BMJ Open

Bearberry in the Treatment of Acute Uncomplicated Cystitis (BRUMI)– Protocol of a Multicentre, Randomized Double-Blind Clinical Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057982
Article Type:	Protocol
Date Submitted by the Author:	04-Oct-2021
Complete List of Authors:	Tóth, Barbara; University of Szeged, Department of Pharmacognosy Jávorházy, András; University of Pécs Nyirády, Péter; Semmelweis University, Department of Urology Csupor-Löffler, Boglárka; University of Pécs Birinyi, Péter; Semmelweis University, Department of Pharmacodynamics Zhanel, George; University of Manitoba, Departmental of Medical Microbiology/Infectious Diseases Csupor, Dezső; University of Szeged, Department of Clinical Pharmacy; University of Pécs Naber, Kurt; Technical University of Munich Länger , Reinhard; AGES Medicine Market Auth Vörhendi, Nóra; Institute for Translational Medicine, University of Pécs Medical School; János Szentágothai Research Center, University of Pécs, Hegyi, Péter; Medical School, University of Pécs, Pécs, Hungary, Institute for Translational Medicine; Semmelweis Egyetem, Centre for Translational Medicine
Keywords:	Urinary tract infections < UROLOGY, Interstitial cystitis < UROLOGY, Clinical trials < THERAPEUTICS

Bear**b**erry in the Treatment of Acute **U**nco**m**pli**c**ated Cystitis (BRUMI)– Protocol of a Multicentre, Randomized Double-Blind Clinical Trial

Barbara Tóth,[a,±] András Jávorházy,[b,±] Péter Nyirády,[c] Boglárka Csupor-Löffler,[d] Péter Birinyi,[e] George Zhanel,[f] Kurt Naber,[g] Reinhard Länger,[h] Nóra Vörhendi,[d] Péter Hegyi,[d,i,j] and Dezső Csupor,[a,d,k,*]

[a] Department of Pharmacognosy, Faculty of Pharmacy, University of Szeged, Szeged, Hungary

[b] Urology Clinic, Medical School, University of Pécs, Pécs, Hungary

[c] Department of Urology, Faculty of Medicine, Semmelweis University, Budapest, Hungary

[d] Institute for Translational Medicine, Szentágothai Research Centre, Medical School, University of Pécs, Pécs, Hungary

[e] Department of Pharmacodynamics, Faculty of Pharmacy, Semmelweis University, Budapest, Hungary

[f] Departmental of Medical Microbiology/Infectious Diseases, University of Manitoba, Manitoba, Canada

[g] Department of Urology, Technical University of Munich, Munich, Germany

[h] Austrian Medicines and Medical Devices Agency, Vienna, Austria

[i] Centre for Translational Medicine, Semmelweis University, Budapest, Hungary

[j] Division of Pancreatic Diseases, Heart and Vascular Center, Semmelweis University, Budapest, Hungary

[k] Department of Clinical Pharmacy, Faculty of Pharmacy, University of Szeged, Szeged, Hungary

*Corresponding author: Dezső Csupor, University of Szeged, Faculty of Pharmacy, Department of Clinical Pharmacy, Szeged, Hungary. Telephone: +36 62 545559; Fax: +36 62 545741, e-mail address: csupor.dezso@szte.hu

[±] these authors contributed equally to the paper

Word count: 3131

ABSTRACT

Background

Bearberry *(Arctostaphylos uva-ursi)* leaf is available as a treatment of uncomplicated cystitis in several European countries. The antimicrobial activity of its extracts and some of its individual constituents has been observed *in vitro*; however, the efficacy of bearberry compared to standard antimicrobial therapy has not been assessed yet.

Objective

The objective of the study is to assess the efficacy of bearberry as an alternative therapy in the treatment of acute uncomplicated cystitis in comparison with standard antibiotic therapy (fosfomycin).

Methods and analysis

This is a randomized controlled double-blinded multicentre trial. Patients with acute uncomplicated cystitis will be randomly assigned to group A (3 g single dose of fosfomycin powder and 2 placebo tablets t.i.d. for 7 days) or B (single dose of placebo powder and 2 tablets containing a dry extract of Uvae ursi folium. At least 504 patients (allocated as 1:1) will need to be enrolled to confirm or reject the hypothesis for the primary endpoint.

Improvement of symptoms of uncomplicated cystitis (based on the ACSS score) at day 7 is defined as the primary endpoint, whereas several secondary endpoints such as the number and ratio of patients with bacteriuria at day 7, frequency and severity of side effects; recurrence of urinary tract infection, concurrent use of other OTC (over the counter) medications and food supplements will be determined to elucidate more detailed differences between the groups. The number of recurrences and medications taken for treatment will be monitored for a follow-up period of 90 days (80-100 days).

Keywords:

bearberry; *Arctostaphylos uva-ursi*; fosfomycin; uncomplicated cystitis, urinary tract infection

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first randomised controlled trial to examine the efficacy of bearberry compared to fosfomycin in the treatment of uncomplicated cystitis
- This is a multicentre, prospective, randomised, non-inferiority study
- A validated score will be used to assess efficacy

INTRODUCTION

Urinary tract infections (UTIs) are the most frequent occurring infections in women, and one of the major reasons for antibiotic prescriptions [1]. UTIs are classified as uncomplicated if anatomical or functional abnormalities are not observed in the urinary system. Regarding UTIs, *Escherichia coli* is the most frequent pathogen, followed by *Staphylococcus saprophyticus* and *Enterococcus faecalis* [2,3]. In clinical practice acute uncomplicated cystitis is diagnosed and treated based on the clinical signs and symptoms, microbiologic investigations are not performed routinely. According to the available guidelines, first-line drugs include fosfomycin trometamol, trimethoprim-sulfamethoxazole, nitrofurantoin, nitroxolin and pivmecillinam [4–7].

Fosfomycin possesses a wide spectrum of antibacterial activity against both Gram-negative and Gram-positive pathogens, including *E. coli* [8,9]. Based on a large scale surveillance study, *E. coli*, the most frequently isolated pathogen from UTI samples, is highly susceptibility to fosfomycin with a susceptibility rate of 98.5% [6]. In the majority of the published trials, the achieved short-term (7–9 days) microbial cure rate was more than 80% [10–12].In a more recent study, bacteriologic success through day 14 after treatment with fosfomycin was 73%, whereas clinical success was 66% [13]. Based on the published evidence, a single 3 g dose of fosfomycin trometamol is considered to be sufficient for the treatment of uncomplicated lower UTIs.

Bacterial resistance is one of the major limiting factors of antibiotic use. Despite fosfomycin's activity against resistant strains (e.g. multi-drug resistant *E. coli*), fosfomycin-resistance is an increasing problem [14]. In Spain, the frequency of fosfomycin-resistance increased from 4% to 11% between 1997 and 2009 [15].

Bearberry leaves have been used in traditional medicine for the treatment of acute cystitis. The European Medicines Agency acknowledged the traditional medicinal use of the herbal tea, the powdered plant material as well as defined extracts for treatment of symptoms of mild recurrent lower urinary tract infections such as burning sensation during urination and/or frequent urination in women [16]. The antimicrobial effect of bearberry leaf extracts and hydroquinone derivatives present in the plant have been confirmed in several *in vitro* studies, including several uropathogens. A bearberry leaf extract (extraction solvent ethanol 70%) exhibited antimicrobial activity towards a variety of organisms, including *E. coli* [17]. The pharmacokinetics of hydroquinones have also been studied, confirming the secretion of these compounds into the urine [18]. Unfortunately, no pharmacokinetic data are available on hydroquinone derivatives in patients with acute uncomplicated cystitis and also no data are available on the antimicrobial activities of secondary metabolites of bearberry leaves other

than hydroquinone derivatives. Overall, although there are data suggesting the antimicrobial activity of bearberry components against *E. coli*, there is no direct evidence for their clinical efficacy in humans.

Herbal preparations of bearberry leaf have been accepted as a traditional medicine, however their efficacy has not been confirmed in clinical trials in comparison with antibiotic treatment. In one study, the efficacy was compared to ibuprofen in terms of symptom improvement [19], and in one ongoing trial fosfomycin is used as comparator [20]. The aim of our study is to assess the non-inferiority of a dry extract of bearberry leaves in terms of clinical efficacy and safety in comparison with standard antibiotics used in acute uUTI.

METHODS

Trial design

The study protocol is structured following the SPIRIT statement 2013 [21]. This study is a prospective, multicentre, randomized, controlled, double-blind trial assessing non-inferiority. The allocation ratio is 1:1. Eligible patients will be randomly assigned to groups A (single dose of fosfomycin powder and 2 placebo tablets t.i.d.) or B (single dose of placebo powder and 2 bearberry tablets t.i.d.).

The trial organization, committees, and boards

The corresponding centre and designer of the BRUMI trial is the Centre for Translational Medicine at the Medical School, University of Pécs (coordinating institution and sponsor, www.tm-centre.org) and the Hungarian Phytotherapy Study Group.

The Steering Committee (SC) will be led by Péter Hegyi (University of Pécs, Hungary). The members will be Dezső Csupor and András Jávorházy (University of Pécs, Hungary). SC will make decisions concerning all relevant questions including the dropouts during the study. There will be independent members as well, and the SC will include a patient representative. The SC will supervise the trial primarily and will make decisions regarding all critical questions (protocol deviations, dropouts, etc.)

The International Translational Advisory Board (ITAB*)* will include urologists, microbiologists, and experts in phytotherapy. ITAB will continuously monitor the progress of the study and will give advice to the SC. The study was designed by the SC and ITAB. The study is financially sponsored by the University of Pécs, the Hungarian Academy of Sciences and the National Research, Development and Innovation Office. Neither sponsors were involved in the design of the study, and they will have no access to the database management or to the randomization code.

Sponsor

The sponsor of the BRUMI study is the University of Pécs, Medical School. The sponsor was not involved in the design of the study and will have no access to the database.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

Participating centres

Study participants are recruited from 2 centres in Hungary: Urology Clinic, University of Pécs, Pécs and Department of Urology, Semmelweis University, Budapest. Participants will be recruited from patients visiting the study centres with the symptoms of acute uncomplicated cystitis.

Study population

All premenopausal female patients diagnosed with uncomplicated urinary tract infection presenting to the participating centres will be informed of the possibility of taking part in the BRUMI study. After the consent form is signed, a computer using a block randomization protocol will randomize the patients (**Figure 1**).

Inclusion and exclusion criteria

Non-pregnant premenopausal adult women having acute uncomplicated cystitis will be included to the study. Acute uncomplicated (simple) cystitis is defined as acute urinary tract infection with the symptoms of dysuria, increased frequency and urgency of urination and lower abdominal pain (suprapubic pain), that is presumed to be confined to the bladder; with no signs or symptoms that suggest an upper tract or systemic infection. Acute uncomplicated (simple) cystitis lack signs or symptoms that suggest an infection extending beyond the bladder, which include: (1) elevated body temperature (>37.7°C) or fever; (2) other signs or symptoms of systemic illness (including chills or rigors, significant fatigue or malaise beyond baseline); (3) flank pain; (4) costovertebral angle tenderness [22]. Eligible patients will be premenopausal women with a sum-score of ≥6 for the typical uUTI symptoms (frequency, urgency, painful urination, incomplete emptying, suprapubic pain, and visible haematuria) reported on the Acute Cystitis Symptom Score (ACSS) typical domain and pyuria (10 white blood cells/mm^3 in a mid-stream specimen) at day 0 [23–25]

The exclusion criteria are: (1) any renal disease; (2) upper urinary tract infection; (3) malformations of the urinary tract; (4) congenital disorders of the urinary tract; (5) catheter use; (6) pregnancy; (7) breastfeeding; (8) self-medication with bearberry or antibiotic use in the last 3 months; (9) 5 or more bearberry treatments in the previous year; (10) concomitant use of other antibiotics and NSAIDs; (11) contraindication for study drugs; (12) active malignancy and (13) immunodeficiency, including immunosuppressive treatment.

Interventions

All eligible patients will be randomized to receive either a single dose of fosfomycin (3 g) powder dissolved in 75 ml water and 2 placebo tablets t.i.d. for 7 days (group A), or single dose of placebo powder dissolved in 75 ml water and 2 bearberry tablets t.i.d. for 7 days (group B).

The study drugs are the following: (1) Fosfomycin trometamol as Monural, containing 3 g fosfomycin [in the form of fosfomycin trometamol (5.631 g)]/sachet); (2) Bearberry tablet as Urzinol

containing dry extract of *Arctostaphylos uva-ursi* (L.) Spreng leaf extract (DER 3.5–5.5:1, extracting solvent 60% v/v ethanol), 238.7–297.5 mg extract/tablet, corresponding to 70 mg hydroquinone derivatives, expressed as anhydrous arbutin. Both bearberry leaf extract and the fosfomycin trometamol would be used according to the recommendations of the SPCs. Placebo products will be identical in appearance (and in case of the placebo of the antibiotic powder also in color and taste) with the active treatments.

The doses of the study drugs (fosfomycin trometamol and bearberry leaf extract) were chosen based on either the international guidelines on the treatment of uncomplicated UTIs and on the European Union herbal monograph on *Arctostaphylos uva-ursi* (L.) Spreng., folium [4,5,16].

Patients will be scheduled for follow-up visits at day 7. At the beginning of the study (day 0) and on day 7, patients will be asked to fill in a self-reported questionnaire [Acute Cystitis Symptom Score (ACSS)] [23]. At the beginning of the study and at the visit at day 7, midstream urine specimens will be collected to evaluate bacteriuria (presence and CFU number of pathogens) and the pH of urine. Urine samples collected at day 0 will also be used to rule out pregnancy.

Outcomes

The primary endpoint of our trial is the improvement of symptoms of uncomplicated cystitis after 7 days of treatment. The improvement of symptoms will be determined by using the validated Hungarian version of the Acute Cystitis Symptom Score on day 0 and day 7 according to predefined thresholds [26,27]. Secondary endpoints include the (1) number of patients with urine with $<10^3$ CFU/ml on day 7 in patients with significant bacteriuria (CFU $\geq 10^5$/ml) at D0; (2) average number of CFU of pathogens (7 days after the start of the therapy) in urine; (3) frequency and severity of side effects; (4) recurrence of UTI (follow-up after better during 90 days; severity and diagnostics of recurrences to be assessed by using the ACSS) and (5) concurrent use of other OTC medications and food supplements that are started taking during the 7 day treatment trial.

Randomization and blinding

Participants will be divided into two groups receiving one of the two study treatments in each centre. The allocation of participants to the different groups will be carried out based on predefined randomization lists created separately for each recruiting centre. The randomization lists will be prepared with a block size of 4 and with an allocation ratio of 1:1. Sequentially numbered, sealed envelopes will contain the assigned treatment group for the next participant provided by the biostatistician group of the Centre for Translational Medicine. The medical staff (e.g., those who will take the patients' history, examine the patients, collect the specimen of urine, distributing the study

drugs, diaries, and questionnaires), statisticians performing data analyses and the patients receiving the study drugs will be blinded regarding treatment assignment.

Statistical analysis and sample size calculation

Sample size estimation

Sample size calculation suggests that 504 patients (1:1) will need to be enrolled to confirm or reject the hypothesis for the primary endpoint (80% vs. 77%; non-inferiority margin: 14%) with a 15% dropout, and power 80%.

Statistical analysis

Descriptive statistics – mean, median, standard deviation, quartiles, and relative frequency – relative risk (dichotomous variables) for the primary endpoint. Affiliated statistical analyses will be performed with an error probability of 0.0294 (type-I error probability). A safety analysis will be performed after reaching 10% of the planned sample size.

Interim analysis

We will calculate statistical power for the primary endpoints which will decide whether additional subjects should be enrolled or not. If no more subjects are needed, early stopping will be applied. We will test our hypotheses first in an interim analysis, and at the end of the study, in the final analysis. For this reason, the p-value should be adjusted to diminish the probability of type I error; therefore, the corrected level of significance (p-value) will be 0.0294. A pre-defined interim analysis will be performed after reaching 50% of the planned sample size.

Study duration

The planned starting date of the study is 1 October 2021, and the planned finishing date of the study is 1 September 2023.

Flow and timing

Enrolment

Patients presenting with symptoms referring to uncomplicated urinary tract infection will be examined by a study physician and assessed for eligibility to participate in the trial in the participating clinical centres. Eligible patients will be asked to give an informed consent to the study. Patients will be asked to complete ACSS symptom questionnaire, and along with detailed medical history, duration and

severity of symptoms and activity impairment will be documented. Symptom evaluation will cover the typical symptoms according to the ACSS questionnaire, such as dysuria, urgency, frequency, and lower abdominal pain, each scored from 0 (none) to 3 (strong). UTI-related activity impairment covers impairment by the symptom (see above), scored as well from 0 (none) to 3 (strong). Data will be transferred to electronic CRF (eCRF) by practice staff. On enrolment, midstream urine specimens will be collected (one sample per participant) to perform microbial analysis of the urine and to rule out pregnancy. After performing the above-mentioned tasks, participants will be divided into two groups receiving one of the two study treatments in each centre (**Figure 1**).

Course of the study and follow-up

After randomization, study drugs, questionnaires for recording adverse events and concurrent use of other medications (pain killers, antibiotics, or other OTC drugs) and food supplements that were started during the 7-day treatment trial will be distributed by a study nurse (**Table 1**).

Patients will be asked to take the study drugs as follows: 1 sachet at the first evening after the last urination before going to sleep, and 2 tablets t.i.d. for 7 consecutive days. Patients will also be asked to record adverse events and concurrent use of other medications (pain medications, antibiotics, or other OTC drugs) and food supplements for 7 consecutive days in diaries. The diaries will be collected on day 7 by the assigned study nurses.

Patients will be asked to return the centre for a follow-up at day 7 to complete an ACSS questionnaire and to return the diaries. Clinical efficacy will be defined as a summary score of the 6 typical symptoms of the ACSS no more than 5, with no item >1 and visible haematuria absent. Moreover, to evaluate the efficacy of the treatment arms midstream urine specimens will also be collected on day 7(one sample per patient). Microbiological efficacy will be determined in the subgroup of patients with significant bacteriuria (CFU $>10^5$/ml) at day 0 and elimination of bacteriuria (CFU $<10^3$/ml) at day 7 according to EMA and FDA guidelines [24,25]. ACSS questionnaires (10 questionnaire/patient) will be distributed to patients with the request to fill in a questionnaire each time when there is a recurrence of UTI.

There will be a long-term follow-up documentation on day 90, when patients will be contacted to collect ACSS questionnaires and will be and interviewed for numbers of UTI recurrences, UTI-related consultations, days of sick leave, and medications and food supplements taken for UTI. The aforementioned data will be transferred to the eCRF by study nurses.

	STUDY PERIOD								
	Enrolment	**Allocation**	**Post-allocation**					**Close-out**	**Follow-up**
TIMEPOINT	**Day 0**	**Day 0**	***Day 1***	***Day2***	***Day3***	***Day4***	***Day 5***	***Day 7***	***Day 90***
ENROLMENT:									
Eligibility screen	X								
Informed consent	X								
Assessment of inclusion/exclusion criteria	X								
Allocation, randomization		X							
INTERVENTIONS:									
Pharmacotherapy		←	—	—	—	—	—	→	
ASSESSMENTS:									
ACSS score	X							X	
Patient diaries								X	
Urine culture	X							X	
Follow-up interview									X

Table 1. SPIRIT flowchart: schedule of enrolment, interventions, and assessments

Data management

Data handling

Data handling will be performed confidentially and anonymously and by the Data Monitoring Committee (DMC). Electronic CRFs (eCRFs) will be used. Principal investigator will have full access for the database. Accuracy, completeness and legibility of the data in the eCRF will be ensured by the Investigator. Detailed data flow will be described in a Data Management Plan (DMP). Data from completed eCRFs will be validated at DMC according to a Data Cleaning Plan (DCP) under the direction of the Data Manager. All changes to eCRFs will be documented.

Ethical principles and patient safety

This clinical study will be conducted following the Declaration of Helsinki. It will be conducted in compliance with the protocol, good clinical practice (GCP) (2001/20/EEC, CPMP/ICH/135/95), designated standard operating procedures, and local laws and regulations relevant to the country of conduct. The study has been approved by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (IV/4225-1/2021/EKU). All patients voluntarily sign the informed consent form, indicating that they agree to participate.

During the study, all investigators will report adverse or serious adverse events on a separate form which must be sent to both SC and DMC. If any adverse or serious adverse effects emerge, SC will discuss and, if the adverse effect is confirmed, it will be reported to the relevant institutional and national ethical committee (http://www.ett.hu/tukeb.htm).

DISCUSSION

Although herbal preparations of bearberry leaves are available as a medicine, their clinical efficacy and safety has not been confirmed in acute uncomplicated cystitis. The assessment of their efficacy is of primary importance: if it does not have a sufficient clinical efficacy, it should not be considered as an alternative to antibiotic treatment; however, if it is non-inferior to fosfomycin, it could be used as an alternative to fosfomycin, a traditional antibiotic. The aim of our study is to provide information regarding the clinical efficacy of bearberry leaf extract in the treatment of acute uncomplicated cystitis compared to standard antibiotic therapy. The study was designed to assess non-inferiority of bearberry leaf compared to fosfomycin for patients with acute uncomplicated cystitis.

The use of bearberry has only been supported by its long-standing usage; therefore, in the European Union traditional herbal medicinal products can be prepared from the plant. However, properly designed and well executed clinical trials may enable the European Medicines Agency's Committee on Herbal Medicinal Products (HMPC) to assess whether a well-established use monograph might be granted for this plant. Results of this clinical trial will help to revise the recommendations on the treatment of uncomplicated cystitis. If bearberry leaf proves to be non-inferior to fosfomycin, the therapeutic approach of uncomplicated cystitis may be changed in a long-term, which might lead to fewer antibiotic prescriptions and subsequent lower antibiotic resistance rates.

COMPETING INTERESTS

There are no financial or other competing interests among the principal investigator, the included participants, or any member of the trial.

FUNDING

Centre costs (IT, biostatistics, trial organization, etc.) are covered by the University of Pécs, Momentum Grant of the Hungarian Academy of Sciences (LP2014-10/2014); and Economic Development and Innovation Operative Programme Grant and Highly Cited Publication Grant of the National Research, Development and Innovation Office (GINOP-2.3.2-15-2016-00015, KH-125678). Since no additional treatment is necessary for the study, the general healthcare costs are covered by the National Healthcare System (grant number not applicable). This study was designed with help of the Centre for Translational Medicine at the University of Pécs. This centre is committed to improve patients' life with research activities (http://www.tm-pte.org/).

AUTHOR CONTRIBUTIONS

BT: conceptualization, writing the protocol

NV: writing the protocol, methodology

AJ: methodology, critical revising of the protocol

PB, GZ, KN, RL, BCL, PH: critical revising of the protocol

DC: conceptualization, writing the protocol, supervision

DISCLAIMER

The contribution of the author R. Länger does not necessarily represent the views of the AGES Medizinmarktaufsicht / BASG in Austria nor of the (committees of the) European Medicines Agency.

ETHICS APPROVAL AND TRIAL REGISTRATION

The study has been approved by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (IV/4225-1/2021/EKU) and has been registered at clinicaltrials.gov (NCT05055544).

Figure legend

Figure 1: Flow chart of participants (SPIRIT 2013 statement)

REFERENCES

[1] K.G. Naber, G. Schito, H. Botto, J. Palou, T. Mazzei, Surveillance Study in Europe and Brazil on Clinical Aspects and Antimicrobial Resistance Epidemiology in Females with Cystitis (ARESC): Implications for Empiric Therapy, Eur. Urol. 54 (2008) 1164–1178. https://doi.org/10.1016/j.eururo.2008.05.010.

[2] G.M. Keating, Fosfomycin trometamol: a review of its use as a single-dose oral treatment for patients with acute lower urinary tract infections and pregnant women with asymptomatic bacteriuria., Drugs. 73 (2013) 1951–66. https://doi.org/10.1007/s40265-013-0143-y.

[3] K. Gupta, T.M. Hooton, K.G. Naber, B. Wullt, R. Colgan, L.G. Miller, G.J. Moran, L.E. Nicolle, R. Raz, A.J. Schaeffer, D.E. Soper, International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases, Clin. Infect. Dis. 52 (2011) e103–e120. https://doi.org/10.1093/cid/ciq257.

[4] J. Kranz, S. Schmidt, C. Lebert, L. Schneidewind, F. Mandraka, M. Kunze, S. Helbig, W. Vahlensieck, K. Naber, G. Schmiemann, F.M. Wagenlehner, The 2017 Update of the German Clinical Guideline on Epidemiology, Diagnostics, Therapy, Prevention, and Management of Uncomplicated Urinary Tract Infections in Adult Patients. Part II: Therapy and Prevention, Urol. Int. 100 (2018) 271–278. https://doi.org/10.1159/000487645.

[5] K. Gupta, T.M. Hooton, K.G. Naber, B. Wullt, R. Colgan, L.G. Miller, G.J. Moran, L.E. Nicolle, R. Raz, A.J. Schaeffer, D.E. Soper, International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases, Clin. Infect. Dis. 52 (2011). https://doi.org/10.1093/cid/ciq257.

[6] J. Kranz, S. Schmidt, C. Lebert, L. Schneidewind, W. Vahlensieck, U. Sester, R. Fünfstück, S. Helbig, W. Hofmann, E. Hummers, M. Kunze, E. Kniehl, K. Naber, F. Mandraka, B. Mündner-Hensen, G. Schmiemann, F.M.E. Wagenlehner, [Epidemiology, diagnostics, therapy, prevention and management of uncomplicated bacterial outpatient acquired urinary tract infections in adult patients : Update 2017 of the interdisciplinary AWMF S3 guideline]., Urologe. A. 56 (2017) 746–758. https://doi.org/10.1007/s00120-017-0389-1.

[7] EAU Guidelines: Urological Infections | Uroweb, (n.d.). https://uroweb.org/guideline/urological-infections/ (accessed March 10, 2020).

[8] B.J. Gardiner, A.J. Stewardson, I.J. Abbott, A.Y. Peleg, Nitrofurantoin and fosfomycin for resistant urinary tract infections: Old drugs for emerging problems, Aust. Prescr. 42 (2019) 14–19. https://doi.org/10.18773/austprescr.2019.002.

[9] M.E. Falagas, E.K. Vouloumanou, G. Samonis, K.Z. Vardakas, Fosfomycin, Clin. Microbiol. Rev.

29 (2016) 321–347. https://doi.org/10.1128/CMR.00068-15.

[10] E. Van Pienbroek, J. Hermans, A.A. Kaptein, J.D. Mulder, Fosfomycin trometamol in a single dose versus seven days nitrofurantoin in the treatment of acute uncomplicated urinary tract infections in women, Pharm. World Sci. 15 (1993) 257–262. https://doi.org/10.1007/BF01871127.

[11] G.E. Stein, Comparison of single-dose fosfomycin and a 7-day course of nitrofurantoin in female patients with uncomplicated urinary tract infection, Clin. Ther. 21 (1999) 1864–1872. https://doi.org/10.1016/S0149-2918(00)86734-X.

[12] M.A. Minassian, D.A. Lewis, D. Chattopadhyay, B. Bovill, G.J. Duckworth, J.D. Williams, A comparison between single-dose fosfomycin trometamol (Monuril®) and a 5-day course of trimethoprim in the treatment of uncomplicated lower urinary tract infection in women, Int. J. Antimicrob. Agents. 10 (1998) 39–47. https://doi.org/10.1016/S0924-8579(98)00021-1.

[13] A. Huttner, A. Kowalczyk, A. Turjeman, T. Babich, C. Brossier, N. Eliakim-Raz, K. Kosiek, B.M. De Tejada, X. Roux, S. Shiber, U. Theuretzbacher, E. Von Dach, D. Yahav, L. Leibovici, M. Godycki-Ćwirko, J.W. Mouton, S. Harbarth, 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 - J. Am. Med. Assoc. 319 (2018) 1781–1789. https://doi.org/10.1001/jama.2018.3627.

[14] C. Loras, A.C. Mendes, L. Peixe, Â. Novais, J.-I. Alós, Escherichia coli resistant to fosfomycin from urinary tract infections: Detection of the fosA3 gene in Spain, J. Glob. Antimicrob. Resist. (2020). https://doi.org/10.1016/j.jgar.2020.01.023.

[15] J. Oteo, V. Bautista, N. Lara, O. Cuevas, M. Arroyo, S. Fernández, E. Lázaro, F.J. de Abajo, J. Campos, Spanish ESBL-EARS-Net Study Group, Parallel increase in community use of fosfomycin and resistance to fosfomycin in extended-spectrum beta-lactamase (ESBL)-producing Escherichia coli., J. Antimicrob. Chemother. 65 (2010) 2459–63. https://doi.org/10.1093/jac/dkq346.

[16] E. Medicines Agency, European Union herbal monograph on Arctostaphylos uva-ursi (L.) Spreng., folium, 2009. www.ema.europa.eu/contact (accessed February 23, 2020).

[17] S.A. Moskalenko, Preliminary screening of far-eastern ethnomedicinal plants for antibacterial activity, J. Ethnopharmacol. 15 (1986) 231–259. https://doi.org/10.1016/0378-8741(86)90163-7.

[18] E. Medicines Agency, Uvae ursi folium - AR, n.d. www.ema.europa.eu/contact (accessed February 23, 2020).

[19] M. Moore, J. Trill, C. Simpson, F. Webley, M. Radford, L. Stanton, T. Maishman, A. Galanopoulou, A. Flower, C. Eyles, M. Willcox, A.D. Hay, E. van der Werf, S. Gibbons, G.

Lewith, P. Little, G. Griffiths, Uva-ursi extract and ibuprofen as alternative treatments for uncomplicated urinary tract infection in women (ATAFUTI): a factorial randomized trial., Clin. Microbiol. Infect. 25 (2019) 973–980. https://doi.org/10.1016/j.cmi.2019.01.011.

[20] K. Afshar, N. Fleischmann, G. Schmiemann, J. Bleidorn, E. Hummers-Pradier, T. Friede, K. Wegscheider, M. Moore, I. Gágyor, Reducing antibiotic use for uncomplicated urinary tract infection in general practice by treatment with uva-ursi (REGATTA) - a double-blind, randomized, controlled comparative effectiveness trial., BMC Complement. Altern. Med. 18 (2018) 203. https://doi.org/10.1186/s12906-018-2266-x.

[21] A.W. Chan, J.M. Tetzlaff, D.G. Altman, A. Laupacis, P.C. Gøtzsche, K. Krleža-Jerić, A. Hróbjartsson, H. Mann, K. Dickersin, J.A. Berlin, C.J. Doré, W.R. Parulekar, W.S.M. Summerskill, T. Groves, K.F. Schulz, H.C. Sox, F.W. Rockhold, D. Rennie, D. Moher, SPIRIT 2013 statement: Defining standard protocol items for clinical trials, Ann. Intern. Med. 158 (2013) 200–207. https://doi.org/10.7326/0003-4819-158-3-201302050-00583.

[22] Acute simple cystitis in women - UpToDate, (n.d.). https://www.uptodate.com/contents/acute-simple-cystitis-in-women (accessed February 24, 2020).

[23] J.F. Alidjanov, U.A. Abdufattaev, S.A. Makhsudov, A. Pilatz, F.A. Akilov, K.G. Naber, F.M. Wagenlehner, New Self-Reporting Questionnaire to Assess Urinary Tract Infections and Differential Diagnosis: Acute Cystitis Symptom Score, Urol. Int. 92 (2014) 230–236. https://doi.org/10.1159/000356177.

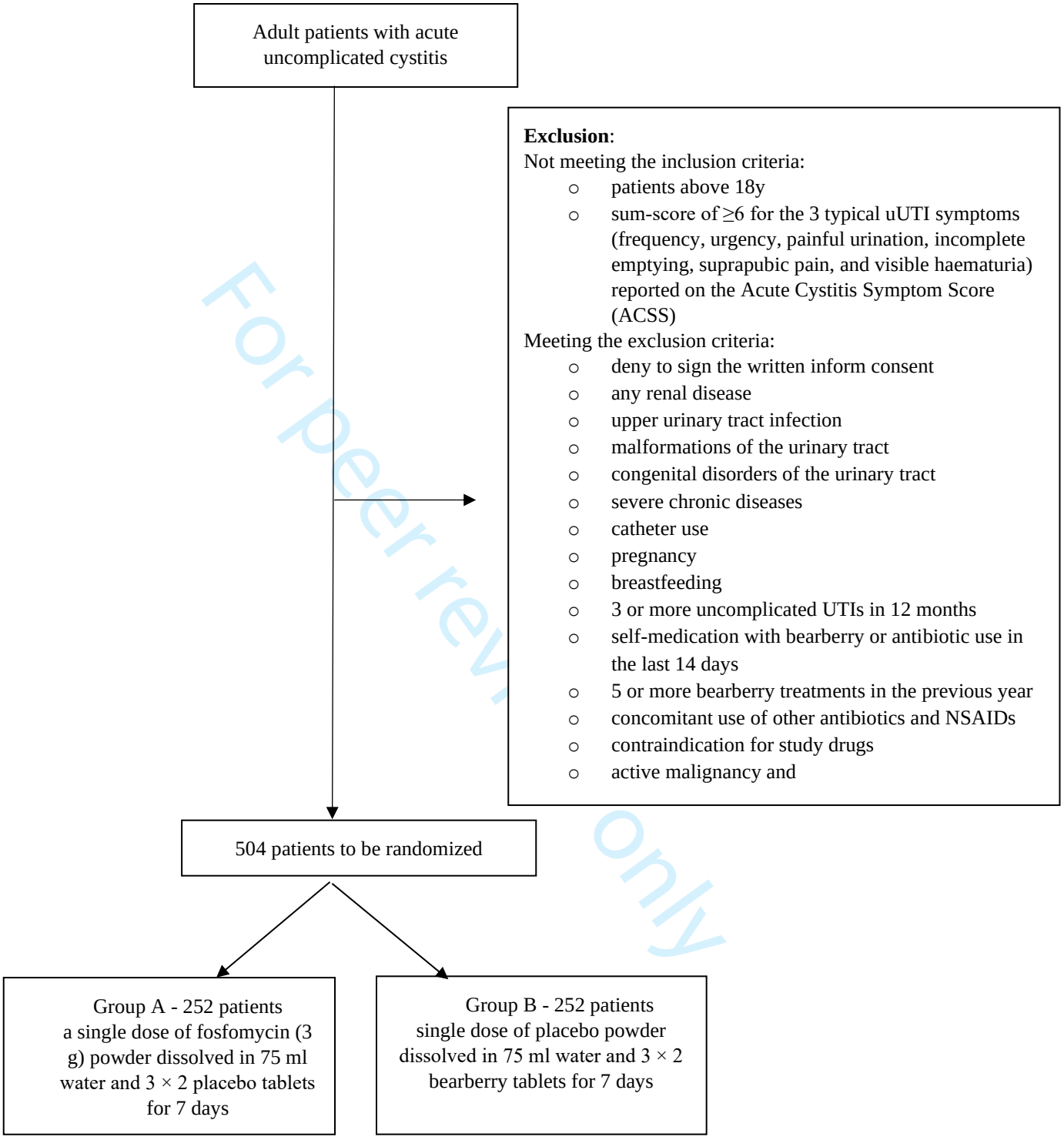
[24] Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections, Rev. 3, London, 2018. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-evaluation-medicinal-products-indicated-treatment-bacterial-infections-revision-3_en.pdf (accessed November 5, 2020).

[25] Uncomplicated Urinary Tract Infections: Developing Drugs for Treatment Guidance for Industry, Rockville, 2019. https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs (accessed August 10, 2021).

[26] A. Magyar, J. Alidjanov, A. Pilatz, K. Nagy, V.K.A. Arthanareeswaran, S. Póth, A. Bécsi, F.M.E. Wagenlehner, K.G. Naber, P. Tenke, B. Köves, The role of the acute cystitis symptom score questionnaire for research and antimicrobial stewardship. Validation of the Hungarian version, Cent. Eur. J. Urol. 71 (2018) 134–141. https://doi.org/10.5173/ceju.2018.1530.

[27] J.F. Alidjanov, K.G. Naber, A. Pilatz, A. Radzhabov, M. Zamuddinov, A. Magyar, P. Tenke, F.M. Wagenlehner, Additional assessment of Acute Cystitis Symptom Score questionnaire for patient-reported outcome measure in female patients with acute uncomplicated cystitis: part II, World J. Urol. 2019 388. 38 (2019) 1977–1988. https://doi.org/10.1007/S00345-019-02948-

8.



Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	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	13
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	13
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	13
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#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	13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	13

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
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	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	4
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, non-inferiority, exploratory)	5
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	5

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
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#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)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
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	7

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)	7
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	8
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,	7

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: 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
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#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	11

Data collection plan: retention	#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	11
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	11
Statistics: outcomes	#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	8
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
Statistics: analysis population and missing data	#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)	n/a
Methods: Monitoring			
Data monitoring: formal committee	#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	11

		details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#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	n/a
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	9
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
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)	n/a

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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	n/a
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Data access	#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	n/a
Dissemination policy: trial results	#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	n/a

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
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

BMJ Open

Bearberry in the Treatment of Acute Uncomplicated Cystitis (BRUMI)– Protocol of a Multicentre, Randomized Double-Blind Clinical Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057982.R1
Article Type:	Protocol
Date Submitted by the Author:	02-Apr-2022
Complete List of Authors:	Tóth, Barbara; University of Szeged, Department of Pharmacognosy Jávorházy, András; University of Pécs Nyirády, Péter; Semmelweis University, Department of Urology Csupor-Löffler, Boglárka; University of Pécs Birinyi, Péter; Semmelweis University, Department of Pharmacodynamics Zhanel, George; University of Manitoba, Departmental of Medical Microbiology/Infectious Diseases Naber, Kurt; Technical University of Munich Länger , Reinhard; AGES Medicine Market Auth Vörhendi, Nóra; Institute for Translational Medicine, University of Pécs Medical School; János Szentágothai Research Center, University of Pécs, Gede, Noémi; Medical School, University of Pécs, Pécs, Hungary, Institute for Translational Medicine Váncsa, Szilárd; University of Pécs; University of Pécs Hegyi, Péter; Medical School, University of Pécs, Pécs, Hungary, Institute for Translational Medicine; Semmelweis Egyetem, Centre for Translational Medicine Csupor, Dezső; University of Szeged, Department of Clinical Pharmacy; University of Pécs
Primary Subject Heading:	Urology
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	Urinary tract infections < UROLOGY, Interstitial cystitis < UROLOGY, Clinical trials < THERAPEUTICS

Bear**b**erry in the Treatment of Acute **U**nco**m**pli**c**ated Cystitis (BRUMI)– Protocol of a Multicentre, Randomized Double-Blind Clinical Trial

Barbara Tóth,[a,±] András Jávorházy,[b,±] Péter Nyirády,[c] Boglárka Csupor-Löffler,[d] Péter Birinyi,[e] George Zhanel,[f] Kurt Naber,[g] Reinhard Länger,[h] Nóra Vörhendi,[d] Noémi Gede,[d] Szilárd Váncsa,[i,j] Péter Hegyi,[d,i,j] and Dezső Csupor,[a,d,k,*]

[a] Department of Pharmacognosy, Faculty of Pharmacy, University of Szeged, Szeged, Hungary

[b] Urology Clinic, Medical School, University of Pécs, Pécs, Hungary

[c] Department of Urology, Faculty of Medicine, Semmelweis University, Budapest, Hungary

[d] Institute for Translational Medicine, Szentágothai Research Centre, Medical School, University of Pécs, Pécs, Hungary

[e] Department of Pharmacodynamics, Faculty of Pharmacy, Semmelweis University, Budapest, Hungary

[f] Departmental of Medical Microbiology/Infectious Diseases, University of Manitoba, Manitoba, Canada

[g] Department of Urology, Technical University of Munich, Munich, Germany

[h] Austrian Medicines and Medical Devices Agency, Vienna, Austria

[i] Centre for Translational Medicine, Semmelweis University, Budapest, Hungary

[j] Division of Pancreatic Diseases, Heart and Vascular Center, Semmelweis University, Budapest, Hungary

[k] Department of Clinical Pharmacy, Faculty of Pharmacy, University of Szeged, Szeged, Hungary

*Corresponding author: Dezső Csupor, University of Szeged, Faculty of Pharmacy, Department of Clinical Pharmacy, Szeged, Hungary. Telephone: +36 62 545559; Fax: +36 62 545741, e-mail address: csupor.dezso@szte.hu

[±] these authors contributed equally to the paper

Word count: 3131

ABSTRACT

Background

Bearberry *(Arctostaphylos uva-ursi)* leaf is available as a treatment of uncomplicated cystitis in several European countries. The antimicrobial activity of its extracts and some of its individual constituents has been observed *in vitro*; however, the efficacy of bearberry compared to standard antimicrobial therapy has not been assessed yet.

Objective

The objective of the study is to assess the safety and non-inferiority of bearberry as an alternative therapy in the treatment of acute uncomplicated cystitis in comparison with standard antibiotic therapy (fosfomycin).

Methods and analysis

This is a randomized controlled double-blinded multicentre trial. Eligible patients will be premenopausal women with a sum-score of ≥6 for the typical acute uncomplicated cystitis symptoms (frequency, urgency, painful urination, incomplete emptying, suprapubic pain, and visible haematuria) reported on the Acute Cystitis Symptom Score (ACSS) typical domain and pyuria. Patients will be randomly assigned to receive 3 g single dose of fosfomycin powder and 2 placebo tablets t.i.d. for 7 days or B a single dose of placebo powder and 2 tablets containing a dry extract of Uvae ursi folium. At least 504 patients (allocated as 1:1) will need to be enrolled to access non-inferiority with a non-inferiority limit of 14% for the primary endpoint.

Improvement of symptoms of uncomplicated cystitis (based on the ACSS score) at day 7 is defined as the primary endpoint, whereas several secondary endpoints such as the number and ratio of patients with bacteriuria at day 7, frequency and severity of side effects; recurrence of urinary tract infection, concurrent use of other OTC (over the counter) medications and food supplements will be determined to elucidate more detailed differences between the groups. The number of recurrences and medications taken for treatment will be monitored for a follow-up period of 90 days (80-100 days).

Keywords:

bearberry; *Arctostaphylos uva-ursi*; fosfomycin; uncomplicated cystitis, urinary tract infection

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first randomised controlled trial to examine the efficacy of bearberry compared to fosfomycin in the treatment of uncomplicated cystitis
- This is a multicentre, prospective, randomised, non-inferiority study
- A validated score will be used to assess efficacy

INTRODUCTION

Urinary tract infections (UTIs) are the most frequent occurring infections in women, and one of the major reasons for antibiotic prescriptions [1]. UTIs are classified as uncomplicated if anatomical or functional abnormalities are not observed in the urinary system. Regarding UTIs, *Escherichia coli* is the most frequent pathogen, followed by *Staphylococcus saprophyticus* and *Enterococcus faecalis* [2,3]. In clinical practice acute uncomplicated cystitis is diagnosed and treated based on the clinical signs and symptoms, microbiologic investigations are not performed routinely. According to the available guidelines, first-line drugs include fosfomycin trometamol, trimethoprim-sulfamethoxazole, nitrofurantoin, nitroxolin and pivmecillinam [4–7].

Fosfomycin, a first-line medication of acute uncomplicated cystitis possesses a wide spectrum of antibacterial activity against both Gram-negative and Gram-positive pathogens, including *E. coli* [8,9]. Based on a large scale surveillance study, *E. coli*, the most frequently isolated pathogen from UTI samples, is highly susceptibility to fosfomycin with a susceptibility rate of 98.5% [6]. In the majority of the published trials, the achieved short-term (7–9 days) microbial cure rate was more than 80% [10–12].In a more recent study, bacteriologic success through day 14 after treatment with fosfomycin was 73%, whereas clinical success was 66% [13]. Based on the published evidence, a single 3 g dose of fosfomycin trometamol is considered to be sufficient for the treatment of uncomplicated lower UTIs.

Bacterial resistance is one of the major limiting factors of antibiotic use. Despite fosfomycin's activity against resistant strains (e.g. multi-drug resistant *E. coli*), fosfomycin-resistance is an increasing problem [14]. In Spain, the frequency of fosfomycin-resistance increased from 4% to 11% between 1997 and 2009 [15].

Bearberry leaves have been used in traditional medicine for the treatment of acute cystitis. The European Medicines Agency acknowledged the traditional medicinal use of the herbal tea, the powdered plant material as well as defined extracts for treatment of symptoms of mild recurrent lower urinary tract infections such as burning sensation during urination and/or frequent urination in women [16]. The antimicrobial effect of bearberry leaf extracts and hydroquinone derivatives present in the plant have been confirmed in several *in vitro* studies, including several uropathogens. A bearberry leaf extract (extraction solvent ethanol 70%) exhibited antimicrobial activity towards a variety of organisms, including *E. coli* [17]. The pharmacokinetics of hydroquinones have also been studied, confirming the secretion of these compounds into the urine [18]. Unfortunately, no pharmacokinetic data are available on hydroquinone derivatives in patients with acute uncomplicated cystitis and also no data are available on the antimicrobial activities of secondary metabolites of bearberry leaves other

than hydroquinone derivatives. Overall, although there are data suggesting the antimicrobial activity of bearberry components against *E. coli*, there is no direct evidence for their clinical efficacy in humans.

Herbal preparations of bearberry leaf have been accepted as a traditional medicine, however their efficacy has not been confirmed in clinical trials in comparison with antibiotic treatment. So far, no resistance has been reported for bearberry. The lack of resistance, together with the cost-effectiveness of the treatment might be the major advantages of the use of this plant as a medicine in the treatment of acute uncomplicated cystitis. In one study, the efficacy was compared to ibuprofen in terms of symptom improvement [19], and in one ongoing trial fosfomycin is used as comparator [20]. The aim of our study is to assess the non-inferiority of a dry extract of bearberry leaves in terms of clinical efficacy and safety in comparison with standard antibiotics used in acute uUTI.

METHODS

Trial design

The study protocol is structured following the SPIRIT statement 2013 [21]. This study is a multicentre, randomized, controlled, double-blind trial assessing non-inferiority. The allocation ratio is 1:1. Eligible patients will be randomly assigned to groups A (single dose of fosfomycin powder and 2 placebo tablets t.i.d.) or B (single dose of placebo powder and 2 bearberry tablets t.i.d.). The trial will be carried out in 2022-2023.

The trial organization, committees, and boards

The corresponding centre and designer of the BRUMI trial is the Centre for Translational Medicine at the Medical School, University of Pécs (coordinating institution and sponsor, www.tm-centre.org) and the Hungarian Phytotherapy Study Group.

The Steering Committee (SC) will be led by Péter Hegyi (University of Pécs, Hungary). The members will be Dezső Csupor and András Jávorházy (University of Pécs, Hungary). SC will make decisions concerning all relevant questions including the dropouts during the study. There will be independent members as well, and the SC will include a patient representative. The SC will supervise the trial primarily and will make decisions regarding all critical questions (protocol deviations, dropouts, etc.)

The International Translational Advisory Board (ITAB*J* will include urologists, microbiologists, and experts in phytotherapy. ITAB will continuously monitor the progress of the study and will give advice to the SC. The study was designed by the SC and ITAB. The study is financially sponsored by the University of Pécs, the Hungarian Academy of Sciences and the National Research, Development and Innovation Office. Neither sponsors were involved in the design of the study, and they will have no access to the database management or to the randomization code.

Sponsor

The sponsor of the BRUMI study is the University of Pécs, Medical School. The sponsor was not involved in the design of the study and will have no access to the database.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

Participating centres

Study participants are recruited from 2 centres in Hungary: Urology Clinic, University of Pécs, Pécs and Department of Urology, Semmelweis University, Budapest. Participants will be recruited from patients visiting the study centres with the symptoms of acute uncomplicated cystitis.

Study population

All premenopausal female patients diagnosed with uncomplicated urinary tract infection presenting to the participating centres will be informed of the possibility of taking part in the BRUMI study. After the consent form is signed, a computer using a block randomization protocol will randomize the patients (**Figure 1**).

Inclusion and exclusion criteria

Non-pregnant adult women before menopause (absence of menses for 1 year) having acute uncomplicated cystitis will be included to the study. Acute uncomplicated (simple) cystitis is defined as acute urinary tract infection with the symptoms of dysuria, increased frequency and urgency of urination and lower abdominal pain (suprapubic pain), that is presumed to be confined to the bladder; with no signs or symptoms that suggest an upper tract or systemic infection. Acute uncomplicated (simple) cystitis lack signs or symptoms that suggest an infection extending beyond the bladder, which include: (1) elevated body temperature (>37.7°C) or fever; (2) other signs or symptoms of systemic illness (including chills or rigors, significant fatigue or malaise beyond baseline); (3) flank pain; (4) costovertebral angle tenderness [22]. Eligible patients will be premenopausal women with a sum-score of ≥6 for the typical uUTI symptoms (frequency, urgency, painful urination, incomplete emptying, suprapubic pain, and visible haematuria) reported on the Acute Cystitis Symptom Score (ACSS) typical domain and pyuria (10 white blood cells/mm^3 in a mid-stream specimen) at day 0 [23–25]

The exclusion criteria are: (1) any renal disease; (2) upper urinary tract infection; (3) malformations of the urinary tract; (4) congenital disorders of the urinary tract; (5) catheter use; (6) pregnancy; (7) breastfeeding; (8) self-medication with bearberry in the last 14 days; (9) 5 or more bearberry treatments in the previous year; (10) any antibiotic therapy or hospitalisation within the last 4 weeks (11) concomitant use of other antibiotics and NSAIDs; (12) contraindication for study drugs; (13) active malignancy and (14) immunodeficiency, including immunosuppressive treatment.

Randomization and blinding

Participants will be divided into two groups (1:1) receiving one of the two study treatments in each centre. Randomization will be performed by using a predefined list with balanced blocked allocation size of four, stratified by recruiting centres, using a computer-generated random sequence. The medical staff (e.g., those who will take the patients' history, examine the patients, collect the specimen

of urine, distributing the study drugs, diaries, and questionnaires), statisticians performing data analyses and the patients receiving the study drugs will be blinded regarding treatment assignment. P. B. (who will be not involved in the clinical study) will coordinate the preparation of medication packages. The packages will be prepared for each patients separately and will be labelled with individual codes only.

Interventions

All eligible patients will be randomized to receive either a single dose of fosfomycin (3 g) powder dissolved in 75 ml water and 2 placebo tablets t.i.d. for 7 days, or single dose of placebo powder dissolved in 75 ml water and 2 bearberry tablets t.i.d. for 7 days.

The study drugs are the following: (1) Fosfomycin trometamol as Monural, containing 3 g fosfomycin [in the form of fosfomycin trometamol (5.631 g)]/sachet); (2) Bearberry tablet as Urzinol containing dry extract of *Arctostaphylos uva-ursi* (L.) Spreng leaf extract (DER 3.5–5.5:1, extracting solvent 60% v/v ethanol), 238.7–297.5 mg extract/tablet, corresponding to 70 mg hydroquinone derivatives, expressed as anhydrous arbutin. Both bearberry leaf extract and the fosfomycin trometamol would be used according to the recommendations of the SPCs. Placebo products will be identical in appearance (and in case of the placebo of the antibiotic powder also in color and taste) with the active treatments.

The doses of the study drugs (fosfomycin trometamol and bearberry leaf extract) were chosen based on either the international guidelines on the treatment of uncomplicated UTIs and on the European Union herbal monograph on *Arctostaphylos uva-ursi* (L.) Spreng., folium [4,5,16].

Patients will be scheduled for follow-up visits at day 7. At the beginning of the study (day 0) and on day 7, patients will be asked to fill in a self-reported questionnaire [Acute Cystitis Symptom Score (ACSS)] [23]. At the beginning of the study and at the visit at day 7, midstream urine specimens will be collected to evaluate bacteriuria (presence and CFU number of pathogens) and the pH of urine. Urine samples collected at day 0 will also be used to rule out pregnancy.

Outcomes

The primary endpoint of our trial is the improvement of symptoms of uncomplicated cystitis after 7 days of treatment. The improvement of symptoms will be determined by using the validated Hungarian version of the Acute Cystitis Symptom Score on day 0 and day 7 according to the following predefined thresholds: summary score of the typical symptoms ≤ 5 scores, no item >1 (mild), and “visible blood in urine” negative [26,27].

Secondary endpoints include the (1) number of patients with urine with $<10^3$ CFU/ml on day 7 in patients with significant bacteriuria (CFU $\geq 10^5$/ml) at D0; (2) average number of CFU of pathogens (7

days after the start of the therapy) in urine; (3) frequency and severity of side effects; (4) recurrence of UTI (follow-up after better during 90 days; severity and diagnostics of recurrences to be assessed by using the ACSS) and (5) concurrent use of other OTC medications and food supplements that are started taking during the 7 day treatment trial.

Statistical analysis and sample size calculation

Sample size estimation

Sample size calculation suggests that 504 patients (1:1) will need to be enrolled to confirm or reject the hypothesis for the primary endpoint, i.e. improvement of symptoms of uncomplicated cystitis based on the ACSS score at day 7 (80% vs. 77%; non-inferiority margin: 14%) with a 15% dropout, and power 80%. For this calculation we considered the clinical cure rates of different antibiotic treatments in UTI (79-92%) [28]. Sample size calculation was performed for the dichotomous primary endpoint by using Stata 16 (Stata Corp).

Statistical analysis

Descriptive statistics – mean, median, standard deviation, quartiles, and relative frequency – relative risk (dichotomous variables) for the primary endpoint. Statistical analyses will be performed with an error probability of 0.0294 (type-I error probability). A safety analysis will be performed after reaching 10% of the planned sample size. Odds ratio will be calculated for the primary endpoint.Statistical analysis will be performed by using R Core Team (2022; R Foundation for Statistical Computing, Vienna, Austria).

Interim analysis

A pre-defined interim analysis will be performed after reaching 50% of the planned sample size. We will calculate statistical power for the primary endpoint which will decide whether additional subjects should be enrolled or not. If 80% statistical power is reached, no more subjects will be needed, and early stopping will be applied. We will test our hypotheses first in an interim analysis, and at the end of the study, in the final analysis. For this reason, the p-value should be adjusted to diminish the probability of type I error; therefore, the corrected level of significance (p-value) will be 0.0294.

Study duration

The planned starting date of the study is 1 October 2021, and the planned finishing date of the study is 1 September 2023.

Flow and timing

Enrolment

Patients presenting with symptoms referring to uncomplicated urinary tract infection will be examined by a study physician and assessed for eligibility to participate in the trial in the participating clinical centres. Eligible patients will be asked to give an informed consent to the study. Patients will be asked to complete ACSS symptom questionnaire, and along with detailed medical history, duration and severity of symptoms and activity impairment will be documented. Symptom evaluation will cover the typical symptoms according to the ACSS questionnaire, such as dysuria, urgency, frequency, and lower abdominal pain, each scored from 0 (none) to 3 (strong). UTI-related activity impairment covers impairment by the symptom (see above), scored as well from 0 (none) to 3 (strong). Data will be transferred to electronic CRF (eCRF) by practice staff. On enrolment, midstream urine specimens will be collected (one sample per participant) to detect pyuria, to perform microbial analysis of the urine and to rule out pregnancy. After performing the above-mentioned tasks, participants will be divided into two groups receiving one of the two study treatments in each centre (**Figure 1**).

Course of the study and follow-up

After randomization, study drugs, questionnaires for recording adverse events and concurrent use of other medications (pain killers, antibiotics, or other OTC drugs) and food supplements that were started during the 7-day treatment trial will be distributed by a study nurse (**Table 1**).

Patients will be asked to take the study drugs as follows: 1 sachet at the first evening after the last urination before going to sleep, and 2 tablets t.i.d. for 7 consecutive days. Patients will also be asked to record adverse events and concurrent use of other medications (pain medications, antibiotics, or other OTC drugs) and food supplements for 7 consecutive days in diaries. The diaries will be collected on day 7 by the assigned study nurses.

Patients will be asked to return the centre for a follow-up at day 7 to complete an ACSS questionnaire and to return the diaries. Clinical efficacy will be defined as a summary score of the 6 typical symptoms of the ACSS no more than 5, with no item >1 and visible haematuria absent. Moreover, to evaluate the efficacy of the treatment arms midstream urine specimens will also be collected on day 7(one sample per patient). Microbiological efficacy will be determined in the subgroups of patients with significant bacteriuria (CFU $>10^5$/ml) vs. those with CFU values of 10^3-10^4/ml vs. $<10^3$/ml at day 0 and elimination of bacteriuria (CFU $<10^3$/ml) at day 7 according to EMA and FDA guidelines [24,25]. ACSS questionnaires (10 questionnaire/patient) will be distributed to patients with the request to fill in a questionnaire each time when there is a recurrence of UTI.

There will be a long-term follow-up documentation on day 90, when patients will be contacted to collect ACSS questionnaires and will be and interviewed for numbers of UTI recurrences, UTI-related consultations, days of sick leave, and medications and food supplements taken for UTI. The aforementioned data will be transferred to the eCRF by study nurses.

	STUDY PERIOD								
	Enrolment	**Allocation**	**Post-allocation**					**Close-out**	**Follow-up**
TIMEPOINT	**Day 0**	**Day 0**	***Day 1***	***Day2***	***Day3***	***Day4***	***Day 5***	***Day 7***	***Day 90***
ENROLMENT:									
Eligibility screen	X								
Informed consent	X								
Assessment of inclusion/exclusion criteria	X								
Allocation, randomization		X							
INTERVENTIONS:									
Pharmacotherapy		←	—	—	—	—	—	→	
ASSESSMENTS:									
ACSS score	X							X	
Patient diaries								X	
Urine culture	X							X	
Follow-up interview									X

Table 1. SPIRIT flowchart: schedule of enrolment, interventions, and assessments

Data management

Data handling

Data handling will be performed confidentially and anonymously and by the Data Monitoring Committee (DMC). Electronic CRFs (eCRFs) will be used. Principal investigator will have full access for the database. Accuracy, completeness and legibility of the data in the eCRF will be ensured by the Investigator. Detailed data flow will be described in a Data Management Plan (DMP). Data from completed eCRFs will be validated at DMC according to a Data Cleaning Plan (DCP) under the direction of the Data Manager. All changes to eCRFs will be documented.

Ethical principles and patient safety

This clinical study will be conducted following the Declaration of Helsinki. It will be conducted in compliance with the protocol, good clinical practice (GCP) (2001/20/EEC, CPMP/ICH/135/95), designated standard operating procedures, and local laws and regulations relevant to the country of conduct. The study has been approved by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (IV/4225-1/2021/EKU). All patients voluntarily sign the informed consent form, indicating that they agree to participate.

During the study, all investigators will report adverse or serious adverse events on a separate form which must be sent to both SC and DMC. If any adverse or serious adverse effects emerge, SC will discuss and, if the adverse effect is confirmed, it will be reported to the relevant institutional and national ethical committee (http://www.ett.hu/tukeb.htm).

DISCUSSION

Although herbal preparations of bearberry leaves are available as a medicine, their clinical efficacy and safety has not been confirmed in acute uncomplicated cystitis. The assessment of their efficacy is of primary importance: if it does not have a sufficient clinical efficacy, it should not be considered as an alternative to antibiotic treatment; however, if it is non-inferior to fosfomycin, it could be used as an alternative to fosfomycin, a traditional antibiotic. The study was designed to assess non-inferiority of bearberry leaf compared to fosfomycin for patients with acute uncomplicated cystitis.

Results of this clinical trial will help to revise the recommendations on the treatment of uncomplicated cystitis. If bearberry leaf proves to be non-inferior to fosfomycin, the therapeutic approach of uncomplicated cystitis may be changed in a long-term, which might lead to fewer antibiotic prescriptions and subsequent lower antibiotic resistance rates.

COMPETING INTERESTS

There are no financial or other competing interests among the principal investigator, the included participants, or any member of the trial.

FUNDING

Centre costs (IT, biostatistics, trial organization, etc.) are covered by the University of Pécs, Momentum Grant of the Hungarian Academy of Sciences (LP2014-10/2014); and Economic Development and Innovation Operative Programme Grant and Highly Cited Publication Grant of the National Research, Development and Innovation Office (GINOP-2.3.2-15-2016-00015, KH-125678). Since no additional treatment is necessary for the study, the general healthcare costs are covered by the National Healthcare System (grant number not applicable). This study was designed with help of the Centre for Translational Medicine at the University of Pécs. This centre is committed to improve patients' life with research activities (http://www.tm-pte.org/).

AUTHOR CONTRIBUTIONS

BT: conceptualization, writing the protocol

NV: writing the protocol, methodology

AJ, SV, NG: methodology, critical revising of the protocol

PB, GZ, KN, RL, BCL, PH, PN: critical revising of the protocol

DC: conceptualization, writing the protocol, supervision

DISCLAIMER

The contribution of the author R. Länger does not necessarily represent the views of the AGES Medizinmarktaufsicht / BASG in Austria nor of the (committees of the) European Medicines Agency.

ETHICS APPROVAL AND TRIAL REGISTRATION

The study has been approved by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (IV/4225-1/2021/EKU) and has been registered at clinicaltrials.gov (NCT05055544).

Figure legend

Figure 1: Flow chart of participants (SPIRIT 2013 statement)

REFERENCES

[1] K.G. Naber, G. Schito, H. Botto, J. Palou, T. Mazzei, Surveillance Study in Europe and Brazil on Clinical Aspects and Antimicrobial Resistance Epidemiology in Females with Cystitis (ARESC): Implications for Empiric Therapy, Eur. Urol. 54 (2008) 1164–1178. https://doi.org/10.1016/j.eururo.2008.05.010.

[2] G.M. Keating, Fosfomycin trometamol: a review of its use as a single-dose oral treatment for patients with acute lower urinary tract infections and pregnant women with asymptomatic bacteriuria., Drugs. 73 (2013) 1951–66. https://doi.org/10.1007/s40265-013-0143-y.

[3] K. Gupta, T.M. Hooton, K.G. Naber, B. Wullt, R. Colgan, L.G. Miller, G.J. Moran, L.E. Nicolle, R. Raz, A.J. Schaeffer, D.E. Soper, International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases, Clin. Infect. Dis. 52 (2011) e103–e120. https://doi.org/10.1093/cid/ciq257.

[4] J. Kranz, S. Schmidt, C. Lebert, L. Schneidewind, F. Mandraka, M. Kunze, S. Helbig, W. Vahlensieck, K. Naber, G. Schmiemann, F.M. Wagenlehner, The 2017 Update of the German Clinical Guideline on Epidemiology, Diagnostics, Therapy, Prevention, and Management of Uncomplicated Urinary Tract Infections in Adult Patients. Part II: Therapy and Prevention, Urol. Int. 100 (2018) 271–278. https://doi.org/10.1159/000487645.

[5] K. Gupta, T.M. Hooton, K.G. Naber, B. Wullt, R. Colgan, L.G. Miller, G.J. Moran, L.E. Nicolle, R. Raz, A.J. Schaeffer, D.E. Soper, International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases, Clin. Infect. Dis. 52 (2011). https://doi.org/10.1093/cid/ciq257.

[6] J. Kranz, S. Schmidt, C. Lebert, L. Schneidewind, W. Vahlensieck, U. Sester, R. Fünfstück, S. Helbig, W. Hofmann, E. Hummers, M. Kunze, E. Kniehl, K. Naber, F. Mandraka, B. Mündner-Hensen, G. Schmiemann, F.M.E. Wagenlehner, [Epidemiology, diagnostics, therapy, prevention and management of uncomplicated bacterial outpatient acquired urinary tract infections in adult patients : Update 2017 of the interdisciplinary AWMF S3 guideline]., Urologe. A. 56 (2017) 746–758. https://doi.org/10.1007/s00120-017-0389-1.

[7] EAU Guidelines: Urological Infections | Uroweb, (n.d.). https://uroweb.org/guideline/urological-infections/ (accessed March 10, 2020).

[8] B.J. Gardiner, A.J. Stewardson, I.J. Abbott, A.Y. Peleg, Nitrofurantoin and fosfomycin for resistant urinary tract infections: Old drugs for emerging problems, Aust. Prescr. 42 (2019) 14–19. https://doi.org/10.18773/austprescr.2019.002.

[9] M.E. Falagas, E.K. Vouloumanou, G. Samonis, K.Z. Vardakas, Fosfomycin, Clin. Microbiol. Rev.

29 (2016) 321–347. https://doi.org/10.1128/CMR.00068-15.

[10] E. Van Pienbroek, J. Hermans, A.A. Kaptein, J.D. Mulder, Fosfomycin trometamol in a single dose versus seven days nitrofurantoin in the treatment of acute uncomplicated urinary tract infections in women, Pharm. World Sci. 15 (1993) 257–262. https://doi.org/10.1007/BF01871127.

[11] G.E. Stein, Comparison of single-dose fosfomycin and a 7-day course of nitrofurantoin in female patients with uncomplicated urinary tract infection, Clin. Ther. 21 (1999) 1864–1872. https://doi.org/10.1016/S0149-2918(00)86734-X.

[12] M.A. Minassian, D.A. Lewis, D. Chattopadhyay, B. Bovill, G.J. Duckworth, J.D. Williams, A comparison between single-dose fosfomycin trometamol (Monuril®) and a 5-day course of trimethoprim in the treatment of uncomplicated lower urinary tract infection in women, Int. J. Antimicrob. Agents. 10 (1998) 39–47. https://doi.org/10.1016/S0924-8579(98)00021-1.

[13] A. Huttner, A. Kowalczyk, A. Turjeman, T. Babich, C. Brossier, N. Eliakim-Raz, K. Kosiek, B.M. De Tejada, X. Roux, S. Shiber, U. Theuretzbacher, E. Von Dach, D. Yahav, L. Leibovici, M. Godycki-Ćwirko, J.W. Mouton, S. Harbarth, 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 - J. Am. Med. Assoc. 319 (2018) 1781–1789. https://doi.org/10.1001/jama.2018.3627.

[14] C. Loras, A.C. Mendes, L. Peixe, Â. Novais, J.-I. Alós, Escherichia coli resistant to fosfomycin from urinary tract infections: Detection of the fosA3 gene in Spain, J. Glob. Antimicrob. Resist. (2020). https://doi.org/10.1016/j.jgar.2020.01.023.

[15] J. Oteo, V. Bautista, N. Lara, O. Cuevas, M. Arroyo, S. Fernández, E. Lázaro, F.J. de Abajo, J. Campos, Spanish ESBL-EARS-Net Study Group, Parallel increase in community use of fosfomycin and resistance to fosfomycin in extended-spectrum beta-lactamase (ESBL)-producing Escherichia coli., J. Antimicrob. Chemother. 65 (2010) 2459–63. https://doi.org/10.1093/jac/dkq346.

[16] E. Medicines Agency, European Union herbal monograph on Arctostaphylos uva-ursi (L.) Spreng., folium, 2009. www.ema.europa.eu/contact (accessed February 23, 2020).

[17] S.A. Moskalenko, Preliminary screening of far-eastern ethnomedicinal plants for antibacterial activity, J. Ethnopharmacol. 15 (1986) 231–259. https://doi.org/10.1016/0378-8741(86)90163-7.

[18] E. Medicines Agency, Uvae ursi folium - AR, n.d. www.ema.europa.eu/contact (accessed February 23, 2020).

[19] M. Moore, J. Trill, C. Simpson, F. Webley, M. Radford, L. Stanton, T. Maishman, A. Galanopoulou, A. Flower, C. Eyles, M. Willcox, A.D. Hay, E. van der Werf, S. Gibbons, G.

Lewith, P. Little, G. Griffiths, Uva-ursi extract and ibuprofen as alternative treatments for uncomplicated urinary tract infection in women (ATAFUTI): a factorial randomized trial., Clin. Microbiol. Infect. 25 (2019) 973–980. https://doi.org/10.1016/j.cmi.2019.01.011.

[20] K. Afshar, N. Fleischmann, G. Schmiemann, J. Bleidorn, E. Hummers-Pradier, T. Friede, K. Wegscheider, M. Moore, I. Gágyor, Reducing antibiotic use for uncomplicated urinary tract infection in general practice by treatment with uva-ursi (REGATTA) - a double-blind, randomized, controlled comparative effectiveness trial., BMC Complement. Altern. Med. 18 (2018) 203. https://doi.org/10.1186/s12906-018-2266-x.

[21] A.W. Chan, J.M. Tetzlaff, D.G. Altman, A. Laupacis, P.C. Gøtzsche, K. Krleža-Jerić, A. Hróbjartsson, H. Mann, K. Dickersin, J.A. Berlin, C.J. Doré, W.R. Parulekar, W.S.M. Summerskill, T. Groves, K.F. Schulz, H.C. Sox, F.W. Rockhold, D. Rennie, D. Moher, SPIRIT 2013 statement: Defining standard protocol items for clinical trials, Ann. Intern. Med. 158 (2013) 200–207. https://doi.org/10.7326/0003-4819-158-3-201302050-00583.

[22] Acute simple cystitis in women - UpToDate, (n.d.). https://www.uptodate.com/contents/acute-simple-cystitis-in-women (accessed February 24, 2020).

[23] J.F. Alidjanov, U.A. Abdufattaev, S.A. Makhsudov, A. Pilatz, F.A. Akilov, K.G. Naber, F.M. Wagenlehner, New Self-Reporting Questionnaire to Assess Urinary Tract Infections and Differential Diagnosis: Acute Cystitis Symptom Score, Urol. Int. 92 (2014) 230–236. https://doi.org/10.1159/000356177.

[24] Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections, Rev. 3, London, 2018.

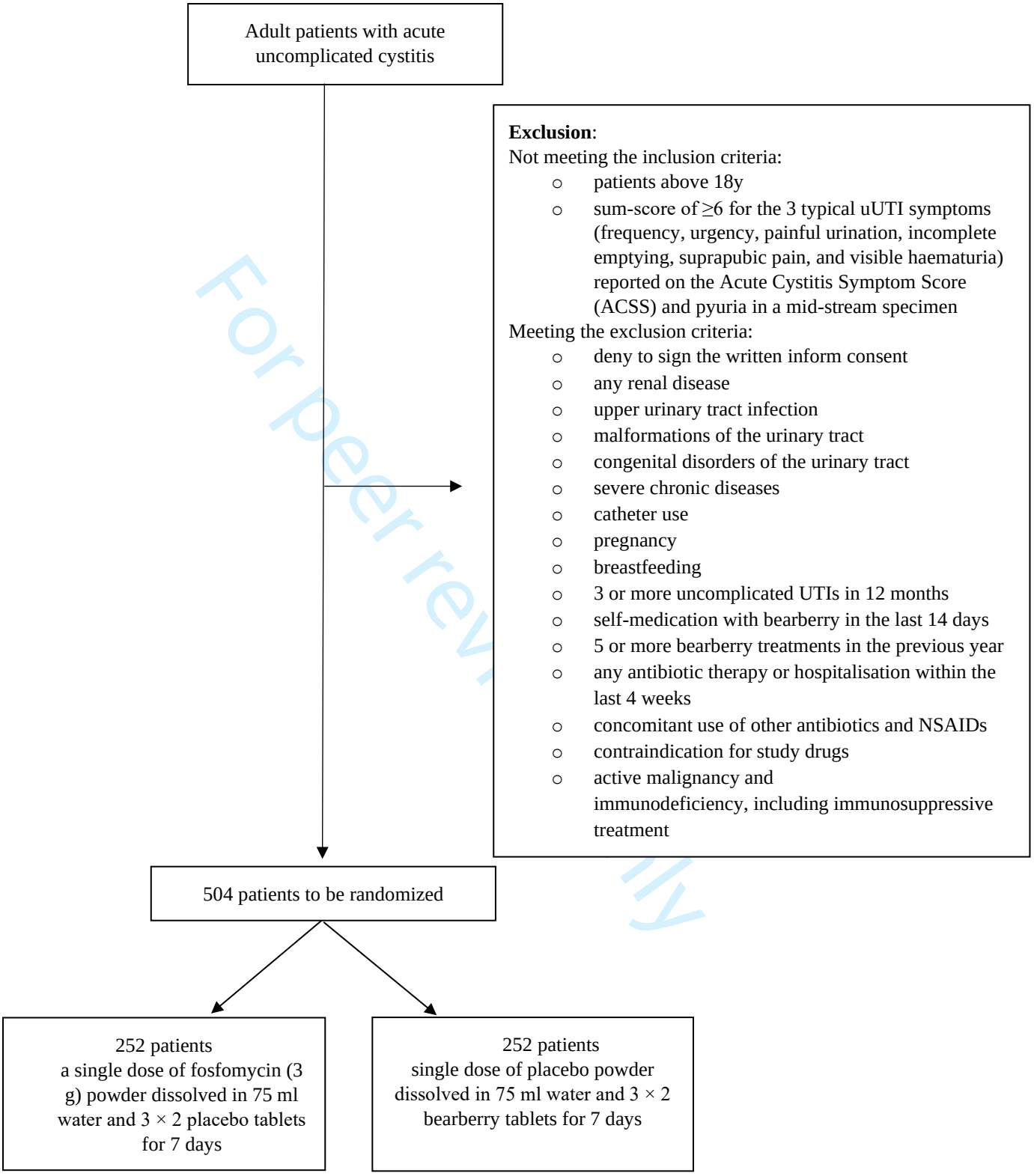
[25] Uncomplicated Urinary Tract Infections: Developing Drugs for Treatment Guidance for Industry, Rockville, 2019. https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs (accessed August 10, 2021).

[26] A. Magyar, J. Alidjanov, A. Pilatz, K. Nagy, V.K.A. Arthanareeswaran, S. Póth, A. Bécsi, F.M.E. Wagenlehner, K.G. Naber, P. Tenke, B. Köves, The role of the acute cystitis symptom score questionnaire for research and antimicrobial stewardship. Validation of the Hungarian version, Cent. Eur. J. Urol. 71 (2018) 134–141. https://doi.org/10.5173/ceju.2018.1530.

[27] J.F. Alidjanov, K.G. Naber, A. Pilatz, A. Radzhabov, M. Zamuddinov, A. Magyar, P. Tenke, F.M. Wagenlehner, Additional assessment of Acute Cystitis Symptom Score questionnaire for patient-reported outcome measure in female patients with acute uncomplicated cystitis: part II, World J. Urol. 2019 388. 38 (2019) 1977–1988. https://doi.org/10.1007/S00345-019-02948-8.

[28] A. Huttner, E.M. Verhaegh, S. Harbarth, A.E. Muller, U. Theuretzbacher, J.W. Mouton,

Nitrofurantoin revisited: a systematic review and meta-analysis of controlled trials, J. Antimicrob. Chemother. 70 (2015) 2456–2464. https://doi.org/10.1093/JAC/DKV147.



Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	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	13
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	13
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	13
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#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	13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	13

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
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	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	4
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, non-inferiority, exploratory)	5
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	5

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
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#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)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
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	7

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)	7
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	8
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,	7

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: 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
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#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	11

Data collection plan: retention	#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	11
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	11
Statistics: outcomes	#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	8
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
Statistics: analysis population and missing data	#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)	n/a
Methods: Monitoring			
Data monitoring: formal committee	#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	11

		details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#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	n/a
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	9
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
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)	n/a

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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	n/a
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Data access	#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	n/a
Dissemination policy: trial results	#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	n/a

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
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

BMJ Open

Bearberry in the Treatment of Acute Uncomplicated Cystitis (BRUMI)– Protocol of a Multicentre, Randomized Double-Blind Clinical Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057982.R2
Article Type:	Protocol
Date Submitted by the Author:	04-May-2022
Complete List of Authors:	Tóth, Barbara; University of Szeged, Department of Pharmacognosy Jávorházy, András; University of Pécs Nyirády, Péter; Semmelweis University, Department of Urology Csupor-Löffler, Boglárka; University of Pécs Birinyi, Péter; Semmelweis University, Department of Pharmacodynamics Zhanel, George; University of Manitoba, Departmental of Medical Microbiology/Infectious Diseases Naber, Kurt; Technical University of Munich Länger , Reinhard; AGES Medicine Market Auth Vörhendi, Nóra; Institute for Translational Medicine, University of Pécs Medical School; János Szentágothai Research Center, University of Pécs, Gede, Noémi; Medical School, University of Pécs, Pécs, Hungary, Institute for Translational Medicine Váncsa, Szilárd; University of Pécs; University of Pécs Hegyi, Péter; Medical School, University of Pécs, Pécs, Hungary, Institute for Translational Medicine; Semmelweis Egyetem, Centre for Translational Medicine Csupor, Dezső; University of Szeged, Department of Clinical Pharmacy; University of Pécs
Primary Subject Heading:	Urology
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	Urinary tract infections < UROLOGY, Interstitial cystitis < UROLOGY, Clinical trials < THERAPEUTICS

Bear**b**erry in the Treatment of Acute **U**nco**m**pli**c**ated Cystitis (BRUMI)– Protocol of a Multicentre, Randomized Double-Blind Clinical Trial

Barbara Tóth,[a,±] András Jávorházy,[b,±] Péter Nyirády,[c] Boglárka Csupor-Löffler,[d] Péter Birinyi,[e] George Zhanel,[f] Kurt Naber,[g] Reinhard Länger,[h] Nóra Vörhendi,[d] Noémi Gede,[d] Szilárd Váncsa,[i,j] Péter Hegyi,[d,i,j] and Dezső Csupor,[a,d,k,*]

[a] Department of Pharmacognosy, Faculty of Pharmacy, University of Szeged, Szeged, Hungary

[b] Urology Clinic, Medical School, University of Pécs, Pécs, Hungary

[c] Department of Urology, Faculty of Medicine, Semmelweis University, Budapest, Hungary

[d] Institute for Translational Medicine, Szentágothai Research Centre, Medical School, University of Pécs, Pécs, Hungary

[e] Department of Pharmacodynamics, Faculty of Pharmacy, Semmelweis University, Budapest, Hungary

[f] Departmental of Medical Microbiology/Infectious Diseases, University of Manitoba, Manitoba, Canada

[g] Department of Urology, Technical University of Munich, Munich, Germany

[h] Austrian Medicines and Medical Devices Agency, Vienna, Austria

[i] Centre for Translational Medicine, Semmelweis University, Budapest, Hungary

[j] Division of Pancreatic Diseases, Heart and Vascular Center, Semmelweis University, Budapest, Hungary

[k] Department of Clinical Pharmacy, Faculty of Pharmacy, University of Szeged, Szeged, Hungary

*Corresponding author: Dezső Csupor, University of Szeged, Faculty of Pharmacy, Department of Clinical Pharmacy, Szeged, Hungary. Telephone: +36 62 545559; Fax: +36 62 545741, e-mail address: csupor.dezso@szte.hu

[±] these authors contributed equally to the paper

Word count: 3131

ABSTRACT

Background

Bearberry *(Arctostaphylos uva-ursi)* leaf is available as a treatment of uncomplicated cystitis in several European countries. The antimicrobial activity of its extracts and some of its individual constituents has been observed *in vitro*; however, the efficacy of bearberry compared to standard antimicrobial therapy has not been assessed yet.

Objective

The objective of the study is to assess the safety and non-inferiority of bearberry as an alternative therapy in the treatment of acute uncomplicated cystitis in comparison with standard antibiotic therapy (fosfomycin).

Methods and analysis

This is a randomized controlled double-blinded multicentre trial. Eligible patients will be premenopausal women with a sum-score of ≥6 for the typical acute uncomplicated cystitis symptoms (frequency, urgency, painful urination, incomplete emptying, suprapubic pain, and visible haematuria) reported on the Acute Cystitis Symptom Score (ACSS) typical domain and pyuria. Patients will be randomly assigned to receive 3 g single dose of fosfomycin powder and 2 placebo tablets t.i.d. for 7 days or B a single dose of placebo powder and 2 tablets containing a dry extract of Uvae ursi folium. At least 504 patients (allocated as 1:1) will need to be enrolled to access non-inferiority with a non-inferiority limit of 14% for the primary endpoint.

Improvement of symptoms of uncomplicated cystitis (based on the ACSS score) at day 7 is defined as the primary endpoint, whereas several secondary endpoints such as the number and ratio of patients with bacteriuria at day 7, frequency and severity of side effects; recurrence of urinary tract infection, concurrent use of other OTC (over the counter) medications and food supplements will be determined to elucidate more detailed differences between the groups. The number of recurrences and medications taken for treatment will be monitored for a follow-up period of 90 days (80-100 days).

Ethics and dissemination This study has been approved by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (IV/4225-1/2021/EKU) and has been registered at clinicaltrials.gov (NCT05055544). The results will be disseminated by publication of peer-reviewed manuscripts.

Keywords:

bearberry; *Arctostaphylos uva-ursi*; fosfomycin; uncomplicated cystitis, urinary tract infection

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first randomised controlled trial to examine the efficacy of bearberry in the treatment of uncomplicated cystitis
- The efficacy will be compared to fosfomycin, a first-line drug
- This is a multicentre, prospective, randomised, non-inferiority study
- A validated score will be used to assess efficacy
- One limitation of this study is that the study population is limited to non-pregnant adult women before menopause

INTRODUCTION

Urinary tract infections (UTIs) are the most frequent occurring infections in women, and one of the major reasons for antibiotic prescriptions [1]. UTIs are classified as uncomplicated if anatomical or functional abnormalities are not observed in the urinary system. Regarding UTIs, *Escherichia coli* is the most frequent pathogen, followed by *Staphylococcus saprophyticus* and *Enterococcus faecalis* [2,3]. In clinical practice acute uncomplicated cystitis is diagnosed and treated based on the clinical signs and symptoms, microbiologic investigations are not performed routinely. According to the available guidelines, first-line drugs include fosfomycin trometamol, trimethoprim-sulfamethoxazole, nitrofurantoin, nitroxolin and pivmecillinam [4–7].

Fosfomycin, a first-line medication of acute uncomplicated cystitis possesses a wide spectrum of antibacterial activity against both Gram-negative and Gram-positive pathogens, including *E. coli* [8,9]. Based on a large scale surveillance study, *E. coli*, the most frequently isolated pathogen from UTI samples, is highly susceptibility to fosfomycin with a susceptibility rate of 98.5% [6]. In the majority of the published trials, the achieved short-term (7–9 days) microbial cure rate was more than 80% [10–12].In a more recent study, bacteriologic success through day 14 after treatment with fosfomycin was 73%, whereas clinical success was 66% [13]. Based on the published evidence, a single 3 g dose of fosfomycin trometamol is considered to be sufficient for the treatment of uncomplicated lower UTIs.

Bacterial resistance is one of the major limiting factors of antibiotic use. Despite fosfomycin's activity against resistant strains (e.g. multi-drug resistant *E. coli*), fosfomycin-resistance is an increasing problem [14]. In Spain, the frequency of fosfomycin-resistance increased from 4% to 11% between 1997 and 2009 [15].

Bearberry leaves have been used in traditional medicine for the treatment of acute cystitis. The European Medicines Agency acknowledged the traditional medicinal use of the herbal tea, the powdered plant material as well as defined extracts for treatment of symptoms of mild recurrent lower urinary tract infections such as burning sensation during urination and/or frequent urination in women [16]. The antimicrobial effect of bearberry leaf extracts and hydroquinone derivatives present in the plant have been confirmed in several *in vitro* studies, including several uropathogens. A bearberry leaf extract (extraction solvent ethanol 70%) exhibited antimicrobial activity towards a variety of organisms, including *E. coli* [17]. The pharmacokinetics of hydroquinones have also been studied, confirming the secretion of these compounds into the urine [18]. Unfortunately, no pharmacokinetic data are available on hydroquinone derivatives in patients with acute uncomplicated cystitis and also no data are available on the antimicrobial activities of secondary metabolites of bearberry leaves other

than hydroquinone derivatives. Overall, although there are data suggesting the antimicrobial activity of bearberry components against *E. coli*, there is no direct evidence for their clinical efficacy in humans.

Herbal preparations of bearberry leaf have been accepted as a traditional medicine, however their efficacy has not been confirmed in clinical trials in comparison with antibiotic treatment. So far, no resistance has been reported for bearberry. The lack of resistance, together with the cost-effectiveness of the treatment might be the major advantages of the use of this plant as a medicine in the treatment of acute uncomplicated cystitis. In one study, the efficacy was compared to ibuprofen in terms of symptom improvement [19], and in one ongoing trial fosfomycin is used as comparator [20]. The aim of our study is to assess the non-inferiority of a dry extract of bearberry leaves in terms of clinical efficacy and safety in comparison with standard antibiotics used in acute uUTI.

METHODS AND ANALYSIS

Trial design

The study protocol is structured following the SPIRIT statement 2013 [21]. This study is a multicentre, randomized, controlled, double-blind trial assessing non-inferiority. The allocation ratio is 1:1. Eligible patients will be randomly assigned to groups A (single dose of fosfomycin powder and 2 placebo tablets t.i.d.) or B (single dose of placebo powder and 2 bearberry tablets t.i.d.). The trial will be carried out in 2022-2023.

The trial organization, committees, and boards

The corresponding centre and designer of the BRUMI trial is the Centre for Translational Medicine at the Medical School, University of Pécs (coordinating institution and sponsor, www.tm-centre.org) and the Hungarian Phytotherapy Study Group.

The Steering Committee (SC) will be led by Péter Hegyi (University of Pécs, Hungary). The members will be Dezső Csupor and András Jávorházy (University of Pécs, Hungary). SC will make decisions concerning all relevant questions including the dropouts during the study. There will be independent members as well, and the SC will include a patient representative. The SC will supervise the trial primarily and will make decisions regarding all critical questions (protocol deviations, dropouts, etc.)

The International Translational Advisory Board (ITAB*J* will include urologists, microbiologists, and experts in phytotherapy. ITAB will continuously monitor the progress of the study and will give advice to the SC. The study was designed by the SC and ITAB. The study is financially sponsored by the University of Pécs, the Hungarian Academy of Sciences and the National Research, Development and Innovation Office. Neither sponsors were involved in the design of the study, and they will have no access to the database management or to the randomization code.

Sponsor

The sponsor of the BRUMI study is the University of Pécs, Medical School. The sponsor was not involved in the design of the study and will have no access to the database.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

Participating centres

Study participants are recruited from 2 centres in Hungary: Urology Clinic, University of Pécs, Pécs and Department of Urology, Semmelweis University, Budapest. Participants will be recruited from patients visiting the study centres with the symptoms of acute uncomplicated cystitis.

Study population

All premenopausal female patients diagnosed with uncomplicated urinary tract infection presenting to the participating centres will be informed of the possibility of taking part in the BRUMI study. After the consent form (Supplementary file) is signed, a computer using a block randomization protocol will randomize the patients (**Figure 1**).

Inclusion and exclusion criteria

Non-pregnant adult women before menopause (absence of menses for 1 year) having acute uncomplicated cystitis will be included to the study. Acute uncomplicated (simple) cystitis is defined as acute urinary tract infection with the symptoms of dysuria, increased frequency and urgency of urination and lower abdominal pain (suprapubic pain), that is presumed to be confined to the bladder; with no signs or symptoms that suggest an upper tract or systemic infection. Acute uncomplicated (simple) cystitis lack signs or symptoms that suggest an infection extending beyond the bladder, which include: (1) elevated body temperature (>37.7°C) or fever; (2) other signs or symptoms of systemic illness (including chills or rigors, significant fatigue or malaise beyond baseline); (3) flank pain; (4) costovertebral angle tenderness [22]. Eligible patients will be premenopausal women with a sum-score of ≥6 for the typical uUTI symptoms (frequency, urgency, painful urination, incomplete emptying, suprapubic pain, and visible haematuria) reported on the Acute Cystitis Symptom Score (ACSS) typical domain and pyuria (10 white blood cells/mm^3 in a mid-stream specimen) at day 0 [23–25]

The exclusion criteria are: (1) any renal disease; (2) upper urinary tract infection; (3) malformations of the urinary tract; (4) congenital disorders of the urinary tract; (5) catheter use; (6) pregnancy; (7) breastfeeding; (8) self-medication with bearberry in the last 14 days; (9) 5 or more bearberry treatments in the previous year; (10) any antibiotic therapy or hospitalisation within the last 4 weeks (11) concomitant use of other antibiotics and NSAIDs; (12) contraindication for study drugs; (13) active malignancy and (14) immunodeficiency, including immunosuppressive treatment.

Randomization and blinding

Participants will be divided into two groups (1:1) receiving one of the two study treatments in each centre. Randomization will be performed by using a predefined list with balanced blocked allocation size of four, stratified by recruiting centres, using a computer-generated random sequence. The medical staff (e.g., those who will take the patients' history, examine the patients, collect the specimen

of urine, distributing the study drugs, diaries, and questionnaires), statisticians performing data analyses and the patients receiving the study drugs will be blinded regarding treatment assignment. P. B. (who will be not involved in the clinical study) will coordinate the preparation of medication packages. The packages will be prepared for each patients separately and will be labelled with individual codes only.

Interventions

All eligible patients will be randomized to receive either a single dose of fosfomycin (3 g) powder dissolved in 75 ml water and 2 placebo tablets t.i.d. for 7 days, or single dose of placebo powder dissolved in 75 ml water and 2 bearberry tablets t.i.d. for 7 days.

The study drugs are the following: (1) Fosfomycin trometamol as Monural, containing 3 g fosfomycin [in the form of fosfomycin trometamol (5.631 g)]/sachet); (2) Bearberry tablet as Urzinol containing dry extract of *Arctostaphylos uva-ursi* (L.) Spreng leaf extract (DER 3.5–5.5:1, extracting solvent 60% v/v ethanol), 238.7–297.5 mg extract/tablet, corresponding to 70 mg hydroquinone derivatives, expressed as anhydrous arbutin. Both bearberry leaf extract and the fosfomycin trometamol would be used according to the recommendations of the SPCs. Placebo products will be identical in appearance (and in case of the placebo of the antibiotic powder also in color and taste) with the active treatments.

The doses of the study drugs (fosfomycin trometamol and bearberry leaf extract) were chosen based on either the international guidelines on the treatment of uncomplicated UTIs and on the European Union herbal monograph on *Arctostaphylos uva-ursi* (L.) Spreng., folium [4,5,16].

Patients will be scheduled for follow-up visits at day 7. At the beginning of the study (day 0) and on day 7, patients will be asked to fill in a self-reported questionnaire [Acute Cystitis Symptom Score (ACSS)] [23]. At the beginning of the study and at the visit at day 7, midstream urine specimens will be collected to evaluate bacteriuria (presence and CFU number of pathogens) and the pH of urine. Urine samples collected at day 0 will also be used to rule out pregnancy.

Outcomes

The primary endpoint of our trial is the improvement of symptoms of uncomplicated cystitis after 7 days of treatment. The improvement of symptoms will be determined by using the validated Hungarian version of the Acute Cystitis Symptom Score on day 0 and day 7 according to the following predefined thresholds: summary score of the typical symptoms ≤ 5 scores, no item >1 (mild), and “visible blood in urine” negative [26,27].

Secondary endpoints include the (1) number of patients with urine with $<10^3$ CFU/ml on day 7 in patients with significant bacteriuria (CFU $\geq 10^5$/ml) at D0; (2) average number of CFU of pathogens (7

days after the start of the therapy) in urine; (3) frequency and severity of side effects; (4) recurrence of UTI (follow-up after better during 90 days; severity and diagnostics of recurrences to be assessed by using the ACSS) and (5) concurrent use of other OTC medications and food supplements that are started taking during the 7 day treatment trial.

Statistical analysis and sample size calculation

Sample size estimation

Sample size calculation suggests that 504 patients (1:1) will need to be enrolled to confirm or reject the hypothesis for the primary endpoint, i.e. improvement of symptoms of uncomplicated cystitis based on the ACSS score at day 7 (80% vs. 77%; non-inferiority margin: 14%) with a 15% dropout, and power 80%. For this calculation we considered the clinical cure rates of different antibiotic treatments in UTI (79-92%) [28]. Sample size calculation was performed for the dichotomous primary endpoint by using Stata 16 (Stata Corp).

Statistical analysis

Descriptive statistics – mean, median, standard deviation, quartiles, and relative frequency – relative risk (dichotomous variables) for the primary endpoint. Statistical analyses will be performed with an error probability of 0.0294 (type-I error probability). A safety analysis will be performed after reaching 10% of the planned sample size. Odds ratio will be calculated for the primary endpoint.Statistical analysis will be performed by using R Core Team (2022; R Foundation for Statistical Computing, Vienna, Austria).

Interim analysis

A pre-defined interim analysis will be performed after reaching 50% of the planned sample size. We will calculate statistical power for the primary endpoint which will decide whether additional subjects should be enrolled or not. If 80% statistical power is reached, no more subjects will be needed, and early stopping will be applied. We will test our hypotheses first in an interim analysis, and at the end of the study, in the final analysis. For this reason, the p-value should be adjusted to diminish the probability of type I error; therefore, the corrected level of significance (p-value) will be 0.0294.

Study duration

The planned starting date of the study is 1 October 2021, and the planned finishing date of the study is 1 September 2023.

Flow and timing

Enrolment

Patients presenting with symptoms referring to uncomplicated urinary tract infection will be examined by a study physician and assessed for eligibility to participate in the trial in the participating clinical centres. Eligible patients will be asked to give an informed consent to the study. Patients will be asked to complete ACSS symptom questionnaire, and along with detailed medical history, duration and severity of symptoms and activity impairment will be documented. Symptom evaluation will cover the typical symptoms according to the ACSS questionnaire, such as dysuria, urgency, frequency, and lower abdominal pain, each scored from 0 (none) to 3 (strong). UTI-related activity impairment covers impairment by the symptom (see above), scored as well from 0 (none) to 3 (strong). Data will be transferred to electronic CRF (eCRF) by practice staff. On enrolment, midstream urine specimens will be collected (one sample per participant) to detect pyuria, to perform microbial analysis of the urine and to rule out pregnancy. After performing the above-mentioned tasks, participants will be divided into two groups receiving one of the two study treatments in each centre (**Figure 1**).

Course of the study and follow-up

After randomization, study drugs, questionnaires for recording adverse events and concurrent use of other medications (pain killers, antibiotics, or other OTC drugs) and food supplements that were started during the 7-day treatment trial will be distributed by a study nurse (**Table 1**).

Patients will be asked to take the study drugs as follows: 1 sachet at the first evening after the last urination before going to sleep, and 2 tablets t.i.d. for 7 consecutive days. Patients will also be asked to record adverse events and concurrent use of other medications (pain medications, antibiotics, or other OTC drugs) and food supplements for 7 consecutive days in diaries. The diaries will be collected on day 7 by the assigned study nurses.

Patients will be asked to return the centre for a follow-up at day 7 to complete an ACSS questionnaire and to return the diaries. Clinical efficacy will be defined as a summary score of the 6 typical symptoms of the ACSS no more than 5, with no item >1 and visible haematuria absent. Moreover, to evaluate the efficacy of the treatment arms midstream urine specimens will also be collected on day 7(one sample per patient). Microbiological efficacy will be determined in the subgroups of patients with significant bacteriuria (CFU $>10^5$/ml) vs. those with CFU values of 10^3-10^4/ml vs. $<10^3$/ml at day 0 and elimination of bacteriuria (CFU $<10^3$/ml) at day 7 according to EMA and FDA guidelines [24,25]. ACSS questionnaires (10 questionnaire/patient) will be distributed to patients with the request to fill in a questionnaire each time when there is a recurrence of UTI.

There will be a long-term follow-up documentation on day 90, when patients will be contacted to collect ACSS questionnaires and will be and interviewed for numbers of UTI recurrences, UTI-related consultations, days of sick leave, and medications and food supplements taken for UTI. The aforementioned data will be transferred to the eCRF by study nurses.

	STUDY PERIOD								
	Enrolment	**Allocation**	**Post-allocation**					**Close-out**	**Follow-up**
TIMEPOINT	**Day 0**	**Day 0**	***Day 1***	***Day2***	***Day3***	***Day4***	***Day 5***	***Day 7***	***Day 90***
ENROLMENT:									
Eligibility screen	X								
Informed consent	X								
Assessment of inclusion/exclusion criteria	X								
Allocation, randomization		X							
INTERVENTIONS:									
Pharmacotherapy		←	—	—	—	—	—	→	
ASSESSMENTS:									
ACSS score	X							X	
Patient diaries								X	
Urine culture	X							X	
Follow-up interview									X

Table 1. SPIRIT flowchart: schedule of enrolment, interventions, and assessments

Data management

Data handling

Data handling will be performed confidentially and anonymously and by the Data Monitoring Committee (DMC). Electronic CRFs (eCRFs) will be used. Principal investigator will have full access for the database. Accuracy, completeness and legibility of the data in the eCRF will be ensured by the Investigator. Detailed data flow will be described in a Data Management Plan (DMP). Data from completed eCRFs will be validated at DMC according to a Data Cleaning Plan (DCP) under the direction of the Data Manager. All changes to eCRFs will be documented.

DISCUSSION

Although herbal preparations of bearberry leaves are available as a medicine, their clinical efficacy and safety has not been confirmed in acute uncomplicated cystitis. The assessment of their efficacy is of primary importance: if it does not have a sufficient clinical efficacy, it should not be considered as an alternative to antibiotic treatment; however, if it is non-inferior to fosfomycin, it could be used as an alternative to fosfomycin, a traditional antibiotic. The study was designed to assess non-inferiority of bearberry leaf compared to fosfomycin for patients with acute uncomplicated cystitis.

Results of this clinical trial will help to revise the recommendations on the treatment of uncomplicated cystitis. If bearberry leaf proves to be non-inferior to fosfomycin, the therapeutic approach of uncomplicated cystitis may be changed in a long-term, which might lead to fewer antibiotic prescriptions and subsequent lower antibiotic resistance rates.

ETHICS AND DISSEMINATION

The study has been approved by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (IV/4225-1/2021/EKU) and has been registered at clinicaltrials.gov (NCT05055544).

This clinical study will be conducted following the Declaration of Helsinki. It will be conducted in compliance with the protocol, good clinical practice (GCP) (2001/20/EEC, CPMP/ICH/135/95), designated standard operating procedures, and local laws and regulations relevant to the country of conduct. The study has been approved by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (IV/4225-1/2021/EKU). All patients voluntarily sign the informed consent form, indicating that they agree to participate.

During the study, all investigators will report adverse or serious adverse events on a separate form which must be sent to both SC and DMC. If any adverse or serious adverse effects emerge, SC will discuss and, if the adverse effect is confirmed, it will be reported to the relevant institutional and national ethical committee (http://www.ett.hu/tukeb.htm).

The results of this study will be disseminated by publication of peer-reviewed manuscripts and presentation at national and international scientific meetings.

Figure legend

Figure 1: Flow chart of participants (SPIRIT 2013 statement)

REFERENCES

[1] K.G. Naber, G. Schito, H. Botto, J. Palou, T. Mazzei, Surveillance Study in Europe and Brazil on Clinical Aspects and Antimicrobial Resistance Epidemiology in Females with Cystitis (ARESC): Implications for Empiric Therapy, Eur. Urol. 54 (2008) 1164–1178. https://doi.org/10.1016/j.eururo.2008.05.010.

[2] G.M. Keating, Fosfomycin trometamol: a review of its use as a single-dose oral treatment for patients with acute lower urinary tract infections and pregnant women with asymptomatic bacteriuria., Drugs. 73 (2013) 1951–66. https://doi.org/10.1007/s40265-013-0143-y.

[3] K. Gupta, T.M. Hooton, K.G. Naber, B. Wullt, R. Colgan, L.G. Miller, G.J. Moran, L.E. Nicolle, R. Raz, A.J. Schaeffer, D.E. Soper, International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases, Clin. Infect. Dis. 52 (2011) e103–e120. https://doi.org/10.1093/cid/ciq257.

[4] J. Kranz, S. Schmidt, C. Lebert, L. Schneidewind, F. Mandraka, M. Kunze, S. Helbig, W. Vahlensieck, K. Naber, G. Schmiemann, F.M. Wagenlehner, The 2017 Update of the German Clinical Guideline on Epidemiology, Diagnostics, Therapy, Prevention, and Management of Uncomplicated Urinary Tract Infections in Adult Patients. Part II: Therapy and Prevention, Urol. Int. 100 (2018) 271–278. https://doi.org/10.1159/000487645.

[5] K. Gupta, T.M. Hooton, K.G. Naber, B. Wullt, R. Colgan, L.G. Miller, G.J. Moran, L.E. Nicolle, R. Raz, A.J. Schaeffer, D.E. Soper, International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases, Clin. Infect. Dis. 52 (2011). https://doi.org/10.1093/cid/ciq257.

[6] J. Kranz, S. Schmidt, C. Lebert, L. Schneidewind, W. Vahlensieck, U. Sester, R. Fünfstück, S. Helbig, W. Hofmann, E. Hummers, M. Kunze, E. Kniehl, K. Naber, F. Mandraka, B. Mündner-Hensen, G. Schmiemann, F.M.E. Wagenlehner, [Epidemiology, diagnostics, therapy, prevention and management of uncomplicated bacterial outpatient acquired urinary tract infections in adult patients : Update 2017 of the interdisciplinary AWMF S3 guideline]., Urologe. A. 56 (2017) 746–758. https://doi.org/10.1007/s00120-017-0389-1.

[7] EAU Guidelines: Urological Infections | Uroweb, (n.d.). https://uroweb.org/guideline/urological-infections/ (accessed March 10, 2020).

[8] B.J. Gardiner, A.J. Stewardson, I.J. Abbott, A.Y. Peleg, Nitrofurantoin and fosfomycin for resistant urinary tract infections: Old drugs for emerging problems, Aust. Prescr. 42 (2019) 14–19. https://doi.org/10.18773/austprescr.2019.002.

[9] M.E. Falagas, E.K. Vouloumanou, G. Samonis, K.Z. Vardakas, Fosfomycin, Clin. Microbiol. Rev.

29 (2016) 321–347. https://doi.org/10.1128/CMR.00068-15.

[10] E. Van Pienbroek, J. Hermans, A.A. Kaptein, J.D. Mulder, Fosfomycin trometamol in a single dose versus seven days nitrofurantoin in the treatment of acute uncomplicated urinary tract infections in women, Pharm. World Sci. 15 (1993) 257–262. https://doi.org/10.1007/BF01871127.

[11] G.E. Stein, Comparison of single-dose fosfomycin and a 7-day course of nitrofurantoin in female patients with uncomplicated urinary tract infection, Clin. Ther. 21 (1999) 1864–1872. https://doi.org/10.1016/S0149-2918(00)86734-X.

[12] M.A. Minassian, D.A. Lewis, D. Chattopadhyay, B. Bovill, G.J. Duckworth, J.D. Williams, A comparison between single-dose fosfomycin trometamol (Monuril®) and a 5-day course of trimethoprim in the treatment of uncomplicated lower urinary tract infection in women, Int. J. Antimicrob. Agents. 10 (1998) 39–47. https://doi.org/10.1016/S0924-8579(98)00021-1.

[13] A. Huttner, A. Kowalczyk, A. Turjeman, T. Babich, C. Brossier, N. Eliakim-Raz, K. Kosiek, B.M. De Tejada, X. Roux, S. Shiber, U. Theuretzbacher, E. Von Dach, D. Yahav, L. Leibovici, M. Godycki-Ćwirko, J.W. Mouton, S. Harbarth, 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 - J. Am. Med. Assoc. 319 (2018) 1781–1789. https://doi.org/10.1001/jama.2018.3627.

[14] C. Loras, A.C. Mendes, L. Peixe, Â. Novais, J.-I. Alós, Escherichia coli resistant to fosfomycin from urinary tract infections: Detection of the fosA3 gene in Spain, J. Glob. Antimicrob. Resist. (2020). https://doi.org/10.1016/j.jgar.2020.01.023.

[15] J. Oteo, V. Bautista, N. Lara, O. Cuevas, M. Arroyo, S. Fernández, E. Lázaro, F.J. de Abajo, J. Campos, Spanish ESBL-EARS-Net Study Group, Parallel increase in community use of fosfomycin and resistance to fosfomycin in extended-spectrum beta-lactamase (ESBL)-producing Escherichia coli., J. Antimicrob. Chemother. 65 (2010) 2459–63. https://doi.org/10.1093/jac/dkq346.

[16] E. Medicines Agency, European Union herbal monograph on Arctostaphylos uva-ursi (L.) Spreng., folium, 2009. www.ema.europa.eu/contact (accessed February 23, 2020).

[17] S.A. Moskalenko, Preliminary screening of far-eastern ethnomedicinal plants for antibacterial activity, J. Ethnopharmacol. 15 (1986) 231–259. https://doi.org/10.1016/0378-8741(86)90163-7.

[18] E. Medicines Agency, Uvae ursi folium - AR, n.d. www.ema.europa.eu/contact (accessed February 23, 2020).

[19] M. Moore, J. Trill, C. Simpson, F. Webley, M. Radford, L. Stanton, T. Maishman, A. Galanopoulou, A. Flower, C. Eyles, M. Willcox, A.D. Hay, E. van der Werf, S. Gibbons, G.

Lewith, P. Little, G. Griffiths, Uva-ursi extract and ibuprofen as alternative treatments for uncomplicated urinary tract infection in women (ATAFUTI): a factorial randomized trial., Clin. Microbiol. Infect. 25 (2019) 973–980. https://doi.org/10.1016/j.cmi.2019.01.011.

[20] K. Afshar, N. Fleischmann, G. Schmiemann, J. Bleidorn, E. Hummers-Pradier, T. Friede, K. Wegscheider, M. Moore, I. Gágyor, Reducing antibiotic use for uncomplicated urinary tract infection in general practice by treatment with uva-ursi (REGATTA) - a double-blind, randomized, controlled comparative effectiveness trial., BMC Complement. Altern. Med. 18 (2018) 203. https://doi.org/10.1186/s12906-018-2266-x.

[21] A.W. Chan, J.M. Tetzlaff, D.G. Altman, A. Laupacis, P.C. Gøtzsche, K. Krleža-Jerić, A. Hróbjartsson, H. Mann, K. Dickersin, J.A. Berlin, C.J. Doré, W.R. Parulekar, W.S.M. Summerskill, T. Groves, K.F. Schulz, H.C. Sox, F.W. Rockhold, D. Rennie, D. Moher, SPIRIT 2013 statement: Defining standard protocol items for clinical trials, Ann. Intern. Med. 158 (2013) 200–207. https://doi.org/10.7326/0003-4819-158-3-201302050-00583.

[22] Acute simple cystitis in women - UpToDate, (n.d.). https://www.uptodate.com/contents/acute-simple-cystitis-in-women (accessed February 24, 2020).

[23] J.F. Alidjanov, U.A. Abdufattaev, S.A. Makhsudov, A. Pilatz, F.A. Akilov, K.G. Naber, F.M. Wagenlehner, New Self-Reporting Questionnaire to Assess Urinary Tract Infections and Differential Diagnosis: Acute Cystitis Symptom Score, Urol. Int. 92 (2014) 230–236. https://doi.org/10.1159/000356177.

[24] Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections, Rev. 3, London, 2018.

[25] Uncomplicated Urinary Tract Infections: Developing Drugs for Treatment Guidance for Industry, Rockville, 2019. https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs (accessed August 10, 2021).

[26] A. Magyar, J. Alidjanov, A. Pilatz, K. Nagy, V.K.A. Arthanareeswaran, S. Póth, A. Bécsi, F.M.E. Wagenlehner, K.G. Naber, P. Tenke, B. Köves, The role of the acute cystitis symptom score questionnaire for research and antimicrobial stewardship. Validation of the Hungarian version, Cent. Eur. J. Urol. 71 (2018) 134–141. https://doi.org/10.5173/ceju.2018.1530.

[27] J.F. Alidjanov, K.G. Naber, A. Pilatz, A. Radzhabov, M. Zamuddinov, A. Magyar, P. Tenke, F.M. Wagenlehner, Additional assessment of Acute Cystitis Symptom Score questionnaire for patient-reported outcome measure in female patients with acute uncomplicated cystitis: part II, World J. Urol. 2019 388. 38 (2019) 1977–1988. https://doi.org/10.1007/S00345-019-02948-8.

[28] A. Huttner, E.M. Verhaegh, S. Harbarth, A.E. Muller, U. Theuretzbacher, J.W. Mouton,

Nitrofurantoin revisited: a systematic review and meta-analysis of controlled trials, J. Antimicrob. Chemother. 70 (2015) 2456–2464. https://doi.org/10.1093/JAC/DKV147.

AUTHOR CONTRIBUTIONS

BT: conceptualization, writing the protocol

NV: writing the protocol, methodology

AJ, SV, NG: methodology, critical revising of the protocol

PB, GZ, KN, RL, BCL, PH, PN, NK: critical revising of the protocol

DC: conceptualization, writing the protocol, supervision

FUNDING

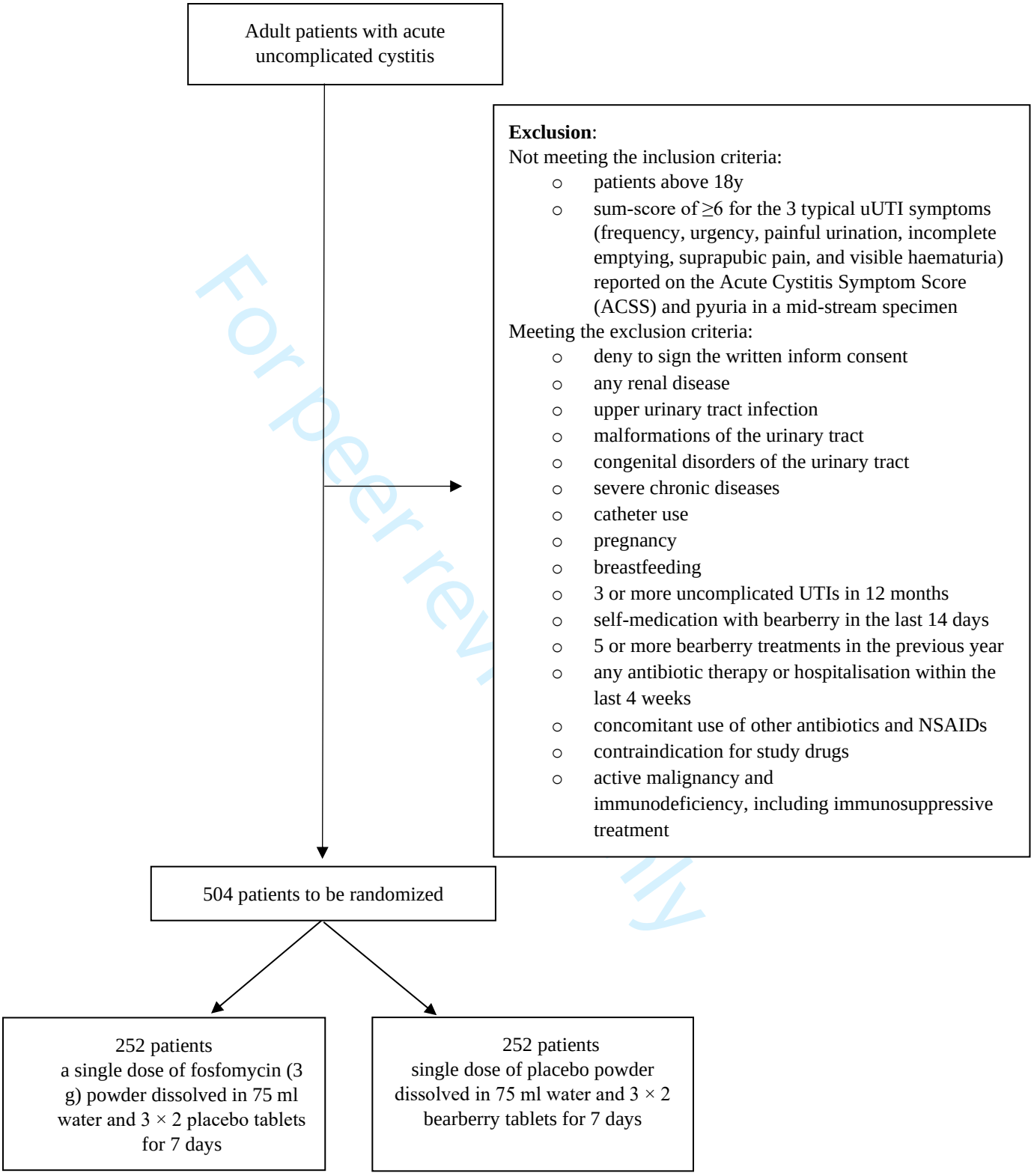
Centre costs (IT, biostatistics, trial organization, etc.) are covered by the University of Pécs, Momentum Grant of the Hungarian Academy of Sciences (LP2014-10/2014); and Economic Development and Innovation Operative Programme Grant and Highly Cited Publication Grant of the National Research, Development and Innovation Office (GINOP-2.3.2-15-2016-00015, KH-125678). Since no additional treatment is necessary for the study, the general healthcare costs are covered by the National Healthcare System (grant number not applicable). This study was designed with help of the Centre for Translational Medicine at the University of Pécs. This centre is committed to improve patients' life with research activities (http://www.tm-pte.org/).

COMPETING INTERESTS

There are no financial or other competing interests among the principal investigator, the included participants, or any member of the trial.

DISCLAIMER

The contribution of the author R. Länger does not necessarily represent the views of the AGES Medizinmarktaufsicht / BASG in Austria nor of the (committees of the) European Medicines Agency.



Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	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	13
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	13
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	13
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#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	13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	13

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
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	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	4
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, non-inferiority, exploratory)	5
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	5

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
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#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)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
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	7

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)	7
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	8
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,	7

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: 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
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#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	11

Data collection plan: retention	#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	11
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	11
Statistics: outcomes	#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	8
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
Statistics: analysis population and missing data	#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)	n/a
Methods: Monitoring			
Data monitoring: formal committee	#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	11

		details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#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	n/a
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	9
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
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)	n/a

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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	n/a
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Data access	#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	n/a
Dissemination policy: trial results	#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	n/a

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
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