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STUDY PROTOCOL

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# Efficacy of a pharmacist care protocol to manage uncomplicated female cystitis in community pharmacies: an open-label, multicenter, randomized, controlled, cluster study: the PharmaCyst' protocol

Arthur Piraux<sup>1\*</sup> , Elsa Parot-Schinkel<sup>2</sup>, Jean-François Hamel<sup>2</sup>, Kurt Naber<sup>3</sup>, Anne-Claire Oger<sup>4</sup>, Alain Guilleminot<sup>4</sup>, Aline Ramond-Roquin<sup>1,5,6</sup> and Sébastien Faure<sup>1</sup>

## Abstract

**Background** Urinary tract infections are common affections, especially for women. Difficult access to a general practitioner to obtain a prescription has led France to offer dispensing under protocol by community pharmacists. The primary objective of this study is to evaluate the effectiveness of a pharmacist care protocol provided to manage women with urinary tract infection symptoms. This objective will be assessed using the Acute Cystitis Symptom Score.

**Methods** PharmaCyst' is an open-label, multicenter, controlled, cluster-randomized study conducted in the Loire region, France. Women aged between 18 and 65 years presenting to a pharmacy complaining of at least one symptom of an uncomplicated urinary tract infection present over the last 3 days (including burning pain during micturition, dysuria, pollakiuria, urgent urination) will be considered for inclusion. All patients will be contacted on day 3, 10, and month 3. A total of 480 patients need to be recruited for the 24 clusters participating in the research. The quantitative data will be described using means and standard deviations and compared using Student's *t*-test. The qualitative data will be described using numbers and percentages and compared using chi<sup>2</sup> test (or Fisher's exact test if necessary). The primary and secondary outcomes analyses will consider the intention-to-treat population.

**Discussion** PharmaCyst' is the first clinical trial conducted in France only by community pharmacists. Its results could lead to an extension of the protocol.

**Trial registration** The protocol has been approved by the French ethics committee on 2022/12/02 and is registered under the number 49RC22\_0240 on ClinicalTrials.gov.

**Keywords** Urinary tract infections, Uncomplicated cystitis, Dispensing under protocol, Community pharmacist, Primary care, Study protocol

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### Administrative information

Note: The numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items.

Title {1}	Efficacy of a pharmacist care protocol to manage uncomplicated female cystitis in community pharmacies: an open-label, multicenter, randomized, controlled, cluster study: the PharmaCyst' protocol
Trial registration {2a and 2b}	This trial is registered under the number 49RC22_0240 on ClinicalTrials.gov
Protocol version {3}	6th version of the protocol, dated 2024/06/26
Funding {4}	This study is supported by a grant from the French Ministry of Health, as part of the "ReSP-IR 2021" program.
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Name and contact information for the trial sponsor {5b}	Angers University Hospital Clinical Research Center Angers University Hospital 4 rue Larrey 49933 Angers Cedex 09 Tel: 02 41 35 57 46

Role of sponsor {5c}	The funder of the study (Ministry of Health) has no power to influence the conduct of the study. In exchange for funding, the sponsor is asked to be acknowledged in the various publications. The study sponsor has contributed its expertise to the design of the study and will provide support for data management and analysis. However, the principal investigator remains solely responsible for the study. He will retain final authority over the various activities, including the publication report.
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### Introduction

#### Background and rationale {6a}

Each year urinary tract infections affect around four to six million people worldwide, most of whom are women [1]. Although little epidemiological research is available to confirm these figures, one American survey from the early 2000s reported that 10% of women had presented with a urinary tract infection within the 12 months prior to the study [2]. In France, the ECOGEN national survey found that in 2.5% of general practitioner consultations [3]. Moreover, 2% of non-trauma emergency department consultations were due to urinary tract infections [4].

Uncomplicated urinary tract infections in women are easy to diagnose. Characteristic clinical features include pollakiuria, dysuria, and post-micturition urge [5, 6]. A urinary dipstick confirms the clinical picture. If no risk factors of complicated infection are present, treatment is an antibiotic such as fosfomycin or pivmecillinam accompanied with lifestyle and dietary advice [6–9]. Early treatment prevents continued discomfort and the risk of developing complications such as pyelonephritis.

This infection is commonly managed by general practitioners, as prescribing an antibiotic requires a medical consultation. Yet, access to general practitioners is increasingly difficult [10, 11], whereas pharmacists are widely available, easily accessed, and distributed geographically throughout most regions [12]. In recent years, numerous countries have involved pharmacists in providing primary care to reduce the workload for general practitioners and emergency specialists [13–16]. Furthermore, patients are highly satisfied with the care provided by the community pharmacist [17, 18].

Community pharmacists in France have been recently entrusted with new responsibilities including influenza vaccination, COVID-19 vaccination and screening, pharmaceutical interviews, shared medication reviews, and dispensing emergency contraception. However, to date, only a small proportion of French community pharmacists are able to offer appropriate care, including the

dispensing of an antibiotic, to women with acute uncomplicated cystitis [19]; the other can only provide lifestyle and dietary advice with food supplements or over the counter medications [20]. To dispense an antibiotic, pharmacists must belong to a coordinated structure and have obtained the agreement of the referring physician to offer this service. Considering the expanding responsibilities pharmacists now have, it seems appropriate to evaluate whether community pharmacists can improve the management of uncomplicated acute cystitis for women presenting to a pharmacy, seeking care for urinary symptoms.

The objective of the study will evaluate the efficacy of a pharmacist-based protocol compared to standard care in the management of urinary tract infections. In Canada, a study with similar inclusion criteria demonstrated the efficacy and safety of pharmacists managing uncomplicated acute cystitis, with clinical cure in 9 out of 10 cases [21]. In Scotland, of the 1189 cases seen by 75 pharmacies, 75.4% were uncomplicated female cystitis. For these cases, pharmacists provided lifestyle and dietary advice to 8.5% of cases ( $n=76$ ), referred the patient to a doctor in 15.5% of cases ( $n=139$ ) mainly due to age or a recent episode, and dispensed an antibiotic in 76.0% of cases ( $n=682$ ) [14]. Furthermore, studies into patient satisfaction revealed that patients trust their pharmacist and are satisfied with the care they provide with one study revealing satisfaction close to 90% [17]. A further study revealed that in 80.4% of cases ( $n=101$ ), patients reported a significant or total improvement in symptoms following the pharmacist’s recommendations [18].

**Objectives {7}**

The primary objective of this study is to evaluate the effectiveness of a pharmacist care protocol provided by a registered pharmacist compared to standard care, to manage women aged between 18 and 65 with urinary tract infection symptoms.

This objective will be assessed using the Acute Cystitis Symptom Score (ACSS) (Appendix 1) [22, 23]. This score includes a section dedicated to the “typical symptoms” of urinary tract infections, comprising 6 items graded from 0 to 3. It also contains a section dedicated to differential signs and quality of life. The translation of this score into French has been linguistically validated (24). The change in score between day 0 (D0) and day 3 (D3) for the “typical symptoms” section will be the primary endpoint.

Secondary objectives evaluate other effectiveness criteria and the safety of the pharmacist care protocol compared with standard care. Pharmacist compliance will also be used to evaluate the feasibility of implementing this pharmacist care protocol.

Based on the previous studies, we anticipate that using a pharmacist-based protocol in the Loire region, France, will significantly improve the management of women with a urinary tract infection. We expect faster symptom relief, with high level of safety, and a satisfactory service.

**Trial design {8}**

PharmaCyst’ is an open-label, multicenter, controlled, cluster-randomized study. Parallel assignment will be performed, with a 1:1 ratio between study arms, to demonstrate the superiority of the intervention.

**Methods: participants, interventions, and outcomes**

**Study setting {9}**

This study is conducted in the Loire region, France. It will involve a total of 24 community pharmacies, across a territory that counts around a thousand. Only pharmacists holding the state diploma of Doctor of Pharmacy and registered with the Order of Pharmacists could participate in the study as investigators. Pharmacies are located in both urban and rural areas. They may be medium-sized (turnover <€1.4 million) or larger (turnover ≥€1.4 million). Pharmacies were stratified according to rural or urban location and average annual sales. Their description is given in Table 1.

**Eligibility criteria {10}**

**Inclusion criteria**

Potential participants for this study will be recruited from participating community pharmacies. Any otherwise healthy, non-febrile, female presenting to a pharmacy complaining of at least one symptom of an uncomplicated urinary tract infection present over the last 3 days (including burning pain during micturition, dysuria, pollakiuria, urgent urination) will be considered for inclusion. Participants must be aged between 18 and 65 years and affiliated with the French national health insurance

**Table 1** Characteristics of pharmacies participating in the clinical study

	Control arm	Experimental arm	Total
<b>Annual turnover &lt;€1.4 million</b>	4	4	8
Rural pharmacy	3	3	6
Urban pharmacy	1	1	2
<b>Annual turnover ≥€1.4 million</b>	8	8	16
Rural pharmacy	4	5	9
Urban pharmacy	4	3	7
<b>Total</b>	12	12	24

scheme. Once enrolled, the pharmacist will check eligibility according to the study population criteria.

#### **Non-inclusion criteria**

Potential participants will be not included if:

- They have had more than three urinary tract infections episodes in the last 12 months or if the previous episode occurred less than 15 days prior to the current episode.
- They have other concomitant urogenital symptoms such as lower back or abdominal pain, urinary tract abnormalities, vaginal discharge, vomiting, diarrhea, or other symptoms that may indicate other pathology.
- They have known risk factors for Enterobacteriaceae resistance to 3rd generation cephalosporins extended spectrum beta-lactamase or have traveled abroad to known geographical risk areas within 3 months.
- They have contraindications to study drugs pivmecillinam and fosfomycin.
- They have been hospitalized 3 months prior to study start or if a urinary tract infection resulted in a hospitalization in the previous 6 months.
- Also, those with renal impairment, are immunosuppressed, or have a known malignancy will be excluded.
- They are breastfeeding or pregnant.

They are unable to understand the study objectives, procedures, or provide informed consent.

#### **Who will take informed consent? {26a}**

If the patient meets all the eligibility criteria for the study, they will be given the information letter. The pharmacist will give a verbal description and be available to answer any questions the subject may have. If the person agrees to participate, they will be asked to provide a signed informed consent form in duplicate.

#### **Additional consent provisions for collection and use of participant data and biological specimens {26b}**

Given the minimal risks and constraints of the study, no additional consent is required.

#### **Interventions**

##### **Explanation for the choice of comparators {6b}**

Those participants cared for by a pharmacy randomized to standard care may be offered at least one of the following: dietary and lifestyle advice, over-the-counter medication, or a food supplement indicated to improve urinary comfort. Management will be adapted to the situation, the patient's preferences, and the pharmacy's habits. The investigating pharmacist will also remind

the patient that she can consult a doctor, especially if the symptoms remain unchanged or worsen.

#### **Intervention description {11a}**

Pharmacists randomized to the interventional group will be trained on providing the intervention protocol, which is in line with the French national health authority guidelines for community pharmacists or state-qualified nurses working within the framework of a multi-professional structure to manage functional urinary symptoms including pollakiuria and dysuria in women aged 16 to 65 years [19].

Those participants cared for by a pharmacy randomized to the intervention group will have their temperature taken and a urine dipstick performed to confirm the urinary tract infection diagnosis. If the patient's temperature is normal ( $\geq 36$  °C and  $\leq 38$  °C), the urine dipstick is positive (positive leukocytes and/or nitrites), and the patient has no pain in the lateral lumbar fossa, the pharmacist will dispense 3 g of fosfomycin in a single-dose sachet. If the patient is allergic to fosfomycin, the pharmacist may prescribe 400 mg of pivmecillinam twice daily for 3 days. The patient will also receive complementary care according to the pharmacists' usual practice, as well as lifestyle and dietary advice. The patient's general practitioner will be informed (phone call, email, letter) of the treatment she has received.

A clinical research technician will contact each patient to obtain study data and the pharmacist will remain available to answer any questions the participant may have about their cystitis episode. All patients will be contacted on day 3, 10, and month 3 (Fig. 1).

#### **Criteria for discontinuing or modifying allocated interventions {11b}**

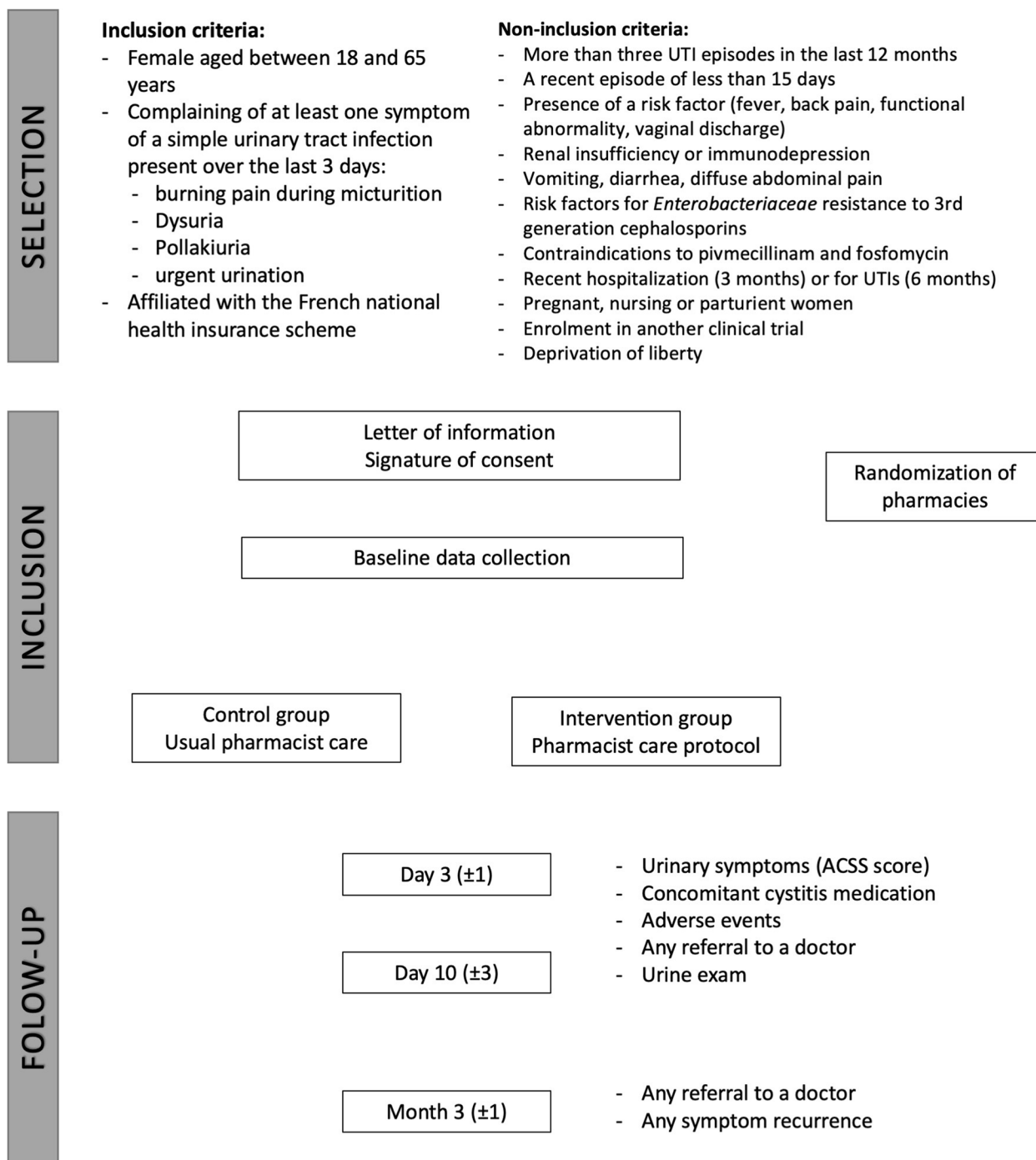
As this is a one-off operation, there will be no change in the patient's care. Close monitoring of patients (D3 and D10) will enable the patient to be referred to a physician if necessary.

#### **Strategies to improve adherence to interventions {11c}**

The single intervention facilitates patient compliance. To maximize telephone follow-up, patients will be asked to indicate a preferred time to call. If necessary, the research technicians will repeat the call at different times of the day, on different numbers or on different days.

#### **Relevant concomitant care permitted or prohibited during the trial {11d}**

Concurrent participation in an interventional study modifying patient care is not authorized for the duration of the patient's participation in the study. Once participation has ended, the protocol does not provide



**Fig. 1** Trial flow chart of the PharmaCyst study

for an exclusion period during which patients must not take part in any other interventional research.

**Provisions for post-trial care {30}**

There is no provision for compensation for the constraints suffered by the people taking part in this study. The promoter has taken out insurance covering its own

civil liability and will also ensure full compensation for any harmful consequences of the research for the person taking part in it.

**Outcomes {12}**

The primary objective of this study is to evaluate the effectiveness of a pharmacist care protocol provided by

a registered pharmacist compared to standard care, to manage women aged between 18 and 65 with urinary tract infection symptoms.

This objective will be assessed using the Acute Cystitis Symptom Score (ACSS) [22, 23]. This score includes a section dedicated to the “typical symptoms” of urinary tract infections, comprising 6 items graded from 0 to 3. It also contains a section dedicated to differential signs and quality of life. The change in score between day 0 (D0) and day 3 (D3) for the “typical symptoms” section will be the primary endpoint.

Secondary objectives evaluate other effectiveness criteria and the safety of the pharmacist care protocol compared with standard care. Pharmacist compliance will also be used to evaluate the feasibility of implementing this pharmacist care protocol.

**Participant timeline {13}**

Patients will be enrolled by community pharmacists (day 0). All data collected will be transcribed onto a paper form and faxed to the centralized monitoring team at Angers University Hospital, where it will be entered into the eCRF. Pharmacists will take the patient’s history and complete the ACSS [21, 22]. This score includes a section dedicated to the “typical symptoms” of urinary tract

infections, comprising 6 items graded from 0 to 3. It also contains a section dedicated to differential signs and quality of life. The translation of this score into French has been linguistically validated [24].

A clinical research technician will conduct follow-up and collect all data via telephone on day 3, 10, and month 3 (Table 2).

Follow-up at day 3 and day 10 included completion of the ACSS part II, new treatments, adverse events, medical consultation, and urinary examination. Patient satisfaction will be collected at day 10 using a questionnaire designed for the purpose of this study (Appendix 2). A quantitative response to each question will be recorded using a 4-point Likert scale and further qualitative data will be captured from the responses to open-ended questions.

At 3 months, participants will be asked if they have consulted a health care professional for cystitis or if a new episode has occurred.

If a participant withdraws prematurely from the study, the reasons will be documented as fully as possible. Participants who are lost to follow-up or withdraw prematurely will not be replaced but will be used during analyses (intention-to-treat analyses), including withdrawal of consent (unless the person requests their

**Table 2** Study schedule (SPIRIT diagram of inclusion, intervention, outcome assessment and evaluation)

Timepoint	Study Period			
	Inclusion	Post-allocation		
		Day 0	Day 3*	Day 10*
<b>Enrolment</b>				
Eligibility screen	X			
Consent form signed	X			
<b>Intervention</b>				
Patient history	X			
Patient temperature measurement	X**			
Urine dipstick test	X**			
Antibiotic dispensing	X**			
OTC drug dispensing	X			
Dietary and lifestyle advice given	X			
Communication sent to GP	X**			
<b>Assessments</b>				
Urinary symptoms (ACSS score)	X	X	X	
Concomitant medication***	X	X	X	
Adverse events since inclusion		X	X	
Any referral to a doctor since inclusion***		X	X	X
Any urinary dipstick, microscopy or culture performed		X	X	
Any symptom of recurrence				X
Patient satisfaction (questionnaire)			X	

\* Follow-up telephone interview, \*\* Interventional group only, \*\*\* For cystitis or its complications

personal data be erased). If the participants request their data be erased, the data required for safety analysis will be kept.

At the end of the study, a satisfaction questionnaire will be sent to all the pharmacists who participated in the study and a semi-structured interview offered to those who wish to provide more information about their experience using the pharmacist care protocol (Appendix 3).

#### **Sample size {14}**

It is difficult to make assumptions about the correlation of patient characteristics within the same clusters. However, in a primary care setting, such intra-class correlations related to different outcomes have been estimated at 0.01 (interquartile range: 0.00–0.03) [25].

Assuming a difference in the ACSS score (typical symptoms section) of one point on day 3 follow-up with a standard deviation of 2.9, as indicated in the Wagenlehner et al. study [26], and considering a power of 80%, an alpha risk of 5%, an intra-class correlation coefficient of 0.03 (corresponding to the most pessimistic situation), an average number of participants per cluster of 20, a coefficient of variation of a cluster size of 0.06, and two sided tests, the number of clusters to be randomized is 12 per arm, i.e., a total of 24 clusters. With an average of 20 participants per cluster, a total of 480 patients need to be recruited for the 24 clusters participating in the research.

#### **Recruitment {15}**

The recruitment capacity of each cluster is determined by the minimum number of participants that the clusters commit to recruit (20 patients per pharmacy) and the expected number of participants recruited per cluster, per month (2 participants per cluster, per month).

The number of patients recruited per center is unlimited.

The patient inclusion period runs from June 30, 2023, to October 29, 2024.

#### **Assignment of interventions: allocation**

##### **Sequence generation {16a}**

Each pharmacy will be defined as an individual cluster and randomized in a 1:1 ratio either to the pharmacist care protocol or standard care. This will ensure that standard care provided in the control group will not be influenced by the intervention care protocol thus reduce the risk of contamination bias. Pharmacy randomization will be stratified according to rural or urban location and average annual turnover (<1.4 M€ or >1.4 M€).

#### **Concealment mechanism {16b}**

This is an open-label, center-randomized trial.

Study site allocation was delayed as long as possible to ensure that sites had signed agreements to participate and final study sites had been identified, ethics approval obtained, and study launch confirmed. Site allocation was revealed on June 30, 2023.

#### **Implementation {16c}**

The biostatistician will assign centers, and therefore patients, to interventions. The investigating pharmacist will implement either the intervention protocol or standard care according to the random allocation.

#### **Assignment of interventions: blinding**

##### **Who will be blinded {17a}**

Both investigators and patients will know their allocation arm.

The data are coded and anonymized in the electronic case report forms (eCRF), enabling blind data analysis.

##### **Procedure for unblinding if needed {17b}**

N/a in an open-label study.

#### **Data collection and management**

##### **Plans for assessment and collection of outcomes {18a}**

All data relating to this study will be collected using an electronic case report form (eCRF) (Ennov Clinical). Patients will be identified only by their study inclusion number. The identity data required for monitoring will be collected on a paper form and faxed to the team responsible for centralized follow-up.

The data from the satisfaction questionnaire of the participating pharmacists as well as their demographic and professional data will be coded and recorded in a case report form and then entered into an EpiData file by a clinical research technician.

The semi-structured interviews will be recorded using a voice recorder and then transcribed using N-Vivo software. The anonymous written transcripts will be analyzed, in particular with the N-Vivo software, and kept under the responsibility of the coordinating investigator. Voice recordings will be deleted after transcription.

##### **Plans to promote participant retention and complete follow-up {18b}**

At the inclusion visit, the patient is asked to provide two separate telephone numbers and her availability.



If the patient cannot be reached on day 3, contact can be attempted again on day 4.

If the patient cannot be reached on day 10, contact attempts can be continue until day 14.

If the patient cannot be contacted at 3 months, the clinical research technician will continue efforts to contact her up to a maximum of 4 months after inclusion.

If a participant withdraws prematurely from the study, the reasons will be documented as fully as possible.

#### **Data management {19}**

Persons with direct access to the data shall take all necessary precautions to ensure the confidentiality of information relating to persons participating in the study, in particular with regard to their identity and the results obtained. These persons are bound by professional secrecy.

The investigator and the sponsor shall ensure that documents and data relating to the research are stored in accordance with the applicable regulations. The means used to store these essential documents must ensure that they remain complete and legible throughout the required retention period.

The investigator is responsible for keeping essential study documents at the research site (in particular, the patient's study file and signed consent).

Data in this study will be managed in accordance with the European General Data Protection Regulation and the French Data Protection Act.

#### **Confidentiality {27}**

Data are collected in the eCRF in coded form, except for patient identity and contact details. Trial participants are identified by a number consisting of the center number and an order number for inclusion in the center. The first letter of the participant's surname, the first letter of her first name, and the month and year of birth are collected.

A correspondence list is kept in each pharmacy under the responsibility of the center's principal investigator. This list is kept for the regulatory period specified for this type of research.

Data from professionals are collected in the EpiData file in coded form, and transcripts of semi-structured interviews are anonymous. Pharmacist investigators are identified by a unique professional number. A correspondence list will be established and maintained under the responsibility of the coordinating investigator at the research center. As part of the process of anonymizing the semi-structured interview transcripts, a copy of this list is sent to the coordinating investigator by secure mail. Once the transcripts have been anonymized, the copy of the correspondence list will be destroyed. This list will be

kept for the period required by the hospital of Angers for this type of research.

#### **Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}**

N/a. No biological samples will be collected.

#### **Statistical methods**

##### **Statistical methods for primary and secondary outcomes {20a}**

The quantitative data will be described using means and standard deviations and compared using Student's *t*-test (or Mann–Whitney *U* test if necessary). The qualitative data will be described using numbers and percentages and compared using chi2 test (or Fisher's exact test if necessary).

##### **Primary analysis**

The changes in symptoms between day 0 and day 3, measured by the ACSS scores (typical symptoms section), will be compared between the 2 groups using a multi-level mixed linear model. This model accounts for the random effect of individual and cluster effects considering the time as a qualitative variable with three modalities: days 0, 3, and 10. The care effect will be assessed using an interaction between the time and randomization arm variable. Such a model will make it possible to verify the expected lack of effect of randomized treatment at day 0. This also makes it possible to assess the interaction between the randomization arm and day 3 measurement, day 10 measurement, and to adjust these results according to the day 0 ACSS score.

##### **Secondary analyses**

Several endpoints will be considered to assess the safety of the experimental care (medical consultation, emergency department visits, and adverse event occurrence), but also the terms and conditions of care (a urine dipstick, microscopy, or culture being performed, taking concomitant medication(s) or food supplement(s) to relieve the cystitis symptoms). For each of these endpoints, a multi-level mixed logistic model will be performed considering the time as a qualitative variable with three modalities: days 0, 3, and 10.

Patient satisfaction will be assessed using the chi<sup>2</sup> test (of the Fischer's exact test if necessary) to compare the Likert scale response distribution. Pharmacist satisfaction will be studied in a similar way.

For these different multi-level models, unstructured variance–covariance matrices will be considered.

In accordance with the principle of intention-to-treat analysis, patients will be analyzed according to their

randomization arm, regardless of whether or not they took the proposed treatment.

All the tests will be carried out bilaterally with the type I error at 5%.

Pharmacists' satisfaction will be measured by semi-directed interview, face-to-face, or by videoconference. Interviews will be recorded and transcribed using NVIVO software (QRS International Pty. Ltd., Doncaster, Victoria, Australia). Qualitative data will be evaluated using a thematic approach [26]. Data collection and analysis will then be considered as simultaneous steps.

#### **Interim analyses {21b}**

No interim analyses will be planned because of the low-risk procedures and the close follow-up of patients.

#### **Methods for additional analyses (e.g., subgroup analyses) {20b}**

No further analysis will be carried out.

#### **Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}**

The primary and secondary outcomes analyses will consider the intention-to-treat population.

If there is missing data, multiple imputations using chained equations will be performed with a total of five imputations per missing datum. A comparison of the initial patient and cluster characteristics will be carried out according to the presence or not of missing data in the patient follow-up, to characterize the nature of the missing data. Finally, a sensitivity analysis will be carried out by analyzing all the observed data, without imputing missing data.

#### **Plans to give access to the full protocol, participant-level data, and statistical code {31c}**

The datasets analyzed during the current study and statistical code are available from the corresponding author on reasonable request, as is the full protocol.

### **Oversight and monitoring**

#### **Composition of the coordinating center and trial steering committee {5d}**

The study is coordinated by the Angers Hospital Clinical Research Center. The principal investigator and the coordinating investigator are pharmacists trained in clinical research. The other investigators are community pharmacists specially trained for the study.

The study management group consists of the principal investigator, the coordinating investigator, a project manager, and a statistician. The data management

team consists of a statistician, a data manager, two clinical researchers, and the coordinator. It is responsible for the collection, storage, and analysis of data. The day-to-day running of the trial is carried out by the research staff, which includes clinical research technicians, the data manager, and the coordinating investigator.

#### **Composition of the data monitoring committee, its role and reporting structure {21a}**

Any problems encountered by the investigators are reported to the coordinating investigators and discussed with the principal investigator (if necessary) and the clinical research technicians. Regular meetings between the coordinating investigator and the clinical research technicians allow monitoring of inclusion and identification of queries.

#### **Adverse event reporting and harms {22}**

In both groups, patients will be informed that persistence over time or aggravation of symptoms or onset of fever are signs their urinary tract infection is worsening. Should this occur or if they have any adverse events, they will be advised to consult a doctor without delay if any of these signs or symptoms occur. The main risk lies in the delayed diagnosis of a more severe upper urinary tract infection such as pyelonephritis. This risk is reduced by the inclusion of low-risk patients, adherence to the dispensing protocol, temperature measurement, and patient follow-up on day 3 and day 10.

#### **Frequency and plans for auditing trial conduct {23}**

The conduct of the study will be monitored to ensure the consistency of the data collected and to limit missing data. Queries will be made regularly (once a month) to check the correct completion of the case report form.

#### **Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}**

Any changes to the protocol must first be approved by the Ethics Committee. Amendments will be sent without delay to the study investigators and posted on the ClinicalTrials.gov website.

#### **Dissemination plans {31a}**

The results of this study will be published in a peer-reviewed journal for the benefit of the investigators and the scientific community. Several presentations at national and international conferences are planned. Specific information will be provided to pharmacists

investigating the trial, as well as to patients (e.g., flyer, posters).

## Discussion

Every year, pharmacies receive an average of 100 women with symptoms of a urinary tract infection who have not consulted a doctor beforehand (unpublished preliminary data). This substantial number suggests sufficient recruitment capacity in the defined region.

The choice of a cluster study, where each participating pharmacy corresponds to a cluster, is justified by the need to leave current practices within the control group pharmacies unchanged. It will also limit the risk contamination bias which would be induced by individual randomization.

Research is deployed in the various departments within the Loire region making it possible to reduce disparities relating to the region, particularly doctor accessibility since these five departments encounter medical demography inequalities [27].

This clinical study involves community pharmacists who are unaccustomed to participating in this type of research. Although we plan to mitigate this as much as possible by providing specific training and adapted materials, nevertheless, we may encounter recruitment difficulties due to the administrative burden or difficulties in data collection. For these reasons, patient follow-up will be ensured by the clinical research technician at the University Hospital of Angers.

Because of the investment required of pharmacists, their lack of time could slow down the recruitment process.

The results of this study could provide solid data to support possible extension of the protocol to pharmacies throughout France (currently restricted to coordinated practice), with a view to facilitating the patient care pathway for women with cystitis. In addition, the proposed methodology could potentially be used in other countries to explore this new approach to dispensing under protocol and move towards pharmaceutical prescribing for minor conditions.

## Trial status

Version 6 of the protocol is currently in force (version 6 dated 2024/06/26). The first investigating center was opened on June 30, 2023, and the first participant was enrolled in the PharmaCyst' clinical study on July 8, 2023. Recruitment is expected to end on October 29, 2024.

## Abbreviations

ACSS	Acute Cystitis Symptom Score
eCRF	Electronic case report form
ICH-GCP	International Consensus on Harmonization—Good Clinical Practice

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13063-024-08476-0>.

Supplementary material 1.

Supplementary material 2.

Supplementary material 3.

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## Authors' contributions {31b}

SF is the chief investigator and AP the coordinating investigator; they conceived the study. AP, EPS, and SF contributed to the study design. JFH developed the statistic plan. KN and AP translated and validated the Acute Cystitis Symptom Score. ACO, AG, and AP recruited the investigators. AP wrote the original draft. ARR and SF supervised the study protocol. All authors read and approved the final manuscript.

## Funding {4}

This study is supported by a grant from the French Ministry of Health, as part of the "ReSP-IR 2021" program.

## Availability of data and materials {29}

Any data required to support the protocol can be supplied on request.

## Declarations

### Ethics approval and consent to participate {24}

The protocol received approval from the French ethics committee "Comité de protection des personnes Ile de France VII, France" (n°-2022-A01874-39 on 2nd December 2022) and of the French "Commission Nationale de l'Informatique et des Libertés" (Data Protection Authority) for centralized monitoring (on 6th June 2023).

The trial is conducted in compliance with French law no. 2012-300 of 12 March 2012 relative to the research involving the human person and following Good Clinical Practice (I.C.H. E6(R2)), the Public Health Code of Ethics, and the Helsinki Declaration (Ethical Principles for Medical Research involving Human Subjects, Tokyo 2004) and other requirements as appropriate. Free and informed consent will be requested before each inclusion.

The study is registered on an open access website (ClinicalTrials.gov) under the number 49RC22\_0240.

### Consent for publication {32}

Not applicable - no identifying images or other personal or clinical details of participants are presented here or will be presented in reports of the trial results. The participant information materials and informed consent form are available from the corresponding author on request.

### Competing interests {28}

The authors declare that they have no competing interests.

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