



Clinical trial results:

Antibiotic treatment for intermittent bladder catheterisation: A randomised controlled trial of once daily prophylaxis (The AnTIC study) Summary

EudraCT number	2013-002556-32
Trial protocol	GB
Global end of trial date	23 February 2017

Results information

Result version number	v1 (current)
This version publication date	09 June 2018
First version publication date	09 June 2018

Trial information

Trial identification

Sponsor protocol code	ANTIC:6672
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Additional study identifiers

ISRCTN number	ISRCTN67145101
ClinicalTrials.gov id (NCT number)	NCT02145338
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Sponsor organisation address	Freeman Hospital, Newcastle upon Tyne, United Kingdom, NE7 7DN
Public contact	Robert Pickard, Newcastle University, 44 1912137139, robert.pickard@ncl.ac.uk
Scientific contact	Robert Pickard, Newcastle University, 44 1912137139, robert.pickard@ncl.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	11 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 February 2017
Global end of trial reached?	Yes
Global end of trial date	23 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal research question was to determine whether use of antibiotic prophylaxis over 12 months resulted in a clinically significant (real and worthwhile) reduction in the rate of symptomatic, antibiotic-treated urinary tract infection (UTI) suffered by people performing intermittent self-bladder catheterisation compared to no prophylaxis. We also calculated which treatment strategy gives best value for money to patients and the NHS by measuring the cost per urinary infection avoided by use of antibiotic prophylaxis.

During the first 12 months of the trial we determined whether recruitment to planned trial duration and sample size was going to succeed by monitoring numbers of randomised participants. Specific objectives for the first phase of the study was to find out how quickly individual research sites could begin to recruit patients to the trial, to find out how many eligible patients are identified and how many of those agree to participate per month.

Protection of trial subjects:

The investigational medicinal products (IMP) used in the trial are all licensed in dosage and form for use in prophylaxis against UTI in the UK and are standard care for this indication. From this it was judged that from an IMP perspective the risk to participants was no higher than that of standard care.

Any adverse effects associated with the use of antibiotic prophylaxis related to individual agents or changes to normal bacterial flora, were described and minimized by carefully worded trial information given to participants to enable selection of the individually most appropriate agent and information concerning use of oral probiotics.

Participants with symptomatic urinary tract infection were encouraged to also take a catheter specimen of urine (CSU) to their treating clinician for local analysis according to local protocols.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	18 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 404
Worldwide total number of subjects	404
EEA total number of subjects	404

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)	223
From 65 to 84 years	172
85 years and over	9

Subject disposition

Recruitment

Recruitment details:

Recruitment took place between November 2013 and January 2016 through 51 primary and secondary care NHS research sites in England and Scotland. Sites were grouped around six UK hubs in Newcastle upon Tyne, Wakefield, Cambridge, Bristol, Southampton, Aberdeen and Glasgow.

Pre-assignment

Screening details:

Participants were identified when attending secondary care clinics, by search of NHS health records and from commercial organisations providing NHS care. Participants meeting inclusion criteria and willing to participate were consented to take part in the study. Those already taking antibiotic prophylaxis underwent a 3-month washout period.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The study design did not allow blinding of participants, clinicians or local research teams to allocation, although outcome assessors including laboratory staff and members of the central trial team involved in outcome adjudication were blinded to allocated group.

Arms

Are arms mutually exclusive?	Yes
Arm title	Antibiotic Prophylaxis

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Trimethoprim
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Once daily Trimethoprim (100mg)

Investigational medicinal product name	Nitrofurantoin
Investigational medicinal product code	
Other name	Aratoin
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Once daily Nitrofurantoin 50 mg (or 100 mg dependent on participant weight).

Investigational medicinal product name	Cefalexin
Investigational medicinal product code	
Other name	Ospexin, Tenkorex, Kiflone
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Once daily Cefalexin 250mg.

Arm title	No Prophylaxis
Arm description: -	
Arm type	Standard Care

Number of subjects in period 1	Antibiotic Prophylaxis	No Prophylaxis
Started	203	201
Completed	203	201

Period 2

Period 2 title	Primary analysis point
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Antibiotic Prophylaxis

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Trimethoprim
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Once daily Trimethoprim (100mg)

Investigational medicinal product name	Nitrofurantoin
Investigational medicinal product code	
Other name	Aratoin
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Once daily Nitrofurantoin 50 mg (or 100 mg dependent on participant weight).

Investigational medicinal product name	Cefalexin
Investigational medicinal product code	
Other name	Ospexin, Tenkorex, Kiflone
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Once daily Cefalexin 250mg.

Arm title	No Prophylaxis
Arm description: -	
Arm type	Standard Care
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Antibiotic Prophylaxis	No Prophylaxis
Started	203	201
Completed	181	180
Not completed	22	21
Consent withdrawn by subject	16	14
Death	-	1
Excluded from analysis insufficient data	6	6

Period 3

Period 3 title	12 month follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Antibiotic Prophylaxis
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Trimethoprim
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Once daily Trimethoprim (100mg)	
Investigational medicinal product name	Nitrofurantoin
Investigational medicinal product code	
Other name	Aratoin
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:	
Once daily Nitrofurantoin 50 mg (or 100 mg dependent on participant weight).	
Investigational medicinal product name	Cefalexin
Investigational medicinal product code	
Other name	Ospexin, Tenkorex, Kiflone
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Once daily Cefalexin 250mg.	
Arm title	No Prophylaxis
Arm description: -	
Arm type	Standard Care
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	Antibiotic Prophylaxis	No Prophylaxis
Started	181	180
Completed	181	180

Baseline characteristics

Reporting groups

Reporting group title	Antibiotic Prophylaxis
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Reporting group description: -

Reporting group title	No Prophylaxis
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Reporting group description: -

Reporting group values	Antibiotic Prophylaxis	No Prophylaxis	Total
Number of subjects	203	201	404
Age categorical			
Units: Subjects			
Adults (18-64 years)	114	109	223
From 65-84 years	86	86	172
85 years and over	3	6	9
Age continuous			
Units: years			
arithmetic mean	59.1	60.1	
standard deviation	± 17.0	± 15.6	-
Gender categorical			
Units: Subjects			
Female	88	87	175
Male	115	114	229
Number of UTI episodes			
Number of UTI episodes suffered in the 12 months prior to randomisation			
Units: Subjects			
<4	71	78	149
>=4	132	123	255
Cause of bladder dysfunction			
Units: Subjects			
Neurological	80	78	158
Non-neurological	123	123	246
Type of intermittent catheterisation			
Units: Subjects			
By self	201	198	399
By spouse/carer	1	2	3
Missing	1	1	2
Planned future duration of need for intermittent catheterisation			
Units: Subjects			
Between 1 and 2 years	0	4	4
Between 2 and 5 years	0	1	1
Indefinite	182	181	363
Not known	20	14	34
Missing	1	1	2
Route of intermittent catheterisation			
Units: Subjects			
Urethra	196	195	391
Mitrofanoff	6	5	11

Missing	1	1	2
Type of catheter used			
Units: Subjects			
Single use	200	199	399
Re-useable	2	2	4
Missing	1	0	1
Hydrophillic coated catheter used?			
Units: Subjects			
No	9	8	17
Yes	189	192	381
Missing	5	1	6
Main functional reason for requiring intermittent catheterisation			
Units: Subjects			
Bladder outlet obstruction	49	56	105
Bladder failure (underactivity)	139	128	267
Bladder augmentation / replacement	13	16	29
Missing	2	1	3
Central laboratory culture of urine at baseline			
Units: Subjects			
Negative	93	84	177
Positive	76	77	153
Missing	34	40	74
Creatinine clearance			
Units: CrCl (mL/min)			
median	89.8	99.1	
inter-quartile range (Q1-Q3)	68.6 to 121.4	71.9 to 124.2	-
Frequency of CISC (/24 hours)			
Frequency of clean intermittent self catheterisation in a 24 hour period.			
Units: Number of times			
arithmetic mean	3.8	4.1	
standard deviation	± 2.2	± 2.9	-
Episodes of UTI in last 12 months			
Episodes of UTI experienced by participant in the last 12 months			
Units: Episodes			
median	4.0	4.0	
inter-quartile range (Q1-Q3)	3.0 to 6.0	3.0 to 7.0	-
Positive urine culture reports in the last 12 months			
Units: Number			
median	2.0	2.0	
inter-quartile range (Q1-Q3)	1.0 to 4.0	1.0 to 4.0	-
Months use of antibiotic prophylaxis in last 12 months			
Units: Months			
median	0.0	0.0	
inter-quartile range (Q1-Q3)	0.0 to 1.0	0.0 to 1.0	-

End points

End points reporting groups

Reporting group title	Antibiotic Prophylaxis
Reporting group description: -	
Reporting group title	No Prophylaxis
Reporting group description: -	
Reporting group title	Antibiotic Prophylaxis
Reporting group description: -	
Reporting group title	No Prophylaxis
Reporting group description: -	
Reporting group title	Antibiotic Prophylaxis
Reporting group description: -	
Reporting group title	No Prophylaxis
Reporting group description: -	

Primary: Occurrence of symptomatic antibiotic-treated UTI

End point title	Occurrence of symptomatic antibiotic-treated UTI
End point description: Occurrence of clinical UTI was defined as the presence of symptoms together with taking a treatment course of antibiotic for UTI. This was measured by participant return of a UTI record for each event, as well as 3-monthly participant questionnaire and 3-monthly trial visit case report form (CRF) completed by the local research team.	
End point type	Primary
End point timeframe: Occurrence of symptomatic antibiotic-treated UTI over 12 months	

End point values	Antibiotic Prophylaxis	No Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	180		
Units: UTI				
All eligible	235	450		

Statistical analyses

Statistical analysis title	Symptomatic antibiotic treated UTI
Statistical analysis description: Results of performing Poisson regression (incidence rate ratio approach) for primary outcome: number of symptomatic antibiotic-treated UTI.	
Comparison groups	Antibiotic Prophylaxis v No Prophylaxis

Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Poisson regression
Parameter estimate	Incidence Rate Ratio
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.61
Variability estimate	Standard error of the mean
Dispersion value	0.04

Primary: Occurrence of symptomatic antibiotic-treated UTI (baseline <4)

End point title	Occurrence of symptomatic antibiotic-treated UTI (baseline <4)
End point description:	
Sub group analysis for participants with Baseline UTI <4	
End point type	Primary
End point timeframe:	
Occurrence of symptomatic antibiotic-treated UTI over 12 months	

End point values	Antibiotic Prophylaxis	No Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: UTI				
Baseline UTI <4	55	118		

Statistical analyses

Statistical analysis title	Symptomatic antibiotic treated UTI
Comparison groups	Antibiotic Prophylaxis v No Prophylaxis
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Poisson regression
Parameter estimate	Incidence Rate Ratio
Point estimate	0.46

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	0.64
Variability estimate	Standard error of the mean
Dispersion value	0.08

Primary: Occurrence of symptomatic antibiotic treated UTI (baseline ≥ 4)

End point title	Occurrence of symptomatic antibiotic treated UTI (baseline ≥ 4)
End point description:	
Sub group analysis for participants with baseline UTI ≥ 4	
End point type	Primary
End point timeframe:	
Occurrence of symptomatic antibiotic-treated UTI over 12 months	

End point values	Antibiotic Prophylaxis	No Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	112		
Units: UTI				
Baseline episodes of UTI ≥ 4	180	332		

Statistical analyses

Statistical analysis title	symptomatic antibiotic-treated UTI
Comparison groups	Antibiotic Prophylaxis v No Prophylaxis
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Poisson Regression
Parameter estimate	Incidence Rate Ratio
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.64
Variability estimate	Standard error of the mean
Dispersion value	0.05

Primary: Occurrence of symptomatic antibiotic-treated UTI (adjusted for days at risk)

End point title	Occurrence of symptomatic antibiotic-treated UTI (adjusted for days at risk)
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End point description:

Secondary analysis of primary outcome, adjusted for days at risk

End point type	Primary
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End point timeframe:

Occurrence of symptomatic antibiotic-treated UTI over 12 months

End point values	Antibiotic Prophylaxis	No Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	180		
Units: UTI				
All eligible	235	450		

Statistical analyses

Statistical analysis title	Symptomatic antibiotic-treated UTI
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Statistical analysis description:

Adjusted for days at risk

Comparison groups	No Prophylaxis v Antibiotic Prophylaxis
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Number of subjects included in analysis	361
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	< 0.001
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Method	Poisson Regression
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Parameter estimate	Incidence Rate Ratio
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Point estimate	0.5
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	0.43
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upper limit	0.58
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Variability estimate	Standard error of the mean
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Dispersion value	0.04
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Primary: Occurrence of symptomatic antibiotic-treated UTI (adjusted for days at risk and stratification)

End point title	Occurrence of symptomatic antibiotic-treated UTI (adjusted
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for days at risk and stratification)

End point description:

Secondary analysis of primary outcome adjusted for days at risk and stratification factors

End point type	Primary
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End point timeframe:

Occurrence of symptomatic antibiotic-treated UTI over 12 months

End point values	Antibiotic Prophylaxis	No Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	180		
Units: UTI				
All eligible	235	450		

Statistical analyses

Statistical analysis title	Occurrence of symptomatic antibiotic-treated UTI
Comparison groups	Antibiotic Prophylaxis v No Prophylaxis
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Poisson Regression
Parameter estimate	Incidence Rate Ratio
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.58
Variability estimate	Standard error of the mean
Dispersion value	0.04

Secondary: Treatment Satisfaction (TSQM)

End point title	Treatment Satisfaction (TSQM)
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End point description:

Satisfaction with treatment measured using the Treatment Satisfaction with Medication Questionnaire (TSQM). Maximum rating = 100 for each domain.

Using ANCOVA modelling to compare arms (adjusting for stratification factors):

Effectiveness $p < 0.001$

Side-effects $p = 0.94$

Convenience $p < 0.001$

Overall $p < 0.001$

Overall satisfaction score for prophylaxis participants was 74. The TSQM is not validated for 'no treatment' strategies in an open-label RCT setting but overall this group rated mean overall satisfaction as 63.

End point type	Secondary
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End point timeframe:

12 months

End point values	Antibiotic Prophylaxis	No Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144 ^[1]	109 ^[2]		
Units: Scale Score				
arithmetic mean (standard deviation)				
Effectiveness	78.0 (± 19.1)	66.3 (± 19.5)		
Side-effects	67.4 (± 23.4)	67.2 (± 24.2)		
Convenience	88.9 (± 13.9)	78.2 (± 21.4)		
Overall satisfaction	73.8 (± 25.4)	63.0 (± 24.3)		

Notes:

[1] - Effectiveness n=144, Side-effects n=22, Convenience n=144, Overall n=143

[2] - Effectiveness n=108, Side-effects n=32, Convenience n=109, Overall n=109

Statistical analyses

No statistical analyses for this end point

Secondary: eGFR at Baseline and 12 months

End point title	eGFR at Baseline and 12 months
End point description:	Estimated Glomerular Filtration Rate (eGFR) measuring kidney function with comparison between arms
End point type	Secondary
End point timeframe:	
Baseline and 12 months	

End point values	Antibiotic Prophylaxis	No Prophylaxis	Antibiotic Prophylaxis	No Prophylaxis
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	200 ^[3]	197 ^[4]	123 ^[5]	140 ^[6]
Units: ml/minute				
arithmetic mean (standard deviation)	86.6 (± 30.2)	88.0 (± 26.1)	82.3 (± 30.0)	83.3 (± 27.6)

Notes:

[3] - Baseline

[4] - Baseline

[5] - 12 months

[6] - 12 months

Statistical analyses

No statistical analyses for this end point

Secondary: Change in eGFR from Baseline

End point title	Change in eGFR from Baseline
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End point description:	
Change in estimated glomerular filtration rate (eGFR) at 12 months from baseline.	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Antibiotic Prophylaxis	No Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	138		
Units: ml/minute				
arithmetic mean (standard deviation)	-2.1 (± 15.0)	-3.4 (± 14.2)		

Statistical analyses

Statistical analysis title	Change in eGFR at 12 months
Comparison groups	No Prophylaxis v Antibiotic Prophylaxis
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48
Method	ANCOVA

Secondary: ALT at Baseline and 12 months

End point title	ALT at Baseline and 12 months
End point description:	
Serum alanine transaminase (ALT) measured at baseline and 12 months, with comparison between arms.	
End point type	Secondary
End point timeframe:	
Baseline and 12 months	

End point values	Antibiotic Prophylaxis	No Prophylaxis	Antibiotic Prophylaxis	No Prophylaxis
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	198 ^[7]	188 ^[8]	118 ^[9]	135 ^[10]
Units: U/L				
arithmetic mean (standard deviation)	24.7 (± 19.9)	24.1 (± 15.6)	26.1 (± 19.1)	24.0 (± 14.1)

Notes:

[7] - Baseline

[8] - Baseline

[9] - 12 months
[10] - 12 months

Statistical analyses

No statistical analyses for this end point

Secondary: Change in ALT at 12 months

End point title	Change in ALT at 12 months
End point description:	Change in serum alanine transaminase (ALT) at 12 months
End point type	Secondary
End point timeframe:	12 months

End point values	Antibiotic Prophylaxis	No Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	128		
Units: U/L				
arithmetic mean (standard deviation)	1.2 ($\pm$ 19.5)	-0.3 ($\pm$ 14.7)		

Statistical analyses

Statistical analysis title	Change in ALT at 12 months
Comparison groups	Antibiotic Prophylaxis v No Prophylaxis
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5
Method	ANCOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported for the duration of the trial and for 4 weeks after the trial intervention was stopped.

Assessment type	Systematic
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Dictionary used

Dictionary name	Verbatim
Dictionary version	1.0

Reporting groups

Reporting group title	Antibiotic Prophylaxis
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Reporting group description: -

Reporting group title	No Prophylaxis
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Reporting group description: -

Serious adverse events	Antibiotic Prophylaxis	No Prophylaxis	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 203 (9.85%)	22 / 201 (10.95%)	
number of deaths (all causes)	0	3	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Bilateral pulmonary embolism			
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Polypharmacy	Additional description: Falls and confusion, left sided pneumonia		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Car accident	Additional description: Admitted for medical observation after car accident		

subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Admitted to hospital for observation and review	Additional description: CT head - new intracranial changes		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain, dizziness and vomiting			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Collapsed while driving	Additional description: ?CVA, ?seizure disorder		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache and nausea	Additional description: Emergency admission to hospital		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache and right-sided neck pain	Additional description: Shunt malfunction		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical fall			

subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rigors	Additional description: On parenteral nutrition		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident	Additional description: bilateral femoral fractures and right distal tibial fracture		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizures and collapse			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unable to catheterise Mitrofanoff adequately			
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasovagal episode			
subjects affected / exposed	0 / 203 (0.00%)	2 / 201 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Abdominal aortic aneurysm			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma attack	Additional description: Acute asthma attack and anxiety		

subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest infection			
subjects affected / exposed	0 / 203 (0.00%)	2 / 201 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Carbon monoxide poisoning			
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Triple bypass surgery			
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dysphagia			
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis relapse			
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right-sided weakness attributed to somatoform disorder			

subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transverse myelitis			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Neuromyelitis optica			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Oesophageal cancer metastatic			
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal pain due to faecal loading			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain/constipation			
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epigastric pain			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecal impaction			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perforated appendix			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Recurrent vomiting and generalised abdominal discomfort			
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Adverse drug reaction	Additional description: Asymptomatic highly raised serum liver enzyme alanine transaminase (ALT)		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Bladder cancer			
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematuria post TURP			
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria post intravesical botulinum toxin			
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trans-urethral resection of bladder tumour			

subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
sub-meatal and urethral strictures			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Follicular thyroid cancer			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (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			
Fall	Additional description: Fall resulting in fractured spine		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute chronic back pain			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis	Additional description: Right foot, diagnosed with Charcot's joint.		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post microdiscectomy recurrent lumbar pain			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ankle stabilisation			
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ruptured left quadriceps tendon subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (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			
Hickman line infection subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Percutaneous gastric feeding tube site infection			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Antibiotic Prophylaxis	No Prophylaxis	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 203 (31.53%)	55 / 201 (27.36%)	
Vascular disorders			
painful varicocele subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Ruptured blood vessel left foot subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
ACE subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Biopsy for microcalcification of lump, left breast subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Biopsy of skin lesion			

subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0
Bladder pressure test for neobladder		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	1
Botox treatment		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	1
Corrective surgery to right foot		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0
Cystoscopy		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	1
Elective admission for dilatation of mitrofanoff and neo bladder washout		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0
Elective admission for SCS insertion		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0
Elective admission for stricture dilatation		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0
Elective day case for embolisation of varicocele		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	1
Elective microdisectomy		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0
Elective perineal proctectomy		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	1
Elective surgery to investigate thickening in bladder wall		

subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	1
Elective TURP		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	1
Elective TURP leading to long term catheterisation		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0
Endoscopy		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0
Fasciectomy (routine planned admission)		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	1
Elective admission for revision of Mitrofanoff		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	1
Knee replacement		
subjects affected / exposed	1 / 203 (0.49%)	1 / 201 (0.50%)
occurrences (all)	1	1
Elective mastoidectomy		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	1
Neo vascular surgery (AMD) to right eye		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	1
Botox injection for overactive bladder		
subjects affected / exposed	2 / 203 (0.99%)	0 / 201 (0.00%)
occurrences (all)	2	0
Sacral nerve stimulation for overactive bladder		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0
Elective thyroid surgery		

subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Elective below knee amputation subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	1 / 201 (0.50%) 1	
Rectal irrigation for constipation subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Biopsy of prostate subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Transurethral prostatectomy subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	1 / 201 (0.50%) 1	
General disorders and administration site conditions			
Abnormal GGT noted on checking routine liver function subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Achilles subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	1 / 201 (0.50%) 1	
Admitted to EAU for headache subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	1 / 201 (0.50%) 1	
Adverse reaction to Nitrofurantoin subjects affected / exposed occurrences (all)	2 / 203 (0.99%) 2	0 / 201 (0.00%) 0	
Attended AE ?DVT subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Attended AE for ? TIA subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Attended ED with ? chest pain. Discharged same night			

subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Attended ED with increase swollen leg, woozy and light-headed	Additional description: possible side effect of Citalopram		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Attended ED for ? obstructed bowel. Discharged same day			
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Migraine (issue with shunt?)			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Attended A&E for ? cause			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Blackout whilst driving			
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Car accident	Additional description: car reversed into patient		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Cat bite			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Collapse of right leg			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Lower back pain and groin pain			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Contusion (head)			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Decline in WCC			

subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0
Dysphagia		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	1
Generalised joint pain of sudden onset		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	1
Head cold		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0
Hoarseness (exacerbation)		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	1
Insomnia		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	1
Laryngitis		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	1
Malaise		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	1
pain right wrist		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0
pain and discomfort in toes of both feet		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0
Reaction to Nitrofurantoin prescribed for UTI		
subjects affected / exposed	1 / 203 (0.49%)	1 / 201 (0.50%)
occurrences (all)	1	1
Elevated potassium		

subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Vulval lumps	Additional description: Antibiotic given for ? infection		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Thinning hair			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Blotchy rash on back			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Rash on inner arms, palms and back of neck			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Patient reported collapse on the way to buy papers			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Pulled VP shunt			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Pressure sore			
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	2	
Pruritis vulvae			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
PV bleed			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Reaction to flucloxacillin			

subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Reaction to trimethoprim			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Scalp itchiness			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Sore throat			
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Stomach discomfort			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Stopped prophylactic cephalixin due to stomach issues			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Stopped prophylactic antibiotics on microbiologist advice			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Vitamin D deficiency			
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Weight loss			
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Breathless			
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Chest infection			
subjects affected / exposed	0 / 203 (0.00%)	2 / 201 (1.00%)	
occurrences (all)	0	2	
Chesty cough			

subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	1 / 201 (0.50%) 1	
Common cold subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	1 / 201 (0.50%) 1	
Cough (exacerbation) subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	1 / 201 (0.50%) 1	
Bronchiectasis subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	1 / 201 (0.50%) 1	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 203 (1.48%) 3	3 / 201 (1.49%) 3	
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	1 / 201 (0.50%) 1	
Investigations Ultrasound investigation subjects affected / exposed occurrences (all)	Additional description: Found hydrocele in right testicle and bilateral epididymal cysts		
	0 / 203 (0.00%) 0	1 / 201 (0.50%) 1	
Routine cystoscopy subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Urodynamics subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Injury, poisoning and procedural complications Burn right foot, infection subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	1 / 201 (0.50%) 1	
Fall due to back pain after sneezing subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	1 / 201 (0.50%) 1	
Fractured ribs due to fall			

subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Injury to urethra from catheter subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Post op redness of second toe subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	1 / 201 (0.50%) 1	
Severe pain right knee due to fall subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Nervous system disorders Migraine subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	1 / 201 (0.50%) 1	
Night sweats increased subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	1 / 201 (0.50%) 1	
Epileptic fit subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	1 / 201 (0.50%) 1	
Blood and lymphatic system disorders Decline in WBC and platelets subjects affected / exposed occurrences (all)	Additional description: Study drug discontinued		
	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Ear and labyrinth disorders Increased tinnitus following VP shunt revision subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Eye disorders Anteria Uveitis left eye			

subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	1 / 201 (0.50%) 1	
Fluid behind eyes bilaterally subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	1 / 201 (0.50%) 1	
Blurred vision subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Diarrhoea and sickness subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Diarrhoea subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	1 / 201 (0.50%) 4	
Diarrhoea and vomiting subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Irritable bowel syndrome subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Mild intermittent nausea subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 4	0 / 201 (0.00%) 0	
Nausea subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	1 / 201 (0.50%) 1	
Pancreatitis subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Viral gastroenteritis subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	1 / 201 (0.50%) 1	

Skin and subcutaneous tissue disorders Two actinic keratoses on left side of upper nose subjects affected / exposed occurrences (all) Rash on chest, legs and feet subjects affected / exposed occurrences (all) Basal cell carcinoma subjects affected / exposed occurrences (all) Blotchy rash subjects affected / exposed occurrences (all) Cellulitis subjects affected / exposed occurrences (all) Exacerbation of dermatitis subjects affected / exposed occurrences (all) Exacerbation of leg ulcers subjects affected / exposed occurrences (all) Itchy rash subjects affected / exposed occurrences (all) Itchy skin with excoriation subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	1 / 201 (0.50%) 1	
	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
	Additional description: Removed with complete excision		
	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
	0 / 203 (0.00%) 0	1 / 201 (0.50%) 2	
	0 / 203 (0.00%) 0	1 / 201 (0.50%) 1	
	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Renal and urinary disorders Admitted to Emergency assessment unit for query renal colic subjects affected / exposed occurrences (all) Attended ED for UTO subjects affected / exposed occurrences (all) Decline in renal function noted in	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
	Additional description: Prophylaxis stopped		

biochemistry		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0
Frank haematuria caused by kink in hi catheter		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	1
Frank haematuria requiring flexible cystoscopy		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	1
Frank haematuria with pre-existing non functioning right kidney		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0
Haematuria and retention		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	1
Left renal cyst increase in size to 5cm		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0
Pain in transplanted kidney		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	1
Nocturia		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	1
Incontinence		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	1
Frank blood in urine		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0
Periodic urethritis		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0
Renal pain		

subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Thickening of bladder wall subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	1 / 201 (0.50%) 1	
Musculoskeletal and connective tissue disorders			
Acupuncture for back pain subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Back pain/fall subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	1 / 201 (0.50%) 1	
Cervical spondylosis (exacerbation) subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	1 / 201 (0.50%) 1	
Tennis elbow, cortisone injection subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Decompression of L4 and L5 through degenerative changes subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Pain base of right thumb subjects affected / exposed occurrences (all)	Additional description: exacerbation osteoarthritis		
	0 / 203 (0.00%) 0	1 / 201 (0.50%) 1	
Infections and infestations			
Dental abscess subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Ear Infection subjects affected / exposed occurrences (all)	0 / 203 (0.00%) 0	1 / 201 (0.50%) 2	
Oral infection subjects affected / exposed occurrences (all)	1 / 203 (0.49%) 1	0 / 201 (0.00%) 0	
Oral thrush and constipation			

subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0
Thrush in mouth		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0
Yeast infection		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0
Oral fungal infection		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	1
Septic toe		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0
Sinus infection		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0
Slight infection to left teste		
subjects affected / exposed	0 / 203 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	1
Tennis elbow, infected soft tissue		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0
Thrush		
subjects affected / exposed	2 / 203 (0.99%)	1 / 201 (0.50%)
occurrences (all)	2	1
Tonsillitis		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0
Wound infection to knee after fall		
subjects affected / exposed	1 / 203 (0.49%)	0 / 201 (0.00%)
occurrences (all)	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 November 2013	Widening of inclusion criteria to include those who had had one serious UTI – in line with options that would be offered in standard care. More frequent participant contact – to help participants as much as possible to complete UTI log and avoid ascertainment bias. Payment of any prescription charge to avoid participants being out of pocket. £20 gift to participants on study entry Use of calculated creatinine clearance rather than eGFR – in line with recent NHS guidance for use of nitrofurantoin as UTI prophylaxis.
13 May 2014	The protocol was updated to make it clear that washout participants should be consented at the beginning of the washout period, but not randomised until the washout period was complete The protocol was also amended to clarify that an active, symptomatic UTI did not exclude a participant from the study and that consent to participate could still be taken, but that the UTI should be treated before a participant could be randomised.
14 May 2014	Update to the contraindications section of the SmPC for Nitrofurantoin concerning patients with kidney dysfunction with an eGFR of less than 45 ml/minute. The study protocol and all study documentation were amended to reflect this update.
30 July 2015	Change to the protocol to allow sites to send a second invitation letter to participants who had not responded to the initial invitation to the study.
17 August 2016	Update to clarify the wording around the approved RSI for the study. The RSI contained in section 4.8 of the SmPC for the three antibiotics used in the study was submitted to MHRA for approval. The updated SmPC for nitrofurantoin, trimethoprim and cefalexin were included in the appendices of the new protocol

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/29766842>