococcus epidermidis*; *S. haemolyticus*, *Staphylococcus haemolyticus*; *S. warneri*, *Staphylococcus warneri*.

Process outcomes

Catheterisation success rate

Catheterisation was successful in 106 (93%) of 114 babies who underwent attempted PCVC placement (figure 1). Online supplemental table S5 shows numbers of anatomical sites having at least one failed catheterisation.

Table 4 Daily skin morbidity scores in the period between catheter insertion and 48 hours post catheter removal

Skin morbidity scores	2% CHG-70% IPA (n=87)	2% CHG-aqueous (n=27)
Worst score for skin dryness throughout safety monitoring period		
Median (IQR)	1 (1–1)	1 (1–1)
Range	(1–2)	(1–2)
1	80 (92.0)	26 (96.3)
2	7 (8.0)	1 (3.7)
3	0	0
Worst score for erythema throughout safety monitoring period		
Median (IQR)	1 (1–1)	1 (1–1)
Range	(1–2)	(1–2)
1	72 (82.8)	22 (81.5)
2	15 (17.2)	5 (18.5)
3	0	0
Worst score for breakdown/excoriation throughout safety monitoring period		
Median (IQR)	1 (1–1)	1 (1–1)
Range	(1–2)	(1–2)
1	82 (94.3)	25 (92.6)
2	5 (5.7)	2 (7.4)
3	0	0
Worst score for totals of all three scores throughout safety monitoring period		
Median (IQR)	3 (3–4)	3 (3–4)
Range	(3–5)	(3–5)
3	65 (74.7)	20 (74.1)
4	20 (23.0)	6 (22.2)
5	2 (2.3)	1 (3.7)
≥6	0	0

Scoring was performed at baseline, within 10-30 minutes of catheterisation, and then daily until 48 hours post catheter removal, including for any infants repatriated to another hospital with their PCVC still in situ. Skin integrity scoring was also recorded until 48 hours post antiseptic application in instances where catheterisation proved unsuccessful. Skin scores were graded as follows:

Dryness	Erythema	Breakdown/excoriation
1=Normal, no sign of dry skin	1=No evidence of erythema	1=None evident
2=Dry skin, visible scaling	2=Visible erythema <50% of skin area exposed to antiseptic	2=Small localised areas
3=Very dry skin, cracking/fissures	3=Visible erythema ≥50% of skin area exposed to antiseptic	3=Extensive

CHG, chlorhexidine gluconate; IPA, isopropyl alcohol; IQR, interquartile range; PCVC, percutaneous central venous catheter.

Adherence to protocol

There was good adherence for the intervention (online supplemental table S5) and no major protocol breaches.

Withdrawals

There were no study infant withdrawals (figure 1).

DISCUSSION

We successfully carried out a feasibility RCT to compare alcohol versus aqueous formulations of 2% CHG. This is the first RCT to evaluate these formulations specifically for skin disinfection before PCVC insertion in preterm neonates. We have demonstrated a very low primary outcome incidence rate of only 4.1% of catheters being colonised with potentially pathogenic bacteria at the time of removal when 2% CHG-70% IPA antiseptic was used for skin disinfection prior to catheterisation. Furthermore, no major antiseptic-related skin injury was reported after application of either formulation under our strict working guideline. We completed recruitment within a 16-month period and had good rates of compliance with study procedures. Completeness of data collection was excellent, and we gathered rigorous prospective safety data for skin integrity. The primary and all planned secondary objectives were achieved. The ARCTIC trial demonstrates that it would in principle be feasible to conduct a definitive multicentre trial comparing the same two antiseptics in a non-inferiority study.

Our primary objective was to determine catheter colonisation rate in infants who received 2% CHG-70% IPA, to allow sample size calculation for a definitive efficacy study. Finding the catheter colonisation rate to be only 4.1% gave a much lower event rate than anticipated (~21%) at the outset.[3] Modelling sample size for a definitive comparative non-inferiority study using the same primary outcome of catheter colonisation, detection of an absolute risk reduction of 2% would require ~n=3250 infants (90% power, two-sided significance level of 0.05). Assessing a composite clinical outcome of CRS+CAS instead: to detect an absolute risk reduction in catheter infections of 4% (from the combined incidence of CRS+CAS of 15% in our reference group down to 11%), we would need ~n=3400 (allowing for 10% loss-to-follow-up). For a non-inferiority hypothesis (to detect a non-inferiority margin of difference of no less than 4%), ~n=3700 would be needed (allowing for 10% loss-to-follow-up). So, while a definitive trial is feasible, these post hoc sample size calculations indicate that a very large trial would be needed.

The ~4% catheter colonisation rate seen in the ARCTIC trial reference group was much lower than the ~30% overall rate seen in our previous multicentre study that used much weaker strength (0.015% and 0.05%) CHG antiseptics.[1] This sevenfold reduction is probably multifactorial: while the stronger CHG-plus-alcohol combined antiseptic trialled has likely played a major part, it is also likely that the rigorous methodology of catheter insertion and other good catheter care practices helped reduce catheter colonisation. We incorporated such practices into our study protocol to harmonise practices between sites and to maximise compliance with the elements of catheter care 'bundles' already collectively known to reduce catheter infection rates.[9 10]

The main limitation of our feasibility study is from the clinical perspective: the findings are inevitably limited for guiding current clinical practice for preferred antiseptic choice—for that requires a definitive large-scale RCT. Nevertheless, some trial findings may assist current practices. Our low outcome rate (~4%) of catheters colonised at removal after using 2% CHG-70% IPA antiseptic at catheterisation/pre-removal is a rigorous benchmark figure that other centres could reference to audit their own units' rates of catheter colonisation using the same or other locally preferred antiseptic formulations. We encourage this and suggest that a national audit or registry may provide useful data. Also, our rigorous prospective safety data collected through daily skin monitoring provide preliminary reassurance that both these two 'stronger' 2% antiseptic formulations of CHG can be safely applied on the skin of preterm babies if used under similar carefully controlled guidelines (online supplemental files 1 and 2). We therefore propose that both agents merit inclusion in catheter care bundles for preterm babies. Our study adds to the existing but limited RCT evidence base for 2% CHG-70% IPA and 2% CHG-aqueous safety in preterm neonates.[24–26] We nevertheless share cautions about their wider use in the first few days postnatal in the lowest gestation babies (<26 weeks) when the burden of skin colonisation is usually lightest yet the risk of chemical injury is greatest.[18] It would therefore presently seem prudent to use lower concentration alcohol-free CHG preparations in the first few postnatal days, for example, 0.2% chlorhexidine acetate,[27] although accepting the trade-off that rates of catheter sepsis may potentially then be higher.

Conclusion and future study

The data from the ARCTIC study suggest that both 2% CHG-aqueous solution and 2% CHG-70% IPA can be used safely in preterm neonates when applied using a strict procedure to limit overexposure. Their use was associated with a large reduction in the risk of catheter colonisation by potentially harmful bacteria compared with historical rates using weaker preparations. A definitive trial is feasible, but based on the very low catheter colonisation rate or combined rate of CRS and CAS, a very large sample size is required. Newer agents such as octenidine[28] now require formal evaluation in preterm neonates. But with such low rates of catheter colonisation and sepsis, conducting any definitive efficacy RCT of antiseptics now poses a formidable challenge. Other ways to distinguish between disinfection agents may be needed, such as registry or real-world data-based assessments of safety and efficacy, or else snapshot audits involving a limited number of centres willing to adopt uniform strict protocols and standardised procedures for catheter care and sampling.

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Contributors PC and PTH conceived the idea for this study. PC designed the study, wrote the protocol and is the chief investigator responsible for all aspects of the study including preparation and submission of the grant application, application for Clinical Trial Authorisation from the Licensing Authority (MHRA), securing funding, obtaining ethics and local NHS approvals, project management and data collection. PTH, CT, LL and EJ contributed to study design and refinement and protocol development. PC, AN, PM, AS, HH and SP undertook patient enrolment and data collection. PC and AS provided research oversight at their sites. MAW was responsible for whole genome sequencing and validation. LL and EJ provided statistical and methodological expertise and JLB assisted in statistical analysis. CP wrote the statistical analysis plan, with input from LL, PC and EJ. AK managed the database, programming and randomisation site. PC wrote the first and final versions of the manuscript. All authors contributed intellectual input and to manuscript revisions, and all approved the final version. PC is the guarantor.

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STANDARDISED GUIDELINE FOR CATHETER INSERTION USING GOOD CATHETER INSERTION AND CARE PRACTICES

This procedure is to be performed with an assistant. Both the operator and assistant must be trained in good catheter insertion and care, and named on the ARCTIC study training or delegation log. The assistant's role is to monitor adherence to this working document. One document must be completed for EACH attempt.

For PCVC insertion equipment, see Appendix 1.

Each pack contains two bottles of the allocated antiseptic (identified by the same pack number) – as above.

Please read thoroughly and complete each point to ensure adherence to current protocol		Initial when done
1	Document number of this attempt (1,2,3,4...) ☐ Date of attempt: ___/___/___	
2	Check that the allocated antiseptic pack no. above corresponds with the pack no. on the bottle.	
3	Bottle No 1 / 2* from above Pack No. *Please circle Date and time bottle opened ____/____/____ ____:____	
4	Document date and time opened on bottle used. NB. Each bottle of study antiseptic can be used for *up to 24 hours* after first being opened. If a second bottle is being used, a new pack will need to be allocated via the randomisation website for use when catheter is removed.	
5	Prescribe IMP on EPMA. (search "TRIAL" and you will find it listed in red as '**High Alert! TRIAL – ARCTIC STUDY Solution**')	
6	Place an ARCTIC IMP prescription label on the 'notice board' section of the baby's hard copy drug prescription chart.	
7	Use the dedicated percutaneous central venous catheter trolley, and ensure equipment from Appendix 1 is complete.	
8	Wash hands and clean trolley with Clinell wipe	
9	Following strict aseptic principles, open out the IV cut down set onto the cleaned trolley surface and add further equipment as required.	
10	Decant 3-5 mL only of the allocated solution into gallipot and ensure the IMP bottle is securely recapped	
11	Measure length of expected catheter insertion from selected insertion site(s) to intended location of catheter tip	
12	Document a baseline assessment of the skin where antiseptic is to be applied on chart on Appendix 2. (If there are any concerns about skin integrity, seek the advice of the research team or attendant consultant neonatologist prior to applying antiseptic)	
13	Apply face mask then wash hands up to elbows.	
14	Put on a sterile gown and double gloves, using strict aseptic non-touch technique.	
15	Prepare your equipment. (Handle the catheter with care, do not stretch or apply tension)	
16	Flush catheter with 0.9% saline and leave the syringe attached. **DO NOT** cut the catheter to alter the length.	
17	Assistant to damp dust the incubator ensuring the portholes are wiped with a Clinell wipe.	
18	Assistant to position the infant to facilitate insertion, ensuring that comfort measures and any pain medication is provided.	
19	With assistant's help, position the blue drape (minor ops pack) over the baby with the required insertion site available via the central aperture with the limb being held, as necessary, by your assistant to keep your field sterile.	

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20	Soak gauze completely in allocated antiseptic and squeeze out thoroughly prior to application.	
21	Apply to the area selected for catheter insertion for a minimum of 10 seconds and maximum of 20 seconds. NB a **single** application of antiseptic is to be applied only. If catheterisation is done via a limb, the assistant should hold the limb through the aperture while the skin is disinfected by the operator. The operator can then fully take over the holding of the baby's limb using sterile gauze, holding the area already disinfected, before cleaning the remainder of the limb. ***NB 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 of antiseptic with the skin.***	
22	Allow the disinfected area to air dry completely (for at least 30 seconds) before proceeding with catheter insertion. Do ***not*** use sterile water to wipe off the disinfected skin area after application of antiseptic solution (***unless*** catheter insertion has been ***unsuccessful)***, because this practice potentially negates the efficacy of the chlorhexidine antiseptic and will therefore potentially confound the study findings, and will constitute a violation of the protocol.	
23	Remove top pair of gloves and insert catheter aseptically as per Appendix 2.	
24	Following catheter insertion but prior to x-ray, assess skin integrity and document on chart on Appendix 2 (10-30 minutes post antiseptic application)	
25	Verify and document satisfactory catheter tip location via an x-ray. If catheter position needs to be adjusted following x-ray, use strict aseptic technique when making any adjustments, and ensure a further check radiograph is obtained to document satisfactory position.	
Is Catheter Insertion successful, confirmed by X-ray? Y / N		
26	If **Y,** ensure the routine catheter insertion sticker is completed in baby's notes. Time of Successful Catheter insertion ____:____ Type of PCVC inserted? (Please tick) – Epicutaneo-Cava Catheter (24G) ☐ – Premicath (28G) ☐	
27	If **N**, Thoroughly clean with sterile water, the whole area that was subject to antiseptic application, and remove the catheter (If inserted) using standard practice. Time of unsuccessful attempt ____:____	
28	Return all opened and unopened bottles of ARCTIC antiseptic to the IMP storage cupboard in Room 4.	
Note that the allocated IMP bottle may be used again within 24 hours of opening for subsequent catheterisation attempts in the same baby.		

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Confirmation of adherence

Please sign below to confirm that you have adhered to this Working Document.

	Operator	Assistant
Name:		
Job Title:		
Date:		
Signature:		

Appendix 1

Equipment

- Percutaneous central venous catheter trolley
- Clinell wipes for surface cleaning
- IV Cut down set
- Good source of light
- Minor ops pack
- Gown
- Mask
- 10 mL syringe
- 2 mL syringe
- Needleless connections (Bionectors)
- Tape measure
- Blunt needle (for drawing up the saline flush)
- 0.9% sodium chloride ampoule 10mls
- Sterile gauze – small and large
- Steristrips (Size 6 mm x 38 mm)
- Transparent sterile dressing
- Vygon: Epicutaneo-Cava Catheter 24G or Premicath 28G percutaneous central venous catheter
- Sterile gloves x2

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Appendix 2

Aseptic Catheter Insertion Technique

Apply tourniquet to limb (if necessary) using gauze, or have an assistant (who would then also need to be surgically gowned) apply pressure above the sterile site if necessary. Anchor the vein by stretching the overlying skin with the thumb and fingers of the free hand.
Insert the green flagged needle/split needle or appropriate cannula through the skin about 0.5-1 cm distal to the intended vein at a low angle (15-30°) When flash back occurs advance chosen cannula/needle appropriately.
Release the tourniquet (if used). Introduce the primed catheter through the needle/cannula using non-toothed forceps and advance percutaneous central venous catheter to the desired length.
Secure the percutaneous central venous catheter in place using Steristrips. If any dried blood needs to be removed from the skin following line insertion, sterile water may be used sparingly for this purpose prior to applying the transparent dressing, (i.e. do **not** use further IMP for this purpose)
When the area is completely dry, use the smallest amount of gauze possible and a transparent dressing to secure the PCVC in place, allowing the greatest area of the antiseptic site coverage to remain visible for skin observations. Aim to use a minimum number of Steristrips and the smallest necessary piece of gauze dressing.
Attach infusion of saline as standard practice at 0.5 mL/hr until line position is confirmed.

Appendix 3

Baseline Skin Assessment

Region of which antiseptic to be applied.	**Date and Time of baseline Skin Assessment** (before application of antiseptic)	**Dryness** *(tick one)* 1 = Normal, no sign of dry skin 2 = Dry skin, visible scaling 3 = Very dry skin, cracking/fissures	**Erythema** *(tick one)* 1 = No evidence of erythema 2 = Visible erythema <50% of skin area to be exposed to antiseptic 3 = Visible erythema ≥50% of skin area to be exposed to antiseptic	**Breakdown/excoriation** *(tick one)* 1 = None evident 2 = Small localised areas 3 = Extensive
	__/__/___ __:__			

Skin Assessment 10 – 30 minutes Post Antiseptic Application

Region of which antiseptic has been applied.	**Date and Time of post antiseptic Skin Assessment**	**Dryness** *(tick one)* 1 = Normal, no sign of dry skin 2 = Dry skin, visible scaling 3 = Very dry skin, cracking/fissures	**Erythema** *(tick one)* 1 = No evidence of erythema 2 = Visible erythema <50% of skin area to be exposed to antiseptic 3 = Visible erythema ≥50% of skin area to be exposed to antiseptic	**Breakdown/excoriation** *(tick one)* 1 = None evident 2 = Small localised areas 3 = Extensive
	__/__/___ __:__			

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WORKING DOCUMENT 2

PCVC Removal Allocated Pack No: __ __ __ __ __

INSTRUCTIONS FOR CATHETER REMOVAL, OBTAINMENT OF STUDY SAMPLES AND SUBMISSION OF STUDY SPECIMENS TO LABORATORY **-**

Catheter removal will be carried out as a sterile procedure. An assistant will be needed to hold the baby still and remove the dressing.

Pre-prepared removal packs have been made up to facilitate catheter removal. These are stored in the clean utility room, on the top of row E/F – See appendix 1 for contents

Please read thoroughly and complete each point to ensure adherence to current protocol		Initial when done
1	Check that the allocated antiseptic pack number matches the pack number documented at the top of this page.	
2	Prescribe on EPMA, as previously done for line insertion. (Search "TRIAL" and you will find it listed in red as '**High Alert! TRIAL – ARCTIC STUDY Solution**').	
3	Place an ARCTIC IMP prescription label on the 'notice board' section of the baby's hard copy drug prescription chart.	
4	Open the sterile pack onto the clean surface and empty a small amount of the allocated antiseptic solution into the gallipot.	
5	Disconnect catheter from fluid line, remove all external covering dressings of the PCVC and all Steristrips; inspect and record skin condition on the skin record form, Form 2 Section B.	
6	Document the catheter insertion length at the point of entry to the skin (see figure 1 overleaf) **__ __.__cm**	
7	Wash hands, dry with sterile dressing towel and put on sterile gloves	
8	**Before** skin disinfection ***and*** **before** PCVC removal, take a first skin swab for microbial culture at the exact point of catheter insertion, covering no more than 0.5-1 cm diameter.	Time sample taken:
9	With the PCVC still in situ: using sterile gauze wetted with a minimal amount of *allocated* solution, squeeze out the gauze to remove excess antiseptic then carefully disinfect about a 1-2 cm diameter area of skin around the entry site of catheter insertion, for between 10 and 20 seconds. ***Ensure the exact puncture site is completely disinfected all around the catheter, including the exposed catheter, prior to removal.*** Take great care to ***avoid*** pooling of antiseptic.	
10	Leave the skin to dry for minimum of 30 seconds, ensuring the site is ***completely dry*** following the skin site disinfection	
11	***After skin site disinfection but before PCVC removal***, take a second skin swab for microbial culture at the ***exact*** point of the disinfected catheter insertion site, covering no more than 0.5-1 cm diameter.	Time sample taken:
12	Gently remove the catheter and place onto a sterile dressing towel, and document the date and time of line removal ___/___/___ ___:___	
13	Using one pair of sterile scissors and a pair of sterile forceps, cut the catheter tip segment (approx. 1 cm length) and place it into the universal sterile pot, labelled '**segment tip**'.	Time sample taken:
14	Using the **other** pair of sterile scissors and the **second** pair of forceps, obtain a segment of approximately 1 cm length by cutting at a distance 1–2 cm *inside* the former point of skin entry, (from the *previously-subcutaneous* portion of the catheter) and place this into the second sterile universal container, labelled '**proximal segment'**. (See figure 1 overleaf)	Time sample taken:
		PTO

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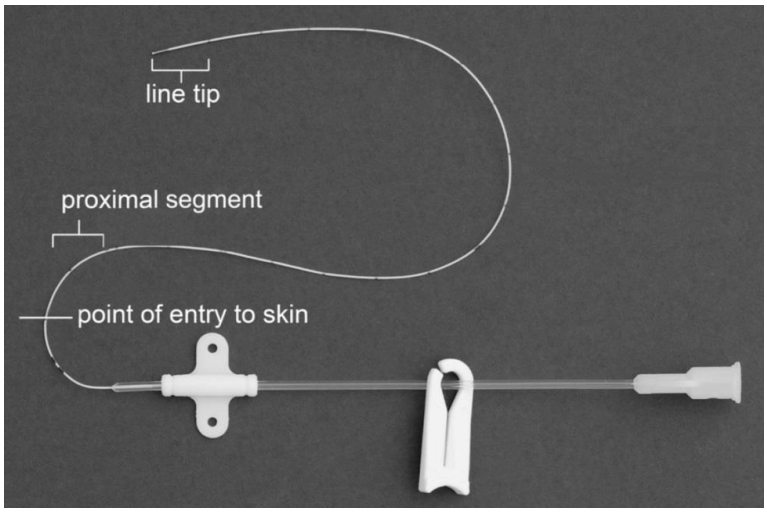
WORKING DOCUMENT 2

PCVC Removal Allocated Pack No: __ __ __ __ __

15	Send all four specimens (catheter segments x2, skin swab x2) to microbiology using the ARCTIC drop down boxes on ICE, for routine culture and antibiotic sensitivities,ensuring that the bottles are labelled with ARCTIC study labels including study number, **as well as baby's own hospital bar code label**. *Please email laura.mansell@nnuh.nhs.uk to inform of specimens being sent and cc.in amy.nichols@nnuh.nhs.uk for her information.*	
16	If baby is considered clinically septic at time of catheter removal please ensure a blood culture is taken concurrently	

Figure 1.



Continue to complete 'Neonatal Skin Condition Assessment' (Form 2, Section B) for 48 hours following catheter removal

N.B. All opened and unopened bottles of ARCTIC antiseptic must be replaced in the IMP cupboard in Room 4 for disposal by the Research Team.

Confirmation of adherence

The team of 'Catheter remover and Assistant' must please sign below to confirm adherence to this Working Document

	Person removing study catheter	Assistant
Name:		
Job Title:		
Date:		
Signature:		

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Working document 2

Norfolk and Norwich University Hospitals NHS

Affix patient ID Label Here

ARCTIC Antiseptic Randomised Controlled Trial for Insertion of Catheters

WORKING DOCUMENT 2

Study no: __ __ __ __ __

PCVC Removal Allocated Pack No: __ __ __ __ __

Appendix 1

- **Catheter Removal Pack – Contents**
- 2 x sterile forceps
- 2 x sterile scissors
- 1 x 'essential 1 wound care' pack containing:
  - *1 dressing towel*
  - *1 gallipot*
  - *Sterile gauze*
- 2 x sterile universal pots, labelled 'segment tip' and 'proximal segment',
- 2 x charcoal skin swabs
- 1 x sterile dressing towel for drying hands

In addition you will require:

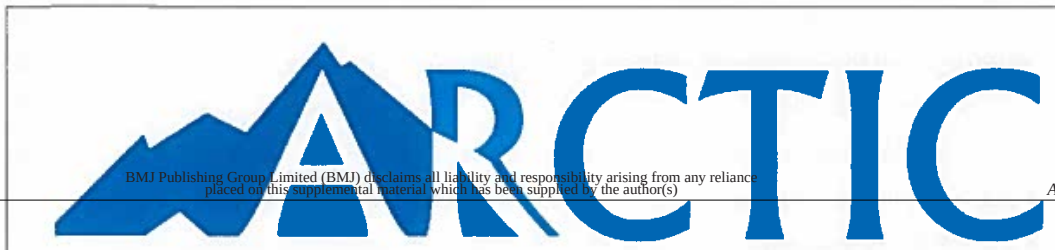
- 1 x pair of sterile gloves
- The **CORRECTLY** labelled ARCTIC antiseptic solution that was allocated to the baby at randomisation (stored in research IMP cupboard in assessment room)

Version 1.7 (NNUH) 06Dec2017
Working document 2

ARCTIC – Antiseptic Randomised Controlled Trial for Insertion of Catheters
Funded by NIHR Research for Patient Benefit Programme
ISRCTN: 82571474
eudraCT number: 2015-000874-36

UKCRC Registered Clinical Trials Units

NPEU Clinical Trials Unit



Antiseptic Randomised Controlled Trial for Insertion of Catheters

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

Statistical Analysis Plan
Version 1.0
Date: 8 August 2018

Author: *Christopher Partlett, Medical Statistician, NPEU CTU*
Reviewers: *Louise Linsell, Senior Medical Statistician, NPEU CTU*
Paul Clarke, Chief Investigator, Norfolk and Norwich University Hospital NICU
Ed Juszczak, Director, NPEU CTU
Kate Costeloe, Chair of TSC, Homerton University Hospital

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Protocol version: v3.0

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1 INTRODUCTION

This document details the proposed presentation and analysis of the paper(s) reporting the two-centre randomised feasibility study ARCTIC, funded by the National Institute of Health Research (NIHR) – Research for Patient Benefit Programme.

The results reported in these papers will follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis, nor to prohibit accepted practices, but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial.

The analysis plan will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis plan; if reported, the source of the suggestion will be acknowledged.

Any deviations from the statistical analysis plan will be described and justified in the final report of the trial. The analysis should be carried out by an identified, appropriately qualified and experienced statistician, who should ensure the integrity of the data during their processing. Examples of such procedures include quality control and evaluation procedures.

2 TRIAL PERSONNEL

Chief Investigator
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3 TRIAL DESIGN AND OBJECTIVES

ARCTIC is a two-centre blinded randomised feasibility study of two topical antiseptics for neonatal skin disinfection prior to insertion of a percutaneous central venous catheter (PCVC) in the neonatal intensive care unit.

Arch Dis Child Fetal Neonatal Ed

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 antisepsis: aqueous-based 2% chlorhexidine gluconate (2%CHG), or 70% isopropyl alcohol-based 2% chlorhexidine gluconate (70%IPA/2%CHG).

The primary objective of this feasibility study is to estimate the prevalence of central venous catheter bacterial colonisation at the time of catheter removal in the 70%IPA/2%CHG arm, in order to inform the sample size calculation for a phase-III trial.

4 DESCRIPTION OF OUTCOMES AND ANALYSIS POPULATIONS

4.1 Primary outcome

Proportion of babies in the 70%IPA/2%CHG arm with catheter colonisation as determined by positive bacterial culture from at least one of the two catheter segments taken at catheter removal.

4.2 Secondary outcomes

4.2.1 Feasibility measures

- Rates of recruitment and retention to the study, and the collection of views of parents and clinicians on factors affecting recruitment and retention
- Proportion of infants completing study with complete data for the primary outcome
- Proportions of infants with missing data collection forms.

4.2.2 Efficacy measures

- Proportion of infants with positive exit-site skin swabs (ESSS) at catheter removal (before and after skin disinfection)
- Number and type of catheter segments culture positive at removal
- Bacterial species (typed via molecular methods) of isolates identified on positive BC, ESSS (before and after skin disinfection), and catheter segment
- 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.

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- 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
- Rate of catheter-related sepsis per 1000 PCVC days
- Rate of catheter-associated sepsis per 1000 PCVC days.

4.2.3 Safety measures

- 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.

4.2.4 Process outcomes

- Number of anatomical sites at which a PCVC insertion was attempted and failed
- Adherence to study protocol
- Study withdrawals.

5 SAMPLE SIZE AND POWER

ARCTIC is using 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 the desired 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% will be estimated with a 95% CI of 65% to 83%. To obtain a sample size in the region of 93 babies having catheters successfully inserted will require parents of at least 124 eligible babies to be consented. Based on our previous collaborative observational study of PCVCs that recruited 127 preterm infants between two tertiary centres in a 14-month study period, we would expect to complete recruitment within 14 months.

6 RANDOM ALLOCATION

Randomisation is carried out using permuted block randomisation with variable block sizes and stratifying on birth gestation (<28 weeks; 28^{+0} to 33^{+6} weeks) and neonatal centre. The randomisation will use a 3:1 allocation ratio in favour of allocating to the alcohol-based antiseptic (70%IPA/2%CHG).

7 PROTOCOL NON-COMPLIANCES

All protocol non-compliances will be listed in the final report. Non-compliances are defined below.

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7.1 Major

The following are pre-defined major protocol non-compliances with a direct bearing on the primary outcome:

- Data considered fraudulent
- Infants randomised without informed maternal consent.

7.2 Minor

7.2.1 Participants randomised in error

These included infants who did not meet the eligibility criteria:

- Born at greater than or equal to 34 weeks' gestation
- Have an underlying skin condition
- Already have an indwelling PCVC in situ or was previously enrolled in respect of an earlier PCVC episode
- Have a positive blood culture in the 7 days prior to randomisation without a subsequent negative blood culture result
- Have had antibiotic treatment for suspected sepsis within the 48 hours preceding randomisation.

7.2.2 Participants who do not receive allocated intervention

- Infants randomised to receive aqueous-based 2% chlorhexidine gluconate (2%CHG) but instead receive alcohol-based (70% isopropyl alcohol) 2% chlorhexidine gluconate (70%IPA/2%CHG)
- Infants randomised to receive alcohol-based (70% isopropyl alcohol) 2% chlorhexidine gluconate (70%IPA/2%CHG) but instead receive aqueous-based 2% chlorhexidine gluconate (2%CHG).
- Infants randomised to either intervention who do not receive either allocated intervention.

8 DATA COLLECTION SCHEDULE

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

- Form 1: Trial Entry and Randomisation Form
- Outcome Data Collection Forms
  - Form 2: Main Outcome Data Form
  - Form 3: Unsuccessful Catheterisation Episode Form
  - Form 4: PCVC Removal Form
  - Form 5: Microbiology Data Form
- Form 6: Discontinuation of Intervention Form
- Form 7: Withdrawal Form
- Form 8: End of Study
- Form 9: Foreseeable Serious Adverse Event Form.

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

- Form 10: Serious Adverse Event (SAE/SUSAR) report Form
- Incident Form (Form for Protocol Deviation, Violation, Breach or Serious Breach of Protocol or GCP) .

9 PATIENT GROUPS FOR ANALYSIS

9.1 Primary analysis strategy

Where possible, infants will be analysed in the groups to which they are randomly assigned, regardless of deviation from the protocol or treatment received (referred to as the Intention to Treat (ITT) population).

However, most outcome measures (including the primary outcome) require a catheter to be successfully inserted. For these outcomes the analysis will be carried out on a 'modified ITT' population: infants with successfully inserted catheters will be analysed in the groups to which they were randomised.

Since ARCTIC is a feasibility study the analysis will be predominantly descriptive. For instance, the primary outcome only relates to infants randomised to a single arm. However, some of the outcomes (i.e. the clinical outcomes listed in section 11.3.3) will be analysed by arm and comparative results will be presented.

9.2 Post-randomisation exclusions

After randomisation, in the following circumstances infants will be excluded from the analysis population(s):

(i) major protocol non-compliance
(ii) infants for whom consent to use their data has been withdrawn
(iii) infants that did not receive either intervention because no study catheter insertion attempt was ever made for them

9.3 Descriptive analysis population

Baseline neonatal and maternal characteristics will be reported for all infants randomised for whom we have data available, excluding post-randomisation exclusions.

9.4 Primary analysis population

All infants randomised, excluding post-randomisation exclusions.

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9.5 Safety analysis population

All infants randomised that received at least one application of one of the study antiseptics, including infants where catheterisation was unsuccessful.

10 BASELINE CHARACTERISTICS

10.1 Representativeness of trial population and participant throughput

The flow of participants through each stage of the trial will be summarised using a CONSORT diagram. We will report the numbers of infants:

- Assessed for eligibility (screened)
- Not eligible
- Eligible
- Could not be recruited because parents declined
- Missed recruitment for other reasons (e.g. staff unavailable)
- Randomised
- Allocated to each intervention
- Did not receive allocated intervention
- Post-randomisation exclusions
- Randomised in error (e.g. duplicate randomisation)
- Withdrawn consent
- Discontinued intervention
- Successfully inserted catheter
- Included in the analysis of safety outcomes
- Included in the analysis of primary outcome.

10.2 Baseline comparability of randomised groups

Participants in the original two randomised groups will be described separately with respect to maternal and infant characteristics at trial entry:

10.2.1 Neonatal characteristics

- Centre
- Sex
- Birthweight
- Gestational age
- Multiple pregnancy
- Mode of delivery
- Membranes ruptured prior to labour
- Membranes ruptured >24 hours before delivery
- Apgar score at 5 minutes
- First recorded temperature on admission to the neonatal unit after birth
- Infant ventilated via an endotracheal tube at the time of randomisation
- Infant born in this hospital
- Any surgical procedure prior to randomisation
- Prophylactic antifungal medication at the time of randomisation
- Infant received antibiotics prior to randomisation
- Devices in situ at time of PCVC insertion.

10.2.2 Maternal characteristics

- Age (years)

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- Any antenatal corticosteroids
- Antibiotics within the week before delivery
- Pyrexial in labour (temperature >38.0 °C)
- Chorioamnionitis suspected clinically before delivery.

Numbers (with percentages) for binary and categorical variables and means (with standard deviations), or medians (with lower and upper quartiles, and minimum and maximum) for continuous variables will be presented. There will be no tests of statistical significance performed nor confidence intervals calculated for differences between randomised groups on any baseline characteristic.

10.3 Losses to follow-up

The number (with percentages) of losses to follow-up among infants will be reported for the two trial arms, and the reasons will be recorded. This is likely to be minimal, as follow-up ends 48 hours after catheter removal (successful insertion and removal of study catheter) or 48 hours after last IMP application (for unsuccessful catheterisation). Any deaths (and their cause) will be reported separately.

There is anticipated to be some loss to follow-up caused by infants with successful or unsuccessful catheter insertions transferring to non-participating sites. For these infants, safety data will be sought up to 48 hours after catheter removal (successful insertion and removal of study catheter) or 48 hours after last IMP application (for unsuccessful catheterisation). For infants lost to recruiting study site with study catheter indwelling, attempts will be made to gather data relevant to important clinical secondary outcome measures, including whether blood culture was done as part of an infection screen while the study catheter remained indwelling or in the 48-hour period following its removal within the non-participating neonatal unit providing ongoing clinical care.

Where possible, the catheter tip will be returned to the recruiting site for microbiological analysis. While these results will not contribute to the primary outcome, they will be useful for a secondary analysis (section 13).

10.4 Adherence to intervention

Adherence to the intervention will be assessed using the following questions from the Main Outcome Data Form:

- **QA3:** Was the insertion done observing strict aseptic technique and in accordance with Working Document "Standardised guideline for catheter insertion utilising good catheter insertion and care practices"?
- **QA7:** Was the insertion site disinfected with the allocated study antiseptic prior to successful PCVC insertion?
- **QA8:** Confirm that baseline skin condition is recorded to describe the PCVC insertion site appearance prior to successful PCVC insertion?
- **QA9:** Was the allocated study antiseptic used to clean the skin before PCVC insertion applied sparingly and for 10 to 20 seconds?

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- **QA10:** Was the allocated study antiseptic allowed to dry for at least 30 seconds prior to the successful PCVC insertion?
- **QA11:** Following skin disinfection preceding the successful PCVC insertion, can you confirm that no other solution was used to wipe off the antiseptic from the skin?

and using the following question from the PCVC Removal Form:

- **QA5:** exit site disinfected after first skin swab taken but before PCVC removal?

Adherence to the protocol can also be assessed from the number of deviation forms.

11 ANALYSIS OF OUTCOMES

11.1 Evaluation/definition of outcomes

The primary outcome will be analysed and reported for infants in the 70%IPA/2%CHG arm only. Rates of recruitment will be analysed and presented for both arms combined, while retention will be summarised by arm and overall. The proportion of infants with missing data collection forms will be summarised for both arms combined. All other secondary outcomes (including process outcomes) will be analysed and presented by arm.

Derivation of variables is described in the data derivation spreadsheet.

11.2 Primary outcome

The primary outcome is the proportion of babies in the 70%IPA/2%CHG arm with catheter colonisation as determined by positive bacterial culture from at least one of the two catheter segments taken at catheter removal.

The proportion of babies with catheter colonisation will be reported along with a 95% confidence interval.

11.3 Secondary outcomes

11.3.1 Feasibility metrics

The following key feasibility metrics will be reported:

- Uptake rate — proportion of eligible infants who are randomised
- Retention — proportion of infants randomised who remain in the study to provide primary outcome data and complete safety data.

These will be reported as proportions with 95% confidence intervals. In addition, the views of parents and clinicians on factors affecting recruitment and retention will be collected and reported.

11.3.2 Bacterial species

The bacterial species (typed via molecular methods) of isolates identified on positive blood culture (BC), ESSS (before and after skin disinfection), and catheter segment will be listed by arm for infants with a positive blood culture.

11.3.3 Clinical outcomes

The following clinical outcomes will be reported as proportions (or rates) in each arm:

- Proportion of infants with positive exit-site skin swabs (ESSS) at catheter removal (before and after skin disinfection)
- Number and type of catheter segments culture positive at removal
- 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
- 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
- Rate of catheter-related sepsis per 1000 PCVC days
- Rate of catheter-associated sepsis per 1000 PCVC days.

11.3.4 Completeness of data

The extent of missing data will be reported for every outcome. The number and percentage of missing forms will be reported for all infants combined for each form.

11.3.5 Safety

Daily skin morbidity scores will be summarised by arm for all infants, including those where catheterisation was unsuccessful. These will be compared between arms using either a difference in means or a difference in medians, along with a 95% confidence interval.

11.4 Pre-specified subgroup analyses

None planned.

11.5 Sensitivity analyses

None planned.

11.6 Missing data

Missing data will be described by presenting the number of individuals in the missing category. As the sample size is small, imputation techniques will not be appropriate.

11.7 Statistical software employed

Stata/SE 13.1 or later for Windows.

12 SAFETY DATA ANALYSIS

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Unforeseeable serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) will be listed by trial allocation.

13 ADDITIONAL EXPLORATORY ANALYSIS

A secondary exploratory analysis of the primary outcome, catheter colonisation, will be carried out to assess the sensitivity of primary outcome if the definition changed to include only proximal line segment alone, or tip segment alone.

14 REFERENCES

14.1 Trial documents

Protocol ARCTIC_protocol_v3.0 dated 18th November 2016
ARCTIC Data Derivation
ARCTIC Dummy Tables

14.2 Other references

None yet.

15 APPROVAL

Senior Statistician	Name: LOUISE LINSELL	
	Signature [redacted]	Date 06/08/18.
Chief Investigator	Name: PAUL CLARKE	
	Signature [redacted]	Date 08/AUG/2018
Chair of Trial Steering Committee (or delegate)	Name: KATE COSTELOE	
	Signature [redacted]	Date 24/08/18

16 DOCUMENT HISTORY

Version	Date	Edited by	Comments/Justification	Timing in relation to interim analysis/unblinding
0.1	20/03/17	CP	Initial draft created	Prior to both
0.2	01/06/17	CP	Changes made following input from PC: Analysis populations for the outcomes clarified & derivation of variables updated.	Prior to both
0.3	05/06/17	CP	Updated following review by LL.	Prior to both
0.4	13/07/17	CP	Updated following outcome mappings meeting with PC.	Prior to both

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			Included details on adherence measures. Added comments relating to changes to be made regarding sample size in version 4.0 of protocol.	
0.5	23/08/17	CP	Minor edits following review by LL.	Prior to both
0.6	13/11/17	CP	Revisions following review by EJ	Prior to both
0.7	15/12/17	CP	Revised following review by PC. Clarified which randomised infants will be excluded from the analysis. Added detail to ESSS (before and after disinfection)	Prior to both
0.8	16/01/18	CP	Revised following further review by PC. Added two extra baseline characteristics. Added details of an exploratory secondary analysis of the primary outcome.	Prior to both
0.9	08/03/18	CP	Revised following DMC meeting on 26th January 2018. Removed RR column from secondary outcomes table. Added details of safety analysis population to CONSORT.	After unblinding and first interim analysis
0.10	06/04/18	CP	Revised following review by TSC. Clarified description of baseline characteristics. Created a new subgroup of outcomes: feasibility measures.	After unblinding and first interim analysis
0.11	21/06/18	CP	Revisions approved by PC. Minor changes to wording. Minor rewording of primary outcome for clarity.	After unblinding and first interim analysis
1.0	08/08/18	JB	Amended section 12 Safety Data Analysis, so SAEs and SUSARs will be listed by allocation instead. Final version for sign-off.	After unblinding and first interim analysis

Supplementary Table S1: Supplementary information related to catheterisation

	70%IPA-2%CHG (n = 79)	2%CHG aqueous (n = 27)	Overall (n = 106)
Postnatal age (days) at line insertion, median (IQR)	5.0 (2.0 to 7.0)	4.0 (2.0 to 8.0)	5.0 (2.0 to 7.0)
Range (min to max)	(0 to 46)	(1 to 19)	(0 to 46)
Catheter inserted in ≤ 3 days after birth, n (%)	31 (39.2)	11 (40.7)	42 (39.6)
Anatomical site of long line insertion			
Upper limb (inc. axilla)	46 (58.2)	15 (55.6)	61 (57.5)
Lower limb	32 (40.5)	11 (40.7)	43 (40.6)
Scalp	1 (1.3)	1 (3.7)	2 (1.9)
At least one blood culture sent while line was in situ, n (%)	25 (33.3)	8 (32.0)	33 (33.0)
Missing	4	2	6
Time (days) to first positive blood culture during line indwell in infants that had bloodstream infection, N	11	4	15
Median (IQR)	7.0 (5.0 to 10.0)	5.5 (5.0 to 9.5)	6.0 (5.0 to 10.0)
Line removal details completed, N	**78**	**26**	**104**
Postnatal age (days) at line removal, median (IQR)	13.0 (10.0 to 19.0)	15.0 (11.0 to 21.0)	14.0 (10.0 to 20.0)
Range (min to max)	(3 to 57)	(3 to 29)	(3 to 57)
Duration of line indwelling, median (IQR)	9.0 (6.0 to 12.0)	9.5 (7.0 to 12.0)	9.0 (6.0 to 12.0)
Range (min to max)	(1 to 32)	(2 to 20)	(1 to 32)
Reason for removal, n (%) (non-exclusive)			
No longer needed	68 (87.2)	20 (76.9)	88 (84.6)
Suspected sepsis	5 (6.4)	3 (11.5)	8 (7.7)
Confirmed sepsis	3 (3.8)	0 (0.0)	3 (2.9)
Damaged	0 (0.0)	1 (3.8)	1 (1.0)
Unintended removal	1 (1.3)	0 (0.0)	1 (1.0)
Blocked	2 (2.6)	1 (3.8)	3 (2.9)
Malposition confirmed by x-ray	4 (5.1)	1 (3.8)	5 (4.8)
Other complications	1 (1.3)	1 (3.8)	2 (1.9)
Missing	1	1	2
Blood culture sent at time of PCVC removal in those with suspected or confirmed sepsis, N	8	3	11
n (%)	5 (62.5)	3 (100.0)	8 (72.7)
Antibiotics received on day of PCVC removal, n (%)	15 (19.2)	6 (23.1)	21 (20.2)
At least one dose prior to removal, n (%)	11 (78.6)	4 (66.7)	15 (75.0)
Missing	1	0	1
Within 7 days before removal, n (%)	10 (100.0)	4 (100.0)	14 (100.0)
Missing	1	0	1

Supplementary Table S2: Rates of recruitment and retention

	Total eligible[1] (n = 178)
Uptake rate	
Number of eligible infants randomised, n (%)	116 (65.2)
Proportion (95% CI)	65.2 (57.7, 72.1)

	70%IPA-2%CHG (n = 88)	**2%CHG aqueous (n = 28)**	**All (n = 116)**
Retention[2]			
Number of infants who remained in the study, n (%)	73 (83.0)	24 (85.7)	97 (83.6)
Proportion (95% CI)	83.0 (73.4, 90.1)	85.7 (67.3, 96.0)	85.1 (77.2, 91.1)

[1]Eligible infants were defined as those who were recruited or not recruited (including those whose parents declined their participation) but who were clinically eligible.
[2]Proportion of infants that remained in the study to provide complete primary outcome and safety data. The overall proportion of randomised infants with complete data for the proposed primary outcome of catheter colonisation was 97/116 (83.6%). Considering only babies who had successfully inserted catheters, 97/106 (91.5%) had both proximal and tip catheter segment cultures available for analysis.

Supplementary Table S3: Parents' and clinicians' views on factors affecting recruitment

Main reasons volunteered by parents for declining consent, n
Not interested in participating in any research, 2
Already enrolled in another study and did not want to join another, 2
Concern about skin reaction to the antiseptic, 3
Felt their baby had been very sick, did not want to impose anything else on them, 3
Parents of twins who did not want one in a study without the other being enrolled, 1
Parents of twins who did not want to participate because they wanted to ensure their babies received the unit's standard alcohol-based 2% chlorhexidine antiseptic for catheterisation as they considered this would be superior, 1
No reason offered, 21
Main reasons provided by clinical staff for factors affecting recruitment
Time pressure – too busy with clinical work to be able to approach/consent
Parents not available to discuss participation
Urgent central venous access needed (eg umbilical venous catheter insertion had been unsuccessful in the first hours after birth so urgent PCVL needed)
New personnel, not yet trained in study procedures
Not GCP certified so unable to obtain consent
Eligibility for the study was overlooked

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Supplementary Table S4: Completeness of data collection

	Total[1] (n = 106)
Infants with no missing data collection forms, n (%)	104 (98.1)
Overall form completeness for required forms, n (%)	
Form 1: Trial Entry and Randomisation Form	106 (100.0)
Form 2: Main Outcome Data Form	106 (100.0)
Form 4: PCVC Removal Form	104 (98.1)[2]
Form 5: Microbiology Data Form	106 (100.0)
Form 8: End of Study	106 (100.0)

[1] Analysed for clinical outcomes – infants who had a successfully inserted catheter and received the intervention

[2] Two participants did not complete the study as they were transferred to non participating hospitals before study catheter removal, and so PCVC Removal Forms were not required.

Supplementary Table S5: Process outcomes and adherence to protocol

	70%IPA-2%CHG (n = 87)	2%CHG aqueous (n = 27)
Number of anatomical sites with at least one failed PCVC insertion		
Median (IQR)	0 (0 to 1)	1 (0 to 2)
Range	(0 to 7)	(0 to 4)
1	18 (20.7)	6 (22.2)
2	10 (11.5)	6 (22.2)
3	1 (1.1)	0
4	1 (1.1)	2 (7.4)
Adherence to intervention		
Successful catheterisation (N)	79	27
Insertion done observing strict aseptic technique and in accordance with Working Document "Standardised guideline for catheter insertion utilising good catheter insertion and care practices", n (%)	79 (100.0)	27 (100.0)
Insertion site disinfected with the allocated study antiseptic prior to successful PCVC insertion, n (%)	79 (100.0)	27 (100.0)
Baseline skin condition is recorded to describe the PCVC insertion site appearance prior to successful PCVC insertion, n (%)	79 (100.0)	27 (100.0)
Allocated study antiseptic used to clean the skin before PCVC insertion applied sparingly and for 10 to 20 seconds, n (%)	79 (100.0)	27 (100.0)
Allocated study antiseptic allowed to dry for at least 30 seconds prior to the successful PCVC insertion, n (%)	79 (100.0)	27 (100.0)
Following skin disinfection preceding the successful PCVC insertion, no other solution was used to wipe off the antiseptic from the skin[1], n (%)	76 (96.2)	26 (96.3)
Exit site disinfected after first skin swab taken but before PCVC removal[2], n (%)	75 (96.2)	24 (92.3)
Missing	1	1

[1] Two infants in the 70%IPA/2%CHG arm and one in the 2%CHG arm who did have another solution had sterile water used.

[2] Three infants in the 70%IPA/2%CHG arm and one in the 2%CHG arm who didn't have their exit site disinfected at this time had their line removed at a non-participating site. For one infant in the 2%CHG arm who didn't, the allocated solution could not be located.