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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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Title

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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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 for these infections. 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 randomised 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. t.i.d, or 5 days of nitrofurantoin 100 mg t.i.d.. Sample: 1,120 patients. This study will include patients as collaborators to the research team, following a patient and public involvement approach. The primary endpoint is clinical effectiveness, defined as cure of symptoms, reported by the patients in a symptom diary at day 7. Follow-up visits are scheduled at days 7 (phone call), 14 and 28 for assessing evolution. Bacterial eradication will be measured at days 14 and 28. Urine samples will be collected in the three on-site visits and urine cultures performed. If positive, antibiograms for the 3 antibiotics studied will be performed.

Ethics and dissemination: The study has been 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: Clinical.gov, reference number NCT04959331. EudraCT Number: 2021-001332-26.

Time schedule: November 2021 to April 2023.

KEY WORDS: Urinary Tract Infections; Women; Patient Outcome Assessment; Bacteriological Eradication; Urinalysis; Anti-Bacterial Agents; Antimicrobial Resistance; Short Course; Primary Health Care.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This will be the first randomised controlled trial to investigate the clinical effectiveness and bacterial eradication of four head-to-head antibiotics administered to women with symptoms of uncomplicated lower urinary tract infection. This will be a multicentre study, carried out in four different Autonomous Communities, and the results will be more generalisable to other settings. In addition, a collaborative patient and public involvement approach will be followed.
- Since this is a pragmatic clinical trial evaluating the effectiveness of four antibiotic regimens, masking techniques will not be used. Despite being an open trial, 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.
- The use of symptom diaries is crucial in this study, and there is always the chance that some will not be returned. However, the symptom diaries only contain four domains and are used for only seven days, and therefore completion will be simple. A phone call will be made at day 7 in case patients do not return the diaries. Notwithstanding, the diary will be used in a pilot study in some centres during two months prior to the initiation of the trial to ensure that its use is feasible and reliable.
- Another limitation is the uncertainty of the COVID-19 pandemic at the time this clinical trial is planned to be initiated (November 2021). However, in the unlikely event that the COVID-19 pandemic is still present at that time, the clinical trial will be initiated later, and in this case, the number of clinicians participating will be increased. Despite this, we do not foresee much risk to fulfil the inclusion of 1,120 patients if the trial is initiated after the summer of 2022.

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 EARS-Net 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, albeit variable, ranges from 20 to 40% in Spain [5-7]. LUTIs caused by resistant microorganisms are associated with longer symptom duration and treatment failure is more likely compared to 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 t.i.d. for five 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 carried out in a country with low resistance rates of uropathogens to common antibiotics found that clinical resolution at day 28 day occurred in 70% of patients taking 100 mg of nitrofurantoin

thrice-daily for 5 days and in 58% of patients assigned to a single 3 g dose of fosfomycin. The authors hypothesized 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]. In conclusion, a single dose of fosfomycin-tromethamine, and short-courses of nitrofurantoin and pivmecillinam are now recommended for the empirical therapy of uncomplicated LUTI, but no study has compared head-to-head more than two short-course antimicrobial agents for uncomplicated LUTIs [24].

OBJECTIVES

The aim of this RCT is to compare three different short-course antibiotic therapies (the preferred two-day fosfomycin regimen, nitrofurantoin and pivmecillinam) with the recommended single-dose fosfomycin regimen for the treatment of cystitis in female adults. The main aim of the trial is to evaluate the clinical effectiveness of the 3 short-course antibiotic regimens (3 g of fosfomycin once daily for two-days; 3 days of pivmecillinam 400 mg. t.i.d.; 5 days of nitrofurantoin 100 mg t.i.d.) and a single 3 g dose of fosfomycin in uncomplicated LUTIs in adult women at day 7.

The 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 efficacy at day 28; (4) Proportion of patients presenting a relapse of symptoms within the first four weeks after inclusion in the study and timing of relapse of symptoms and/or bacteriuria; (5) Proportion of patients developing complications (i.e. 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, i.e. 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 4 treatment groups: (1) single 3 g dose of fosfomycin-tromethamine; (2) 3 g of fosfomycin-tromethamine once daily 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 autonomous communities 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 [25,26]. Assuming a clinical efficacy of 75% for a single dose fosfomycin as demonstrated in a recent systematic review [27], 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 1,120 LUTIs).

Settings

This RCT will be conducted in 15-20 primary care centres in four Autonomous Communities in Spain: Aragon, Balearic Islands, Catalonia and Madrid.

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 (i.e. symptoms suggestive of sexually-transmitted infection or vulvovaginitis), and (2) a urine dipstick analysis positive for either nitrites or leukocyte esterase.

Exclusion criteria

Patients with any of the following criteria will be excluded from this trial: (1), male sex; (2) high suspicion of pyelonephritis (i.e. fever ≥ 37.5°C or flank pain/tenderness); (3) any condition that may lead or predispose to complicated urinary infection (i.e. indwelling urinary catheter, pregnancy, immunosuppressive therapy, abnormal urinary tract, recurrent UTI, severe neurological disease affecting the bladder); (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 (i.e. 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 (i.e. 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 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 1,000 colony-forming units per millilitre (CFU/ml). Failure will be defined as bacteriuria ≥ 1,000 CFU/ml with the infecting strain; (3) Bacteriological efficacy at day 28 (i.e. proportion of patients bacteriologically cured at the final urine sample); (4) Proportion of patients presenting a relapse of symptoms within the first four 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 November 2021 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 4 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. 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 [28], 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 two months prior to the initiation of the trial to ensure that its use is feasible and reliable. A maximum length of 15 minutes 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 at day 14 (two weeks after patient inclusion) to evaluate their clinical evolution, collect the diaries and collect a new urine sample. The last visit will be at day 28, and patients will also be asked to collect another urine sample. An evaluation of adverse events, re-attendance 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 Autonomous Communities for examination of the presence and counting of uropathogenic bacteria.

In the presence of significant bacteriuria (i.e. ≥ 1,000 bacteria/ml of a single pathogen according to current European guidelines for women with symptoms of LUTI) [29], 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 (EUCAST) [30]. A urine culture with less than 1,000 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 randomised clinical trials using the same inclusion criteria as in our trial [19,31].

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 (i.e., pyelonephritis), treatment failure, serious adverse effects or allergic reactions to the medicine will be withdrawn from the study. Patients presenting treatment failure (i.e., ongoing or worsening symptoms) will receive a different antibiotic according to the pre-treatment (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 Chi-square test of the 3 short-course antibiotic regimens (3 g of fosfomycin once daily for 2 days; 3 days of pivmecillinam 400 mg. t.i.d.; 5 days of nitrofurantoin 100 mg t.i.d.) compared to a single 3 g 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 hazard ratios with associated 95% confidence intervals 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 Autonomous Community. Missing outcomes will be accounted for using multiple imputation with chained equation [32]. Twenty imputed samples will be generated, and estimates will be

combined using Rubin rules [33]. Direct health care costs will be calculated by adding the costs derived from medication consumption, medical tests, use of health-related services, 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 [34]. 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, autonomous community, UTI recurrence and socioeconomic characteristics were taken into consideration. Our patient and public involvement framework is defined as study-focused [35] following a collaborative strategy [36]. 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 collaborating patients will be informed of the study results 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 as well as from a national medicines Research Ethics Committee (IDIAPJGol) will be obtained before starting the trial. 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. The trial is registered in the ClinicalTrials.gov Protocol registry (NCT04959331) and in the European Clinical Trial Database (EudraCT) (2021-001332-26).

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 to 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 hypothesize 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 head-to-head 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.

Rest of the members of the SCOUT Study Group

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,

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Contributors

AGS, RMor, and CL drafted the research protocol and both AGS and CL wrote the manuscript. All authors were involved in the protocol development. LMP, ALR, JR and MMM are involved in PPI management. ALR, JR, MMM, CBBM, RMMB, JMC, JMMG and AM are involved in trial conduct and recruitment. AGS, RMor, RMon and CL are involved in trial supervision. AMT is involved in study drug management. MAS is involved in microbiology coordination. ALR and JR contributed to the statistical design and analysis. All authors have contributed to the conception of this clinical trial.

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Competing interests

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

Patient consent

Obtained.

REFERENCES

1. Palou J, Pigrau C, Molina I, Ledesma JM, Angulo J; Grupo Colaborador Español del Estudio ARESC. Etiology and sensitivity of uropathogens identified in uncomplicated lower urinary tract infections in women (ARESC Study): implications on empiric therapy. Med Clin (Barc) 2011;136:1–7.
2. Andreu A, Planells I, Grupo cooperativo español para el estudio de la sensibilidad antimicrobiana de los patógenos urinarios. Etiology of community-acquired lower urinary infections and antimicrobial resistance of Escherichia coli: a national surveillance study. Med Clin (Barc) 2008;130:481–6.
3. Jiménez-Guerra G, Heras-Cañas V, Béjar-Molina L, Sorlózano-Puerto A, Navarro-Marí JM, Gutiérrez-Fernández J. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae from urinary tract infections: Evolution of antimicrobial resistance and treatment options. Med Clin (Barc) 2018;150:262–5.
4. European Centre for Disease Prevention and Control (ECDC). Antimicrobial resistance surveillance in Europe 2019. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2020. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/surveillance-antimicrobial-resistance-Europe-2019.pdf [accessed 25 July 2021]
5. Cuevas O, Oteo J, Lázaro E, Aracil B, de Abajo F, García-Cobos Set al; Spanish EARS-Net Study Group. Significant ecological impact on the progression of fluoroquinolone resistance in Escherichia coli with increased community use of moxifloxacin, levofloxacin and amoxicillin/clavulanic acid. J Antimicrob Chemother 2011;66:664–9.
6. Llor C, Aspiroz C, Cano A, Barranco M. The use of amoxicillin and clavulanic acid and quinolones as first choice antibiotics in uncomplicated urinary tract infections in Spain should be reviewed. Aten Primaria 2012;44:443–4.

7. Rodríguez-Baño J, Oteo J, Ortega A, Villar M, Conejo MC, Bou G, e al. Epidemiological and clinical complexity of amoxicillin-clavulanate-resistant Escherichia coli. J Clin Microbiol 2013;51:2414–7.
8. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol 2015;13:269-84.
9. van Hecke O, Wang K, Lee JJ, Roberts NW, Butler CC. Implications of antibiotic resistance for patients' recovery from common infections in the community: A systematic review and meta-analysis. Clin Infect Dis 2017;65:371–82.
10. Vallano A, Rodríguez D, Barceló ME, López A, Cano A, Viñado B, et al; Grupo de Estudio de las Infecciones del Tracto Urinario en Atención Primaria. Antimicrobial susceptibility of uropathogens and outcome following antibiotic treatment for urinary tract infections in primary health care. Enferm Infecc Microbiol Clin 2006;24:418–25.
11. Guay DR. Contemporary management of uncomplicated urinary tract infections. Drugs 2008;68:1169-205.
12. Patología infecciosa. En: Grupo de Trabajo de Enfermedades Infecciosas de la semFYC. Manual de enfermedades infecciosas en Atención Primaria, 4.a ed. Sociedad Española de Medicina de Familia y Comunitaria; 2017; pp. 815–47.
13. Guía de terapéutica antimicrobiana del área Aljarafe. Distrito Sanitario Aljarafe y Hospital San Juan de Dios del Aljarafe, 3a. Edición, 2018. http://www.juntadeandalucia.es/servicioandaluzdesalud/guiaterapeuticaaljarafe/guiaTerapeuticaAljarafe/ [accessed 25 July 2021]
14. Cai T, Tamanini I, Tascini C, Köves B, Bonkat G, Gacci M, et al. Fosfomycin trometamol versus comparator antibiotics for the treatment of acute uncomplicated urinary tract infections in women: A systematic review and meta-analysis. J Urol 2020;203:570–8.
15. Llor C, Moragas A, Hernández S, Crispi S, Cots JM. Misconceptions of Spanish general practitioners' attitudes toward the management of urinary tract infections and asymptomatic bacteriuria: an internet-based questionnaire study. Rev Esp Quimioter 2017;30:372–8.
16. Bollestad M, Grude N, Solhaug S, Raffelsberger N, Handal N, Schjelderup Nilsen HJ, et al; the Norwegian ESBL UTI study group. Clinical and bacteriological efficacy of pivmecillinam treatment for uncomplicated urinary tract infections caused by ESBL-producing Escherichia coli: a prospective, multicentre, observational cohort study. J Antimicrob Chemother 2018;73:2503–9.

17. Bjerrum L, Gahrn-Hansen B, Grinsted P. Pivmecillinam versus sulfamethizole for short-term treatment of uncomplicated acute cystitis in general practice: a randomized controlled trial. Scand J Prim Health Care 2009;27:6–11.
18. Pinart M, Kranz J, Jensen K, Proctor T, Naber K, Kunath K, et al. Optimal dosage and duration of pivmecillinam treatment for uncomplicated lower urinary tract infections: a systematic review and meta-analysis. Int J Infect Dis 2017;58:96–109.
19. Huttner A, Kowalczyk A, Turjeman A, Babich T, Brossier C, Eliakim-Raz N, et al. Effect of 5-day nitrofurantoin vs single dose fosfomycin on clinical resolution of uncomplicated lower urinary tract infection in women: a randomized clinical trial. JAMA 2018;319:1781–9.
20. Giske CG. Contemporary resistance trends and mechanisms for the old antibiotics colistin, temocillin, fosfomycin, mecillinam and nitrofurantoin. Clin Microbiol Infect 2015;21:899–905.
21. Falagas ME, Athanasaki F, Voulgaris GL, Triarides NA, Vardakas KZ. Resistance to fosfomycin: mechanisms, frequency and clinical consequences. Int J Antimicrob Agents 2019;53:22–8.
22. Cattoir V, Pourbaix A, Magnan M, Chau F, de Lastours V, Felden B, et al. Novel chromosomal mutations responsible for fosfomycin resistance in Escherichia coli. Front Microbiol 2020;11:575031
23. Fajfr M, Balik M, Cermakova E, Bostik P. Effective treatment for uncomplicated urinary tract infections with oral fosfomycin, single center four year retrospective study. Antibiotics (Basel) 2020;9:511.
24. Pitout JD, Chan WW, Church DL. Tackling antimicrobial resistance in lower urinary tract infections: treatment options. Expert Rev Anti Infect Ther 2016;14:621–32.
25. European Medicines Agency. Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections, Rev 3, 2018 (EMA/844951/2018 Rev. 3).
26. Infectious Diseases Society of America. White paper: recommendations on the conduct of superiority and organism-specific clinical trials of antibacterial agents for the treatment of infections caused by drug-resistant bacterial pathogens. Clin Infect Dis. 2012;55:1031–46.
27. Konwar M, Gogtay NJ, Ravi R, Thatte UM, Bose D. Evaluation of efficacy and safety of fosfomycin versus nitrofurantoin for the treatment of uncomplicated lower urinary tract infection (UTI) in women – A systematic review and meta-analysis. J Chemother 2021;Jun 21:1-10. doi: 10.1080/1120009X.2021.1938949.
28. Gágyor I, Bleidorn J, Kochen MM, Schmiemann G, Wegscheider K, Hummers-Pradier E. Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: randomised controlled trial. BMJ 2015;351:h6544.

29. Aspevall O, Hallander H, Gant V, Kouri T. European guidelines for urinalysis: a collaborative document produced by European clinical microbiologists and clinical chemists under ECLM in collaboration with ESCMID. Clin Microbiol Infect 2001;7:173–8.
30. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters, version 10.0, 2020. Available at: http://www.eucast.org/clinical_breakpoints/ [accessed 25 July 2021]
31. Kronenberg A, Bütikofer L, Odutayo A, Mühlemann K, da Costa BR, Battaglia M, et al. Symptomatic treatment of uncomplicated lower urinary tract infections in the ambulatory setting: randomised, double blind trial. BMJ 2017;359:j4784.
32. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med 2011;30:377–99.
33. Rubin DB. Multiple imputation for nonresponse in surveys. Wiley: New York, NY, 2004.
34. Vallejo-Torres L, García-Lorenzo B, Serrano-Aguilar P. Estimating a cost-effectiveness threshold for the Spanish NHS. Health Econ 2018;27:746-61.
35. Greenhalgh T, Hinton L, Finlay T, Macfarlane A, Fahy N, Clyde B, et al. Frameworks for supporting patient and public involvement in research: Systematic review and co-design pilot. Health Expect 2019;22:785–801.
36. Jacques-Aviñó C, Pons-Vigués M, Mcghie JE, Rodríguez-Giralt I, Medina-Perucha L, Mahtani-Chugani V, et al. [Public participation in research projects: ways of creating collective knowledge in health]. Gac Sanit 2020;34:200–3.

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 re-attendance to healthcare services and complications with relation to the infection		X	X	X

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_2,abstract_____ _____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	_ 2_____
Funding	4	Sources and types of financial, material, and other support	14, funding _____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_1,14_____
	5b	Name and contact information for the trial sponsor	_14_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__14_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___14_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	4,5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6,7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	table 1
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___6_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___7_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____7_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____7_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____7_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____7_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___unblinded___
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	____8-10_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____10_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	___8_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	___10_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___10,11_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	___10_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	__8_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__not planned___
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__10,11_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	___11_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___11_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	____11_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	11
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8-10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	11
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	13,14
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	attached (suppl)
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	not included
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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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Title

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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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. t.i.d, or 5 days of nitrofurantoin 100 mg t.i.d. A total sample of 1,120 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 3 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: Clinical.gov, reference number NCT04959331. EudraCT Number: 2021-001332-26.

Time schedule: November 2021 to April 2023.

KEY WORDS: Urinary Tract Infections; Women; Patient Outcome Assessment; Bacteriological Eradication; Urinalysis; Anti-Bacterial Agents; Antimicrobial Resistance; Short Course; Primary Health Care.

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 seven 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, albeit 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 to 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 t.i.d. for five 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 day occurred in 70% of patients taking 100 mg of nitrofurantoin

thrice-daily for 5 days and in 58% of patients assigned to a single 3 g dose of fosfomycin. The authors hypothesized 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 3 short-course antibiotic regimens (3 g of fosfomycin once daily for two-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 vs 3 days of pivmecillinam 400 mg. t.i.d, 3 g of fosfomycin 2-days vs 5 days of nitrofurantoin 100 mg t.i.d. and 3 days of pivmecillinam 400 mg. t.i.d. vs 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 four weeks after inclusion in the study and timing of relapse of symptoms and/or bacteriuria; (5) Proportion of patients developing complications (i.e. 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, i.e. 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 4 treatment groups: (1) single 3 g dose of fosfomycin-tromethamine; (2) 3 g of fosfomycin-tromethamine once daily 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 1,120 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 (i.e. symptoms suggestive

of sexually-transmitted infection or vulvovaginitis), and (2) a urine dipstick analysis positive for either nitrites or leukocyte esterase.

Exclusion criteria

Patients with any of the following criteria will be excluded from this trial: (1), male sex; (2) high suspicion of pyelonephritis (i.e. 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 2 in the previous six 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 (i.e. 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 (i.e. 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 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 1,000 colony-forming units per millilitre (CFU/ml). Failure will be defined as bacteriuria ≥ 1,000 CFU/ml with the infecting strain; (3) Bacteriological eradication at day 28 (i.e. proportion of patients bacteriologically cured at the final urine sample); (4) Proportion of patients presenting a relapse of symptoms within the first four 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 November 2021 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 4 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 two months prior to the initiation of the trial to ensure that its use is feasible and reliable. A maximum length of 15 minutes 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 at day 14 (two weeks after patient inclusion) to evaluate their clinical evolution, collect the diaries and collect a new urine sample. The last visit will be at day 28, and patients will also be asked to collect another urine sample. An evaluation of adverse events, re-attendance 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 (i.e. ≥ 1,000 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 (EUCAST) [31]. A urine culture with less than 1,000 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 randomised clinical trials 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 (i.e., pyelonephritis), treatment failure, serious adverse effects or allergic reactions to the medicine will be withdrawn from the study. Patients presenting treatment failure (i.e., ongoing or worsening symptoms) will receive a different antibiotic according to the pre-treatment (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 chi-square 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 hazard ratios with associated 95% confidence intervals 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 health care 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 (September 6, 2021) as well as from a national medicines Research Ethics Committee (IDIAPJGol) have been obtained (reference code 21/173-AC, authorised on September 23, 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. The trial is registered in the ClinicalTrials.gov Protocol registry (NCT04959331) and in the European Clinical Trial Database (EudraCT) (2021-001332-26).

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 to 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 hypothesize 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.

Rest of the members of the SCOUT Study Group

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Contributors

AGS, RMor, and CL drafted the research protocol and both AGS and CL wrote the manuscript. All authors were involved in the protocol development. LMP, ALR, JR and MMM are involved in PPI management. ALR, JR, MMM, CBBM, RMMB, JMC, JMMG and AM are involved in trial conduct and recruitment. AGS, RMor, RMon and CL are involved in trial supervision. AMT is involved in study drug management. MAS is involved in microbiology coordination. ALR and JR contributed to the statistical design and analysis. All authors have contributed to the conception of this clinical trial.

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Competing interests

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

Patient consent

Obtained.

REFERENCES

1. Palou J, Pigrau C, Molina I, Ledesma JM, Angulo J; Grupo Colaborador Español del Estudio ARESC. Etiology and sensitivity of uropathogens identified in uncomplicated lower urinary tract infections in women (ARESC Study): implications on empiric therapy. Med Clin (Barc) 2011;136:1–7.
2. Andreu A, Planells I, Grupo cooperativo español para el estudio de la sensibilidad antimicrobiana de los patógenos urinarios. Etiology of community-acquired lower urinary infections and antimicrobial resistance of Escherichia coli: a national surveillance study. Med Clin (Barc) 2008;130:481–6.
3. Jiménez-Guerra G, Heras-Cañas V, Béjar-Molina L, Sorlózano-Puerto A, Navarro-Marí JM, Gutiérrez-Fernández J. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae from urinary tract infections: Evolution of antimicrobial resistance and treatment options. Med Clin (Barc) 2018;150:262–5.
4. European Centre for Disease Prevention and Control (ECDC). Antimicrobial resistance surveillance in Europe 2019. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2020. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/surveillance-antimicrobial-resistance-Europe-2019.pdf [accessed 25 October 2021]

5. Cuevas O, Oteo J, Lázaro E, Aracil B, de Abajo F, García-Cobos Set al; Spanish EARS-Net Study Group. Significant ecological impact on the progression of fluoroquinolone resistance in Escherichia coli with increased community use of moxifloxacin, levofloxacin and amoxicillin/clavulanic acid. J Antimicrob Chemother 2011;66:664–9.
6. Llor C, Aspiroz C, Cano A, Barranco M. The use of amoxicillin and clavulanic acid and quinolones as first choice antibiotics in uncomplicated urinary tract infections in Spain should be reviewed. Aten Primaria 2012;44:443–4.
7. Rodríguez-Baño J, Oteo J, Ortega A, Villar M, Conejo MC, Bou G, e al. Epidemiological and clinical complexity of amoxicillin-clavulanate-resistant Escherichia coli. J Clin Microbiol 2013;51:2414–7.
8. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol 2015;13:269-84.
9. van Hecke O, Wang K, Lee JJ, Roberts NW, Butler CC. Implications of antibiotic resistance for patients' recovery from common infections in the community: A systematic review and meta-analysis. Clin Infect Dis 2017;65:371–82.
10. Vallano A, Rodríguez D, Barceló ME, López A, Cano A, Viñado B, et al; Grupo de Estudio de las Infecciones del Tracto Urinario en Atención Primaria. Antimicrobial susceptibility of uropathogens and outcome following antibiotic treatment for urinary tract infections in primary health care. Enferm Infecc Microbiol Clin 2006;24:418–25.
11. Guay DR. Contemporary management of uncomplicated urinary tract infections. Drugs 2008;68:1169-205.
12. Patología infecciosa. En: Grupo de Trabajo de Enfermedades Infecciosas de la semFYC. Manual de enfermedades infecciosas en Atención Primaria, 4.a ed. Sociedad Española de Medicina de Familia y Comunitaria; 2017; pp. 815–47.
13. Guía de terapéutica antimicrobiana del área Aljarafe. Distrito Sanitario Aljarafe y Hospital San Juan de Dios del Aljarafe, 3a. Edición, 2018. http://www.juntadeandalucia.es/servicioandaluzdesalud/guiaterapeuticaaljarafe/guiaTerapeuticaAljarafe/ [accessed 25 October 2021]
14. Cai T, Tamanini I, Tascini C, Köves B, Bonkat G, Gacci M, et al. Fosfomycin trometamol versus comparator antibiotics for the treatment of acute uncomplicated urinary tract infections in women: A systematic review and meta-analysis. J Urol 2020;203:570–8.
15. Llor C, Moragas A, Hernández S, Crispi S, Cots JM. Misconceptions of Spanish general practitioners' attitudes toward the management of urinary tract infections and

asymptomatic bacteriuria: an internet-based questionnaire study. Rev Esp Quimioter 2017;30:372–8.

16. Bollestad M, Grude N, Solhaug S, Raffelsberger N, Handal N, Schjelderup Nilsen HJ, et al; the Norwegian ESBL UTI study group. Clinical and bacteriological efficacy of pivmecillinam treatment for uncomplicated urinary tract infections caused by ESBL-producing Escherichia coli: a prospective, multicentre, observational cohort study. J Antimicrob Chemother 2018;73:2503–9.
17. Bjerrum L, Gahrn-Hansen B, Grinsted P. Pivmecillinam versus sulfamethizole for short-term treatment of uncomplicated acute cystitis in general practice: a randomized controlled trial. Scand J Prim Health Care 2009;27:6–11.
18. Pinart M, Kranz J, Jensen K, Proctor T, Naber K, Kunath K, et al. Optimal dosage and duration of pivmecillinam treatment for uncomplicated lower urinary tract infections: a systematic review and meta-analysis. Int J Infect Dis 2017;58:96–109.
19. Huttner A, Kowalczyk A, Turjeman A, Babich T, Brossier C, Eliakim-Raz N, et al. Effect of 5-day nitrofurantoin vs single dose fosfomycin on clinical resolution of uncomplicated lower urinary tract infection in women: a randomized clinical trial. JAMA 2018;319:1781–9.
20. Giske CG. Contemporary resistance trends and mechanisms for the old antibiotics colistin, temocillin, fosfomycin, mecillinam and nitrofurantoin. Clin Microbiol Infect 2015;21:899–905.
21. Falagas ME, Athanasaki F, Voulgaris GL, Triarides NA, Vardakas KZ. Resistance to fosfomycin: mechanisms, frequency and clinical consequences. Int J Antimicrob Agents 2019;53:22–8.
22. Cattoir V, Pourbaix A, Magnan M, Chau F, de Lastours V, Felden B, et al. Novel chromosomal mutations responsible for fosfomycin resistance in Escherichia coli. Front Microbiol 2020;11:575031
23. Fajfr M, Balik M, Cermakova E, Bostik P. Effective treatment for uncomplicated urinary tract infections with oral fosfomycin, single center four year retrospective study. Antibiotics (Basel) 2020;9:511.
24. Bonkat G, Pickard R, Bartoletti R, Cai T, Bruyère F, Geerlings SE, et al. EUA Guidelines on Urological Infections. European Association of Urology, 2018. https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Urological-Infections-2018-large-text.pdf [accessed 25 October 2021]
25. Pitout JD, Chan WW, Church DL. Tackling antimicrobial resistance in lower urinary tract infections: treatment options. Expert Rev Anti Infect Ther 2016;14:621–32.

26. European Medicines Agency. Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections, Rev 3, 2018 (EMA/844951/2018 Rev. 3).
27. Infectious Diseases Society of America. White paper: recommendations on the conduct of superiority and organism-specific clinical trials of antibacterial agents for the treatment of infections caused by drug-resistant bacterial pathogens. Clin Infect Dis. 2012;55:1031–46.
28. Konwar M, Gogtay NJ, Ravi R, Thatte UM, Bose D. Evaluation of efficacy and safety of fosfomycin versus nitrofurantoin for the treatment of uncomplicated lower urinary tract infection (UTI) in women – A systematic review and meta-analysis. J Chemother 2021;Jun 21:1-10. doi: 10.1080/1120009X.2021.1938949.
29. Gágyor I, Bleidorn J, Kochen MM, Schmiemann G, Wegscheider K, Hummers-Pradier E. Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: randomised controlled trial. BMJ 2015;351:h6544.
30. Aspevall O, Hallander H, Gant V, Kouri T. European guidelines for urinalysis: a collaborative document produced by European clinical microbiologists and clinical chemists under ECLM in collaboration with ESCMID. Clin Microbiol Infect 2001;7:173–8.
31. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters, version 10.0, 2020. Available at: http://www.eucast.org/clinical_breakpoints/ [accessed 25 October 2021]
32. Kronenberg A, Bütikofer L, Odutayo A, Mühlemann K, da Costa BR, Battaglia M, et al. Symptomatic treatment of uncomplicated lower urinary tract infections in the ambulatory setting: randomised, double blind trial. BMJ 2017;359:j4784.
33. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med 2011;30:377–99.
34. Rubin DB. Multiple imputation for nonresponse in surveys. Wiley: New York, NY, 2004.
35. Vallejo-Torres L, García-Lorenzo B, Serrano-Aguilar P. Estimating a cost-effectiveness threshold for the Spanish NHS. Health Econ 2018;27:746-61.
36. Greenhalgh T, Hinton L, Finlay T, Macfarlane A, Fahy N, Clyde B, et al. Frameworks for supporting patient and public involvement in research: Systematic review and co-design pilot. Health Expect 2019;22:785–801.
37. Jacques-Aviñó C, Pons-Vigués M, Mcghie JE, Rodríguez-Giralt I, Medina-Perucha L, Mahtani-Chugani V, et al. [Public participation in research projects: ways of creating collective knowledge in health]. Gac Sanit 2020;34:200–3.

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 re-attendance to healthcare services and complications with relation to the infection		X	X	X

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_2,abstract_____ _____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	_ 2_____
Funding	4	Sources and types of financial, material, and other support	14, funding _____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_1,14_____
	5b	Name and contact information for the trial sponsor	_14_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__14_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___14_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	4,5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6,7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	table 1
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___6_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___7_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____7_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____7_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____7_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____7_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___unblinded___
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	____8-10_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____10_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	___8_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	___10_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___10,11_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	___10_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	__8_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__not planned___
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__10,11_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	___11_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___11_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	____11_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	11
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8-10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	11
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	13,14
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	attached (suppl)
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	not included
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.