BMJ Open

Clinical effectiveness and bacteriological eradication of three different Short-COurse antibiotic regimens and single-dose fosfomycin for uncomplicated lower Urinary Tract infections in adult women (SCOUT study): study protocol for a randomised clinical trial

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To cite: Garcia-Sangenís A, Morros R, Aguilar-Sánchez M, *et al*. Clinical effectiveness and bacteriological eradication of three different Short-COurse antibiotic regimens and single-dose fosfomycin for uncomplicated lower Urinary Tract infections in adult women (SCOUT study): study protocol for a randomised clinical trial. *BMJ Open* 2021;**11**:e055898. doi:10.1136/bmjopen-2021-055898

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-055898).

Received 28 July 2021
Accepted 01 November 2021

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ABSTRACT

Introduction Uncomplicated lower urinary tract infections (uLUTI) are a common problem in primary care. Current local guidelines recommend the use of a single 3 g dose of fosfomycin. However, most general practitioners (GP) prefer short-course therapies to single-dose therapy. No study has compared head-to-head short-course antimicrobial agents for uLUTIs. Therefore, the aim of this randomised clinical trial is to compare three different short-course antibiotic therapies with a single-dose of fosfomycin for these infections.

Methods and analysis This will be a pragmatic, multicentre, parallel group, open trial. Women aged 18 or older and with symptoms of uLUTI and a positive urine dipstick analysis will be randomised to one of the following four groups: a single dose of 3 g of fosfomycin, 2 days of 3 g of fosfomycin o.d., 3 days of pivmecillinam 400 mg three times per day (t.i.d) or 5 days of nitrofurantoin 100 mg t.i.d. A total sample of 1120 patients was calculated. The primary endpoint is clinical effectiveness at day 7, defined as cure of symptoms reported by the patients in a diary including four symptoms: dysuria, urgency, frequency and suprapubic pain, which will be scored on a 4-point severity scale (not present/mild/moderate/severe). Follow-up visits are scheduled at days 7 (phone call), 14 and 28 for assessing evolution. Urine samples will be collected in the three on-site visits and urine cultures performed. If positive, antibiograms for the three antibiotics studied will be performed. Bacterial eradication will be measured at days 14 and 28.

Ethics and dissemination The study was approved by the Ethical Board of IDIAP Jordi Gol (reference number: 21/173-AC) and Spanish Agency of Medicines and Medical Devices. The findings of this trial will be disseminated through research conferences and peer-review journals.

Trial registration number NCT04959331; EudraCT Number: 2021-001332-26.

Time schedule January 2022 to April 2023.

Strengths and limitations of this study

- This will be the first randomised controlled trial to investigate the clinical effectiveness and bacterial eradication of four antibiotic regimens administered to women with symptoms of uncomplicated lower urinary tract infection.
- Although masking techniques are not used, observer bias will be reduced to a minimum as the primary objective and some of the secondary objectives will be based on symptoms recorded by the patients themselves and on urine cultures.
- Symptom diaries only contain four domains and are used for only 7 days, and therefore completion is simple. Nonetheless, if symptom diaries are not returned, a phone call will be made at day 7.
- In the unlikely event that the COVID-19 pandemic is still present throughout the period that the clinical trial is conducted, and this hampers the inclusion of patients, the number of clinicians participating will be increased.

INTRODUCTION

Lower urinary tract infections (LUTI) are a common problem in primary care consultations. More than 50% of all women experience at least one episode during their lifetime.[1] In more than 80% of cases, LUTI is caused by *Escherichia coli*.[1 2] In many clinical settings, urine cultures are not routinely performed, and women with symptoms of acute cystitis are treated empirically. Thus, empirical treatment in LUTIs should cover *E. coli*. Resistance of uropathogens to the classical antibiotics has significantly increased in the last years in Spain, mainly because of the high use of antibiotics.[3] The resistance of enterobacteria to third generation cephalosporins, mediated by the production of extended spectrum β lactamases (ESBL), is a growing problem in *E. coli* and *Klebsiella pneumoniae* strains. Indeed, in 2019, more than half of the *E. coli* isolates reported to the European Antimicrobial Resistance Surveillance Network and more than a third of the *K. pneumoniae* isolates were resistant to at least one antimicrobial group under surveillance.[4] According to recent data, the percentage of *E. coli* resistance to quinolones, cotrimoxazole and amoxicillin and clavulanate, although variable, ranges from 20% to 40% in Spain and approximately 10% of the isolates of *E. coli* are ESBL-producers.[5–7] LUTIs caused by resistant microorganisms are associated with longer symptom duration and treatment failure is more likely compared with infections caused by susceptible strains.[8–10] According to the recommendations of the Infectious Diseases Society of America, empiric antibiotic therapy should be substituted when the rates of resistance surpass 20%.[11] This means that the use of amoxicillin and clavulanate as well as quinolones are no longer recommended for the empirical treatment of LUTIs in our country.

Current guidelines recommend prescribing a single 3 g dose of fosfomycin or nitrofurantoin 100 mg three times per day (t.i.d.) for 5 days.[12 13] The rationale for this strategy is based on the narrow spectrum of aetiologic agents causing acute cystitis and knowledge of their local antimicrobial resistance patterns.[14] Over the last years, the use of fosfomycin as the preferred therapy for these infections has significantly increased in Spain. However, more than half of the Spanish doctors prefer the use of short-course therapies over single-dose therapy.[15] Pivmecillinam, an antibiotic widely used in Scandinavian countries for the treatment of LUTIs, has been authorised by the Spanish Agency of Drugs and Medicine Products (2017), although it is still not marketed. Its effectiveness has been demonstrated in different randomised clinical trials (RCT) and is also recommended for the treatment of uncomplicated LUTI.[16 17] The dose that will be used in our RCT has been shown to be the more effective in a recent systematic review.[18] A recent RCT including a total of 513 women with uncomplicated LUTIs found that clinical resolution at day 28 occurred in 70% of patients taking 100 mg of nitrofurantoin three times per day for 5 days and in 58% of patients assigned to a single 3 g dose of fosfomycin. The authors hypothesised that a single 3 g dose does not appear to be optimal.[19] Fosfomycin resistance is rare in areas with limited use but is on the rise in countries with higher usage, although the susceptibility rates are variable and do not exceed 10% of the isolates.[20–22] However, the use of a single dose is associated with a higher percentage of relapses, mainly in patients with recurrent LUTIs.[23] A single dose of fosfomycin–tromethamine and short-courses of nitrofurantoin and pivmecillinam are now recommended by the latest guideline of the European Association of Urology for empirical therapy of uncomplicated LUTI,[24] but no study has compared more than two short-course antimicrobial agents for uncomplicated LUTIs.[25]

OBJECTIVES

The main aim of the trial is to compare the clinical effectiveness of three short-course antibiotic regimens (3 g of fosfomycin one time per day for 2 days; 3 days of pivmecillinam 400 mg. t.i.d.; 5 days of nitrofurantoin 100 mg t.i.d.) with a single 3 g dose of fosfomycin in uncomplicated LUTIs in adult women at day 7. The clinical effectiveness of the short-course antibiotics will be evaluated as a secondary objective of the trial: 3 g of fosfomycin 2 days versus 3 days of pivmecillinam 400 mg. t.i.d, 3 g of fosfomycin 2 days versus 5 days of nitrofurantoin 100 mg t.i.d. and 3 days of pivmecillinam 400 mg. t.i.d. versus 5 days of nitrofurantoin 100 mg t.i.d.

The other secondary objectives are aimed at evaluating the following parameters in the four medication arms: (1) duration of symptoms; (2) bacteriological eradication measured at day 14; (3) bacteriological eradication at day 28; (4) proportion of patients presenting a relapse of symptoms within the first 4 weeks after inclusion in the study and timing of relapse of symptoms and/or bacteriuria; (5) proportion of patients developing complications (ie, pyelonephritis and/or urosepsis) within the first 4 weeks; (6) proportion of patients presenting adverse and serious adverse events; (7) predictive value of the different clinical criteria collected with microbiologically-confirmed LUTI; (8) bacteriological findings, (ie ESBL-producing bacteria, resistance rates to the study medications); (9) cost-effectiveness of each of the treatment arms and (10) change in quality of life in the first week.

METHODS AND ANALYSIS

Trial design

This study is a phase IV, multicentre, pragmatic, parallel group, open randomised trial.

Study arms

Once the patients are included in the trial, they will be randomised into one of the four treatment groups: (1) single 3 g dose of fosfomycin–tromethamine; (2) 3 g of fosfomycin–tromethamine one time per day for 2 days; (3) 3 days of pivmecillinam 400 mg t.i.d. and (4) 5 days of nitrofurantoin 100 mg t.i.d. All the drugs and products

used in this study are already marketed, and therefore, the manufacturers are responsible for the elaboration and control of samples. The study drugs will be provided free to the participants by the sponsor. The provision, secondary conditioning and distribution of the study drugs will be performed by the Barcelona Primary Care Pharmacy Service. Study drugs will be distributed to the Primary Care Pharmacy Services of the four regions taking part in the study, which will be in charge of providing their primary care sites with the medication. All the study drugs will be kept at room temperature.

Sample size

A minimal clinically important difference of 10% was chosen in line with guidance provided by both the European Medicine Agency and the Infectious Disease Society of America.[26 27] Assuming a clinical efficacy of 75% for a single-dose fosfomycin as demonstrated in a recent systematic review,[28] a two-sided type I error of 5%, and a statistical power of 80%, we need 253 patients in each group for the intention-to-treat analysis. Considering an estimated drop-out rate of 10% in each study arm, we aim to recruit 280 in each group (total number 1120 LUTIs).

Settings

This RCT will be conducted in 15–20 primary care centres in four regions in Spain: Aragon, Balearic Islands, Catalonia and Madrid. In each area, a total of 280 patients will be recruited, with three to eight primary care centres and one or two microbiology departments being involved.

Participants

Inclusion criteria

Potential participants are women of 18 years of age or older, with clinical features of uncomplicated community-acquired LUTI including: (1) at least one of four key symptoms of LUTI: dysuria, urgency including nocturia, frequency and suprapubic tenderness that could be attributed to an uncomplicated LUTI, and no alternative explanation (ie, symptoms suggestive of sexually-transmitted infection or vulvovaginitis), and (2) a urine dipstick analysis positive for either nitrites or leucocyte esterase.

Exclusion criteria

Patients with any of the following criteria will be excluded from this trial: (1), male sex; (2) high suspicion of pyelonephritis (ie, fever ≥37.5°C or flank pain/tenderness); (3) any condition that may lead or predispose to complicated urinary infection, such as indwelling urinary catheter, pregnancy, immunosuppressive therapy, abnormal urinary tract, severe neurological disease affecting the bladder or recurrent UTIs, defined as the presence of more than 3 UTIs in the previous year or more than two in the previous 6 months; (4) pregnancy or planned pregnancy; (5) symptoms consistent with UTI in the preceding 4 weeks; (6) patients taking long-term antibiotic prophylaxis; (7) ongoing antibiotic therapy or use of any systemic antibiotic in the previous 7 days; (8) symptoms correlated with differential diagnosis (ie, vaginal discharge or pain); (9) hypersensitivity or allergy to β lactams, nitrofurantoin and/or fosfomycin; (10) moderate to severe chronic renal insufficiency; (11) pre-existing polyneuropathy; (12) history of lung or liver reaction or peripheral neuropathy after previous use of nitrofurantoin; (13) glucose-6-phosphate dehydrogenase deficiency; (14) porphyria or systemic primary carnitine deficiency or of the type organic aciduria (ie, methylmalonic aciduria and propionacidanaemia); (15) oesophageal stricture; (16) current intake of allopurinol (increases the risk of allergic skin reaction to mecillinam), probenecid (decreases the renal excretion of mecillinam) or valproate; (17) currently part of another RCT; (18) previous enrolment in the proposed study; (19) patients living in long-term institutions and/or (20) difficulty in conducting scheduled follow-up visits.

Randomisation

Patients will be sequentially assigned as they enter the study. Randomisation of patients will be performed by registering the patient in an electronic case report form (CRF) during the index visit. Since this study is open-label to patients and investigators, randomisation will be based on investigator-blinded blocks of randomly varying size to protect against potential predictability of treatment assignments. Blocks will be small in order to decrease the potential for mid-block inequality. Since this is a multicentre study, a block procedure will be performed to assign patients to each of the health centres at a 1:1:1:1 treatment ratio.

Blinding

This is an open study. Neither physicians nor patients will be blind to the patient's assignment to the drug study group. The open nature of the RCT ensures that the results obtained in this study are very close to the reality of primary care, considering that both the participating general practitioners (GPs) and the patients with uncomplicated LUTI will be aware of the treatment given.

Outcome measures

Primary outcome

Clinical effectiveness is defined as the proportion of patients who report being cured by day 7, defined as the resolution of all symptoms (scoring 0 in the symptom diary) and those who report an improvement of the symptoms related to the LUTI (persistence of symptoms without objective evidence of infection). We will consider failure in case of need for additional or a change in antibiotic treatment due to UTI or discontinuation due to lack of efficacy.

Secondary outcomes

(1) Duration of symptoms (number of days until the last day the patient scores 0 in any of the four symptoms); (2) bacteriological eradication at day 14, defined as eradication of the infecting strain with no recurrence of bacteriuria—less than 1000 colony-forming units per millilitre (CFU/mL). Failure will be defined as

bacteriuria ≥1000 CFU/mL with the infecting strain; (3) bacteriological eradication at day 28 (ie, proportion of patients bacteriologically cured at the final urine sample); (4) proportion of patients presenting a relapse of symptoms within the first 4 weeks after inclusion in the study and timing of relapse of symptoms and/or bacteriuria; (5) proportion of patients developing complications within the first 4 weeks; (6) proportion of patients presenting adverse and serious adverse events; (7) predictive value of the different clinical criteria with microbiologically confirmed LUTI; (8) bacteriological findings (ESBL-producing bacteria, resistance rates to the study medications); (9) cost-effectiveness (drug costs, health resources used, days until recovery and days with limitation of activity (productive and non-productive) and (10) quality of life by means of the EQ-5D-5L validated questionnaire (Spanish version).

Time schedule

The recruiting GPs will commence the study in January 2022 and will attempt to recruit all eligible patients by 30 April 2023. If the necessary sample size is met before this date, the recruitment period will end at the time of inclusion of the last patient.

Data management and monitoring

The investigators will follow the standard operating procedures of the trial for better quality of assessment and outcome data collection. All assessment data and case reports in the different arms will be collected at the baseline visit and at the various follow-up visits. Collected documents and data will be managed by electronic CRF. Only the principal investigator or those who have permission can access the data. The CRFs and other documents will be stored at a separate and secure location for 25 years after trial completion. A risk approach monitoring plan will be developed and followed via periodic on-site/online visits.

Ascertainment of visits

The patients will be randomised to one of the four treatment strategies. Women will receive information on the study by the participating GPs, and if they are interested in participating, they will be provided with an informed consent form to read and sign. The participating GPs will explain the study scheme and the visit programme to the patient (table 1). After randomisation, information on the strategy to which they have been allocated will be given to the participants, and they will be given the study medication and will be informed as to the appropriate measures to take in case of worsening or no improvement of their condition. Patients will be asked about the prior duration of symptoms. In addition, they will be given a paper-based diary to be completed by themselves daily for a total of 7 days. Patients will be asked to score a simple symptom diary, which has been slightly modified from one used in another RCT on uncomplicated LUTI,[29] with only four symptoms: dysuria, urgency, frequency and suprapubic pain. Each symptom will be scored by the patient on a 4-point severity scale (not present/mild/moderate/severe). Patients will be given instructions on how to fill in the diary, how to take the study medication and reminders of the following visits, and they will be asked on which day they felt cured. This diary will be used in a pilot study in some centres during 2 months prior to

Table 1 Timetable of the study period

Visit	Baseline visit	Day 7 (phone visit)	Day 14	Day 28
History taking and clinical examination	X			
Eligibility	X			
Explanation of the study and informed consent	X			
Initial case report form	X			
Urine dipstick	X			
Urine culture, including antibiogram if positive	X		X	X
Randomisation	X			
Dispensing the study medication	X			
Giving out of the symptom diary	X			
Assessment of the change in the quality of life	X	X		
Assessment of the clinical outcome		X	X	X
Adherence to the study drug		X		
Collection of the symptom diary			X	
Monitoring concomitant treatment and use of other antibiotics		X	X	X
Evaluation of adverse events		X	X	X
Evaluation of reattendance to healthcare services and complications with relation to the infection		X	X	X

the initiation of the trial to ensure that its use is feasible and reliable. A maximum length of 15 min is expected for the baseline visit including interview, randomisation, collection of the urine sample and the introduction of the data.

GPs will call patients 7 days after their inclusion in the study to monitor their progress and obtain information about their symptoms. Patients will be scheduled for a second visit on day 14 (2 weeks after patient inclusion) to evaluate their clinical evolution, collect the diaries and collect a new urine sample. The last visit will be on day 28, and patients will also be asked to collect another urine sample. An evaluation of adverse events, reattendance to healthcare services and complications with relation to the LUTI will be carried out.

The face-to-face visits will coincide with the delivery of the urine sample, thus facilitating the patient to deliver the sample. The procedure of urine sample collection will be decided according to the results of a systematic review and meta-analysis on what the most adequate non-invasive method to collect a urine specimen for diagnosing UTI in symptomatic non-pregnant women is, currently being performed by some of the same study authors (PROSPERO CRD42021241758). The three urine samples will be sent to the Departments of Microbiology in each of the four regions for examination of the presence and counting of uropathogenic bacteria.

In the presence of significant bacteriuria (ie, ≥1000 bacteria/mL of a single pathogen according to current European guidelines for women with symptoms of LUTI),[30] the isolates will also be examined for resistance mechanisms and patterns and minimal inhibitory concentration to common antibiotics, including fosfomycin, nitrofurantoin and pivmecillinam. All urine samples will be processed according to routine laboratory procedures and susceptibility tested according to the European Committee on Antimicrobial Susceptibility Testing.[31] A urine culture with less than 1000 CFU/mL, multiple pathogens or normal flora will be considered contamination and will not be defined as LUTI. We consider that about 25% of the suspected LUTIs will not be microbiologically confirmed based on two recent RCTs using the same inclusion criteria as in our trial.[19 32]

Patients will be free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to provide the reason for withdrawal. In addition, patients presenting signs of upper UTI (ie, pyelonephritis), treatment failure, serious adverse effects or allergic reactions to the medicine will be withdrawn from the study. Patients presenting treatment failure (ie, ongoing or worsening symptoms) will receive a different antibiotic according to the pretreatment (day 0) urine culture results. During the trial, patients will be asked to inform about any signs of worsening symptoms, and investigators will evaluate appropriate measures if they need additional therapy. Since this is a pragmatic trial, patients who decide interrupting the study drug treatment will be withdrawn from the study.

Statistical analysis

All treatment strategy comparisons among the randomised groups will be performed according to the principle of intention-to-treat; that is, all initially enrolled patients will be included in the analysis according to the treatment strategy to which the subjects are randomised regardless of non-adherence to treatment or treatment failure. The primary statistical comparison of the primary outcome will be a two-sided χ^2 test of the three short-course antibiotic regimens with the single dose of fosfomycin. Time-to-event analysis will be used to analyse the clinical effectiveness of the four treatment strategies. Relative risks will be expressed as HRs with associated 95% CIs derived using the Cox proportional hazards model. The overall level of significance for the assessment of primary and secondary endpoints will be α=0.05. A per-protocol analysis of those who complete the entire trial without violating the protocol, will also be performed as a sensitivity analysis of the primary results. A subgroup analyses of the main variables will be carried out by age groups (premenopausal, postmenopausal) and by region. Missing outcomes will be accounted for using multiple imputation with chained equation.[33] Twenty imputed samples will be generated, and estimates will be combined using Rubin rules.[34] Direct healthcare costs will be calculated by adding the costs derived from medication consumption, medical tests, use of health-related services, cost of relapses and cost of the staff running the intervention, for each arm. Indirect costs will be calculated considering the proportion part of quality adjusted life year indicator, the number of days with symptoms and sick days taken.[35] All the analyses will be carried out with the statistical software R V.4.0 or higher, and the level of significance will be 0.05.

Patient and public involvement

Women with previous LUTI experience have been invited to be part of our study team. Participants were selected using purposive sampling to cover a wide range of opinions and discourses. Age, region, UTI recurrence and socioeconomic characteristics were taken into consideration. Our patient and public involvement framework is defined as study-focused[36] following a collaborative strategy.[37] Participants have been and will be asked to assess all patient-related materials, as well as well key procedures and documents such as the study protocol and patient information sheets, case report files, recruitment strategy and results reports. They will be present throughout the whole project. All the RCT participants and all the patients who are interested in the study results will receive a layman study newsletter with a summary of the results obtained at the end of the trial.

ETHICS AND DISSEMINATION

Ethical issues

The trial will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines,

national and European legislation on clinical trials and data protection and with the study protocol. Consolidated Standards of Reporting Trials guidelines will be followed to inform of the study results.

Approval from the Spanish Agency of Medicines and Medical Devices (6 September 2021) as well as from a national medicines Research Ethics Committee (IDIAPJGol) have been obtained (reference code 21/173-AC, authorised on 23 September 2021. Investigators will be required to provide all information related to the clinical trial to every patient, including the possible benefits and harms, other therapeutic choices, right to withdraw and use of their data, via a written patient information sheet and oral interview. After the patient has been provided with enough time and opportunity to ask questions and decide whether to participate, written informed consent will be obtained from all participants before study inclusion.

Adverse events and serious adverse events

According to European legislation on clinical trials, this is a low intervention clinical trial: the drugs administered are used in accordance with the terms of the marketing authorisation with a well-known safety profile, and the clinical trial procedures in the patient pose no additional risk to the subject compared with usual clinical practice. The study medications used in this clinical trial have been widely prescribed and consumed for a long time, and the safety profile of these drugs is well documented. Pivmecillinam has been widely used in Nordic countries and is now approved in Spain, although it is not yet marketed.

Considering the low intervention characteristics of the trial, only adverse events related to the trial medication and all serious adverse events (regardless of the relationship with the study drugs) will be recorded, followed and analysed. The remaining events will be treated as in normal clinical practice.

Dissemination

A range of dissemination activities at national and international conferences is planned. At the end of the trial, we will publish the final report in an open access peer-review journal even in the case of negative results, and the study results will also be disseminated via conference presentations. National stakeholders will be informed about clinical trial results. A summary of the findings will be sent to the participating practices on completion of the RCT, and the participants will also be informed of the results. We will design a booklet to be used in LUTI consultations with the results of our clinical trial and qualitative studies, and a layman version of the trial results will be developed for public dissemination.

Complementary studies

After the RCT, two qualitative studies are planned, one with former patients of our clinical trial and one with healthcare professionals who have also participated in the clinical trial as investigators. Qualitative studies will explore the experiences, needs and preferences of patients and professionals regarding LUTIs and their treatment, giving information on patients' values and preferences to consider in decision-making.

DISCUSSION

Antimicrobial resistance is a growing problem threatening societal development and human health. LUTIs caused by antibiotic resistant bacteria are associated with increased morbidity and mortality, as well as with higher treatment costs due to an increased risk of complications (urosepsis and pyelonephritis) and admission to hospital and productive losses.[9 10] The use of broad-spectrum antibiotics for women with uncomplicated LUTIs has been shown to increase and spread the antimicrobial resistance of uropathogens. After two decades of increased antibiotic resistance, the urgency of the problem is now widely understood and inappropriate use of antibiotics is the main driver for the growing development and spread of antimicrobial resistance. The SCOUT study will mark a significant move forward from theory to practice in relation to promoting responsible stewardship regarding treatment of uncomplicated LUTIs in women. In our country, the increase in resistance to antibiotics used empirically in LUTIs, such as amoxicillin and clavulanic acid and quinolones, is very worrisome, and even more so at this time in which quinolones have restrictions due to safety problems. This problem, along with the fact that most GPs are reluctant to follow the national guidelines and avoid the prescribing of a single 3 g-dose of fosfomycin, makes this study very important in an area such as Spain with high resistance rates. Therefore, having comparative data in real-life can constitute the basis for implementing the most efficient option with less exposure to antibiotic treatment and contribute to reducing the increase in resistance.

Very importantly, we are conducting an independent clinical trial with medicines without commercial interest. Our aim is to compare different short-course regimens of most antibiotics used in the empiric treatment of LUTIs and will provide valuable information about the most effective treatment for a common infection seen in primary care. We hypothesise that short-course treatments will be more effective than the recommended 3 g single dose of fosfomycin, resembling what clinicians usually do in routine practice. Since no RCT comparing the four available regimens has been carried out to date, we still do not know which of the three short courses is more effective in terms of clinical effectiveness and bacteriological eradication.

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Acknowledgements We would like to acknowledge the work of the lay participants in our team (PPI): Maribel Dorado, Magdalena Serra and B Jolanta Wyzynska. We thank the Advisory Board of this study: Carlos Pigrau-Serrallach (Internal Medicine Department, Hospital Vall d'Hebron), Lars Bjerrum (Department of General Practice and Public Health, University of Copenhagen), Antonio López (Medicines and Health Products Spanish Agency) and J Manuel Izquierdo-Palomares (Pharmacy and Health Products Management Area).

Collaborators We wish to acknowledge the rest of the members of the SCOUT Study Group: Bonaventura Bolíbar, Dan Ouchi-Vernet, Anna Berenguera, Josep M Cots, Sílvia Cobo, Fede Gómez (Catalonia), Ignacio Ricci Cabello, Catalina Vicens-Caldentey, José I Ramírez-Manent, Aina Soler-Mieras, Lourdes Quintana-Torres, Joan Llobera-Cànaves, Antonia Roca-Casas, Aina M Yáñez-Juan, Eva Alcoceba-Cruixent, Antonio Ballester-Camps, Oana Bulilete, M Consuelo Camionero-Soto, Joan Pou Bordoy (Balearic Islands), M Antonia Sánchez-Calavera, Pilar Royán-Molero, Nima Peyman-Fard Shafi-Tabatebaei, África García-Roy, Raquel Jabal-Calvillo, Lucía Lasilla-Fernández, Andrea Hurtado-Gutiérrez (Aragón), Pilar Vich-Pérez, Rocío C Triano-Sánchez, M José Ávila-Sánchez, Manuel Gómez-García, Isabel Prieto-Checa, Mar Nogueol-Álvarez, Cristina Sánchez-Iñigo, A Carla Ferreyra-Lanatta, Maria Victoria Garcia Espinosa, Marta Lor Leandro, Lidia Escribano González, Luís Benito Ortiz (Madrid).

Contributors AG-S, RMor and CL drafted the research protocol and both AG-S and CL wrote the manuscript. All authors were involved in the protocol development. LM-P, AL, JR and MM-P are involved in PPI management. AL, JR, MM-P, CBB-M, RMB, JM-C, JMM and AM are involved in trial conduct and recruitment. AG-S, RMor, RMon and CL are involved in trial supervision. AT is involved in study drug management. MA-S is involved in microbiology coordination. AL and JR contributed to the statistical design and analysis. All authors have contributed to the conception of this clinical trial.

Funding The SCOUT Study received a research grant from the Carlos III Institute of Health (ISCIII), Ministry of Science and Innovation (Spain), awarded in the 2020 call under the Academic Clinical Trials Call, with reference ICI20/00100, by Primary Care Prevention and Heath Promotion Network GRenSSAP (code RD16/0007/0001), Balearic Islands (code RD16/0007/0008), Aragón (code RD16/0007/0005), Madrid (code RD16/0007/0013) and by European Union ERDF funds (European Regional Development Fund).

Competing interests CL reports receiving research grants from Abbott Diagnostics. The other authors have nothing to declare.

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).

Provenance and peer review Not commissioned; externally peer reviewed.

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