Full Title:	**AL**ternatives **T**o prophylactic **A**ntibiotics for the treatment of **R**ecurrent urinary tract infection in women
Short Title/Acronym:	ALTAR
Protocol Version Number & Date:	Version 1.4 20/06/2018

Statement:

This protocol has regard for the HRA guidance.

NHS National Institute for Health Research

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2 SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted. The Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, the relevant Standard Operating Procedures and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

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Trial Website	https://research.ncl.ac.uk/altar/

4 TRIAL SUMMARY

Trial Title	**AL**ternatives **T**o prophylactic **A**ntibiotics for the treatment of **R**ecurrent urinary tract infection in women
Acronym	ALTAR
Clinical Phase	Phase IV
Summary of Trial Design	A multicentre, pragmatic patient-randomised non-inferiority trial comparing two drugs for the prevention of recurrent urinary tract infection in women both during a 12-month period of use and in the subsequent 6-months following completion of the prophylactic medication.
Summary of Participant Population	Adult females with recurrent uncomplicated urinary tract infection.
Planned Sample Size	240 participants
Planned Number of Sites	4 initial sites (with capacity to increase if required)
Treatment Duration	12 months
Follow Up Duration	6 months
Planned Trial Period	54 Months
Primary Objectives	To determine the relative clinical effectiveness and cost-effectiveness for the NHS of two types of licensed preventative treatments for women with recurrent uncomplicated urinary tract infection (rUTI) over a 12 month treatment period.
Secondary Objectives	To determine the relative impact on incidence of symptomatic antibiotic-treated UTI self-reported by patients during the 6 month follow-up period after completion of 12 months of allocated treatment. To determine the total number of days spent on urinary specific antibiotics (prophylactic or treatment) during the 12 month treatment period and 6 months of follow up. To determine if there is any longitudinal ecological change in terms of phenotype and genotype of bacteria and their resistance patterns in

	isolates from individual participant's i) urine and ii) faecal reservoir during the 12 month treatment period and in the 6 months following completion of treatment.
	To determine the number of microbiologically proven urinary tract infections during the 12 month treatment and 6 month follow-up periods.
	To determine the incidence of asymptomatic bacteriuria (ABU) during the study period.
	To determine the incidence rate of hospitalisation due to urinary tract infections during the study period.
	To determine overall patients satisfaction with antibiotic versus antiseptic treatment.
	To determine patients and clinicians views regarding trial processes and participation via an embedded qualitative study.
	To determine the Incremental Cost per Quality of Life Year (QALY) gained at 18-month periods based on responses to EQ-5D-5L.
	To determine the Incremental Costs to the NHS, personal social services measured at the end of the 18-month study period.
	To determine the relative health economic efficiency over the longer term estimated using a modelling exercise.
Primary Outcome Measures	Incidence of symptomatic antibiotic-treated UTI self-reported by participants and verified where necessary from medical records during the 12 month period of preventative treatment.
	Incremental cost per quality-adjusted life year (QALY) gained during the 12 month treatment period. Incremental costs to the NHS, personal social services, and the patient at 12 months.
Secondary Outcome Measures	The number of symptomatic antibiotic-treated UTI self-reported by participants in the 6 months follow up period after completing the allocated preventative therapy.
	Total antibiotic use during the study period, reported by patients and verified where necessary from medical records.

Phenotype and genotype of *Escherichia coli* (*E. coli*) isolated from urine and perineal swabs sent by participants directly to the central reference laboratory.

The number of microbiologically confirmed urinary tract infections occurring during both the 12 months of treatment and the subsequent 6 months of follow-up . A positive culture will be classified according to standard Public Health England (PHE) definitions; the laboratory report of two isolates at ≥ 10^5 cfu/mL or a single isolate at ≥ 10^4 cfu/mL.

Presence of asymptomatic bacteriuria (ABU) identified by urine culture performed at patient visits for study follow-up. ABU is defined as the presence of bacteria in the urine in the absence of symptoms suggestive of urinary tract infection. For the purposes of this study, a positive culture was defined in line with the routine PHE definitions above.

The incidence rate of hospitalisation due to urinary tract infections during the treatment and follow-up phases of the study.

Overall satisfaction with treatment measured by Treatment Questionnaire on Satisfaction with Medication (TQSM) administered at both the end of treatment (12 months) and then again at the end of follow-up (18 months).

Qualitative analysis of patients and clinicians views regarding trial processes and participation.

QALYs based on responses to the EQ-5D -5L at 3, 6, 9, 12, 15 and 18 months and after a UTI episode.

Treatment costs for drug and healthcare services from a standard NHS source such as British Formulary (BNF) and published tariffs from NHS reference costs.

Health resource utilisation questionnaire at 3, 6, 9, 12, 15 and 18 months.

Incremental cost per quality-adjusted life year (QALY) gained during the total 18 month trial period. Incremental costs to the NHS, personal social services, and the patient at 18 months.

Costs and QALYs will be combined in a cost-utility analysis for both a “within” trial analysis and modelled over the patient’s lifetime using previously developed methods and data from other relevant RCTs that collected patient costs.

Investigational Medicinal Product(s)	Experimental: Methenamine hippurate. Control: Nitrofurantoin or Trimethoprim or Cefalexin.
Formulation, Dose & Route of Administration	Methenamine hippurate 1g oral twice daily. Nitrofurantoin 50mg or 100mg oral once daily. Trimethoprim 100mg oral once daily. Cefalexin 250mg oral once daily.

5 Contents

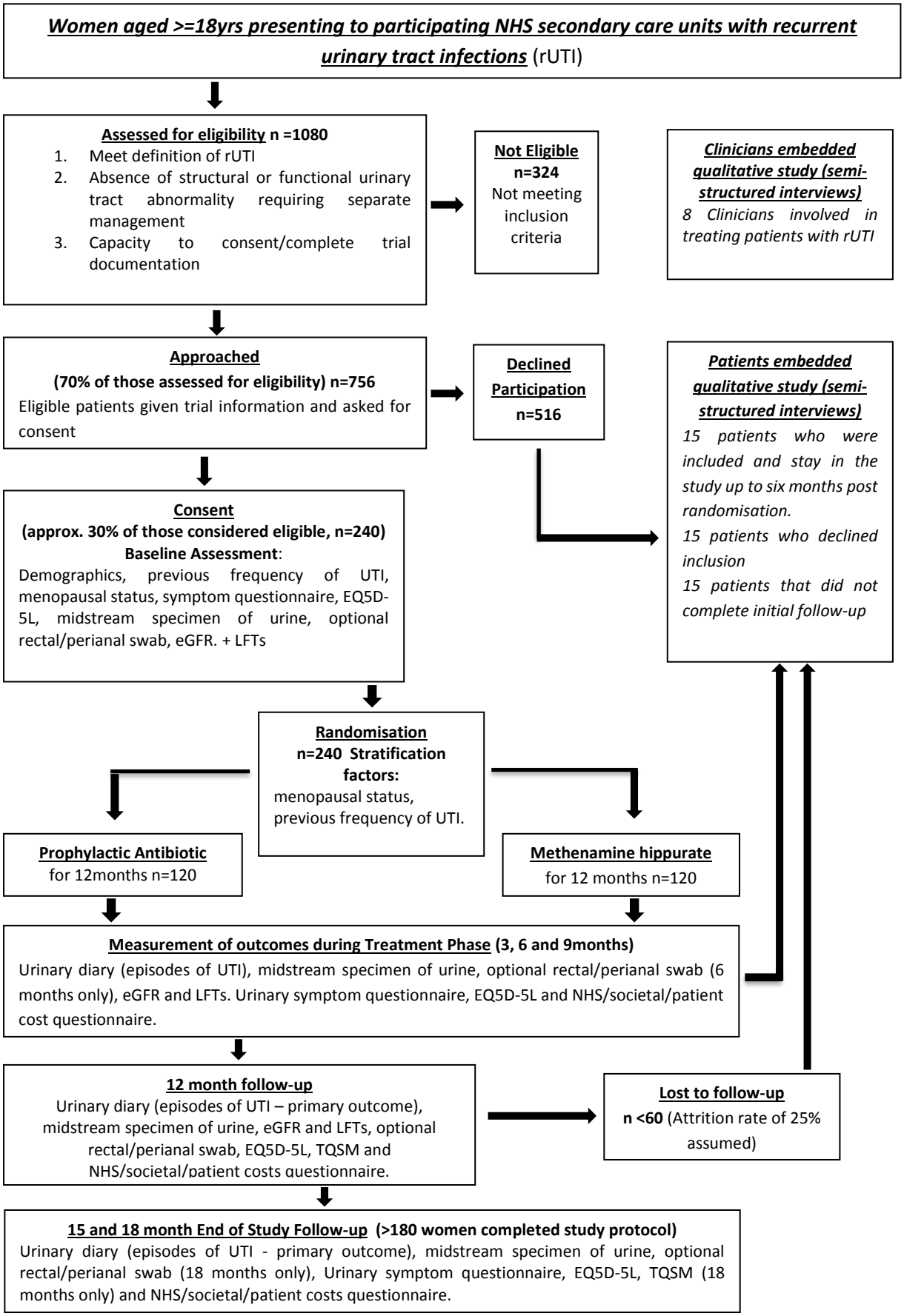
GLOSSARY OF ABREVIATIONS

ABBREVIATION	DEFINITION
ABU	Asymptomatic bacteriuria
AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CDI	Clostridium difficile infection
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
E. coli	*Escherichia coli*
eGFR	Estimated Glomerular Filtration Rate
EQ5D-5L	EuroQoL 5 Dimension Questionnaire
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
HPA	Health Protection Agency
HRA	Health Research Authority
HTA	Health Technology Assessment
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
IMP	Investigational Medicinal Product

IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
LFT	Liver function test
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MRSA	Meticillin-resistant *staphylococcus aureus*
MSU	Mid-stream Urine
NCTU	Newcastle Clinical Trials Unit
NHS	National Health Service
PHE	Public Health England
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PK	Pharmacokinetic
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
R&D	Research & Development
RCT	Randomised Control Trial
REC	Research Ethics Committee
RR	Relative risk
rUTI	Recurrent urinary tract infection
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure

SmPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File
TQSM	Treatment Satisfaction Questionnaire for Medication
UTI	Urinary tract infection

6 TRIAL FLOW CHART



1. BACKGROUND

1.1. Size of the Problem

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 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 affected by rUTI of over 300,000 women annually 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 are not part of the target population for this trial.

1.2. The current body of evidence and the contribution of this study

Continuous low-dose prophylactic antibiotic therapy is the current standard of care for the prevention of rUTI and is recommended for this use by both UK and European guidelines[4, 5]. The largest meta-analysis examining efficacy of prophylactic antibiotics found an 85% reduction in symptomatic UTI over placebo (RR 0.15, 95% CI 0.08 to 0.28)[6]. This meta-analysis included 19 studies with data from 1120 women. The authors concluded that continuous antibiotic prophylaxis for 6-12 months reduced the rate of UTI during prophylaxis when compared to placebo. There were however more adverse events in the antibiotic group and these included vaginal and oral candidiasis and gastrointestinal symptoms. The observation that following ending of prophylaxis the rate of symptomatic UTI returned to similar levels in both women who had taken prophylactic antibiotics and those that received placebo comes from only two studies. This suggests that antibiotic prophylaxis does not have a sustained benefit following completion of a standard duration of treatment.

Use of the urinary antiseptic, Methenamine hippurate as a preventative treatment for rUTI has also been the subject of a Cochrane meta-analysis[7] including 13 studies involving 2043 patients. The mean reduction in rUTI was 76% (RR 0.24, 95% CI 0.07 to 0.89). The authors did however comment that the quality of the included studies was mixed and that pooled estimates for the major outcome measures were not interpretable because of underlying heterogeneity. They did state that Methenamine hippurate may be effective for preventing UTI in patients with uncomplicated rUTI, particularly when used for short-term prophylaxis. The rate of adverse events was low, but poorly described. The need for large well-conducted clinical trials to clarify the effectiveness of Methenamine hippurate in the setting of prevention of rUTI was highlighted.

Although continuous antibiotic treatment has been shown to prevent rUTI[6] previous randomised trials have demonstrated a threefold increase in antimicrobial resistance compared with placebo[8]. Several studies have confirmed the emergence of resistant organisms in the faecal reservoir and urine of women who take prolonged low dose antibiotic[8, 9]. The resistance pattern observed was not confined to the prescribed antibiotic but to a range of other antibiotic agents commonly used to treat symptomatic UTI[10]. Furthermore the detection of resistant microorganisms can occur after just a few weeks of prophylactic antibiotic therapy[8]. The prevalence of antimicrobial multi-resistance within post-menopausal women suffering from rUTI is around 25% and was shown to rise to more than 80% following prolonged antibiotics[10]. The use of effective non-antibiotic UTI prevention strategies is highly likely to reduce risk to patients of both emergence of resistant organisms and subsequent difficult-to-treat clinical infection with these bacteria provided that the number of clinical episodes of UTI is reduced. The ALTAR study will address the question of whether the reduction in incidence of symptomatic UTIs in women with rUTI using the urinary antiseptic Methenamine hippurate (a non-antibiotic preventative treatment) for 12 months is no worse compared to women using prophylactic antibiotic therapy. In addition we will assess the possible carried over effectiveness of these two treatments by following up all participants for 6 months after treatment has ended. We will also comparatively value these treatments in terms of their effect on overall quality of life (QoL) and cost-effectiveness. The unit cost difference between medications is small but healthcare costs associated with each strategy may differ in terms of frequency of breakthrough UTI or side effects. Furthermore, the assessment of QoL over the treatment and follow-up periods will seek to capture the effect of both longer term trends in QoL as well as more transient effects associated with a UTI. Secondary outcomes will assess whether use of Methenamine hippurate reduces the number of days participants use antibiotics for UTI and reduces development of antimicrobial resistance associated with antibiotic use focussing on the main pathogen *Escherichia coli (E . coli)*. These data will be interpreted alongside the results of the economic evaluation to highlight the choices and trade-offs made in any given policy decision on the use/non-use of antibiotic preventative treatments.

1.3. Summary with implications for trial design

This background has summarised evidence of the importance of the association between antibiotic use as prophylaxis for rUTI and antimicrobial resistance. ALTAR is a robust pragmatically designed trial to evaluate the clinical benefit and cost-effectiveness of the best candidate alternative treatment for prevention of rUTI, the urinary antiseptic Methenamine hippurate. Estimates of prevalence, effectiveness and harms from Cochrane reviews have informed the power calculation conservatively based on what we, guided by a patient panel, consider

to be a minimum threshold difference that would drive patient and clinician acceptability together with change of practice prompted by inclusion of trial results in future meta-analyses and guidance for management of rUTI in the NHS and internationally.

2. RATIONALE

2.1. Risk Assessment

We have made a risk assessment of the potential hazards associated with this trial including those occurring and resulting in harm to the participants or researchers. The investigational medicinal products (IMP) to be used in the trial are all licensed in dosage and form for use against rUTI in the UK and are standard care for this indication[11]. From this we judge that from an IMP perspective there is low risk to trial participants. Apart from the interventions, participants in both arms of the trial will be subject to routine clinical care only and we therefore consider that risk associated with trial participation other than those related to the IMP are also low. Risks associated with the design and methods of the trial including the clinical procedures specified in the protocol, participants' rights related to consent and protection of data and the reliability of trial results have also been assessed. The robust design of the study to mitigate and manage these risks has led to the decision to submit this trial as a 'Type A' status (low risk - notification only) to the MHRA and allow for a risk-proportionate trial management and monitoring approach to the trial. A structured Safety Monitoring Plan will be made to assess risk management by all relevant parties including the sponsor, regulators, pharmacists, and regulatory and governance staff. This will be submitted to the MHRA along with the notification application.

2.2. Rationale for the study

A recent meta-analysis reviewed trials of non-antibiotic treatments as prophylaxis against rUTI and found that robust evidence of effectiveness was limited[12]. The report concluded; "Although sometimes statistically significant, pooled findings for the other (non-antibiotic) interventions should be considered tentative until corroborated by more research" and "Large head-to-head trials should be performed to optimally inform clinical decision making". It would appear that one of the barriers to clinicians recommending non-antibiotic alternatives for the treatment of rUTI is the lack of evidence of effectiveness particularly in direct comparison to antibiotic prophylaxis. The continuing drive for antibiotic stewardship and more prudent prescribing of antibiotic agents can only be strengthened by further work giving unequivocal evidence concerning whether or

not non-antibiotic alternatives are effective and cost-effective in prevention of UTI.

The need for the ALTAR study is emphasised by evidence statements in current guidance documents. The 2012 Scottish Intercollegiate Guideline Network (SIGN) guideline 88[4] forcibly illustrates why this study is essential and needed promptly. The SIGN literature review identified "considerable evidence of practice variation" and variation in "initiation of antibiotic treatment" for UTI. In addition one of the constant themes in this report is the need to avoid "unnecessary antibiotic prescribing" which is associated with "clinical adverse events including *Clostridium difficile* infection (CDI) or methicillin-resistant *Staphylococcus aureus* (MRSA) infection, and the development of antibiotic-resistant [*E. coli*] UTIs". The UK antimicrobial resistance strategy and action plan[13]states "the increasing prevalence of antimicrobial resistant micro-organisms is causing international concern" and identifies that "the emergence of resistance represents adaptive selection by micro-organisms which is an inevitable result of therapeutic use of antimicrobial agents". This document reflects an urgent need for prudent antibiotic use as one of three key elements of the strategy to control antibiotic resistance. The predominant UTI pathogen, *E. coli*, is the subject of a recent paper identifying the overuse of antibiotics in Asia as a potential causative factor for the development of a new mechanism of bacteria producing extended spectrum beta lactamase (ESBL) antibiotic resistance detected in the UK[14]. Limiting the use of broad spectrum antibiotics is a key measure in addressing this problem, and has been the driver for recent UK guideline updates[12]. The development of antimicrobial stewardship programmes which encourage prudent antibiotic prescribing have already been shown to reduce antibiotic use and consequently incidence of healthcare-acquired infection (HAI) which until recently was increasing[18, 19]. Avoidance of antibiotic administration, where possible, is believed to be the single most important factor leading to the observed decline in HAI in Scotland[19]. The advisability of using non-antibiotic preventative treatments for rUTI has been highlighted by current UK, European and USA guidelines to reduce the "collateral damage" of antibiotic use by minimising risk of resistance[12, 15]. Policy-makers in the UK have included antibiotic avoidance and prudent antibiotic prescribing as key components of strategies to reduce antimicrobial resistance[10, 11, 17]. A well-designed research study providing robust evidence of at least no-worse effectiveness for non-antibiotic treatment is needed to further inform guideline-writers and policy-makers and allow recommendation of alternative treatments avoiding prolonged antibiotic use. The ALTAR study aims to provide this in the context of a routine NHS care setting in order to achieve consistent practice in this area.

3. OBJECTIVES AND OUTCOME MEASURES

3.1. 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 recurrent uncomplicated urinary tract infection (UTI).

The treatments under investigation are:

i) Methenamine hippurate a urinary antiseptic that is taken as a twice daily oral tablet for 12 months and is excreted into the urine by the kidneys as formaldehyde which is bacteriocidal.

ii) Prophylactic antibiotic taken as a single daily dose oral tablet for 12 months in order to prevent colonisation of the urinary tract by uropathogenic bacteria.

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

3.2. Secondary Objective(s)

Secondary objectives will determine the following:

i) The occurrence of symptomatic UTI in the 6 months 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.

3.3. Outcome Measures

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 completion of planned course of preventative treatment (making up a total observation period of 18 months for each participant) and analysed at trial completion.

3.3.1. Primary Outcome Measures

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

This will be 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) [20] together with taking a discrete treatment course of antibiotic for UTI prescribed by a clinician or as part of patient-initiated self-start treatment. Symptom diary format will conform to the recommendations of British Infection Association (BIA) [20]. The symptoms with the clinical UTI severity category in brackets that will be recorded are dysuria, urinary frequency, urinary urgency, polyuria, haematuria, suprapubic tenderness (cystitis), and pyrexia (temperature > 38°C; (febrile cystitis), and loin pain (pyelonephritis). We will ask participants to notify local research staff using a telephone number with answerphone of the occurrence of a UTI within 48 hours of the onset of symptoms in order for necessary assessments to be promptly undertaken. The rate of UTI will be defined firstly as a simple incident rate and secondly as the incident density rate; the number of UTI suffered during the 12 months of therapy minus days spent taking treatment courses of antibiotics active against urinary tract organisms. We will determine this outcome by collection of the following data:

Occurrence of symptomatic UTI with prescription and taking of a treatment course of antibiotic for UTI

- Participant log with report alert from participant to local or central trial staff
- Regular (at least monthly) participant review/contact by local trial staff
- Review of healthcare records at 12 and 18 months or more frequently if needed by local trial staff.

For any identified treatment course of antibiotics for UTI the participant will be asked to complete a checklist of symptoms that precipitated the request for antibiotic treatment. To ensure consistent attribution the primary outcome will be based on a hierarchy of evidence. 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.

During the first six months of the trial we will randomly select a sample of 10% reported positive primary outcome episodes without details of allocated group and present these as vignettes to the clinician members of the Trial Steering Committee (TSC) and ask them to determine whether the primary outcome was fulfilled. If there is disagreement for more than 10% of vignettes we will investigate further to determine the cause of altered attribution. We will also ask local research staff, local PIs and trial coordinators to flag any uncertain attributions of outcome. Following completion of the trial we will re-examine these flagged episodes and if necessary use clinician members of the TSC blinded to participant group to attribute the outcome by consensus.

The primary health-economic outcome measured during the 12 month treatment period is Incremental Cost per Quality-Adjusted Life Year (QALY) gained (based on responses to the Euroqol 5 dimension, 5 level (EQ-5D 5L) health status questionnaire completed at baseline and 3, 6, 9 and 12 months.

Costs will be based on those of the interventions themselves (antiseptic and antibiotic medications), the use of subsequent services including subsequent treatments for UTI and the cost of treating any adverse events. Treatment costs such as medications and healthcare services will come from standard NHS sources such as the British National Formulary[24] and published tariffs from NHS reference costs. Use of services will come from a health resource use questionnaire (including use of private health care and over the counter care)

completed at each 3 month follow-up visit. Personal costs will be estimated using existing data from other RCTS due to the burden of collecting this type of information on participants

QALYs will be estimated using the area under the curve methods from the responses from the EQ-5D 5L administered every 3 months and when a participant suffers a UTI. Responses to the EQ-5D 5L will be converted into utility values using UK population tariffs. Tariffs are not currently available for the EQ-5D 5L but responses can be cross-walked to scores for the EQ-5D 3L and this scoring will be used unless EQ-5D 5L scoring system becomes available during the lifetime of the trial.

3.3.2. Secondary Outcome Measures

- ***The occurrence of symptomatic UTI in the 6 months follow up period after stopping the allocated preventative therapy****:* This will be 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)[20] together with taking a discrete treatment course of antibiotic for UTI prescribed by a clinician or as part of patient-initiated self-start treatment.

- ***Antibiotic use***: The use of both prophylactic and therapeutic antibiotics will be recorded. For prophylactic antibiotics 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. The use of therapeutic antibiotics will also be recorded and this will be defined as the number of days patients are prescribed 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. Antibiotics taken for reasons other than UTI will also be recorded given the potential activity against uropathogens. We will also 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.

- ***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. Participants will be requested to submit urine samples to the central laboratory when they suspect a UTI based on symptoms. GP or hospital records will be checked if necessary to confirm any additional urine culture

results. Resistance patterns of bacteria cultured from these samples will be recorded. We also plan to longitudinally monitor development of antimicrobial resistance in the primary uropathogen *Escherichia coli* (*E. coli*) isolated from urine by collecting specimens sent by participants directly to our central reference laboratory at the time of each UTI and during asymptomatic periods at baseline, 3, 6, 9, 12, 15, and 18 months. We will also assess resistance pattern change in *E. coli* within the faecal reservoir by obtaining isolates from perineal swabs sent at baseline, 6, 12 and 18 months. For the purposes of the study sensitivity testing will use a panel of 12 antibiotics and carry out the tests in triplicate, choosing three different colonies from positive *E.coli* cultures to check for the possibility of mixed infections with more than one *E.coli* strain. These techniques will allow the demonstration of ecological changes in bacteria in particular the development of antimicrobial resistance at phenotypic level. All *E. coli* isolates will be stored for later molecular study to determine whether any identified change in resistance has been acquired or is the result of infection by a different strain. We will examine this by either pulsed field gel electrophoresis or whole genome sequencing of isolates responsible for apparent recurrent infection with a changed phenotype.

- ***Number of microbiological-proven UTIs***: Defined as the occurrence of symptomatic UTI and the demonstration of a positive urine culture. Participants will be requested to submit urine samples to the central laboratory in Newcastle when they suspect a UTI based on symptoms. A positive culture will be classified according to standard Public Health England (PHE) definitions; the laboratory report of two isolates at ≥ 10^5 cfu/mL or a single isolate at ≥ 10^4 cfu/mL[21].

- ***Occurrence of asymptomatic bacteriuria (ABU)***: defined as a positive urine culture in the absence of symptoms. This will be detected from the routine urine samples taken during 3-monthly hospital visits throughout the 18 month period of participation. Both the presence of ABU and the type of bacteria and their resistance patterns will be recorded.

- **Hospitalisation due to UTI:** Defined as an unplanned visit to hospital for treatment of a UTI. These data will be collected from healthcare record review and checked from participant report. 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) administered at both the end of the 12 month treatment period and then again at 18 months the end of follow-up

- **Embedded Qualitative Study:** The early phase of the recruitment period will include an embedded qualitative study analysis involving both patients

approached to participate and recruiting clinicians. This will be used to inform the study team of potential barriers to recruitment and full participation as the trial progresses. Specific questions to be addressed are:

- What are the factors that are of most importance to women with rUTI in deciding between different treatment options and agreeing to trial participation?
- What are the factors that clinicians take into account when recommending one treatment over another?
- Patients' understanding and views of: the different treatment arms of the study; the treatment group they are randomised to; patient study information and consent process, trial design (outcome measures, length of participation); and reasons for participating, declining to participate and dropping out of the study.

- ***HRQoL***: Measured using the EQ-5D 5L questionnaire at 3-monthly intervals. Measurement of health-related quality of life (HRQoL) change due to UTI is difficult in this patient group as UTI causes transient deficit. We will therefore encourage completion of the EQ-5D 5L during periods of UTI – participants will be asked to do this within 48 hours of onset of UTI symptoms. Local research staff will ensure each participant has a helpline telephone number to facilitate this process.

- **Incremental costs to the NHS, personal social services, and the patient at the end of the 12-month treatment and 18-month follow-up phases:** Within this study both a 'within trial' and model based economic evaluation will be conducted. These analyses will take the form of a cost-utility and a cost-benefit analysis. The 'within trial' analysis will take the perspective of the NHS and personal and social services, but will also take a wider perspective by including costs by the participants and their families. The model based analysis will take the perspective of the NHS and personal and social services.

- **Model based estimates of costs, QALYs and net benefits over the longer terms, potentially over the patients estimated lifetime:** Drawing upon existing modelling expertise in the Health Economics Group at Newcastle University, an economic model describing recurrent UTIs will be developed. The model will be constructed following guidelines for best practice in economic modelling.

4. TRIAL DESIGN

4.1. Research Methods

4.1.1. Target Population and Trial Duration

Adult (>18 years) women with recurrent urinary tract infection, for whom prophylactic antibiotics would be considered as a therapeutic option e.g. at least three episodes of symptomatic antibiotic-treated urinary infection in the previous 12 months, two episodes of UTI in the last 6 months or a single occurrence of severe UTI requiring hospital admission in the preceding 1 year. The trial duration is 54 months in total with recruitment expected to be complete by the end of month 30. The initial 3 months will incorporate trial set up including appointment of staff and local site approvals. The following 6-month phase will commence at the beginning of month 4 with approval for all four primary sites in place by end of month 6. The feasibility of trial progression to completion using this recruitment strategy will be assessed at this stage using recruitment data and early results from the embedded qualitative study. Follow-up will conclude by month 39. Data analysis will be carried out for the primary outcomes after month 33 and for all other outcomes in the final 6 months of the study.

4.1.2. Design

A multicentre, pragmatic patient-randomised non-inferiority trial comparing two treatments for the prevention of rUTI in women during a 12-month period of treatment and in the 6-months following treatment completion. The standard is once daily prophylactic antibiotic, using either trimethoprim 100 mg, nitrofurantoin 50 or 100 mg depending on body weight or cefalexin 250 mg once daily for 12 months which are the recommended drugs licensed for this purpose. The choice of antibiotic will be decided by considering previous bacterial sensitivities, safety, and patient or clinician preference. The alternative (experimental) treatment is a 1 g twice daily oral urinary antiseptic Methenamine hippurate for 12 months. Participants in both arms would continue to receive treatment courses of antibiotic for UTI as needed.

Apart from random allocation to either option, all participants will receive usual care including use of on demand discrete treatment antibiotic courses for UTI. We have formulated a recruitment plan to progressively build to a target of 240 participants over an 18 month recruitment window.

4.1.3. Sources of Bias

Selection bias will be minimised by including all adult female patients with recurrent uncomplicated UTI as eligible participants. We have deliberately set few exclusion criteria to enable the findings of this study to be generalisable. Both treatments are licensed for this condition, exhibit a low side-effect profile

and have little interaction with other common medications which limits absolute contra-indications to either therapy. We will stratify randomisation on the basis of number of UTIs [<4 episodes per year vs 4 or more episodes per year] and menopausal state [pre-menopausal vs menopausal/post-menopausal] of the participants to ensure equivalent proportions of these groups at differential risk in both arms.

Eligible patients and their responsible clinicians will need to be sufficiently uncertain of the optimum treatment for rUTI to allow randomisation. The "Background and Rationale" section (sections 1 and 2) of this document sets out the existing evidence for both treatments and describes Level 1 evidence to support the use of both prophylactic antibiotics and Methenamine hippurate. Similar reductions in the frequency of episodes of UTI are reported for both treatments and clinicians should therefore have equipoise based on these data. This should ensure that any selection bias in terms of characteristics of rUTI sufferers put forward and willing to be randomised compared with those who are eligible but not willing to participate is minimised. We will keep an anonymised screening log at each centre listing demographic and clinical characteristics and reasons for declining randomisation (if offered) and compare this group with those entering and those completing the trial. Secondly the characteristics of participants who switch treatment arm during the 12-month treatment period, may differ from those completing the allocated strategy. We will address this by comparison of demographic data and QoL scores between these groups measured at baseline prior to randomisation and following treatment.

4.2. Planned Interventions

This trial is pragmatic in design and, apart from random allocation of treatment option and participant completion of diaries and questionnaires; participant care will follow standard pathways in participating secondary care NHS sites. Both prophylactic antibiotic and Methenamine hippurate are licensed and approved for routine NHS use. We will ensure that all participants have access as desired to the use of other measures to reduce the risk of UTI such as adequate fluid intake, avoidance of constipation, and, for post-menopausal women, vaginal oestrogen supplements. We will also ensure all participants are informed regarding the possible benefit of other alternative options including cranberry extract. Participants in both trial groups will receive on demand discrete courses of antibiotics as decided by the responsible clinician for symptomatic UTI. Use of all these adjunctive treatments will be recorded on case report forms.

4.2.1. Antibiotic prophylaxis

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. Renal function will be determined by eGFR at baseline and if this is less than 45 ml/min nitrofurantoin will not be used. Patients randomised to receive antibiotic prophylaxis will have blood samples taken at 3, 6, 9 and 12 months to monitor kidney and liver function (eGFR and LFT). If there are any abnormalities in these tests during the period of treatment then a further sample will be taken at 18 months to ensure these have resolved. If clinically indicated then blood tests may be more frequent. Participants will be asked to take the once-daily antibiotic prophylaxis as a single dose at bedtime. If there are specific and intolerable adverse effects such as nausea with nitrofurantoin, or candidiasis with cefalexin then switching to an alternative agent would be advised in consultation with the relevant clinician with the reasons for the change recorded. The aim will be to maintain participants on antibiotic prophylaxis using any one of the three agents for as long as possible during the 12-month treatment period within tolerance and safety constraints. Participants intolerant of prophylactic antibiotic despite trying alternative agents will have the opportunity to discontinue the medication and be offered an alternative treatment which may include Methenamine hippurate. This information will be recorded and the participant will continue on study. If a participant in the antibiotic prophylaxis group develops symptoms and signs suggestive of breakthrough UTI then they will seek treatment in their usual way mostly by contacting their GP and starting a discrete treatment course of antibiotics. In this scenario they will be instructed to stop the prophylactic antibiotic whilst they are taking a treatment course and restart it again the day following the last dose they take of the treatment course. Clinicians and participants will be advised to use a different agent for treatment than the one they are taking for prophylaxis. Details of all treatment antibiotic courses will be recorded including the agent used and the number of days participants actually took the prescribed antibiotic. The rate of UTI will be defined firstly as a simple incidence rate and secondly as the incident density rate; the number of UTI suffered during the observation period minus days spent taking treatment courses of antibiotics active against urinary tract organisms. This number will be annualised for the purposes of standardisation.

4.2.2. Methenamine hippurate

For those women randomised to receive Methenamine hippurate a twice daily dose of 1 g to be taken 12 hours apart will be prescribed for 12 months (as recommended in the British National Formulary; BNF). An eGFR of less than 10

ml/min will be an exclusion criterion for the study. Other exclusion criteria will be patients with gout which is a contra-indication to treatment with Methenamine and those with liver dysfunction as determined by pre-study serum Liver Function Tests (analysis of blood sample). Patients randomised to receive Methenamine hippurate or antibiotic prophylaxis will have blood samples taken at 3, 6, 9 and 12 months to monitor kidney and liver function (eGFR and LFT). If there are any abnormalities in these tests during the period of treatment then a further sample will be taken at 18 months to ensure these have resolved. If clinically indicated then blood tests may be more frequent. If there are specific and intolerable side effects such as nausea, gastrointestinal disturbance, itching or skin rashes then participants will be given the opportunity to discontinue treatment and be offered an alternative treatment which may include prophylactic antibiotic. This information will be recorded and the participant will continue on study. If a participant in the Methenamine group develops symptoms and signs suggestive of breakthrough UTI then they will seek treatment in their usual way predominantly by contacting their GP and starting a discrete treatment course of antibiotics. They will be instructed to continue taking Methenamine during this antibiotic treatment course. Details of all treatment antibiotic courses will be recorded including the agent used and the number of days participants actually took the prescribed antibiotic. The rate of UTI will be defined firstly as a simple incident rate and secondly as the incident density rate as described above and annualised for the purpose of standardisation.

4.2.3. Trial adherence

Some participants or their clinicians will seek to change their allocated group at some point during trial participation either due to lack of efficacy or adverse effects for either treatment. Trial literature will emphasise the need to adhere to the allocated strategy during the 12 month trial period if possible and will record any deviation. Multiple switching between prophylactic antibiotic agents will be allowed. If participants do stop their allocated treatment within the 12-month treatment period or if they re-commence prophylaxis during the subsequent 6-month observation period this will be recorded and the participant will continue on study unless they withdraw consent.

5. STUDY SETTING

Large, secondary care Urology Centres with a consistent clinical assessment pathway for women with rUTI will be selected as sites for this multicentre clinical trial. Centres will be sufficiently resourced and have a proven track record of delivering clinical research with established links to their respective Clinical Research Networks (CRN). The Principal Investigator or delegated individual will be responsible for coordinating participant recruitment by screening women with rUTI who are

routinely referred from primary care to these centres. We initially plan to open 4 sites and we will consider opening further sites if the rate of recruitment is slower than anticipated.

6. ELIGIBILITY CRITERIA

6.1. 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.

6.2. 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.

NB: Enrolling a patient onto the trial who does not meet the inclusion/exclusion criteria is considered a protocol waiver and is in breach of Regulation 29 (SI 2004/1031) of the Medicines for Human Use (Clinical Trials) Regulations 2004. PROTOCOL WAIVERS ARE NOT PERMITTED.

7. TRIAL PROCEDURES

7.1. Recruitment

7.1.1. Patient Identification

We will aim to ensure that all adult women referred to each site with rUTI are aware of the study prior to their clinic appointment and those eligible can consider whether they wish to participate prior to assessment. Each research site lead will publicise the study within their own departments and referral catchment areas and ensure that colleagues in allied specialities such as urogynaecology and nephrology, who may receive referrals of women with rUTI, are aware of the study and willing to identify potential participants. We will use established CRN links to ensure that referring GPs are aware of the study; can identify potential eligible participants and direct referrals accordingly, we will register GP practices or other secondary sites as participant identification centres (PIC) if needed. All sites will have an established clinical research track record and effective infrastructure in place for patient recruitment.

In order for the results from the ALTAR study to be generalisable across the wider NHS, the demographic mix of patients recruited to the study must reflect that of patients currently being referred to urologists. Recurrent UTI is generally defined as 3 episodes of infection within a 12 month period[4] and the patient group most affected by rUTI are adult females making up over 80% of all people presenting with UTI[5]; this will constitute the majority of our target population. We have expanded the inclusion criteria to other groups that would also be considered for antibiotic prophylaxis including women who have had 2 episodes of UTI in the preceding 6 months and patients who have had one episode of serious UTI resulting in hospitalisation in the preceding 12 months. Furthermore patients that are being treated by their General Practitioners (GP) in primary care will also be identified by liaison of the lead clinician in each site with primary care leads at LCRN.

ALTAR study sites will consist of large UK urology/urogynaecology centres, with the majority of referrals coming from primary care through the standard NHS 'Choose and Book' pathway. These centres have well-defined existing clinical pathways in place for the investigation of such patients which initially focusses on

the exclusion of underlying structural or functional abnormalities of the urinary tract. This is usually done by renal tract ultrasound scan (USS) and an endoscopic examination of the bladder under local anaesthesia (flexible cystoscopy). A recent local audit in Newcastle (unpublished data, n=200) has revealed that contributory structural or functional abnormalities are detected in less than 10% of patients. Therefore we estimate approximately 90% of patients referred with rUTI to these centres will be eligible to be approached for inclusion to the ALTAR study. We will compare ratios of screened to randomised patients throughout the trial which will enable us to estimate recruitment rates and ensure targets are met.

Participant Identification Centres (PICs) will be considered as a means to maximise recruitment at each site. Participants will be identified by the PIC and information about the study will be provided. Any participants interested in the study will be referred to the main site for possible recruitment into the study through the usual recruitment procedures.

Recruitment will be carried out by research staff in each of the centres and will involve a clear explanation of the trial including the background, study protocol and aims.

7.1.2. Screening

Clinical staff at each site will identify eligible participants through direct contact or by searches of electronic records held in each Trust. They will then give or send potentially eligible patients brief study information. If interested potential participants can then agree to be approached by research staff and provided with further study information. Trial invitation information will include brief details of the need and purpose of the study and eligibility criteria. It will emphasise the pragmatic nature of the study and give a realistic indication of the burden to participants. All patients given trial information will be recorded in the screening logs at each site. All subjects who agree to consider participation will be seen by local research staff or the trial coordinator at the respective site to go through the consent and randomisation procedure. A case report form will be initiated and baseline data collected.

A screening log will be kept by local site research staff to document details of subjects invited to participate in the study and reasons for non-participation. Non-identifying patient details and reasons for non-participation will be uploaded to the study eCRF for subsequent analysis. The log will also ensure potential participants who are ineligible or decline participation are approached only once. Participants who do not respond to written information about the study may be contacted a second time to ensure they have received the information and been given the opportunity to participate.

7.2. Consent

All participants will undergo a process of informed consent. Participants will be free to withdraw their consent at any time.

The informed consent discussion will be undertaken by appropriately trained staff from the main trial sites as detailed in the site delegation log. This will include medical staff and research nurses/trial coordinators involved in the study who will give time for participants to ask any questions they may have following review of the trial information pack. The consent process will include provision of balanced written information concerning the need and overall benefit of the trial followed up by discussion with a local trial coordinator. This discussion will include a check of understanding concerning benefits and risks and ensuring that participants accept that the treatment will be allocated at random regardless of any personal preference they may have.

In relation to the qualitative interviews, recruiting staff will also explain why it is important to understand why people do and do not participate and how an interview study can help to improve the way trials are conducted. Participants who are willing to be approached will be provided with a separate information sheet about the interview study, this will include an expression of interest form with a reply-paid envelope.

Following receipt of information about the study, participants will be given at least 24 hours and up to as much time as they need to decide whether or not they would like to participate. Those wishing to take part will provide written informed consent by signing and dating the study consent form, which will be witnessed and dated by a member of the research team with documented, delegated responsibility to do so. Written informed consent will always be obtained prior to randomisation. The original signed consent form will be retained in the Investigator Site File, with a copy filed in the clinical notes, a copy given to the participant and a copy faxed to the central trial office. The participant will specifically consent to their General Practitioner (GP) being informed of their participation in the study. The right to refuse to participate without giving reasons will be respected. Consent for the interviews will be taken over the telephone, digitally recorded, and the consent form filled in by the researcher. A copy of the consent form will be made available to participants and a copy faxed to the central trial office.

During study set up we will consider requests for trial participant literature including the information sheet and consent form to be translated into other languages. Ability by the participant or their carer to complete the primary outcome questionnaires in English will be required for trial participation. If local NHS circumstances permit, sign interpreters will be arranged for all visits with patients who require them for deaf patients wishing to take part in the study. Interpreters will be used where necessary to explain the consent form and information sheet; great priority will be placed on finding the most direct means

of communication. If local research staff are in any doubt with regards to patient understanding of crucial aspects of the trial or ability to collect the outcome measures in English, then consent for randomisation will not be sought.

Participants will be given the option of consenting to storage of blood, urine and perianal swab for future research. They will also be asked if they would be willing for the inclusion of data collected for this study in future research. Any further research would be subject to separate review by an ethics committee.

7.3. Randomisation

Randomisation will be administered centrally by the Newcastle Clinical Trials Unit (CTU) secure web-based system. Permuted random 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 will produce the final randomisation schedule. Stratification 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) will be performed prior to randomisation to ensure balanced allocation within these factors.

Local research staff will access the web-based randomisation system with a login and password. The treatment allocation and randomisation number will be provided to the research staff once the correct details have been entered into the system. Following randomisation an appointment will be arranged, facilitated by trial staff, with the prescribing clinician to commence allocated treatment and ensure continued supply for the 12-month treatment period usually through hospital prescription or via the participant's GP. The antibiotic selected for use as prophylaxis will be chosen by the patient and clinician with regard to individual participant characteristics, local guidance, and standardised trial information with preferred agents being: nitrofurantoin first, trimethoprim second, cefalexin third.

7.4. Blinding

There is no participant blinding in this study. The members of the local research team that will carry out the follow-up process will not be blinded to the allocated treatment for each participant. We will however ensure that central trial staff inputting trial data onto trial database will, as far as possible, be unaware of allocated group.

7.5. Baseline Assessments and Data

Baseline data will include demographics, menopausal status, previous frequency of UTI, and associated usage of healthcare, past urine microbiological reports, together with symptom and QoL measures recorded prior to randomisation.

- **Screening:**
  - Eligibility checks

- **Consent for:**
  - Randomisation
  - Trial participation
  - Contact regarding telephone interview (Information sheet with reply sheet and prepaid envelope for the interviews given to patients approached for the trial)
  - Storage of blood, urine and swab for future research
  - Agreement to be approached for future studies in this area

- **Complete Baseline CRF which will include:**
  - Demographic Review/document eligibility including UTI details (stratify UTI frequency for randomisation)
  - Pre/post menopause (stratify for randomisation)
  - Document adjunctive treatments e.g. cranberry/ oestrogens/ d-mannose/ probiotics.
  - eGFR and LFTs, plus optional sample for storage and DNA analysis
  - Health Resource Use questionnaire
  - EQ5D-5L
  - Urine for MSU (plus urine for central lab with storage)
  - Optional perineal swab (central lab only)
  - Randomisation
  - Post-randomisation discussion of trial documentation

7.6. Trial Assessments

Samples of urine (baseline, 3, 6, 9, 12, 15 and 18 months), blood (baseline), and if agreed a perineal swab (baseline, 6, 12 and 18 months) will also be collected for shipment to the central laboratory for immediate testing and banking for studies additional to the trial. Health-related QoL will be measured by the EQ-5D 5L questionnaire completed at each 3-monthly follow-up and at the time of occurrence of UTI. Treatment satisfaction questionnaires will be recorded at the end of both the treatment and follow-up periods. Details of participant progress will be recorded on case report forms at baseline, 1, 3, 6, 9, 12, 15 and 18 months.

Monthly checks (telephone)

- Trial staff contact with participant:
- Completion of monthly check CRF by trial staff

3, 6 and 9 month visit

- UTI diary review
- Completion of CRF by trial staff
- Urine for MSU (plus urine for central lab)
- Optional perineal swab (central lab only at 6 month visit)
- eGFR and LFTs blood tests

Mailed direct to participant:

- UTI Symptom questionnaire
- EQ 5D 5L
- Health resource use questionnaire

At the time of UTI

Participant to complete and return:

- Participant UTI record
- EQ 5D 5L
- Urine for MSU (plus urine for central lab)
- Trial staff to complete report alert after telephone call from participant

12 month visit

- UTI diary review
- Completion of CRF by trial staff
- Urine for MSU (plus urine for central lab)
- Optional perineal swab (central lab only)
- eGFR and LFTs blood tests

Mailed direct to participant:

- UTI Symptom questionnaire
- EQ 5D 5L
- Health resource use questionnaire
- TSQM

15 and 18 month visits

- UTI diary review
- Completion of CRF by trial staff
- Urine for MSU (plus urine for central lab)
- Optional perineal swab (18 month and central lab only)

- eGFR and LFTs blood tests

Mailed direct to participant:

- UTI Symptom questionnaire
- EQ 5D 5L
- Health resource use questionnaire (18 month visit only)
- TSQM (18 month visit only)

7.6.1 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***				

*Screening data values may be used for baseline if taken within 2 months from the date of randomisation. **15 patients who declined to participate in main study but consented to interview study. ***15 patients who do not complete the treatment and 15 patients who stay in the study up to 6 months post randomisation will be interviewed. Time points will vary.

7.7. Withdrawal Criteria

Participants have the right to withdraw from the trial at any time without having to give a reason. Investigator sites should try to ascertain the reason for withdrawal and document this reason within the Case Report Form and participant's medical notes.

The Investigator may discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason including:

- Pregnancy
- Participant withdrawal of consent
- Investigator's discretion that it is in the best interest of the participant to withdraw
- An adverse event that renders the participant unable to continue in the trial
- Termination of the clinical trial by the sponsor

Participants who withdraw from the trial will not be replaced.

There are three withdrawal options:

1.) Withdrawing completely (i.e. withdrawal from allocated treatment and provision of follow-up data, including follow up through patient healthcare records)

2.) Withdrawing from the allocated treatment (moving to the alternative treatment arm) in the trial but allowing continued full follow up (including questionnaires) and review by research team of healthcare records

3.) Withdrawing from the allocated treatment in the trial and the active follow up but allowing the research team to follow up through healthcare records

A proportion of participants who discontinue participation in the study will be invited to take part in the qualitative interviews as it is important to understand why some participants withdraw from the trial.

7.8. Storage and Analysis of Samples

It is the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with the trial procedures to comply with the Data Protection Act. Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes

and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and 2006 Human Tissue (Scotland) Act.

1.) Urine samples

To measure the secondary outcomes of microbiologically proven urinary tract infection and altered bacterial phenotype and genotype, mid-stream urine (MSU) specimens will be collected and sent to the central reference laboratory (Freeman Hospital, Newcastle upon Tyne, NE7 7DN). The specimens will be collected by the participants according to standard instructions for mid-stream urine included in their trial information packs. MSU specimens will be collected at baseline and at 3, 6, 9, 12, 15 and 18 months after randomisation and during the early part of all episodes of urinary tract infection prior to antibiotic treatment. Using the labelling and Royal Mail-approved safe-boxes provided, the specimens will be sent to the central laboratory using surface mail. On arrival in the laboratory the specimens will be cultured for bacteria and any isolates tested for antibiotic sensitivity. Any isolated *Escherichia coli (E. coli)* species will be temporarily stored in the laboratory for later genotyping using specific DNA probes. Samples will be destroyed once the study and necessary analysis is complete.

2.) Perianal swabs

To measure the secondary outcome of altered gut commensal bacterial phenotype and genotype, perianal swabs will be collected from participants and sent to the central reference laboratory (Freeman Hospital, Newcastle upon Tyne, NE7 7DN). The specimens will be collected by the participants according to standard instructions for perineal swab collection. Perineal swabs will be collected at baseline and at 6, 12 and 18 months after randomisation. Using the labelling and Royal Mail-approved safe-boxes provided, the specimens will be sent to the central laboratory using surface mail. On arrival in the laboratory the specimens will be cultured for bacteria and isolates tested for antibiotic sensitivity. Any isolated *Escherichia coli (E. coli)* species will be temporarily stored in the laboratory for later genotyping using specific DNA probes. Samples will be destroyed once the study and necessary analysis is complete.

3.) Blood samples

As a subsidiary study, participant DNA will be obtained from blood samples taken during trial participation and probed for known genetic polymorphisms that predispose to urinary tract infection. Typically at the baseline visit a blood sample will be taken by the local research team from the participant using the study standard operating procedure. It will be immediately sent to the central reference laboratory (Freeman Hospital, Newcastle upon Tyne, NE7 7DN) using the labelling and Royal Mail-approved safe-boxes provided. The specimens will then be stored at -80°C at the central laboratory. At appropriate points during the recruitment period the samples will be transferred to the urinary tract

infection laboratory at Newcastle University for DNA extraction and analysis. Samples will be destroyed once the study and necessary analysis is complete.

7.9. End of Trial

The definition of the end of the trial will be the last participant's last follow-up visit at 18 months post-randomisation. And end of trial declaration will be submitted to the REC and MHRA.

8. TRIAL MEDICATION

8.1. Name and Description of IMP

SmPC will be used for all IMPs in the study (see Appendix 4 or www.medicines.org.uk for more information):

- Methenamine hippurate (Hiprex) – 1g scored tablets
- Nitrofurantoin (non-proprietary) – 50mg or 100mg tablets or 50mg capsules
- Trimethoprim (non-proprietary) – 100mg tablets
- Cefalexin (non-proprietary) – 250mg capsules or 250mg tablets

8.2. Drug Storage and Supply

The IMPs listed above are commercially available, UK-licensed drugs taken from routine hospital stock. They are not supplied by the Sponsor as trial drugs and should be ordered, stored and destroyed in the usual way according to local hospital policy. Any generic brand may be used (with the exception of nitrofurantoin m/r capsules which are not licensed for use in prophylaxis). Only licensed EU formulations may be used.

8.3. Preparation and Labelling of IMP

Normal manufacturing labelling requirements apply to all IMPs and no additional clinical trial information is required on the manufacturing or hospital dispensing label.

8.4. Dosage Schedule & Modifications

Methenamine hippurate: a twice daily dose of 1g to be taken 12 hours apart

Nitrofurantoin: 50 mg or 100 mg daily

Trimethoprim: 100 mg daily

Cefalexin: 250 mg daily

8.5. Known Drug Reactions and Interactions

See sample SmPCs for Nitrofurantoin, Trimethoprim, Cefalexin and Methenamine hippurate in Appendix 4.

8.6. Concomitant Medications

It is the responsibility of the prescribing clinician to check for interactions between trial drugs and other medications. For further guidance please refer to SmPCs for Nitrofurantoin, Trimethoprim, Cefalexin and Methenamine hippurate in Appendix 4.

8.7. Assessment of Compliance

Patients will be contacted on a monthly basis to assess compliance with study medication.

9. PHARMACOVIGILANCE

9.1. Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR)	An untoward or unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death • Is life-threatening* • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect • Other important medical events that jeopardise the participant or require intervention to prevent one of the above consequences * Life-threatening refers to an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based upon the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the SmPC (if the product holds a marketing authorisation) or the Investigator Brochure.

9.2. Recording and Reporting AEs and SAEs

Any adverse events occurring during the period of participation will be recorded in line with Good Clinical Practice[21]. The expected rate of adverse events is low for both treatment arms. For daily prophylactic antibiotics the Cochrane meta-analysis[6] reported a RR against placebo for severe side effects of 1.58 (95% CI 0.47 to 5.28) with the most common being skin rash and nausea. Other side effects occurred with a RR of 1.78 (CI 1.06 to 3.00) and included vaginal itching.

Of the three prophylactic antibiotics (nitrofurantoin, trimethoprim and cefalexin) that we have specified for use in the trial there was only two reported cases of a severe side effect in the published RCTs; both with cefalexin. The Cochrane meta-analysis examining the urinary antiseptic Methenamine hippurate[7] stated "All the studies that reported adverse events showed low rates" and "Nausea was the most common symptom… constipation was described once … and rash was described in four single instances".]

All non-serious adverse reactions will be recorded on the e-CRF at visits/contacts/records review at one, three, six, nine and 12 and 18 months for the duration of the trial.

Any serious adverse events will be recorded throughout the duration of the trial until four weeks after trial intervention is stopped on the specific trial SAE form.

Serious adverse events exclude any pre-planned hospitalisations (e.g. elective surgery) not associated with clinical deterioration.

Serious adverse events exclude routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.

Serious adverse events exclude elective or scheduled treatment for pre-existing conditions that did not worsen during the study.

Serious adverse events exclude UTIs which are the primary outcome measure, already documented and monitored within study.

For each SAE the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Causality in the opinion of the investigator
- Whether the event is considered expected or unexpected.

Any change of condition or other follow-up information should be faxed to the NCTU as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

9.3. Recording and Reporting SUSARs

All SUSARs occurring from first administration of IMP until 4 weeks post termination of trial treatment must be reported to the MHRA and REC. The Sponsor will perform this reporting.

The assessment of expectedness will be performed by the CI against the Reference Safety Information (RSI) for the trial. The RSI is in section 4.8 of the SmPC for each of the IMPs.

Fatal and life-threatening SUSARS must be reported no later than 7 calendar days after the sponsor, CI or NCTU has first knowledge of the event. Any relevant follow-up information must be sought and reported within a further 8 calendar days.

Non-fatal SUSARs must be reported no later than 15 calendar days after the sponsor, CI or NCTU has first knowledge of the event. Any relevant follow-up information should be sought and reported as soon as possible after the initial report.

As soon as a site suspects that a SAR may be a SUSAR they must contact the CI, sponsor representative and the trial manager immediately. The reporting timeframe starts at day 0 when the sponsor, or NCTU is in receipt of a minimum set of information:

- Sponsor trial reference and trial name (sponsor reference)
- EudraCT number
- Patient trial number and date of birth
- Name of IMP(s)
- Date of notification of the event
- Medical description of the event
- Date and time of the onset of the event (including event end date if applicable)
- Causality assessment
- Seriousness of the event, particularly if life threatening or fatal
- An identifiable reporter (e.g., Principal Investigator)

This information must be provided by secure fax or secure email. The site is expected to fully cooperate with the sponsor, CI and NCTU in order that a full and detailed report can be submitted to the MHRA and REC within the required timelines.

PIs will be informed of all SUSARs by the NCTU.

9.4. Responsibilities

Principal Investigator

- Checking for AEs and ARs when participants attend for treatment or follow-up
- Using medical judgement in assigning seriousness and causality and providing an opinion on expectedness of events using the Reference Safety Information approved for the trial.
- Ensuring that all SAEs and SARs, including SUSARs, are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.
- Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.

Chief Investigator

- Clinical oversight of the safety of trial participants, including an ongoing review of the risk/benefit.
- Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
- Using medical judgement in assigning expectedness to SARs.
- Immediate review of all SUSARs.
- Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol.

Sponsor

- Assessment of expectedness of any SUSARs
- Expedited reporting of SUSARs to the CA and REC within required timelines
- Notification of all investigator sites of any SUSAR that occurs

TSC and DMEC

- Review of safety data collected to date (TSC and DMEC)
- Carry out a cumulative review of unblinded safety information at each meeting to identify any trends (DMEC)

9.5. Notification of Deaths

All deaths that are assessed to have a causal relationship to the IMP will be reported to the sponsor. This report will be immediate.

9.6. Pregnancy Reporting

Participants on the methenamine hippurate arm of the trial should stop taking their allocated intervention if they become pregnant during the study. They should contact the research team so that their future treatment can be assessed and whether an alternate form of prophylaxis should be prescribed. If a participant becomes pregnant while on the antibiotic arm of the trial there will be further discussion between patient and clinician to decide whether continuation in the trial is in the woman's best interests and whether any change should be made to the prophylactic antibiotic (it is likely that medical advice will say that some form of prophylaxis should continue). Standard CTiMP procedures will be followed in terms of ongoing care and surveillance, i.e. the pregnancy should be reported to the treating clinician (normally her General Practitioner). The pregnancy must be followed up to determine outcome. Additional follow-up will no longer be required once the newborn is determined to be healthy.

9.7. Overdose

Overdoses will be recorded and notified to the sponsor by completion of a deviation report by the Trial Manager.

Overdoses may be identified during follow-up with the participant, participant notification, notification by participant's GP.

9.8. Reporting Urgent Safety Measures

An Urgent Safety Measure (USM) is an action that the Sponsor or an Investigator may take in order to protect the subjects of a trial against any immediate hazard to their health or safety. Upon implementation of an USM by an Investigator, the Sponsor, CI and NCTU must be notified immediately and details of the USM given. The NCTU must inform the MHRA and the NHS REC within 3 days of the USM taking place in accordance with the NCTU's standard operating procedures.

9.9. Development Safety Update Reports

The Development Safety Update Report will be prepared by the NCTU for review by the CI. The Sponsor will review the final version of the report before submission to the MHRA.

10. STATISTICS AND DATA ANALYSIS

10.1. Sample Size Calculation

The clinical trial has a planned recruitment target of 240 patients, 120 in each of the treatment arms. 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.

We have discussed extensively the relative merits of non-inferiority against superiority comparison and believe the key issue is that oral urinary antiseptic would be acceptable to the patient group provided that their effectiveness for UTI prevention is no worse than antibiotic prophylaxis and that the burden of adverse effects is similar or better. There is also the key added potential benefit of reduced rates of resistant organisms and subsequent collateral harm to the individual and community. The sample size calculation is based on the following assumptions:

- 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[6] and Methenamine hippurate[7] 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 difference in number of episodes per year between prophylactic antibiotics and Methenamine hippurate to be 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[6, 7] and has been conservatively estimated at 0.9 episodes per year.
- The type 1 error rate for a two group comparison is set at 5% thus the calculation of a one-sided 95% confidence interval (or a two sided 90% confidence interval).
- The attrition rate of participants in this study has been conservatively estimated at 25%.

10.2. Planned Recruitment Rate

Feasibility of recruitment will be monitored by returns to the web-based trial management system and further informed via the embedded qualitative study. We have set the following targets to ensure recruitment is kept to target over the 18 month recruitment phase (64 site months) estimating that one-third of participants will be recruited in the first half of the study and as a result of increasing awareness and momentum in each centre and the staggered set up of the initial four centres. The remaining two-thirds of required participants will be recruited in the second half of the study;

- End of 12 site months – 18 patients recruited in total (8%)
- End of 24 site months – 48 patients recruited in total (20%)
- End of 36 site months – 108 patients recruited in total (45%)
- End of 48 site months– 168 patients recruited in total (70%)
- End of 60 site months – 228 patients recruited in total (95%)
- End of recruitment (64 site months) – 240 patients recruited in total (100%)

We have introduced criteria for progression covering the first 24 site months of the trial. Our target recruitment in that period is 48 participants. We will regard recruitment of less than 24 participants at this stage as indicating that the trial is not feasible in its present design and, unless there are compelling mitigating circumstances such as zero recruitment due to circumstances beyond our control at some of the sites, terminate the project. Recruitment of between 24 and 44 participants would trigger major alteration to the recruitment plan; such as increasing the number of planned sites and extension to recruitment period. Recruitment of 44 or more participants would be considered within sampling variability of the target of 48 and entail only minor finessing of the recruitment strategy. If any of these 6 recruitment targets are not met then an extra meeting of the TSC will be called in order to explore any common themes or barriers to recruitment.

In the embedded qualitative study which we propose to conduct in the early phase of recruitment we will carry out in-depth telephone interviews with up to 15 patients in each of three groups (those who agree to participate, those who decline and if available those who drop out of the study before the end of the follow up period). Also we will conduct telephone interviews with up to eight clinicians recruiting to the trial. This will provide information regarding both patients' willingness to be randomised and clinicians' views on treatment randomisation. A descriptive report with proposed action will be prepared and

sent to the Trial Steering Committee for approval this will include rate and reasons of declining randomisation and participant attrition.

10.3. Statistical Analysis Plan

The main analysis will comprise a comparison of patients randomised to antiseptic with patients randomised to antibiotic ("intention to treat").The primary clinical outcome is the occurrence of symptomatic UTI during the 12-month period of treatment. Our hypothesis is that treatment with antiseptic is not inferior to treatment with antibiotic. When considering an inferiority limit the variable that patients most readily relate to is the number of episodes experienced during treatment. The inferiority limit adopted for this study will be one episode per year. A 90% confidence interval for the difference between groups (antiseptic - antibiotic) will be calculated using a resampling (bootstrap) procedure. 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.

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/post-menopausal) will be included as fixed effects. This will yield an estimate of the incidence rate ratio. A binary indicator of at least one patient reported or clinician recorded symptom of UTI will be analysed using the same approach but with a binomial error structure. The same methods will be used to analyse the relative frequency of episodes of UTI during the 6 month post treatment period as a secondary outcome.

Analysis of the secondary outcomes will follow a broadly similar strategy although non-inferiority will not be assessed as this is only relevant for the pre-specified primary outcome. Incidence or occurrence type outcomes will be analysed in a manner analogous to that previously described for the primary outcome. Patient satisfaction will be compared between arms using an analysis of variance/covariance approach adjusting for stratification variables and other pre-defined baseline covariates. Health related quality of life will be analysed as part of the Health Economics analysis.

A full statistical analysis plan (SAP) will be produced and finalised prior to data lock and analysis commencing.

10.4. Interim Analysis and Criteria for the Premature Termination of the Trial

Data will be analysed at the end of the study; there are no planned interim analyses. An independent Data Monitoring Committee (DMC) will be convened to undertake independent review. The purpose of this committee will be to monitor efficacy and safety endpoints and will operate according to a written terms of reference linked to DAMOCLES charter. Only the DMC will have access to full unblinded study data, if requested, prior to completion of the trial. All analyses will follow a carefully documented Statistical Analysis Plan. The DMC will be asked to review and comment on this Plan prior to analysis. A single main analysis will be performed at the end of the trial when all follow up has been completed. The DMC will meet initially to agree terms of reference and other procedures. 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.

10.5. Subject Population

The main analysis will comprise a comparison of patients randomised to antiseptic with patients randomised to antibiotic (“intention to treat”).

We will also undertake a per protocol analysis. The primary analysis will be repeated but on the subset of patients who have been treated in accordance with the treatment protocol for the arm to which they were randomised. Patients who switch treatments will still be analysed within the group to which they were randomised but only if that switching has been undertaken in accordance with the specified protocol.

10.6. Procedure to Account for Missing or Spurious Data

Data with missing observations 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 missing to a sufficient extent, the use of appropriate multiple imputation techniques will be considered. Data management processes will include checking for data outliers and unusual data patterns.

10.7. Qualitative Analysis

Topic guides for both patient and clinician telephone interviews will be developed with the input of the study team and PPI group. Interviews will be digitally recorded with the permission of the interviewee and transcribed verbatim. NVivo will be used as a tool to manage and code the transcript data. Data will be analysed drawing upon the constant comparative method. Issues identified that impact on recruitment and are resolvable, such as lack of clarity in the patient study information or consent process, will be addressed immediately. We plan the headline results to be available to inform change in study procedures at an early stage of the recruitment phase.

10.8. Health Economic Analysis

Within this study both a 'within trial' and model based economic evaluation will be conducted. These analyses will take the form of a cost-utility analysis. The 'within trial' analysis will take the perspective of the NHS and personal and social services, but will also take a wider perspective by including costs by the participants and their families. The model based analysis will take the perspective of the NHS and personal and social services.

10.8.1. Within Trial Analysis

For each trial participant the use of health and social care services will be recorded. The use of services for the initial treatments (medications) including time in hospital will be collected on the CRF. Also collected on the CRF will be the use of secondary care services such as duration of any hospital stay, number of outpatient visits, use of tests, and any change in medications. Use of primary care services such as general practitioner visits will be collected via questionnaire at baseline, 3, 6, 9, 12 and 18 months. Information of further patient costs will be sourced from other relevant RCTs that collected patient costs due to the burden on respondents from collecting this type of data.

Costs for health care services will be obtained from standard sources such as NHS reference Healthcare Resource Group (HRG) tariffs, the British National Formulary[25] (BNF) for medications, and Unit Costs of Health and Social Care[26] for primary care usage. Further data will come from the study centres themselves such as the cost of consumables and other equipment used for treatment. The price year adopted for the base case analysis will be the year when the final analysis is conducted. For each participant measures of use of resources will be combined with unit costs to provide a cost for that participant.

The relative changes in health related quality of life resulting from reductions in recurrent UTIs together with any harms associated with each of the treatment strategies and with subsequent treatments for UTIs will be captured by the EQ-5D-5L. Tariffs are currently not available for the EQ-5D-5L but responses can be crosswalked to scores from the EQ-5D-3L and this scoring will be used unless EQ-5D-5L scoring becomes available during the lifetime of the trial. Health State Utilities from the EQ-5D will be used to estimate QALYs for each participant using the area under the curve approach.

Data on costs and QALYs will be used to estimate the mean cost and QALYs for each intervention group. The cost and QALY data will then be used to estimate incremental costs and QALYs and incremental costs per QALY. These data will be presented as point estimates and bootstrapping techniques will be used to estimate the statistical imprecision surrounding them. The results of this stochastic analysis will be presented as cost and QALY plots and as cost-effectiveness acceptability curves[27].

10.8.2. Model Based Analysis

Drawing upon existing modelling expertise in the Health Economics Group at Newcastle University, an economic model describing recurrent UTIs will be developed. The model will be constructed following guidelines for best practice in economic modelling[29].

The use of services both for the treatment and management for recurrent UTIs will be modelled and the costs of these events will be based upon the estimates for these events derived from within the trial. The trial based data will be the main source of data for the economic model but it will be supplemented by focused searches of the literature and health economic data bases (e.g. the Centre for the Evaluation of Value and Risk in Health (CEVR) Cost Effectiveness Analysis (CEA) Registry; https://research.tufts-nemc.org/cear4/; NHS Economic Evaluation Database).

Discounting will be applied to costs and outcomes at the UK recommended rate of 3.5%[31]. Further data required for the model relates to the transition and other probabilities of events occurring over the lifetime of patients. These probabilities include the risk of recurrence as well as probabilities of receiving different types of intervention should recurrence occur.

The model will be used to produce estimates of costs and QALYs (from the EQ-5D). Cost-effectiveness will be reported as incremental cost per QALY gained (at both 12 months and over the patient's lifetime). The model will be probabilistic and distributions will be attached to all parameters, the shape and type of distribution will depend upon the data available and recommendations for good practice in modelling[32]. The results will also be presented as point estimates of costs, effects, incremental costs, QALYS, and measures cost-utility. They will also be presented as plots of costs and QALYs derived from the probabilistic analysis

and cost-effectiveness acceptability curves. Deterministic sensitivity analyses will be combined with the probabilistic analysis to explore other forms of uncertainty.

11. DATA HANDLING

11.1. Data Collection Tools and Source Document Identification

Data will be collected using Case Report Forms, participant completed questionnaires and information retrieved from medical notes. Data will be recorded by site staff authorised by delegation log on electronic Case Report Forms (eCRF) in the clinical data management software package (MACRO™). Participant completed questionnaires and UTI diaries which are entered into the eCRF at a later date will be classed as source documentation. Results of urine and perineal swab analysis will also be uploaded into the MACRO database from reports produced by the central laboratory (see section 7.8 Storage and analysis of samples). Data transferred from site to the secure validated database by remote access will be secure and encrypted. Data will be handled, computerised and stored in accordance with the Data Protection Act 1998. Under the trial participant consent, identifiable data will be stored in a separate and limited access database to allow preparation and sending of follow up documentation. The quality and retention of study data will be the responsibility of the Newcastle Clinical Trials Unit (CTU). All study data will be retained in accordance with the latest Directive on Good Clinical Practice (GCP) and local policy.

11.2. Data Handling and Record Keeping

Caldicott approval for use, transfer and storage of participant identifiable information will be obtained at each site. Clinical data will be entered into the database (MACRO™) remotely at each site by the local investigator or another member of the site research team with delegated responsibility for this activity, together with data from case report forms completed at face-to-face visits or telephone calls with participants.

All research data will be kept in accordance with Newcastle University's Information security policy (http://www.ncl.ac.uk/itservice/policies/). Newcastle University maintains a series of regular backups and off-site mirror servers to ensure continuity and disaster recovery.

The MACRO™ database is an electronic data capture system which complies with the requirements of regulatory bodies and maintains an audit trail of any changes to the data. All data stored in MACRO benefit from Infermeds' hosting service in

collaboration with Rackspace which features redundancy and backup measures in case of disaster.

Questionnaires returned by post to the trial management office in Newcastle will be entered there. Trial management staff in the Newcastle trial office in collaboration with database management staff will work closely with local site research teams to ensure that the data are as complete and accurate as possible. The Newcastle CTU will be responsible for chasing missing data. Two reminders will be sent to participants to prompt return of questionnaires. Extensive range and consistency checks will further enhance the quality of the data. Data collected during the course of the research will be kept strictly confidential and accessed only by members of the trial team. Patient's details will be stored on a secure database under the guidelines of the 1998 Data Protection Act. Patients will be allocated an individual specific trial number to allow anonymised versions of the secure database to be available to the trial team and subsequently more widely under open data access arrangements. Identifiable data will be kept separately from the trial data in a password protected database within Newcastle CTU with access limited to those members of the trial team responsible for sending out the questionnaires and logging their return. The database will be used to ensure trial correspondence is sent to each participant using their preferred mode of delivery. Participants will be asked to give their preferred contact details for communication with trial staff. To comply with the 5th Principle of the Data Protection Act 1998, personal data will not be kept for longer than is required for the purpose for which it has been acquired.

11.3. Access to Data

Direct access may be granted to representatives of the Sponsor, host institution, regulatory authorities or NCTU employees for monitoring or auditing purposes.

11.4. Archiving

Data will be archived in accordance with the NCTU SOP and European Commission Directive 2005/28/EC Article 17. Essential data will be retained for a period of at least 15 years following close of study in line with sponsor policy and the latest Directive on GCP (2005/28/EC). Archiving will be authorised by the Sponsor following submission of the end of study report. Authorisation will be requested from the Sponsor to destroy the documentation at the end of the archiving period.

12. MONITORING, AUDIT & INSPECTION

A trial monitoring plan will be developed, based upon the trial risk assessment, and this plan will be agreed by the Trial Management Group, the Trial Steering Committee and the Sponsor.

Monitoring of study conduct and data collected will be performed by a combination of central review and site monitoring visits to ensure the study is conducted in accordance with GCP. Study site monitoring will be undertaken by members of the TMG. The main areas of focus will include consent, serious adverse events and essential documents in study. Site monitoring will include:

- All original consent forms will be reviewed as part of the study file; confirmation of the presence of a copy in the patient hospital notes may be requested for 10% of participants
- All original consent forms will be compared against the study participant identification list
- All reported serious adverse events will be verified against clinical records (source data verification)
- The presence of essential documents in the investigator site file and study files will be checked
- Verification of primary endpoint data and eligibility data for 10% of participants entered in the study may be requested

Central monitoring will include:

- All applications for study authorisations and submissions of progress/safety reports will be reviewed for accuracy and completeness, prior to submission
- All documentation essential for study initiation will be reviewed prior to site authorisation
- Statistical monitoring for outlier sites and unusual data patterns

All monitoring findings will be reported and followed up with the appropriate personnel in a timely manner.

The trial may be subject to audit by representatives of the Sponsor or inspection by the MHRA or HTA. Each investigator site will permit trial-related monitoring, audits and regulatory inspection including access to all essential and source data relating to the trial.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Research Ethics Committee Review and Reports

The NCTU will obtain a favourable ethical opinion from an NHS Research Ethics Committee (REC) prior to the start of the trial. All parties will conduct the trial in accordance with this ethical opinion.

The NCTU will notify the REC of all required substantial amendments to the trial and those non-substantial amendments that result in a change to trial documentation (e.g. protocol or patient information sheet). Substantial amendments that require a REC favourable opinion will not be implemented until this REC favourable opinion is obtained. The NCTU will notify the REC of any serious

breaches of GCP or the protocol, urgent safety measures or SUSARs that occur during the trial.

An annual progress report will be submitted each year to the REC by the NCTU until the end of the trial. This report will be submitted within 30 days of the anniversary date on which the original favourable ethical opinion was granted.

The NCTU will notify the REC of the early termination or end of trial in accordance with the required timelines.

13.2. Peer Review

The study has undergone peer review by independent reviewers as part of the grant award process. The protocol has been reviewed by the study co-investigators, the sponsor and the North East - Tyne & Wear South Research Ethics Committee.

13.3. Public and Patient Involvement

Identification and prioritisation of the research topic was directly patient driven. We have set up a patient interest group locally which has helped refine the methodology of the study and aims to further inform the study to completion. A member of this patient interest group will be invited onto the TSC. The Cambridge PPI panel have also been involved with specific help reviewing the application. We have discussed our research plans with Alison Irving, at Cystitis and Overactive Bladder (COB) Foundation who strongly support studies investigating non-antibiotic treatment for cystitis and will help recruitment and dissemination of findings. A representative from the COB foundation has agreed to membership of the TSC. The COB foundation has previously advised the team on issues relating to reporting of research and assisted in its dissemination through the national press and their own monthly magazine. As a relatively under-studied area, the involvement of patient groups will be critical to disseminating the results of the study to a wider audience, particularly as the impetus for the research has come directly from patient frustrations at the lack of alternative non-antibiotic based treatment.

13.4. Regulatory Compliance

The trial will be conducted in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments. All parties must abide by these regulations and the ICH GCP guidelines.

The NCTU will obtain a Clinical Trial Authorisation from the MHRA prior to the start of the trial and will notify the MHRA of any substantial amendments that require review by the competent authority. These substantial amendments will not be implemented until the MHRA have issued an acceptance of the amendment.

The NCTU will notify the MHRA of any serious breaches of GCP or the protocol, urgent safety measures or SUSARs that occur during the trial.

The Development Safety Update Report will be submitted each year to the MHRA by the NCTU until the end of the trial.

The NCTU will notify the MHRA of the early termination or end of trial in accordance with the required timelines.

13.5. Protocol Compliance

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used. Unintentional protocol deviations will be documented and reported to the Sponsor in accordance with NCTU SOPs. Deviations that are found to frequently recur at a site are not acceptable and could be classified as a serious breach.

13.6. Notification of Serious Breaches to GCP and/or the Protocol

A serious breach is a breach which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the subjects of the trial.
- The scientific value of the trial.

The sponsor must be notified immediately of any incident that may be classified as a serious breach. The NCTU will notify the MHRA and the NHS REC within the required timelines in accordance with the NCTU SOP.

13.7. Data Protection and Patient Confidentiality

All investigators and trial staff must comply with the requirements of the Data Protection Act 1998 with regards to collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to data will be limited to the minimum number of individuals necessary for quality control, audit, and analysis.

Data will be archived in accordance with the Newcastle CTU SOP and European Commission Directive 2005/28/EC Article 17 and made permanently available to the wider community through deposition at UK Data Archive. Research participants will be protected through the removal of personal, confidential and sensitive data. In addition to data files (rendered as csv-delimited text), data list files will provide descriptions of all variables, including how each variable was constructed and calculated where appropriate.

Essential data will be retained for a period of at least 15 years following close of study in line with sponsor policy and the latest Directive on GCP (2005/28/EC).

The CI will be the data custodian.

13.8. Indemnity

The sponsor will provide indemnity in the event that trial participants suffer negligent harm due to the management of the trial. This indemnity will be provided under the NHS indemnity arrangements for clinical negligence claims in the NHS.

The substantial employers of the protocol authors will provide indemnity in the event that trial participants suffer negligent harm due to the design of the trial.

The study sites will provide indemnity in the event that trial participants suffer negligent harm due to the conduct of the trial at their site. For NHS Organisations this indemnity will be provided under the NHS indemnity arrangements for clinical negligence claims in the NHS. NHS Organisations must ensure that site staff without substantive NHS contract hold honorary contracts to ensure they can access patients and are covered under the NHS indemnity arrangements. Study staff without NHS contracts, e.g. General Practitioners will provide their own professional indemnity.

13.9. Amendments

It is the responsibility of the Research Sponsor to determine if an amendment is substantial or not and study procedures must not be changed without the mutual agreement of the CI, Sponsor, the Trial Management Group, and the Trial Steering Committee where appropriate.

Substantial amendments will be submitted to the REC and/or MHRA (as appropriate) and will not be implemented until this approval is in place. It is the responsibility of the NCTU to submit substantial amendments.

Non-substantial amendments may be made at any time with a record of the amendment held in the Trial Master File. Any non-substantial amendment that requires an update to the trial documentation will be submitted to the NHS REC for acknowledgement of the revised version of the document.

Substantial amendments and those minor amendments which may impact sites will be submitted to the relevant NHS R&D Departments for notification to determine if the amendment affects the NHS permission for that site. Amendment documentation will provide to sites by the NCTU.

13.10. Post-Trial Care

The discontinuation of prophylaxis (antibiotics or antiseptic) after 12 months of treatment is part of the protocol and participants will be encouraged to abstain from prophylactic medication for the 6 months of the follow-up phase. It is recognised however that recurrence of urinary tract infections may mandate further prophylactic treatment within the follow-up period and this will be recorded in individual CRF's. If the participant wishes and if the clinician responsible for their routine care agrees, then one of the methods of prophylaxis can be continued beyond the 18-month trial participation period. This will take place without further active monitoring from the trial research team. This information will be stated in the patient documentation.

13.11. Access to the Final Trial Dataset

The TSC, DMC, trial statistician, data manager and other members of the central trial team as required will have access to the full trial dataset. The full trial dataset will not be available to individual site investigators prior to publication of the main trial results. Site investigators will be allowed to access the full dataset after publication of the main trial results if a formal request describing their plans is approved by the TSC.

14. DISSEMINATION POLICY

The results of the study will be presented at topic-specific national or international conferences and published in a general medical journal with the monograph published by HTA. Authorship of all publications will be on a named individual authorship basis. For each publication all individuals who fulfil the authorship definition for the publishing journal or site will be included as individually named authors. Authorship order will be decided by the Chief Investigator. Any disputes regarding

Authorship will be adjudicated by the Trial Steering Committee. To safeguard the integrity of the main trial, reports of explanatory or satellite studies will not be submitted for publication without prior agreement from the Trial Management Group and Trial Steering Committee. We will also send outputs to the funder prior to submission for publication. The full study report will be available from the NIHR HTA website. The trial will provide high-level evidence to include in systematic reviews such as those published by Cochrane and SIGN. The results will also be submitted for inclusion in relevant urology guidance documents

Participants will be provided with a lay summary of results. They will also have access to a copy of journal articles through the trial website. Members of the PPI focus groups will review results and they will be involved in writing lay summaries of results for dissemination to relevant patient groups such as the Cystitis and Overactive Bladder Foundation (COB) and the Bladder and Bowel Foundation (BBF). The COB expertise will be utilised on how best to deliver these results to the other participants and patient-specific groups. These will be in formats accessible to all. The most significant anticipated outcome from this study will be demonstration of the comparable effectiveness of a non-antibiotic treatment for the prevention of recurrent UTI, Methenamine hippurate. If our alternative hypothesis holds true the study will represent a significant step forward in the treatment of recurrent urinary infection, with high level evidence for the effectiveness of a treatment strategy that avoids prolonged antibiotic use and which is directly in line with the UK government's strategy to combat antimicrobial resistance. It is likely that national and international media will pick up the story and inform the wider public of the results and their significance. We will also engage with Commissioning Groups, relevant NHS Managers and other Trust Representatives to facilitate prompt change to local NHS practice and promote this alternative preventative treatment for recurrent UTI. The results will be publicised on hospital websites and discussed at departmental meetings. The results will be disseminated to members of professional groups such as BAUS and EAU through updates and presentations.

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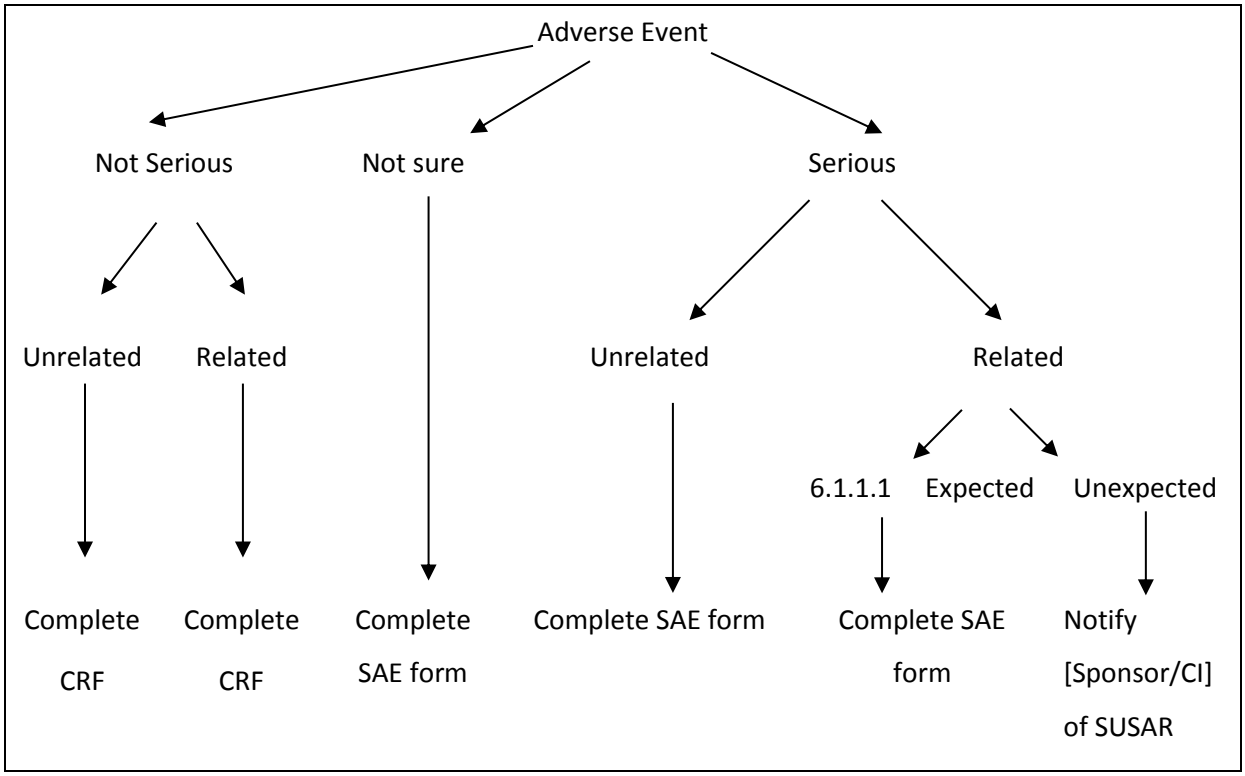
16. APPENDICES

Appendix 1 - Safety Reporting Diagram



{The diagram may require editing depending upon the requirements of the trial and the sponsor}

Contact details for reporting SAEs and SUSARs

Please send [**] form(s) via [Fax number]

or

[Telephone number] [Availability]

Appendix 2 – Amendment History

• Amendment Number	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
Substantial Amendment 1	1.1	7th April 2016	R. Brown	• Updated participant questionnaires for baseline, 3, 6 ,9 ,12, 15 and 18 month time points to take account of slightly different combinations of the questionnaires at some timepoints • An updated PIS to account for an additional blood test at 15 months and an additional questionnaire at 15 months • Corrections to the protocol and clarification of the schedule of events. Addition of paragraph describing the use of PICs. • Changes to qualitative interview sections in the protocol to allow for change from face to face interviews to telephone interviews and verbal consent to be taken. • Other minor administrative changes to protocol • Revised participant information sheet for interviews • Topic guide for interviews • New consent form for interviews to allow verbal consent to be taken for telephone interviews
Substantial Amendment 2	1.1	6th September 2016	R Brown	• Updated letter to GP, clarification of treatment during a breakthrough UTI • Updated participant Identification card, clarification of treatment during breakthrough UTI

				• Updated sample shipment form, administrative changes to the form • Updated UTI Record, addition of symptom questions and reordering of items • Addition of a short Participant Information Sheet • Addition of a participant thank you letter
Substantial Amendment 3 (addition of new sites)	1.1	20th Feb 2017	C Brennand	Addition of 2 new sites: • Liverpool • Oldham
Substantial Amendment 4	1.1	20th March 2017	C Brennand	• ALTAR actions for participants at time of UTI, v1.0, 02/12/2016. Additional guidance for participants, produced as a result of feedback from sites, giving more information on the actions to be completed when a participant has a urinary tract infection. • Letter to patient's General Practitioner washout period, v1.0, 02-12-2016. Additional letter to participant's GP, only to be used if a participant requires a washout period. • Update to Clinician Trial Information Sheet, to clarify that antibiotic prophylaxis should be temporarily discontinued during a Urinary Tract Infection treated with antibiotics.
Substantial Amendment 5	1.2	REC: 7th August 2017 MHRA: 23rd August 2017	C Brennand	• The change to the study involves an update to the Reference Safety Information (RSI) for Trimethoprim, one of the antibiotics used in the study, which was submitted to MHRA and approved with the original application. The sample SmPC (any generic brand may be used) submitted as the updated RSI for this study as there are changes to section 4.8 (undesirable effects) which may be relevant to the ALTAR study population:

				Trimethoprim 100mg tablets (Kent Pharmaceuticals Ltd) last updated 18 April 2017 • The SmPCs for the other drugs used in the trial have also been reviewed and, whilst there have been no changes to the RSI for Nitrofurantoin, there have been updates to the SmPC for this antibiotic and, for completeness, the 16 May 2016 version has been included in this update to the protocol. Therefore this version will be referred to as the SmPC containing the RSI for the study: • Minor typographical errors in the errors corrected
Non substantial amendment 1	1.2	HRA: 25th October 2017	R Forbes	• Extension to the study – 9 months extension to the trial.
Substantial Amendment 6 (addition of new sites)	1.2	27th November 2017	R Forbes	Addition of 2 new sites: • Coventry • East Kent
Substantial Amendment 7	1.3	3rd April 2018	R Forbes	• ALTAR Protocol v1.3 dated 13 December 2017. The protocol with a number of administrative changes (trial staff), update the trial period following a recent extension to the study. There has also been a change to the time period that the screening data values can be used for the baseline values from 2 weeks to 2 months. This was due to feedback from sites and to make the study reflect normal clinical practice. • ALTAR Participant Information Sheet v1.3 13 December 2017 and ALTAR Consent Form Main study v1.1 13 December 2017. The patient information sheet and informed consent form have been updated to include information regarding

				pregnancy and birth data being collected for participants who become pregnant while on the trial. • ALTAR Completion of randomised treatment letter to Participant v1.0 13 December 2017. This is a new/additional document to be sent to participants to thank them for participating in the trial and what they need to do next for further treatment. • ALTAR Discharge letter to Clinician v1.0 13 Dec 2017. This is a new/additional document to be sent the participant's GP to confirm that the participant has completed the trial and to thank them for their support during the trial.

{Enter all amendments to the protocol here whether substantial or non-substantial. Substantial amendments will require approval by the NHS REC and MHRA. Non-substantial amendments should be sent to the NHS REC for acknowledgement only

Appendix 3 - Childs – Pugh classification and scoring system for hepatic impairment.

Measure	1 point	2 points	3 points
Total bilirubin, µmol/l (mg/dl)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/dl	>3.5	2.8-3.5	<2.8
Prothrombin time, prolongation (secs)	<4.0	4.0-6.0	> 6.0
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Points	Class
5-6	A
7-9	B
10-15	C

Appendix 4 – Sample SmPCs for Trimethoprim, Nitrofurantoin, Cefalexin, Methenamine Hippurate

Any generic brand may be used (with the exception of nitrofurantoin m/r capsules which are not licensed for use in prophylaxis). Only licensed EU formulations may be used.

Trimethoprim 100mg Tablets

Summary of Product Characteristics Updated 18-Apr-2017 | Kent Pharmaceuticals Ltd

1. Name of the medicinal product

Trimethoprim 100mg Tablets

2. Qualitative and quantitative composition

Each tablet contains Trimethoprim 100 mg

3. Pharmaceutical form

Uncoated tablet

Flat white tablet, with bevelled edges and embossed with 'TR100'on one side.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of susceptible infections (caused by trimethoprim sensitive organisms including urinary and respiratory tract infections.

Prophylaxis of recurrent urinary tract infections.

4.2 Posology and method of administration

Acute infections:

Treatment should continue for a period of between 3 days (eg, uncomplicated bacterial cystitis in women) to 2 weeks depending on the nature and severity of the infection. The first dose may be doubled.

Adults: 200mg twice daily Paediatric population:

Children over 12 years: Same as adult dose Children 6 - 12 years: 100mg twice daily

Children under 6 years: This dosage form is not suitable for use in children younger than 6 years. Elderly: Dosage is dependent on renal function. See special dosage schedule below.

Advised dosage schedule where there is reduced kidney function:

Creatinine Clearance (ml/sec)	Plasma creatinine (micromol/l)	Dosage advised
Over 0.45	Men <250 Women <175	Normal
0.25 - 0.45	Men 250-600 Women 175-400	Normal for 3 days then half dose
Under 0.25	Men >600 Women >400	Half the normal dose

Trimethoprim is removed by dialysis. However, it should not be administered to dialysis patients unless plasma concentrations can be estimated regularly.

Long-term treatment and prevention therapy:

Adults: 100mg at night

Paediatric Population:

Children over 12 years: Same as adult dose

Children 6-12 years: 50mg at night. Where a single daily dose is required, dosage at bedtime may maximise urinary concentrations. The approximate dosage in children is 2mg trimethoprim per kg body weight per day.

Elderly: Dose depends on renal function. Refer to special dosage schedule above.

Method of administration

For oral administration.

4.3 Contraindications

Severe hepatic insufficiency. Severe renal insufficiency. Megaloblastic anaemia and other blood dyscrasias. Trimethoprim should not be administered to premature infants or children under 4 months of age. Trimethoprim should not be administered to pregnant women.

Hypersensitivity to trimethoprim or any other constituents of the medication (listed in section 6.1).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

Trimethoprim should not be administered to pregnant women, premature infants or infants during the first few weeks of life.

Patients with marked impairment of renal function: Care should be taken to avoid accumulation and resulting adverse hepatological effect.

Regular haematological examination should be performed during long-term therapy.

Trimethoprim may cause depression of haemopoiesis. Regular haematological tests should be undertaken in patients receiving long term treatment and those predisposed to folate deficiency, (e.g. the elderly), to check for possible pancytopaenia. Although an effect on folate metabolism is possible, interference with haematopoiesis rarely occurs at the recommended dose. If any such change is seen, folinic acid should reverse the effect. Elderly people may be more susceptible and a lower dose may be advisable. If there is evidence of folic acid deficiency, calcium folinate should be administered and response checked by haematologic monitoring. It may be necessary to discontinue trimethoprim. Particular care should be exercised in the haematological monitoring of children on long term therapy.

Close monitoring of serum electrolytes is advised in patients at risk forhyperkalaemia (see section 4.8).

Concomitant use of medicinal products known to cause hyperkalaemia with Trimethoprim may result in severe hyperkalaemia.

Monitoring of blood glucose is advised if co-administered with repaglinide (see section 4.5).

Acute porphyria

4.5 Interaction with other medicinal products and other forms of interaction

Folate antagonists and anticonvulsants: Trimethoprim may induce folate deficiency in patients predisposed to folate deficiency such as those receiving concomitant folate antagonists or anticonvulsants.

Bone marrow depressants: Trimethoprim may increase the risk for bone marrow aplasia. Cytotoxic agents such as azathioprine, mercaptopurine and methotrexate increase the risk of haematologic toxicity when given with trimethoprim.

Special care is necessary in patients receiving pyrimethamine in addition to trimethoprim.

Phenytoin and Digoxin: Careful monitoring of patients treated with digoxin or phenytoin is advised as trimethoprim may increase plasma concentration of these agents by increasing their elimination half life.

Rifampicin may decrease trimethoprim concentrations.

Diuretics: In elderly patients taking diuretics, particularly thiazides, there is an increased incidence of thrombocytopaenia with purpura.

Hyperkalaemia may be exacerbated by concomitant administration of diuretics, particularly potassium sparing diuretics and/or thiazide diuretics and eplerenone.

In addition to other medicinal products known to cause hyperkalaemia concomitant use of trimethoprim with spironolactone may result in clinically relevant hyperkalaemia

Cyclosporin: Increased risk of nephrotoxicity.

Procainamide: Trimethoprim increases plasma concentrations of procainamide.

Dapsone: Plasma concentrations of trimethoprim and dapsone may increase when taken together.

Repaglinide: Trimethoprim may enhance the hypoglycaemic effects of repaglinide.

Anticoagulants: Trimethoprim may potentate the anticoagulant effect of warfarin and other coumarins.

Antibacterials: Plasma concentration of trimethoprim is possibly reduced by rifampicin. Plasma concentration of both drugs may increase when trimethoprim is given with dapsone.

Antimalarials: Increased antifolate effect when trimethoprim is given with pyrimethamine.

4.6 Pregnancy and breast-feeding

Pregnancy

Trimethoprim is contraindicated in pregnant women, premature infants or infants during the first few weeks of life.

Breast-Feeding

Although Trimethoprim is excreted in breast milk, it is not necessarily contraindicated for short-term therapy during lactation. This should be kept in mind when considering administration to breast- feeding women.

4.7 Effects on ability to drive and use machines

None that are known.

4.8 Undesirable effects

The following list of undesirable effects have been reported by health care professionals. Sometimes it may be difficult to distinguish reactions caused by the condition being treated from adverse drug reactions, which means that not all the listed reactions were caused by drug administration.

The most frequent adverse effects at usual doses are pruritus and skin rash (in about 3 to 7% of patients) and mild, gastrointestinal disturbances including nausea, vomiting and glossitis. These effects are generally mild and quickly reversible on withdrawal of the drug.

Infections and Infestations

Common: Monilial overgrowth

Blood and lymphatic system disorders

Very rare: Leucopenia, neutropenia, thrombocytopenia, pancytopaenia, bone marrow depression, agranulocytosis, aplastic anaemia, haemolytic anaemia, eosinophilia, purpura, haemolysis,

Unknown: Megaloblastic anaemia, methaemoglobinaemia, hyperkalaemia (particularly in the elderly and in HIV patients), methaemoglobinaemia. Trimethoprim therapy may affect haematopoiesis.

Fatalities have been reported (especially in the elderly, or those with impairment of renal or hepatic function in whom careful monitoring is advised- refer to Section 4.3 Contraindications), however the majority of haematological changes are mild and reversible when treatment is stopped.

Immune system disorders

Very rare: Hypersensitivity, anaphylaxis, anaphylactoid reaction, drug fever, allergic vasculitis resembling Henoch-Schoenlein purpura, periarteritis nodosa, systemic lupus erythematosus.

Metabolism and nutrition disorders

Very common: Hyperkalaemia

Very rare: Hypoglycaemia, hyponatraemia, anorexia

Close supervision is recommended when Trimoptin is used in elderly patients or in patients taking high doses as these patients may be more susceptible to hyperkalaemia and hyponatraemia

Psychiatric disorders

Very rare: Depression, hallucinations, confusional states, agitation, anxiety, abnormal behavior, insomnia and nightmares.

Nervous system disorders Common: Headache

Very rare: Dyskinesias, aseptic meningitis, tremor, ataxia, dizziness, lethargy, syncope, paraesthesiae, convulsions, peripheral neuritis, vertigo, tinnitus.

Aseptic meningitis was rapidly reversible on withdrawal of the drug, but recurred in a number of cases on re-exposure to either co-trimoxazole or to Trimoptin alone.

Eye disorders

Very rare: uveitis

Respiratory, thoracic and mediastinal disorders

Very rare: Cough, shortness of breath, wheeze, epistaxis

Gastrointestinal disorders

Common: Nausea, diarrhoea, vomiting.

Very rare: Constipation, glossitis, stomatitis, pseudomembranous colitis, pancreatitis.

Unknown: Sore mouth, gastrointestinal disturbances

Hepatobiliary disorders

Very rare: Disturbance in liver enzyme values, elevation of serum transaminases, elevation of bilirubin levels, cholestatic jaundice, hepatic necrosis. Cholestatic jaundice and hepatic necrosis may be fatal.

Skin and subcutaneous tissue disorders

Common: Skin rashes, urticaria

Very rare: Photosensitivity, exfoliative dermatitis, fixed drug eruption, erythema multiforme, erythema nodusum, Stevens-Johnson Syndrome, toxic epidermal necrolysis, bullous dermatitis, purpura, angioedema

Unknown: Pruritis,

Lyell's syndrome (toxic epidermal necrolysis) carries a high mortality.

Musculoskeletal and connective tissue disorders

Very rare: Arthralgia, myalgia and uveitis

Renal and urinary disorders

Very rare: Impaired renal function (sometimes reported as renal failure), haematuria,

Unknown: Raised serum creatinine and blood urea nitrogen levels. It is not known however, whether this represents inhibition of creatinine tubular secretion or genuine renal dysfunction.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the yellow card scheme at www.mhra.gov.uk/yellowcard.

4.9 Overdose

Treat symptomatically, gastric lavage and forced diuresis can be used.

Depression of haematopoiesis by trimethoprim can be counteracted by intramuscular injections of calcium folinate.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Systemic antibacterial. ATC Code: J01EA01

Mechanisms of action

Trimethoprim is a dihydrofolate reductase inhibitor which affects the nucleoprotein metabolism of micro-organisms by interference in the folic-folinic acid systems, inhibiting the conversion of bacterial dihydrofolic acid to tetrahydrofolic acid, required for the synthesis of some amino acids. Its effects are considerably greater on the cells of micro-organisms than on the mammalian cells. Trimethoprim may be bactericidal or bacteriostatic depending on growth conditions.

In vitro trimethoprim has effects on most Gram-positive and Gram-negative aerobic organisms, including enterobacteria such as *E Coli*, Proteus, *Klebsiella pneumoniae, Streptococcus faecalis, Streptococcus pneumoniae, Haemophilus influenzae* and *Staphylococcus aureus.*

It has no effect on *Mycobacterium tuberculosis, Neisseria gonorrhoeae, Nocardia species, Pseudomonas aeruginosa, Treponema pallidum, Brucella abortis* or anaerobic bacteria.

Mechanism(s) of resistance

Resistance to trimethoprim may be due to several mechanisms. Clinical resistance is often due to plasmid mediated dihydrofolate reductases that are resistant to trimethoprim: such genes may become incorporated into the chromosome via transposons. Resistance may also be due to overproduction of dihydrofolate reductase, changes in cell permeability, or bacterial mutants which are intrinsically resistant to trimethoprim because they depend on exogenous thymidine and thymine for growth. Emergence of resistance to trimethoprim does not appear to be any higher in areas where it is used alone than in areas where trimethoprim is used in combination with sulphonamides. Nonetheless, trimethoprim resistance has been reported in many species, and very high frequencies of resistance have been seen in some developing countries, particularly among Enterobacteriaceae.

EUCAST clinical MIC breakpoints to separate susceptible (S) pathogens from resistant (R) pathogens are:

EUCAST Species-related breakpoints (Susceptible -		
Enterobacteriac	***Staphylococ***	***Enterococc***
- 2/**>**4	**-** 2/**>**4	**-** 0.032/**>**1 *

*The activity of trimethoprim is uncertain against enterococci. Hence the wild type population is categorized asintermediate.

5.2 Pharmacokinetic properties

Trimethoprim is rapidly and almost completely absorbed from the gastrointestinal track and peak concentration in the circulation occur about 1-4 hours after an oral dose. Peak plasma concentrations of about 1µg/ml have been reported after a single dose of 100mg. Approximately 40-70% is bound to plasma proteins. Tissue concentrations are reported to be higher than serum concentrations with particularly high concentrations occurring in the kidneys and lungs but concentrations in the cerebrospinal fluid are about one half of those in the blood. About 40 to 60% of a dose is excreted in the urine within 24 hours (mainly as unchanged drug) together with metabolites; hence, patients with

impairment of renal function such as the elderly may require a reduction in dosage due to accumulation. Urinary concentrations are generally well above the MIC of common pathogens for more than 24 hours after the last dose. The half-life is approximately 8-10 hours. It appears in breast milk.

5.3 Preclinical safety data

Not relevant

6. Pharmaceutical particulars

6.1 List of excipients

Lactose

monohydrate

Povidone K30

Crospovidone

Sodium starch glycolate

(Type A) Magnesium

stearate

Purified water

6.2 Incompatibilities

None reported

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 25°C in a dry place. Protect from light.

6.5 Nature and contents of container

Polypropylene securitainer of 15/18/20/21/28/30/100/500 100 or 500 tablets with appropriate bellows or polyurethane foam wads. Also available in a PVC blister with aluminium lidding foil containing 28 tablets.

6.6 Special precautions for disposal and other handling

No special instructions

7. Marketing authorisation holder

Athlone Laboratories

Limited Ballymurray

Co. Roscommon

Ireland

8. Marketing authorisation number(s)

PL 06453/0043

9. Date of first authorisation/renewal of the authorisation

22/09/2005

10. Date of revision of the text

April 2017

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Nitrofurantoin 50 mg Tablets

Summary of Product Characteristics Updated 16-May-2016 | Dr. Reddy's Laboratories (UK) Ltd

1. Name of the medicinal product

Nitrofurantoin 50 mg Tablets

Aratoin 50 mg Tablets

2. Qualitative and quantitative composition

Nitrofurantoin 50.00 mg

For excipients see 6.1.

3. Pharmaceutical form

Tablet to be taken orally.

Flat yellow, bevelled and scored tablets.

4. Clinical particulars

4.1 Therapeutic indications

For the treatment of and prophylaxis against acute or recurrent, uncomplicated lower urinary tract infections or pyelitis either spontaneous or following surgical procedures.

Nitrofurantoin is specifically indicated for the treatment of infections due to susceptible strains of *Escherichia coli, Enterococci, Staphylococci, Citrobacter, Klebsiella* and *Enterobacter.*

4.2 Posology and method of administration

Dosage

Adults

Acute Uncomplicated Urinary Tract Infections: 50mg four times daily for seven days.

Severe Chronic Recurrence: 100mg four times daily for seven days.

Long Term Suppression: 50-100mg once a day.

Prophylaxis: 50mg four times daily for the duration of the procedure and for the 3 days thereafter.

Children and Infants over three months of age

Acute Urinary Tract Infections 3mg/kg/day in four divided doses for seven days.

Suppressive therapy: 1mg/kg/day once a day.

Elderly

Provided there is no significant renal impairment in which Nitrofurantoin is contraindicated, the dosage should be that for any normal adult. See precautions and risks to elderly patients associated with long term therapy (Section 4.8).

4.3 Contraindications

Patients with known hypersensitivity to nitrofurantoin or other nitrofurans.

Patients suffering from renal dysfunction with an eGFR of less than 45 ml/minute. Nitrofurantoin may be used with caution as short-course therapy only for the treatment of uncomplicated lower urinary tract infection in individual cases with an eGFR between 30-44 ml/min to treat resistant pathogens, when the benefits are expected to outweigh the risks.

G6PD deficiency (see also Section 4.6)

Acute porphyria.

In infants under three months of age as well as pregnant patients at term (during labour and delivery) because of the theoretical possibility of haemolytic anaemia in the foetus or in the newborn infant due to immature erythrocyte enzyme systems.

4.4 Special warnings and precautions for use

Nitrofurantoin is not effective for the treatment of parenchymal infections of unilaterally non-functioning kidney. A surgical cause for infection should be excluded in recurrent or severe cases.

Since pre-existing conditions may mask adverse reactions, Nitrofurantoin should be used with caution in patients with pulmonary disease, hepatic dysfunction, neurological disorders, and allergic diathesis.

Peripheral neuropathy and susceptibility to peripheral neuropathy, which may become severe or irreversible, has occurred and may be life threatening. Therefore, treatment should be stopped at the first signs of neural involvement (paraesthesiae).

Nitrofurantoin should be used in caution with patients with anaemia, diabetes mellitus, electrolyte imbalance, debilitating conditions and vitamin B (particularly folate) deficiency.

Acute, subacute and chronic pulmonary reactions have been observed in patients treated with Nitrofurantoin. If these reactions occur, nitrofurantoin should be discontinued immediately.

Chronic pulmonary reactions (including pulmonary fibrosis and diffuse interstitial pneumonitis) can develop insidiously, and may occur commonly in elderly patients. Close monitoring of pulmonary conditions of patients receiving long-term therapy is warranted (especially in the elderly).

Patients should be monitored closely for signs of hepatitis (particularly in long-term use). Urine may be coloured yellow or brown after taking Nitrofurantoin. Patients on Nitrofurantoin are susceptible to false positive urinary glucose (if tested for reducing substances).

Nitrofurantoin should be discontinued at any sign of haemolysis in those with suspected glucose-6-phosphate dehydogenase deficiency.

Gastrointestinal reactions may be minimised by taking the drug with food or milk, or by adjustment of dosage.

For long-term treatment, monitor patients closely for evidence of hepatitis or pulmonary symptoms or other evidence of toxicity.

Discontinue treatment with Nitrofurantoin if otherwise unexplained pulmonary, hepatic, haematological or neurological syndromes occur.

4.5 Interaction with other medicinal products and other forms of interaction

1. Increased absorption with food or agents delaying gastric emptying.
2. Decreased absorption with magnesium trisilicate.
3. Decreased renal excretion of Nitrofurantoin by probenecid and sulphinpyrazene.
4. Decreased anti-bacterial activity by carbonic anhydrase inhibitors and urine alkalisation.
5. Anti-bacterial antagonism by quinolone anti-infectives.
6. Interference with some tests for glucose in urine.
7. As Nitrofurantoin belongs to the group of Antibacterials, it will have the following resulting interactions:

• Typhoid Vaccine (oral): Antibacterials inactivate oral typhoid vaccine.

4.6 Fertility, pregnancy and lactation

Animal studies with nitrofurantoin have shown no teratogenic effects. Nitrofurantoin has been in extensive clinical use since 1952 and its suitability in human pregnancy has been well documented. However as with all drugs, the maternal side effects may adversely affect the course of pregnancy. The drug should be used at the lowest does appropriate for the specific indication, only after careful assessment.

Nitrofurantoin is however contraindicated in infants under three months of age and in pregnant women during labour and delivery, because of the possible risk of haemolysis of the infants' immature red cells. Breast feeding an infant known or suspected to have an erythrocyte enzyme deficiency (including G6PD deficiency), must be temporarily avoided, since Nitrofurantoin is detected in trace amounts in breast milk.

4.7 Effects on ability to drive and use machines

Nitrofurantoin may cause dizziness and drowsiness and the patient should not drive or operate machinery if affected this way.

4.8 Undesirable effects

Respiratory

If any of the following respiratory reactions occur the drug should be discontinued.

Acute pulmonary reactions usually occur within the first week of treatment and are reversible with cessation of therapy. Acute pulmonary reactions are commonly manifested by fever, chills, cough, chest pain, dyspnoea, pulmonary infiltration with consolidation or pleural effusion on chest x-ray, and eosinophilia. In subacute pulmonary reactions, fever and eosinophilia occur less often than in the acute form.

Chronic pulmonary reactions occur rarely in patients who have received continuous therapy for six months or longer and are more common in elderly patients. Changes in ECG have occurred, associated with pulmonary reactions.

Minor symptoms such as fever, chills, cough and dyspnoea may be significant. Collapse and cyanosis have been reported rarely. The severity of chronic pulmonary reactions and their degree of resolution appear to be related to the duration of therapy after the first clinical signs appear. It is important to recognise symptoms as early as possible. Pulmonary function may be impaired permanently, even after cessation of therapy.

Hepatic

Hepatic reactions including cholestatic jaundice and chronic active hepatitis, occur rarely. Fatalities have been reported. Cholestatic jaundice is generally associated with short-term therapy (usually up to two weeks). Chronic active hepatitis, occasionally leading to hepatic necrosis is generally associated with long-term therapy (usually after six months). The onset may be insidious. Treatment should be stopped at the first sign of hepatotoxicity.

Neurological

Peripheral neuropathy (including optical neuritis) with symptoms of sensory as well as motor involvement, which may become severe or irreversible, has been reported infrequently. Less frequent reactions of unknown causal relationship are depression, euphoria, confusion, psychotic reactions, nystagmus, vertigo, dizziness, asthenia, headache and drowsiness. Treatment should be stopped at the first sign of neurological involvement.

Gastrointestinal

Nausea and anorexia have been reported. Emesis, abdominal pain and diarrhoea are less common gastrointestinal reactions.

Haematological

Agranulocytosis, leucopenia, granulocytopenia, haemolytic anaemia, thrombocytopenia, megaloblastic anaemia, glucose-6-phosphate dehydrogenase deficiency anaemia, and eosinophilia have been reported. Aplastic anaemia has been reported rarely. Cessation of therapy has generally returned the blood picture to normal.

Hypersensitivity

Allergic skin reactions manifesting as angioneurotic oedema, maculopapular, erythematous or eczematous eruptions, urticaria, rash, and pruritus have occurred.

Lupus-like syndrome associated with pulmonary reaction to nitrofurantoin has been reported.

Exfoliative dermatitis and erythema multiforme (including Stevens-Johnson Syndrome) have been reported rarely.

Other hypersensitivity reactions include anaphylaxis, sialadenitis, pancreatitis, drug fever, and arthralgia.

Miscellaneous

Transient alopecia and benign intracranial hypertension.

As with other antimicrobial agents, superinfections by fungi or resistant organisms such as Pseudomonas may occur.

However, these are limited to the genito-urinary tract because suppression of normal bacterial flora does not occur elsewhere in the body.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

4.9 Overdose

Symptoms and signs of overdosage include gastric irritation, nausea and vomiting. There is no known specific antidote. Nitrofurantoin can be haemodialysed. Standard treatment is by induction of emesis or by gastric lavage in cases of recent ingestion. Monitoring of full blood count, liver function tests and pulmonary function, are recommended. A high fluid intake should be maintained to promote urinary excretion of the drug.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Nitrofurantoin is a broad spectrum antibacterial agent, active against the majority of urinary pathogens. The wide range of organisms sensitive to the bactericidal activity include:

Escherichia coli

Enterococcus Faecalis

Klebsiella Species

Enterobacter Species

Staphylococcus Species e.g. S. Aureus, S. Saprophyticus, S. Epidermidis

Citrobacter Species

Clinically most common urinary pathogens are sensitive to nitrofurantoin. Most strains of *Proteus* and *Serratia* are resistant. All *Pseudomonas* strains are resistant.

5.2 Pharmacokinetic properties

Orally administered nitrofurantoin is readily absorbed in the upper gastrointestinal tract and is rapidly excreted in the urine. Blood concentrations at therapeutic dosages are usually low with an elimination half-life of about 30 minutes.

Maximum urinary excretion usually occurs 2-4 hours after administration of nitrofurantoin. Urinary drug dose recoveries of about 40-45% are obtained.

5.3 Preclinical safety data

Carcinogenic effect of nitrofurantoin in animal studies was observed. However, human data and extensive use of nitrofurantoin over 50 years do not support such suggestion.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose

Maize starch

Pregelatinised maize starch

Sodium starch glycollate

Magnesium stearate

Purified water

6.2 Incompatibilities

None stated.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package. Keep blister in the outer carton/keep container tightly closed.

6.5 Nature and contents of container

High density polystyrene containers with polythene lids and/or polypropylene containers with polypropylene or polythene lids.

Pack sizes: 28, 30, 50, 56, 60, 84, 100, 250, 500 & 1000

250 micron, pharmaceutical grade, green rigid PVC

20 micron, hard-tempered aluminium foil, coated on the dull side with 6-7 gsm heat-seal lacquer and printed on the bright side.

Pack sizes: 28, 30, 50, 56, 60, 84, 100, 250, 500 & 1000

6.6 Special precautions for disposal and other handling

None

7. Marketing authorisation holder

Dr Reddy's Laboratories (UK) Limited,

6 Riverview Road,

Beverley,

East Yorkshire,

HU17 0LD

8. Marketing authorisation number(s)

08553/0087

9. Date of first authorisation/renewal of the authorisation

14/03/2011

10. Date of revision of the text

04/05/2016

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Cefalexin Tablets 250mg

Summary of Product Characteristics Updated 30-Jul-2014 | Sandoz Limited

1. Name of the medicinal product

Cefalexin tablets BP 250mg/Ospexin tablets 250mg/Tenkorex tablets 250mg/Kiflone tablets 250mg

2. Qualitative and quantitative composition

Each tablet contains Cefalexin BP equivalent to 250 mg anhydrous cefalexin.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablets.

Round, biconvex, white to yellowish. Scored on one side, with “CX” above the score and “250” below the score. Odour - slightly peppermint to characteristic of the active ingredient.

4. Clinical particulars

4.1 Therapeutic indications

Cefalexin is indicated for the treatment of respiratory tract infections (R.T.I's), urinary tract infections (U.T.I's), skin and soft tissue infections, otitis media and other infections due to sensitive organisms.

4.2 Posology and method of administration

Cefalexin tablets BP 250mg/Ospexin tablets 250mg/Tenkorex tablets 250 mg/Kiflone tablets 250mg are for oral use. Each tablet should be swallowed whole with water.

DOSAGE

Adults

The dosage is 1-4 g daily in divided doses. Most infections will respond to 500 mg every 8 hours. For skin and soft tissue infections, streptococcal pharyngitis and mild uncomplicated U.T.I's, the usual dosage is 250 mg every 6 hours or 500 mg every 12 hours. For more severe infections or those caused by less susceptible organisms, larger doses may be needed.

Older people

The dosage is as for adults. The dosage should be reduced if renal function is markedly impaired.

Use in children and adolescents

The usual recommended daily dosage for children is 25-50 mg/kg in divided doses. For skin and soft tissue infections, streptococcal pharyngitis and mild, uncomplicated urinary tract infections, the total daily dose may be divided and administered every 12 hours. For most infections the following schedule is suggested:

children under 5 years:	125 mg every 8 hours
children 5 years and over:	250 mg every 8 hours

In severe infections the dosage may be doubled. In the therapy of otitis media, clinical studies have shown that a dosage of 75-100mg/kg/day in 4 divided doses is required. In the treatment of beta-haemolytic streptococcal infections, a therapeutic dose should be administered for at least 10 days.

4.3 Contraindications

Cefalexin is contra-indicated in patients with known allergy to the cephalosporin group of antibiotics.

Severe systemic infections, which require parenteral cephalosporin treatment, should not be treated orally during the acute stage.

4.4 Special warnings and precautions for use

Cefalexin should be given cautiously to patients who have shown hypersensitivity to other drugs. Cephalosporins should be given with caution to penicillin-sensitive patients, as there is some evidence of partial cross-allergenicity between the penicillins and cephalosporins. Patients have had severe reactions

(including anaphylaxis) to both drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics, including macrolides, semisynthetic penicillins and cephalosporins. It is important, therefore, to consider its diagnosis in patients who develop diarrhoea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening. Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, appropriate measures should be taken.

If the patient experiences an allergic reaction cefalexin should be discontinued and treatment with the appropriate agents initiated.

Prolonged use of cefalexin may result in the overgrowth of non-susceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Cefalexin should be administered with caution in the presence of markedly impaired renal function as it is excreted mainly by the kidneys. Careful clinical and laboratory studies should be made because the safe dosage may be lower than that usually recommended.

Positive direct Coombs' tests have been reported during treatment with cephalosporin antibiotics. For haematological studies, or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side, or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognised that a positive Coombs' test may be due to the drug.

A false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solutions or with copper sulphate test tablets. Tests based on glucose oxidation reactions may be safely used.

4.5 Interaction with other medicinal products and other forms of interaction

As cephalosporins like cefalexin are only active against proliferating microorganisms, they should not be combined with bacteriostatic antibiotics.

Concomitant use of uricosuric drugs (e.g. probenicid) suppresses renal drug elimination. As a result, cefalexin plasma levels are increased and sustained for longer periods.

If associated with highly potent diuretics (ethacrynic acid, furosemide) or other potentially nephrotoxic antibiotics (aminoglycosides, polymyxin, colistin), cephalosprins may show higher nephrotoxicity.

Combined use of cephalosporins and oral anticoagulants may prolong prothrombin time.

Cefalexin may reduce the effects of oral contraceptives.

A potential interaction between cefalexin and metformin may result in an accumulation of metformin and could result in fatal lactic acidosis.

Hypokalaemia has been described in patient taking cytotoxic drugs for leukaemia when they were given gentamicin and cefalexin.

4.6. Pregnancy and breast-feeding

Pregnancy

Although laboratory and clinical studies have shown no evidence of teratogenicity, caution should be exercised when prescribing for the pregnant patient.

Breastfeedings

The excretion of cefalexin in human breast milk increased up to 4 hours following a 500mg dose. The drug reached a maximum level of 4 micrograms/ml, then decreased gradually and had disappeared 8 hours after administration. Caution should be exercised when cefalexin is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

There are no effects on ability to drive or to operate machinery.

4.8 Undesirable effects

Side effects of cefalexin include gastro-intestinal disturbances such as nausea, vomiting, diarrhoea and abdominal discomfort. The most common of these effects is diarrhoea, but this is rarely severe enough to warrant cessation of therapy. Dyspepsia has also occurred. Transient hepatitis and cholestatic jaundice have rarely been reported.

Allergic reactions have been reported such as rash, urticaria, angioedema and rarely erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis (exanthematic necrolysis). These reactions usually subsided upon discontinuation of the drug, although in some cases supportive therapy may be necessary. Anaphylaxis has also been reported.

Other side effects such as genital and anal pruritus, genital candidiasis, vaginitis and vaginal discharge, dizziness, fatigue, headache, agitation, confusion, hallucinations, arthralgia, arthritis and joint disorders have been reported.

As with other cephalosporins interstitial nephritis has rarely been reported.

Eosinophilia, neutropenia, thrombocytopenia, haemolytic anaemia and slight elevations in AST and ALT have been reported.

As with other broad-spectrum antibiotics prolonged use may result in the overgrowth of non-susceptible organisms, e.g. candida. This may present a vulvo-vaginitis.

There is a possibility of development of pseudomembranous colitis and it is therefore important to consider its diagnosis in patients who develop diarrhoea while taking cefalexin. It may range in severity from mild to life threatening with mild case usually responding to cessation of therapy. Appropriate measures should be taken with moderate to severe cases.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product, Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms of oral overdose include nausea, vomiting, epigastric distress, diarrhoea and haematuria.

General management consists of close clinical and laboratory monitoring of haematological, renal and hepatic functions and coagulation status until the patient is stable.

Serum levels of cefalexin can be reduced by haemodialysis or peritoneal dialysis.

Unless 5 to 10 times the normal total daily dose has been ingested, gastro-intestinal decontamination should not be necessary.

There have been reports of haematuria without impairment of renal function in children accidentally ingesting more than 3.5g of cefalexin in a day. Treatment has been supportive (fluids) and no sequelae have been reported.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Cefalexin is an oral broad-spectrum antibiotic belonging to the group known as cephalosporins. In adequate concentrations it is bacteriocidal for sensitive proliferating microorganisms by inhibiting the biosynthesis of the cell wall. It is active against the following pathogens:

Gram Positive

Staphylococci (coagulase positive as well as penicillinase-producing strains), Streptococci, pneumococci, Corynebacterium diphtheriae, Baccillus anthracis, Clostridia, Listeria monocytogenes, Bacillus subtilis and Bacteroides melaninogenicus.

Gram Negative

Escherichia coli, Salmonellae, Shigellae, Neisseria, Proteus mirabilis, Haemophilus influenzae (some strains), Brucellae, Klebsiella species, Treponema pallidum and actinomycetes.

5.2 Pharmacokinetic properties

Cefalexin is almost completely absorbed from the gastrointestinal tract and produces peak plasma concentrations about 1 hour after administration.

A dose of 500 mg produces a peak plasma concentration of about 18 µg per ml; doubling the dose doubles the peak concentration. Cefalexin readily diffuses into tissues, including bone, joints and the pericardial as well as pleural cavities. Only 10-15% of the dose is bound to plasma proteins. Elimination is mainly renal with 80% of the dose, recovered from the urine, therapeutically active, in the first 6 hours.

Cefalexin does not enter cerebrospinal fluid in significant quantities. Cefalexin crosses the placenta and small quantities are found in the milk of nursing mothers. Therapeutically effective concentrations may be found in the bile and some may be excreted by this route.

The half-life has been reported to range from 0.5 to 2 hours and this increases with reduced renal function.

5.3 Preclinical safety data

None stated.

6. Pharmaceutical particulars

6.1 List of excipients

<u>Core</u>

Macrogol 6000

Magnesium stearate

Sodium starch glycollate

Povidone (E1201)

Lactose

Saccharin sodium (E954)

Peppermint oil

Talc (E553b)

Coat

Titanium dioxide (E171)

Hypromellose (E464)

6.2 Incompatibilities

There are no known incompatibilities.

6.3 Shelf life

This medicinal product as packaged for sale has a shelf life of 48 months.

6.4 Special precautions for storage

The following applies to the storage of Cefalexin tablets BP 250 mg/Tenkorex tablets 250mg/Ospexin tablets 250mg/ Kiflone tablets 250mg;

- Do not store above 25°C.

- Store in the original packaging (blister pack presentations only).

- Keep the container tightly closed (securitainer presentations only).

6.5 Nature and contents of container

Package No. 1

The 250mg film coated tablets are in white polypropylene securitainers with white polyethylene snap on caps. Each container contains 20 or 21 or 28 or 50 or 100 or 500 tablets.

Package No. 2

Blister packs of duplex PVC/PVDC foil 200/36 micron with aluminium foil 20 micron backing. One blister pack contains 20 or 21 or 28 tablets.

6.6 Special precautions for disposal and other handling

Each tablet should be swallowed whole with water. There are no particular instructions for handling.

7. Marketing authorisation holder

Sandoz GmbH

Biochemiestrasse 10

A-6250 Kundl

Austria.

8. Marketing authorisation number(s)

PL 04520/0032

9. Date of first authorisation/renewal of the authorisation

16 August 1996

10. Date of revision of the text

09/07/2014

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SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Hiprex 1 g Tablets

2. Qualitative and quantitative composition

Each Hiprex tablet contains methenamine hippurate 1 g.

For the full list of excipients, see 6.1.

3. Pharmaceutical form

White, oblong tablet with breakline marked HX on one side and 3M on the other.

4. Clinical particulars

4.1 Therapeutic indications

Hiprex is indicated in the prophylaxis and treatment of urinary tract infections:

1. As maintenance therapy after successful initial treatment of acute infections with antibiotics.

2. As long-term therapy in the prevention of recurrent cystitis.

3. To suppress urinary infection in patients with indwelling catheters and to reduce the incidence of catheter blockage.

4. To provide prophylaxis against the introduction of infection into the urinary tract during instrumental procedures.

5. Asymptomatic bacteriuria.

4.2 Posology and method of administration

Posology

Adults: 1g twice daily.

In patients with catheters the dosage may be increased to 1g three times daily.

Paediatric population:

Children under 6 years: Not recommended.

Children: 6-12 years: 500mg twice daily.

Older people: No special dosage recommendations.

Method of administration

The tablets may be halved, or they can be crushed and taken with a drink of milk or fruit juice if the patient prefers.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hepatic dysfunction, renal parenchymal infection, severe dehydration, metabolic acidosis, severe renal failure (creatinine clearance or GFR<10 ml/min.) or gout. Hiprex may be used where mild (20-50 ml/min.) to moderate (10-20 ml/min.) renal insufficiency is present. (If the GFR is not available the serum creatinine concentration can be used as a guide.). Hiprex should not be administered concurrently with sulphonamides because of the possibility of crystalluria, or with alkalising agents, such as a mixture of potassium citrate.

4.4 Special warnings and precautions for use

None.

4.5 Interaction with other medicinal products and other forms of interaction

Methenamine hippurate should not be given/administered concurrently with sulphonamides because of the possibility of crystalluria, or with alkalising agents such as potassium citrate. Concurrent use with acetazolamide should be avoided as the desired effect of hexamine will be lost.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is inadequate evidence of safety of the drug in human pregnancy but it has been in wide use for many years without apparent ill consequence, animal studies having shown no hazard.

Breast-feeding

Methenamine is excreted in breast milk but the quantities will be insignificant to the infant. Mothers can therefore breast feed their infants.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as:

Very common (≥1/l0)

Common (≥1/100 and <1/10)

Uncommon (≥1/1000 and <1/100)

Rare (≥ 1/10,000 and <1/1000)

Very rare (<1/10,000)

Not known (cannot be estimated from the available data).

Uncommon: rashes, pruritis, gastric irritation, irritation of the bladder

All side effects are reversible on the withdrawal of the drug.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Vomiting and haematuria may occur. These can be treated by the use of an anti-emetic and drinking copious quantities of water respectively. Bladder symptoms can be treated by the consumption of copious quantities of water and 2-3 teaspoonfuls of bicarbonate of soda.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group G04A A01

Hiprex is a urinary antibacterial agent with a wide antibacterial spectrum covering both gram-positive and gram-negative organisms. Urinary antibacterial activity can be shown within 30 minutes of administration.

The chemical structure of methenamine hippurate is such that a two-fold antibacterial action is obtained:

1. The slow release of the bactericidal formaldehyde, from the methenamine part, in the urine; acid pH is necessary for this reaction to occur. It is obtained and maintained there by the presence of hippuric acid.

2. The bacteriostatic effect of hippuric acid itself on urinary tract pathogens.

5.2 Pharmacokinetic properties

Methenamine hippurate is readily absorbed from the gastro-intestinal tract and excreted via the kidney.

Plasma concentrations of methenamine hippurate reach maximum 1-2 hours after a single dose and then decline with a half-life of about 4 hours. Methenamine recovered in the urine corresponds to about 80% of the dose given per 12 hours.

5.3 Preclinical safety data

Not applicable

6. Pharmaceutical particulars

6.1 List of excipients

Magnesium Stearate

Povidone

Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 30°C. Keep bottle tightly closed.

6.5 Nature and contents of container

Glass bottles of 60 tablets

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Meda Pharmaceuticals Ltd

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CM22 6PU

United Kingdom

8. Marketing authorisation number(s)

PL 15142/0099

9. Date of first authorisation/renewal of the authorisation

12 October 1989/13 September 2005

10. Date of revision of the text

March 2015