BMJ Open

Cost-effectiveness of methenamine hippurate compared with antibiotic prophylaxis for the management of recurrent urinary tract infections in secondary care: a multicentre, open-label, randomised, non-inferiority trial

William King ,[1] Tara Homer ,[1] Chris Harding,[2] Helen Mossop,[3] Thomas Chadwick,[3] Alaa Abouhajar,[4] Luke Vale[1]

To cite: King W, Homer T, Harding C, *et al*. Cost-effectiveness of methenamine hippurate compared with antibiotic prophylaxis for the management of recurrent urinary tract infections in secondary care: a multicentre, open-label, randomised, non-inferiority trial. *BMJ Open* 2024;**14**:e074445. doi:10.1136/bmjopen-2023-074445

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2023-074445).

Received 08 August 2023
Accepted 05 April 2024

Check for updates

© Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to
Dr Tara Homer;
tara.homer@newcastle.ac.uk

ABSTRACT

Objectives To estimate the cost-effectiveness of methenamine hippurate compared with antibiotic prophylaxis in the management of recurrent urinary tract infections.

Design Multicentre, open-label, randomised, non-inferiority trial.

Setting Eight centres in the UK, recruiting from June 2016 to June 2018.

Participants Women aged ≥18 years with recurrent urinary tract infections, requiring prophylactic treatment.

Interventions Women were randomised to receive once-daily antibiotic prophylaxis or twice-daily methenamine hippurate for 12 months. Treatment allocation was not masked and crossover between arms was allowed.

Primary and secondary outcome measures The primary economic outcome was the incremental cost per quality-adjusted life year (QALY) gained at 18 months. All costs were collected from a UK National Health Service perspective. QALYs were estimated based on responses to the EQ-5D-5L administered at baseline, 3, 6, 9, 12 and 18 months. Incremental costs and QALYs were estimated using an adjusted analysis which controlled for observed and unobserved characteristics. Stochastic sensitivity analysis was used to illustrate uncertainty on a cost-effectiveness plane and a cost-effectiveness acceptability curve. A sensitivity analysis, not specified in the protocol, considered the costs associated with antibiotic resistance.

Results Data on 205 participants were included in the economic analysis. On average, methenamine hippurate was less costly (−£40; 95% CI: −684 to 603) and more effective (0.014 QALYs; 95% CI: −0.05 to 0.07) than antibiotic prophylaxis. Over the range of values considered for an additional QALY, the probability of methenamine hippurate being considered cost-effective ranged from 51% to 67%.

Conclusions On average, methenamine hippurate was less costly and more effective than antibiotic prophylaxis but these results are subject to uncertainty. Methenamine hippurate is more likely to be considered cost-effective when the benefits of reduced antibiotic use were included in the analysis.

Trial registration number ISRCTN70219762.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Data used were collected and analysed following a prespecified health economics analysis plan, which followed best practice methods. These data were collected as part of the study and thus ensure robust and generalisable results.

⇒ This study employed techniques for handling missing data, allowing us to maximise the richness of the available data used in the analysis. Sensitivity analyses were also used to test the robustness of these results.

⇒ The inclusion of the economic cost of antimicrobial resistance as a sensitivity analysis is a key strength of this paper.

⇒ Participant overburden contributed to progressive loss to response rates, particularly to the participant self-reported cost questionnaires, which limited the quantity of complete data available.

INTRODUCTION

Urinary tract infections (UTIs) are common in adult women with up to 50% experiencing at least a single episode during their lifetime.[1–3] Of women who experience a UTI, 20%–30% of episodes will become recurrent urinary tract infections (rUTIs).[2 4] UTIs have a high economic burden, affect quality of life and lead to time off work and usual activities.[5] Additionally, the burden of UTIs is likely to increase due to antibiotic resistance.[6] The burden of UTIs has been shown to be an international problem and there is emerging evidence of a globally rising trend in the burden of UTIs.[7 8] Identifying a cost-effective

management strategy for rUTIs is vital. Current international guidelines recommend low-dose antimicrobial therapy in the prevention of rUTIs which has been shown to reduce the recurrence rate by up to 80%.[3 9 10] Antibiotic prophylaxis has been shown to be both clinical effective and cost-effective in the management of rUTIs compared with no prophylaxis.[11]

However, the global progression of antimicrobial resistance (AMR) has led to calls for more judicious prescribing of antibiotic agents to halt the progression of AMR.[12 13] Consequently, alternatives to antimicrobial therapy in the prevention of rUTIs have been investigated and methenamine hippurate (an oral antiseptic) has shown promising effectiveness results.[14 15] Methenamine hippurate is a urinary antiseptic. The compound is metabolised to formaldehyde in the kidneys, and this has a bacteriostatic effect.[15] It can be used to treat or help to treat rUTI but there is limited information available on the cost-effectiveness of methenamine hippurate compared with antibiotic prophylaxis. To our knowledge, no study has determined the clinical-effectiveness and cost-effectiveness of methenamine hippurate in the management of rUTI.

The ALternatives To prophylactic Antibiotics for the treatment of Recurrent urinary tract infection in women (ALTAR) trial was a multicentre, pragmatic, open-label randomised non-inferiority trial evaluating the clinical-effectiveness and cost-effectiveness of the urinary antiseptic methenamine hippurate for the prevention of rUTI and comparing it to the current standard treatment of low-dose antibiotic prophylaxis.[16] This paper reports the results of the economic evaluation which was undertaken alongside the clinical trial. Trial clinical outcomes are presented elsewhere.[17]

METHODS

Reporting for this trial follows the Consolidated Health Economic Evaluation Reporting Standards.[18] The ALTAR trial was conducted across eight sites in England and Scotland. A description of the trial design, inclusion criteria and clinical-effectiveness outcomes is presented elsewhere.[16 17] The analysis was prespecified and presented in a health economic analysis plan.[19] The perspective chosen for the economic analysis was the UK National Health Service and personal social services. Costs and effects that were incurred after 12 months were discounted at 3.5%.[20] Data analysis was conducted using both R and STATA software.[21 22]

Estimation of costs

Costs were based on the intervention medications, the use of healthcare services, medications used to manage UTIs and concomitant medications, and, in a sensitivity analysis, the cost of AMR was estimated.

Intervention medications varied depending on the treatment arm participants were randomised to. Participants randomised to the antibiotic prophylaxis arm received a once-daily low-dose antibiotic. Participants randomised to the methenamine hippurate arm received a twice-daily dose of methenamine hippurate. Both medications were prescribed for 12 months. Following this, data were still collected on participants for 6 months, until 18 months post-randomisation.

Healthcare service use was comprised of both primary and secondary care use. Primary care use included consultations with general practitioners (GPs) and nurses which could occur at a GP practice, at home, via telephone or out-of-hours. Secondary care use included accident and emergency attendances, outpatient visits, hospital admissions and telephone or out-of-hours consultations with a hospital doctor. These data were captured via a bespoke self-completed health utilisation questionnaire which was administered at baseline, 3, 6, 9, 12 and 18 months post-randomisation.

If a woman experienced a UTI during their 18-month follow-up they were prescribed a course of antibiotics, regardless of their randomised allocation. Information on the type and duration of antibiotics was captured in Case Report Forms (CRFs).[16] Information on the concomitant medications taken by participants was collected in a separate concomitant medications CRF. For all medications, where dosage and frequency data were incomplete, assumptions were informed using the British National Formulary prescribing guidelines.[23]

Unit costs for medications and healthcare services were obtained from routine sources.[24–26] Unit costs are presented in online supplemental table 1 and all costs are in 2019 Great British pounds.

Estimation of total healthcare resource use cost per participant was conducted by multiplying the frequency of resource use by the corresponding unit cost and summing across all healthcare resources used. Similarly, the total medication cost per participant, which included the intervention medications, medications to treat a UTI and concomitant medications, was estimated by combining the frequency and dosage information from the CRF with the relevant cost. The total cost per participant was estimated by summing all healthcare resource use and medication costs over the 18-month trial duration. An average total cost per randomised arm was calculated by combining the total cost per participant in each arm and dividing it by the number of participants in each arm with cost data. The difference in the average total cost between the treatment arms was estimated.

Estimation of effects

Effectiveness was measured using quality-adjusted life years (QALYs). QALYs were based on responses to the EQ-5D-5L collected at scheduled timepoints (baseline, 3, 6, 9, 12, 15 and 18 months post-randomisation) and when a UTI episode occurred. The EQ-5D-5L responses collected at unscheduled timepoints were incorporated in a sensitivity analysis which considered the quality of life decrement associated with UTIs. Utility scores were estimated by cross-walking responses to the EQ-5D-5L onto

the EQ-5D-3L value set.[27] In this framework, utility values with higher values correspond to better states of health. Utilities were estimated for each participant at each timepoint and these values were combined with time-weights, using the area under the curve method, to estimate QALYs.[28]

Dealing with missing data

Costs

Provided that participants had responded to at least one question, for a given health utilisation questionnaire, it was assumed for the missing questions that they did not use this resource and were assigned a cost of zero. This approach was chosen to maximise the data available due to the granularity of the data.

QALYs

It was anticipated that there would be incomplete responses to the EQ-5D-5L questionnaire given the frequency of data collection so again assumptions were made to maximise the data available. Methods used for handling missing utility data followed on from work by Shen *et al*.[29] Provided participants had at least 4 out of 7 responses to the EQ-5D-5L, including baseline, QALYs were estimated based on data available. Calculation of QALYs assumed that missing EQ-5D-5L data were missing-at-random (MAR). To validate the MAR assumption, t-tests were undertaken on baseline cost and utility data to identify whether there were any differences between those with complete data and those with missing data.

Cost-effectiveness analysis

Similar to the primary outcome the economic analysis was conducted using data from participants who satisfied the modified intention-to-treat criteria.[17] Average total costs and QALYs for each randomised arm were estimated. The incremental differences in costs and effects were estimated using a seemingly unrelated regression (SUR) model.[30] Additional variables included in the SUR model were baseline costs, baseline utility, baseline severity of disease (number of UTIs in previous 6 months) and menopausal status.

Based on the SUR results if one intervention was more costly and less effective than the comparator it was considered to be dominated. If an intervention was not dominated, then an incremental cost-effectiveness ratio (ICER) was estimated. The ICER is the difference in mean costs divided by the difference in mean effects and gives an estimate of the incremental cost per additional unit of effect.[31]

Sensitivity analysis

Stochastic sensitivity analyses using non-parametric bootstrapping were used to estimate the statistical imprecision surrounding the estimates of costs, effects and cost-effectiveness. Bootstrap replications of the ICER were presented on the cost-effectiveness plane.[32] Cost-effectiveness acceptability curves (CEACs) were also plotted to illustrate which treatment option maximised net benefits at a variety of values for an additional QALY. These values varied from £0 to £50 000 per QALY gained.[20]

Following on from work conducted by Pickard *et al*,[33] a sensitivity analysis which incorporated the cost of AMR was also undertaken.[33] An estimate of the annual cost of AMR for the UK population[34] was inflated to price year 2019 and combined with the total number of antibiotics prescribed in the UK[35] to identify an AMR cost per prescription (£20bn/27m=£741). A mean AMR cost per participant was estimated by combining the number of antibiotic prescriptions a participant received and the AMR cost per prescription. We conservatively assumed that participants in the antibiotic prophylaxis arm incurred this AMR cost once due to their intervention medication and then each time antibiotics were prescribed for a UTI episode. Participants in the methenamine hippurate arm only incurred the cost of AMR when antibiotics were prescribed during a UTI episode.

Patient and public involvement

Patient representatives were involved in the initial planning stages of this study including defining the primary outcome. Patient representatives were invited to join the Trial Steering Committee and were involved with the interpretation of the findings of this research.

RESULTS

Data on 205 participants (antibiotic prophylaxis (N=102), methenamine hippurate (N=103)) were used in the economic analysis. As to be expected with self-completed questionnaires the was a progressive reduction in response rates to both the health utilisation questionnaire and the EQ-5D-5L questionnaire.

Missing data were assumed to be MAR as there was no evidence of a difference in baseline costs (£16; 95% CI: -£200 to £232) or baseline utility (0.03; 95% CI: −0.05 to 0.11) between those with complete data and those with missing data.

Resource use and costs

Table 1 presents the average total costs for each healthcare resource by randomised arm. On average, participants reported higher costs in the methenamine hippurate arm compared with those in the antibiotic prophylaxis arm. The difference in average total costs between arms was due to intervention medication costs. The daily cost associated with methenamine hippurate was higher than the daily costs associated with taking a prophylactic antibiotic.

Effectiveness outcomes

Table 2 presents the average utility values at each scheduled timepoint and the average total QALYs per randomised arm. On average, participants randomised to antibiotic prophylaxis reported higher utilities and QALYs than those randomised to methenamine hippurate.

Incremental cost-effectiveness

Table 3 presents the incremental cost-effectiveness results over the 18-month follow-up. Total average cost and

Table 1 Average total costs (£) per randomised arm

	Antibiotic prophylaxis (N=89)		Methenamine hippurate (N=94)	
Healthcare costs	n	Mean (SD)	n	Mean (SD)
Intervention costs	89	89 (76)	94	188 (67)
Concomitant medication costs	89	2 (8)	94	1 (7)
Antibiotic costs (due to UTI)	89	4 (5)	94	8 (28)
Primary care costs	89	201 (265)	94	236 (236)
Secondary care costs	89	636 (1814)	94	580 (876)
Average total NHS costs per participant	89	931 (2015)	94	1013 (1024)

NHS, National Health Service; UTI, urinary tract infection.

utility data were available for 129 participants (antibiotic prophylaxis (N=58), methenamine hippurate (N=71)). For the incremental adjusted analysis data were available on 121 participants (antibiotic prophylaxis (N=57), methenamine hippurate (N=64)). Based on the unadjusted average total costs and QALYs presented in table 3 for each randomised arm, methenamine hippurate was, on average, more costly and less effective when compared with antibiotic prophylaxis. However, in the adjusted analysis which estimated the incremental results, methenamine hippurate was, on average, less costly and more effective in terms of QALYs gained. Therefore, methenamine hippurate was dominant in the adjusted analysis.

The uncertainty in the cost-effectiveness results is illustrated in figures 1 and 2. Figure 1 illustrates the results of the 1000 bootstrap iterations and illustrates the uncertainty around the incremental costs and effects estimated using the SUR. The iterations are spread across all four quadrants which suggests that the incremental results are highly uncertain.

Figure 2 illustrates the probability of methenamine hippurate being considered cost-effective over different willingness to pay thresholds for an additional QALY. If we were not willing to pay for an additional QALY methenamine hippurate had a 51% probability of being considered cost-effective. This probability increased as the value placed on an additional QALYs increased but it never exceeded 67%.

Sensitivity analysis—the cost of AMR

Participants in the methenamine hippurate arm experienced, on average, more UTI episodes than those in the antibiotic prophylaxis arm (unadjusted absolute difference=0.49 (95% CI: 0.15 to 0.84)).[17] On average, the cost of AMR per participant was £1471 (95% CI: £1304 to £1637) for the antibiotic prophylaxis arm and £1111 (95% CI: £881 to £1348) for the methenamine hippurate arm. When the cost of AMR was incorporated into the analysis, methenamine hippurate was, on average, less costly and more effective than antibiotic prophylaxis. If we were not willing to pay for an additional QALY, methenamine hippurate had a 69% probability of being considered cost-effective. Over the range of threshold values considered for an additional QALY, the probability of methenamine hippurate being considered cost-effective never exceeded 76%. These results are presented in online supplemental table 2 and online supplemental figures 1 and 2.

DISCUSSION

On average, those randomised to the methenamine hippurate arm reported higher overall healthcare costs

Table 2 Mean utilities and QALYs per randomised arm

	Antibiotic prophylaxis (N=102)		Methenamine hippurate (N=103)	
	n	Mean (SD)	n	Mean (SD)
Baseline utility	95	0.813 (0.21)	98	0.750 (0.28)
3 months	76	0.792 (0.28)	76	0.765 (0.27)
6 months	64	0.783 (0.26)	76	0.791 (0.21)
9 months	66	0.780 (0.28)	76	0.768 (0.24)
12 months	66	0.764 (0.27)	73	0.743 (0.26)
15 months	60	0.783 (0.26)	69	0.739 (0.28)
18 months	59	0.795 (0.18)	67	0.746 (0.24)
QALYs* (18 months)	58	1.182 (0.35)	71	1.133 (0.34)

*QALYs were estimated for those who had utility data at baseline and at least three other timepoints.
QALYs, quality-adjusted life years.

Table 3 Cost-utility results

Strategy	Cost (£) (SD)	Incremental cost (£) (95% CI)*	QALYs (SD)	Incremental QALYs (95% CI)*	ICER
Antibiotic prophylaxis	931 (2015)		1.182 (0.35)		
Methenamine hippurate	1013 (1024)	−40 (−684 to 603)	1.133 (0.35)	0.014 (−0.05 to 0.07)	Dominant

*Incremental results based on adjusted analysis n=121 (antibiotic prophylaxis, n=57; methenamine hippurate, n=64).
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

than those randomised to the antibiotic prophylaxis arm. This difference in costs is largely attributable to the difference in intervention medication unit costs. The daily intervention medication cost of taking methenamine hippurate (£0.66) was higher than the average antibiotic prophylaxis cost (£0.22) and this difference (£0.44) was compounded daily over the 12-month treatment period (£160.60=£0.44*365). Otherwise, similar healthcare resources were reported in both of the randomised arms.

When considering the unadjusted analysis, methenamine hippurate had on average higher costs and lower QALYs than antibiotic prophylaxis. This meant that when estimating costs and utilities independently and not controlling for covariates, such as baseline utilities and costs, methenamine hippurate was dominated by antibiotic prophylaxis. However, when the difference in costs and QALYs was estimated using SUR, antibiotic prophylaxis was no longer the dominant strategy. In the adjusted analysis, methenamine hippurate had on average lower costs and higher QALYs than antibiotic prophylaxis. If we were not willing to pay for an additional QALY, methenamine hippurate had a 51% probability of being considered cost-effective. If society were willing to pay for an additional QALY then the probability that methenamine hippurate was cost-effective compared with antibiotic prophylaxis increased as the threshold value for an additional QALY increased. This change in conclusions could, in part, be explained by the higher average baseline utility values reported in the antibiotic prophylaxis arm (which were not statistically significant (difference in baseline utility 0.06; 95% CI: −0.13 to 0.01)). This difference in average baseline utility values likely due to sampling uncertainty highlights the importance of using adjusted models like SUR when using individual patient data.[36] Additionally, the change in our conclusions could be attributable to the decreased number of participants included in the adjusted analysis. There were fewer participants with complete data included in the adjusted analysis as the simultaneous estimation of costs and effects required that participants were not missing data in either the dependent variables (costs and QALYs) or the independent variables. Ultimately, the variation in our conclusions across each type of analysis highlights the imprecision in our estimates and the uncertainty in our conclusions. However, given the wide confidence intervals surrounding the difference in costs and effects, there does not appear to be strong economic evidence to support the adoption of one treatment over the other in the management of rUTIs in women. Therefore, other factors need to be considered such as women's preferences for each treatment and other clinical considerations such as antibiotic resistance. It is for this reason that we considered the cost associated with AMR in the economic analysis.

The inclusion of an AMR cost per prescription led to a relative increase in average total cost in both randomised arms however, it was greater in the antibiotic prophylaxis arm despite this arm reporting, on average, fewer UTI episodes. After the inclusion of the cost of AMR into the economic evaluation, our conclusions based on the adjusted analysis were unchanged with methenamine hippurate dominating antibiotic prophylaxis. A conservative assumption was made for the antibiotic prophylaxis arm by only assigning the AMR cost associated with randomised treatment once. It is likely that larger

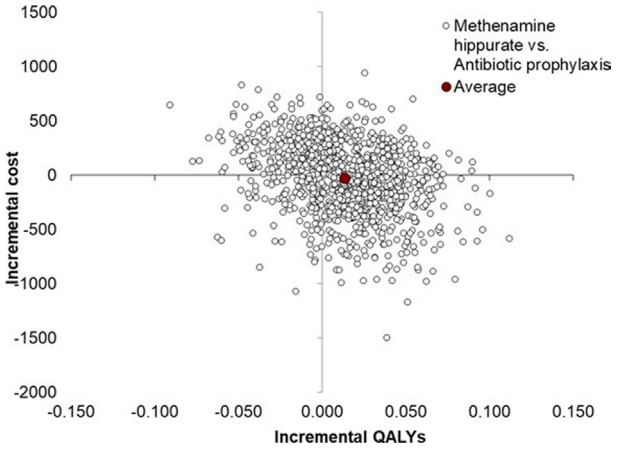

Figure 1 Cost-effectiveness plane. QALYs, quality-adjusted life years.

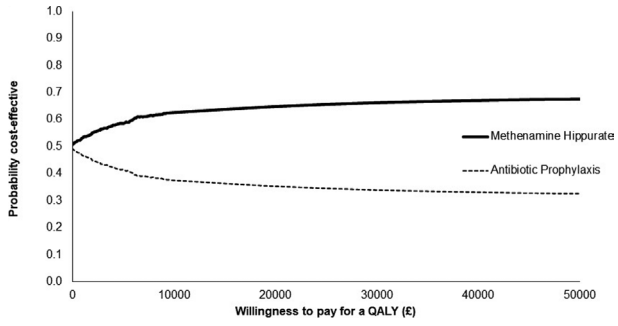

Figure 2 Cost-effectiveness acceptability curve. QALY, quality-adjusted life year.

differences in costs would be observed if other assumptions were made. The inclusion of AMR costs increases the level of confidence in our conclusions as the probability of methenamine hippurate being considered cost-effective increased to 76% at the current NICE willingness-to-pay threshold value,[20] although more robust estimates of the cost of AMR are needed.[37]

Although our study was conducted in a secondary care setting, there are other reports[38] describing research carried out in primary care that have also shown significant reductions in UTI frequency and antibiotic use. The definition of rUTI is now widely accepted (patients who experienced 3 UTIs in the preceding year) and this ensures comparable study populations irrespective of the trial setting. Other studies, currently in progress should confirm that the clinical results from our trial can be generalised across both primary and secondary care.[39]

The economic analysis had several strengths. We used missing data methods used previously by Shen *et al*,[29] which enabled us to maximise the quantity of data available to use in the analysis.[29] Additionally, another strength of the analysis was that the trial was pre-planned and the data used were collected as part of a randomised non-inferiority trial.[16]

The inclusion of the economic cost of AMR as a sensitivity analysis is another key strength of the analysis. Studies have shown that the economic cost of AMR is non-zero and failing to include this cost in evaluation can lead to misleading results.[16 37] In light of this, while the cost of AMR was not measured directly in the trial, information from secondary sources was used to incorporate the cost of AMR into the analysis.

However, the economic analysis is not without limitations. As mentioned in the results, the analysis was limited by a progressive loss in response rates to self-completed questionnaires. Although, we were able to overcome this through the use of missing data methods.[29] The reduction in response rates over time is consistent with other studies in this area with similar data collection timepoints.[11] Recommendations for future research in this area would be to consider the balance of reliable recall and participant burden, we would suggest 6-monthly recall for both cost and utility data. The AMR costs derived by Pickard *et al*[33] are subject to uncertainty, however, even though we made conservative assumptions, methenamine hippurate was the preferred management strategy when AMR costs were considered.[33]

CONCLUSION

In the primary economic analysis, there does not appear to be strong economic evidence to support the adoption of one treatment over the other in the management of rUTIs in women. However, when the costs of antibiotic resistance were considered, methenamine hippurate had a 76% probability of being considered cost-effective at a £20 000 cost per QALY threshold.

Take home message

There is no strong economic evidence to support the adoption of either methenamine hippurate or antibiotic prophylaxis in the management of rUITs. Other factors need to be considered when offering treatment to women, including the effect of AMR. When the economic cost of AMR was considered, methenamine hippurate was the preferred treatment option and had a 76% probability of being considered cost-effective if we were willing to pay £20 000 for an additional QALY.

Author affiliations
[1]Health Economics Group, Newcastle University Population Health Sciences Institute, Newcastle upon Tyne, UK
[2]Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[3]Newcastle University Population Health Sciences Institute, Newcastle upon Tyne, UK
[4]Newcastle Clinical Trials Unit, Newcastle University, Newcastle upon Tyne, UK

X Chris Harding @chrisharding123

Contributors CH, TC and LV designed the trial and provided intellectual input into the study protocol. WK conducted the main economic analysis under the supervision of TH and LV. WK and TH co-wrote the manuscript. CH was the chief investigator and guarantor. HM conducted the main statistical analysis under the supervision of CH. AA designed and set up databases and managed central data processes. All authors reviewed and commented on the manuscript before submission and gave approval to submit for publication.

Funding Funding was provided by the National Institute for Health Research Health Technology Assessment Programme, project number 13/88/21.

Competing interests CH reports personal fees from Astellas Pharma (Tokyo, Japan), Medtronic plc (Dublin, Ireland), Allergan Ltd (Dublin, Ireland), GlaxoSmithKline plc (Brentford, UK), Teleflex Medical Inc (Temecula, California, USA), Viatris (Canonsburg, Pennsylvania, USA) and grants from Medtronic plc, the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme (HTA 15/40/05) and The Urology Foundation (London, UK) outside the submitted work. LV reports being the co-ordinating editor of Cochrane Incontinence (from 2016) and being a member of NIHR HTA, Clinical Evaluation and Trials Panel from 2015 to 2018. TC reports grants from the NIHR HTA programme (HTA 16/154/01, HTA 15/130/94 and HTA 11/72/01) during the conduct of the study.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by NHS Research Ethics Service Committee North East Tyne and Wear South (reference 15/NE/0381). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data requests should be submitted to the chief investigator, CH (c.harding@nhs.net), for consideration. Access to de-identified data collected during the trial, alongside a data dictionary, may be granted to researchers upon approval of their study protocol and analysis plan, by a committee of the ALTAR team.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially,

and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
William King http://orcid.org/0000-0001-7040-9133
Tara Homer http://orcid.org/0000-0002-6664-0671

REFERENCES

1 Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. *Dis Mon* 2003;49:53–70.
2 Fu Z, Liska D, Talan D, *et al*. Cranberry reduces the risk of urinary tract infection recurrence in otherwise healthy women: a systematic review and meta-analysis. *J Nutr* 2017;147:2282–8.
3 European Association of Urology. *EAU guidelines – urological infections. EAU Annual Congress*. Amsterdam, the Netherlands, 2020.
4 Beerepoot MAJ, ter Riet G, Nys S, *et al*. Lactobacilli vs antibiotics to prevent urinary tract infections: a randomized, double-blind, Noninferiority trial in postmenopausal women. *Arch Intern Med* 2012;172:704–12.
5 Wagenlehner F, Wullt B, Ballarini S, *et al*. Social and economic burden of recurrent urinary tract infections and quality of life: a patient web-based study (GESPRIT). *Expert Rev Pharmacoecon Outcomes Res* 2018;18:107–17.
6 Medina M, Castillo-Pino E. An introduction to the epidemiology and burden of urinary tract infections. *Ther Adv Urol* 2019;11:1756287219832172.
7 François M, Hanslik T, Dervaux B, *et al*. The economic burden of urinary tract infections in women visiting general practices in France: a cross-sectional survey. *BMC Health Serv Res* 2016;16:365.
8 Zeng Z, Zhan J, Zhang K, *et al*. Global, regional, and national burden of urinary tract infections from 1990 to 2019: an analysis of the Global Burden of Disease Study 2019. *World J Urol* 2022;40:755–63.
9 National Institute for Health and Care Excellence (NICE). Urinary tract infection (lower) - women. 2020. Available: https://cks.nice.org.uk/topics/urinary-tract-infection-lower-women/
10 Scottish Intercollegiate Guideline Network (SIGN). Management of suspected bacterial urinary tract infection in adults. 2012.
11 Fisher H, Oluboyede Y, Chadwick T, *et al*. Continuous low-dose antibiotic prophylaxis for adults with repeated urinary tract infections (antic): a randomised, open-label trial. *Lancet Infect Dis* 2018;18:957–68.
12 Scottish Government. The Scottish management of antimicrobial resistance action plan [ScotMARAP]. 2008. Available: https://www.webarchive.org.uk/wayback/archive/20150220072927/http://www.gov.scot/Publications/2008/03/12153030/10
13 Department of Health. UK antimicrobial resistance strategy and action plan. 2000.
14 Barclay J, Veeratterapillay R, Harding C. Non-antibiotic options for recurrent urinary tract infections in women. *BMJ* 2017;359:j5193.
15 Lee BSB, Bhuta T, Simpson JM, *et al*. Methenamine hippurate for preventing urinary tract infections. *Cochrane Database Syst Rev* 2012;10:CD003265.
16 Forbes R, Ali A, Abouhajar A, *et al*. Alternatives to prophylactic antibiotics for the treatment of recurrent urinary tract infection in women (ALTAR): study protocol for a Multicentre, pragmatic, patient-randomised, non-inferiority trial. *Trials* 2018;19:616.
17 Harding C, Mossop H, Homer T, *et al*. Alternative to prophylactic antibiotics for the treatment of recurrent urinary tract infections in women: multicentre, open label, randomised, non-inferiority trial. *BMJ* 2022;376:e068229.
18 Husereau D, Drummond M, Augustovski F, *et al*. Consolidated health economic evaluation reporting standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. *Int J Technol Assess Health Care* 2022;38:e13.
19 King W, Homer T, Vale L. Alternative to prophylactic antibiotics for the treatment of recurrent urinary tract infections in women (ALTAR) - health economics analysis plan. 2020. Available: https://fundingawards.nihr.ac.uk/award/13/88/21
20 National Institute for Clinical Excellence (NICE). *Guide to the methods of technology appraisal*. London: National Institute for Health and Care Excellence, 2013.
21 StataCorp. *Stata statistical software: release 15*. College Station, TX: StataCorp LP, 2017.
22 R Development Core Team. *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing, 2010.
23 Joint Formulary Committee. *British national formulary (Online*). London: BMJ Group and Pharmaceutical Press, Available: http://www.medicinescomplete.com
24 Curtis LA, Burns A. *Unit costs of health and social care 2019*. Personal Social Services Research Unit, 2019.
25 NHS Improvement. NHS reference costs 2020-2021. n.d. Available: https://improvement.nhs.uk/resources/reference-costs/
26 NICE. British national formulary. n.d. Available: https://www.medicinescomplete.com/mc/bnf/current/
27 van Hout B, Janssen MF, Feng Y-S, *et al*. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value SETS. *Value Health* 2012;15:708–15.
28 Matthews JN, Altman DG, Campbell MJ, *et al*. Analysis of serial measurements in medical research. *BMJ* 1990;300:230–5.
29 Shen J, Vale L, Goulao B, *et al*. Endoscopic Urethrotomy vs open Urethroplasty for men with Bulbar Urethral Stricture: the open randomised trial cost-effectiveness analysis. *In Review* [Preprint] 2021.
30 Fiebig DG. *Seemingly unrelated regression. a companion to theoretical econometrics*.2001:101–21.
31 Drummond MF, Sculpher MJ, Claxton K, *et al*. *Methods for the economic evaluation of health care programmes*. Oxford university press, 2015.
32 Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ* 2001;10:779–87.
33 Pickard R, Chadwick T, Oluboyede Y, *et al*. Continuous low-dose antibiotic prophylaxis to prevent urinary tract infection in adults who perform clean intermittent self-catheterisation: the antic RCT. *Health Technol Assess* 2018;22:1–102.
34 O'Neill J. Antimicrobial resistance: tackling a crisis for the health and wealth of nations: review on antimicrobial resistance. 2014.
35 NHS England. Antibiotic quality premium monitoring dashboard 2020/21. n.d. Available: https://www.england.nhs.uk/publication/antibiotic-quality-premium-monitoring-dashboard/
36 Willan AR, Lin DY, Manca A. Regression methods for cost-effectiveness analysis with censored data. *Stat Med* 2005;24:131–45.
37 Oppong R, Smith RD, Little P, *et al*. Cost effectiveness of amoxicillin for lower respiratory tract infections in primary care: an economic evaluation accounting for the cost of antimicrobial resistance. *Br J Gen Pract* 2016;66:e633–9.
38 Rui L, Lindbaek M, Gjelstad S. Preventive effect of methenamine in women with recurrent urinary tract infections - a case-control study. *Scand J Prim Health Care* 2022;40:331–8.
39 Heltveit-Olsen SR, Sundvall P-D, Gunnarsson R, *et al*. Methenamine hippurate to prevent recurrent urinary tract infections in older women: protocol for a randomised, placebo-controlled trial (ImpresU). *BMJ Open* 2022;12:e065217.