Newcastle University

Alternatives to prophylactic antibiotics for the treatment of recurrent urinary tract infection in women (ALTAR)

Health Economics Analysis Plan

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Table of abbreviations

Abbreviation	
ALTAR	ALternatives To prophylactic Antibiotics for the treatment of Recurrent urinary tract infection in women.
CEA	Cost-Effectiveness Analysis
CUA	Cost-Utility Analysis
HEAP	Health Economics Analysis Plan
HRUQ	Health Resource Use Questionnaire
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness ratio
ITT	Intention-to-treat
NHS	National Health Service
NIHR	National Institute of Health Research
OUA	Oral urinary antiseptic
QALY	Quality-Adjusted Life Year
rUTI	Recurrent urinary tract infection
SAP	Statistical Analysis Plan
SUR	Seemingly unrelated regression

1. Brief summary of the trial – protocol

Background

Continuous low-dose prophylactic antibiotic therapy is the current standard of care for the prevention of recurrent urinary tract infection (rUTI), although this can lead to a rise in antimicrobial resistance and subsequent difficult to treat infections. The **AL**ternatives **T**o prophylactic **A**ntibiotics for the treatment of **R**ecurrent urinary tract infection in women (ALTAR) was funded by National Institute for Health Research (NIHR) Health Technology Assessment (HTA). The aim of this trial is to determine the relative clinical- and cost-effectiveness of two preventative treatments for women with rUTI over a 12-month treatment period and an 18-month follow up period. The design of the trial is a multicentre, pragmatic patient-randomised non-inferiority trial comparing daily prophylactic antibiotic with twice daily oral urinary antiseptic.

Recurrent urinary tract infection in adult women is common. Bacteria from the faecal reservoir inoculate the vaginal periurethral area and then the bladder, causing uncomfortable urinary symptoms termed cystitis. The lifetime risk of a urinary tract infection (UTI) is around 40% in adult women and peaks in the 3rd and 9th decades. The annual incidence of a single UTI is 3% (1) with up to 44% of these women experiencing recurrence within 1 year (2). This equates to an adult female population of over 300,000 annually affected by rUTI in the UK (3). Male UTIs are generally regarded as complicated as they are often associated with underlying structural or functional urinary tract abnormalities therefore men with rUTI were not considered eligible for this trial.

The primary clinical objective of ALTAR is to compare the incidence of symptomatic antibiotic-treated UTI during the 12-month treatment period. Participants will be followed up for 18-months post-randomisation, including the 12-month treatment period. The primary economic objective is to compare the difference in incremental cost per quality-adjusted life year (QALY) over the 12-month treatment period between the treatment arm (oral urinary antiseptic) and the control arm (prophylactic antibiotics). Secondary economic objectives include: 1) incremental cost per QALY over the 18-months follow-up period, 2) incremental cost per UTI avoided over the 12-month treatment period, and 3) incremental cost per UTI avoided over the 18-month follow-up period. Data will be collected at baseline, 3, 6, 9, 12, 15 and 18 months post-randomisation.

2. Outline of the economic analysis

The key objective of this health economic analysis plan (HEAP) is to outline the framework and methodology of the economic evaluation that will be utilised in the ALTAR trial. The methodology employed in the analysis will be twofold: 1) a within trial analysis, and 2) a model-based analysis, which will consider the longer-term implications of the intervention. This within trial economic evaluation will include both cost-effectiveness analyses (CEA) and cost-utility analyses (CUA). All analyses will estimate costs using the same methodology but will differ in how outcomes are measured; the CEA will estimate the cost per UTI avoided and the CUA will estimate the cost per QALY gained. Further details of these analyses are presented in Section 3.

The perspective of the trial is that of the UK National Health Service (NHS) and Personal Social Services. In a further sensitivity analysis a wider societal perspective, considering participant costs, will be adopted. The main costs will be healthcare resource use costs i.e. the average total cost per patient to the NHS to manage UTIs. Participant costs will include direct (e.g. out of pocket purchases of private health care costs) and indirect (e.g. time off paid work/usual activities and travel) costs.

For the economic evaluation the following outcomes will be reported at both 12 months (end of the treatment phase) and 18 months (end of the follow-up period) post-randomisation:

- NHS and Personal Social Services costs of managing rUTI
- Participant costs associated with rUTI
- Total number of UTI's
- QALYs estimated based on responses to the EQ-5D-5L administered at baseline, 3, 6, 9, 12, 15 and 18 months.
- Incremental cost per UTI avoided
- Incremental cost per QALY gained

3. Within Trial Analysis

Using cost and effectiveness data derived from the trial allows us to estimate the relative cost-effectiveness of the intervention in comparison to the current treatment. The economic analysis will be conducted as a modified intention-to-treat (ITT) and will adopt the same assumptions as the statistical ITT analysis set out in the SAP (v2.0) Section 3.3. A sensitivity analysis may consider the implications of a modified ITT analysis and conduct a strict ITT and per protocol analysis for comparison (SAP).

3.1 Structure of within trial analysis

The within trial analysis is structured as a two-arm comparison estimating the cost-effectiveness between the treatment (oral urinary antiseptic) and control (prophylactic antibiotic). The primary objective of the within trial analysis considers the relative cost-effectiveness of the two treatments over the 12-month treatment phase, while a secondary objective considers the implications of the intervention over an 18 month time-horizon (the 12-month treatment phase plus 6-months additional follow-up). Information on timing and type of data collected is presented in table 13.

3.1.1 Description of treatment options

As briefly described above in the study summary and in more detail in the study protocol (4) the treatment and control being analysed within ALTAR are:

C = Prophylactic antibiotic

For those women randomised to receive antibiotic, a once-daily prophylactic low dose will be prescribed for 12 months. The agent to be used will be active against common urinary pathogens and selected by the responsible clinician depending on patient characteristics such as previous use, allergy, renal function, liver function, prior urine cultures and local guidance. Available evidence suggests use of nitrofurantoin 50 mg or 100 mg, trimethoprim 100 mg, or cefalexin 250 mg, in that order of preference.

T = Oral urinary antiseptic (Methenamine hippurate)

For those women randomised to receive Methenamine hippurate a twice daily dose of 1g to be taken 12 hours apart will be prescribed for 12 months (as recommended in the British National Formulary; BNF).

3.1.2 Format of the incremental analysis

Table 3.1.2 is an illustrative example of how costs, effects and the ICER will be presented for all analyses in the economic evaluation.

Table 3.1.2: Incremental cost-effectiveness of oral urinary antiseptic vs. prophylactic antibiotics (an illustrative example)

Treatment Arm	Costs	Incremental costs	Effects	Incremental effects	ICER
C. Prophylactic antibiotic	C		C		-
T. Oral urinary antiseptic	T	Δ costs	T	Δ effects	ΔCosts/ΔEffects

*ICER = Incremental cost-effectiveness ratio; Δ = difference between C & T.

Differences between costs and effects between the treatment and control groups will be identified from the presentation of the results and the treatment option most likely to be considered cost-effective for prevention of rUTI will be identified.

3.2 Costs and frequency of services

NHS costs and participant costs included in the economic analysis are summarised in Figure 1. NHS costs included intervention costs, primary care resource use, secondary care resource use, and medication costs. These costs were estimated based on the frequency of healthcare reported in the Health Resource Use Questionnaire (HRUQ) at baseline, 3, 6, 9, 12 and 18 months and the unit cost for each healthcare resource collected from routine sources (5, 6). Costs to the participant and their main caregiver will be estimated based on responses to the HRUQ for private healthcare costs while time and travel costs were obtained from prior research. All costs will be reported in GBP (£).

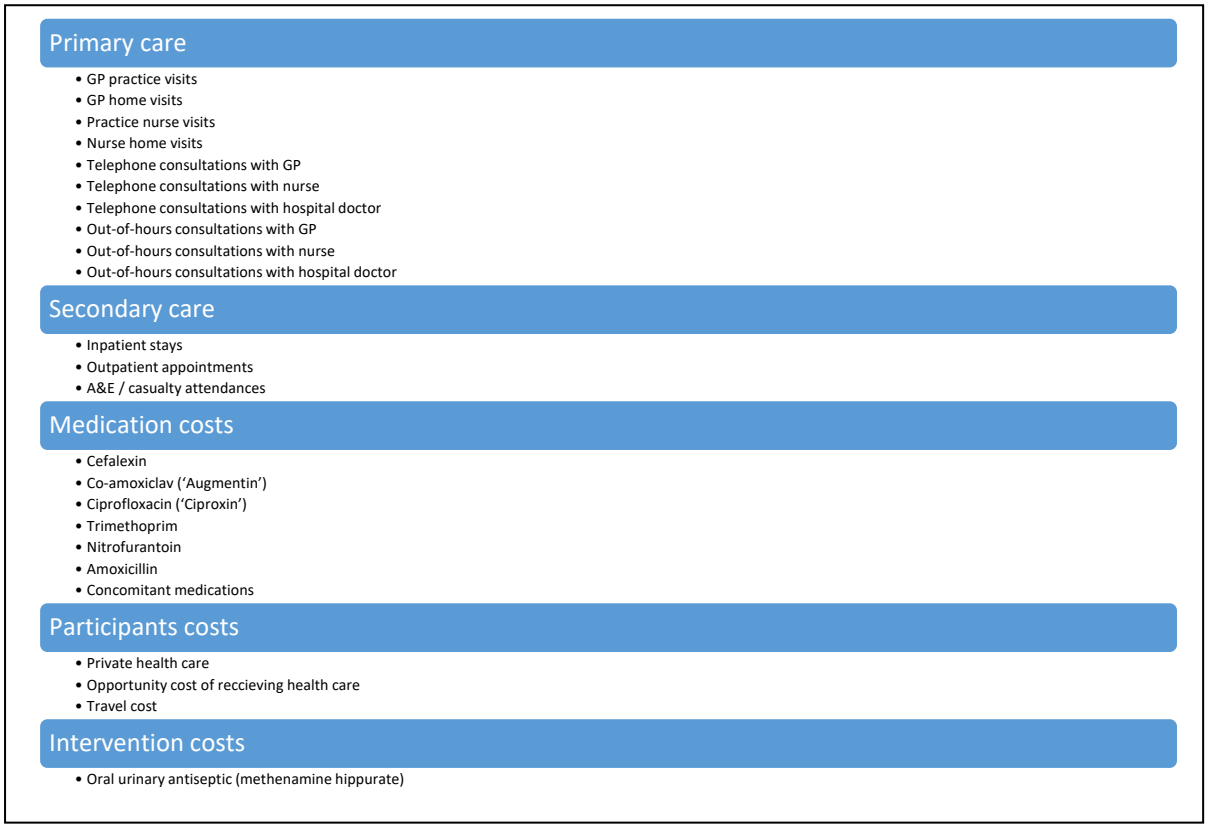

Figure 1: NHS resource use and cost to the participant and their main caregiver

3.2.1 Intervention costs

Information on the intervention medications will be collected in the CRF completed at baseline, 3, 6, 9, 12, 15 and 18 months. The CRF contains information on the dosage, frequency, and duration of the medications taken by participants over their 12-month treatment phase. The unit cost of each medication will be combined with the dosage, frequency, and duration for each participant to estimate the total intervention cost per participant.

3.2.2 Follow-up costs

Primary care costs

Primary care costs can be categorised as consultations with general practitioners (GPs), pharmacists, dentists, optometrists or nurses (7). These consultations can be broken down further to specify the type of consultation (i.e. practice consultations, home visits, phone consultations and out-of-hours consultations). It is necessary to specify this information because each different permutation of primary care consultation incurs a different unit cost. The number of primary care consultations will be quantified based on responses to the HRUQ and the unit costs for each consultation will be obtained from routine sources (5). The number of consultations will be multiplied by the unit cost of that consultation for each participant to estimate the total primary care cost per participant and total primary care cost per randomised arm. The average total cost per participant will be estimated for both the treatment and control arms and presented as summary statistics (mean(standard deviation), median(Interquartile range)) and any potential differences in primary care costs between the two arms can be identified.

Secondary care costs

Secondary care can be broken down into inpatient and outpatient visits. The data collected in the HRUQ informs us on the duration of the stay as an inpatient and this can be combined with the inpatient bed day cost. The inpatient bed day cost will be assumed to be the average inpatient bed day cost which is presented in the NHS Reference Costs 2017/18. In calculating the total A&E cost per person, the A&E visit unit cost will be combined with the number of visits (given in the HRUQ). The unit costs for secondary care will be collected from routine sources such as the NHS Reference Costs 2017/18 (6).

Similarly to inpatient data, the number of hospital outpatient appointments obtained by each patient are recorded in the HRUQ although information on the type of appointment is not given. We will assume hospital outpatient appointments occur in urological clinics and use the urology outpatient appointment unit cost to calculate total outpatient cost per person. The total cost of secondary care and the average cost of secondary care per participant will be presented in table 5 for both the treatment group and control group.

Medications

Information regarding concomitant medication will be derived from the concomitant medication form and will be combined with the unit costs which are collected from routine sources (8). The medication type, dose, duration and frequency is recorded in the concomitant medication form. Reported medication use will be combined with the corresponding unit costs from routine sources (8) to estimate the total medication cost

per participant. The average total cost of medications per participant will then be estimated for both the treatment and control arms as summary statistics.

3.2.3 Participant costs

The vast majority of costs involved in managing rUTI are incurred by the NHS, however there are certain costs that are borne by the participants and their caregivers. These can be broken down into either time and travel costs or private healthcare costs. Data on private healthcare utilisation are recorded in the HRUQ and is expressed in monetary terms (GBP/£). Information on the type of private healthcare used is specified in the HRUQ and relevant healthcare costs will be included in the cost analysis. Participant costs are totalled for each participant so the average total participant cost can be estimated for both treatment arms.

Time and travel data was not collected as part of this trial to reduce participant burden. Alternatively, time and travel cost information will be derived from prior research, namely, the continuous low-dose antibiotic prophylaxis for adults with repeated urinary tract infections (AnTIC) trial (9). The AnTIC trial investigated the clinical- and cost-effectiveness of antibiotic prophylaxis in the reduction of symptomatic, antibiotic-treated UTIs suffered by patients performing intermittent bladder catheterisation over a 12-month follow-up period (9).

It is assumed that the time and travel costs incurred by participants in the AnTIC trial will be similar to the costs incurred by participants in the ALTAR trial due to similar treatment procedures in a similar population. This assumption will be verified by summarising the baseline characteristics in each trial to ensure comparability. The time and travel costs provided in the AnTIC report will be inflated to the correct price year to account for inflation (9).

Therefore, total time and travel cost per participant will be estimated by using the average costs for time and travel derived from the data obtained in the AnTIC study (9). The time and travel costs associated with each resource will be combined with the frequency of use to yield a patient time and travel cost estimate. Unit time and travel costs for each resource used are presented in the table below.

Table 3.2.3: Average Time and Travel Costs per resource use as presented in the AnTIC study

	Time and Travel Cost		
	Total	**Intervention**	**Control**
Inpatient	100.10	102.62	98.17
Outpatient	38.26	38.78	37.76
GP	15.66	20.84	10.87

*Mean costs per visit (£)

Total Cost

In order to satisfy the objectives of the economic evaluation it is necessary to estimate a total cost per participant across both arms of the trial. This was conducted by adding together the intervention costs, follow-up costs, and participant costs reported by each participant over the 12-month treatment phase. This calculation will be replicated to account for the additional 6-month follow-up and the total treatment cost per participant will be estimated for the total 18-month follow-up period. Once all costs are

aggregated, average total costs for each type of care will be estimated for both treatment arms. Table 10 and 11 summarise how this data will be presented.

3.3 Effectiveness

Two effectiveness measures will be used in this economic evaluation, one for each of the analyses; incidence of UTI's for the CEA and QALYs for the CUA.

3.3.1 Estimation of incidence of UTI's

Estimation of the UTI incidence rate will follow the same methodology as the SAP v2.0 (section 5.1) and be calculated as the number of episodes divided by the total observation time. Episodes of UTI that take place after the treatment phase (>12 months) will be discounted at the NICE recommended rate of 3.5% (10). Table 7 summarises how the clinical effectiveness estimates will be presented.

3.3.2 Estimation of QALYs gained

QALYs will be estimated based on the responses to the EQ-5D-5L administered at baseline, 3, 6, 9, 12, 15 and 18 months. The EQ-5D-5L is also administered at the time of UTI during the trial. Responses to the EQ-5D-5L will be 'crosswalked' to the EQ-5D-3L value sets using the van Hout et al (2012) mapping function (11). This method is currently recommended by NICE (12). Once the utility values have been estimated then they are combined with the duration of time (expressed in months) that an individual 'receives' the level of utility for. The combination of these two pieces of information results in the estimation of a QALY using the Morris et al (2006) 'area under the curve' method (13). This can be calculated mathematically using the equation in the example below. Table 9 summarises how the utility and QALY data will be presented.

QALY estimation over the 12-month treatment phase with no UTI's occurring

$$QALY = \frac{EQ5D_{bl} + EQ5D_{3mths}}{2} * \frac{3}{12} + \frac{EQ5D_{3mths} + EQ5D_{6mths}}{2} * \frac{3}{12} + \frac{EQ5D_{6mths} + EQ5D_{9mths}}{2} * \frac{3}{12} + \frac{EQ5D_{9mths} + EQ5D_{12mths}}{2} * \frac{3}{12}$$

QALY estimation over the 12-month treatment phase and 6-month follow-up with no UTI's occurring

$$QALY = \frac{EQ5D_{bl} + EQ5D_{3mths}}{2} * \frac{3}{12} + \frac{EQ5D_{3mths} + EQ5D_{6mths}}{2} * \frac{3}{12} + \frac{EQ5D_{6mths} + EQ5D_{9mths}}{2} * \frac{3}{12} + \frac{EQ5D_{9mths} + EQ5D_{12mths}}{2} * \frac{3}{12} + \frac{EQ5D_{12mths} + EQ5D_{15mths}}{2} * \frac{3}{12} * \beta + \frac{EQ5D_{15mths} + EQ5D_{18mths}}{2} * \frac{3}{12} * \beta$$

*QALY's accrued past 12 months will be adjusted by discount factor (β) as recommended by NICE

Additionally, participants could report experiencing a UTI between the fixed timepoints the EQ-5D-5L is collected. This UTI could lead to a fall in utility which may only be partially captured by the EQ-5D-5L score at the fixed time points. Participants were asked to complete an EQ-5D-5L questionnaire for each UTI they had so that QALYs can be estimated with the impact of a UTI on utility accounted for. The QALY equation and graph below illustrate the effect of having a UTI on utility and take account of this when calculating QALY values.

A sensitivity analysis will consider the effect of UTIs on utility and QALY values. The analysis will assume that UTIs have a three day duration before the symptoms begin to resolve and will use the utility value obtained from the UTI Record. A three day duration was based on clinical guidance, this duration will be changed to five days in a sensitivity analysis to equate to the same duration of UTIs chosen in a previous study (9).

QALY estimation over the 12-month treatment phase with a UTI occurring at 7 months

$$QALY = \frac{EQ5D_{bl} + EQ5D_{3mths}}{2} * \frac{3}{12} + \frac{EQ5D_{3mths} + EQ5D_{6mths}}{2} * \frac{3}{12} + \frac{EQ5D_{6mths} + EQ5D_{9mths}}{2} * \frac{91.4 - 3}{365} + EQ5D_{UTI} * \frac{3}{365} + \frac{EQ5D_{9mths} + EQ5D_{12mths}}{2} * \frac{3}{12}$$

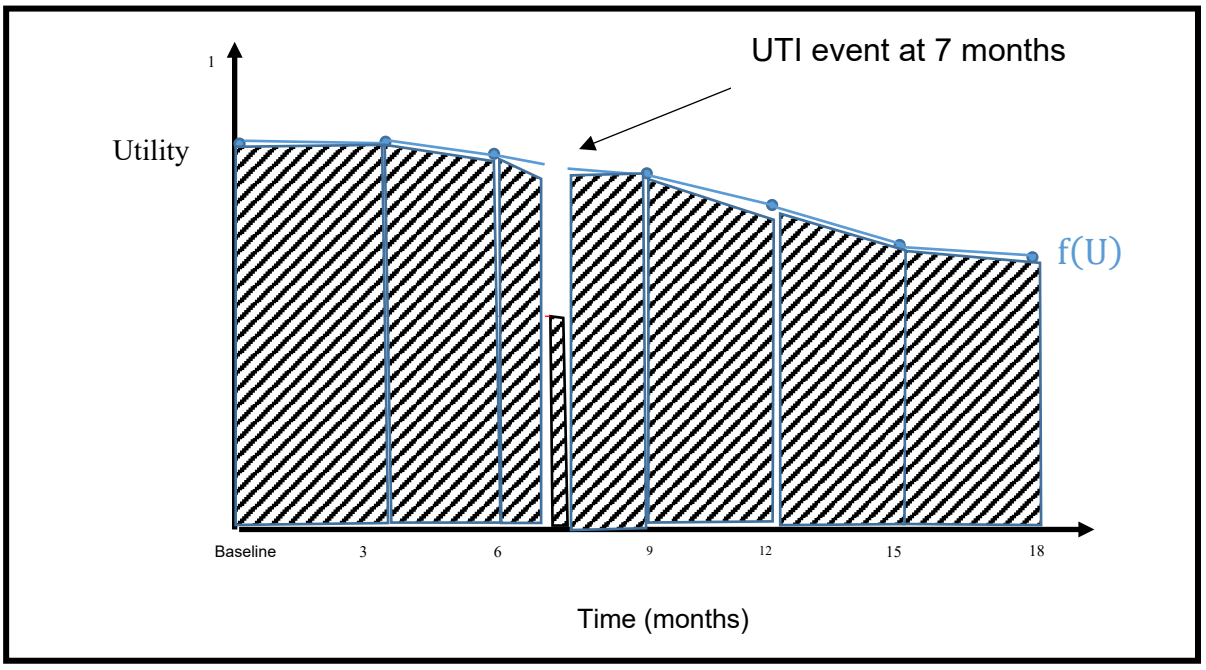

Figure 1: Effect of UTI on utility

3.4 Discounting

All participants are being followed up for 18-months post-randomisation. As a result, costs and effects that are incurred beyond the 12-month time horizon will be discounted by discount factor (β) which is set at the UK recommended rate (10).

3.5 Economic Evaluation

Both unadjusted and adjusted analyses will be performed to estimate the cost-effectiveness of urinary antiseptics compared to prophylactic antibiotics. All results will be presented as point estimates of mean incremental costs, effects and cost-effectiveness.

If one arm is found to be less costly and more effective, it is the dominant strategy and hence is considered to be cost-effective (14). If however, one arm is on average, more costly and more effective, a judgement has to be made as to whether this

treatment is cost-effective. Judgements are made based on the incremental cost-effectiveness ratio (ICER) and society's willingness-to-pay for an additional unit of benefit.

3.5.1 Cost-effectiveness analysis

The cost-effectiveness analysis will be based on the incremental cost per UTI avoided. The average total cost and average number of UTIs will be estimated for both treatment groups. These will be presented as point estimates of the mean incremental costs and effects and the mean incremental cost per UTI avoided. There is currently no NICE threshold from which the cost per UTI avoided can be compared. However, as part of the AnTIC study (9) participants' willingness-to-pay to avoid a UTI was estimated. This value will be used to assist in interpreting the results from the CEA if neither treatment strategies is dominant.

3.5.2 Cost-utility analysis

The cost-utility analysis will be based on the incremental cost per QALY gained. The average total cost and average total QALYs will be estimated for both treatment groups. These will be presented as point estimates of the mean incremental costs and effects (QALYs) and the incremental cost per QALY gained. Society's current willingness-to-pay in the UK is approximately £20,000 per additional QALY hence if the oral urinary antiseptic is not dominant but the ICER is within this threshold it could be considered cost-effective by NHS decision-makers.

3.5.3 Adjusted Analysis

Calculation of the adjusted ICER will be conducted using a seemingly-unrelated-regression model (SUR) which estimates the costs and effects simultaneously to account for unobservable individual characteristics that could affect the estimates (15). In addition to controlling for unobservable individual characteristics, the SUR allows for the inclusion of covariates into the regression model (baseline utility, number of UTI's in the past, menopausal status) to control for confounding variables. Variables included as covariates in the SUR model will replicate those included in the SAP v2.0 section 5.1. A 95% confidence interval surrounding the adjusted mean difference will be estimated. The adjusted incidence rate in each treatment group is presented in Table 12.

3.6 Sensitivity Analysis

Sensitivity analyses will be conducted to assess the robustness of the results to realistic variations in the levels of underlying data. Deterministic sensitivity analysis will be conducted to assess the implications of the assumptions made during the economic evaluation (e.g. the effect of UTIs on QALYs). A stochastic sensitivity analysis will be conducted using non-parametric bootstrapping to explore the statistical precision surrounding the estimates for costs, effects and cost-effectiveness. Bootstrapping results will be used to estimate confidence intervals for costs and effects.

Bootstrapped estimates of ICERs from the cost-utility and cost-effectiveness analyses will be used to populate the cost-effectiveness plane to illustrate the uncertainty in costs and effects.

Cost-effectiveness acceptability curves (CEACs) will be presented for both the cost-utility and cost-effectiveness analyses to graphically illustrate the probability of each treatment being considered cost-effective at different societal willingness-to-pay values.

3.7 Missing Data

Economic evaluations that occur alongside RCTs are often subject to missing data due to withdrawals, mistakes in questionnaire completion and loss-to-follow-up. Decisions on data imputation will be made based on the pattern of missing data However a number of methods that will be considered are: 1) a complete case analysis which only includes participants with complete data and 2) multiple imputation methods can be undertaken under the assumption that those with missing data are missing-completely-at-random (MCAR) (16). Comparisons in baseline characteristics between those missing data and those with complete data will be undertaken to assess the plausibility of the missing at random assumption.

4. Dummy Tables

Table 1: Unit costs – Antibiotics and Antiseptic - During treatment and daily usage

	Unit	£	Source
Antibiotics			
Cefalexin	Per dosage		Bnf.org
Co-amoxiclav ('Augmentin')	Per dosage		Bnf.org
Ciprofloxacin ('Ciproxin')	Per dosage		Bnf.org
Trimethoprim	Per dosage		Bnf.org
Nitrofurantoin	Per dosage		Bnf.org
Amoxicillin	Per dosage		Bnf.org
Other	Per dosage		Bnf.org
Antiseptic			
Methenamine hippurate	Per dosage		Bnf.org

Table 2: Unit costs – Secondary care

	Unit	£	Source
Inpatient (overnight or longer)	Per bed day		NHS ref costs
Outpatient appointment (Urology dept.)	Per appointment	£110	NHS ref costs
A&E/casualty attendance	Per visit	£136	NHS ref costs

Table 3: Unit costs – Primary care

	Unit	£	Source
GP practice visit	Per visit	£39	PSSRU
GP home visit	Per visit		PSSRU
Practice nurse visits	Per visit		PSSRU
Nurse home visit	Per visit		PSSRU
Telephone consultation with GP	Per consultation		PSSRU
Telephone consultation with nurse	Per consultation		PSSRU
Telephone consultation with hospital doctor	Per consultation		PSSRU
Telephone consultation with other health professional	Per consultation		PSSRU
Out-of-hours consultation with GP	Per consultation		PSSRU

Out-of-hours consultation with nurse	Per consultation		PSSRU
Out-of-hours consultation with hospital doctor	Per consultation		PSSRU
Out-of-hours consultation with other health professional	Per consultation		PSSRU

Table 4: Unit Costs – Societal (including participant and main caregiver costs) – Ref Participant Time and Travel Questionnaire (ANTIC)

Average time and travel cost to attend healthcare services			
	Unit	**£**	**Source**
Hospital admission	Per visit		Time-travel questionnaire q1
Outpatient visit	Per visit		Time-travel questionnaire q11
GP visit	Per visit		Time-travel questionnaire q11
Practice nurse visit	Per visit		Time-travel questionnaire q11

Table 5: NHS resource use - Health utilisation questionnaire (ref: participant reported / participant questionnaire 3-6-9-12 months booklet & UTI Record)

Resource use	**Mean usage (SD)**				**Primary source**
	Intervention group	**n**	**Control group**	**n**	
Secondary care					
Inpatient stay					Health utilisation questionnaire q1
Outpatient appointment					Health utilisation questionnaire q2
A&E / casualty attendance					Health utilisation questionnaire q3
Primary care					
GP practice visits					Health utilisation questionnaire q4
GP home visits					Health utilisation questionnaire q5
Practice nurse visits					Health utilisation questionnaire q6
Nurse home visits					Health utilisation questionnaire q7
Telephone consultations with GP					Health utilisation questionnaire q8
Telephone consultations with nurse					Health utilisation questionnaire q8

Telephone consultations with hospital doctor					Health utilisation questionnaire q8
Out-of-hours consultations with GP					Health utilisation questionnaire q9
Out-of-hours consultations with nurse					Health utilisation questionnaire q9
Out-of-hours consultations with hospital doctor					Health utilisation questionnaire q9
Private Health Care					
Private health/Personal Care					Health utilisation questionnaire q11
Antibiotics					
Cefalexin					CRF
Co-amoxiclav ('Augmentin')					CRF
Ciprofloxacin ('Ciproxin')					CRF
Trimethoprim					CRF
Nitrofurantoin					CRF
Amoxicillin					CRF
Antiseptic					
Methenamine hippurate					CRF

** Table will be repeated for each time point (e.g. baseline, 3, 6, 9, 12, 15, 18 months)

Table 6: Average NHS costs - Health utilisation questionnaire (ref: participant reported / participant questionnaire Baseline 3,6,9,12,15, 18 months booklet & UTI Record) ****Timepoint: 0-12 months, 12-18 months, total study period****

Resource use	**NHS Costs (£) (SD)/Median (IQR)**	
	Intervention group	**Control group**
Secondary care		
Inpatient stay		
Outpatient appointment		
A&E / casualty attendance		
Primary care		
GP practice visits		
GP home visits		
Practice nurse visits		
Nurse home visits		
Telephone consultations with GP		
Telephone consultations with nurse		

Telephone consultations with hospital doctor		
Out-of-hours consultations with GP		
Out-of-hours consultations with nurse		
Out-of-hours consultations with hospital doctor		
Antibiotics		
Cefalexin		
Co-amoxiclav (‘Augmentin’)		
Ciprofloxacin (‘Ciproxin’)		
Trimethoprim		
Nitrofurantoin		
Amoxicillin		
Antiseptic		
Methenamine hippurate		

Table 7: Frequency and incidence of symptomatic UTI during the 12 month treatment period (taken from SAP Table xxx)

Outcome measure	Antibiotic (N=)	Methenamine hippurate (N=)
Episodes of symptomatic UTI Mean (SD)	Mean (SD)	Mean (SD)
Simple incident rate	Total # episodes / Total observation time (y)	Total # episodes / Total observation time (y)
Difference (90% CI)	Difference (90% CI)	

Table 8: Frequency and incidence of symptomatic UTI during the 18 month treatment period

Outcome measure	Antibiotic (N=)	Methenamine hippurate (N=)
Episodes of symptomatic UTI Mean (SD)	Mean (SD)	Mean (SD)
Simple incident rate	Total # episodes / Total observation time (y)	Total # episodes / Total observation time (y)
Difference (90% CI)	Difference (90% CI)	

Table 9: Average health utility (EQ-5D) and QALY per participant

	Control **Mean (SD)**	**Intervention** **Mean (SD)**	**Difference** **Mean difference (95% CI)**
Baseline EQ-5D-5L			Not estimated
3 months EQ-5D-5L			
6 months EQ-5D-5L			
12 months EQ-5D-5L			
15 month EQ-5D-5L			
18 month EQ-5D-5L			
QALYs 0-12 months			
QALYs 12-18 months			
QALYs at 18 months			

Table 10: Cumulative average cost per participant in prior 3 month period

Cumulative Average Cost			
	Control **Mean (SD)**	**Intervention** **Mean (SD)**	**Difference** **Mean difference (95% CI)**
Baseline			Not estimated
3 months			
6 months			
12 months			
15 months			
18 months			

Table 11: Economic evaluation at 12 and 18 months (unadjusted)

Treatment Arm	Costs Mean (SD)	Outcome Mean (SD)	ICER	Probability of C/E at £0/ £5k/£10k/£20k/30k				
Treatment period: 12 month								
Cost-effectiveness analysis								
Control	£	# UTIs	ΔC/ΔE					
Intervention	£	# UTIs						
Cost-utility analysis								
Control	£	# QALYs	ΔC/ΔE					
Intervention	£	# QALYs						
Treatment period: 18 month								
Cost-effectiveness analysis								
Control	£	# UTIs	ΔC/ΔE					
Intervention	£	# UTIs						
Cost-utility analysis								
Control	£	# QALYs	ΔC/ΔE					
Intervention	£	# QALYs						

Table 12: Economic evaluation at 12 and 18 months (adjusted)

Treatment Arm	Costs Mean (SD)	Outcome Mean (SD)	ICER	Probability of C/E at £0/ £5k/£10k/£20k/£30k				
Treatment period: 12 month								
Cost-effectiveness analysis								
Control	£	# UTIs	ΔC/ΔE					
Intervention	£	# UTIs						
Cost-utility analysis								
Control	£	# QALYs	ΔC/ΔE					
Intervention	£	# QALYs						
Treatment period: 18 month								
Cost-effectiveness analysis								
Control	£	# UTIs	ΔC/ΔE					
Intervention	£	# UTIs						
Cost-utility analysis								
Control	£	# QALYs	ΔC/ΔE					
Intervention	£	# QALYs						

Table 13: 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 (a sample for DNA will be taken at one of these time points)	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					

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
Compliance			X	X	X	X	X	X	X	X
UTI Record							X			
UTI questionnaire			X	X	X	X			X	X
EQ5D-5L		X	X	X	X	X	X		X	X
Health Resource Use Questionnaire		X	X	X	X	X				X
TSQM						X				X
Adverse event assessments			X	X	X	X	X		X	X
CRF completion	X	X	X	X	X	X	X	X	X	X
Qualitative Interviews	X					X				

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