Biostatistics Research Group,
Population Health Sciences Institute,
Newcastle University

ALternatives **T**o prophylactic **A**ntibiotics for the treatment of **R**ecurrent urinary tract infection in women

Statistical Analysis Plan
SAP Version number: 2.0
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This statistical analysis plan is based on protocol version 1.4 [20/06/2018]

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This current version of the SAP and all preceding versions will be stored in the Statistical Section of Trial Master File held by the Biostatistics Research Group, Newcastle University.

This statistical analysis plan (SAP) provides a framework and guidelines for the statistical analysis and reporting of the ALTAR trial.

This SAP applies to a clean and validated dataset. Detailed information on data collection tools, data validation, consistency and accuracy checks and data storage and archiving can be found in the current version of the Data Management Plan (version 2.0 [08/01/2019]).

Any deviation from the methods outlined in this SAP will be documented in the statistical end of trial report. Example Tables, Figures and Listings are for illustrative purposes only and are subject to change.

This SAP, along with all other documents relating to the analysis of this trial, will be stored in the 'Statistical Section' of the Trial Master File (TMF) held and maintained by the Biostatistics Research Group, Newcastle University. The final signed SAP will also be stored in section 16 of the main TMF (16. Statistics / 16.1 Final signed Statistical Analysis Plan).

Document history

Version	Date	Main changes made	Justification for change
1.0	19/11/2016	First version	
1.1	02/08/2017	Further explanation added to sample size calculation	For clarity and reproducibility
		Figures and tables for DMC and end of trial reporting updated and added to main body of analysis plan	Further detail required
		Definition of incidence and incident density rate expanded	For clarity
		Further clarification of analysis strategy	For clarity
2.0	04/11/2019	Clarification of the principal population for analysis of the primary outcome measure: a modified ITT population including all patients randomised with at least 6 months follow-up data.	To account for loss to follow-up. At least 6 month data felt to be needed to reliably estimate UTI rate.
		Definition of per-protocol population expanded to define participants who received treatment in accordance with the protocol as those who achieved 90% compliance. Added that exclusions from the per-protocol population will be listed.	More detail required. Exclusions will be listed as per GCP recommendations.
		Added detail on coding of primary outcome and primary outcome review.	More technical detail and elaboration required for clarity and reproducibility
		Expanded definition of secondary outcomes	More technical detail and elaboration required for clarity and reproducibility
		Tolerability of prophylactic treatment and problems with treatment antibiotics reported by the participant added to the analysis of safety data	This data is to be reported descriptively to supplement AE data.
		Formatting changes made to reflect Biostatistics Research Group SAP Template v0.8 [24/01/2018].	To comply with most recent SAP template
		Removed Valentina Mamasoula as trial statistician	Change in staff

Contents

1. INTRODUCTION

1.1 Background and rational

Continuous low-dose prophylactic antibiotic therapy is the current standard of care for the prevention of recurrent urinary tract infection (rUTI), however this can lead to an increase in antimicrobial resistance and subsequent difficult-to-treat infections. The ALTAR trial is designed to evaluate the clinical benefit, as assessed by the incidence of symptomatic antibiotic-treated UTI's over 12 months, of the best candidate alternative treatment for the prevention of rUTI, the urinary antiseptic Methenamine hippurate.

1.2 Objectives

Primary objective:

The primary objective is to determine the relative clinical effectiveness and cost effectiveness for the NHS of two licensed preventative treatments for women with rUTI over a 12 month treatment period.

Secondary objectives:

i. The occurrence of symptomatic UTI in the 6 month follow up period after discontinuing the allocated preventative therapy.
ii. Total urinary specific antibiotic use during both the treatment (12 months) and follow-up (6 months) phases of the trial.
iii. Antimicrobial resistance in the primary uropathogen *Escherichia coli* during both the treatment and follow-up phases of the trial.
iv. Number of microbiological-proven UTIs.
v. Incidence of asymptomatic bacteriuria (ABU).
vi. Hospitalisation due to UTI.
vii. Participant satisfaction with treatment.
viii. Embedded qualitative analysis of patients' and clinicians' views of the study processes and experience of participation. The aim is to explore patient and clinicians' observations on trial recruitment, conduct and acceptability
ix. Incremental Cost per Quality of Life Year (QALY) gained over the 18-month period based on responses to EQ-5D-5L.
x. Incremental Costs to the NHS, personal social services measured at the end of the 18-month period.
xi. Relative health economic efficiency over the longer term estimated using a modelling exercise.

Details of the cost effectiveness component of the primary objective, as well as secondary health economic objectives (ix-xi) will be documented elsewhere (health economic analysis plan) and are outside the scope of this statistical analysis plan. Details of qualitative analyses (objective viii) are also outside the scope of this statistical analysis plan.

2. STUDY METHODS

2.1 Trial design

ALTAR is a randomised, multicentre, pragmatic open-label phase IV non-inferiority trial comparing two licensed treatments for the prevention of rUTI. Adult women with rUTI who have decided that prophylaxis is an appropriate option will be randomised (1:1) to receive daily antibiotic (nitrofurantoin, trimethoprim or cefalexin) or twice daily antiseptic (Methenamine hippurate) for 12 months.

The antibiotic selected for use as prophylaxis will be determined by the responsible clinician with regard to patient characteristics such as previous use, allergy, renal function, liver function and prior urine cultures, local guidance, and standardised trial information with preferred agents being: nitrofurantoin first, trimethoprim second, cefalexin third.

In addition to trial treatment all participants will receive usual care including use of on demand discrete treatment antibiotic courses for UTI.

The trial hypothesis is that the non-antibiotic treatment (Methenamine hippurate) is non-inferior to the standard treatment of extended course prophylactic antibiotic for prevention of rUTI in women.

2.2 Study setting and patient population

Patients will be recruited from large, secondary care urology centres with a consistent clinical assessment pathway for women with rUTI.

Inclusion criteria:

- Women aged 18 years and over.
- Women with rUTI who, in consultation with a clinician, have decided that prophylaxis is an appropriate option (to include women who have suffered at least three episodes of symptomatic UTI within the preceding 12 months or two episodes in the last 6 months or a single severe infection requiring hospitalisation).
- Able to take a once daily oral dose of at least one of nitrofurantoin, or trimethoprim, or cephalexin.
- Able to take Methenamine hippurate.
- Women who agree to take part in the trial but who are already taking Methenamine or antibiotic prophylaxis will be consented for participation and will stop their preventative therapy for a 3-month washout period. They will then be reassessed and if still eligible undergo baseline assessment and randomisation.
- Able to give informed consent for participation in trial.
- Able and willing to adhere to an 18-month study period.

Exclusion criteria:

- Women unable to take Methenamine hippurate e.g. known allergy to Methenamine hippurate, severe hepatic impairment (Childs–Pugh class C, score of 10 or more, see appendix 3), gout, eGFR < 10 ml/min, Proteus sp. As consistent proven causative organism for rUTIs.
- Women who are unable to take nitrofurantoin and trimethoprim and cefalexin
- Women with correctable urinary tract abnormalities that are considered to be contributory to the occurrence of rUTI.
- Presence of symptomatic UTI – this will be treated and symptoms resolved prior to randomisation.
- Pregnancy or intended pregnancy in next 12 months.

- Women who are breast feeding.
- Women already taking Methenamine or antibiotic prophylaxis and declining a 3-month washout period.

2.3 Randomisation and blinding

Randomisation will be administered centrally by the Newcastle Clinical Trials Unit (NCTU) secure web-based system. Random permuted blocks of variable length will be used to allocate participants 1:1 to the antibiotic and antiseptic groups. An individual not otherwise involved with the study produced the final randomisation schedule. Stratification was by two variables; prior frequency of UTI (<4 episodes per year or ≥ 4 episodes per year), and menopausal status of participants (pre-menopausal or menopausal/post-menopausal) to ensure balanced allocation within these factors.

There is no participant blinding in this study. The members of the local research team who carry out the follow-up process will not be blind to the allocated treatment for each participant. The trial statistician (Helen Mossop) has been involved in preparing unblind reports to the DMC. The senior statistician responsible for approving this Statistical Analysis Plan has not reviewed any unblind data by randomised treatment group and will remain blind until the data is locked for the primary analysis.

2.4 Definition of outcome measures

2.4.1 Primary endpoint

The primary clinical outcome will be the incidence of symptomatic, antibiotic treated UTI, self-reported by participants over the 12 month treatment period.

The ***incidence of UTI*** will primarily be defined simply in each group as;

$$\frac{\textit{Total episodes of symptomatic UTI}}{\textit{Total observational period (years)}}$$

Secondary analysis will also be based on the ***incident density rate***, calculated in each group as;

$$\frac{\textit{Total episodes of symptomatic UTI}}{\textit{Total observational period (years)-Total time taking therapeutic antibiotics for UTI (years)}}$$

The 'observational period' will be calculated for each participant as the time from randomisation to the date of the Month 12 participant review. If the Month 12 review took place more than 1 year from randomisation the observational time will be capped at 1 year. If the participant did not attend their Month 12 visit the observational period will be calculated as the time from randomisation to their last attended monthly visit (either face-to-face or telephone contact) or the completion date of the last UTI Log or Phone reported UTI record prior to Month 12, whichever is later. For participants who have withdrawn but allowed continued use of routine data sites will be requested to check healthcare records for episodes of UTI once the participant would have reached the 12 month time point. Where this is done the participants observation time will be 1 year.

The time spent taking therapeutic antibiotics for UTI will be defined as for the therapeutic component (for UTI) of the secondary outcome 'Antibiotic use during treatment (12 months) and follow-up (6 months)', see below.

An episode of UTI will be defined as the presence of at least one patient-reported or clinician recorded symptom from a predefined list (fever, shivers, cloudy urine, smelly urine, visible blood in urine, urinary

leakage, lower abdominal pain, feeling generally unwell, frequent passing of urine, pain when passing urine) together with taking a discrete treatment course of antibiotic prescribed by a clinician or as part of patient-initiated self-start treatment. The end of a single episode of UTI is defined as 14 days after the end of the final treatment course of antibiotics. If a further course of antibiotics is prescribed, or symptoms re-started, before the end of the 14 days this is not counted as a separate episode.

The primary outcome will be determined by collection of the following data:

Form	Time point of data collection	Data captured
Participant UTI Log	Completed by the participant at the time of UTI and posted to central trial office for data entry	Antibiotic treatments and symptoms are reported
Antibiotic treated UTI Episode	Completed with trial staff at 3 monthly follow up visits	Antibiotic treatments and symptoms are reported
Phone Reported UTI	Completed by trial staff if a participant calls to report a UTI	Antibiotic treatments and symptoms are reported
Antibiotic Treatments	3 monthly review of hospital and primary care records for antibiotic treatments for UTIs	Antibiotic treatments are reported
Participant Questionnaire UTI Episodes	3 monthly participant completed questionnaire. Antibiotic treatments for UTI's are reported	Antibiotic treatments are reported

Where there are multiple reports of the same antibiotic treatment course but with inconsistent dates then one copy is kept based on the following hierarchy of evidence;

1) Antibiotic Treatments
2) Participant UTI Log
3) Phone reported UTI
4) Antibiotic treated UTI Episode
5) Participant Questionnaire UTI Episodes

A maximum of 30 days from the start of symptoms to the start of an antibiotic course is allowed for the data to count towards the same episode.

Episodes of UTI will primarily be identified by the trial statistician using statistical programming. A more technical elaboration of the data coding process is detailed in the document ALTAR Primary Outcome Coding Process v1.1 [18/07/2019], located in (S:\School Statistics\NCTU\ALTAR\3. Statistical Analysis Plan\Primary Outcome Coding) and stored as a hardcopy in the Statistical Section of the TMF.

A clinician not otherwise involved in the trial will independently review a random selection of participants to determine episodes of UTI, blind to treatment allocation. Should there be major discrepancies in the attribution of primary outcome events between the independent reviewer and trial statistician a further sample may be required to be checked or changes made to the statistical programming, as necessary. In addition to reviewing a random sample of cases the independent reviewer will also review any participants reporting only an 'other' symptom and not a pre-specified symptom to determine if the symptom is attributable to UTI (these will also be confirmed by the Chief Investigator (CI), blind to treatment allocation), any cases with a missing end date of antibiotic use and any other complicated cases requiring manual review, at the discretion of the trial statistician.

Further details of the primary outcome review process is documented in the Primary outcome review document v0.2 [29/10/2018], located in (S:\School Statistics\NCTU\ALTAR\PRIMARY OUTCOME REVIEW\Documentation\Instructions) and as a hardcopy in the Statistical Section of the TMF.

2.4.2 Secondary endpoints

Occurrence of symptomatic UTI in the 6 months follow up period after stopping the allocated preventative therapy

The incidence and incident density rate of symptomatic UTI in the 6 month follow up period will be defined as for the primary endpoint. The 6 month follow up period will be defined as the 6 months following the planned treatment end date, i.e. 12 months from randomisation. The definition of an episode of UTI will be as for the primary endpoint.

Antibiotic use during treatment (12 months) and follow-up (6 months)

The use of both prophylactic and therapeutic antibiotics will be recorded.

Prophylactic - this will be defined as the number of days patients are *prescribed* antibiotics at a low-dose intended for prophylaxis against UTIs. Although for one arm of the study this will be their allocated treatment measuring this outcome is intended to capture the prophylactic antibiotic use of patients who are initially allocated to the urinary antiseptic arm and need to change treatment for any reason.

Definition of prophylactic antibiotic use during treatment:

- For participants randomised to antibiotic prophylaxis this be defined as the time from their first prescription (or randomisation if the date of first prescription is unavailable) until their Month 12 visit or, if the Month 12 review took place more than 1 year from randomisation the time will be capped at 1 year. If the participant did not attend their Month 12 visit the time will be calculated as the time from randomisation to their last attended monthly visit (either face-to-face or telephone contact). If the participant has stopped treatment or switched to Methenamine hippurate then the time will be calculated as the time from randomisation to the date of stopping or switching.
- For participants randomised to Methenamine hippurate this will be defined as the time from switching treatment to antibiotic prophylaxis until their Month 12 visit or, if the Month 12 review took place more than 1 year from randomisation the end date will be capped at 1 year from randomisation. If the participant did not attend their Month 12 visit the end date will be their last attended monthly visit (either face-to-face or telephone contact). If the participant has stopped treatment with antibiotic prophylaxis then the end date will be the date of stopping.

Note that this outcome will report the number of days of prescribed prophylactic antibiotics. Compliance with prescribed treatment will be summarised as described in Section 4.3: Treatment Compliance.

Prophylactic antibiotic use during follow-up will be calculated as the time from the start to end of prophylactic antibiotic treatment reported on the Month 15 and Month 18 Staff Actions eCRF. If the participant is continuing treatment after Month 18 the time will be capped at 6 months.

Therapeutic for UTI - the use of therapeutic antibiotics will also be recorded and this will be defined as the number of days patients are prescribed (including previous prescription for self-start therapy) therapeutic (as opposed to prophylactic) doses of antibiotics for breakthrough UTIs during the treatment period of 12 months following allocation to either the prophylactic antibiotic or urinary antiseptic groups and also, separately, the 6 month follow up period. Antibiotic treatment courses will be those identified following data processing from the primary outcome measure and will include antibiotic treatment courses for UTI but where there are no symptoms reported. Care will be taken to avoid double counting of any overlapping treatment courses. Where an end date of a treatment course is missing a period of 5 days will be used as a surrogate.

The rate of therapeutic antibiotic use will be calculated as the total number of days therapeutic antibiotics were prescribed in each randomised group divided by the total observational period (in days).

Therapeutic for other reason **-** antibiotics taken for reasons other than UTI will also be recorded given the potential activity against uropathogens. The number of days patients are prescribed therapeutic antibiotics for reasons other than UTI will be calculated. Care will be taken to avoid double counting of any overlapping treatment courses. The rate of therapeutic antibiotic use for reasons other than UTI will be calculated as the total number of days therapeutic antibiotics were prescribed for reasons other than UTI in each randomised group divided by the total observational period (in days).

Adverse effects

We will analyse and report the adverse effects reported by participants and clinicians related to both antiseptic and prophylactic antibiotic use over the 12 month treatment and subsequent 6 month follow-up period. Further detail can be found in Section 6: Safety.

Antimicrobial resistance

Ecological change in terms of type of bacteria and their resistance patterns in isolates from i) mid-stream urine samples and ii) faecal reservoir (via optional rectal or perineal swabs) during the 12 month treatment period and in the 6 months following completion of treatment will be explored.

Participants will be requested to submit urine samples to the central laboratory when they suspect a UTI based on symptoms and routinely at baseline, 3, 6, 9, 12, 15, and 18 months. Optional perineal swabs will also be requested at baseline, 6, 12 and 18 months. Antimicrobial resistance of up to two types of bacteria isolated from each urine sample will be reported and of E.coli isolated from perineal swabs.

Antibiotic resistance in routine urine samples – these samples will be those taken at routine baseline and 3 monthly visits. Primarily we will report antimicrobial resistance to E.coli. At each time point and for each antibiotic tested (with sufficient data available) the proportion of participants with E.coli isolates resistant to the antibiotic will be tabulated. The denominator will be the number of participants with resistance status available at that time point and for that antibiotic. We will also report at each time point the number and proportion of participants with no growth isolated. Additionally, in the same way we will report antimicrobial resistance to any isolate, not just E.coli.

Antibiotic resistance in routine perineal swabs – as per Antibiotic resistance in routine urine samples (antimicrobial resistance to E.coli only).

Antibiotic resistance in symptomatic urine samples – these will be all remaining urine samples taken at time points other than for routine baseline and 3 monthly visits. Primarily we will report antimicrobial resistance to E.coli. For each antibiotic (with sufficient data available) the cumulative proportion of isolates resistant to the antibiotic (out of the cumulative number of samples tested for that antibiotic) will be calculated in each treatment group over time. Additionally, in the same way, we will report antimicrobial resistance to any isolate.

Ever-resistant **-** We will also report the number and proportion of participants ever-resistant to each antibiotic at baseline and at any follow-up time-point (routine and symptomatic samples will be included). The denominator will be the number of participants with a resistance status available for that antibiotic at baseline or at any follow-up time point (including routine and symptomatic samples) respectively. We will also report the number of participants who developed resistance since baseline out of those known not to be resistant at baseline (note that this requires a positive sample at baseline and so numbers will likely be very small). Primarily we will report ever-resistance to E.coli but will also report ever-resistance to any isolate, not just E.coli. We will also report ever-resistance based on perineal swabs (E.coli only).

Multi-drug resistant - will be defined as resistance to at least one antimicrobial agent in at least three antimicrobial categories, following the principles described by Magiorakos et al.[1] For this study, the antimicrobial agents and categories have been tailored to be specific to UTIs and are given in the below Table. Multidrug-resistance will focus only on E.coli isolates. Multi-drug resistance will be reported as for ever-resistant but for only E.coli isolates (urine and perineal swab samples will be reported separately).

Antimicrobial category	**Antimicrobial agent**
Aminoglycosides	Gentamicin
Antipseudomonal penicillin	Piperacillin/tazobactam
Carbapenems	Ertapenem; Meropenem
Non-extended spectrum cephalosporins	Cefuroxime; Cefalexin
Fluoroquinolones	Ciprofloxacin
Folate pathway inhibitors	Trimethoprim-sulphamethoxazole (co-trimoxazole); Trimethoprim
Monobactams	Aztreonam
Penicillins	Amoxicillin; Mecillinam;
Penicillins + β-lactamase inhibitors	Amoxicillin-clavulanic acid (co-amoxiclav)
β-lactamase resistant penicillin	Temocillin
Phosphonic acids	Fosfomycin
Nitrofuran	Nitrofurantoin

Multi-drug resistant: resistant to ≥1 antimicrobial agent in ≥3 antimicrobial categories

Note that for these outcomes we will only use data from analyses conducted by the central laboratory and not those collected from GP and hospital records (on the Antibiotic Treatments eCRF).

Number of microbiological-proven UTIs

Symptomatic UTI episodes, identified as per the primary outcome, will be considered microbiologically proven if a positive urine culture from a urine sample sent to the central laboratory, or if no sample was received, a positive culture reported by a local laboratory, is available from between 14 days prior to starting antibiotic treatment up to the end of antibiotic treatment. A positive culture will be classified according to standard Public Health England (PHE) definitions; the laboratory report of two isolates at $\geq 10^5$ cfu/mL or a single isolate at $\geq 10^4$ cfu/mL.

Occurrence of asymptomatic bacteriuria (ABU)

This will be defined as a positive urine culture from the routine urine samples taken and sent to the central laboratory during 3 monthly hospital visits throughout the 18 month period of participation.

Hospitalisation due to UTI

This will be defined as a visit to hospital for treatment of a UTI. These data will be collected from healthcare record review and checked from participant report. Reasons for hospital admission will be coded by the CI, blind to treatment allocation. Those episodes with evidence of systemic sepsis will be severity categorised as urosepsis.

Participant satisfaction with treatment

This will be measured using the Treatment Questionnaire on Satisfaction with Medication (TQSM)[2] administered at both the end of the 12 month treatment period and then again at the 18 months end of follow-up visit. Four separate subscale scores (Effectiveness, Side-effects, Convenience & Global Satisfaction) will be calculated as per the scoring algorithm.

2.4.3 Exploratory endpoints

There are no exploratory endpoints pre-specified for this study.

2.5 Study assessments

Outcomes will be collected for each participant over the 12 month treatment period following randomisation and also during a follow up period of 6 months after the planned preventative treatment period (making up a total observation period of 18 months for each participant).

Schedule of procedures

Procedures	Screening	Baseline	Treatment Phase						Follow Up	
			3 months	6 months	9 months	12 months	At time of UTI	Monthly checks	15 months	18 months
Informed consent		X								
Demographics	X	X*								
Medical history		X								
Physical examination		X								
eGFR and LFTs	X	X*	X	X	X	X			X	X
MSU (local lab)		X	X	X	X	X	X		X	X
MSU (central lab)		X	X	X	X	X	X		X	X
Perineal swab		X		X		X				X
Concomitant medications	X	X*								
Eligibility assessment	X									
Randomisation		X								
Dispensing of trial drugs		X	X	X	X					
Compliance			X	X	X	X	X	X	X	X
UTI Record							X			
UTI questionnaire			X	X	X	X			X	X
TSQM						X				X
Adverse event assessments			X	X	X	X	X		X	X

*Screening data values may be used for baseline if taken within 2 months from the date of randomisation.

2.6 Sample size and power

The recruitment target for this trial is a total of 240 patients, 120 in each treatment group.

Semi-structured interviews with a patient panel of 12 women identified that any reduction in UTI episodes even by 1 per year would be deemed worthwhile. Therefore we have set the minimum clinically important difference between the treatment arms of 1 UTI per 12 months as our non-inferiority margin.

The two existing meta-analyses of studies examining prophylactic antibiotics[2] and Methenamine hippurate[3] have quoted mean relative risk of UTI versus placebo of 0.15 and 0.24 respectively. Using these values and data from a local audit (unpublished, n=200) suggesting that the average number of UTI episodes per year in this patient group is 6.5 we have estimated that the number of UTI episodes will be 0.975 and 1.56 in those randomised to antibiotics and antiseptic respectively. This equates to a difference in number of episodes per year between prophylactic antibiotics and Methenamine hippurate of around 0.6 episodes (in favour of antibiotics).

The standard deviation of episodes of UTI per year is taken from the placebo groups in the studies included in the Cochrane meta-analyses[3, 4] and has been conservatively estimated at 0.9 episodes per year.

If there is an actual difference of 0.6 episodes (in favour of treatment with antibiotics), then two groups of 87 patients are required to be 90% sure that the lower limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will be above the non-inferiority limit of 1 UTI episode assuming a standard deviation of 0.9 episodes per year. Total sample size assuming 2 groups and an attrition rate of 25% = 232, rounded up to 240.

3. STATISTICAL CONSIDERATIONS

3.1 Timing of analyses

The primary analysis will commence following data cleaning and data lock once all patients have completed their 18 month follow up visit.

3.2 Interim analyses, data monitoring and stopping guidelines

Other than any analyses requested by the Data Monitoring Committee, data will not be analysed until the end of the study. There are no planned interim analyses and no formal stopping rules for efficacy or safety.

Data snapshots will be taken during the recruitment and follow up period for DMC reporting and for any data cleaning and statistical monitoring. The DMC will meet at least annually over the total trial duration. Interim meetings may be arranged at the request of the DMC. The trial statistician will have overall responsibility for the production of the report to the DMC, which will contain data summaries corresponding to the specific roles of the DMC as outlined in the DMC charter [Version 2.1, 16/12/2016]. Data will be presented to the DMC broadly as set out in this analysis plan, however formal statistical comparisons will be not made, unless specifically requested by the DMC.

3.3 Analysis populations

Intention-to-treat: This population contains all patients randomised into the study (regardless of whether they were later found to be ineligible, a protocol violator, given the wrong treatment allocation, never treated etc.).

Modified intention-to-treat: This population contains all patients randomised into the study with an observational period (as per the primary outcome definition) of at least 6 months.

Per-Protocol: This population contains all patients randomised to the study who achieved ≥90% compliance with the planned 12 month study treatment period (missed doses of antibiotic prophylaxis during periods of taking treatment antibiotics will be considered compliant as per the treatment protocol). Patients who switch treatments will still be analysed within the group to which they were randomised if switching has been undertaken in accordance with the protocol. Patients later found to be ineligible or patients with major protocol violations will also be excluded from the per-protocol population. A line listing of all participants excluded from the per-protocol analysis will be provided. Inclusion/exclusion of participants from the per-protocol population will be checked (blind to treatment allocation) by a statistician who has not reviewed any unblind outcome data.

Safety population: This population contains all patients randomised to the study and received at least one dose of any trial treatment.

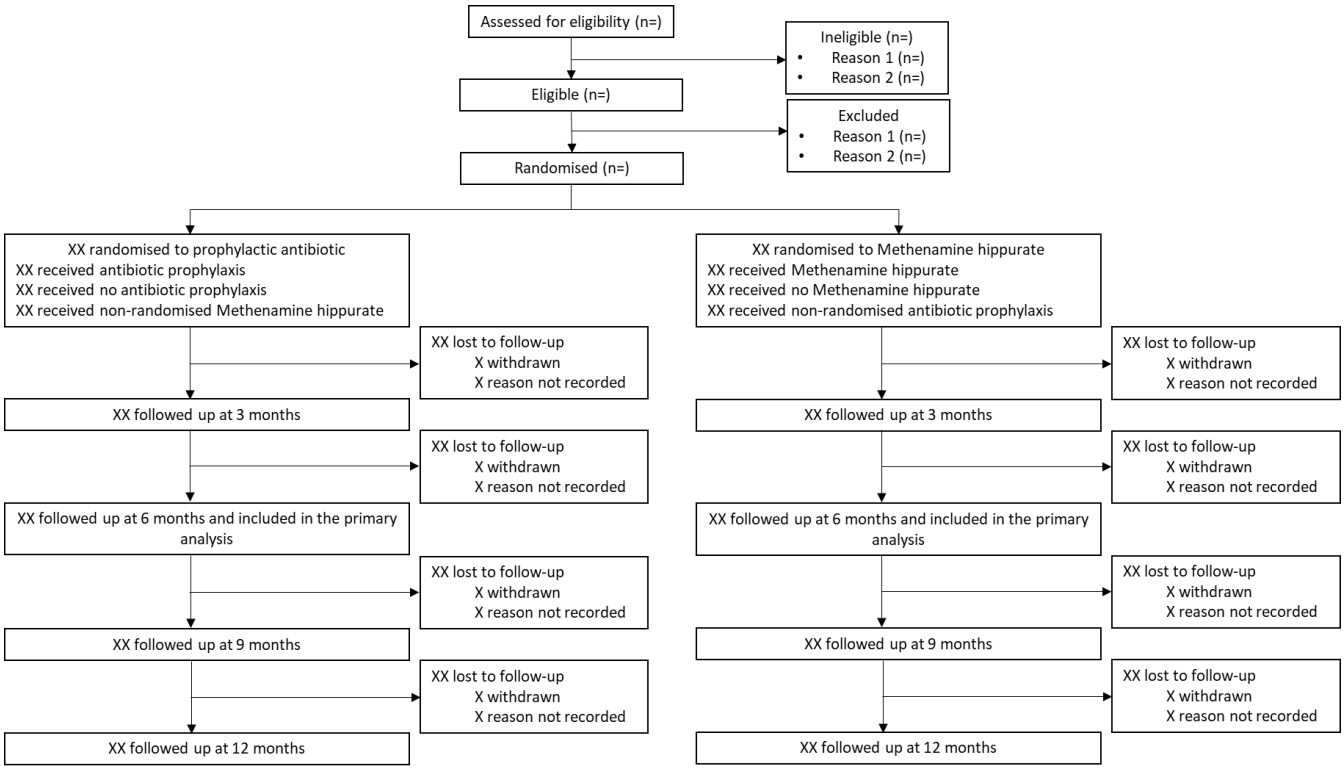
The main analysis will be conducted in the modified intention-to-treat population with sensitivity analyses in the strict intention-to-treat population and also the per-protocol population if more than 10% of participants would be excluded from either randomised group when compared to the modified intention to treat population.

4. STUDY POPULATION

4.1 Participant flow through trial

Patient flow through the trial will be presented using a CONSORT diagram. Information may be provided on numbers and reasons (where appropriate) for: screened patients not being eligible; eligible patients not being randomised; patients found to be ineligible after randomisation; patients deviating from allocated treatment; patients not evaluable for the primary endpoints; withdrawal from follow-up; withdrawal of consent and major protocol violations.

Example Figure 1: CONSORT flow diagram



4.1.1 Screening, eligibility and recruitment

The representativeness of the study sample will be presented with the following data, e.g. Example Table 1, Example Table 2:

- The number of patients identified at screening
- The number of patients excluded at screening due to ineligibility (with reasons)
- The number of eligible patients identified at screening
- The number of eligible patients not taking part in the study (with reasons)
- The number of eligible patients randomised into the study.

Observed and target accrual will be presented graphically, e.g. Example Figure 2. Accrual will also be tabulated overall and by month and by centre, e.g. Example Table 3. The trial opened to recruitment in June 2016 and, according to the original recruitment plan, was anticipated to close to recruitment in October 2017. Due to slower than anticipated accrual the original planned recruitment duration was extended by 9 months with a revised recruitment end date of July 2018.

Example Table 1: Summary of screening and recruitment by site

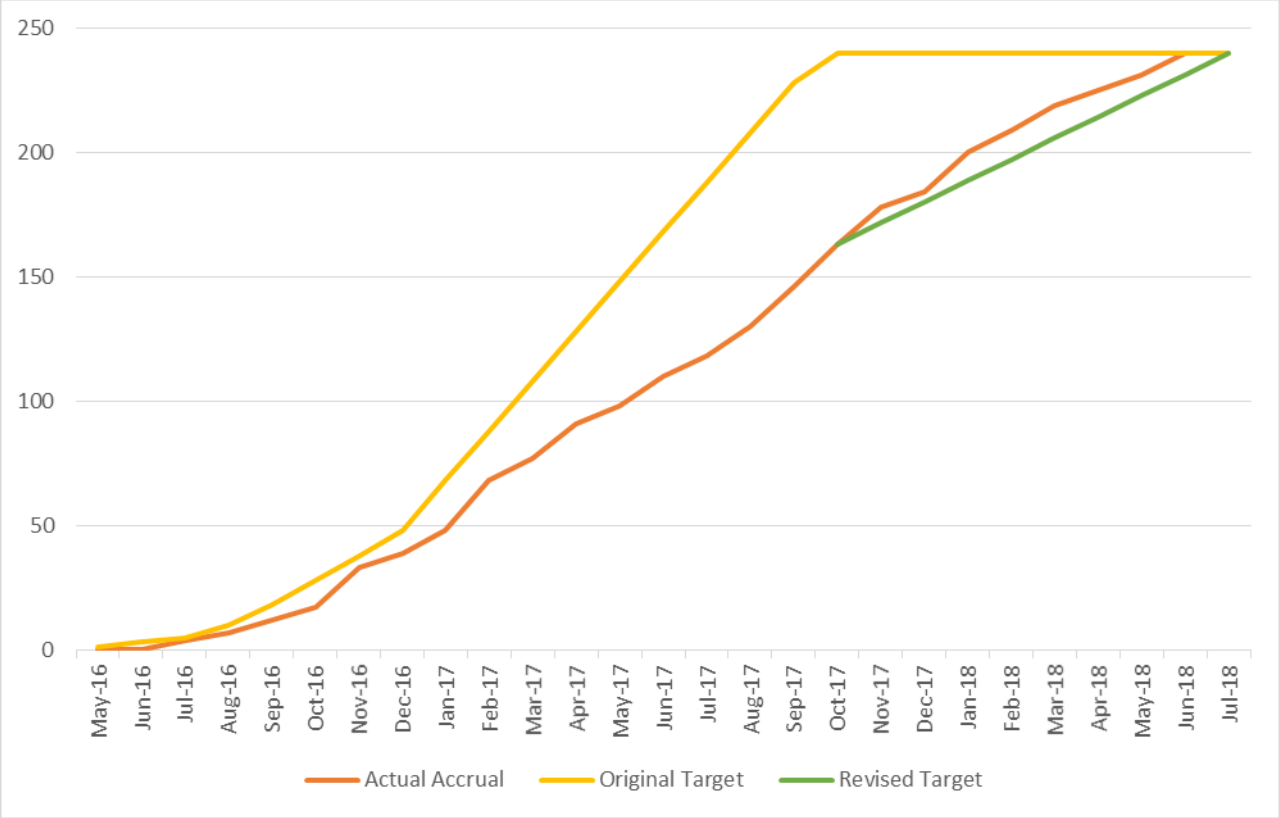
Site	Assessed for eligibility N_{Ass}	Approached[1] N_{App} (%, of N_{ass})	Consented N_C (%, of N_{App})	Declined N_D (%, of N_{App})	Not enrolled for other reasons N_{Oth} (%, of N_{App})	Randomised N_R (%, of N_{App})
Newcastle						
Cambridge						
Wakefield						
Glasgow						
Manchester						
Leeds						
Oldham						
Liverpool						
Total						

[1] considered eligible

Example Table 2: Summary by site of reasons for eligible patients not being recruited

Reason not recruited	**Reason 1**	**Reason 2**	**…**	**…**	**…**	**Total**
Newcastle						
Cambridge						
Wakefield						
Glasgow						
Manchester						
Leeds						
Oldham						
Liverpool						
Total						

Example Figure 2: Target accrual



Example Table 3: Monthly and cumulative summary of actual and target accrual by site

Site	Date open	May-16	Jun-16	Jul-16	….	….	….	Jul-18	Total
Newcastle	23/06/16								
Cambridge	18/08/16								
Wakefield	28/09/16								
Glasgow	31/10/16								
Manchester	07/11/16								
Leeds	18/11/16								
Oldham	09/05/17								
Liverpool	28/06/17								
Participants recruited									
Cumulative accrual									
Site months									
Cumulative site months									

4.1.2 Follow-Up

The frequency and percentage of patients with data available for each assessment at each follow-up visit will be tabulated overall and in each randomised group (e.g. Example Table 4a). The total observation time for during treatment (12 months) and follow-up (6 months) periods will be calculated (as per Section 2.4) for each patient and summarised descriptively in each randomised group (e.g. Example Table 4b).

Withdrawals and losses to follow-up will be tabulated by randomised group. Participants withdrawing from follow-up may allow the research team to continue to access follow-up data through healthcare records. This will be cross-tabulated against time on study (e.g. Example Table 4c).

Example Table 4a: Assessments available during follow up

Follow up visit	Number expected	Assessment	Antibiotic (N=)	Methenamine hippurate (N=)	Total (N=)
Month 3		Attended follow-up assessment / visit			
		MSU sample available			
Month 6		Attended follow-up assessment / visit			
		MSU sample available			
		Perineal swab available			
Month 9		Attended follow-up assessment / visit			
		MSU sample available			
Month 12		Attended follow-up assessment / visit			
		MSU sample available			
		Perineal swab available			
Month 15		Attended follow-up assessment / visit			
		MSU sample available			
Month 18		Attended follow-up assessment / visit			
		MSU sample available			
		Perineal swab available			

Example Table 4b: Summary of overall and per-patient observation time

	Antibiotic (N=)	Methenamine hippurate (N=)	Total (N=)
During treatment (12 months)			
Total observation time (months)			
Mean (SD)			
Median (IQR)			
Range			
Patient observation time (months)			
<3			
≥3, <6			
≥6, <9			
≥9, <12			
12			
Follow-up (6 months)			
Total observation time (months)			
Mean (SD)			
Median (IQR)			
Range			
Patient observation time (months)			
<3			
≥3, <6			
6			

Example Table 4c: Summary of withdrawals and loss to follow-up

	Antibiotic (N=)	Methenamine hippurate (N=)	Total (N=)
Total withdrawn / lost to follow-up			
Last follow-up visit < 6 months Permission to collect outcome data via hospital & GP records Yes No Missing/Unknown			
Last follow-up visit ≥6, <12 months Permission to collect outcome data via hospital & GP records Yes No Missing/Unknown			
Last follow-up visit ≥12 months Permission to collect outcome data via hospital & GP records Yes No Missing/Unknown			

4.1.3 Protocol deviations

Protocol deviations will be reported overall and by randomised group. Protocol deviations may include, but are not limited to; deviations from allocated treatment strategy not in accordance with the protocol (treatment switching is permitted), deviations from visit schedule, withdrawal from trial specific follow-up, losses to follow-up and ineligible patients.

Major deviations will include ineligible patients and withdrawal from the study within the first 6 months. Minor deviations will include withdrawal from study visits, deviation from the study visit schedule and deviations from allocated treatment strategy not made in accordance with the protocol.

Protocol deviations will be reported in a line listing, sorted by type (for ineligible patients, reasons for ineligibility will be reported), or tabulated for minor deviations such as missing visits or deviations from the study visit schedule. How each deviation contributed to analysis populations will be noted (e.g. whether they were included/excluded from the per-protocol population). Data may also be summarised by frequency and percentage of the number of patients reporting each type of deviation. Note that protocol deviations which are administrative in nature, e.g. SAEs reported outside allowable time windows, identifiable data sent to unsecured email accounts will not be summarised as part of the statistical report.

Example Table 5: Line listing of protocol deviations

Trial ID	Randomised group	Deviation type	Details	Contribution to analysis populations
		e.g. ineligible/deviation from treatment schedule/withdrawal/lost to follow-up/deviation from visit schedule		

4.2 Baseline characteristics

Demographic, clinical and baseline characteristics and trial stratification factors at randomisation will be summarised across treatment groups descriptively. We will report the number and percentage in each group for all categorical variables and mean, SD or median, IQR and range, as appropriate, for all continuous variables. No significance testing will be carried out due to the randomised nature of the study.

Example Table 6: Patient demographics and UTI history reported at baseline

	Antibiotic prophylaxis (N=)	Methenamine hippurate (N=)	Total (N=)
Demographics			
Age (years)			
Weight Missing/Not available			
Menopausal status Pre Peri/Post			
UTI History			
Reported episodes of UTI in the last 12m <4 >=4			
Patient-reported antibiotic treated UTI episodes in last 12m			
Positive urine cultures in last 12m Missing/Not available			
Previous use of antibiotic prophylaxis None Trimethoprim Nitrofurantoin Cefalexin Co-amoxyclav Ciprofloxacin Amoxycillin Pivmecillinam			
Approx. months of antibiotic prophylaxis use over previous 12m			
Use of antibiotic prophylaxis in last 6m			
Undertook 3 month washout period before randomisation			
Previous use of Methenamine Hippurate			
Preventative measures over last 3m			
Drinking more fluid Stopping cigarette smoking Vaginal oestrogen tablet or cream Cranberry product (juice, capsule or other) Substances like potassium citrate or sodium bicarb Foods or drinks with anti-bacterial properties Probiotics such as live yoghurt Dietary modifications to reduce urinary acidity			
Bloods			
ALT (U/L) Missing / Not available			
AST (U/L) Missing / Not available			

	Antibiotic prophylaxis (N=)	Methenamine hippurate (N=)	Total (N=)
Alkaline Phosphatase (U/L) Missing / Not available			
Bilirubin (µmol/L) Missing / Not available			
Creatinine eGFR (µmol/L) Missing / Not available			
Creatinine clearance (mL/min) Missing / Not available			
Child-Pugh score 5 6 7 8 Missing/Not available			
Urinalysis			
WBC count thousands/ml 0 <10 10-40 41-200 >200 Missing/Not available			

4.3 Treatment compliance

In the group allocated to antibiotic treatment the type of prophylactic antibiotic agent (e.g. Nitrofurantoin, Trimethoprim, Cefalexin) chosen at randomisation will be tabulated. This data will also be reported by centre.

Example Table 7a: Antibiotic agent chosen at randomisation by centre (antibiotic group only)

Centre	Nitrofurantoin	Trimethoprim	Cefalexin
Newcastle	n(row %)	n(row %)	n(row %)
Cambridge	n(row %)	n(row %)	n(row %)
Manchester	n(row %)	n(row %)	n(row %)
Leeds	n(row %)	n(row %)	n(row %)
Centre 1	n(row %)	n(row %)	n(row %)
Centre 2	n(row %)	n(row %)	n(row %)
Total	**n(row %)**	**n(row %)**	**n(row %)**

Switching between antibiotic agents, including multiple switching, due to lack of efficacy or adverse effects is permitted. Some participants or their clinicians may also seek to change their allocated strategy (antibiotic or antiseptic) at some point during trial participation, again either due to lack of efficacy or adverse effects. The need to adhere to the allocated strategy where possible during the 12 month trial period will however be emphasised in trial literature.

Compliance with prophylactic treatment will be recorded on the eCRFs at each monthly follow-up assessment. Any changes in prescribed treatment will also be captured along with reason for switching. Compliance with trial treatment will also be captured as days missed, categorised as 1, 2, 3, 4, 5-10, 11-20, 21-31. For the purpose of summing days missed over multiple months the mid-point of the category will be used.

Percentage compliance will be calculated as compliance with any trial prophylactic treatment. It will be calculated as follows:

- For those completing the 12 month treatment period:
  - % compliance = (365 - days missed* while on treatment) / 365 *100
- For those known to have withdrawn from all trial treatment:
  - % compliance = [(Treatment stop date – randomisation date) - days missed* while on treatment] / 365 *100
- For those lost to follow-up during the 12 month treatment period (with no known stop date):
  - % compliance = [(Last monthly follow-up visit date – randomisation date) - days missed* while on treatment] / 365 *100

*Missed days of antibiotic prophylaxis whilst taking treatment antibiotics is permitted and will not be counted.

Treatment received, including switching between antibiotic agents and allocated treatment strategies, will be summarised descriptively. Full detail of participants switching treatment, withdrawing from trial treatment or will be reported in a line listing.

Example Table 7b: Summary of preventative agents received

	Antibiotic (N=)	Methenamine hippurate (N=)	Total (N=)
Number of prophylactic treatment(s) received 1 2 3 4			
Treatment(s) received			
Nitrofurantoin	n (%)	n (%)	n (%)
Days on treatment Median (IQR) Range			
Number stopping* early			
Reason for stopping Allergy Anaphylaxis Adverse effect Ineffective Other			
Trimethoprim	n (%)	n (%)	n (%)
Days on treatment Median (IQR) Range			
Number stopping* early			
Reason for stopping Allergy Anaphylaxis Adverse effect Ineffective Other			
Cefalexin	n (%)	n (%)	n (%)
Days on treatment Median (IQR) Range			
Number stopping* early			
Reason for stopping Allergy Anaphylaxis Adverse effect Ineffective Other			
Methenamine Hippurate	n (%)	n (%)	n (%)
Days on treatment Median (IQR) Range			
Number stopping* early			
Reason for stopping Allergy Anaphylaxis Adverse effect Ineffective Other			

**Stopping and switching to alternative prophylaxis or stopping all/any trial prophylactic treatment.*

Example Table 7c: Summary of treatment compliance

	Antibiotic (N=)	Methenamine hippurate (N=)	Total (N=)
% Compliance with any trial preventative treatment			
≥90% compliant			
<90% compliant			
Time on any trial preventative treatment			
<6 months			
≥6, <12 months			
12 months			
Median (IQR); Range			
Changed allocated treatment strategy			
Yes			
No			
If Yes, time from randomisation to change in allocated treatment strategy			
<3 months			
≥3, <6 months			
≥6, <9 months			
≥9 months			
Median (IQR); Range			

Example Table 7d: Summary of treatment compliance by time on treatment

	Antibiotic (N=)	Methenamine hippurate (N=)	Total (N=)
Completed 12 month treatment period			
≥90% compliant			
<90% compliant			
Changed allocated treatment strategy			
Yes			
No			
If yes, time on allocated treatment			
< 6 months			
≥6 months			
Median (IQR); Range			
Treatment period ≥ 6, <12 months			
≥90% compliant			
<90% compliant			
Changed allocated treatment strategy			
Yes			
No			
If yes, time on allocated treatment			
< 6 months			
≥6 months			
Median (IQR); Range			
Treatment period < 6 months			
Changed allocated treatment strategy			
Yes			
No			
If yes, time on allocated treatment			
Median (IQR); Range			

Use of preventative treatment (antibiotic prophylaxis or Methenamine Hippurate) during the 6 month follow-up period will be summarised descriptively.

5. ANALYSIS METHODS

5.1 Analysis of primary outcome

Incidence of symptomatic UTI during the 12 month period of treatment

The hypothesis to be tested is: treatment with antiseptic is non-inferior to treatment with antibiotic, with an inferiority limit of one episode per year.

The simple incident rate of UTI will be calculated in each randomised group. The difference between groups (antiseptic - antibiotic) will be estimated along with a 90% confidence interval calculated using a resampling (bootstrap) procedure with at least 1000 replicates. Provided that the lower 90% confidence limit is greater than the inferiority limit of 1, we will infer that treatment with antiseptic is not inferior to treatment with antibiotic. Analyses will also be repeated using the incident density rate.

A secondary analysis of the primary outcome will involve the modelling of the number of episodes of UTI using a negative binomial regression model with differences between centre included as a random effect and a binary indicator of previous annual frequency of UTI at baseline (more than 4 episodes versus 4 or less episodes) and menopausal status (pre-menopausal vs menopausal/postmenopausal) will be included as fixed effects. The log of the exposure variable (study observation period) will be included in the model with coefficient constrained to be one. This will yield an estimate of the incidence rate ratio.

A binary indicator of at least one patient episode of symptomatic UTI will be analysed using the same approach but with a logistic regression model.

Example Table 8: Frequency and incidence of symptomatic UTI during the 12 month treatment period

Outcome measure	Antibiotic (N=)	Methenamine hippurate (N=)
Episodes of symptomatic UTI		
0	n (%)	n (%)
1	n (%)	n (%)
2	n (%)	n (%)
3	n (%)	n (%)
4+	n (%)	n (%)
Mean (SD)	Mean (SD)	Mean (SD)
Median (IQR)	Median (IQR)	Median (IQR)
Range	Range	Range
Simple incident rate	Total # episodes / Total observation time (y)	Total # episodes / Total observation time (y)
Difference (90% CI)	Difference (90% CI)	
Unadjusted incidence rate ratio (95% CI)	IRR (95% CI), p-value	
Adjusted incidence rate ratio (95% CI)	IRR (95% CI), p-value	
Incident density rate	Total # episodes / Total observation time (y) - Total time taking antibiotics (y)	Total # episodes / Total observation time (y) - Total time taking antibiotics (y)
Difference (90% CI)	Difference (90% CI)	
Unadjusted incidence rate ratio (95% CI)	IRR (95% CI), p-value	
Adjusted incidence rate ratio (95% CI)	IRR (95% CI), p-value	
At least one episode of symptomatic UTI	# participants with 1+ UTI / N	# participants with 1+ UTI / N
Unadjusted odds ratio (95% CI)	OR (95% CI), p-value	
Adjusted odds ratio (95% CI)	OR (95% CI), p-value	

y=years

5.2 Analysis of secondary outcomes

Occurrence of symptomatic UTI in the 6 months follow up period after stopping the allocated preventative therapy

The simple incident rate of UTI in the 6 month follow up period will be calculated in each randomised group. The difference between groups (antiseptic - antibiotic) will be estimated along with a 95% confidence interval calculated using a resampling (bootstrap) procedure. Analyses will also be repeated using the incident density rate.

A further analysis will involve the modelling of the number of episodes of UTI in the 6 month follow up period using a negative binomial regression model with differences between centre included as a random effect and a binary indicator of previous annual frequency of UTI at baseline (more than 4 episodes versus 4 or less episodes) and menopausal status (pre-menopausal vs menopausal/postmenopausal) will be included as fixed effects. This will yield an estimate of the incidence rate ratio.

A binary indicator of at least one episode of symptomatic UTI during the 6 month post treatment period will be analysed using the same approach but with a logistic regression model.

Data will be presented as in Table 8, but with 95% CI for the difference in the simple incident rate and the incident density rate between randomised treatment groups.

Antibiotic use during treatment (12 months) and follow-up (6 months)

The number of days patients are prescribed low-dose antibiotics intended for prophylaxis against UTIs during the 12 month treatment period will be calculated and reported descriptively in each randomised treatment group using median, IQR and range. The number of days of prophylactic antibiotic use during the 6 month follow up period will also be presented using the same methods.

The number of days patients are prescribed therapeutic doses of antibiotics for breakthrough UTI's during the 12 month treatment period, and separately the 6 month follow-up period, will be calculated and reported in each randomised group descriptively using methods as for prophylactic antibiotic use. The rate of therapeutic antibiotic use will also be calculated and summarised descriptively.

Antimicrobial resistance

Antibiotic resistance in routine urine samples – data will be tabulated and also summarised graphically with 95% CI's. The number of resistant antibiotic agents at each time point will be summarised descriptively by median, IQR and range.

Example Table 9: E-coli resistance from routine urine samples

	Antibiotic (N=)							Methenamine hippurate (N=)						
	Baseline	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Baseline	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18
Samples available [n]														
E.coli isolated [n(%)] Yes No														
Antibiotic resistance [n(%); 95% CI] Antibiotic agent 1 Antibiotic agent 2 Antibiotic agent 3 Antibiotic agent 4 Antibiotic agent 5 Antibiotic agent 6														
Number of resistant agents Median (IQR); Range														
Number of resistant categories* Median (IQR); Range														

**as per multi-drug resistance definition*

Antibiotic resistance in routine perineal swabs – E.coli resistance data will be summarised as described above.

Antibiotic resistance in symptomatic urine samples - From samples submitted at the time of each UTI, for each antibiotic, the cumulative proportion of isolates resistant to the antibiotic (out of the cumulative number of samples tested for that antibiotic) will be plotted graphically over time in each treatment group with 95% CI's.

Ever-resistant and multi-drug resistant – data will be summarised descriptively as frequencies and percentages.

Example Table 10: Individual antibiotic agent resistance and multi-drug resistance status

	Antibiotic*	Methenamine hippurate
Antibiotic agent 1		
Resistant at baseline		
Resistant post-baseline		
Known resistant since baseline		
Antibiotic agent 2		
Resistant at baseline		
Resistant post-baseline		
Known resistant since baseline		
Antibiotic agent …		
Resistant at baseline		
Resistant post-baseline		
Known resistant since baseline		
Multi-drug resistant		
MDR at baseline		
MDR post-baseline		
Known MDR since baseline		

**May also be tabulated by preventative antibiotic agent (cefalexin, nitrofurantoin or trimethoprim)*

Number of microbiological-proven UTIs

The simple incident rate of microbiological-proven UTIs in the 12 month treatment period will be calculated in each randomised group. The difference between groups (antiseptic - antibiotic) will be estimated along with a 95% confidence interval calculated using a resampling (bootstrap) procedure. Analyses will also be repeated using the incident density rate.

A further analysis will involve the modelling of the number of episodes of UTI in the 12 month treatment period using a negative binomial regression model with differences between centre included as a random effect and a binary indicator of previous annual frequency of UTI at baseline (more than 4 episodes versus 4 or less episodes) and menopausal status (pre-menopausal vs menopausal/postmenopausal) will be included as fixed effects. This will yield an estimate of the incidence rate ratio.

A binary indicator of at least one microbiological-proven UTI during the 12 month treatment period will be analysed using the same approach but with a logistic regression model.

The above analyses will be repeated using microbiological-proven UTIs during the 6 month follow-up period.

Data will be presented as in Table 8, but with 95% CI for the difference in the simple incident rate and the incident density rate between randomised treatment groups.

Occurrence of asymptomatic bacteriuria (ABU)

The number of cases of asymptomatic bacteriuria will be reported out of the total number of routine urine samples taken in each randomised group.

Hospitalisation due to UTI

The total number of hospitalisations due to UTI during the 18 month trial period will be reported along with the number of participants hospitalised due to UTI at least once. Data will be summarised descriptively and frequencies and percentages in each randomised group.

Participant satisfaction with treatment

Four separate subscale scores (Effectiveness, Side-effects, Convenience & Global Satisfaction) from the Treatment Questionnaire on Satisfaction with Medication will be calculated as per the scoring algorithm at 12 months and 18 months. An analysis of covariance approach will be used to assess the difference in each subscale score between randomised treatment groups, with TQSM subscale score as the outcome and randomised treatment group, stratification variables and age as predictors.

5.3 Additional / Exploratory Analyses

The primary analyses will principally be conducted in the modified intention-to-treat (ITT) population, however we will also undertake analyses of the primary outcome measure in the strict ITT population and the per-protocol population if more than 10% of participants would be excluded in either randomised group when compared to the modified intention to treat population.

Further multivariable analyses may be conducted adjusting for the influence of age as well as the variables described above (centre, frequency of UTI and menopausal status).

5.4 Missing data

Missing primary outcome data due to participant withdrawal or loss to follow-up will be summarised and may be examined to determine both its extent and whether it is missing at random or is informative. If data are missing to a sufficient extent (more than 25% accounted for), then the use of appropriate multiple imputation techniques will be considered.

Levels of missing data may also be summarised by form type, e.g. as per Section 4.1.2.

Missing items from a partially completed TQSM questionnaire will be handled as described in the scoring manual.

Multivariable analyses will be based on a complete case analysis. A sensitivity analysis based on imputation of missing covariate data may also be carried out if more than 25% of participants have incomplete covariate data. Simple imputation methods would be used, performed separately within each randomised group, where continuous variables will be imputed using the mean and categorical values using the mode.

6. SAFETY DATA

6.1 Adverse events

Adverse events occurring throughout the trial period (up to 18 month follow-up) will be recorded on the eCRF. All events will be graded as mild, moderate or severe and relationship to study medication as unrelated, unlikely, possible, probable or definite. Adverse events will be coded systematically at the end of the study.

Safety data will be reported in the safety population by randomised treatment group, retaining participants in the group to which they were randomised, and also by the number exposed to each treatment group (taking into account changes in treatment strategy).

The number of adverse events per participant will be reported descriptively, for all adverse events and also only for those possibly, probably or definitely related to treatment. The number of non-serious adverse events reported per-participant will also be summarised descriptively in line with EudraCT reporting requirements.

All adverse events will be tabulated by worst grade reported during the study. This will be repeated in only non-serious adverse events in line with EudraCT reporting requirements and in only related adverse events.

Example Table 11: Summary of all adverse events – by randomised treatment group*

	Antibiotic (N=)		Methenamine hippurate (N=)		Total (N=)	
	N	%	N	%	N	%
All AEs – regardless of relatedness						
Number reported per participant						
0						
1						
2						
3						
4						
5+						
Median (IQR); Range						
Worst grade reported per participant						
None						
Mild						
Moderate						
Severe						
AEs possibly / probably / definitely related to treatment						
Number reported per participant						
0						
1						
2						
3						
4						
5+						

	Antibiotic (N=)		Methenamine hippurate (N=)		Total (N=)	
	N	%	N	%	N	%
Worst grade reported per participant						
None						
Mild						
Moderate						
Severe						
Non-serious AEs						
Number reported per participant						
0						
1						
2						
3						
4						
5+						
Worst grade reported per participant						
None						
Mild						
Moderate						
Severe						

**Table 11 will also be presented by numbers exposed to each treatment to account for treatment switching.*

Example Table 12a: All adverse events (regardless of relatedness or seriousness) – by randomised treatment group*

Adverse event	Worst grade reported	Antibiotic (N=)	Methenamine hippurate (N=)	Total (N=)
AE 1	Mild Moderate Severe			
AE 2	Mild Moderate Severe			
AE 3	Mild Moderate Severe			
…	Mild Moderate Severe			
Any event	Mild Moderate Severe			

**Table 11a will also be presented by numbers exposed to each treatment to account for treatment switching.*

Example Table 12b: Related adverse events (regardless of seriousness) – by randomised treatment group*

Adverse event	Worst grade reported	Antibiotic (N=)	Methenamine hippurate (N=)	Total (N=)
AE 1	Mild Moderate Severe			
AE 2	Mild Moderate Severe			
AE 3	Mild Moderate Severe			
…	Mild Moderate Severe			
Any event	Mild Moderate Severe			

**Table 11b will also be presented by numbers exposed to each treatment to account for treatment switching.*

Example Table 12c: Non-serious adverse events (regardless of relatedness) – by randomised treatment group*

Adverse event	Worst grade reported	Antibiotic (N=)	Methenamine hippurate (N=)	Total (N=)
AE 1	Mild Moderate Severe			
AE 2	Mild Moderate Severe			
AE 3	Mild Moderate Severe			
…	Mild Moderate Severe			
Any event	Mild Moderate Severe			

**Table 11c will also be presented by numbers exposed to each treatment to account for treatment switching.*

Adverse effects are also reported on treatment compliance eCRFs at each monthly follow-up visit. The number of participants reporting to have not tolerated the study drug or to have tolerated it but with adverse effects will be tabulated by randomised treatment group. The adverse effect reported will be summarised for each treatment group. Each adverse effect will only be counted once per participant per treatment strategy received.

Example Table 13: Tolerability of treatment as reported by the participant at monthly follow-up appointments

	Antibiotic (N=)	Methenamine hippurate (N=)	Total (N=)
1 month Questionnaires complete Agent - antibiotic Not tolerated/tolerated with adverse effect Agent - Methenamine hippurate Not tolerated/tolerated with adverse effect			
2 months Questionnaires complete Agent - antibiotic Not tolerated/tolerated with adverse effect Agent - Methenamine hippurate Not tolerated/tolerated with adverse effect			
3 months Questionnaires complete Agent - antibiotic Not tolerated/tolerated with adverse effect Agent - Methenamine hippurate Not tolerated/tolerated with adverse effect			
4 months Questionnaires complete Agent - antibiotic Not tolerated/tolerated with adverse effect Agent - Methenamine hippurate Not tolerated/tolerated with adverse effect			
5 months Questionnaires complete Agent - antibiotic Not tolerated/tolerated with adverse effect Agent - Methenamine hippurate Not tolerated/tolerated with adverse effect			
6 months Questionnaires complete Agent - antibiotic Not tolerated/tolerated with adverse effect Agent - Methenamine hippurate Not tolerated/tolerated with adverse effect			
7 months Questionnaires complete Agent - antibiotic Not tolerated/tolerated with adverse effect Agent - Methenamine hippurate Not tolerated/tolerated with adverse effect			
8 months Questionnaires complete Agent - antibiotic Not tolerated/tolerated with adverse effect Agent - Methenamine hippurate Not tolerated/tolerated with adverse effect			
9 months			

	Antibiotic (N=)	Methenamine hippurate (N=)	Total (N=)
Questionnaires complete Agent - antibiotic Not tolerated/tolerated with adverse effect Agent - Methenamine hippurate Not tolerated/tolerated with adverse effect			
10 months Questionnaires complete Agent - antibiotic Not tolerated/tolerated with adverse effect Agent - Methenamine hippurate Not tolerated/tolerated with adverse effect			
11 months Questionnaires complete Agent - antibiotic Not tolerated/tolerated with adverse effect Agent - Methenamine hippurate Not tolerated/tolerated with adverse effect			
12 months Questionnaires complete Agent - antibiotic Not tolerated/tolerated with adverse effect Agent - Methenamine hippurate Not tolerated/tolerated with adverse effect			

Example Table 14: Adverse effects reported by the participant at monthly follow-up visits

	Antibiotic (N=)	Methenamine hippurate (N=)	Total (N=)
Antibiotic Number exposed Number not tolerated/tolerated with adverse effects Adverse effect* AE 1 AE 2 AE 3 …			
Methenamine Hippurate Number exposed Number not tolerated/tolerated with adverse effects Adverse effect* AE 1 AE 2 AE 3 …			

Problems with treatment antibiotics (for UTI or other reasons, excluding the prophylactic antibiotic for UTI) are also reported by the participant on UTI logs and on the 3 monthly participant questionnaire. Any problems reported will be summarised descriptively.

Example Table 15: Problems with treatment antibiotics reported by the participant

	Antibiotic (N=)	Methenamine hippurate (N=)	Total (N=)
Skin rash			
Feeling sick (nauseated)			
Being sick (vomiting)			
Looser or more frequent bowel movements (diarrhoea)			
Thrush (candidal fungal infection) in the vagina			
Thrush (candidal fungal infection) in the mouth			
Antibiotic side effects - Other			

6.2 Serious adverse events

Serious adverse events will be summarised as a line listing. A summary of the number of SAEs reported per participant will also be tabulated by treatment group.

Example Table 16: Line listing of all reported SAEs

**If participant switched treatment, each start and end date will be reported*

ID	SAE no.	Randomised treatment group	Treatment start date*	Treatment end date*	Onset date	Description	Severity [A]	Seriousness criteria [B]	Causality [C]	Expected [D]	Outcome [E]	Outcome date

**If participant switched treatment, each start and end date will be reported*

A: Mild / Moderate / Severe

B: Death / Life-threatening / Hospitalisation or prolongation of hospitalisation / Persistent or significant disability or incapacity / Congenital anomaly or birth defect / Other significant medical event

C: Related / Unrelated / Indeterminate

D: Expected / Unexpected

E: Recovered / Condition improved / Condition deteriorated / Condition unchanged / Recovered with sequalae / Condition stable and no change anticipated / Participant died

6.3 Other safety measures

No other analyses of safety measures are planned.

7. STATISTICAL SOFTWARE

Data will be downloaded directly from MACRO into a Stata format by the NCTU at time-points agreed by the TMG. Statistical analyses will be carried out by the Trial Statistician at the Biostatistics Research Group, Newcastle University. All programs will be stored in the School Statistics folder on the IHS server.

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