# Continuous low-dose antibiotic prophylaxis to prevent urinary tract infection in adults who perform clean intermittent self-catheterisation: the AnTIC RCT

Robert Pickard,[1*†] Thomas Chadwick,[2] Yemi Oluboyede,[2] Catherine Brennand,[3] Alexander von Wilamowitz-Moellendorff,[3] Doreen McClurg,[4] Jennifer Wilkinson,[3] Laura Ternent,[2] Holly Fisher,[2] Katherine Walton,[5] Elaine McColl,[2] Luke Vale,[2] Ruth Wood,[3] Mohamed Abdel-Fattah,[6] Paul Hilton,[7] Mandy Fader,[8] Simon Harrison,[9] James Larcombe,[10] Paul Little,[11] Anthony Timoney,[12] James N'Dow,[6] Heather Armstrong,[13] Nicola Morris,[12] Kerry Walker[4] and Nikesh Thiruchelvam[14]

[1]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK
[2]Institute of Health and Society, Newcastle University, Newcastle upon Tyne, UK
[3]Newcastle Clinical Trials Unit, Newcastle University, Newcastle upon Tyne, UK
[4]Nursing, Midwifery and Allied Health Professions Research Unit, Glasgow Caledonian University, Glasgow, UK
[5]Department of Microbiology, Newcastle upon Tyne Hospitals NHS Foundation Trust, Freeman Hospital, Newcastle upon Tyne, UK
[6]Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, UK
[7]Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK
[8]Health Sciences, University of Southampton, Southampton, UK
[9]Department of Urology, Mid-Yorkshire Hospitals NHS Trust, Pinderfields Hospital, Wakefield, UK
[10]Skerne Medical Centre, Sedgefield, UK
[11]Primary Care and Population Sciences, University of Southampton, Southampton, UK
[12]Bristol Urological Institute, North Bristol NHS Trust, Bristol, UK
[13]Patient representative, no affiliation
[14]Department of Urology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

*Corresponding author robert.pickard@newcastle.ac.uk
†Chief investigator

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# Scientific summary

## The AnTIC RCT

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# Scientific summary

## Background

Clean intermittent self-catheterisation (CISC) is an important management option for people who cannot empty their bladder naturally due to bladder outlet obstruction or the failure of bladder muscle contraction, often associated with neurological disease. Recurrent urinary tract infection (UTI) is common among CISC users, affecting 12–88% of patients.

This trial was motivated by the need to determine whether or not the possible benefit of continuous, once-daily low-dose antibiotic (prophylaxis) for recurrent UTI seen in small trials in specific groups could be applied to the wider population of adult CISC users. Any benefit must be worthwhile to patients and society in terms of financial costs and harms, including the emergence of antimicrobial resistance.

## Objectives

The hypothesis addressed is that an experimental strategy of once-daily low-dose antibiotic prophylaxis will reduce the rate of symptomatic antibiotic-treated UTI by ≥ 20% compared with a control strategy of no prophylaxis over a 12-month trial period. To investigate this hypothesis, the following objectives were set.

### *Primary objectives*

- Determine the impact of prophylaxis on incidence of symptomatic antibiotic-treated UTI.
- Determine the incremental cost per symptomatic UTI avoided.

### *Secondary objectives*

- Determine the effect of prophylaxis on incidence of microbiologically confirmed UTI.
- Determine the rates of fever and hospitalisation because of UTI.
- Determine the rates of asymptomatic bacteriuria.
- Record adverse events (AEs) related to use of prophylactic and treatment antibiotics.
- Assess change in resistance of pathogens isolated from urine and from perianal swabs.
- Measure overall satisfaction with prophylactic antibiotic treatment.
- Determine the relative effect on health status.
- Measure the incremental cost per quality-adjusted life-year (QALY) gained.
- Assess participants' willingness to pay (WTP) to avoid a UTI.
- Qualitatively assess the experience and impact of using CISC and suffering recurrent UTI, exploring health beliefs concerning trial interventions, antibiotic use and antimicrobial resistance.

## Methods

### *Design*

An open-label, patient-randomised, parallel-group superiority trial comparing an experimental strategy of once-daily low-dose antibiotic prophylaxis using 50 mg of nitrofurantoin, 100 mg of trimethoprim (Kent Pharmaceuticals, Ashford, UK) or 250 mg of cefalexin (Sandoz Ltd, Holzkirchen, Germany) with a control strategy of no prophylaxis in adults using CISC who suffer recurrent UTI over 12 months. A centralised randomisation system using random block allocation set by an independent statistician allocated

participants to each group. Central trials office and laboratory staff assessed outcomes without knowledge of participants' allocated group.

### Setting and participants

The trial was set in the UK, recruiting participants from primary, community and secondary care NHS organisations.

### Inclusion criteria

- Adult aged ≥ 18 years.
- Established user of CISC who was predicted to continue using it for ≥ 12 months.
- Able to give informed consent for participation in the trial.
- Able and willing to adhere to a 12-month follow-up period.
- Had suffered either at least two episodes of UTI related to CISC in the previous 12 months or at least one episode of UTI requiring hospitalisation. Or, for those already using prophylaxis, the completion of a 3-month washout period without prophylaxis.
- Able to take a once-daily oral dose of at least one of 50 mg of nitrofurantoin, 100 mg of trimethoprim or 250 mg of cefalexin.

Patients were excluded if they were taking prophylactic antibiotic against UTI and declining the 3-month washout period. Women who were pregnant or breastfeeding, or who intended to become pregnant during the trial period, and people unable to give informed consent were excluded.

### Measurement of clinical outcomes

#### Primary

Occurrence of clinical UTI was defined as the presence of symptoms together with taking a treatment course of antibiotic for UTI. This was measured by participant return of a UTI record for each event, as well as a 3-monthly participant questionnaire and a 3-monthly trial visit case report form (CRF) completed by the local research team. At the end of the trial, these records were reviewed by two members of the central trial team and the primary outcome adjudicated in accordance with a written protocol to avoid double-counting of episodes. Any disagreement or uncertainty was arbitrated by a third member of the central trial team, who also checked 10% of episodes. All outcome assessors were unaware of allocated group.

#### Secondary

Microbiologically proven UTI was defined as the confirmed report of symptomatic antibiotic-treated UTI (primary outcome) together with a positive urine culture. In addition, a fever of > 38 °C and hospitalisation for UTI were recorded. We defined a positive culture as the presence of one or two isolates at $\geq 10 \times 10^4$ colony-forming units/ml. Asymptomatic bacteriuria was defined as a positive culture from urine specimens submitted at baseline and 3, 6, 9 and 12 months in the absence of clinical UTI.

Adverse reactions related to prophylaxis and the treatment antibiotic were recorded by a participant-completed UTI record and a 3-monthly participant questionnaire, in addition to a 3-monthly visit CRF and health record review completed by local research staff. AEs were collected by 3-monthly health record review and those deemed serious (serious adverse events) were sent urgently to the central trial office by fax transmission.

Bacterial ecological change was assessed by comparing resistance patterns of pathogens isolated from urine specimens sent to the central laboratory by participants at the time of UTI with pathogens isolated during asymptomatic periods at the time of 3-monthly review visits. Changes to *Escherichia coli* colonising the faecal microbiome were assessed by culture of perianal swabs taken at baseline and 6- and 12-month trial visits.

Satisfaction with prophylactic antibiotic treatment was measured by participant completion of the Treatment Satisfaction Questionnaire for Medication (TSQM) at 12 months encompassing domains for effectiveness, side effects and convenience.

Health status over 12 months was assessed by participant completion of the Short Form questionnaire-36 items version 2 (SF-36v2) at baseline and 6 and 12 months. The analysis focused on the mental component summary (MCS) score and the physical component summary (PCS) score. Participants were also asked to complete and return the SF-36v2 at the time of symptomatic UTI as part of the UTI questionnaire. Data from complete SF-36v2 were also used to generate utility values and QALYs for the cost–utility analysis.

Participant attitudes towards use of antibiotic prophylaxis were assessed by an exploratory case-based study with thematic analysis of semistructured interviews.

### *Measurement of health economic outcomes*

#### Primary

Incremental cost per symptomatic UTI avoided was calculated from collected costs associated with prophylaxis and no prophylaxis strategies. Health-care costs were assessed by a participant-completed health resource utilisation questionnaire at 6 and 12 months and 3-monthly record review. Monetary costs of these events were derived from standard UK sources. For patient costs, participants completed a time and travel questionnaire at 12 months.

#### Secondary

Cost–utility analysis was based on estimated QALYs from responses to the SF-36v2, including at the time of symptomatic UTI. Participants' WTP to avoid a UTI was assessed by a completion of a bespoke contingent valuation questionnaire after the 12-month trial period.

### *Statistical analysis*

It was assumed that an overall 20% reduction in symptomatic UTI rate from an average of three episodes to 2.4 episodes over 12 months was the minimum clinically important difference. Using the Poisson rate test, completion of the trial by 158 participants in each group, 316 participants in total, would give 90% power to detect this difference at the 5% level. A total of 372 participants would allow for a 15% attrition rate. This gave 92% power to detect a 25% difference in the high-frequency subgroup (from four to three episodes per year) and 99% power for a 50% reduction in the low-frequency subgroup (from two to one episodes per year). All statistical analyses were carried out on a modified intention-to-treat basis, retaining participants in their allocated groups and including all participants in the primary outcome analysis for whom $\geq 6$ months of continuous follow-up data had been collected.

The relative rate of symptomatic antibiotic-treated UTI was defined as the incident rate ratio (IRR), calculated by dividing the UTI rate in the prophylaxis group by that found in the no-prophylaxis group, allowing for different durations of follow-up. Analysis of the primary outcome measure was performed as a univariate approach using the Poisson rate test and a Poisson regression modelling approach allowing for days not at risk while taking treatment courses of antibiotics. Regression modelling was used to detect effects of covariates including stratification factors and other baseline variables suggested to increase risk of UTI. The univariate analysis was considered to be the primary analysis for reporting.

For TSQM scores, the two-sample *t*-test was used as a simple univariate analysis. Chi-squared test and tests for trend were used for analysis of resistance patterns. For univariate analysis of the MCS and PCS components of the SF-36v2, the simple '*t*'-test was used. For adjusted analyses of the TSQM scores and the components of the SF-36v2, a linear regression/analysis of covariance was performed with the same covariates used in the primary outcome analysis.

### Health economic analysis

Cost-effectiveness was measured by summing treatment and participant costs and taking an average across participants in each trial group. The number of UTIs was derived from primary outcome data. The incremental cost-effectiveness ratio was then calculated by dividing the difference in costs by the difference in the number of UTIs for each group.

From participant responses to the SF-36v2 completed at 6 and 12 months and at the time of symptomatic UTI, health state utilities were estimated using an established algorithm applied to the Short Form questionnaire-6 Dimensions. QALYs were then derived using an area-under-the-curve approach. The difference in mean QALYs between groups was calculated. Costs were summed from trial and NHS sources and means calculated for each group. Cost utility was expressed as the incremental cost per QALY gained.

Data from the contingent valuation questionnaire were incorporated into the economic evaluation using a cost–benefit analysis framework.

### Qualitative analysis

Those participants who consented to being approached by a qualitative researcher were purposively sampled to ensure that interviews were conducted with both men and women of various ages in each trial group, geographically spread across seven sites. Semistructured interviews were conducted using a topic guide for consistency, while also allowing participants to raise any other relevant issues. The researcher carried out all interviews by telephone from a private room with audio-recording. Interviews were transcribed, checked for accuracy and manually coded. Data were then subjected to thematic analysis to generate categories and themes appropriate to the quantitative research questions.

## Results

We identified 1743 patients, of whom 404 were randomised. Trial participants were recruited from clinics in secondary care ($n = 340$; 84%), primary care ($n = 50$; 12%) and community NHS services ($n = 14$; 4%) over a 26-month period (25 November 2013 to 29 January 2016). A total of 332 (82%) participants completed the 12-month trial of allocated intervention and follow-up, with an additional 29 participants having $\geq 6$ months of follow-up data, which were required for inclusion in the primary analysis. Thus, 361 (89%) of the randomised participants were included in the primary analysis.

Participants allocated to prophylaxis ($n = 203$) were well matched at baseline to those in the no-prophylaxis group ($n = 201$) with regard to demographics, cause of bladder dysfunction, regimen of CISC use, previous frequency of UTI and presence of risk factors for UTI. The number of participants with asymptomatic bacteriuria in each group at baseline was comparable [prophylaxis, $n = 76$ (37%); no prophylaxis, $n = 77$ (38%)].

In univariate analysis, the IRR for symptomatic antibiotic-treated UTI over 12 months in the prophylaxis group relative to no prophylaxis was 0.52 [95% confidence interval (CI) 0.44 to 0.61]. Reduction in frequency of microbiologically proven UTI was similar (IRR 0.49, 95% CI 0.39 to 0.60). The absolute reduction in UTI episodes over 12 months was 50% from a median (interquartile range) of 2 (1–4) in the no-prophylaxis group to 1 (0–2) in the prophylaxis group. These results were unchanged in the Poisson regression model including days at risk of UTI, prior frequency of UTI and other possible confounders. There was no clinically significant difference in measured health status between the two groups over 12 months and no difference in utility value at the time of UTI. Pathogens, predominantly *E. coli* (58%), isolated from 3-monthly urine specimens submitted by the prophylaxis group were more likely to have a higher frequency of resistance to trimethoprim ($p < 0.001$), co-trimoxazole ($p = 0.002$) and nitrofurantoin ($p = 0.038$) at 12 months than isolates from the no-prophylaxis group. We found significant trends over 12 months in increased resistance of pathogens isolated from urine specimens provided by the prophylaxis

group to amoxicillin ($p = 0.004$), cefalexin ($p = 0.005$), trimethoprim ($p = 0.016$) and co-trimoxazole ($p = 0.006$). No such trends were seen in the no-prophylaxis group.

The incremental cost of use of prophylaxis to avoid UTI over 12 months was £99 per UTI. The incremental cost per QALY over 12 months was £12,452. Participants in the prophylaxis group were willing to pay approximately £50 more than those in the no-prophylaxis group to avoid one episode of UTI over 12 months in the contingent valuation exercise.

Qualitative findings were that the emotional and practical burden of CISC and UTI in participants' lives was considerable and influenced their perception of well-being. Psychological adjustment to CISC and UTI was complex, characterised by cognitive, attitudinal and situational factors. Generally, participants had an unconcerned attitude about using antibiotics for UTI. A minority felt concerned that prophylaxis would reduce future effectiveness by inducing antimicrobial resistance. These attitudes affected behaviour towards using prophylaxis, which was also influenced by clinician recommendation. Finally, adhering to the trial schedule was deemed straightforward, and those allocated to the prophylaxis group exploited habitual tendencies to incorporate it into their lives.

## Conclusions

This trial, designed and conducted in accordance with best practice, provides robust evidence that taking a once-daily low-dose antibiotic chosen from a restricted range of agents results in a substantial reduction in UTI frequency. The result was unchanged by inclusion of possible confounders in the analysis and use of alternative definitions for UTI. The representative sample of adult CISC users enrolled in the trial and the lack of effect of inclusion of patient subgroups as exploratory covariates in the primary outcome model suggests generalisability to the overall population of CISC users. The intervention was well tolerated, with few participants suffering overt harm. The benefit offered appears affordable to patients and the NHS. The increase in antimicrobial resistance of pathogens causing UTI to commonly used antibiotics may reduce the long-term efficacy of prophylaxis in individuals continuing to perform CISC and is also a major public health concern.

## Recommendations for research

In priority order:

1. longer-term studies of the emergence of antimicrobial resistance
2. studies of clinical effectiveness and cost-effectiveness of non-antibiotic strategies to prevent UTI
3. patient and bacterial phenotypic and genotypic studies to identify groups that benefit most from prophylaxis and pathogens most likely to develop antimicrobial resistance.

## Trial registration

This trial is registered as ISRCTN67145101 and EudraCT 2013-002556-32.

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