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

Trial registration

Protocol version: 1.5

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2. Protocol signature page

Protocol authorisation signatories

Signature …… Date ……

Professor Robert Pickard, Chief Investigator

Signature …… Date ……

Dr Thomas Chadwick, Lead Statistician

Signature …… Date ……

Miss Catherine Brennand, Trial Manager

Principal Investigator at each study site signature

I confirm that I have read and understood protocol version 1.5 dated 17th August 2016. I agree to comply with the study protocol, the principles of GCP, research governance, clinical trial regulations and appropriate reporting requirements.

Signature …… Date ……

Print Name ……

Site Name/I.D. ……

3. Contents Page

Figures and Tables

Appendices

4. Glossary of Abbreviations

Abbreviation	Definition
ACA	Association for Continence Advice
BAUS	British Association of Urological Surgeons
BIA	British Infection Association
BNF	British National Formulary
BSUG	British Society for Urogynaecology
CDC	Centres for Disease Control and Prevention
CI	confidence interval
CISC	clean intermittent self-catheterisation
CLRN	Comprehensive Local Research Network
CSU	**c**atheter specimen of urine
CTiMP	clinical trial of an investigational medicinal product
CTU	clinical trials unit
CRC	Clinical Research Collaboration
DMEC	Data Monitoring & Ethics Committee
E. coli	*Escherichia coli*
e-CRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
EU	European Union
GCP	Good Clinical Practice
GP	General Practitioner
HRQoL	health-related quality of life
HTA	Health Technology Assessment Programme
IMP	investigational medicinal product
LFT	liver function test
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NIHR CSP	National Institute for Health Research coordinated system for gaining national central NHS permission
PI	Principal Investigator
PIC	participant identification centre
PCRN	Primary Care Research Network
RCT	randomised controlled trial

rUTI	Recurrent urinary tract infection
QALY	quality-adjusted life year
QoL	quality of life
R&D	Research and Development Departments of NHS Trusts
SF-12	Medical Outcomes Short Form 12 item questionnaire
SF-36	Medical Outcomes Short Form 36 item questionnaire
SmPC	Summary of Product Characteristics
SOP	standard operating procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
UTI	urinary tract infection
WTP	Willingness to pay

5. Responsibilities

Sponsor: The Newcastle upon Tyne Hospitals NHS Foundation Trust will act as the sponsor for this study.

Funder: The National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA) is funding this study, project reference 11-72-01

Trial Management: A Trial Management Group (TMG) will be convened and will be responsible for overseeing the progress of the trial. The day-to-day management of the trial will be co-ordinated by Cath Brennand as Trial manager and Robert Pickard as Chief Investigator.

Principal Investigator: The Principal Investigator at each site will have overall responsibility for the conduct of the study at that site. Further details will be covered by clinical trial site agreements between individual sites and Sponsor.

Trial Management:

The following functions falling under the responsibility of the sponsor will be delegated to Robert Pickard as Chief Investigator:

- Authorisation and Ethics Committee Opinion; including Clinical Trial Agreement (CTA) request, research ethics committee (REC) opinion, notification of protocol amendments and end of trial, site specific assessment & local approval.
- Good Clinical Practice (GCP) and trial conduct; including GCP arrangements, management of investigational medicinal product (IMP), data monitoring, emergency & safety procedures.
- Pharmacovigilance; including defining & recording adverse events/reactions, reporting suspected unexpected serious adverse reactions (SUSAR), notifying investigators of SUSARs, ensuring serious adverse events (SAE) are reviewed by an appropriate committee for safety monitoring, annual listings & safety report.
- Administration of funding for the study.

Trial conduct at site:

Investigator responsibilities:

- Study conduct and the welfare of study subjects.
- Familiarity with the use of the investigational medicinal products as described in the product information.
- Compliance with the protocol, documentation of any protocol deviations and reporting of all serious adverse events.
- Screening and recruitment of subjects.
- Ensuring that all trial-related medical decisions are made by a qualified physician, who is an investigator or co-investigator for the trial.
- Provision of adequate medical care in the event of an adverse event.
- Obtaining local approval and abiding by the policies of Research Governance.
    - Assistance will be provided by Cath Brennand.

- Compliance with the Principles of GCP, the Research Governance Framework for Health and Social Care, and any national legislation implementing the European Union (EU) Clinical Trials Directive (2001/20/EC) and subsequent amendments.
- Ensuring that no participant is recruited into the study until all relevant regulatory permissions and approvals have been obtained.
- Obtaining written informed consent from participants prior to any study specific procedures.
- The Principal Investigator (PI) shall be qualified by education, training and experience to assume responsibility for the proper conduct of the trial. S/he shall provide a current signed & dated curriculum vitae as evidence for the Trial Master File.
- Ensuring Study Site team members are appropriately qualified by education, training and experience to undertake the conduct of the study.
- Availability for Investigator meetings, monitoring visits and in the case of an audit.
- Maintaining study documentation and compliance with reporting requests.
- Maintaining a site file, including copies of study approval, list of subjects and their signed informed consent forms.
- Documenting appropriate delegation of tasks to study personnel e.g. Pharmacist, Research Nurse, Investigator(s).
- Ensuring data collected is accurate, timely & complete.
- Providing updates on the progress of the trial.
- Ensuring subject confidentiality is maintained during the project and archival period.
- Ensuring archival of study documentation for a minimum of 15 years following the end of the study, unless local arrangements require a longer period.

6. Protocol Summary

Short title:	Antibiotic prophylaxis for clean intermittent catheterisation (The AnTIC Study)
Protocol version:	1.5
Protocol date:	17th August 2016
Chief Investigator:	Professor Robert Pickard
Sponsor:	Newcastle upon Tyne Hospitals NHS Foundation Trust
Funder:	NIHR HTA Programme
Study design:	Pragmatic, superiority patient randomised controlled trial
Study Interventions:	Experimental: Daily antibiotic prophylaxis for 12 months Control: No antibiotic prophylaxis
Primary objective:	To determine whether antibiotic prophylaxis results in a clinically significant reduction in the rate of symptomatic, antibiotic-treated urinary tract infection suffered by people performing intermittent self-bladder catheterisation over 12 months and is cost-effective for the UK NHS.
Secondary objectives:	To determine whether use of antibiotic prophylaxis results in better quality of life, better satisfaction with treatment and has an acceptable safety profile including antibiotic stewardship.
Primary outcome:	Relative incidence of symptomatic antibiotic-treated UTI between the trial groups over 12 months
Number of study sites:	40
Study population/size:	372
Study duration:	42 months (12 months active participation)

7. Background

7.1. Need for clean intermittent self-catheterisation

Clean intermittent self-catheterisation (CISC) is an important management option for people who cannot empty their bladder naturally due to bladder outlet obstruction, or due to failure or incoordination of bladder muscle contraction which is most frequently associated with neurological disease.[1] Patients needing CISC are taught how to insert a catheter, drain the bladder, and then remove the catheter.[2] Single-use disposable catheters, typically with a hydrophilic coating, are the preferred option in the UK.[3]

7.2. Prevalence of use of clean intermittent self-catheterisation in the United Kingdom

There are no accurate prevalence data for CISC use in the United Kingdom (UK). The National Health Service (NHS) England prescription database shows that approximately 47 million CISC catheters were prescribed in 2010 at a cost of £64 million.[4] Assuming each individual uses an average of 25 catheters per week; this suggests that there are about 36,000 CISC-users in England and perhaps 43,000 in the UK as a whole. This estimate ties in with calculations for marketing purposes made by two catheter manufacturers; both suggesting that there were between 40,000 and 60,000 regular CISC-users in the UK (McClurg D., personal communication, February 2012). A primary care-based estimate found a prevalence of approximately 7-8 per 10,000 adults suggesting an approximate total of 43,000 - 49,000 adults in the UK (Fader M., personal communication, August 2011).

7.3. Recurrent urinary tract infection amongst people using intermittent catheterisation

Recurrent urinary tract infection (UTI) is the commonest adverse event experienced by CISC-users affecting between 12% and 88% of cohorts.[5] Separation of rates of asymptomatic bacteriuria, which would not normally be treated, and symptomatic UTI in these studies is difficult with the best estimate being that 50% of users have chronic bacteriuria and at least 25% suffer two or more symptomatic UTI episodes per year.[6] This has been confirmed by early results from our own ongoing audit in Newcastle (Lake H., personal communication, November 2012). Neurological disease, female gender, young age, and high bladder volumes have been associated with higher prevalence of UTI.[1] Rates will also vary according to the definition of symptomatic UTI used; in particular whether microbiological proof is required.[7] The most frequently isolated organism is *Escherichia coli* (*E. coli*) accounting for 60-70% of isolates.[6] Most episodes are associated with transient symptoms such as lower abdominal pain, urethral pain, and flu-like symptoms; occasionally systemic upset can occur with fever and loin pain. Those with reduced bladder sensation may alternatively complain of cloudy urine, increased odour and worse incontinence.[8] Recurrent UTI is distressing and an additional burden for patients on top of their underlying disease and functional disability.[5] For some there is a risk of renal damage in the longer term.[8] In one cohort 59% experienced 'mild', 14% 'moderate' and 3% 'major' UTI symptoms over 12 months;[1] the rate of bacteriuria was 60% with symptomatic UTI occurring in 12-18%. Conservatively this suggests that 6,000 CISC-users in the UK suffer recurrent UTI; the target population for this trial.

A number of simple interventions have been trialled to reduce UTI risk for CISC-users including single use and hydrophilic catheters, and antiseptics but none showed efficacy.[2] A recent randomised controlled trial (RCT) reported benefit of hydrophilic catheters for patients with spinal cord injury during initial hospitalisation.[7] The need for strategies to reduce prevalence of UTI in this population has been emphasised by recent reports from the James Lind Alliance and the National Institute for Health and Clinical Excellence (NICE).[9,10]

7.4. Evidence for use of antibiotic prophylaxis

Once-daily low dose antibiotic prophylaxis is effective for women without bladder emptying problems who suffer simple recurrent UTI. Systematic review and meta-analysis of trials in this patient group showed a relative risk for UTI (95% Confidence Interval; CI) of 0.15 (0.08 – 0.28).[11] Three crossover trials were identified but not included in the review; of these one trial with a fluoroquinolone had a 4-month washout period at crossover whilst two had no washout period. Adverse events in trials using nitrofurantoin, trimethoprim or cephalexin were mild and rarely associated with withdrawal, but were more frequent in the antibiotic group with a relative risk of 1.78 (1.06 – 3.0); gastro-intestinal upset, skin rash and vaginal candidiasis predominated. Nitrofurantoin appeared more effective than trimethoprim but resulted in more withdrawals. These two drugs together with cefalexin are recommended and licensed for this purpose in the UK.[12] There were no reports of serious adverse effects such as neuropathy or pulmonary fibrosis in the nitrofurantoin arms of

randomised studies included in the Cochrane review but an observation study of prophylactic nitrofurantoin noted one episode of possible neuropathy in 219 patients over 12 months use[13] and awareness of these conditions together with the possibility of liver inflammation is advised on the Medicines and Healthcare Products Regulatory Agency (MHRA) licence[14].

Evidence for use of antibiotic prophylaxis for CISC-users, the focus for this trial, has been summarised in a Cochrane review updated to September 2011.[15] We were unable to identify any new published or ongoing trials since this date up to March 2013. The review found six RCTs involving adults (four trials) or children (three trials) performing CISC for neurological bladder dysfunction with a total of 406 randomised participants. Five had placebo as a comparator with either a crossover or parallel group design and three each used clinical or microbiological definition for UTI outcome; the latest report was 2011. Two of the crossover trials had duration of three months for each intervention without washout whilst one had duration of five months for each intervention and a one month washout period. The prophylactic agents used were trimethoprim -sulfamethoxizole (two trials) and nitrofurantoin (four trials) and a variety of agents (one trial). Participant attrition after randomisation ranged from 2 – 35%. For clinically-defined symptomatic UTI, evidence from one trial showed a relative incidence rate (95% CI) of 0.50 (0.17 – 1.44) in favour of antibiotic prophylaxis whilst another trial found no difference. For microbiologically-proven symptomatic UTI, one trial found a relative risk of 0.78 (0.62 – 0.79) in favour of prophylaxis. Evidence from four trials showed an overall relative incidence rate (95% CI) for bacteriuria of 0.61 (0.44 – 0.87) in favour of prophylaxis. The review authors concluded that although results were promising, there was a lack of unequivocal evidence for effectiveness of antibiotic prophylaxis for CISC-users, agreeing with a previous review.[16] Recommendations for future trials were:

- Use incidence of symptomatic UTI as the primary outcome
- Measure antibiotic resistance
- Control for factors increasing UTI risk: sex, frequency of catheterization, neurological cause, frequency of previous UTI, prior use of antibiotic prophylaxis.

None of these trials found any excess harms in the prophylaxis groups but changes in bacterial pathogens were not studied. These results and the need for further research has been highlighted in a further narrative review[17].

7.5. Health economics

A previous study constructed a decision analytical model that predicted use of prophylactic nitrofurantoin in women performing CISC after gynaecological surgery would reduce the UTI rate from 33% to 17%.[18] Measurement of health-related quality of life (HRQoL) change due to UTI is difficult in this patient group as UTI causes transient deficit within a background of a fluctuating chronic health condition. One possibility is to estimate the cost per day of UTI saved and model the probability of different strategies being cost effective.[19] Another possibility is to measure the short-term disutility by completion of a HRQoL measure such as the SF-36 at baseline and whilst suffering a UTI and use the difference in a cost-utility analysis.[20]

7.6. Antibiotic stewardship

The impact of prophylactic antibiotic therapy for UTI on bacterial ecology particularly of gut flora was not explored in any of the trials included in the two relevant Cochrane reviews[11,15] and monitoring of these during future treatment trials was recommended. An observational study found no evidence of development of faecal organisms resistant to nitrofurantoin or loss of sensitive organisms in the gut suggesting this drug does not have potentially harmful effects on gut commensals[13]. In a large RCT of antibiotic prophylaxis of rUTI in women with normal voiding it was found that faecal and urinary carriage of resistant *E. coli* was increased from 40% to 80% by use of trimethoprim-sulphamethoxazole once-daily prophylaxis but that this returned to baseline three months after discontinuing the antibiotic prophylactic therapy[21]. There remains public health concern regarding the empiric use of antibiotics given the rapid emergence of resistant strains of particularly *E. coli*.

7.7. Summary with implications for trial design

This background has convinced us that a robust pragmatically designed trial is required to determine whether the apparent benefit of antibiotic prophylaxis seen in small trials amongst specific groups of CISC-users is seen

in a routine care setting and whether the benefits are worth the costs both financial and in terms of harms. The estimates of prevalence, effectiveness and harms have allowed us to power the trial conservatively based on what we consider to be a minimum important difference from clinician, patient, and economic perspectives.

8. Objectives

8.1. Summary of research objectives

The primary objective is to determine the relative clinical effectiveness and cost-effectiveness of an experimental UTI prevention strategy of continuous once-daily prophylactic antibiotic therapy against the control strategy of no prophylaxis in people carrying out intermittent bladder catheterisation who suffer recurrent UTI. Outcomes will be collected over 12 months for each participant and analysed at trial termination according to intention to treat.

8.2. Hypothesis

The null hypothesis is that the effectiveness and cost-effectiveness of a strategy of prophylactic antibiotic is not superior to no prophylaxis over 12 months.

8.3. Feasibility phase

In the first 12 months of the trial we will determine whether recruitment to planned trial duration and sample size is feasible by monitoring numbers of randomised participants through the web-based trial management system. Specific objectives for this internal pilot phase and initiation of each site are:

- Determine the rate of site initiation and participant recruitment
- Document whether patients accept their treatment group allocation after randomisation

8.4 Full trial phase

If recruitment to target is deemed feasible by the Trial Steering Committee (TSC) and Funder we will progress seamlessly to the full trial phase and increase the number of centres and accelerate the rate of recruitment.

Primary objectives are:

- Determine the relative impact on incidence of UTI over 12 months
- Determine the incremental cost per symptomatic UTI avoided

Secondary objectives are:

- Clinical
    - Determine the relative effect on quality of life (QoL) amongst trial participants
    - Measure overall satisfaction with prophylactic antibiotic treatment
    - Assess participants' perception of benefit at 12 months
    - Record adverse effects related to both prophylaxis and treatment antibiotic use
    - Determine relative rates of hospitalisation because of UTI
    - Measure difference in estimated glomerular filtration rate (eGFR) at 12 months
    - Determine rates of asymptomatic bacteriuria at 12 months
    - Assess ecological change in *E. coli* isolated from urine and perianal swabs

- Economic
    - Measure incremental cost per QALY gained through repeated completion of SF-36
    - Assess participants' willingness to pay to avoid a UTI by contingent valuation at end of trial participation and incorporate these data in the economic evaluation using a cost-benefit framework.

9. Study Design

9.1 Summary

This is a 40-site, pragmatic, patient randomised superiority trial comparing an experimental strategy of once daily antibiotic prophylaxis against a control strategy of no prophylaxis. Both groups will otherwise receive usual care including on demand discrete treatment courses of antibiotic treatment for UTI. The trial will be set in both primary and secondary National Health Service (NHS) care. Participants and their clinicians will not be blinded to the allocated intervention but central trial staff managing and analysing trial data will, as far as possible, be unaware of participant allocation. We will also assess participant perception of benefit firstly by completion of a treatment satisfaction questionnaire on exit and secondly by qualitative analysis of semi-structured interviews on trial completion exploring the views and attitudes of a purposive sample of participants towards the trial intervention. The primary economic analysis will assess the cost per UTI avoided but we will also perform a cost-utility analysis and a contingent valuation study. Bacterial ecological change will be assessed by comparing changes in resistance patterns of *E. coli* in urine and perianal swabs. We have formulated a recruitment plan to progressively build to a target of 372 participants over 24 months.

9.2 Criteria for progression from feasibility

Feasibility of recruitment will be analysed at end of month 12 during which we aim to incrementally set up 17 research sites and monitor participant recruitment. We will use the first three months to initiate the first site and then establish two sites per month over the next nine months. This will give us at least 36 whole site-months from 11 sites at month nine and 81 site-months from 17 sites at month 12 to assess strength of recruitment. We will report on end of month nine data to the TSC and Funder in month ten with an additional safety report submitted to the DMC but will continue to assess recruitment up to month 12 to prevent any pause in trial schedule. At an approximate start-up recruitment rate of 0.8 participants per month per site we expect to recruit about 30 participants by end of month nine and 64 by end of month 12. We will regard recruitment of less than 20 participants at month nine as indicating that the trial is not feasible and, unless there are compelling mitigating circumstances such as zero recruitment due to circumstances beyond our control at some of the start-up sites, terminate the project. Recruitment of between 20 and 25 participants would trigger major alteration to the recruitment plan; such as increasing the number of planned sites and extension to recruitment period. Recruitment of 26 or more participants would be considered within sampling variability of the target of 30 and entail only minor finessing of the recruitment strategy. Recruitment will be monitored by the Trial Management Group (TMG) through returns to the trial website. A descriptive report with proposed action will be prepared and sent to the TSC and Funder at end of month nine for approval with rate and reasons of participant attrition.

9.3. Consort diagram

The anticipated trial flow for participants is illustrated in Figure 1.

9.4. Trial participants, Duration and Setting

We will recruit from the population of adult uses of CISC. The setting is NHS hospitals and community sites throughout the UK where CISC use is taught and/or monitored. We expect to randomise at least 372 participants over a 24 month period. For primary outcome purposes, follow up will continue for 12 months after intervention. We will separately consent participants to submit an additional urine sample and perianal swab six months after trial completion (18-month timepoint) to assess return to baseline of *E. coli* ecology. Separate consent will also be asked for permission to access clinical records for extended follow up for a further nine years (ten years in total) and for life-long linkage to central NHS databases. Allowing for a four-month analysis phase, the total planned trial duration is 42 months (Appendix – Gantt Chart).

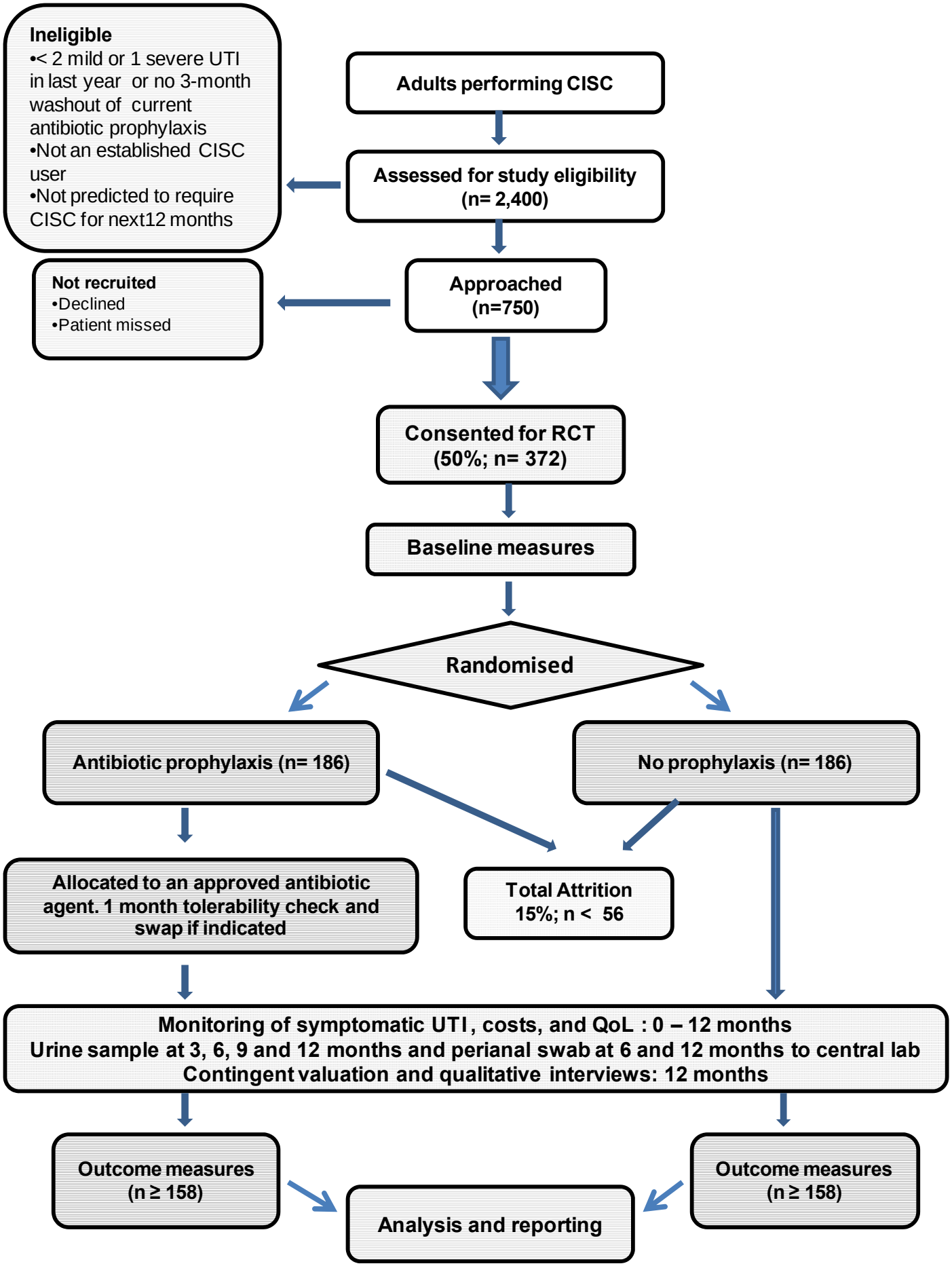

Figure 1: CONSORT diagram showing flow of trial participants through the trial

9.5 Primary effectiveness outcome measure

Difference in **incidence of symptomatic UTI** during the 12-month observation period defined as the presence of at least one patient-reported or clinician-recorded symptom from a predefined list encompassing the recommendations of the British Infection Association (BIA)[22], the Centres for Disease Control and Prevention (CDC)[23] and spinal cord injury UTI consensus statement[8] together with taking a discrete treatment course of antibiotics prescribed by a clinician or as part of a patient-initiated self-start policy. The rate of UTI will be defined 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. We will determine this outcome by collection of the following data:

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

To ensure consistent attribution we will set a hierarchy of evidence on which to base the primary outcome. First will be participant-reported episodes of symptoms that they considered to be due to UTI and for which they obtained treatment with an appropriate antibiotic. If in discussion with the participant there is uncertainty as to whether an antibiotic was taken or if the stated antibiotic was not of a type normally used for UTI, the relevant GP or hospital record will be checked for confirmation that a prescription for an antibiotic to treat UTI was issued (including previous prescription for self-start therapy). Where no antibiotic prescription was found in the record we will ask the participant to confirm the origin of the prescription. If we were unable to confirm issuing of either a single course or self-start supply of antibiotics then the primary outcome will not be fulfilled. The second type of event would be the identification of a prescription of an antibiotic during planned 3-monthly interrogation of healthcare records without a participant report of a UTI. In this case the participant will be contacted to check that they did take a treatment course of antibiotics at that time and assess their symptom status. If the participant had no recollection of the antibiotic course or if there was no evidence from the participant or healthcare records of any change to baseline urinary symptoms then the episode will be judged not to have fulfilled the primary outcome. During the first six months of the trial we will randomly select a sample of 10% reported positive primary outcome episodes and present these as vignettes to the members of the 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 but before unblinding of data we will re-examine these flagged episodes and if necessary use members of the Trial Steering Committee to attribute the outcome by consensus.

9.6. Secondary clinical outcomes

These will be collected either as additional criteria to the primary outcome from inspection of participant health care records, or by participant questionnaire, or by clinical test performed at specific time points.

- **Febrile UTI** defined as the primary outcome + presence of a recorded fever of more than 38°C
    - Confirmed by inspection of primary or secondary healthcare record by research staff
- **Microbiologically-confirmed symptomatic UTI** defined as the primary outcome + positive urine culture#

- Participants will provide an intermittent catheter specimen of urine (CSU) for local analysis as requested by the treating clinician. This will be analysed according to clinician decision by the local microbiology using local SOP. We will also ask the participant to send an CSU using provided packaging which conforms to current Royal Mail regulations to the central microbiology laboratory in Newcastle upon Tyne each time they consider they have symptoms suggestive of UTI and intend to commence a treatment course of antibiotic. This will be analysed and cultured on receipt in the central laboratory and the result used for outcome purposes but not for routine care.

- **Antibiotic prescription for asymptomatic UTI** without participant-reported or clinician recorded evidence of symptom change
- **Asymptomatic bacteriuria** defined as a positive urine culture in the absence of symptoms
  - Participants will be asked to provide a CSU sent to the central laboratory in provided packaging at baseline prior to randomisation and during asymptomatic periods in months 3, 6, 9 and 12 of their trial participation. They will also be separately consented to provide a CSU six months after completion of trial (18-month timepoint).
- **Hospitalisation due to UTI** defined as an unplanned visit to hospital for treatment of a UTI which required at least one overnight stay in hospital.
  - Collected from healthcare record review and checked from participant report or enquiry
- **Participant perception of benefit**
  - We will record and analyse semi-structured interviews with up to 30 participants purposively sampled from both trial arms on completion of their 12-month trial period.
- **Overall satisfaction with allocated treatment strategy**
  - Participants will complete the treatment satisfaction questionnaire for medication at 12 months as part of their completion of trial questionnaire.
- **Generic health-related quality of life**
  - Participant completion of the SF-36 1-week recall questionnaire at baseline, 3, 6, 9 and 12 months and within the first 2 days of each episode of symptomatic antibiotic-treated UTI prompted by telephone, e mail or text message

#Standard definition in a symptomatic participant is the laboratory report of one or two isolates at ≥ 10^5 cfu/mL or a single isolate at ≥ 10^4 cfu/mL.[24] The central laboratory result will be used preferentially for this outcome with the local result used only if a suitable sample was not received by the central laboratory.

9.7. Adverse effects

- **Adverse effects of antibiotic therapy**
  - During antibiotic prophylaxis use
    - Collected by participation checklist completed at 3, 6, 9 and 12 months
    - Recording of relevant data from primary and secondary care records at 12 months
  - During treatment antibiotic use
    - Collected as part of participant log during episode of antibiotic-treated UTI
    - Recording of relevant data from primary and secondary care records at 12 months
- **Change in renal function** defined as estimated creatinine clearance measured by serum creatinine blood test at baseline before randomisation and during an asymptomatic period in month 12
- **Change in liver function** defined as clinically significant change in liver function indices measured by serum liver function tests (LFT) at baseline and at 12 months

- **Bacterial ecological changes** to type and resistance patterns of *E. coli* isolated from CSU and perianal swabs collected and sent to the central laboratory in provided packaging at baseline prior to randomisation and at 3 (CSU only), 6, 9 (CSU only) and 12 months after randomisation and from surveillance of other CSU specimens submitted to the central laboratory. Participants will also be separately consented to provide a CSU and perianal swab together with an antibiotic use questionnaire six months after completion of trial (18-month timepoint).

9.8. Primary economic outcome

The incremental cost per symptomatic UTI avoided.

- Costs associated with the prophylaxis and no prophylaxis strategies including cost of harms
    - Treatment costs – drugs and healthcare services from standard NHS sources such as the British National Formulary (BNF) and published tariffs from NHS reference costs
    - Health resource utilisation questionnaire at baseline, and at 3, 6, 9 and 12 months
    - Patient costs from a time and travel questionnaire as part of the 12 months exit assessment

9.9. Secondary economic outcomes

- **incremental cost per QALY gained**
    - QALY estimated from responses to repeated administration of the SF-36 as described above
- **Participants' willingness to pay (wtp) to avoid a UTI**
    - Measured by completion of a contingent valuation questionnaire at end of month 12

9.10. Sources of bias

To allow randomisation, eligible participants and the responsible clinician will both need to be sufficiently uncertain of whether the experimental or control strategy is better for relief of recurrent UTI considering each individual's particular circumstances. Given the lack of high level evidence as to which is more effective we will provide trial information illustrating the uncertainty and the need for a definitive trial. This will act to ensure that any selection bias in terms of characteristics of CISC-users willing to be randomised compared with those who are eligible but not willing to participate is minimised. An anonymised screening log will be kept 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 crossover at randomisation or at a later stage, withdraw, or regret their allocated treatment option may differ from those completing the allocated strategy. We will address this by comparison of SF-36 scores between these groups measured at baseline prior to randomisation and following treatment. Trial literature given to all participants and to their clinicians will detail other measures to reduce the risk of UTI such as adequate fluid intake, increased frequency of catheterization, cranberry products, and, if appropriate for post-menopausal women, vaginal estrogen supplements. Given lack of blinding it is possible that participants allocated to the control of no prophylaxis will be more likely to seek treatment for symptoms suggestive of UTI, and that their clinicians may be more likely to prescribe treatment antibiotic introducing bias to our primary outcome. To reduce the potential for this bias we will give information on use of antibiotic treatment describing indication and choice of agent in trial literature to participants and their General Practitioners (GP) according to established guidance from the BIA and other groups. We will also include in the participant information packs advice when to seek help regarding symptoms suggestive of UTI and use of simple measures to avoid or avert symptomatic UTI. To ensure uniformity of processing and culture techniques, we will ask participants to post a CSU taken at the onset of symptomatic UTI to the central laboratory in addition to the routine diagnostic sample sent to their usual microbiology service provider. The local result will be used for clinical management purposes, while the culture result from the sample processed at the central laboratory will be the basis of the microbiological secondary outcomes for the purposes of the

study. The local result will be used for the study if the central result is missing. Packaging will conform to current Royal Mail standards. The local result will only be used if the central result is missing. Details of strategies to minimise ascertainment and attribution bias for the primary outcome are given in section 9.5.

10.9. Definition of end of study

The end of study is the last participant's final study contact, at 12 months after their randomisation. We will separately consent for the sending of a CSU and perianal swab at 6 months after end of study (18-month time point) together with completion of an antibiotic usage questionnaire. This is to determine the final bacterial ecology outcome.

10. Subject Population

10.1. Target population

Adult established CISC-users predicted to continue its use for at least 12 months who have:

A. Suffered at least two episodes of CISC-related symptomatic oral antibiotic-treated UTI within the previous 12 months managed in the community.

Or

B. Suffered at least one episode of severe CISC-related symptomatic parenteral antibiotic-treated UTI within the previous 12 months requiring hospital care

Or

C. Have previously received prophylactic antibiotic therapy for recurrent symptomatic UTI within the 12 months prior to starting prophylactic antibiotic therapy and who have completed a 3-month washout period without taking antibiotic prophylaxis prior to randomisation.

10.2. Planned inclusion/exclusion criteria

10.2.1 Inclusion criteria

- Adult men and women aged ≥ 18 years
- Completed training of CISC and predicted to continue use for at least 12 months
- Able to give informed consent for participation in trial
- Able and willing to adhere to a 12-month follow up period
- Have either suffered at least two episodes of symptomatic UTI related to CISC within last 12 months. or at least one episode of UTI requiring hospitalization, or for those previously prescribed prophylactic antibiotic for UTI, have completed a 3-month washout period without antibiotic prophylaxis. Any active symptomatic UTI will be treated prior to randomisation
- Able to take a once daily oral dose of at least one of nitrofurantoin, or trimethoprim, or cefalexin
- Intermittent catheterisation may be performed by participant, spouse, or carer
- No restriction on type of catheter used

10.2.2. Exclusion criteria

- Age < 18 years
- In learning phase of CISC
- Already taking prophylactic antibiotic against UTI and declining 3-month washout period without antibiotic prophylaxis (this will be specifically monitored in the screening log)
- Inability to take any of the three prophylactic antibiotic agents due to multiple drug sensitivities
- Women who intend to become pregnant during planned period of trial participation or who are pregnant or who are breastfeeding
- Previous participation in this study
- Inability to give informed consent or have primary outcome information collected

11. Screening, recruitment and consent

11.1. Setting

We aim to recruit participants in primary care and secondary care NHS organizations throughout the UK. Site and participant recruitment will be coordinated through seven 'hubs' each with a named co-applicant research lead and recruitment coordinator. Hub staff will engage with local secondary care sites and the appropriate Primary Care Research Network (PCRN), the latter being facilitated by two primary care lead co-applicants; James Larcombe and Paul Little to establish further research sites and Participant Identification Centres (PIC). The hubs (Lead; number of identified secondary care sites) are Newcastle upon Tyne (Pickard; 10), Wakefield (Harrison; 11), Bristol (Timoney; 8), Cambridge (Thiruchelvam; 6), Southampton (Fader; 7), Glasgow (McClurg; 7), Aberdeen (Abdel-Fattah/N'Dow; 6).

11.2. Participant identification and invitation to participate

We will try to ensure that all users of CISC in the UK are aware of the study and can consider whether they are eligible and wish to participate. We ask GP staff to identify eligible patients from electronic search of primary care records using relevant Read codes coordinated through the PCRNs. The feasibility of this will be tested in three 'Pathfinder' Primary Care Research Networks. We will preferentially ask research-active practices, particularly those with a large list size, and other large practices willing to act as participation identification centres (PIC), as guided and facilitated by PCRN staff. Identified potentially eligible patients will then be sent brief details of the need and purpose of the study and eligibility criteria. This will emphasise the pragmatic nature of the study and give a realistic indication of the burden to participants. Contact details of central and local trial teams will be provided so that interested patients can express a willingness to know more about the project and agree to be contacted by the research team. For secondary care we will establish in which services eligible patients are seen in each recruitment hub. This is likely to include urology, urogynaecology, neurological rehabilitation, and community continence clinics found using our links with professional groups including British Association of Urological Surgeons (BAUS), British Association of Urogynaecology (BSUG) and the Association for Continence Advice (ACA). Again we will ask clinical staff to 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. We will ask catheter delivery companies to enclose brief study information including central trial contact details with catheter supply packages delivered to people carrying out CISC and will also advertise the study in relevant media. Once identified and expressing a desire to know more about participating in the study and agreeing to be contacted by the research team, eligible potential participants will be contacted by trial staff and if willing will be sent or given the trial participant information material. This recruitment activity will be coordinated centrally but administered through the seven trial hubs. All subjects who agree to participate will be seen by local research staff or the trial coordinator at the respective hub to go through the consent and randomisation procedure. A screening log will be kept by local site research staff to document details of subjects invited to participate in the study. Non-identifying patient details to allow assessment of selection bias such as age, number of episodes of UTI in past 12 months, previous use of antibiotic prophylaxis for UTI, type of bladder dysfunction and type of catheter used will be uploaded to the secure study website for subsequent analysis. For subjects who decline participation, the log will document reason for non-participation. The log will also ensure potential participants who are ineligible or decline participation are approached only once. Participants who do not respond after being sent or given 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. The projected recruitment timetable is attached as an Appendix.

11.3. Consent procedures

Informed consent discussion will be untaken by appropriate staff at the main trial sites as detailed in the site delegation log. This will include medical staff and research nurses involved in the study who will give time for participants to ask any questions they may have following review of the trial information pack. 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. 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 subjects 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.

11.4. Participant expenses

Reasonable expenses incurred by participants as a result of for example extra hospital visits for study purposes outside of normal clinical care will be reimbursed. We will reimburse any NHS prescription charges for study medication. Participants will be given a gift of £20 when they start the study.

11.5. Subject Withdrawal

Patients will remain on the study unless they withdraw consent or in the unlikely event that the local Principal Investigator (PI), Chief Investigator (CI) or trial office feel it is no longer appropriate for the patient to continue. If a participant chooses to withdraw we will seek permission for the research team to continue to collect outcome data from their clinical records.

12. Details of Study Medication

12.1. Planned Interventions

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

12.1.1. Antibiotic prophylaxis (experimental)

The experimental intervention is the use for 12 months of a once-daily low dose of an antibiotic active against common urinary pathogens. The agent to be used will be selected by the responsible clinician depending on patient characteristics such as previous use, allergy, any possibility of pregnancy, renal function, prior urine cultures and local guidance. There is no universally agreed national guidance but available evidence suggest use of nitrofurantoin 50 mg (or 100 mg dependent on participant weight), trimethoprim 100 mg, or cefalexin 250 mg, in that order of preference.[14,25,26] Renal function will be determined by eGFR at baseline and if this is less than 45 ml/min nitrofurantoin will not be used. Otherwise participants and their clinicians will be asked to review the prescribing information for each drug given in the trial documentation to guide selection of the most appropriate initial agent. At the planned one-month telephone review, local trial staff will ask about tolerability of the prescribed medication. If there are specific and intolerable adverse effects then switching to an alternative agent would be advised in consultation with the relevant clinician with the reasons for the change recorded. This process would then be repeated at planned 3-monthly reviews and a third agent advised if necessary. More frequent telephone follow up will be undertaken if needed to help the participants become established on a suitable agent. The aim will be to maintain participants allocated to the prophylaxis group on prophylaxis for as long as possible during the 12-month trial period within tolerance and safety constraints. Participants will be asked to take the once-daily antibiotic prophylaxis as a single dose at bedtime. If a participant in the prophylaxis 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. 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 will be recorded on the patient log and trial case report form (CRF). All adverse events will also be recorded (see Section 19).

12.1.2. No prophylaxis

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

12.1.3. Standard care for both groups

Apart from the randomized allocation to prophylaxis and the avoidance of the prophylactic agent as treatment for symptomatic UTI, there will not be any differences in the trial protocol concerning care of experimental and control groups of participants. We will ensure as far as is possible that participants in both groups receive their usual care in terms of identification and treatment of UTI, health surveillance and support related to use of CISC, and monitoring and treatment of the underlying cause of their lower urinary tract dysfunction. For purposes of generalisability of trial results and to input into relevant trial outcomes and sub-group analysis we will record all healthcare episodes for each participant. We consider standard care for users

of clean intermittent self-catheterisation (CISC) who suffer recurrent urinary tract infection (UTI) to be the use of discrete treatment courses of antibiotics as indicated by symptoms or signs of UTI. Treatment will typically involve a 3 or 7-day course of an antibiotic active against urinary pathogens depending on severity of symptoms. A urine specimen would normally be sent for microbiological examination at the time of starting antibiotic treatment. If therapy was successful no further action would be required whereas if symptoms did not resolve the choice and duration of antibiotic would be reconsidered in the light of urine culture result and if necessary a further urine sample submitted for analysis.[22] This suggested standard of care will be emphasised in participant and clinician trial documentation. Regular renal surveillance using serum creatinine and ultrasound would also be expected. Guidance will be provided to participants in both groups, and their clinicians regarding use of urine testing and antibiotic options in terms of agents used and their duration. Participants in both groups will continue their regular care with primary and secondary care clinic visits, access to continence advice and relevant patient support groups according to local practice and individual preference.

12.2. Delivery of interventions

Local clinicians at the NHS site of randomisation will be responsible for initiating trial medication for those participants allocated to prophylaxis whether in secondary (typically) or primary care with a 3-month supply of the relevant medication. The participants' GP will then be asked to provide further supplies until the end of the 12-month trial treatment period. If this is not possible then the clinician at the NHS site of randomisation will continue to supply the medication. If the participant wishes and if the clinician responsible for their routine care agrees, then the antibiotic prophylaxis can be continued beyond the 12-month trial participation period but without further active monitoring from the trial research team.

12.3. Funding of trial intervention

The interventions will be funded by standing NHS contracting mechanisms having been sanctioned by local commissioning groups through local approval mechanisms. The NHS excess treatment costs have been approved by the Sponsor. Any prescription charges for trial drugs incurred by participants will be reimbursed. The trial intervention is low cost.

13. Randomisation

13.1. Participant allocation

Randomisation will be administered centrally by the Newcastle CTU secure web-based system. Permuted random blocks of variable length will be used to allocate participants 1:1 to the control and experimental groups and ensure concealment of allocation from central trial staff. An individual not otherwise involved with the study will produce the final randomisation schedule. Stratification by three variables; prior frequency of UTI: < 4 episodes per year and ≥ 4 episodes per year, a diagnosis of neurogenic lower urinary tract dysfunction: yes or no, and sex: female or male, will be performed prior to randomisation to ensure balanced allocation within these factors. For those allocated to prophylaxis an appointment will be arranged, facilitated by trial staff, with the prescribing clinician to commence prophylaxis. This may be a hospital consultant, a general practitioner (GP), or a continence nurse specialist. The prophylaxis agent will be chosen by the clinician with regard to individual participant characteristics, local guidance, previous urine culture and sensitivity results, and standardised trial information with preferred agents being: nitrofurantoin first, trimethoprim second, cefalexin third. Continued supply will be ensured typically through repeat prescription from the individual participant's primary care practice.

Patients may only be randomised into the study by an authorised member of staff at the study research site, as detailed on the Delegation Log.

Contact details for Randomisation: http://apps.ncl.ac.uk/random/

(Available 24 hours a day)

14. Blinding

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

15. Data Collection

15.1 Summary

Outcome data will be recorded on questionnaires by the participant, which will be made available in paper-based and electronic format, and on the worksheet by local research staff under a unique identifier with subsequent electronic entry onto electronic case report forms (e-CRF) by local research staff or the hub trial coordinator onto the web-based secure clinical data management system for storage at Newcastle CTU. Baseline data will include demographics, underlying disease characteristics, details of catheterisation, prior frequency of UTI and associated usage of healthcare, past urine microbiological reports, together with symptom and QoL measures recorded prior to randomisation. Samples of urine, blood, and perianal swab will also be collected at baseline for immediate testing and banking of serum, urine and *E. coli isolates* for studies additional to the trial. During the 12 months of study participation, participants will be asked to keep a simple log recording episodes of suspected UTI from a symptom and help-seeking point of view. If required trial staff will contact participants approximately monthly to help completion of UTI logs within a reasonable recall window. The patient logs will be validated if necessary by data from regular inspection of primary and secondary health care records for UTI events and subsequent direct checking with participants by their preferred means (telephone, text, e-mail). Other outcome data will be collected by patient questionnaire at 3, 6, 9, and 12 months supplemented by regular inspection of health records. Details of participant progress will be recorded on case report forms. For a tabulated schedule of events see Table 1. Timings in bold refer to duration of participant time required.

15.1.1. ***Screening****: clinical records and face-to-face* ***20 minutes***

- Demographics
- Eligibility criteria checklist
- Decision: eligible or not eligible?
    - If experiencing symptomatic UTI currently treat with standard antibiotic therapy and randomise when symptom free
    - If already on antibiotic prophylaxis for UTI – agree to 3-month washout period before randomisation
- Trial Information provided
- Consent for
    - Randomisation
    - Informing GP of participation in trial
    - Contact by researcher for semi-structured interview at end of trial participation (12 months)
    - Send CSU and perianal swab to central laboratory six months after trial completion (18 months)
    - Access by research team to clinical records after active trial participation has ended
    - Storage and use of blood, urine and perianal swab samples for further research

15.1.2. ***Baseline*** *(before randomisation): face-to-face*

- Baseline personal and disease details completed with research staff on the CRF **10 minutes**
- Completion of SF-36 questionnaire **10 minutes**
- Creatinine and LFT (blood test) and creatinine clearance (from clinical records if within 2 months of baseline) with storage of blood sample for future research
- CSU for central microbiological analysis and storage **5 minutes**

- Perianal swab for central microbiological analysis **5 minutes**
- Decision with regard to preferred means of questionnaire delivery, alerts, and best time for contact by trial staff

15.1.3. ***Randomisation***

Randomisation will be performed as close as possible to the date of consent (normally immediately after). Those participants willing to undergo a 3-month washout period will consent to the study at the beginning of the washout period, but will not be randomised or complete the other baseline measures until the washout period is complete at which point their continued eligibility for trial participation will be checked.

15.1.4. ***Post randomisation*** *discussion of trial documentation: face to face* ***30 minutes***

- Participant log
- Means and frequency of contact with trial staff
- Means of supply and use of antibiotic prophylaxis (if allocated)
- Trial definition of UTI
- What to do if UTI experienced
- Delivery of urine specimens and perianal swabs to central laboratory

15.1.5. ***One month*** *after randomisation and repeated if required: telephone* ***5 – 10 minutes***

- Contact by trial staff regarding
    - General concerns
    - Understanding of trial documentation
    - Tolerance of prophylactic antibiotic agent (if allocated)

15.1.6. ***Three months*** *after randomisation: telephone/postal or face-to-face (according to local circumstance)*

- Participant
    - Trial outcome questionnaire **10 minutes**
        - Report of UTIs during months 1 to 3
        - Report of symptoms associated with any episode of UTI during months 1 to 3
        - Report of adverse effects during months 1 to 3
        - Adherence to prophylaxis if allocated
    - SF-36 **10 minutes**
    - Health care resource use questionnaire **10 minutes**
    - CSU (during asymptomatic period) posted to central laboratory for analysis and storage **5 minutes**

- Trial or local clinical staff
    - Search of clinical records (secondary and primary care)
        - Episodes of UTI

- Episodes of UTI associated with fever greater than 38°C
- Antibiotic prescription
    - For UTI prophylaxis
    - For UTI
    - For other reasons
- Episodes of hospitalisation
    - For UTI
    - For other reasons
- Results of local laboratory urine culture

*15.1.7. **Six months** after randomisation: telephone/postal or face-to-face (according to local circumstance)*

- Participant
    - Trial outcome questionnaire **10 minutes**
        - Report of UTIs during months 4 to 6
        - Report of symptoms associated with any episode of UTI during months 4 to 6
        - Report of adverse effects during months 4 to 6
        - Adherence to prophylaxis if allocated
    - SF-36 **10 minutes**
    - Health care resource use questionnaire **10 minutes**
    - CSU (during asymptomatic period) and perianal swab to central laboratory for analysis and storage **10 minutes**

- Trial or local clinical staff
    - Search of clinical records (secondary and primary care)
        - Episodes of UTI
        - Episodes of UTI associated with fever greater than 38°C
        - Antibiotic prescription
            - For UTI prophylaxis
            - For UTI
            - For other reasons
        - Episodes of hospitalisation
            - For UTI
            - For other reasons
        - Results of local laboratory urine culture

*15.1.8. **Nine months** after randomisation: telephone or face-to-face (according to local circumstance and policy)*

- Participant
    - Trial outcome questionnaire **10 minutes**
        - Report of UTIs during months 7 to 9

        - Report of symptoms associated with any episode of UTI during months 7 to 9
        - Report of adverse effects during months 7 to 9
        - Adherence to prophylaxis if allocated
    - SF-36 **10 minutes**
    - Health care resource use questionnaire **10 minutes**
    - CSU (during asymptomatic period) posted to central laboratory for analysis and storage **5 minutes**

- Trial or local clinical staff
    - Search of clinical records (secondary and primary care)
        - Episodes of UTI
        - Episodes of UTI associated with fever greater than 38°C
        - Antibiotic prescription
            - For UTI prophylaxis
            - For UTI
            - For other reasons
        - Episodes of hospitalisation
            - For UTI
            - For other reasons
        - Results of local laboratory urine culture

15.1.9. ***During episode of symptomatic antibiotic-treated UTI:*** *telephone/postal or face-to-face (according to local circumstance)*

- Participant
    - Trial outcome questionnaire **10 minutes**
        - Report of UTI
        - Report of symptoms associated with current episode of UTI
        - Report of adverse effects of treatment for UTI
        - Continued adherence to prophylaxis if allocated
    - SF-36 **10 minutes**
    - CSU to central and local laboratory prior to commencing treatment course of antibiotics for analysis and storage **5 minutes**

- Trial or local clinical staff
    - Check of clinical records (secondary and primary care)
        - Documented visit for UTI
        - Recorded fever greater than 38°C
        - Antibiotic prescription UTI
        - Hospitalisation

- Results of local laboratory urine culture

*15.1.10. **Twelve months** after randomisation: telephone or face-to-face (according to local circumstance and policy)*

- Participant
    - Trial outcome questionnaire **10 minutes**
        - Report of UTIs during months 10 to 12
        - Report of symptoms associated with any episode of UTI during months 10 to 12
        - Report of adverse effects during months 10 to 12
        - Adherence to prophylaxis if allocated
    - SF-36 **10 minutes**
    - Health care resource use questionnaire **10 minutes**
    - Patient costs (time and travel) questionnaire for months 6 to 12 **15 minutes**
    - CSU (during asymptomatic period) and perianal swab to central laboratory for analysis and storage **10 minutes**
    - Creatinine and LFT (blood test) and creatinine clearance or eGFR during asymptomatic period **5 minutes**
    - Completion of satisfaction with medication questionnaire **5 minutes**
    - Completion of contingent valuation questionnaire **20 minutes**
    - Semi-structured interview (if agreed and selected) **45 minutes**

- Trial or local clinical staff
    - Search of clinical records (secondary and primary care) over 12 months of participation
        - Episodes of UTI
        - Episodes of UTI associated with fever greater than 38°C
        - Antibiotic prescription
            - For UTI prophylaxis
            - For UTI
            - For other reasons
        - Episodes of hospitalisation
            - For UTI
            - For other reasons
        - Results of local laboratory urine culture

	Visit 1 Initial Screen	Visit 2 Consent (C), Baseline(B) and Randomisation (R)			Visit 3 3 months	Visit 4 6 months	Visit 5 9 months	Visit 6 12 months	At time of UTI
		C	B	R					
Eligibility checklist	X								
Trial discussed and PIS given	X								
Informed Consent		X							
UTI questionnaire			X		X	X	X	X	X
Adverse events					X	X	X	X	X
SF-36			X		X	X	X	X	X
Resource use questionnaire					X	X	X	X	
Patient costs questionnaire								X	
Treatment satisfaction questionnaire								X	
Contingent valuation questionnaire								X	
CSU to central laboratory			X		X	X	X	X	X
Perianal swab			X			X		X	
Creatinine (eGFR) and LFT			X					X	

Table 1: Schedule of study interventions and outcome data collection from participant

15.2. Data handling and record keeping

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™). 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.

Clinical data will be entered into the database 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 questionnaires completed at face-to-face visits with participants. 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. Encrypted identifiable data will be kept on the trial database within Newcastle CTU. The management system 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. This will include access by qualitative researchers to contact details of participants who consent to the semi-structured interview. 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. The sponsor is responsible for ensuring that trial data is archived appropriately. 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). Caldicott approval for use, transfer and storage of participant identifiable information will be obtained at each site.

16. Statistical Considerations

16.1. Statistical analysis

An analysis of the primary outcome measure (incidence of UTI as defined in section 9.5) for the full study will be performed both for the full data set and for the separate subgroups defined by high and low baseline UTI rate (as specified during stratification for the randomisation process) using both the Poisson rate test and an incidence density ratio approach to allow for the different treatment durations; regression or generalised linear modelling approaches will be used to adjust for the effects of covariates. The model selection process will include the stratification factors (prior rate of UTI, presence of neurological disease and gender) and other baseline variables [person doing CISC (self or other), asymptomatic bacteriuria, age, type of catheter, use of antibiotic prophylaxis for UTI in the previous 12 months prior to randomisation, presence of bladder augmentation]. The inclusion of interaction terms such as site will also be explored. The inclusion of baseline values as covariates will additionally enable the examination of possible interactions between effects observed and these values. Not all covariates mentioned above will be included in the final model but will be considered during the model selection process. A number of additional secondary analyses will also be undertaken to examine the secondary outcome variables. Febrile and microbiologically-confirmed UTI, asymptomatic bacteriuria and hospitalisation due to UTI will be analysed in a manner analogous to the primary outcome. Analysis of other outcomes will use similar regression or analysis of variance/covariance based approaches as described above to compare between treatment groups while allowing for the effects of covariates. Baseline measures would be included in the analysis, either considered as possible covariates or by exploring changes in outcome measures from baseline. Analysis will be carried out primarily on an intention-to-treat basis although other exploratory analyses such as per-protocol may also be considered. Data will be analysed at the end of the study; there are no planned interim analyses. Safety data will not be subjected to statistical analysis. 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.

16.2 Sample size calculation

We plan to recruit 372 participants to the trial. Based on systematic reviews[11,15] and expert opinion we believe that an overall 20% reduction in symptomatic UTI rate from an average of 3 to 2.4 episodes per year represents the minimum clinically important difference. Using the Poisson rate test, completion of the study by 158 participants in each arm, 316 in total, would give 90% power to detect this difference at the 5% level. A total of 372 would allow for a 15% attrition rate estimated from previous trials included in the systematic review. Attrition rate will be monitored and sample size increased if necessary. Half this sample size would

give 92% power to detect a 25% difference in the high frequency sub-group (from 4 to 3 episodes per year) and more than 99% power for a 50% reduction in the low frequency group (from 2 to 1) without allowance for multiple testing. We will approach approximately 750 eligible patients anticipating a 50% recruitment rate. We plan to recruit from 40 of the 58 sites who have expressed an interest in the trial coordinated through seven trial hubs. This number will be adjusted according to site, and overall recruitment rate. The hubs, the secondary care sites who expressed an interest, and the PCRN that we will target, cover a population of over 30 million people. Making the conservative assumptions that there are 40,000 CISC users in the UK and that 15% suffer recurrent UTIs this gives a pool of 2,400 eligible participants to recruit from. For the qualitative sub-study of participant perception of benefit we will interview 30 trial participants who, at the time of trial consent, expressed a willingness to be interviewed at completion. We will create a purposive sample of approximately 20 participants from the prophylaxis arm and ten from the no prophylaxis arm including some with neurological disability and some who did not complete the trial as allocated. We anticipate this will be sufficient to saturate themes arising from qualitative analysis of interviews transcripts. For contingent valuation a sample of 100 participants in each group; 200 in total will complete an exit questionnaire.

16.3. Health economic analysis

Analyses will be carried out from the perspective of the NHS and personal and social services, but we will also take a wider perspective by including costs borne by the participants and their families. All unit costs will be derived using routine data sources[27] and study specific estimates. Where appropriate, discounting will be applied to costs and outcomes at UK recommended rates.[28] Data on use of services will be combined with appropriate unit costs to produce a cost for each trial participant. From these a mean cost per intervention and a mean cost taking into account patient and carer costs will be estimated. Results for cost-effectiveness will be presented as point estimates of mean incremental costs and effects. The within trial analysis will also compare changes in HRQoL based on responses to the SF-36 and converted into the SF-6D[29] to estimate QALYs using the area under the curve approach. They will subsequently be used in a cost-utility analysis. The results will be presented as point estimates of mean incremental costs and QALYs. Both cost-effectiveness and cost-utility analyses will include deterministic and stochastic sensitivity analysis, presented as point estimates and cost-effectiveness acceptability curves. Contingent valuation study at 12 months will collect individuals' willingness to pay, for a reduction in the number of UTI. For a given level of income, higher monetary values indicate that they would derive greater benefit. This method will enable us to place a monetary value on the health outcome, going beyond the QALY framework and also conduct a cost-benefit analysis. Cost-benefit analysis expresses both costs and benefits in commensurate units which enables comparison to be made between strategies.[30] The decision rule for cost-benefit analysis is therefore relatively simple, if the benefits measured in sterling (£) exceed the costs this represents a gain in welfare and the strategy is deemed worthwhile.[31] Results will be presented as incremental net benefits (net benefits = mean willingness to pay – mean cost of intervention). Both stochastic and deterministic sensitivity analyses will be conducted and the results presented as incremental net benefit curves and as the probability that each treatment would be considered cost-effective.

16.4. Qualitative analysis of participant exit interviews

We will use qualitative methodology to conduct and analyse semi-structured interviews with a purposive sample of 30 trial participants to explore their views and experiences of self-catheterisation, the impact of UTI on their QoL, attitudes towards prophylactic antibiotics, and adherence to treatment. This will inform interpretation of measures of effectiveness, particularly regarding adherence and will also add insights that can further refine implementation of the intervention into practice. The sample will be weighted towards the prophylaxis arm in order to better explore the comparative experiences of this intervention for people with neurological and non-neurological conditions. Interviews lasting approximately 45 minutes will be conducted by telephone with development of the schedule conducted in an iterative fashion in order to follow up unanticipated themes. Constant comparison techniques to check experiences against those of others in the sample will be used to ensure that the analysis represents all perspectives. Interviews will be recorded, transcribed verbatim, anonymised and stored electronically with restricted access. Data will be transcribed and uploaded into NVivo 9 software and coded for recurrent themes drawing on a framework analysis

approach.[32] Transcripts will be charted, classified, and organised according to key themes, concepts and emergent categories. The analytic matrix will include key attributes such as: antibiotic use; gender; degree of adherence; and neurological/non-neurological condition and will facilitate cross-referencing attributes with nodes/themes. Transcripts will be read by more than one researcher and discussed with the wider team to establish a rigorous analytical framework to find true patterns in the data. This will go beyond description to evaluate meanings of participants' experiences in greater depth. Negative cases will be sought and further interrogated to explore the reasons for variation of experience or views[33] and unanticipated themes will be searched for.[34] A sample (n=5) of coded transcripts will be checked and verified by a second researcher to ensure reliability.

16.5. Feasibility and acceptability analysis

Feasibility of recruitment will be analysed at end of month nine of the initial recruitment period (trial month 12). Recruitment will be monitored by the Trial Management Group (TMG) through returns to the trial website. A descriptive report with proposed action will be prepared and sent to the Board for approval this will include rate and reasons of participant attrition.

17. Compliance and withdrawal

17.1. Assessment of Adherence

Outcome data will be collected remotely whenever feasible by participant completion of postal or secure web-based questionnaires. This will be supplemented by e-mail or text alerts to participants notifying them to complete questionnaires with additionally up to two reminders in these formats for non-responders. Local research staff will make use of planned routine clinical visits whether for the underlying health condition or urinary tract monitoring to check completion of trial documentation and collect clinical outcome information such as CSU and perianal swab. We will telephone participants allocated to prophylaxis after one month to assess tolerability and if necessary allow change to alternative agent with re-checking of tolerability after a further month. We will assess adherence to the allocated arm (prophylaxis or no prophylaxis) by 3-monthly contact with the participant to check tolerability and surveillance of their primary healthcare record to record issuing of relevant prescriptions and consultations involving discussion of UTI treatment. We will contact participants more frequently if they need assistance to complete trial documents particularly the UTI log. All information will be recorded in the 3-monthly CRF. If we do detect crossover between the arms we will explore and record the reasons for this with the participant and the relevant clinician by telephone or face-to-face contact. Wherever possible participants will remain on study and continue collection of planned outcome information. 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 agents will be allowed. Previous studies suggests that this will affect approximately 12% of participants[35] although a higher rate was seen in children (48%).[36] The trial statistician will monitor attrition rate against our anticipated maximum of 15% and report to the TMG, TSC and Data Monitoring Committee (DMC) as appropriate.

17.2. Withdrawal of participants

Participants have the right to withdraw from the study at any time for any reason, and without giving a reason. The investigator also has the right to withdraw patients from the study intervention if it is judged to be in the patient's best interests. It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable and therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible.

There are three withdrawal options:

1. Withdrawing completely (i.e. withdrawal from allocated treatment and provision of follow-up data)
2. Withdrawing active participation in trial but allowing continued review by research team of healthcare records

3. Withdrawing partially (i.e. a request to move to alternative treatment arm) but continuing to provide follow-up data by attending clinic and/or completing questionnaires).

We will encourage participants that decide to withdraw to choose option 2 or 3 but if they wish to withdraw completely we will retain data collected up to the point of withdrawal. Participants will be asked if they would be happy for the reason for the decision to withdraw to be recorded. Participants who withdraw completely will not be replaced but the rate of withdrawal will be monitored and reported to the DMC.

Investigator-led participant change in status would be considered for the following reasons:

- Prophylaxis arm
    - Unable to tolerate any suitable antibiotic agent
    - Pregnancy
- No prophylaxis arm
    - Change in circumstance whereby starting prophylaxis is an urgent clinical necessity
    - Pregnancy

18. Data Monitoring, Quality Control and Quality Assurance

18.1. Monitoring, Quality control/assurance

Quality control will be maintained through adherence to SOP published by the Newcastle CTU, study protocol, the principles of GCP, research governance and clinical trial regulations. An independent Data Monitoring and Ethics Committee (DMC) will be set up to include one methodologist, one physician not connected to the trial, and one statistician (Chair). It 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 TSC and 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.

A Trial Steering Committee (TSC) will be established to provide overall supervision of the trial. The TSC will consist of an independent Chair, two further independent clinicians, independent statistician, independent lay representatives, Chief Investigator & members of the TMG as required or requested by the chair. The committee will meet approximately every six months during recruitment, and annually thereafter for the duration of the trial.

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% 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 authorization
- 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 study may be subject to inspection and audit by the Research and Development Directorate, Newcastle upon Tyne Hospitals NHS Foundation Trust under their remit as sponsor, and other regulatory bodies to ensure adherence to GCP. The investigator(s) / institutions will permit trial-related monitoring, audits, REC review and regulatory inspection(s), providing direct access to source data/documents.

18.2. Discontinuation Rules

The trial may be prematurely discontinued on the basis of new safety information, or for other reasons given by the DMC and/or TSC, Sponsor, regulatory authority or ethics committee concerned. The study will be terminated if recruitment to target is found not to be feasible in consultation with the funder. Following 9 months of recruitment, initial rates of recruitment will be used to project total recruitment to ensure sufficient participants to power the trial. The criteria for recruitment feasibility are described in section 9.2. The TSC will give advice on whether to continue or discontinue the study and make a recommendation to the funder and sponsor. If the study is prematurely discontinued, active participants will be informed and no further participant data will be collected.

18.3 Data Sharing

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.

19. Pharmacovigilance

19.1. Definitions

Adverse event (AE): Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE, therefore, does not necessarily have a causal relationship with the treatment. In this context, "treatment" includes all investigational agents (including comparative agents) administered during the course of the study. Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment.

Adverse Reaction (AR)/Adverse Drug Reaction (ADR): Any untoward and unintended responses to an Investigational Medicinal Product (IMP) which related to any dose administered to that subject. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression "reasonable causal relationship" means to convey in general that there is evidence or argument to suggest a causal relationship.

Causality: Assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in Table 2. All adverse events judged as having a reasonable suspected causal relationship to the IMP (definitely, probably or possibly related) are considered to be adverse reactions. If any doubt about the causality exists, the local investigator (PI) should inform the Chief Investigator. In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA, main REC and other bodies will be informed of both points of view.

Relationship	**Description**
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

Table 2: Definitions of terms of use in categorisation of causality of adverse event

Unexpected Adverse Reaction: An adverse reaction the nature and severity of which is inconsistent with information about the medicinal product as set out in the relevant Summary of Product Characteristics.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR): an adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

1. Results in death

2. Is life-threatening (refers to an event in which the subject was at 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)
3. Requires hospitalisation, or prolongation of existing hospitalisation
4. Results in persistent or significant disability or incapacity
5. Consists of a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important medical events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Suspected, Unexpected Serious Adverse Reaction (SUSAR): an adverse reaction that is both unexpected and serious. An adverse reaction is 'unexpected' if its nature or severity is not consistent with the applicable product information (see section 19.2).

Severity (intensity) of Adverse Events and Adverse Reactions: Severity of all AEs and ARs will be graded on a three-point scale of intensity (mild, moderate, severe).

- Mild: Discomfort is noticed, but there is no disruption of normal daily activities.
- Moderate: Discomfort is sufficient to reduce or affect normal daily activities.
- Severe: Discomfort is incapacitating, with inability to work or to perform normal daily activities.

An AE or AR may be severe but not serious.

19.2. Expected adverse reactions:

Most adverse events and adverse drug reactions that occur in this study, whether they are serious or not, will be expected treatment-related toxicities due to the drugs used in this study. For a full list of expected undesirable effects of nitrofurantoin, trimethoprim, and cefalexin, please refer to the reference safety information (RSI) in the Summary of Product Characteristics (SmPC) Section 4.8, for each of these drugs (Appendix 2).

19.3. Protocol Specifications

For purposes of this protocol:

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

19.4. Recording & Reporting Serious Adverse Events or Reactions:

Adverse events that occur but are not covered by the exclusion criteria listed in section 19.3 should be reported. The reporting procedure to be followed will depend on the seriousness of the adverse event and are described in the following section. Any questions concerning the need or process of adverse event reporting should be directed to the Trial Manager or Chief Investigator. The flow chart summarises reporting procedures (Figure 2).

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

Serious Adverse Event / Reaction (SAE/SAR, including SUSARs): All SAEs, SARs & SUSARs during antibiotic prophylaxis treatment shall be reported to the Trial Manager and Chief Investigator within 24 hours of the site learning of its occurrence. The initial report can be made by secure fax which will also generate an email copy to the Chief Investigator, Senior Trial Manager and Trial Manager. In the case of incomplete information at the time of initial reporting, all appropriate information should be provided as follow-up as soon as this becomes available. Relationship of the SAE to the treatment should be assessed by the investigator at site, as should the expected or unexpected nature of any serious adverse reactions.

The MHRA and main REC will be notified by the Trial Management Team or Chief Investigator (on behalf of the Sponsor) of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. SUSARS will be reported using a CIOMS1 form, specifying the EudraCT number, CTA number, protocol number and study name, and the data elements listed in Annex 3 of the document "*Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use – April 2006*". All investigators will be informed of all SUSARs occurring throughout the study on a case-by-case basis. The Trial Manager and Chief Investigator will ensure the Newcastle upon Tyne Hospitals NHS Foundation Trust as Sponsor is notified of any SUSARs in accordance with local trust policy. If required local investigators should report any SUSARs /SAEs to their local Research & Development Office.

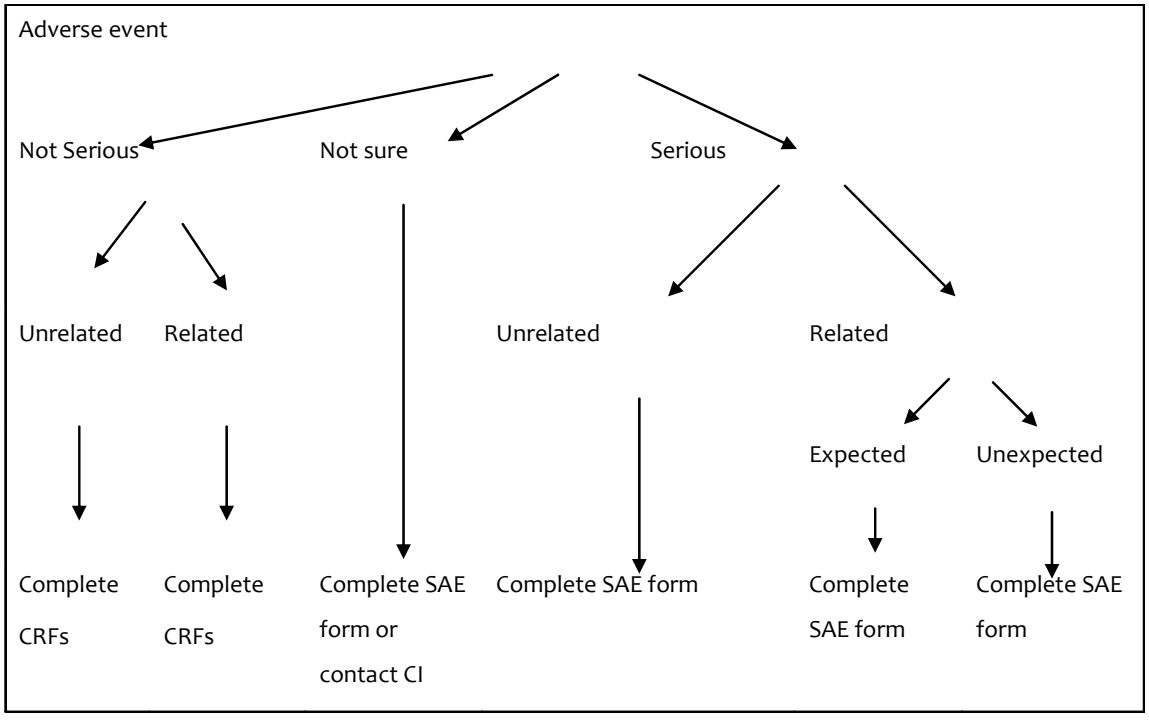

Figure 2: Flow chart illustrating adverse event reporting procedures

Contact details for reporting SAEs and SUSARs
Please send SAE form(s) via FAO AnTIC Trial Manager [Fax: 0191 580 0725]

The initial report can be made by secure fax which will also generate an email copy to the Chief Investigator, Senior Trial Manager and Trial Manager. In the case of incomplete information at the time of initial reporting, all appropriate information should be provided as a follow-up communication on the appropriate SAE form. As detailed above, relationship of the SAE to the treatment (causality) should be assessed by the investigator at site, as should the expected or unexpected nature (by reference to the SmPC for nitrofurantoin, trimethoprim, and cefalexin) of any serious adverse reactions.

Pregnancy: If a female participant allocated to the prophylaxis arm becomes pregnant while participating in the trial, the prophylaxis agent will be discontinued immediately. Details of the pregnancy should be reported to the treating clinician (normally her General Practitioner) within 24 hours of learning of its occurrence. 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.

20. Ethics & Regulatory Issues

20.1. Summary

The conduct of this study will be in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions. Favourable ethical opinion from an appropriate REC and R&D approval has been obtained. Local approvals will be sought before recruitment may commence at each site. The Newcastle CTU will require a written copy of local approval documentation before initiating each centre and accepting participants into the study. Information sheets will be provided to all eligible subjects and written informed consent obtained prior to any study procedures.

20.2. Specific ethical issues

This pragmatic trial seeks to follow standard local patterns and pathways of care with the only additional intervention being randomisation between the two strategies under test and collection of baseline and outcome information. Given the degree of uncertainty regarding the use of antibiotic prophylaxis against UTI in this patient group there is as yet no definitive evidence that randomisation to either arm will result in greater benefit or harm for participants; this being the reason for the trial. Collection of outcome information by participant questionnaire may be onerous for some participants because of co-morbidities and disabilities linked to their underlying health condition. Local research staff, local clinical staff and, where appropriate, the carers of participant will be asked to help with completion of documentation using as frequent contact with participants as is needed. The primary outcome will be validated from primary care records and we will need to ensure full compliance with personal data protection. We will need to ensure that we achieve a correct balance between supporting participants so that they stay in their allocated group and record UTI events whilst avoiding causing distress or bias.

20.3. Risks and benefits for trial participants and society

The use of antibiotic prophylaxis may be associated with adverse effects related to individual agents or changes to normal bacterial flora, these are described in Section 19. These risks will be minimized by carefully worded trial information given to participants to enable selection of the individually most appropriate agent and information concerning use of oral probiotics. The order of preference of prophylactic agents we will advise together with guidance to avoid use of other agents will ensure that the great majority of participants will use one of the three recommended agents and switch between them if necessary. We have planned what we believe is a sufficiently comprehensive but feasible programme of bacterial surveillance that will detect potentially serious changes to bacterial ecology in the trial groups. The main benefit will be to resolve uncertainty concerning effectiveness of antibiotic prophylaxis in this group thereby reducing variation in practice. Specimens of urine (CSU) and perianal swabs will be submitted regularly by participants during the trial to the central laboratory for selective culture of *E. coli*. These are trial samples that would not normally be collected during routine care and the participants will be asymptomatic for UTI at the time of specimen collection. We therefore do not plan to inform the participant or the clinicians responsible for their care of the results of the centrally performed urine and perianal skin *E. coli* cultures. This policy would be sensitive to clinical concerns and exceptions readily made if, for example, the participant suffered an episode of severe sepsis and the results of the cultures would be helpful to clinical care. Similarly we will not routinely inform treating clinicians of the result of any positive culture from CSU sent to the central laboratory during an episode of symptomatic UTI. The reason for this is the delayed transit time and hence prolonged period before any result is available. This in most cases would make the result unhelpful to clinical care. Participants will be encouraged to also take a CSU to their treating clinician for local analysis according to local protocols.

20.4. Informed consent

All participants will undergo a process of informed consent which will include the delivery 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. Participants will be free to withdraw their consent at any time and if this happened they would be given the opportunity of withdrawing their data collected up to that time.

20.5. Compliance with 'Medicines for Human Use (Clinical Trials)' Regulations

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 in prophylaxis against UTI in the UK and are standard care for this indication.[14,25,26] From this we judge that from an IMP perspective there is low risk to trial participants. Apart from the intervention in the experimental arm participants in both arms of the trial will be subject to routine clinical care only and we therefore consider that risks 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, supported by the sponsor, to be granted 'Type A' status (low risk - notification only) from 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 was submitted to the MHRA along with the notification application.

21. Confidentiality

Personal data will be regarded as strictly confidential. To preserve anonymity, any data leaving the site will identify participants by their initials and a unique study identification code only. With participants' consent, details required to send postal/web-based or e-mailed questionnaires and associated prompts will be provided to the trial data management centre in Newcastle CTU to enable remote follow up. The study will comply with the Data Protection Act, 1998. All study records and Investigator Site Files will be kept at site in a locked filing cabinet with restricted access. All trial laboratory samples will be labelled with a unique study identification number and patient date of birth only (linked in anonymised form).

22. Insurance and Finance

The Newcastle upon Tyne Hospitals NHS Foundation Trust has liability for clinical negligence that harms individuals toward whom they have a duty of care. NHS Indemnity covers NHS staff and medical academic staff with honorary contracts conducting the trial for potential liability in respect of negligent harm arising from the conduct of the study. The Newcastle upon Tyne Hospitals NHS Foundation Trust is Sponsor and through the Sponsor, NHS indemnity is provided in respect of potential liability and negligent harm arising from study management. Indemnity in respect of potential liability arising from negligent harm related to study design is provided by NHS schemes for those protocol authors who have their substantive contracts of employment with the NHS and by Newcastle University Insurance schemes for those protocol authors who have their substantive contract of employment with this organisation. This is a non-commercial study and there are no arrangements for non-negligent compensation. The NIHR HTA Programme is funding the study.

23. Study Report / Publications

The data will be the property of the Chief Investigator and Co-Investigators. Publication will be the responsibility of the Chief Investigator. It is planned to publish this study in peer reviewed articles and to present data at national and international meetings. Results of the study will also be reported to the Sponsor and Funder by monograph, and will be available on their web sites. All manuscripts, abstracts or other modes of presentation will be reviewed by the Trial Steering Committee and Funder prior to submission. Participants will be informed about their treatment and their contribution to the study at the end of the study, including a lay summary of the results. At a minimum this trial will have a results paper published in a peer-reviewed medical journal. 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.

24. Satellite Studies

The funds provided by NIHR-HTA Programme are to conduct the main study as described in this protocol. It is recognised, however, that the value of the study may be enhanced by smaller satellite studies of specific aspects. Plans for these will be submitted to the Trial Management Group and tabled at meetings of the Trial Steering Committee. The agreement of these groups and of the funder will be required for satellite studies to proceed to submission for regulatory approval.

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26. Appendices

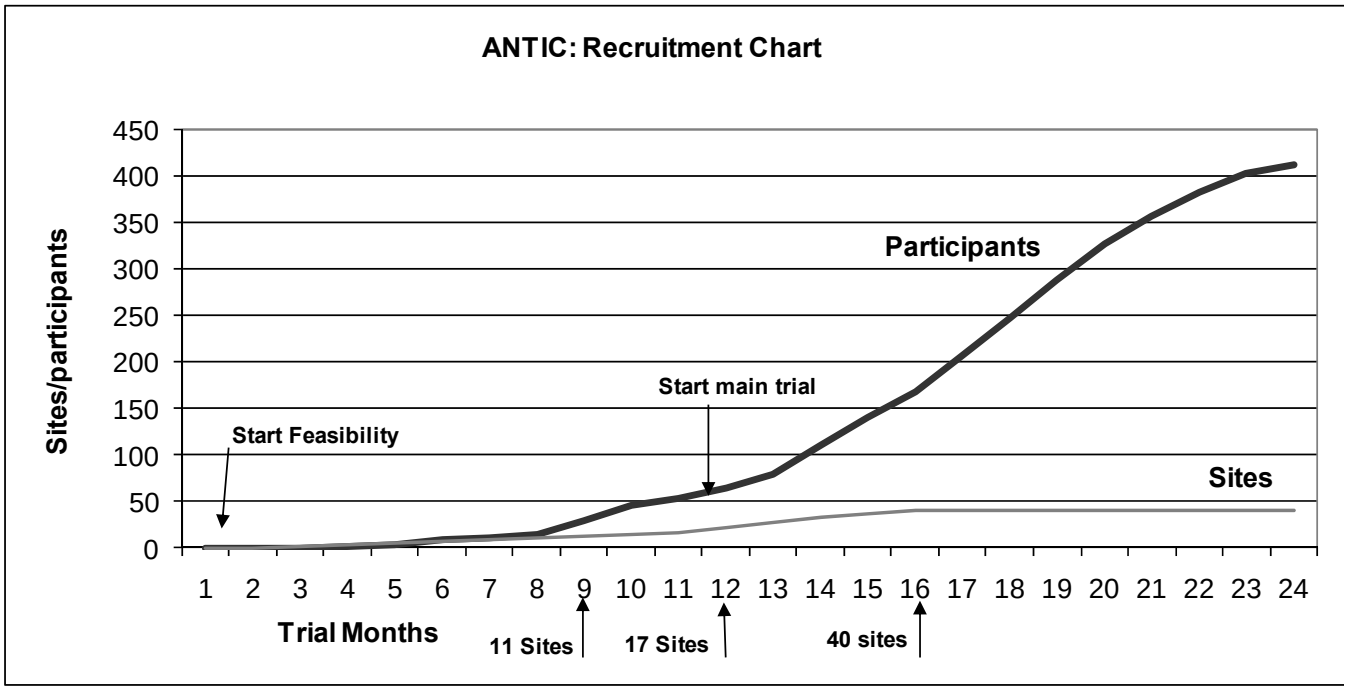
1. Trial Recruitment and Gantt Charts
2. SmPCs for nitrofurantoin, trimethoprim, and cefalexin
3. Questionnaires / Measurement tools (& validation where appropriate)
    a. SF-36
    b. Health care resource use questionnaire
    c. AnTIC participant outcome questionnaire
    d. Urinary tract infection log questionnaire (Participant UTI Record)
    e. Patient costs (Time and Travel) questionnaire
    f. Treatment Satisfaction with medication questionnaire (TSQM)
    g. Contingent valuation questionnaire
4. Declaration of Helsinki

Appendix 1

Project: 11/72/01 ANTIC			
Key Milestones			
A		Finalise feasibility/full trial site arrangements	31 Jul 2013
B		Obtain central regulatory approvals	31 Aug 2013
C		Appoint staff to commence Sep 2013	30 Jun 2013
D		Commence trial	01 Sep 2013
E		Completion feasibility phase (at least 31 site-months of active recruitment by month 9)	31 May 2014
F		Report of feasibility phase to funder	14 June 2014
G		Commence main trial	01 Sep 2014
H		Complete recruitment (target 372 participants randomised)	31 Aug 2015
I		Complete follow up phase	31 Aug 2016
J		Complete data analysis	31 Jan 2017
K		Submit final report to funder	28 Feb 2017

Activity/Project Plan		2013				2014				2015				2016				2017	
Work Package		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2
1	Trial set up and approvals																		
2	Feasibility phase																		
3	Full trial phase																		
4	Analysis and writing up																		
5	Full project management group meetings		X	X		X		X		X		X			X		X	X	
6	Trial steering group meetings	X		X					X				X					X	
7	Data monitoring committee meetings	X		X				X				X					X		
8	Progress report to funder						X		X			X				X		X	
HTA Funding (42 months)																			
9	Follow up urine specimen for bacterial ecology																		

Gantt chart for AnTIC study with start date 1st September 2013



Projected recruitment chart for AnTIC

Appendix 2:

Summary of Product Characteristics

- **Nitrofurantoin**
- **Trimethoprim**
- **Cefalexin**

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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Trimethoprim 100mg Tablets

Summary of Product Characteristics Updated 14-Oct-2013 | Kent Pharmaceuticals Ltd

1. Name of the medicinal product

Trimethoprim 100mg Tablets and Trimid

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 and children over 12 years: 200mg twice daily

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 and children over 12 years: 100mg at night

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.

Route of administration

For oral administration.

4.3 Contraindications

Severe hepatic insufficiency. Severe renal insufficiency, unless plasma levels can be monitored regularly. Megaloblastic anaemia and other blooddyscrasias. 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.

4.4 Special warnings and precautions for use

Patients with marked impairment of renal function:

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. 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 for hyperkalaemia (see section 4.8).

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.

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 lactation

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

Trimethoprim is excreted in breast milk. Effects on the suckling child are likely if therapeutic doses are administered to breast-feeding mothers. Trimethoprim is contraindicated if the breast fed infant is less than 4 months of age.

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.

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

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, angioedema, 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

Hepatobiliary disorders

Very rare: 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.

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

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

Mode of action

Trimethoprim is a dihydrofolate reductase inhibitor, 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, 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≤/Resistant>) Units: mg/L		
Enterobacteriaceae	***Staphylococcus***	***Enterococcus***
≤2/>4	≤2/>4	≤0.032/>1*

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

5.2 Pharmacokinetic properties

Trimethoprim is readily absorbed from the gastro-intestinal tract and peak concentrations in the circulation occur about 3 hours after a dose is taken. It 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 50% of a dose is excreted in the urine within 24 hours mainly as unchanged drug. Urinary concentrations are generally well above the MIC of common pathogens for more than 24 hours after the last dose.

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

14/08/2013

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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

Core

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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Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one week ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

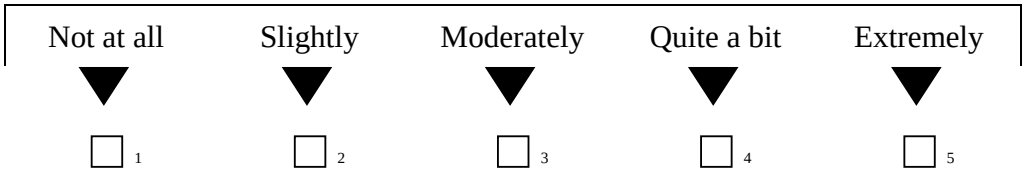
4. During the <u>past week</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the <u>kind</u> of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

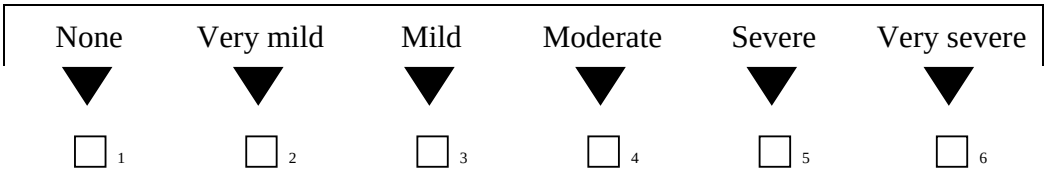
5. During the <u>past week</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities <u>less carefully than usual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

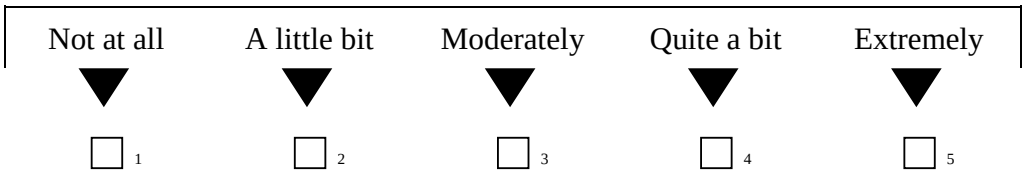
6. During the <u>past week</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?



7. How much <u>bodily</u> pain have you had during the <u>past week</u>?



8. During the <u>past week</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?



9. These questions are about how you feel and how things have been with you <u>during the past week</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past week</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past week</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a	I seem to get ill more easily than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Participant Study Number: ☐☐ - ☐☐☐ - ☐☐☐☐
Hub Centre Participant No.

Health Service Utilisation Questionnaire - ANTIC

Please complete this questionnaire with details of your treatment over the last 3 months. These questions ask about visits to hospital and your GP. Please tick the appropriate boxes and answer the questions where required.

1. In the last 3 months, have you been admitted to hospital as an inpatient (stayed in hospital overnight or longer)?

Yes ☐ 1 **If Yes, go to Q1a**

No ☐ 2 **If No, go to Q2**

1a. If Yes, approximately how many nights in total did you spend in hospital in the last 3 months?

Enter number of nights that you stayed in hospital ☐☐ **Go to Q2**

2. In the last 3 months, have you had any hospital outpatient appointments (did not stay overnight)?

Yes ☐ 1 **If Yes, go to Q2a**

No ☐ 2 **If No, go to Q3**

2a. If Yes, approximately how many outpatient appointments in total did you have in the last 3 months?

Enter number of times you attended hospital as an outpatient

☐☐ **Go to Q3**

3. In the last 3 months, have you had to attend the A&E/casualty department but were not admitted overnight?

Yes ☐ 1 **If Yes, go to Q3a**

No ☐ 2 **If No, go to Q4**

3a. If Yes, approximately how many times in total did you attend the A&E/casualty department in the last 3 months?

Enter number of times you attended the A&E/casualty department ☐☐ **Go to Q4**

4. In the last 3 months, have you had any consultations with a **GP at their practice**?

Yes ☐ 1 **If Yes, go to Q4a**

No ☐ 2 **If No, go to Q5**

4a. If Yes, approximately how many consultations in total did you have with a GP at their practice in the last 3 months?

Enter number of consultations you had with a GP at their practice ☐☐ **Go to Q5**

5. In the last 3 months, have you had any consultations with a **GP at your home**?

Yes ☐ 1 **If Yes, go to Q5a**

No ☐ 2 **If No, go to Q6**

5a. If Yes, approximately how many consultations in total did you have with a GP at your home in the last 3 months?

Enter number of consultations you had with a GP at your home ☐☐ **Go to Q6**

6. In the last 3 months, have you had any consultations with a **practice nurse at their practice**?

Yes ☐ 1 **If Yes, go to Q6a**

No ☐ 2 **If No, go to Q7**

6a. If Yes, approximately how many consultations in total did you have with a practice nurse at their practice in the last 3 months?

Enter number of consultations you had with a practice nurse at their practice ☐☐ **Go to Q7**

7. In the last 3 months, have you had any consultations with a **nurse at your home**? (E.G. district nurse, specialist nurse, etc.)

Yes ☐ 1 **If Yes, go to Q7a**

No ☐ 2 **If No, go to Q8**

7a. If Yes, approximately how many consultations in total did you have with a nurse at your home in the last 3 months?

Enter number of consultations you had with a nurse at your home ☐☐ **Go to Q8**

8. In the last 3 months have you had any **telephone consultations** with a health care professional?

Yes ☐ 1 **If Yes, go to 8a**

No ☐ 2 **If No, go to Q9**

8a. If Yes, please indicate what health care professional provided this telephone consultation and approximately how many telephone consultations in total you have had in the past 3 months. Please tick as many as apply.

Health Care Professional	**Yes** 1	✓ **No** 2	**Number of consultations**
GP	☐	☐	☐☐
Hospital Doctor	☐	☐	☐☐
Nurse	☐	☐	☐☐
Other health professional	☐	☐	☐☐

If Other please provide details _____

9. In the last 3 months have you had any **out-of-hours consultations** with a health care professional?

Yes ☐ 1 **If Yes, go to Q10a**

No ☐ 2 **If No, go to Q11**

10a. If Yes, please indicate what health care professional provided this out-of-hours consultation and approximately how many out-of-hours-consultations in total you have had in the past 3 months. Please tick as many as apply.

Health Care Professional	**Yes** 1	✓ **No** 2	**Number of consultations**
GP	☐	☐	☐☐
Hospital Doctor	☐	☐	☐☐
Nurse	☐	☐	☐☐
Other health professional	☐	☐	☐☐

If Other please provide details _____

11. In the past 3 months have you paid for any private health care and/or personal care?

Yes ☐ 1 **If Yes, go to Q11a**

No ☐ 2 **If No, please continue to the end of the questionnaire**

11a. If Yes, please indicate what type of health care you have paid for in the past 3 months and what was the cost of this health care to you.

What heath care have you paid for?	**What was the cost of this health care?**
1._____	£☐☐☐☐☐☐.☐☐p
2._____	£☐☐☐☐☐☐.☐☐p
3._____	£☐☐☐☐☐☐.☐☐p

Date of completion:

If you wish to provide any further information, please do so below.

Thank-you for taking the time to complete this questionnaire

AnTIC Participant Questionnaire – 3, 6, 9, 12 months

Participant Study Number: ☐☐ - ☐☐☐ - ☐☐☐☐ (Hub - Centre - Participant No.)	Participant initials ☐☐☐

A. Date of Completion: [DD/MM/YYYY] ☐☐ ☐☐ ☐☐☐☐

B. Have you experienced any episodes of **urinary infection** treated with antibiotics during the **past three months**? Please tick '✓' to indicate yes or no as appropriate for each question.

Yes ☐ 1 **If yes how many urinary infections (e.g if two: insert 2 in the box)** ☐

No ☐ 2 **[please go to Q2]**

For each episode, if you have not done so already, you should complete a separate AnTIC urinary tract infection questionnaire supplied to you.

EPISODE 1

1a. Name of antibiotic treatment taken:		Code for antibiotic **OFFICE USE ONLY**	
1b. Date treatment antibiotic started D D M M Y Y Y Y		1c. Date treatment antibiotic stopped D D M M Y Y Y Y	
1d. Urinary tract infection questionnaire completed	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
1e. Urine specimen sent to AnTIC trial office	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
1f. Urine specimen given to GP's surgery	Yes ☐ 1	No ☐ 2	Don't know ☐ 3

EPISODE 2

2a. Name of antibiotic treatment taken:		Code for antibiotic **OFFICE USE ONLY**	
2b. Date treatment antibiotic started D D M M Y Y Y Y		2c. Date treatment antibiotic stopped D D M M Y Y Y Y	
2d. Urinary tract infection questionnaire completed	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
2e. Urine specimen sent to AnTIC trial office	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
2f. Urine specimen given to GP's surgery	Yes ☐ 1	No ☐ 2	Don't know ☐ 3

EPISODE 3

3a. Name of antibiotic treatment taken:		Code for antibiotic **OFFICE USE ONLY**	
3b. Date treatment antibiotic started D D M M Y Y Y Y		3c. Date treatment antibiotic stopped D D M M Y Y Y Y	
3d. Urinary tract infection questionnaire completed	Yes ☐ 1 No ☐ 2 Don't know ☐ 3		
3e. Urine specimen sent to AnTIC trial office	Yes ☐ 1 No ☐ 2 Don't know ☐ 3		
3f. Urine specimen given to GP's surgery	Yes ☐ 1 No ☐ 2 Don't know ☐ 3		

EPISODE 4

4a. Name of antibiotic treatment taken:		Code for antibiotic **OFFICE USE ONLY**	
4b. Date treatment antibiotic started D D M M Y Y Y Y		4c. Date treatment antibiotic stopped D D M M Y Y Y Y	
4d. Urinary tract infection questionnaire completed	Yes ☐ 1 No ☐ 2 Don't know ☐ 3		
4e. Urine specimen sent to AnTIC trial office	Yes ☐ 1 No ☐ 2 Don't know ☐ 3		
4f. Urine specimen given to GP's surgery	Yes ☐ 1 No ☐ 2 Don't know ☐ 3		

EPISODE 5

5a. Name of antibiotic treatment taken:		Code for antibiotic **OFFICE USE ONLY**	
5b. Date treatment antibiotic started D D M M Y Y Y Y		5c. Date treatment antibiotic stopped D D M M Y Y Y Y	
5d. Urinary tract infection questionnaire completed	Yes ☐ 1 No ☐ 2 Don't know ☐ 3		
5e. Urine specimen sent to AnTIC trial office	Yes ☐ 1 No ☐ 2 Don't know ☐ 3		
5f. Urine specimen given to GP's surgery	Yes ☐ 1 No ☐ 2 Don't know ☐ 3		

C. Have you made any of the following changes to your intermittent catheterisation use in the last three months (please tick '✓' to indicate yes or no as appropriate for each question)?

Change in catheter use	**Yes$_1$**	**No$_2$**
1. Increased number of catheterisation each day	☐	☐
2. Decreased number of catheterisations each day	☐	☐
3. Changed type or brand of catheter	☐	☐
4. Changed size of catheter	☐	☐

D. During the last three months have you made any lifestyle changes or used any 'over-the-counter' home remedies to help prevent urinary tract infection (please tick '✓' to indicate yes or no as appropriate for each question)?

Lifestyle/home remedy use change	**Yes$_1$**	**No$_2$**
1. Drinking more fluid	☐	☐
2. Stopping cigarette smoking	☐	☐
3. Vaginal oestrogen tablet or cream	☐	☐
4. Cranberry product (juice, capsule or other)	☐	☐
5. Substances like potassium citrate or sodium bicarbonate to alter the acidity of your urine	☐	☐
6. Foods or drinks with anti-bacterial properties such as manuka honey or nettle tea	☐	☐
7. Probiotics such as live yoghurt, 'Actimel', 'Yakult' or 'acidophyllus' and others.	☐	☐

E. Have you taken any courses of antibiotic for **any other reason** apart from urinary infection during the past three months?	**Yes$_1$** ☐	**No$_1$ [please go to Q5]** ☐

If yes how many urinary infections (e.g. if two: insert 2 in the box) ☐

If **yes**, please now fill in the boxes for each episode.

Episode:	**1**	**2**	**3**
a. Name of treatment antibiotic taken			
Code for antibiotic OFFICE USE			

Episode:	**1**	**2**	**3**
ONLY*			
b. Date antibiotic treatment started:	D D M M Y Y Y Y	D D M M Y Y Y Y	D D M M Y Y Y Y
c. Date treatment antibiotic stopped:	D D M M Y Y Y Y	D D M M Y Y Y Y	D D M M Y Y Y Y
d. Reason for antibiotic [type of infection]			
Code for infection OFFICE USE ONLY*			

Episode:	**4**	**5**
a. Name of treatment antibiotic taken		
Code for antibiotic OFFICE USE ONLY*		
b. Date antibiotic treatment started:	D D M M Y Y Y Y	D D M M Y Y Y Y
c. Date treatment antibiotic stopped:	D D M M Y Y Y Y	D D M M Y Y Y Y
d. Reason for antibiotic [type of infection]		
Code for infection OFFICE USE ONLY*		

F. Did you experience any of the following health problems while you were taking treatment courses of antibiotics for **any reason** [excluding the once daily prophylactic antibiotic for UTI] during the last three months and did you have to stop taking the antibiotic because of the problem? For each question please tick '✓' to indicate yes or no as appropriate). **Please fill in a separate table for each antibiotic that you had problems with.**

Problem with antiobiotic 1:		**Code - OFFICE USE ONLY***
1a. Name of antibiotic:		
1b. Reason for taking antibiotic:		

			Action: Did you……			
Problem whilst taking antibiotics: Did you experience any of the following?			**Stop taking the antibiotic**		**Change to a different antibiotic**	
	Yes	**No**	**Yes**	**No**	**Yes**	**No**
1c. Skin rash	☐	☐	☐	☐	☐	☐
1d. Feeling sick (nauseated)	☐	☐	☐	☐	☐	☐
1e. Being sick (vomiting)	☐	☐	☐	☐	☐	☐
1f. Looser or more frequent bowel movements (diarrhoea)	☐	☐	☐	☐	☐	☐
1g.Thrush (candidal fungal infection) in the vagina	☐	☐	☐	☐	☐	☐
1h.Thrush (candidal fungal infection) in the mouth	☐	☐	☐	☐	☐	☐
1i.Other: please describe side effect(s) in the space below						

Code - OFFICE USE ONLY

Problem with antibiotic 2		**Code - OFFICE USE ONLY**					
2a.Name of antibiotic:							
2b.Reason for taking antibiotic:							
			Action: Did you……				
Problem whilst taking antibiotics: Did you experience any of the following?			**Stop taking the antibiotic**		**Change to a different antibiotic**		
	Yes	**No**	**Yes**	**No**	**Yes**	**No**	
2c. Skin rash	☐	☐	☐	☐	☐	☐	
2d. Feeling sick (nauseated)	☐	☐	☐	☐	☐	☐	
2e. Being sick (vomiting)	☐	☐	☐	☐	☐	☐	
2f. Looser or more frequent bowel movements (diarrhoea)	☐	☐	☐	☐	☐	☐	
2g.Thrush (candidal fungal infection) in the vagina	☐	☐	☐	☐	☐	☐	
2h.Thrush (candidal fungal infection) in the mouth	☐	☐	☐	☐	☐	☐	
2i.Other: please describe side effect(s) in the space below							

Code - OFFICE USE ONLY

Problem with antibiotic 3

Code - OFFICE USE ONLY*

3a. Name of antibiotic:

3b. Reason for taking antibiotic:

Problem whilst taking antibiotics: Did you experience any of the following?			**Action: Did you…… Stop taking the antibiotic**		**Change to a different antibiotic**	
	Yes	**No**	**Yes**	**No**	**Yes**	**No**
3c. Skin rash	☐	☐	☐	☐	☐	☐
3d. Feeling sick (nauseated)	☐	☐	☐	☐	☐	☐
3e. Being sick (vomiting)	☐	☐	☐	☐	☐	☐
3f. Looser or more frequent bowel movements (diarrhoea)	☐	☐	☐	☐	☐	☐
3g.Thrush (candidal fungal infection) in the vagina	☐	☐	☐	☐	☐	☐
3h.Thrush (candidal fungal infection) in the mouth	☐	☐	☐	☐	☐	☐
3i.Other: please describe side effect(s) in the space below						

Code - OFFICE USE ONLY

G. Finally just a checklist of the other things we would like you to do at this point. For each please tick '✓' yes or no according to whether you have completed them.

Trial Task	**Completed**		**Sent back to trial office**	
	Yes	**No**	**Yes**	**No**
'Your Health and Well-Being' questionnaire	☐	☐	☐	☐
Healthcare visits questionnaire	☐	☐	☐	☐
Personal costs questionnaire (12 months)	☐	☐	☐	☐
Treatment satisfaction questionnaire (12 months)	☐	☐	☐	☐
Willingness to pay questionnaire (12 months)	☐	☐	☐	☐
Asymptomatic urine specimen sent to trial office	☐	☐	☐	☐

Perianal swab sent to trial office (6 and 12 months) ☐ ☐ ☐ ☐

Thank you very much for completing all your trial tasks. Please don't hesitate to contact your local research team if you have any further questions or need to clarify anything.

Local Principal Investigator:		Local Research Nurse:	
Address:		Address:	

Phone:		Phone:	
Fax:		Fax:	
Email:		Email:	

Participant UTI Record

A. Symptoms	
1. Date symptoms started:	**Date:** ☐☐ ☐☐ ☐☐☐☐ D D M M Y Y Y Y

During this episode of antibiotic-treated urinary infection which symptoms did you experience? Please put a tick '✓' in the appropriate box for each symptom that you experienced during this urinary infection episode

	Yes	**No**	**Don't Know**
2. Fever (hot and sweaty)	☐ 1	☐ 2	☐ 3
3. Shivers	☐ 1	☐ 2	☐ 3
4. Cloudy urine	☐ 1	☐ 2	☐ 3
5. Smelly urine	☐ 1	☐ 2	☐ 3
6. Visible blood in urine	☐ 1	☐ 2	☐ 3
7. Urinary leakage (incontinence)	☐ 1	☐ 2	☐ 3
8. Lower abdominal (tummy) pain	☐ 1	☐ 2	☐ 3
9. Having to catheterise more often	☐ 1	☐ 2	☐ 3
10. Having to rush to catheterise	☐ 1	☐ 2	☐ 3
11. Pain when you put the catheter in	☐ 1	☐ 2	☐ 3
12. Feeling generally unwell ('fluey')	☐ 1	☐ 2	☐ 3
13. Stiffness or worsening stiffness (spasticity) of arms and legs	☐ 1	☐ 2	☐ 3
14. Other (please describe symptom(s) below)	☐ 1	☐ 2	☐ 3

15. During this episode of antibiotic-treated urinary infection was your body temperature measured?	Yes ☐ 1 No ☐ 2

16. If yes what was the reading? [e.g. 37.0 or 38.5]	☐☐.☐ °C

B. Treatment that you took for the UTI:

Non-antibiotic treatments

During this episode of antibiotic-treated urinary infection did you use any of the following? Please put a tick '✓' in the appropriate box for each option that you used during this urinary infection episode.

	Yes	No	Don't Know
1. Increased fluid intake (drinking more)	☐ 1	☐ 2	☐ 3
2. Catheterising more often	☐ 1	☐ 2	☐ 3
3. Cranberry products (juice or tablets for example)	☐ 1	☐ 2	☐ 3
4. Probiotics such as natural 'live' yoghurt or 'Actimel' or 'Yakult'	☐ 1	☐ 2	☐ 3
5. Vaginal hormonal supplements (oestrogen creams or pessaries)	☐ 1	☐ 2	☐ 3
6. Herbal teas or infusions	☐ 1	☐ 2	☐ 3
7. Medicines form your chemist or doctor to make the urine more acid or alkaline (such as potassium citrate)	☐ 1	☐ 2	☐ 3
8. Bladder washes or irrigations	☐ 1	☐ 2	☐ 3

Antibiotic

Please describe your antibiotic usage during this episode of antibiotic-treated urinary infection

How did you get the supply for antibiotic? Please put a tick '✓' in the appropriate box for each option that you used during this urinary infection episode.

	Yes	No	Don't Know
9. Prescription from GP	☐ 1	☐ 2	☐ 3
10. Self-start supply at home from own supply	☐ 1	☐ 2	☐ 3
11. On what date did you start taking antibiotic?	**Date:** ☐☐ ☐☐ ☐☐☐☐ D D M M Y Y Y Y		

Which antibiotic did you **first** take for treatment during this episode of antibiotic-treated urinary infection? Please tick '✓' the relevant box.

	Yes	No	Don't Know
12. Cefalexin	☐ 1	☐ 2	☐ 3
13. Co-amoxiclav ('Augmentin')	☐ 1	☐ 2	☐ 3
14. Ciprofloxacin ('Ciproxin')	☐ 1	☐ 2	☐ 3
15. Trimethoprim	☐ 1	☐ 2	☐ 3
16. Nitrofurantoin	☐ 1	☐ 2	☐ 3
17. Amoxicillin	☐ 1	☐ 2	☐ 3
18. Other (please write name of antibiotic below)	☐ 1	☐ 2	☐ 3

CODE* (For Trial Office Use Only) ☐☐

For how many days did you take the first antibiotic during this episode of antibiotic-treated urinary infection? Please write the number of days in the box below:

19. Number of days: ☐☐

Did you need a second lot of antibiotic during this episode of antibiotic-treated urinary infection? Please write the details in the appropriate place below:

20. Date started second antibiotic	☐☐ ☐☐ ☐☐☐☐ D D M M Y Y Y Y
21. Name of antibiotic:	**CODE* (for trial office use only)** ☐☐
22. Number of days second antibiotic taken for:	☐☐

C. Other questions:

1. During this episode of antibiotic-treated urinary infection did you have to go into hospital because of the urinary infection? **Yes** ☐ 1 **No** ☐ 2

If Yes:	
2. Name of Hospital:	
3. Date of admission to hospital	☐☐ ☐☐ ☐☐☐☐ D D M M Y Y Y Y
4. Date of discharge home from hospital	☐☐ ☐☐ ☐☐☐☐ D D M M Y Y Y Y

Did you experience and side effects whilst taking the antibiotic(s) to treat this infection? Please put a tick '✓' in the appropriate box for each side effect that you experienced during this urinary infection episode.

	Yes	**No**	**Don't Know**
5. Skin rash	☐ 1	☐ 2	☐ 3
6. Feeling sick (nauseated)	☐ 1	☐ 2	☐ 3
7. Diarrhoea (more loose or more frequent bowel movements)	☐ 1	☐ 2	☐ 3
8. Thrush (candidal fungal infection) in the vagina	☐ 1	☐ 2	☐ 3
9. Thrush (candidal fungal infection) in the mouth	☐ 1	☐ 2	☐ 3
10. Other (please describe side effect in the box)	☐ 1	☐ 2	☐ 3

11. Overall, how would you rate the severity of this infection compared to others that you have experienced? Please tick '✓' the most appropriate option.

Very mild	**Mild**	**Between mild and severe**	**Severe**	**Very severe**
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Participant Time and Travel Questionnaire

Please complete this questionnaire with details of your **most recent** travel for treatment over the last 12 months. Please tick (✓) the appropriate boxes and answer the questions where required.

Section 1 Hospital Admissions:

*Please answer the following questions for your **most recent** HOSPITAL ADMISSION only.*

*If you **have not** been admitted to hospital in the last 12 months, please go to SECTION 2.*

1. How did you travel to the hospital?

Car	☐ **Go to Q1a**	Taxi	☐ **Go to Q1b**
Public Transport	☐ **Go to Q1c**	Other	☐ **Go to Q1d**
Ambulance	☐ **Go to Q2**	Hospital vehicle	☐ **Go to Q2**
Walked	☐ **Go to Q2**		

1a. If you travelled by **private car** please answer the following:

How many miles did you travel to the hospital (one way)? ____ miles

How much did you have to pay to park the car? £____

Go to Q2

1b. If you travelled by **taxi,** how much was the taxi fare (one way)? £____

Go to Q2

1c. If you travelled by **public transport**, how much did you pay (one way)? £____

Go to Q2

1d. If you travelled by **another form of transport** please answer the following:

What form of transport did you use? ____

What costs were incurred by you using this form of transport? £____

Go to Q2

2. What would you have been doing as your main activity if you had not been admitted to hospital?

Paid Work ☐	Housework ☐
Childcare ☐	Caring for someone ☐
Voluntary work ☐	Leisure activities ☐
Other **Please provide details:**_____ ☐	

3. Were you accompanied to hospital by a relative or carer?

Yes ☐ **If Yes, go to Q4**

No ☐ **If No, go to Section 2**

4. How much time did your main relative or carer spend in the hospital with you when you were admitted to hospital (**this includes time spent travelling and waiting to be admitted but not visiting times**)? Please ✓ the box that best applies to your last hospital admission when you were accompanied by a relative or carer.

Less than 30 minutes ☐

30 minutes – less than I hour ☐

1 hour – less than 2 hours ☐

2 hours – less than 3 hours ☐

3 hours – less than 4 hours ☐

4 hours – less than 5 hours ☐

5 hours or greater ☐

If greater than 5 hours, please specify the number of hours they spent in the hospital_____

5. What would your <u>main relative or carer</u> have been doing as their main activity if they had not accompanied you to your last hospital admission?

Paid Work ☐	Housework ☐
Childcare ☐	Caring for someone ☐
Voluntary work ☐	Leisure activities ☐
Other **Please provide details:**_____ ☐	

Section 2: Outpatient Appointments

*Please answer the following questions for your **most recent** HOSPITAL OUTPATIENT APPOINTMENT only.*

*If you **did not** have an outpatient appointment in the last 12 months, please go to SECTION 3.*

6. How did you travel to the hospital/clinic?

Car ☐ **Go to Q6a**	Taxi ☐ **Go to Q6b**
Public Transport ☐ **Go to Q6c**	Other ☐ **Go to Q6d**
Ambulance ☐ **Go to Q7**	Hospital vehicle ☐ **Go to Q7**
Walked ☐ **Go to Q7**	

6a. If you travelled by **private car** please answer the following:

How many miles did you travel to the hospital/clinic (one way)? ____ miles

How much did you have to pay to park the car? £____

Go to Q7

6b. If you travelled by **taxi**, how much was the taxi fare (one way)? £____

Go to Q7

6c. If you travelled by **public transport,** how much was the fare (one way)? £____

Go to Q7

6d. If you travelled by **another form of transport** please answer the following:

What form of transport did you use? ____

What costs were incurred by you using this form of transport? £____

Go to Q7

7. What would you have been doing as your main activity if you had not attended your last outpatient appointment?

Paid Work ☐	Housework ☐
Childcare ☐	Caring for someone ☐
Voluntary work ☐	Leisure activities ☐
Other **Please provide details:**_____ ☐	

8. How much time did you spend in the hospital/clinic at your last outpatient appointment (**this includes time spent travelling and waiting**)? Please ✓ the box that best applies to your last outpatient appointment.

Less than 30 minutes	☐
30 minutes – less than I hour	☐
1 hour – less than 2 hours	☐
2 hours – less than 3 hours	☐
3 hours – less than 4 hours	☐
4 hours – less than 5 hours	☐
5 hours or greater	☐

If greater than 5 hours, please specify the number of hours you spent in the hospital/clinic_____

9. Were you accompanied by a relative or carer to your last outpatient appointment?

Yes	☐	**If Yes, go to Q10**
No	☐	**If No, go to Section 3**

10. What would your <u>main relative or carer</u> have been doing as their main activity if they had not attended your last outpatient appointment with you?

Paid Work ☐	Housework ☐
Childcare ☐	Caring for someone ☐
Voluntary work ☐	Leisure activities ☐
Other **Please provide details:**_____ ☐	

Section 3: GP Consultations

*Please answer the following questions for your **most recent** GP CONSULTATIONS only.*

*If you **did not** have a GP consultation in the last 12 months, please go to SECTION 4.*

11. How did you travel to the GP surgery?

Car ☐ **Go to Q11a**	Taxi ☐ **Go to Q11b**
Public Transport ☐ **Go to Q11c**	Other ☐ **Go to Q11d**
Walked ☐ **Go to Q12**	

11a. If you travelled by **private car** please answer the following:

How many miles did you travel to the GP surgery (one way)? miles

How much did you have to pay to park the car? £

Go to Q12

11b. If you travelled by **taxi**, how much was the taxi fare (one way)? £

Go to Q12

11c. If you travelled by **public transport**, how much was the fare (one way)? £

Go to Q12

11d. If you travelled by **another form of transport** please answer the following:

What form of transport did you use?

What costs were incurred by you using this form of transport? £

Go to Q12

12. What would you have been doing as your main activity if you had not attended your last GP consultation?

Paid Work ☐	Housework ☐
Childcare ☐	Caring for someone ☐
Voluntary work ☐	Leisure activities ☐
Other **Please provide details:**_____ ☐	

13. How much time did you spend in the GP surgery at your last GP consultation (**this includes time spent travelling and waiting**)? Please ✓ the box that best applies to your last GP consultation.

Less than 30 minutes	☐
30 minutes – less than I hour	☐
1 hour – less than 2 hours	☐
2 hours – less than 3 hours	☐
3 hours – less than 4 hours	☐
4 hours – less than 5 hours	☐
5 hours or greater	☐

If greater than 5 hours, please specify the number of hours you spent in the GP surgery_____

14. Were you accompanied by a relative or carer to your last GP consultation?

Yes	☐	**If Yes, go to Q15**
No	☐	**If No, go to Section 4**

15. What would your <u>main relative or carer</u> have been doing as their main activity if they had not attended your last GP consultation with you?

Paid Work ☐	Housework ☐
Childcare ☐	Caring for someone ☐
Voluntary work ☐	Leisure activities ☐
Other **Please provide details:**_____ ☐	

Section 4: Practice Nurse Consultations

*Please answer the following questions for your **most recent** PRACTICE NURSE CONSULTATIONS only.*

*If you **did not** have a practice nurse consultation in the past 12 months, please go to SECTION 5.*

16. What would you have been doing as your main activity if you had not attended your last practice nurse consultation?

Paid Work ☐	Housework ☐
Childcare ☐	Caring for someone ☐
Voluntary work ☐	Leisure activities ☐
Other **Please provide details:**_____ ☐	

17. How much time did you spend at your last practice nurse consultation (**this includes time spent travelling and waiting**)? Please ✓ the box that best applies to your last practice nurse consultation.

Less than 30 minutes	☐
30 minutes – less than I hour	☐
1 hour – less than 2 hours	☐
2 hours – less than 3 hours	☐
3 hours – less than 4 hours	☐
4 hours – less than 5 hours	☐
5 hours or greater	☐

If greater than 5 hours, please specify the number of hours you spent in the practice_____

18. Were you accompanied by a relative or carer to your last practice nurse consultation?

Yes	☐	**If Yes, go to Q19**
No	☐	**If No, go to Section 5**

19. What would your main relative or carer have been doing as their main activity if they had not attended your last practice nurse consultation with you?

Paid Work ☐	Housework ☐
Childcare ☐	Caring for someone ☐
Voluntary work ☐	Leisure activities ☐
Other **Please provide details:**_____ ☐	

Section 6: Work Affected by illness

Please answer the following questions regarding your current employment status and the effect your ill health has on your employment status (if any).

22. What is your current employment status?

Full Employment ☐	Part-time Employment ☐
Student ☐	Retired ☐
Housework ☐	Caring for someone ☐
Unemployed, not actively seeking work ☐	Unemployed, actively seeking work ☐
Other **Please provide details:**_____ ☐	

23. How many days off work (to the nearest ½ day) have you had in the past 2 months because of health problems?

Days in total ☐☐ • ☐

Days because of a urinary tract infection ☐☐ • ☐

Section 7: Income

24. Could you please provide an estimate of your annual household income from all sources (before tax and including your partner/spouse)? (*Please ✓ appropriate box.*)

Less that £6,000	☐
£6,000 to £10,000	☐
£10,001 to £15,000	☐
£15,001 to £20,000	☐
£20,001 to £25,000	☐
£25,001 to £30,000	☐
£30,001 to £35,000	☐
£35,001 and greater	☐

Section 8: Other Information

If you wish to provide any further information, please do so below.

Thank-you for taking the time to complete this questionnaire.

Australian and UK English TSQM, *version 1.4*
Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about how satisfied or dissatisfied you are with the medication you are taking in this clinical trial. We are interested in what you think about the effectiveness, side effects, and convenience experienced when using the medication over the last two to three weeks, or since you last used it. For each question, please place one tick next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Dissatisfied
☐$_4$ Somewhat Satisfied
☐$_5$ Satisfied
☐$_6$ Very Satisfied
☐$_7$ Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Dissatisfied
☐$_4$ Somewhat Satisfied
☐$_5$ Satisfied
☐$_6$ Very Satisfied
☐$_7$ Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Dissatisfied
☐$_4$ Somewhat Satisfied
☐$_5$ Satisfied
☐$_6$ Very Satisfied
☐$_7$ Extremely Satisfied

4. As a result of taking this medication, do you experience any (even slight) side effects?

☐$_1$ Yes
☐$_0$ No (if No, then please go to Question 9)

5. How much do the side effects of the medication you take to treat your condition bother you?

☐$_1$ Extremely
☐$_2$ Very much
☐$_3$ Somewhat
☐$_4$ A Little
☐$_5$ Not at All

6. To what extent do the side effects interfere with your physical health and ability to function (e.g., strength, energy levels, etc.)?

☐$_1$ A Great Deal
☐$_2$ Quite a Bit
☐$_3$ Somewhat
☐$_4$ A little Bit
☐$_5$ Not at All

7. To what extent do the side effects interfere with your mental function (e.g., ability to think clearly, stay awake, etc.)?

☐$_1$ A Great Deal
☐$_2$ Quite a Bit
☐$_3$ Somewhat
☐$_4$ Minimally
☐$_5$ Not at All

8. To what degree have medication side effects affected your overall satisfaction with the medication?

☐$_1$ A Great Deal
☐$_2$ Quite a Bit
☐$_3$ Somewhat
☐$_4$ Minimally
☐$_5$ Not at All

9. How easy or difficult is it to use the medication in its current form?

☐$_1$ Extremely Difficult
☐$_2$ Very Difficult
☐$_3$ Difficult
☐$_4$ Somewhat Easy
☐$_5$ Easy
☐$_6$ Very Easy
☐$_7$ Extremely Easy

10. How easy or difficult is it to plan when you will use the medication each time?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

11. How convenient or inconvenient is it to take the medication as instructed?

☐1 Extremely Inconvenient
☐2 Very Inconvenient
☐3 Inconvenient
☐4 Somewhat Convenient
☐5 Convenient
☐6 Very Convenient
☐7 Extremely Convenient

12. Overall, how confident are you that taking this medication is a good thing for you?

☐1 Not at All Confident
☐2 A Little Confident
☐3 Somewhat Confident
☐4 Very Confident
☐5 Extremely Confident

13. How certain are you that the good things about your medication outweigh the bad things?

☐1 Not at All Certain
☐2 A Little Certain
☐3 Somewhat Certain
☐4 Very Certain
☐5 Extremely Certain

14. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

Valuing the benefits of avoiding a urinary tract infection

Recurrent **Urinary Tract Infection (UTI)** is one of the most common side effects experienced by Clean Intermittent Self-Catheterisation users. Common symptoms associated with a UTI episode include things like pain (e.g in the genitals or lower abdomen), flu-like symptoms and fever among other things.

We are interested in your views about UTIs. We would like to know how valuable it would be to you to avoid having a UTI. We would also like to identify what issues surrounding UTIs are important to people who experience it.

The information you provide will be treated as **STRICTLY CONFIDENTIAL**. Your individual responses to the questionnaire will be anonymous as they will be grouped together with the responses provided by all the participants who complete the survey. No personally identifiable information about you will appear in any report or article based on the findings of this study.

If you have any questions regarding this questionnaire please contact:
Dr. Laura Ternent or Dr Yemi Oluboyede
Institute of Health & Society, Newcastle University, Newcastle NE24 AX
Telephone 0191 208 7083 or 0191 208 7349
Email laura.ternent@ncl.ac.uk or yemi.oluboyede@ncl.ac.uk

Please answer <u>all</u> the questions in <u>Section 1</u> and <u>Section 2</u> in this questionnaire.

Valuing the benefits of avoiding urinary tract infections

Section 1

An episode of **Urinary Tract Infection (UTI)** can affect people in different ways. In order for us to understand more about your UTI we would like you to think about the different aspects of your life that are typically affected when you have a UTI

Q1. From the list below choose those aspects that TYPICALLY AFFECT YOU when you have a UTI episode.

		(Please tick all that apply)
a	Pain /cramps	☐ 1
b	Feeling down	☐ 2
c	Discomfort	☐ 3
d	Feeling tired / lethargic	☐ 4
e	Difficulty doing activities of daily life	☐ 5
f	Negative effect on family life	☐ 6
g	Reduced ability to work	☐ 7
h	Difficulty doing social activities	☐ 8
i	Other symptoms or activities affected by UTI *(please, specify)*	……..…….. ……

Q2. Have you had a symptomatic UTI over the past year?

		(Please tick one box)
a	No	☐ 2
	Yes	☐ 1
b	If **Yes**, how many?	☐☐
c If **Yes**, how long did the most recent episode last (*including the time prior to taking antibiotics*)?		☐☐☐ days

There are various ways of asking about your views regarding the value you place on avoiding a UTI episode. One way is to ask what money value you would place on avoiding a UTI. The money value you put on avoiding a UTI is a good way to compare how important this issue is to you.

We would like to know the **maximum amount** you are willing to spend as a **one-off payment** to avoid one UTI over one year period. This information gives us a good indication of how much you value the affect that a UTI has on your life. This information also gives us an indication of the value that you place on avoiding a UTI compared with other things you might spent your money on.

You will not be asked to pay anything towards your health care; we simply want to know the value in money you place on avoiding UTIs.

Q3. We would like you to imagine a hypothetical scenario. Think about your last UTI episode, imagine you could have avoided having it. Would you be willing to pay a one-off sum of money to have avoided having this UTI episode?

	(Please tick one box)	
Yes	☐ 1	Go to Q.5
No	☐ 2	Go to Q.4

Q4. Please state the reasons you are not prepared to pay to avoid a UTI.
(Please continue to question 7)

……..……..……

……

…….

…….

Q.5 We would like to know the maximum amount you are willing to spend as a one-off payment to avoid having this UTI episode over a one year period. For each of the amounts stated below, please tick if you are sure you would be willing to pay the amount stated to avoid having this UTI. Stop ticking when you have reached your maximum willingness to pay.
(For example if you were willing to pay up to £70 you would tick £5, £10, £20, £40, £50, and £70)

Amount	I would **definitely** be prepared to pay the amount	
£5	☐	Go to Q.6
£10	☐	
£20	☐	
£40	☐	
£50	☐	
£70	☐	
£90	☐	
£100	☐	
£200	☐	
£300	☐	
£400	☐	
£500	☐	
More than £500	☐	Go to Q.6

Q6. Referring back to your answer in Q5, please state the maximum one-off amount you would be willing to pay to avoid <u>one</u> episode of UTI over a one year period below.
(For example if you stop ticking at £70 write the maximum amount you are willing to pay below as this can range between £70 and £90)

Maximum you are willing to pay **£** | | | | | |

On the following scale of 1 to 5, please state how difficult or easy it was to provide the value above (the maximum one-off amount you would be willing to pay).

Please circle one number only

Extremely Easy				Extremely Difficult
1	2	3	4	5

Q7. When answering how much you were willing to pay to avoid a UTI episode what was/were the most important factors you were considering when thinking of your maximum willingness to pay?

		(Please tick <u>all</u> boxes that apply)
a	Personal income/savings	☐1
b	Other financial commitments	☐2
c	Impact of UTI on family life	☐3
d	Impact of UTI on ability to work	☐4
e	Other *(please, specify)*	……..…….……

Q8. What is the highest level of education you and your partner (if applicable) have completed?

	*(Please tick **one** box)*	
	a Yourself	**b Your partner**
Post-graduate	☐1	☐1
Degree/professional/vocational (e.g. NVQ level 4)	☐2	☐2
Higher/A level/National grade/vocational (e.g. HND)	☐3	☐3
O Level/O Grade/GCSE/Standard Grade/vocational (e.g. HNC)	☐4	☐4
No educational qualification	☐5	☐5
Other (*please, specify*)	…….. 6	…….. 6

Q9. Please select the category that best describes your current employment status

	*(Please tick **one** box)*	
	a Yourself	**b Your partner**
In full or part time employment / Maternity leave	☐1	☐1
Unemployed	☐2	☐2
Long term sick or disabled	☐3	☐3
Full / part time study	☐4	☐4
Retired from paid work altogether	☐5	☐5
Other (please, specify)	…….. 6	…….. 6

Q10. How would you describe your ethnic origin?

	*(Please tick **one** box)*
White	☐1
Asian (of Indian, Pakistani, Bangladeshi ancestry)	☐2
Other Asian	☐3
Black or Afro-Caribbean (of African or Caribbean ancestry)	☐4
Other (please, specify)	…….5

Q11: Overall, how would you rate your health during the past 12 months?

	*(Please tick **one** box)*
Excellent	☐1
Good	☐2
Fair	☐3
Poor	☐4
Very Poor	☐5

Q12: Could you please tell us how much do you earn compared to the national average estimates?

The average annual income (from all sources) for <u>one individual</u> in the UK is around £25,000 (pre-tax 2014-15). ***Taking into account all sources of income (including benefits) where would you say you fall in relation to the UK average?***	*(Please tick **one** box)*
Below average	☐1
Average	☐2
Above average	☐3

Q13: Do you have access to private health insurance?

	*(Please tick **one** box)*
No	☐2
Yes	☐1

Q14. Are there any comments that you would like to make about how a UTI episode affects you?

……

……

……

……

Section 2

An episode of Urinary Tract Infection (UTI) can affect people in different ways. We would like to understand more about the different aspects of your life that are affected when you have a UTI. The next question is divided into three parts:

- In **Part 1** we would like you to select up to five areas of your life affected when you have a UTI. There is an extra category provided indicating all the other areas of your life affected by a UTI episode.

- In **Part 2** we would like you to score all six of the items listed in Part 1 on a scale of 0 (the worst you could imagine) to 10 (exactly as you would like to be).

- In **Part 3** you can spend 10 imaginary points to improve the six aspects listed in Part 1. You can spend more points improving areas that are important to you and to spend less or nothing on areas of less importance.

Please read through the example on the next page then complete all three parts of Question 15

**********THIS IS AN ILLUSTRATIVE MADE-UP EXAMPLE**********

Part 1: List Areas	Part 2: Scoring each area	Part 3: Spending points
Identify FIVE areas of your life affected by your condition in the boxes below. Some examples are shown below: **Pain; Social activities; Feeling depressed/anxious; Relationships**	Please score each area out of 10 using this scale: 10 Exactly as you would like to be 9 Close to how you would like to be 8 Very good but not how you would like to be 7 Good, but not how you would like to be 6 Between good and fair 5 Fair 4 Between poor and fair 3 Poor but not the worst you could imagine 2 Very poor but not the worst you could imagine 1 Close to the worst you could imagine 0 The worst you could imagine	We want you to imagine that any or all the areas of your life could be improved. You have 10 imaginary points to spend to show which areas you would most like to see improve. Spend more points on areas you would most like to see improve and less on areas that are not so important. You don't have to spend points in every area. You can't spend more than 10 points in total.

School	10/10	0
Vision	0/10	7
Speech	4/10	1
Sports	5/10	1
Self-confidence	9/10	0
	PLEASE USE THE LAST BOX TO SCORE ALL AREAS OF YOUR LIFE AFFECTED	
ALL OTHER AREAS OF YOUR LIFE AFFECTED BY YOUR UTI	9/10	1

Remember total must add up to 10

Q15. Please complete Part 1, Part 2 & Part 3 in the grid below to tell us how your life is currently affected by a UTI episode and its treatment and how you would like to see it improve

Part 1: List Areas	Part 2: Scoring each area	Part 3: Spending points
We would like you to think of the most important areas of your life affected when you have a UTI. Please write up to FIVE areas in the boxes below. Some examples are shown below: **Pain; Social activities; Feeling depressed/anxious; Relationships**	We would like you to score the areas you mentioned in Part 1. This score should show how badly you were affected by your last UTI episode. Please score each area out of 10 using this scale: 10 Exactly as you would like to be 9 Close to how you would like to be 8 Very good but not how you would like to be 7 Good, but not how you would like to be 6 Between good and fair 5 Fair 4 Between poor and fair 3 Poor but not the worst you could imagine 2 Very poor but not the worst you could imagine 1 Close to the worst you could imagine 0 The worst you could imagine	We want you to imagine that any or all the areas of your life could be improved. You have 10 imaginary points to spend to show which areas you would most like to see improve. Spend more points on areas you would most like to see improve and less on areas that are not so important. You don't have to spend points in every area. You can't spend more than 10 points in total.
	PLEASE USE THE LAST BOX TO SCORE ALL AREAS OF YOUR LIFE AFFECTED	
ALL OTHER AREAS OF YOUR LIFE AFFECTED BY YOUR UTI		

Remember total must add up to 10

Q16. Are there any comments that you would like to make regarding the questionnaire?

……

……

……

……

……

Thank you for taking time to complete this questionnaire.

Please post it back to us in the enclosed pre-paid envelope.

Appendix 4

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities

involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition

to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.