Newcastle Clinical Trials Unit

Statistical Analysis Plan for the AnTIC Trial

Antibiotic **T**reatment for **I**ntermittent Bladder **C**atheterisation: A Randomised Controlled Trial of Once Daily Prophylaxis (The **AnTIC** study)

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Trial Statisticians:
Valentina Mamasoula, Holly Ainsworth

Signature: H. Ainsworth **Date**: 18/10/2017

Reviewed and Approved by:

Signature: Thomas Chadwick (Senior statistician) **Date**: 18/10/17

Signature: Robert Pickard (Chief investigator) **Date**: 18th October 2017

This document and any preceding versions will be stored in the Trial Master File.

Changes in Version 1.1

- Page 1: Updated date. Note also that Version 1.0 was incorrectly dated – this should have been recorded as 23/03/2017.
- Page 3: Table of contents updated.
- Page 15: Additional analysis added for microbiological data up to 12 months.
  Reason: This was intended to be included in Version 1.0 (and is mentioned as an outcome measure in the protocol) but analysis before the later 18 month time point was overlooked in error.

Changes in Version 1.2

- Page 1: Updated date.
- Page 3: Table of contents updated.
- Pages 15-16: Clarification and expansion of future analysis plans, particularly around the 18 month microbiological data and an additional summary measure.
  Reason: Although noted that the 18 month data is not considered part of the RCT it was decided to document the planned analysis in greater detail prior to the lock and release of this data. The measure to be tabulated by arm was overlooked prior to this point.

Contents

1. INTRODUCTION

This statistical analysis plan provides guidelines for the analysis and presentation of the results of the ANTIC trial. The plan, along with all other documents relating to the analysis of this trial, will be stored in the 'Statistical Documentation' section of the Trial Master File.

1.1 Summary

Clean intermittent self-catheterisation (CISC) is an important management option for people who cannot empty their bladder naturally due to bladder outlet obstruction, or due to failure or incoordination of bladder muscle contraction which is most frequently associated with neurological disease [1]. Patients needing CISC are taught how to insert a catheter, drain the bladder, and then remove the catheter [2]. Single-use disposable catheters, typically with a hydrophilic coating, are the preferred option in the UK. There are no accurate prevalence data for CISC use in the United Kingdom (UK). Recurrent urinary tract infection (UTI) is the commonest adverse event experienced by CISC-users affecting between 12% and 88% of cohorts [3]. Separation of rates of asymptomatic bacteriuria, which would not normally be treated, and symptomatic UTI in these studies is difficult with the best estimate being that 50% of users have chronic bacteriuria and at least 25% suffer two or more symptomatic UTI episodes per year [4]. Neurological disease, female gender, young age, and high bladder volumes have been associated with higher prevalence of UTI [1]. Rates will also vary according to the definition of symptomatic UTI used; in particular whether microbiological proof is required [5]. It is estimated that 6,000 CISC-users in the UK suffer recurrent UTI; the target population for this trial.

Once-daily low dose antibiotic prophylaxis is effective for women without bladder emptying problems who suffer simple recurrent UTI. Systematic review and meta-analysis of trials in this patient group showed a relative risk for UTI (95% Confidence Interval; CI) of 0.15 (0.08 – 0.28) [6]. Three crossover trials were identified but not included in the review; of these one trial with a fluoroquinolone had a 4-month washout period at crossover whilst two had no washout period.

This background has convinced us that a robust pragmatically designed trial is required to determine whether the apparent benefit of antibiotic prophylaxis seen in small trials amongst specific groups of CISC-users is seen in a routine care setting and whether any benefits are worth the costs both financial and in terms of harms.

The estimates of prevalence, effectiveness and harms have allowed us to power the trial conservatively based on what we consider to be a minimum important difference from clinician, patient, and economic perspectives.

Trial hypothesis: The statistical null hypothesis is that the effectiveness of a strategy of prophylactic antibiotic is not superior to no prophylaxis over 12 months.

Primary objective: To determine whether antibiotic prophylaxis results in a clinically significant reduction in the rate of symptomatic, antibiotic-treated urinary tract infection suffered by people performing intermittent bladder catheterisation over 12 months and is cost-effective for the UK NHS.

Secondary objectives: To determine whether use of antibiotic prophylaxis results in better quality of life, better satisfaction with treatment and has an acceptable safety profile including antibiotic stewardship.

Study design: Pragmatic, superiority patient randomised (1:1) controlled trial of once daily prophylaxis without masking of participants or clinicians.

Study Interventions: Daily antibiotic prophylaxis for 12 months compared to no prophylaxis

Primary outcome: Relative incidence of symptomatic antibiotic-treated UTI between the trial groups over 12 months

Number of study sites: 40

Target study population/size: 372 (404 achieved)

Planned study duration: 42 months (12 months active participation)

1.2 Planned Trial Diagram/Flowchart

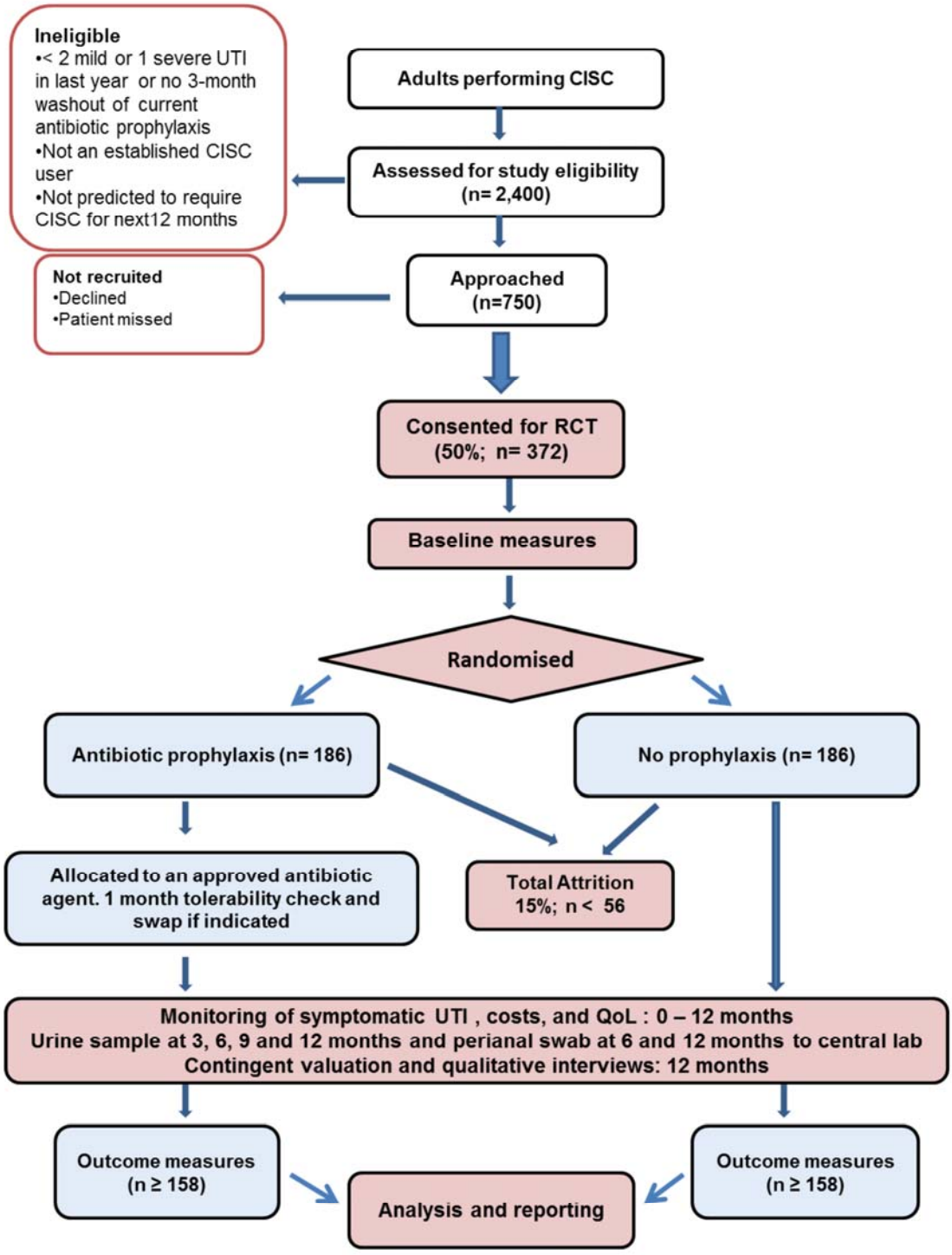

Figure 1: CONSORT diagram showing planned flow of trial participants through the trial

2. TIMING AND REPORTING INTERIM AND FINAL ANALYSES

Data will be analysed at the end of the study; other than as requested for DMC reporting there are no planned interim analyses. The final trial report will contain full detail of the analytical methodology.

The DMC will meet at least 3 times, at the start, middle and completion of the study. At the first meeting, the committee will agree on its charter of operation, and discuss and advise on the inclusion of an interim analysis and possible adoption of a formal stopping rule for efficacy or safety.

3. RECRUITMENT AND RANDOMISATION

3.1 Recruitment

Initially planned recruitment was a target of 372 participants over 24 months. Slower than anticipated recruitment led to this being extended in time by 5 months and permission was also obtained for all available time to be used in order to allow for a possibility higher than anticipated loss to follow-up rate. The first patient was randomised on 26 November 2013. The study closed to recruitment on the 29th January 2016. Final recruitment was 404 participants.

Data snapshots were taken for production of closed DMC reports for meetings dated 17 November 2014, 12 June 2015, 15 January 2016, 10 June 2016 & 9 December 2016. An initial DMC meeting took place on 29 April 2014 without data analysis.

After last patient last visit an unblinded data snapshot is planned to be taken on 31 March 2017 to allow development of data analysis and data cleaning. A final data-lock and data download is intended to take place on 30 April 2017.

Figure 2: Plot of recruitment over time

3.2 Randomisation

Randomisation was administered centrally by the Newcastle CTU secure web-based system. Permuted random blocks of variable length were used to allocate participants 1:1 to the control and experimental groups and ensure concealment of allocation from central trial staff. An individual not otherwise involved with the study produced the final randomisation schedule. Stratification by three variables; prior frequency of UTI: < 4 episodes per year and ≥4 episodes per year, a diagnosis of neurogenic lower urinary tract dysfunction: yes or no, and gender: female or male, was performed prior to randomisation to ensure balanced allocation within these factors.

Number of patients randomised in each treatment arm will be tabulated by strata during analysis.

3.3 Blinding

Assignment to either prophylaxis or no prophylaxis was not blinded to either the participant or investigator or the local research staff (non-blinded study). However central trial staff responsible for data management, entry and analysis were unaware of allocated intervention where possible.

4. STUDY POPULATION

4.1 Baseline Patient Characteristics

Demographic and clinical baseline characteristics, and trial stratification factors at randomisation will be compared across treatment groups descriptively. Descriptive statistics will be tabulated by treatment group and overall participant population.

No significance testing will be carried out due to the randomised nature of the study.

Demographic characteristics for comparison are age, and gender.

Clinical characteristics for comparison will include the individual performing CISC (self or other), presence of asymptomatic bacteriuria, type of catheter (hydrophilic or non-hydrophilic, use of antibiotic prophylaxis for UTI in the 12 months prior to randomisation, use of non-antibiotic prophylaxis, presence of intestinal segment transposed to bladder. Additionally, we will tabulate the average number of catheters used per 24 hours (≤5 and >5), average duration of use of catheterisation (months) and calculated glomerular filtration rate (GFR).

In addition to gender (above), stratification factors for comparison are prior rate of UTI – both as stratification group & actual recorded value, and presence of neurological cause for bladder dysfunction.

4.2 Defining Populations for Analysis

An analysis of the primary outcome measure for the full study will be performed both for the full data set and for the separate subgroups defined by high and low baseline UTI rate (as specified during stratification for the randomisation process) using both the Poisson rate test and an incidence density ratio approach to allow for the different treatment durations; regression or generalised linear modelling approaches will be used to adjust for the effects of covariates.

All statistical analyses will be carried out on an intention to treat basis, retaining patients in their randomised treatment groups and including protocol violators, patients found to be ineligible post-randomisation and patients who, despite having withdrawn from treatment have consented to continued follow-up. In addition to this, patients who have been affected by errors during the randomisation process (such as incorrect stratification values being entered) will be retained within their allocated arms. The number of these will be reported and the true values of these potential covariates used during the analysis.

Ineligible patients will be classed as those randomised patients who are found to subsequently not adhere to the eligibility criteria of the trial. The number of ineligible patients and reasons for ineligibility will be reported. A sensitivity analysis may be conducted and reported if the number of ineligible patients is > 10%. Similarly, the number of patients switching treatment arms during the study will be reported. If the number here is > 10%, alternative analyses (i.e. per-protocol) may be explored.

Additionally, participants whose follow-up visits or telephone calls fall outside of the specified time window may have affected outcomes excluded from the analysis. However, much of the data collected at these visits/calls is duplicated in returned questionnaires. Should questionnaire data be available within the visit time window then this data will be used in preference in the event of any discrepancy. A sensitivity analysis may be untaken to compare the analyses with and without data from these participants.

5. TREATMENT RECEIVED

Planned Interventions
This trial is pragmatic in design and, apart from randomisation to prophylaxis/no prophylaxis strategies and collection of outcome data, participant care will follow standard pathways in participating NHS sites across both primary and secondary care. Participants in both trial groups will receive discrete courses of antibiotics as decided by the responsible clinician for treatment of symptomatic UTI. Both experimental and control strategies are in routine NHS use and we will, by consensus amongst clinician co-applicants and patient representatives, specify these strategies clearly in the trial information literature.

Antibiotic prophylaxis (experimental arm)
The experimental intervention is the use for 12 months of a once-daily low dose of an antibiotic active against common urinary pathogens. The agent to be used (nitrofurantoin, trimethoprim or cefalexin) will be selected by the responsible clinician depending on patient characteristics such as previous use, allergy, renal function, prior urine cultures and local guidance.

No prophylaxis
The control arm will be a strategy of no prophylaxis. Participants will self-monitor their symptoms as usual and report to their GP if they develop symptoms and signs suggestive of UTI requiring treatment.

The numbers randomised into each group in addition to the number of protocol violators (including those discontinuing the allocated intervention) and reasons for violation will be reported.

6. SAFETY ANALYSIS

The number of treatment related serious adverse events (SAE), including treatment related deaths, are reported divided by their relatedness. Related SAEs are those assessed as ‘definitely’, ‘probably’ and ‘possibly’ related to treatment and unrelated SAEs are those assessed as ‘unlikely’ and ‘unrelated’. The proportions of patients experiencing AEs with severity judged as mild, moderate and severe (categories 1, 2 and 3 respectively) will be compared descriptively across treatments and differences assessed for clinical significance but not statistical significance. Similarly the proportions of patients with SAEs judged as ‘life-threatening’, ‘involved prolonged inpatient hospitalisation’, ‘involved persistent or significant disability or incapacity’ and ‘other significant medical event’ (categories 1, 2, 3 and 4 respectively) or an SAE that resulted in death will be compared descriptively across treatments and differences assessed for clinical significance.

6.1 Recording & Reporting of Adverse and Serious Adverse Events or Reactions:

Adverse events that occur but are not covered by the exclusion criteria listed in section 19.3 of the protocol should be reported. The reporting procedure to be followed will depend on the seriousness of the adverse event and are described in the following section.

6.2 Adverse Event (including Adverse Reaction):
All non-serious adverse events /reactions during antibiotic prophylaxis will be reported on the study eCRF and monitored on the trial database by the NCTU management team. Severity of AEs will be graded on a three-point scale (mild, moderate, severe). Relation of the AE to the treatment should be assessed by the investigator at site.

Additional to this reporting, the subset of adverse events related to prophylaxis and treatment antibiotics will be considered as a secondary outcome as detailed later in the document.

6.3 Serious Adverse Event / Reaction (SAE/SAR, including SUSARs):
All SAEs, SARs & SUSARs shall be reported to the Trial Manager and Chief Investigator within 24 hours of the site learning of its occurrence. In the case of incomplete information at the time of initial reporting, all appropriate information should be provided as follow-up as soon as this becomes available. Relationship of the SAE to the treatment should be assessed by the investigator at site, as should the expected or unexpected nature of any serious adverse reactions. The MHRA and main REC will be notified by the Sponsor of all SUSARs occurring during the study according to the following timelines; fatal and life threatening within 7 days of notification and non-life threatening within 15 days.

7. EFFICACY ANALYSIS

7.1 Definition and Calculation of Efficacy Outcome Measures

Primary outcome measure
Difference in incidence of symptomatic UTI during the 12-month observation period defined as the presence of at least one patient-reported or clinician-recorded symptom from a predefined list encompassing the recommendations of the British Infection Association (BIA) [7], the Centres for Disease Control and Prevention (CDC) [8] and spinal cord injury UTI consensus statement [9] together with taking a discrete treatment course of antibiotics prescribed by a clinician or as part of a patient-initiated self-start policy.

The rate of UTI in each arm will be defined as the incident density rate; the total number of UTI suffered across all patients during the total observation period minus days spent taking treatment courses of antibiotics active against urinary tract organisms.

More formally, the incident density rate in each arm is defined to be

$$\frac{\text{Total \# of UTI suffered across all patients}}{\text{(Total observation period)} - \text{(Total \# days spent taking treatment)}}.$$

Where data on the treatment course duration is not available this will be assumed to be 1 week. We will determine this outcome by collection of the following data:

Variable: Occurrence of symptomatic UTI with prescription of a treatment course of antibiotic

- Participant log with report alert sent by participant to trial staff
- Contact with each participant at least every three months by local trial staff and more frequently if required to aid participant recording of UTI episodes
- Response to specific enquiry in participant questionnaire completed at 3, 6, 9 and 12 months
- End of trial review of hospital and primary care record at 12 months
- For any identified treatment course of antibiotics for UTI the participant will be asked to complete a multiple-choice description of symptoms that precipitated the request for antibiotic treatment.

To ensure consistent attribution we will set a hierarchy of evidence on which to base the primary outcome with notes on each circumstance:

First will be participant-reported episodes of symptoms that they considered to be due to UTI and for which they obtained treatment with an appropriate antibiotic.

- If in discussion with the participant there is uncertainty as to whether an antibiotic was taken or if the stated antibiotic was not of a type normally used for UTI, the relevant GP or hospital record will be checked for confirmation that a prescription for an antibiotic to treat UTI was issued (including previous prescription for self-start therapy).
- Where no antibiotic prescription was found in the record we will ask the participant to confirm the origin of the prescription.
- If we were unable to confirm issuing of either a single course or self-start supply of antibiotics then the primary outcome will not be fulfilled.

The second type of event would be the identification of a prescription of an antibiotic during planned 3-monthly interrogation of healthcare records without a participant report of a UTI.

- In this case the participant will be contacted to check that they did take a treatment course of antibiotics at that time and assess their symptom status.
- If the participant had no recollection of the antibiotic course or if there was no evidence from the participant or healthcare records of any change to baseline urinary symptoms then the episode will be judged not to have fulfilled the primary outcome.

UTI records are reviewed by trial staff to determine whether the requirements of the primary outcome are fulfilled.

- Should there be any uncertainty regarding the attribution of primary outcome queries are raised with the site concerned in order to source additional information before a final decision on attribution is reached.

Similar processes are followed for a number of the secondary outcomes listed below.

For clarity, the end of a UTI is to be considered as 14 days after the end of the final treatment antibiotic course; this means that should a further course of treatment antibiotics be prescribed for UTI before the end of 14 days since the previous this will be considered a single UTI episode.

We may further consider a sensitivity analysis where participants with UTIs confirmed microbiologically and/or treated with antibiotics but without evidence of symptoms are added to those with a fully confirmed symptomatic UTI primary outcome. This would be

reported in addition to the main analysis and undertaken as described for the formal secondary outcomes.

Secondary outcome measures

Secondary outcomes will be collected either as additional criteria to the primary outcome from inspection of participant health care records, or by participant questionnaire, or by clinical test performed at specific time points. For the following secondary outcome measures, rates are defined in an analogously to the primary outcome.

Febrile UTI rate

This is defined as the primary outcome measure combined with the presence of a recorded fever of more than 38°C. For clarity, a febrile UTI event would consist of an event confirmed as meeting the primary outcome criteria with the additional requirement of a recorded temperature of more than 38°C.

Hospitalisation due to UTI over 12 months rate

Hospitalisation due to UTI defined as an unplanned visit to hospital for treatment of a UTI which required at least one overnight stay in hospital.

Microbiologically-confirmed symptomatic UTI rate

This is defined as the primary outcome measure combined with a positive urine culture result from the central laboratory

Antibiotic prescription for asymptomatic UTI rate

This is defined as the presence of an antibiotic prescription for UTI without participant-reported or clinician recorded evidence of symptom change.

Asymptomatic bacteriuria rate

Asymptomatic bacteriuria defined as a positive urine culture in the absence of symptoms

Overall satisfaction with allocated treatment strategy

Participants will complete the treatment satisfaction questionnaire for medication (TSQM, version 1.4) at 12 months as part of their completion of trial questionnaire. This will be reported as four separate scores from the subscales (Effectiveness, Side-effects, Convenience & Global Satisfaction).

Additionally, the generic health-related quality of life SF36 questionnaire will be analysed by the health economics team. As such, is beyond the scope of the statistical analysis plan and will be detailed separately in a similar health economics document.

Adverse events related to prophylaxis and treatment antibiotics

The rate of these events will be determined from the safety monitoring as described previously. For clarity, the earlier reporting is purely from a safety perspective whereas here we consider only this specific subset of the safety data as an outcome measure for analysis.

Renal and liver function

These will be measured by calculated glomerular filtration rate (GFR) and serum level of alanine transaminase (ALT) respectively. These will be checked at randomisation and at 12 months and the change reported per arm.

7.2 Descriptive Analyses

In addition to the baseline characteristics (defined in section 4.1), the outcome measures defined above (section 7.1) will be tabulated by group at baseline where possible*. No statistical testing between groups will be performed. They will be presented, by group, as summary statistics (e.g. mean, standard deviation and 95% confidence interval or number and percentage as appropriate).

*The TSQM scales scores are only available at 12 months and so will not be presented at baseline.

7.3 Hypothesis Testing

The primary hypothesis to be tested is:

"There is no difference in UTI rate (primary outcome) between groups treated with and without prophylactic antibiotics".

Similar null hypotheses of no difference between the arms will be examined in relation to the other specified outcome measures.

All analyses will compare the outcome measures between the trial arms, either with simple univariate testing, or by inclusion of arm as a modelling covariate.

Primary Outcome

Analyses of the primary outcome measure for the full study will be performed using both the Poisson rate test (as a simple univariate approach) and an incidence density ratio modelling approach to allow for the different treatment durations; regression or generalised linear modelling approaches will be used to adjust for the effects of covariates. For clarity, the simple univariate analysis will be considered the primary analysis for reporting purposes. This will be the case for all analyses of this and other outcome measures described.

Specifically, Poisson regression will be used with an offset variable to allow for different durations of exposure measured in person-years in terms of available follow-up in patients at the 12 month time point. Patients will be considered to have available follow-up and a valid estimate of UTI rate should reliable follow-up be established for at least 6 of the 12 months post-randomisation. For clarity, this can be any 6 months of the 12 rather than any specific 6 month block.

The model selection process will include the stratification factors (prior rate of UTI, presence of neurological disease and gender) and other baseline variables (individual performing CISC (self or other), asymptomatic bacteriuria, age, type of catheter, use of antibiotic prophylaxis for UTI in the previous 12 months prior to randomisation, presence of intestinal segment transposed to bladder). The inclusion of interaction terms such as site will also be explored. The inclusion of baseline values as covariates will additionally enable the examination of possible interactions between effects observed and these values. Not all covariates mentioned above will be included in the final model but all will be considered during the model selection process.

Analysis will concern events during the full (12 month) study period. The optional 18 month follow-up data will be considered as part of future analysis plans below.

A two-sided significance level of $p<0.05$ will be used throughout.

Secondary clinical outcomes

- Febrile UTI rate
- Hospitalisation rate due to UTI during the 12 months
- Microbiologically-confirmed symptomatic UTI rate
- Antibiotic prescription for asymptomatic UTI rate
- Asymptomatic bacteriuria rate
- Adverse events rate (those related to prophylaxis and treatment antibiotics)

Analyses of these outcome measures will follow the same approaches as for the primary outcome and will use the model developed during the primary outcome analysis. The incidence density ratio approach will not be used for adverse events (those related to prophylaxis and treatment antibiotics).

Overall satisfaction with allocated treatment strategy

Participants will complete the treatment satisfaction questionnaire for medication (TSQM) at 12 months as part of their completion of trial questionnaire.

This consists of four separate scores from subscales (Effectiveness, Side-effects, Convenience & Global Satisfaction). Subscales will be scored using the algorithm for TSQM version I [16]

In addition to univariate analyses using the 2-sample t-test, an Analysis of Covariance (ANCOVA) approach will be employed for each subscale using the covariates identified during the primary outcome modelling.

Adverse events related to prophylaxis and treatment antibiotics

Will be analysed analogously to other secondary clinical outcomes (see above).

Renal and liver function

The change from baseline at 12 months (as measured by calculated glomerular filtration rate and serum level of alanine transaminase (ALT)) will be analysed as follows:
In addition to univariate analyses via the 2-sample t-test, an Analysis of Covariance (ANCOVA) approach will be employed for each measure using the covariates identified during the primary outcome modelling.

Microbiological data

Resistance patterns, specifically the detection rate for resistance to specific antibiotics at any point during 3 month time periods ((0,3], (3,6], (6,9], (9,12] months) (for those patients with available samples), will be summarised by trial arm. In line with other outcome measures, these will be compared for each antibiotic in the (9,12] month time period using the chi-squared test should numbers available be felt sufficient. Tests for trend, potentially including difference in trend between arms, over the 12 month time period may also be considered.

Antibiotics to be included here are:

- Amoxicillin
- Cefalexin
- Ciprofloxacin
- Co-trimoxazole
- Coamoxiclav
- Mecillnam
- Nitrofurantion
- Trimethoprim

See also future analysis plans below.

7.4 Future analysis plans

Following the completion of the RCT at 12-months, participants will be additionally followed up at 18 months post-randomisation for changes in bacterial ecology and clinical decision whether to continue or commence antibiotic prophylaxis. Analysis of data from this time point will not form part of the main study report to funder and will not be considered as part of the main RCT analysis.

It is intended to perform the following analyses on an Intention to Treat (ITT) basis:

Microbiological data

Resistance patterns, specifically the detection rate for resistance to any of the antibiotics tested as part of the central laboratory protocol for urine and perianal swab specimens at any point during 3 month time periods between baseline and 18 months for those participants with available samples, will be summarised by trial arm and by continuation or non-continuation of prophylaxis after the 12 month trial period. These will be compared for each antibiotic using the chi-squared test should numbers available be considered sufficient. Tests for trend, potentially including difference in trend between arms, over the full 18 month time period will also be considered.

Antibiotics to be included here are:

- Amoxicillin
- Cefalexin
- Ciprofloxacin
- Co-trimoxazole
- Coamoxiclav
- Mecillnam
- Nitrofurantion
- Trimethoprim

We will also examine changes in bacterial ecology such as resistance patterns and species of pathogen. Resistance rates (defined as development of resistance to at least one antibiotic at any time point) will also be summarised by group at 3, 6, 9 and 12 months

Clinical Decision

The proportion of patients remaining on their allocated trial intervention at 18 months will be reported by trial arm.

Additional Summary Measure

Additionally, a further measure will be summarised by arm as reported in participant questionnaires at months 3, 6, 9 and 12:

The proportion of patients reporting the use of lifestyle changes/home remedies over the past 3 months, both for the individual items listed below and as a composite measure of use of any of these. Consideration will also be given to tabulating by arm the proportion using these at any point in the full twelve month period.

The items to be considered are:

- Drinking more fluid
- Stopping cigarette smoking
- Vaginal oestrogen tablet or cream
- Cranberry product
- Substances like potassium citrate or sodium bicarbonate to alter the acidity of urine
- Foods or drinks with anti-bacterial properties
- Probiotics

Further Analyses

Additional further analyses may be carried out in future, possibly without the involvement of the full original trial team or the support of IHS Biostatistics.

7.5 Statistical Software

Trial data are input by individual site staff into a MACRO database held and maintained by the Newcastle Clinical Trials Unit.

Data will be downloaded directly from MACRO into statistical software packages including SAS, Stata and R. Statistical analyses will be carried out by the Trial Statistician at NCTU downloading snapshots of the data at time-points agreed by the TMG.

7.6 Missing data

Data with missing observations for the primary outcome due to loss to follow-up will be examined to determine both its extent and whether it is missing at random or is informative. If data are judged to be missing to a sufficient extent (greater than 10%), the use of appropriate multiple imputation techniques will be considered.

More specifically, we may be in a position to calculate a UTI rate from participants who have been lost to follow-up at a later time in the study by using the information known at the point of withdrawal/loss to follow-up. We will endeavour to have as complete outcome data as possible after taking into account the various sources from which it will be possible to confirm UTI events but should this information not cover the full study period then we would use an offset variable in the Poisson regression model in order to allow for the actual duration of follow-up for each individual. As stated above, we would consider participants with available follow-up of 6 months or more of the 12 months post-randomisation as having a valid estimate of UTI rate available.

Should data be collected outside the recognised time window (+/- 4 weeks) then consideration will be given to excluding the patient from the analysis depending on the availability of data from other sources to determine whether outcome criteria have been fulfilled. Should this be thought necessary it would take the form of a sensitivity analysis comparing the analysis with these included or excluded.

8. SUBGROUP ANALYSIS

Analyses as described above will also be performed for the separate subgroups defined by high and low baseline UTI rate (as specified during stratification for the randomisation process: Prior frequency of UTI: < 4 episodes per year and ≥ 4 episodes per year)

Note that the model used for the full data primary outcome will be used rather than a separate modelling process applied for each subgroup. This model will, however, exclude the prior frequency of UTI as a covariate as the separate subgroups for analysis are defined in relation to this measure.

9. STORAGE AND ARCHIVING

The AnTIC study database is stored on the MACRO Clinical Data Management System, on Newcastle University's database on the hosted server (Rackspace in London) provided by Elsevier. Only authorised staff can grant and have control of user permissions and access as outlined in DM-011: Database Setup and Maintenance. Each Data entry clerk/Trial Manager/Trial co-ordinator is assigned a unique password and permissions relating to their role. Any snapshots of the database taken will made in accordance with NCTU DM-012: Release of Data and Database Lock; and be kept on the NCTU server which is backed up daily in accordance with DM-011: Database Setup and Maintenance. Once the final report and related analysis and activities are completed each site will be provided with a copy of their own data, on CD/DVD according to the current NCTU DM-012: Release of Data and Database Lock. A copy of all the sites' data is also filed and archived with the central Trial Master File. In addition the data will remain on MACRO with all user permissions removed. The separate statistics section of the Trial Master File will also be archived alongside the central Trial Master File with a copy of the final data used for analysis after any processing has taken place.

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Appendix: Dummy Tables

These will be repeated as necessary for any subgroup analyses.

Results

Table 1 – Summary of baseline characteristics

	Prophylaxis Group (N =)	No Prophylaxis Group (N =)	Overall (N =)
Stratification Factors:			
Female Gender	n (%)	n (%)	n (%)
Neurological bladder dysfunction	n (%)	n (%)	n (%)
Prior frequency of UTI ≥ 4/year	n (%)	n (%)	n (%)
Other characteristics:			
Age (years)	mean (sd)	mean(sd)	mean(sd)
Catheterisation by self	n (%)	n (%)	n (%)
Duration intermittent catheterisation (months)	mean (sd)	mean(sd)	mean(sd)
Prior rate of UTI (/year)	mean (sd)	mean(sd)	mean(sd)
Intestinal segment transposed to bladder	n (%)	n (%)	n (%)
Previous use of antibiotic prophylaxis in past 12 months	n (%)	n (%)	n (%)
Use of non-antibiotic prophylaxis	n (%)	n (%)	n (%)
Bacteriuria present on baseline urine specimen	n (%)	n (%)	n (%)
Estimated Glomerular Filtration Rate (mL/min/1.73m^2)	mean (sd)	mean(sd)	mean(sd)
Use of hydrophilic catheter	n (%)	n (%)	n (%)
Catheterisation frequency ≤ 5 per day	n (%)	n (%)	n (%)

Table 2 – Primary Outcome

	Prophylaxis group (N=)	No prophylaxis group (N =)	Ratio	P-value
Frequency of symptomatic UTI :				
0	n (%)	n (%)	-	-
1	n (%)	n (%)	-	-
2	n (%)	n (%)	-	-
3	n (%)	n (%)	-	-
≥4	n (%)	n (%)	-	-
Incidence of (at least one) episode of symptomatic UTI over observation period	n/N (%)	n/N (%)	-	-
Mean (sd) episodes of symptomatic UTI	mean (sd)	mean (sd)	-	-
Symptomatic UTI rate (/year)	(Total # episodes)/N	(Total # episodes)/N	Rate Ratio	*
Incidence density rate:				
Unadjusted for covariates (95% CI)	Incidence density rate	Incidence density rate	Rate Ratio	**
Adjusted for covariates (95% CI)	-	-	Rate Ratio	**

* Poisson rate test
** Incidence rate ratio test

Table 3 – Secondary clinical outcomes

Secondary clinical outcomes will be presented in an analogously to that of the primary outcome (see Table 2).

Table 4 – Microbiological outcomes

Variable	Prophylaxis (N =)			No prophylaxis (N =)			P-value
Microbiological UTI frequency:							
0	n (%)			n (%)			
1	n (%)			n (%)			
2	n (%)			n (%)			
3	n (%)			n (%)			
≥4	n (%)			n (%)			
Asymptomatic bacteriuria (any time point during participation)	n/N (%)			n/N (%)			
E. coli isolated during SYMPTOMATIC UTI	n/N (%)			n/N (%)			
E. coli isolated during ASYMPTOMATIC state	n/N (%)			n/N (%)			
	Baseline	**0 < months ≤6**	**6 < months ≤12**	**Baseline**	**0 < months ≤6**	**6 < months ≤12**	
Resistance E. coli to panel antibiotic (during SYMPTOMATIC UTI) :							
amoxicillin							
cefalexin							
ciprofloxacin							
coamoxiclav							
nitrofurantion							
trimethoprim							
Resistance E. coli to panel antibiotic (during ASYMPTOMATIC state) :							
amoxicillin							
cefalexin							
ciprofloxacin							
coamoxiclav							
nitrofurantion							
trimethoprim							
Resistance of perineal isolates of *E. coli* to panel antibiotics:							
amoxicillin							
cefalexin							
ciprofloxacin							
coamoxiclav							
nitrofurantion							
trimethoprim							

Table 5 – Adverse event outcomes

Variable	Prophylaxis (N=)	No prophylaxis (N =)	P-value
Severity:			
None			
Mild			
Severe			
Renal function			
Change in cGFR over 12 months			
Liver Function			
Change in ALT over 12 months			
Bacterial ecology			
Worsening (≥1 additional resistance) of sensitivity of infecting organism (symptomatic UTI)			
Worsening (≥1 additional resistance) of sensitivity of perineal E. coli			