Clinical trial results:
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

Summary

EudraCT number	2015-000874-36
Trial protocol	GB
Global end of trial date	15 October 2019

Results information

Result version number	v1 (current)
This version publication date	01 May 2020
First version publication date	01 May 2020

Trial information

Trial identification

Sponsor protocol code	2014PAED13L

Additional study identifiers

ISRCTN number	ISRCTN82571474
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Norfolk and Norwich University Hospitals NHS Foundation Trust
Sponsor organisation address	Colney Lane, Norwich, United Kingdom, NR4 7UY
Public contact	R+D Office, Norfolk and Norwich University Hospitals NHS Trust, +44 01603 286614, Lisa.Chalkley@nnuh.nhs.uk
Scientific contact	R+D Office, Norfolk and Norwich University Hospitals NHS Foundation Trust, +44 01603 286614, Lisa.Chalkley@nnuh.nhs.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 October 2019
Global end of trial reached?	Yes
Global end of trial date	15 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a small feasibility study of a group of babies whose skin will get cleaned with either aqueous- or alcohol-based formulations of 2% chlorhexidine antiseptic at the time of percutaneous central venous catheter (PCVC) insertion. Both the active ingredients in these antiseptics are presently very widely used, either alone or in combination, for skin disinfection in neonates in the UK, Europe, and North America. The primary objective is to obtain an estimate of what proportion of babies treated with the alcoholic version (2% chlorhexidine in 70% isopropyl alcohol) have PCVCs that are colonised with bacteria at the time that their catheters are removed. This will directly inform the sample size calculation for a future large-scale trial.

Protection of trial subjects:

not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 116
Worldwide total number of subjects	116
EEA total number of subjects	116

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	116
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

207 assessed for eligibility. 29 were not eligible, 62 were eligible but not recruited, 116 were randomised.

Period 1

Period 1 title	Trial entry
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Subject, Assessor

Blinding implementation details:

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.

Arms

Are arms mutually exclusive?	Yes
Arm title	2%CHG

Arm description:

Aqueous-based 2% chlorhexidine gluconate

Arm type	Active comparator
Investigational medicinal product name	Chlorhexidine Gluconate 2% aqueous solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Topical use

Dosage and administration details:

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

Arm title	70%IPA/2%CHG

Arm description:

Alcohol-based (70% isopropyl alcohol) 2% chlorhexidine gluconate

Arm type	Active comparator

Investigational medicinal product name	Chlorhexidine Gluconate 2% in isopropyl alcohol 70% solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Topical use

Dosage and administration details:

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

Number of subjects in period 1	2%CHG	70%IPA/2%CHG
Started	28	88
Completed	27	87
Not completed	1	1
Protocol deviation	1	1

Period 2

Period 2 title	Outcomes
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	2%CHG

Arm description:

Aqueous-based 2% chlorhexidine gluconate

Arm type	Active comparator
Investigational medicinal product name	Chlorhexidine Gluconate 2% aqueous solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Topical use

Dosage and administration details:

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

Arm title	70%IPA/2%CHG

Arm description:

Alcohol-based (70% isopropyl alcohol) 2% chlorhexidine gluconate

Arm type	Active comparator
Investigational medicinal product name	Chlorhexidine Gluconate 2% in isopropyl alcohol 70% solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Topical use

Dosage and administration details:

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

Number of subjects in period 2[1]	2%CHG	70%IPA/2%CHG
Started	27	79
Completed	24	73
Not completed	3	6
culture result not available for both prox and tip	3	6

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: In the 70%IPA/2%CHG arm, 87 participants provided baseline information, but for 8 of these their line insertion was never successful, so they could not go on to provide clinical outcomes. Therefore, the number starting the outcomes period is 79, rather than 87.

Baseline characteristics

Reporting groups	
Reporting group title	2%CHG
Reporting group description:	
Aqueous-based 2% chlorhexidine gluconate	
Reporting group title	70%IPA/2%CHG
Reporting group description:	
Alcohol-based (70% isopropyl alcohol) 2% chlorhexidine gluconate	

Reporting group values	2%CHG	70%IPA/2%CHG	Total
Number of subjects	28	88	116
Age categorical			
Gestational age at trial entry			
Units: Subjects			
<26+0 weeks	5	20	25
26+1 to 27+6 weeks	7	19	26
28+0 to 33+6 weeks	15	48	63
Not recorded	1	1	2
Age continuous			
Gestational age (completed weeks)			
Units: weeks			
median	28	28	
inter-quartile range (Q1-Q3)	26 to 30	26 to 30	-
Gender categorical			
Units: Subjects			
Female	14	41	55
Male	13	46	59
Not recorded	1	1	2

Subject analysis sets	
Subject analysis set title	2%CHG - inc in baseline characteristics
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
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 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.	
Subject analysis set title	70%IPA/2%CHG - inc in baseline characteristics
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
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

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.

Subject analysis set title	2%CHG - analysed for clinical outcomes
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Excluding infants with no line insertion attempted (1) or line insertion never successful (0).	
Subject analysis set title	70%IPA/2%CHG - analysed for clinical outcomes
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Excluding infants with no line insertion attempted (1) or line insertion never successful (8).	
Subject analysis set title	Analysed for clinical outcomes (total)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All participants randomised who had a successfully inserted catheter and received the intervention	

Reporting group values	2%CHG - inc in baseline characteristics	70%IPA/2%CHG - inc in baseline characteristics	2%CHG - analysed for clinical outcomes
Number of subjects	27	87	27
Age categorical			
Gestational age at trial entry			
Units: Subjects			
<26+0 weeks	5	20	
26+1 to 27+6 weeks	7	19	
28+0 to 33+6 weeks	15	48	
Not recorded	0	0	
Age continuous			
Gestational age (completed weeks)			
Units: weeks			
median	28	28	
inter-quartile range (Q1-Q3)	26 to 30	26 to 30	
Gender categorical			
Units: Subjects			
Female	14	41	
Male	13	46	
Not recorded	0	0	

Reporting group values	70%IPA/2%CHG - analysed for clinical outcomes	Analysed for clinical outcomes (total)	
Number of subjects	79	106	
Age categorical			
Gestational age at trial entry			
Units: Subjects			
<26+0 weeks			
26+1 to 27+6 weeks			
28+0 to 33+6 weeks			
Not recorded			

Age continuous			
Gestational age (completed weeks)			
Units: weeks median inter-quartile range (Q1-Q3)			
Gender categorical Units: Subjects			
Female Male Not recorded			

End points

End points reporting groups

Reporting group title	2%CHG
Reporting group description:	
Aqueous-based 2% chlorhexidine gluconate	
Reporting group title	70%IPA/2%CHG
Reporting group description:	
Alcohol-based (70% isopropyl alcohol) 2% chlorhexidine gluconate	
Reporting group title	2%CHG
Reporting group description:	
Aqueous-based 2% chlorhexidine gluconate	
Reporting group title	70%IPA/2%CHG
Reporting group description:	
Alcohol-based (70% isopropyl alcohol) 2% chlorhexidine gluconate	
Subject analysis set title	2%CHG - inc in baseline characteristics
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
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 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.	
Subject analysis set title	70%IPA/2%CHG - inc in baseline characteristics
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
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 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.	
Subject analysis set title	2%CHG - analysed for clinical outcomes
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Excluding infants with no line insertion attempted (1) or line insertion never successful (0).	
Subject analysis set title	70%IPA/2%CHG - analysed for clinical outcomes
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Excluding infants with no line insertion attempted (1) or line insertion never successful (8).	
Subject analysis set title	Analysed for clinical outcomes (total)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All participants randomised who had a successfully inserted catheter and received the intervention	

Primary: Catheter colonisation as determined by positive bacterial culture from at least one of the two catheter segments taken at catheter removal

End point title	Catheter colonisation as determined by positive bacterial culture from at least one of the two catheter segments taken at catheter removal[1]

End point description:

End point type	Primary

End point timeframe:

At catheter removal

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Feasibility study, no comparative analysis planned

End point values	70%IPA/2%CHG - analysed for clinical outcomes			
Subject group type	Subject analysis set			
Number of subjects analysed	79			
Units: Infants				
Yes	3			
No	70			
Missing	6			

Statistical analyses

No statistical analyses for this end point

Primary: Proportion of babies with catheter colonisation

End point title	Proportion of babies with catheter colonisation[2]

End point description:

End point type	Primary

End point timeframe:

At catheter removal

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Feasibility study, no comparative analysis planned

End point values	70%IPA/2%CHG - analysed for clinical outcomes			
Subject group type	Subject analysis set			
Number of subjects analysed	79			
Units: Proportion				
number (confidence interval 95%)	4.1 (0.9 to 11.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Positive exit-site skin swab at catheter removal (before disinfection)

End point title	Positive exit-site skin swab at catheter removal (before disinfection)

End point description:

End point type	Secondary

End point timeframe:

At catheter removal

End point values	2%CHG - analysed for clinical outcomes	70%IPA/2%CHG - analysed for clinical outcomes		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	79		
Units: Infants				
Yes	4	11		
No	20	62		
Missing	3	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Positive exit site skin swab at catheter removal (after disinfection)

End point title	Positive exit site skin swab at catheter removal (after disinfection)

End point description:

End point type	Secondary

End point timeframe:

At catheter removal

End point values	2%CHG - analysed for clinical outcomes	70%IPA/2%CHG - analysed for clinical outcomes		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	79		
Units: Infants				
Yes	1	1		
No	22	71		
Missing	4	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Culture positive catheter segments at removal

End point title	Culture positive catheter segments at removal

End point description:

End point type	Secondary

End point timeframe:

At catheter removal

End point values	2%CHG - analysed for clinical outcomes	70%IPA/2%CHG - analysed for clinical outcomes		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	79		
Units: Infants				
Yes	2	3		
No	22	70		
Missing	3	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Culture positive catheter segments at removal: Positive tip alone

End point title	Culture positive catheter segments at removal: Positive tip alone

End point description:

End point type	Secondary

End point timeframe:

At catheter removal

End point values	2%CHG - analysed for clinical outcomes	70%IPA/2%CHG - analysed for clinical outcomes		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	79		
Units: Infants				
Yes	1	1		
No	26	78		
Missing	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Culture positive catheter segments at removal: Positive proximal segment alone

End point title	Culture positive catheter segments at removal: Positive proximal segment alone

End point description:

End point type	Secondary

End point timeframe:

At catheter removal

End point values	2%CHG - analysed for clinical outcomes	70%IPA/2%CHG - analysed for clinical outcomes		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	79		
Units: Infants				
Yes	0	2		
No	27	77		

Statistical analyses

No statistical analyses for this end point

Secondary: Culture positive catheter segments at removal: Both tip and proximal segment positive

End point title	Culture positive catheter segments at removal: Both tip and proximal segment positive

End point description:

End point type	Secondary

End point timeframe:

At catheter removal

End point values	2%CHG - analysed for clinical outcomes	70%IPA/2%CHG - analysed for clinical outcomes		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	79		
Units: Infants				
Yes	1	0		
No	23	73		
Missing	3	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Definite catheter-related sepsis

End point title	Definite catheter-related sepsis

End point description:

End point type	Secondary

End point timeframe:

After catheter removal

End point values	2%CHG - analysed for clinical outcomes	70%IPA/2%CHG - analysed for clinical outcomes		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	79		
Units: Infant				
Yes	1	1		
No	21	65		
Missing	5	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Catheter-associated sepsis

End point title	Catheter-associated sepsis

End point description:

End point type	Secondary

End point timeframe:

After catheter removal

End point values	2%CHG - analysed for clinical outcomes	70%IPA/2%CHG - analysed for clinical outcomes		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	79		
Units: Infants				
Yes	3	10		
No	21	63		
Missing	3	6		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Retention: Remained in the study

End point title	Retention: Remained in the study

End point description:

Feasibility metric. Proportion of infants that remained in the study to provide complete primary outcome and safety data.

End point type	Other pre-specified

End point timeframe:

Randomisation to end

End point values	2%CHG	70%IPA/2%CHG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	88		
Units: Infants				
Yes	24	88		
No	4	73		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Retention: Proportion who remained in the study

End point title	Retention: Proportion who remained in the study

End point description:

Feasibility metric. Proportion of infants that remained in the study to provide complete primary outcome and safety data.

End point type	Other pre-specified

End point timeframe:

Randomisation to end

End point values	2%CHG	70%IPA/2%CHG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	88		
Units: Proportion				
number (confidence interval 95%)	85.7 (67.3 to 96.0)	83.0 (73.4 to 90.1)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Infants with no missing data collection forms

End point title	Infants with no missing data collection forms

End point description:

Feasibility metric.

End point type	Other pre-specified

End point timeframe:

Randomisation to end

End point values	Analysed for clinical outcomes (total)			
Subject group type	Subject analysis set			
Number of subjects analysed	106			
Units: Infants				
Yes	104			
No	2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

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.

Adverse event reporting additional description:

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.

Assessment type	Non-systematic

Dictionary used

Dictionary name	N/A
Dictionary version	0

Reporting groups

Reporting group title	2%CHG

Reporting group description:

Aqueous-based 2% chlorhexidine gluconate

Reporting group title	70%IPA/2%CHG

Reporting group description:

Alcohol-based (70% isopropyl alcohol) 2% chlorhexidine gluconate

Serious adverse events	2%CHG	70%IPA/2%CHG	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	0 / 87 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	2%CHG	70%IPA/2%CHG	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	0 / 87 (0.00%)	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: As per protocol, not reported

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported