Clinical trial results:
Perineural Local Anaesthetic Catheter aftEr Major lowEr limb amputatioN Trial (PLACEMENT)

Summary

EudraCT number	2016-003544-37
Trial protocol	GB
Global end of trial date	31 August 2018

Results information

Result version number	v1 (current)
This version publication date	11 June 2020
First version publication date	11 June 2020

Trial information

Trial identification

Sponsor protocol code	ABUHB/01/0816/1

Additional study identifiers

ISRCTN number	ISRCTN85710690
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aneurin Bevan Univeristy Health Board
Sponsor organisation address	Cardiff Road, Newport, United Kingdom, NP20 2UB
Public contact	Trial Manager, Centre for Trials Research, Cardiff University, 02920 687609, PLACEMENT-Trial@cardiff.ac.uk
Scientific contact	Trial Manager, Centre for Trials Research, Cardiff University, 02920 687609, PLACEMENT-Trial@cardiff.ac.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	22 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2018
Global end of trial reached?	Yes
Global end of trial date	31 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal research question is whether it is feasible to run a pragmatic randomised controlled trial to investigate the effect of a perineural catheter (PNC) use plus usual care compared to usual care alone on post-operative pain.

Protection of trial subjects:

TSC took on the role of IDMC, PID

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
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)	14
From 65 to 84 years	34
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The first patient was recruited on 06.02.2017 and the final patient on 15.11.2017. Follow up continued for 6 months post-surgery.

Pre-assignment

Screening details:

Patients listed for major lower limb amputation will be screened by members of the clinical care team against the above inclusion/exclusion criteria. Those who are considered potentially suitable for inclusion will be approached and provided with a Patient Information Sheet (PIS) by a member of the clinical care team.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Usual Care

Arm description:

Best available standard care

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Peri-neural catheter

Arm description:

Received peri-neural catheter to infuse local anaesthesia into amputation area intra-operatively

Arm type	Experimental
Investigational medicinal product name	Levobupivacaine hydrochloride 0.125%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Perineural use

Dosage and administration details:

The local anaesthetic used in this trial is Levobupivacaine hydrochloride 0.125%, which will be administered via the above described epidural catheter and infusion device at a rate of 2-12 ml per hour (2.5-15 mg/hr).

Number of subjects in period 1	Usual Care	Peri-neural catheter
Started	27	23
Completed	26	23
Not completed	1	0
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Usual Care
Reporting group description:	
Best available standard care	
Reporting group title	Peri-neural catheter
Reporting group description:	
Received peri-neural catheter to infuse local anaesthesia into amputation area intra-operatively	

Reporting group values	Usual Care	Peri-neural catheter	Total
Number of subjects	27	23	50
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
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 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	69.9	69.7	
standard deviation	± 10.20	± 9.99	-
Gender categorical			
Units: Subjects			
Female	6	4	10
Male	21	19	40
Level of amputation			
Units: Subjects			
Below knee	15	16	31
Above knee	12	7	19
Site			
Units: Subjects			
Royal Gwent Hospital	11	9	20
Morriston Hospital	16	14	30
Opioid Use			
Units: Morphine Equivalance Scale			
median	5.3	4.6	
inter-quartile range (Q1-Q3)	1.8 to 23.7	0.0 to 18.0	-

Subject analysis sets	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised

Reporting group values	ITT		
Number of subjects	50		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	69.8		
standard deviation	± 10.00		
Gender categorical Units: Subjects			
Female	10		
Male	40		
Level of amputation Units: Subjects			
Below knee	31		
Above knee	19		
Site Units: Subjects			
Royal Gwent Hospital	20		
Morriston Hospital	30		
Opioid Use Units: Morphine Equivalance Scale			
median	4.6		
inter-quartile range (Q1-Q3)	0.0 to 18.0		

End points

End points reporting groups

Reporting group title	Usual Care
Reporting group description:	
Best available standard care	
Reporting group title	Peri-neural catheter
Reporting group description:	
Received peri-neural catheter to infuse local anaesthesia into amputation area intra-operatively	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomised	

Primary: Provide data on alternative primary outcome of those included

End point title	Provide data on alternative primary outcome of those included

End point description:

Definition of alternative primary outcome: modal value of potential 17 post surgery pain scores. These scores are a combination of patient-reported 11-point pain scores converted to 4-point and, where the patient-reported version is not available, nurse-reported 4-point pain scores. The modal calculation is only made if 9 or more values are available. This alternative was calculated (as defined in the SAP) because the original primary outcome (using just patient-reported 11-point pain scores) was only available for 34/49 (62.1), which was less than the pre-specified 90%.

A 'traffic light' system will be used to identify levels deemed acceptable (green), possibly acceptable with discussion and amendments (amber) and unacceptable (red). These criteria are:
- For the proportion of randomised patients that provide data for the primary outcome:
  - greater than 0.9 - green;
  - 0.9 to 0.6 - amber;
  - less than 0.6 - red.

End point type	Primary

End point timeframe:

5 days post-surgery

End point values	Usual Care	Peri-neural catheter	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	26	23	49[1]	
Units: Subjects				
No	3	1	4	
Yes	23	22	45	

Notes:

[1] - All randomised minus 1 peri-operative exclusion (SAE - Non-fatal) that had no ability to provide

Statistical analyses

Statistical analysis title	95% Confidence Interval (Wilson's Method)
Comparison groups	Peri-neural catheter v Usual Care v ITT

Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage
Point estimate	91.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	80.81
upper limit	96.78

Primary: Provide data on original primary outcome of those included

End point title	Provide data on original primary outcome of those included

End point description:

Definition of original primary outcome: mean value of potential 17 post surgery pain scores. These scores are patient-reported 11-point pain scores.

A 'traffic light' system will be used to identify levels deemed acceptable (green), possibly acceptable with discussion and amendments (amber) and unacceptable (red). These criteria are:

- For the proportion of randomised patients that provide data for the primary outcome:
  - greater than 0.9 - green;
  - 0.9 to 0.6 - amber;
  - less than 0.6 - red.

End point type	Primary

End point timeframe:

5 days post-surgery

End point values	Usual Care	Peri-neural catheter	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	26	23	49[2]	
Units: Subjects				
No	8	7	15	
Yes	18	16	34	

Notes:

[2] - All randomised minus 1 peri-operative exclusion (SAE - Non-fatal) that had no ability to provide

Statistical analyses

Statistical analysis title	95% Confidence Interval (Wilson's Method)
Comparison groups	Usual Care v Peri-neural catheter v ITT
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage
Point estimate	69.39

Confidence interval	
level	95 %
sides	2-sided
lower limit	55.47
upper limit	80.48

Primary: Provide data on Chronic Stump Pain of those reaching 6 weeks

End point title	Provide data on Chronic Stump Pain of those reaching 6 weeks

End point description:

End point type	Primary

End point timeframe:

6 weeks post-surgery

End point values	Usual Care	Peri-neural catheter	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	23	22	45[3]	
Units: Subjects				
No	11	5	16	
Yes	12	17	29	

Notes:

[3] - All randomised minus 1 peri-operative exclusion (SAE - Non-fatal) and 4 deceased before 6 weeks

Statistical analyses

Statistical analysis title	95% Confidence Interval (Wilson's Method)
Comparison groups	Usual Care v Peri-neural catheter v ITT
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage
Point estimate	64.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	49.84
upper limit	76.78

Primary: Provide data on Phantom Limb Pain of those reaching 6 weeks

End point title	Provide data on Phantom Limb Pain of those reaching 6 weeks

End point description:

End point type	Primary

End point timeframe:

6 weeks post-surgery

End point values	Usual Care	Peri-neural catheter	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	23	22	45[4]	
Units: Subjects				
No	11	7	18	
Yes	12	15	27	

Notes:

[4] - All randomised minus 1 peri-operative exclusion (SAE - Non-fatal) and 4 deceased before 6 weeks

Statistical analyses

Statistical analysis title	95% Confidence Interval (Wilson's Method)
Comparison groups	Usual Care v Peri-neural catheter v ITT
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage
Point estimate	60
Confidence interval	
level	95 %
sides	2-sided
lower limit	45.45
upper limit	72.98

Primary: Provide data on Chronic Stump Pain of those reaching 6 months

End point title	Provide data on Chronic Stump Pain of those reaching 6 months

End point description:

End point type	Primary

End point timeframe:

6 months post-surgery

End point values	Usual Care	Peri-neural catheter	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	21	20	41[5]	
Units: Subjects				
No	12	11	23	
Yes	9	9	18	

Notes:

[5] - All randomised minus 1 peri-operative exclusion (SAE - Non-fatal) and 8 deceased before 6 months

Statistical analyses

Statistical analysis title	95% Confidence Interval (Wilson's Method)
Comparison groups	Usual Care v Peri-neural catheter v ITT
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage
Point estimate	43.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	29.89
upper limit	58.96

Primary: Provide data on Phantom Limb Pain of those reaching 6 months

End point title	Provide data on Phantom Limb Pain of those reaching 6 months

End point description:

End point type	Primary

End point timeframe:

6 months post-surgery

End point values	Usual Care	Peri-neural catheter	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	21	20	41[6]	
Units: Subjects				
No	14	13	27	
Yes	7	7	14	

Notes:

[6] - All randomised minus 1 peri-operative exclusion (SAE - Non-fatal) and 8 deceased before 6 months

Statistical analyses

Statistical analysis title	95% Confidence Interval (Wilson's Method)
Comparison groups	Usual Care v Peri-neural catheter v ITT
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage
Point estimate	34.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.56
upper limit	49.45

Primary: Alternative primary outcome

End point title	Alternative primary outcome

End point description:

End point type	Primary

End point timeframe:

5 days post-surgery

End point values	Usual Care	Peri-neural catheter	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	23[7]	22[8]	45[9]	
Units: Subjects				
None	11	14	25	
Mild	6	5	11	
Moderate	3	2	5	
Severe	3	1	4	

Notes:

[7] - All randomised minus 1 peri-operative exclusion (SAE - Non-fatal) and 3 missing alternative primary

[8] - All randomised minus 1 missing alternative primary

[9] - All randomised minus 1 peri-operative exclusion (SAE - Non-fatal) and 4 missing alternative primary

Statistical analyses

Statistical analysis title	Ordinal logistic modelling
Comparison groups	Usual Care v Peri-neural catheter

Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.376
Method	Regression, ordinal logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.571
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.165
upper limit	1.975

Notes:

[10] - Exploratory analysis of potential future primary outcome. The analysis undertaken with site, gender, level of amputation, age, opioid use at baseline, history of diabetes mellitus and (additional) regional Anaesthesia (variable) as covariates. BMI was planned to be included but was not collected fully. An original regional Anaesthesia variable was to be included as a covariate but a new variable with merged categories had to be used instead as only 1 subject received Continuous infusion.

Secondary: HADS Anxiety Score at 6 weeks

End point title	HADS Anxiety Score at 6 weeks
End point description:	
End point type	Secondary
End point timeframe:	
6 weeks post-surgery	

End point values	Usual Care	Peri-neural catheter		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	15		
Units: HADS Scale				
arithmetic mean (standard deviation)	4.6 (± 4.50)	5.7 (± 5.56)		

Statistical analyses

Statistical analysis title	Difference in means
Comparison groups	Usual Care v Peri-neural catheter
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.291
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.835

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.244
upper limit	1.574

Notes:

[11] - Exploratory analysis. Analysis undertaken with site, gender, level of amputation, age, opioid use at baseline, history of diabetes mellitus and (additional) regional Anaesthesia (variable) as covariates.

Secondary: HADS Anxiety Score at 6 months

End point title	HADS Anxiety Score at 6 months

End point description:

End point type	Secondary

End point timeframe:

6 months post-surgery

End point values	Usual Care	Peri-neural catheter		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: HADS Anxiety Scale				
arithmetic mean (standard deviation)	7.0 (± 6.68)	7.6 (± 4.28)		

Statistical analyses

Statistical analysis title	Difference in means
Comparison groups	Usual Care v Peri-neural catheter
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.978
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.111
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.83
upper limit	7.609

Notes:

[12] - Exploratory analysis. Analysis undertaken with site, gender, level of amputation, age, opioid use at baseline, history of diabetes mellitus and (additional) regional Anaesthesia (variable) as covariates.

Secondary: HADS Depression Score at 6 weeks

End point title	HADS Depression Score at 6 weeks

End point description:

End point type	Secondary

End point timeframe:

6 weeks post-surgery

End point values	Usual Care	Peri-neural catheter		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	16		
Units: HADS Depression Scale				
arithmetic mean (standard deviation)	7.2 (± 5.79)	5.8 (± 3.55)		

Statistical analyses

Statistical analysis title	Difference in means
Comparison groups	Usual Care v Peri-neural catheter
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.155
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.912
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.549
upper limit	0.725

Notes:

[13] - Exploratory analysis. Analysis undertaken with site, gender, level of amputation, age, opioid use at baseline, history of diabetes mellitus and (additional) regional Anaesthesia (variable) as covariates.

Secondary: HADS Depression Score at 6 months

End point title	HADS Depression Score at 6 months

End point description:

End point type	Secondary

End point timeframe:

6 months post-surgery

End point values	Usual Care	Peri-neural catheter		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: HADS Depression Scale				
arithmetic mean (standard deviation)	7.9 (± 6.60)	8.0 (± 2.89)		

Statistical analyses

Statistical analysis title	Difference in means
Comparison groups	Usual Care v Peri-neural catheter
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.411
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.211
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.099
upper limit	1.676

Notes:

[14] - Exploratory analysis. Analysis undertaken with site, gender, level of amputation, age, opioid use at baseline, history of diabetes mellitus and (additional) regional Anaesthesia (variable) as covariates.

Secondary: EQ-5D Health today VAS at 6 weeks

End point title	EQ-5D Health today VAS at 6 weeks

End point description:

End point type	Secondary

End point timeframe:

6 weeks post-surgery

End point values	Usual Care	Peri-neural catheter		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	17		
Units: EQ-5D VAS				
arithmetic mean (standard deviation)	66.2 (± 23.99)	70.1 (± 23.99)		

Statistical analyses

Statistical analysis title	Difference in means
Comparison groups	Usual Care v Peri-neural catheter
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.347
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	6.977
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.558
upper limit	21.512

Notes:

[15] - Exploratory analysis. Analysis undertaken with site, gender, level of amputation, age, opioid use at baseline, history of diabetes mellitus and (additional) regional Anaesthesia (variable) as covariates.

Secondary: EQ-5D Health today VAS at 6 months

End point title	EQ-5D Health today VAS at 6 months
End point description:	
End point type	Secondary
End point timeframe:	
6 months post-surgery	

End point values	Usual Care	Peri-neural catheter		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: EQ-5D VAS				
arithmetic mean (standard deviation)	60.6 (± 25.42)	71.9 (± 11.63)		

Statistical analyses

Statistical analysis title	Difference in means
Comparison groups	Usual Care v Peri-neural catheter
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.148
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	9.705

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.459
upper limit	22.87

Notes:

[16] - Exploratory analysis. Analysis undertaken with site, gender, level of amputation, age, opioid use at baseline, history of diabetes mellitus and (additional) regional Anaesthesia (variable) as covariates.

Secondary: Natural log of EQ-5D-5L Crosswalk to EQ-5D-3L at 6 weeks

End point title	Natural log of EQ-5D-5L Crosswalk to EQ-5D-3L at 6 weeks

End point description:

End point type	Secondary

End point timeframe:

6 weeks post-surgery

End point values	Usual Care	Peri-neural catheter		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	17		
Units: Natural log scale				
arithmetic mean (standard deviation)	0.1365 (± 0.31765)	0.0619 (± 0.16781)		

Statistical analyses

Statistical analysis title	Difference in means
Comparison groups	Usual Care v Peri-neural catheter
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.376
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.067
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.215
upper limit	0.081

Notes:

[17] - Exploratory analysis. Analysis undertaken with site, gender, level of amputation, age, opioid use at baseline, history of diabetes mellitus and (additional) regional Anaesthesia (variable) as covariates.

Secondary: Natural log of EQ-5D-5L Crosswalk to EQ-5D-3L at 6 months

End point title	Natural log of EQ-5D-5L Crosswalk to EQ-5D-3L at 6 months

End point description:

End point type	Secondary

End point timeframe:

6 months post-surgery

End point values	Usual Care	Peri-neural catheter		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: Natural log scale				
arithmetic mean (standard deviation)	0.1644 (± 0.23361)	0.0076 (± 0.18991)		

Statistical analyses

Statistical analysis title	Difference in means
Comparison groups	Usual Care v Peri-neural catheter
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.311
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.459
upper limit	-0.163

Notes:

[18] - Exploratory analysis. Analysis undertaken with site, gender, level of amputation, age, opioid use at baseline, history of diabetes mellitus and (additional) regional Anaesthesia (variable) as covariates.

Secondary: Treatment failure

End point title	Treatment failure

End point description:

1 required emergency surgery so the baseline pain scale (a covariate in the model) was not collected and thus only 48 are reported in this analysis

End point type	Secondary

End point timeframe:

5 days post-surgery

End point values	Usual Care	Peri-neural catheter		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	23		
Units: Subjects				
No	3	6		
Yes	22	17		

Statistical analyses

Statistical analysis title	Odds ratio
Comparison groups	Usual Care v Peri-neural catheter
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.376
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.571
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.165
upper limit	1.975

Notes:

[19] - Exploratory analysis. Analysis undertaken with site, gender, level of amputation, age, opioid use at baseline, history of diabetes mellitus and (additional) regional Anaesthesia (variable) as covariates.

Secondary: Surgical site infection

End point title	Surgical site infection

End point description:

End point type	Secondary

End point timeframe:

At discharge

End point values	Usual Care	Peri-neural catheter		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: Subjects				
No	21	22		
Yes	2	1		

Statistical analyses

Statistical analysis title	Odds ratio
Comparison groups	Usual Care v Peri-neural catheter
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	= 0.655
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.554
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.042
upper limit	7.369

Notes:

[20] - Exploratory analysis. Analysis undertaken with site, level of amputation, age, opioid use at baseline and history of diabetes mellitus.

NB. Estimate made without gender and (Additional Regional Anaesthesia (Variable) covariates, as co-linear.

Secondary: Nausea and vomiting

End point title	Nausea and vomiting

End point description:

End point type	Secondary

End point timeframe:

At discharge

End point values	Usual Care	Peri-neural catheter		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: Subjects				
No	17	21		
Yes	6	2		

Statistical analyses

Statistical analysis title	Odds ratio
Comparison groups	Usual Care v Peri-neural catheter

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	= 0.127
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.249
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.042
upper limit	1.487

Notes:

[21] - Exploratory analysis. Analysis undertaken with site, gender, level of amputation, age, opioid use at baseline, history of diabetes mellitus and (additional) regional Anaesthesia (variable) as covariates.

Secondary: Chronic Stump Pain at 6 weeks

End point title	Chronic Stump Pain at 6 weeks

End point description:

End point type	Secondary

End point timeframe:

6 weeks post-surgery

End point values	Usual Care	Peri-neural catheter		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	15		
Units: Subjects				
Absent	8	14		
Present	4	3		

Statistical analyses

Statistical analysis title	Odds ratio
Comparison groups	Usual Care v Peri-neural catheter
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other[22]
P-value	= 0.332
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.228

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.012
upper limit	4.535

Notes:

[22] - Exploratory analysis. Analysis undertaken with site, gender, level of amputation, age, opioid use at baseline, history of diabetes mellitus and (additional) regional Anaesthesia (variable) as covariates.

Secondary: Phantom Limb Pain at 6 weeks

End point title	Phantom Limb Pain at 6 weeks

End point description:

End point type	Secondary

End point timeframe:

6 weeks post-surgery

End point values	Usual Care	Peri-neural catheter		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	15		
Units: Subjects				
Absent	7	11		
Present	5	4		

Statistical analyses

Statistical analysis title	Odds ratio
Comparison groups	Usual Care v Peri-neural catheter
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 0.12
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.158
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.015
upper limit	1.623

Notes:

[23] - Exploratory analysis. Analysis undertaken with site, gender, level of amputation, age, opioid use at baseline, history of diabetes mellitus and (additional) regional Anaesthesia (variable) as covariates.

Secondary: Chronic Stump Pain at 6 months

End point title	Chronic Stump Pain at 6 months

End point description:

End point type	Secondary

End point timeframe:

6 months post-surgery

End point values	Usual Care	Peri-neural catheter		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: Subjects				
Absent	6	7		
Present	3	2		

Statistical analyses

Statistical analysis title	Odds ratio
Comparison groups	Usual Care v Peri-neural catheter
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other[24]
P-value	= 0.207
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.137
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.006
upper limit	3.015

Notes:

[24] - Exploratory analysis. Analysis undertaken with site, level of amputation, age, opioid use at baseline, history of diabetes mellitus and (additional) regional Anaesthesia (variable) as covariates.

NB. Estimate made without gender covariate, as co-linear.

Secondary: Phantom Limb Pain at 6 months

End point title	Phantom Limb Pain at 6 months

End point description:

End point type	Secondary

End point timeframe:

6 months post-surgery

End point values	Usual Care	Peri-neural catheter		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	7		
Units: Subjects				
Absent	5	4		
Present	2	3		

Statistical analyses

Statistical analysis title	Odds ratio
Comparison groups	Usual Care v Peri-neural catheter
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	= 0.56
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.286
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.142
upper limit	36.808

Notes:

[25] - Exploratory analysis. Analysis undertaken with gender, level of amputation, age, opioid use at baseline, history of diabetes mellitus and (additional) regional Anaesthesia (variable) as covariates.

NB. Estimate made without Site covariate, else no convergence

Secondary: Natural log of OBAS

End point title	Natural log of OBAS

End point description:

End point type	Secondary

End point timeframe:

5 days post-surgery

End point values	Usual Care	Peri-neural catheter		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	23		
Units: Natural log scale				
arithmetic mean (standard deviation)	1.3 (± 0.57)	1.2 (± 0.63)		

Statistical analyses

Statistical analysis title	Difference in means
Comparison groups	Usual Care v Peri-neural catheter
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other[26]
P-value	= 0.16
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.528
upper limit	0.087

Notes:

[26] - Exploratory analysis. Analysis undertaken with site, gender, level of amputation, age, opioid use at baseline, history of diabetes mellitus and (additional) regional Anaesthesia (variable) as covariates.

Secondary: Successful identification of nerve

End point title	Successful identification of nerve[27]

End point description:

End point type	Secondary

End point timeframe:

At surgery

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This end point is only relevant to the Peri-neural Catheter arm.

End point values	Peri-neural catheter			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: Subjects				
No	0			
Yes	23			

Statistical analyses

No statistical analyses for this end point

Secondary: Successful placement of Peri-neural Catheter

End point title	Successful placement of Peri-neural Catheter[28]

End point description:

End point type	Secondary

End point timeframe:

At surgery

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point is only relevant to the Peri-neural Catheter arm.

End point values	Peri-neural catheter			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: Subjects				
No	0			
Yes	23			

Statistical analyses

No statistical analyses for this end point

Secondary: S-LANSS at 5 days

End point title	S-LANSS at 5 days

End point description:

End point type	Secondary

End point timeframe:

5 days post-surgery

End point values	Usual Care	Peri-neural catheter		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	20		
Units: S-LANSS Scale				
median (inter-quartile range (Q1-Q3))	12.0 (3.0 to 14.0)	6.5 (0.0 to 13.5)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Usual Care v Peri-neural catheter

Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other[29]
P-value	= 0.331
Method	Wilcoxon (Mann-Whitney)

Notes:

[29] - Exploratory analysis.

Secondary: S-LANSS at 6 weeks

End point title	S-LANSS at 6 weeks

End point description:

End point type	Secondary

End point timeframe:

6 weeks post-surgery

End point values	Usual Care	Peri-neural catheter		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	16		
Units: S-LANSS Scale				
median (inter-quartile range (Q1-Q3))	0.0 (0.0 to 6.0)	5.0 (2.0 to 11.0)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Usual Care v Peri-neural catheter
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[30]
P-value	= 0.159 [31]
Method	Wilcoxon (Mann-Whitney)

Notes:

[30] - Exploratory analysis.

[31] - Exact, rather than asymptotic, p-value displayed based on algorithm of Dineen and Blakesley

Secondary: S-LANSS at 6 months

End point title	S-LANSS at 6 months

End point description:

End point type	Secondary

End point timeframe:

6 months post-surgery

End point values	Usual Care	Peri-neural catheter		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: S-LANSS Scale				
median (inter-quartile range (Q1-Q3))	9.0 (1.0 to 13.0)	10 (2.5 to 16.5)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Usual Care v Peri-neural catheter
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other[32]
P-value	= 0.721 [33]
Method	Wilcoxon (Mann-Whitney)

Notes:

[32] - Exploratory analysis.

[33] - Exact, rather than asymptotic, p-value based on algorithm of Dineen and Blakesley

Secondary: Opioid Use

End point title	Opioid Use

End point description:

End point type	Secondary

End point timeframe:

5 days post-surgery

End point values	Usual Care	Peri-neural catheter		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	23		
Units: Equivalent Morphine Use				
median (inter-quartile range (Q1-Q3))	12.2 (7.0 to 22.5)	8.0 (3.0 to 21.0)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Usual Care v Peri-neural catheter

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other[34]
P-value	= 0.302
Method	Wilcoxon (Mann-Whitney)

Notes:
[34] - Exploratory analysis.

Other pre-specified: Provide data on Treatment Failure

End point title	Provide data on Treatment Failure

End point description:

End point type	Other pre-specified

End point timeframe:
5 days post-surgery

End point values	Usual Care	Peri-neural catheter	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	26	23	49[35]	
Units: Subjects				
No	0	0	0	
Yes	26	23	49	

Notes:
[35] - All randomised minus 1 peri-operative exclusion (SAE - Non-fatal) that had no ability to provide

Statistical analyses

Statistical analysis title	95% Confidence Interval (Wilson's Method)
Comparison groups	Usual Care v Peri-neural catheter v ITT
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage
Point estimate	100
Confidence interval	
level	95 %
sides	2-sided
lower limit	92.73
upper limit	100

Other pre-specified: Provide data on OBAS

End point title	Provide data on OBAS

End point description:

End point type	Other pre-specified

End point timeframe:

5 days post-surgery

End point values	Usual Care	Peri-neural catheter	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	26	23	49[36]	
Units: Subjects				
No	2	0	2	
Yes	24	23	47	

Notes:

[36] - All randomised minus 1 peri-operative exclusion (SAE - Non-fatal) that had no ability to provide

Statistical analyses

Statistical analysis title	95% Confidence Interval (Wilson's Method)
Comparison groups	Usual Care v Peri-neural catheter v ITT
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage
Point estimate	95.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	86.29
upper limit	98.87

Other pre-specified: Provide data on Opioid Use

End point title	Provide data on Opioid Use

End point description:

End point type	Other pre-specified

End point timeframe:

5 days post-surgery

End point values	Usual Care	Peri-neural catheter	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	26	23	49[37]	
Units: Subjects				
No	1	0	1	
Yes	25	23	48	

Notes:
[37] - All randomised minus 1 peri-operative exclusion (SAE - Non-fatal) that had no ability to provide

Statistical analyses

Statistical analysis title	95% Confidence Interval (Wilson's Method)
Comparison groups	Peri-neural catheter v Usual Care v ITT
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage
Point estimate	97.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	89.31
upper limit	99.64

Other pre-specified: Provide data on S-LANSS at Day 5

End point title	Provide data on S-LANSS at Day 5

End point description:

End point type	Other pre-specified

End point timeframe:
5 days post-surgery

End point values	Usual Care	Peri-neural catheter	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	26	23	49[38]	
Units: Subjects				
No	5	3	8	
Yes	21	29	41	

Notes:
[38] - All randomised minus 1 peri-operative exclusion (SAE - Non-fatal) that had no ability to provide

Statistical analyses

Statistical analysis title	95% Confidence Interval (Wilson's Method)
Comparison groups	Usual Care v Peri-neural catheter v ITT

Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage
Point estimate	83.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	70.96
upper limit	91.49

Other pre-specified: Provide data on Clavien-Dindo

End point title	Provide data on Clavien-Dindo

End point description:

Clavien-Dindo used to assess Nausea and vomiting, and Surgical Site Infection outcomes

End point type	Other pre-specified

End point timeframe:

At discharge

End point values	Usual Care	Peri-neural catheter	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	26	23	49[39]	
Units: Subjects				
No	3	0	3	
Yes	23	23	46	

Notes:

[39] - All randomised minus 1 peri-operative exclusion (SAE - Non-fatal) that had no ability to provide

Statistical analyses

Statistical analysis title	95% Confidence Interval (Wilson's Method)
Comparison groups	Usual Care v Peri-neural catheter v ITT
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage
Point estimate	93.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	83.48
upper limit	97.9

Other pre-specified: Provide data on S-LANSS at 6 weeks

End point title	Provide data on S-LANSS at 6 weeks

End point description:

End point type	Other pre-specified

End point timeframe:

6 weeks post-surgery

End point values	Usual Care	Peri-neural catheter	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	23	22	45[40]	
Units: Subjects				
No	11	6	17	
Yes	12	16	28	

Notes:

[40] - All randomised minus 1 peri-operative exclusion (SAE - Non-fatal) and 4 deceased before 6 weeks

Statistical analyses

Statistical analysis title	95% Confidence Interval (Wilson's Method)
Comparison groups	Usual Care v Peri-neural catheter v ITT
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage
Point estimate	62.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	47.63
upper limit	74.89

Other pre-specified: Provide data on S-LANSS at 6 months

End point title	Provide data on S-LANSS at 6 months

End point description:

End point type	Other pre-specified

End point timeframe:

6 months post-surgery

End point values	Usual Care	Peri-neural catheter	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	21	20	41[41]	
Units: Subjects				
No	13	12	25	
Yes	8	8	16	

Notes:

[41] - All randomised minus 1 peri-operative exclusion (SAE - Non-fatal) and 8 deceased before 6 months

Statistical analyses

Statistical analysis title	95% Confidence Interval (Wilson's Method)
Comparison groups	Usual Care v Peri-neural catheter v ITT
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage
Point estimate	39.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	25.66
upper limit	54.27

Other pre-specified: Provide data on HADS at 6 weeks

End point title	Provide data on HADS at 6 weeks

End point description:

End point type	Other pre-specified

End point timeframe:

6 weeks post-surgery

End point values	Usual Care	Peri-neural catheter	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	23	22	45[42]	
Units: Subjects				
No	10	5	15	
Yes	13	17	30	

Notes:

[42] - All randomised minus 1 peri-operative exclusion (SAE - Non-fatal) and 4 deceased before 6 weeks

Statistical analyses

Statistical analysis title	95% Confidence Interval (Wilson's Method)
Comparison groups	Usual Care v Peri-neural catheter v ITT
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage
Point estimate	66.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	52.07
upper limit	78.64

Other pre-specified: Provide data on HADS at 6 months

End point title	Provide data on HADS at 6 months

End point description:

End point type	Other pre-specified

End point timeframe:

6 months post-surgery

End point values	Usual Care	Peri-neural catheter	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	21	20	41[43]	
Units: Subjects				
No	12	12	24	
Yes	9	8	17	

Notes:

[43] - All randomised minus 1 peri-operative exclusion (SAE - Non-fatal) and 8 deceased before 6 months

Statistical analyses

Statistical analysis title	95% Confidence Interval (Wilson's Method)
Comparison groups	Usual Care v Peri-neural catheter v ITT
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage
Point estimate	41.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	27.76
upper limit	56.63

Other pre-specified: Provide data on EQ-5D at 6 weeks

End point title	Provide data on EQ-5D at 6 weeks

End point description:

End point type	Other pre-specified

End point timeframe:

6 weeks post-surgery

End point values	Usual Care	Peri-neural catheter	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	23	22	45[44]	
Units: Subjects				
No	11	5	16	
Yes	12	17	29	

Notes:

[44] - All randomised minus 1 peri-operative exclusion (SAE - Non-fatal) and 4 deceased before 6 weeks

Statistical analyses

Statistical analysis title	95% Confidence Interval (Wilson's Method)
Comparison groups	Usual Care v Peri-neural catheter v ITT
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage
Point estimate	64.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	49.84
upper limit	76.78

Other pre-specified: Provide data on EQ-5D at 6 months

End point title	Provide data on EQ-5D at 6 months

End point description:

End point type	Other pre-specified

End point timeframe:

6 months post-surgery

End point values	Usual Care	Peri-neural catheter	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	21	20	41[45]	
Units: Subjects				
No	12	11	23	
Yes	9	9	18	

Notes:

[45] - All randomised minus 1 peri-operative exclusion (SAE - Non-fatal) and 8 deceased before 6 months

Statistical analyses

Statistical analysis title	95% Confidence Interval (Wilson's Method)
Comparison groups	Usual Care v Peri-neural catheter v ITT
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage
Point estimate	43.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	29.89
upper limit	58.96

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs reported from time the patient goes into theatre, throughout the treatment period up to, and including 7 days post-operation. Serious adverse reactions (such as long term side effects of trial treatment) reported until the end of follow up.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	4.02

Reporting groups

Reporting group title	Usual care
Reporting group description: -	
Reporting group title	Peri-neural catheter (Levobupivacaine)

Reporting group description: -

Serious adverse events	Usual care	Peri-neural catheter (Levobupivacaine)	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 27 (22.22%)	3 / 23 (13.04%)	
number of deaths (all causes)	4	3	
number of deaths resulting from adverse events	0	1	
Injury, poisoning and procedural complications			
Opioid toxicity			
subjects affected / exposed	2 / 27 (7.41%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
(L) MCA territory ischemic stroke			
subjects affected / exposed	0 / 27 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arterial bleed			
subjects affected / exposed	1 / 27 (3.70%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

fractured neck of femur			
subjects affected / exposed	1 / 27 (3.70%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
wound infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
stump infection			
subjects affected / exposed	1 / 27 (3.70%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Usual care	Peri-neural catheter (Levobupivacaine)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 27 (25.93%)	9 / 23 (39.13%)	
Injury, poisoning and procedural complications			
Other - Falls & wound dehiscence	Additional description: fell on stump- slight bleeding, fell on stump - wound dehiscence, fall - no injuries, wound dehiscence, above knee amputation non-viable stump, non healing stump with minimal blood loss, fall - small cut to head, pressure ulcer, death.		
alternative dictionary used: Clavien-Dindo system 1			
subjects affected / exposed	3 / 27 (11.11%)	3 / 23 (13.04%)	
occurrences (all)	5	4	
Cardiac disorders			
Cardiopulmonary	Additional description: Pleural drain, hypotensive		
alternative dictionary used: Clavien-Dindo system 1			
subjects affected / exposed	1 / 27 (3.70%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Nervous system disorders			

Neurologic	Additional description: Stroke		
alternative dictionary used: Clavien-Dindo system 1			
subjects affected / exposed	0 / 27 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Bleeding/hematoma	Additional description: Blood transfusion, blood transfusion in theatre, blood transfusion post op, Low HB - blood transfusion, PR bleeding, blood loss.		
alternative dictionary used: Clavien-Dindo system 1			
subjects affected / exposed	6 / 27 (22.22%)	3 / 23 (13.04%)	
occurrences (all)	7	3	
Gastrointestinal disorders			
Nausea and vomiting			
alternative dictionary used: Clavien-Dindo system 1			
subjects affected / exposed	6 / 27 (22.22%)	2 / 23 (8.70%)	
occurrences (all)	6	2	
Skin and subcutaneous tissue disorders			
Other - Rash	Additional description: Rash - iliac fossa		
alternative dictionary used: Clavien Dindo system 1			
subjects affected / exposed	0 / 27 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Psychiatric disorders			
Pain	Additional description: Pain		
alternative dictionary used: Clavien-Dindo system 1			
subjects affected / exposed	0 / 27 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Endocrine disorders			
Other - Hypoglycaemia	Additional description: Hypoglycaemic event		
alternative dictionary used: Clavien-Dindo system 1			
subjects affected / exposed	0 / 27 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	2	
Infections and infestations			
Infection	Additional description: Hospital acquired pneumonia, UTI, septic from UTI with cardiovascular and renal failure, recurrent UTI, wound infection, urosepsis		
alternative dictionary used: Clavien-Dindo system 1			
subjects affected / exposed	3 / 27 (11.11%)	3 / 23 (13.04%)	
occurrences (all)	4	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 July 2017	Substantial amendment to consent form. Added permission for a nominated alternative contact person to be contacted if a participant cannot be reached for their 6 week and 6 month follow ups. Substantial amendment - addition of follow up letter. Sent out if a participant cannot be reached for their follow ups. It gives options for completing the follow up questionnaires by post, return to the research nurse at next clinic appointment, or complete at home and research nurse will call to record answers over the telephone. This letter has been created to improve follow up rates.
16 January 2018	Addition of peri-operative risk modelling work. An analysis of national registry data to allow better quantification of peri-operative risk for patients undergoing major lower limb amputation.
20 February 2018	Addition of a consent form and participant information sheet for the qualitative study for relatives. To be used if both the patient decides they would like the relative present, and the relative decides they wish to contribute in the qualitative interviews. Also, addition of the Healthcare Professional consent to contact form to be used for Healthcare Professional details to be passed onto the qualitative researcher so they can contact the Healthcare Professional about participating in the qualitative interviews for the process evaluation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31719071