Clinical trial results:
A randomised control trial to determine whether a 5 day course of antibiotics is more clinically and cost effective than a 24 hour prophylactic course for the prevention of surgical site infection following lower limb amputation surgery

Summary

EudraCT number	2012-003146-32
Trial protocol	GB
Global end of trial date	28 December 2016

Results information

Result version number	v1 (current)
This version publication date	07 October 2020
First version publication date	07 October 2020
Summary attachment (see zip file)	ASSIT main results and summary report (ASSITStudymainresultsandfindingsSummaryreport.docx) ASSIT Choice of Statistical Tests (Choice of statistical tests.docx)

Trial information

Trial identification

Sponsor protocol code	ASSIT

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Hull University Teaching Hospital NHS Trust
Sponsor organisation address	Anlaby Road, Hull, United Kingdom, HU3 2JZ
Public contact	Judith Long, Academic Vascular Surgical Unit, Hull Royal Infirmary, 01482 675784, judith.long@hey.nhs.uk
Scientific contact	Panos Souroullas, Academic Vascular Surgical Unit, Hull Royal Infirmary, 01482 675784, sourou@doctors.org.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	12 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 January 2016
Global end of trial reached?	Yes
Global end of trial date	28 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective: to establish if a 5 day course of antibiotics is more clinically and cost effective than a 24 hour prophylactic course in preventing surgical site infection in patients undergoing lower limb amputation.

Protection of trial subjects:

Full written informed consent was received from all participants prior to any study procedures. Patients were free to withdraw from the study at any time.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 January 2013
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: 161
Worldwide total number of subjects	161
EEA total number of subjects	161

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)	73
From 65 to 84 years	77
85 years and over	11

Subject disposition

Recruitment

Recruitment details:

A total of 208 patients were screened for eligibility of which 161 patients were recruited and randomised between 17th October 2013 and 12th December 2015.

Pre-assignment

Screening details:

All patients undergoing either transfemoral, transtibial or transmetatasal amputation were screened:
Inclusion
Adults ≥18 yrs undergoing MLLA.

Exclusion
Allergies to chlorhexidine/alcohol/ iodophors
Admitted to hospital requiring emergency amputation due to severe sepsis
Use of investigational drug/device therapy within preceding 4 weeks

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

Blinding of treating surgical team and participant was not performed. Blinding of the investigator assessing outcomes was achieved by having outcome assessments performed by a member of the research team who was unaware of treatment allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	5-day Antibiotic Group

Arm description:

Both treatment groups received 24 hours of intravenous (IV) treatment, consisting of three doses of 1.2g of amoxicillin with clavulanic acid and 500mg of metronidazole eight hours apart starting on induction of anaesthesia. In cases of amputations proximal to the transtibial level, a single weight-adjusted dose of gentamicin (7mg/Kg) was also administered on induction.

Those in the five-day treatment arm received further oral antibiotic prophylaxis with 625mg of Co-amoxiclav TDS and 400mg metronidazole administered three times a day for four days.

Arm type	Active comparator
Investigational medicinal product name	Co-amoxiclav
Investigational medicinal product code	
Other name	Augmentin
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Augmentin 1.2g IV three times daily for 24 hours. If the patient is randomised to the 5-day duration antibiotic arm then Augmentin 625mg oral tablets three times daily are added to the 24 hour course for a further 4 days.

Investigational medicinal product name	Metronidazole
Investigational medicinal product code	
Other name	Flagyl
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

500mg IV three times daily for 24 hours. If the patient is randomised to 5-day duration arm, then

another 4 days of oral metronidazole at 400mg three times daily is added to the course

Investigational medicinal product name	Iodine
Investigational medicinal product code	
Other name	Povidone iodine
Pharmaceutical forms	Cutaneous solution
Routes of administration	Topical use

Dosage and administration details:

Intra-operative skin preparation prior to incision to skin.

Investigational medicinal product name	Chlorhexidine
Investigational medicinal product code	
Other name	Hydrex
Pharmaceutical forms	Cutaneous solution
Routes of administration	Topical use

Dosage and administration details:

Alcoholic Chlorhexidine skin pre-op preparation

Investigational medicinal product name	Teicoplanin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Teicoplanin 400mg on induction. If penicillin allergic and on 5-day antibiotic arm then add clindamycin 300mg 4 times daily for further 4 days

Investigational medicinal product name	Clindamycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Clindamycin 300mg 4 times daily orally to be used in case of penicillin allergy

Arm title	24 Hour Antibiotic Group

Arm description:

Both treatment groups received 24 hours of intravenous (IV) treatment, consisting of three doses of 1.2g of amoxicillin with clavulanic acid and 500mg of metronidazole eight hours apart starting on induction of anaesthesia. In cases of amputations proximal to the transtibial level, a single weight-adjusted dose of gentamicin (7mg/Kg) was also administered on induction. Participants in the 24-hour treatment arm received no further antibiotics

Arm type	Active comparator
Investigational medicinal product name	Co-amoxiclav
Investigational medicinal product code	
Other name	Augmentin
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Augmentin 1.2g IV three times daily for 24 hours. If the patient is randomised to the 5-day duration antibiotic arm then Augmentin 625mg oral tablets three times daily are added to the 24 hour course for a further 4 days.

Investigational medicinal product name	Iodine
Investigational medicinal product code	
Other name	Povidone iodine
Pharmaceutical forms	Cutaneous solution
Routes of administration	Topical use

Dosage and administration details:	
Intra-operative skin preparation prior to incision to skin.	
Investigational medicinal product name	Metronidazole
Investigational medicinal product code	
Other name	Flagyl
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
500mg IV three times daily for 24 hours. If the patient is randomised to 5-day duration arm, then another 4 days of oral metronidazole at 400mg three times daily is added to the course	
Investigational medicinal product name	Chlorhexidine
Investigational medicinal product code	
Other name	Hydrex
Pharmaceutical forms	Cutaneous solution
Routes of administration	Topical use
Dosage and administration details:	
Alcoholic Chlorhexidine skin pre-op preparation	
Investigational medicinal product name	Teicoplanin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use
Dosage and administration details:	
Teicoplanin 400mg on induction. If penicillin allergic and on 5-day antibiotic arm then add clindamycin 300mg 4 times daily for further 4 days	

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Blinding of treating surgical team and participant was not performed. Blinding of the investigator assessing outcomes was achieved by having outcome assessments performed by a member of the research team who was unaware of treatment allocation.

Number of subjects in period 1	5-day Antibiotic Group	24 Hour Antibiotic Group
Started	81	80
Completed	76	76
Not completed	5	4
Death	5	4

Baseline characteristics

Reporting groups	
Reporting group title	5-day Antibiotic Group

Reporting group description:

Both treatment groups received 24 hours of intravenous (IV) treatment, consisting of three doses of 1.2g of amoxicillin with clavulanic acid and 500mg of metronidazole eight hours apart starting on induction of anaesthesia. In cases of amputations proximal to the transtibial level, a single weight-adjusted dose of gentamicin (7mg/Kg) was also administered on induction.

Those in the five-day treatment arm received further oral antibiotic prophylaxis with 625mg of Co-amoxiclav TDS and 400mg metronidazole administered three times a day for four days.

Reporting group title	24 Hour Antibiotic Group

Reporting group description:

Both treatment groups received 24 hours of intravenous (IV) treatment, consisting of three doses of 1.2g of amoxicillin with clavulanic acid and 500mg of metronidazole eight hours apart starting on induction of anaesthesia. In cases of amputations proximal to the transtibial level, a single weight-adjusted dose of gentamicin (7mg/Kg) was also administered on induction. Participants in the 24-hour treatment arm received no further antibiotics

Reporting group values	5-day Antibiotic Group	24 Hour Antibiotic Group	Total
Number of subjects	81	80	161
Age categorical Units: Subjects			
Age continuous Units: years			
median	65	66	
full range (min-max)	26 to 93	30 to 93	-
Gender categorical Units: Subjects			
Female	22	19	41
Male	59	61	120

End points

End points reporting groups

Reporting group title	5-day Antibiotic Group

Reporting group description:

Both treatment groups received 24 hours of intravenous (IV) treatment, consisting of three doses of 1.2g of amoxicillin with clavulanic acid and 500mg of metronidazole eight hours apart starting on induction of anaesthesia. In cases of amputations proximal to the transtibial level, a single weight-adjusted dose of gentamicin (7mg/Kg) was also administered on induction.

Those in the five-day treatment arm received further oral antibiotic prophylaxis with 625mg of Co-amoxiclav TDS and 400mg metronidazole administered three times a day for four days.

Reporting group title	24 Hour Antibiotic Group

Reporting group description:

Both treatment groups received 24 hours of intravenous (IV) treatment, consisting of three doses of 1.2g of amoxicillin with clavulanic acid and 500mg of metronidazole eight hours apart starting on induction of anaesthesia. In cases of amputations proximal to the transtibial level, a single weight-adjusted dose of gentamicin (7mg/Kg) was also administered on induction. Participants in the 24-hour treatment arm received no further antibiotics

Primary: Incidence of Surgical Site Infection

End point title	Incidence of Surgical Site Infection

End point description:

Incidence of SSI within 30 days of the procedure using the ASEPSIS score as an objective measure of wound healing. Occurrence of a SSI was defined as positive finding at any of the three follow-ups with an ASEPSIS score of ≥ 21.

End point type	Primary

End point timeframe:

30 days

End point values	5-day Antibiotic Group	24 Hour Antibiotic Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	76		
Units: score of ≥ 21				
number (not applicable)	9	30		

Attachments (see zip file)	ASSIT Choice of Statistical Tests/Choice of statistical tests.pdf

Statistical analyses

Statistical analysis title	Logistic regression analysis

Statistical analysis description:

Continuous data: If the data appeared normally distributed the Kolmogorov statistic or Shapiro Wilk statistic was utilized to confirm this, with a P value > 0.05 indicating normality. P values are quoted to 3 decimal places with values of less than 0.05 being considered significant

Categorical data: The primary test utilized was Pearson’s Chi squared test. If more than 20% of the expected frequencies were <5 or if any were <1 then the Fisher’s exact test was utilized.

Comparison groups	5-day Antibiotic Group v 24 Hour Antibiotic Group
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.05 [2]
Method	Chi-squared

Notes:

[1] - SPSS - see uploaded results for full analysis

[2] - The use of a 5-day antibiotic course was found to be associated with statistically significant 27.7% absolute risk reduction in the incidence of SSI (P=0.000096-Pearson’s $\chi 2$ test)

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events will be reported in accordance with the Trust's R&D department's Safety Reporting standard operating procedure (R&D GCP SOP 07) to ensure compliance with UK Clinical Trial Regulations.

Adverse event reporting additional description:

The AE reporting period for this trial begins as soon as patients have consented to the trial and ends 30 days after patient's operation date, which signifies the endpoint for the primary objective of this clinical trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

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

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: See plot 7 in study main results and findings file to see percentage of complications amongst all groups.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 August 2013	Change of antibiotics for patients with penicillin allergies.
12 February 2014	Patient sample size changed from 164 to 168 and SAE reporting requirements clarified
26 June 2014	To add third pre-op skin preparation alcoholic povidone iodine

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported