

Sudy of Antibiotics You Stop for Treatment Of Pyelonephritis (SAYSTOP)

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Lead Principal Investigator: Brett Faine/David Talan

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STATEMENT OF COMPLIANCE

The study trial will be carried out in accordance with Good Clinical Practice (GCP) and as required by the following:

- United States Code of Federal Regulations (CFR) 45 CFR Part 46: Protection of Human Subjects
- Food and Drug Administration (FDA) Regulations, as applicable: 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (Institutional Review Boards), 21 CFR Part 11, and 21 CFR Part 312 (Investigational New Drug Application), 21 CFR 812 (Investigational Device Exemptions)
- International Conference on Harmonisation: Good Clinical Practice (ICH E6); 62 Federal Register 25691 (1997); and future revisions
- Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- National Institutes of Health (NIH) Office of Extramural Research, Research Involving Human Subjects, as applicable
- National Institute of Allergy and Infectious Diseases (NIAID) Clinical Terms of Award, as applicable
- Applicable Federal, State, and Local Regulations and Guidance
- The trial will be conducted in compliance with the protocol, International Conference on Harmonisation E6: Good Clinical Practice: Consolidated Guideline (ICH E6) and the applicable regulatory requirements.

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
AUP	Acute Uncomplicated Pyelonephritis
BID	Twice A Day
BLA	Biologics License Applications
CDI	Clostridium Difficile Infection
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CMS	Clinical Material Services
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
ED	Emergency Department
ESBL	Extended Spectrum Beta-Lactamase
EOT	End Of Treatment
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FQ	Fluoroquinolone

FWA	Federal Wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IDSA	Infectious Diseases Society of America
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
JAMA	Journal of the American Medical Association
MedDRA [®]	Medical Dictionary for Regulatory Activities
mITT	Modified-Intention-To-Treat
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NDA	New Drug Application
NEJM	New England Journal of Medicine
NGS	Next-Generation Sequencing
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
OHRP	Office for Human Research Protections

OHSR	Office for Human Subjects Research
PD	Pharmacodynamics
PDAD	Patient-directed antimicrobial duration
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetics
PFGE	Pulse Field Gel Electrophoresis
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
SR	Symptom Resolution
TMP-SMX	Trimethoprim/Sulfamethoxazole
US	United States
UTI	Urinary Tract Infection
WHO	World Health Organization

PROTOCOL SUMMARY

Title:	Study of Antibiotics You Stop for Treatment Of Pyelonephritis (SAYSTOP trial)
Design of the Study:	Double-blinded Randomized Controlled Trial.
Study Phase:	4
Study Population:	Females ≥ 18 to < 65 years of age (n=40) diagnosed with acute uncomplicated pyelonephritis and who can be discharged home on antimicrobial treatment
Number of Sites:	2
Description of Study Product or Intervention:	Cephalexin 500 mg capsules, Placebo capsules
Study Objectives:	<u>Primary:</u> The primary objective of the study is to evaluate trial feasibility based on achieving threshold proportions for the following performance indicators: 1) Patients with acute uncomplicated pyelonephritis (AUP) are identified, 2) Eligible patients provide consent to participate, 3) Participants are followed through EOT visit, and 4) Participants are followed through 30 days. <u>Secondary:</u> The secondary objective of the study is to evaluate trial safety defined by: 1) The upper bound of the 95% CI around the 30-day sustained clinical cure rate for the patient-directed antimicrobial duration (PDAD) group exceeds the lower

bound of the 95% CI for that of the standard treatment duration group.

Exploratory:

- 1) Analysis of Microbiological Failure Strain Types by Next Generation Sequencing.

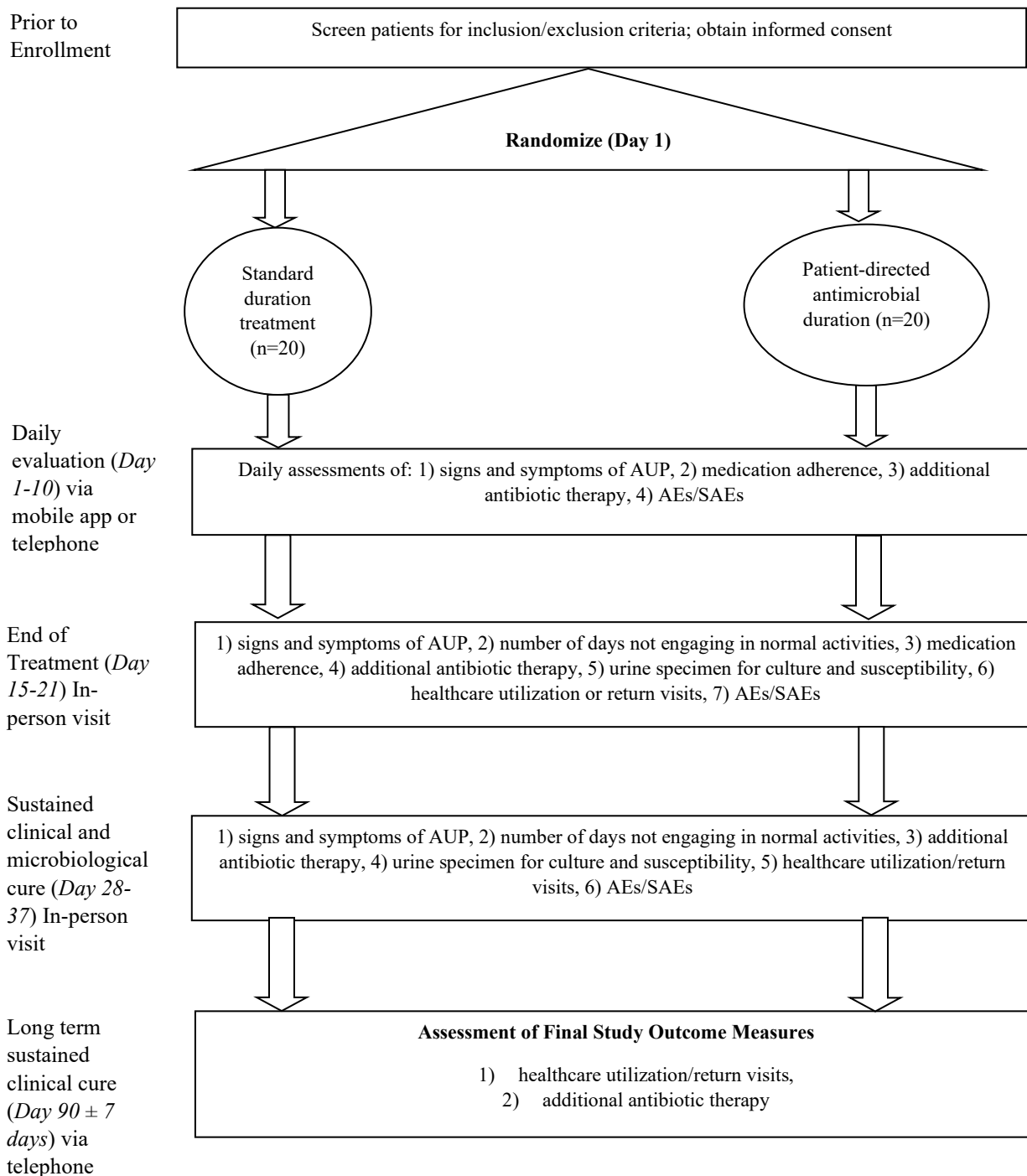
**Duration of Individual
Subject Participation:**

90 days

Table 1: Treatment Arms

Standard duration treatment (complete full 10-day course of Cephalexin)	Cephalexin 500 mg, take two capsules orally three times daily (<i>Pack A</i>)	Once the participant reports symptom resolution for 24 hours, they will be instructed to switch to Pack B
	Cephalexin 500 mg, take two capsules orally three times daily (<i>Pack B</i>)	

Patient-directed antimicrobial duration (PDAD) - Discontinue treatment 24 hours after complete symptom resolution (after a minimum of 3 days of treatment)	Cephalexin 500 mg, take two capsules orally three times daily (<i>Pack A</i>)	Once the participant reports symptom resolution for 24 hours, they will be instructed to switch to Pack B after a minimum of 3 days of taking Pack A
	Placebo capsules, take two capsules orally three times daily (<i>Pack B</i>)	

Figure 1: Schematic of Study Design (n=40)

1 KEY ROLES

Principal Investigators:	Brett Faine, PharmD, MS Clinical Associate Professor Department of Pharmacy and Emergency Medicine University of Iowa Hospitals and Clinics 200 Hawkins Dr. Iowa City, IA, 52242 Email: brett-faine@uiowa.edu David A. Talan, MD Professor of Medicine/Infectious Diseases and Emergency Medicine, David Geffen School of Medicine at UCLA Department of Emergency Medicine Ronald Reagan UCLA Medical Center 757 Westwood Plaza Los Angeles, CA 90095 Email: dtalan@ucla.edu
Co-Investigator/Project Manager	Anusha Krishnadasan, PhD Project Director/Epidemiologist Olive View-UCLA Education and Research Institute 14445 Olive View Drive, North Annex Sylmar, CA 91342 Email: idnet@ucla.edu
Co-Investigators	Gregory J. Moran, MD Professor of Medicine/Infectious Diseases and Emergency Medicine, David Geffen School of Medicine at UCLA Olive View-UCLA Medical Center Department of Emergency Medicine 14445 Olive View Drive, North Annex Sylmar, CA 91342 Email: gmoran@ucla.edu Scott Evans, PhD Professor Chair of the Department of Biostatistics George Washington University College of Public Health

950 New Hampshire Ave, NW, Suite 750
Washington, DC, 20052
Email: sevans@bsc.gwu.edu

William R. Mower, MD, PhD
Professor of Medicine, David Geffen School of Medicine at UCLA
UCLA Emergency Department
924 Westwood Blvd., Suite 300
Los Angeles, CA 90024
Phone: 310-794-0582
Email: wmower@ucla.edu

Anne Zepeski, PharmD
Clinical Assistant Professor
Department of Emergency Medicine
University of Iowa Hospitals and Clinics
200 Hawkins Dr.
Iowa City, IA, 52242
Email: anne-zepeski@uiowa.edu

Kavitha Pathmarajah, MPH
Project Manager
Department of Emergency Medicine
Olive View-UCLA Medical Center
14445 Olive View Drive, North Annex Bldg.
Sylmar, CA 91342
Email: kpathmarajah@dhs.lacounty.gov

2 BACKGROUND AND SCIENTIFIC RATIONALE

2.1 Background

Urinary tract infections (UTI) in the setting of rising fluoroquinolone (FQ) resistance

UTIs account for over 3 million emergency department (ED) visits annually and remain one of the most common indications for antibiotics.¹⁻⁵ Societal costs of UTIs, including healthcare costs and time missed from work, are approximately \$3.5 billion annually in the US.⁶ Additionally, UTIs are associated with a significant cause of morbidity, including recurrences, pyelonephritis with sepsis, and antibiotic-related adverse events (AEs).^{2,6}

The 2010 Infectious Diseases Society of America (IDSA) guidelines recommend FQs as 1st-line therapy of acute uncomplicated pyelonephritis (AUP) if the prevalence of *Escherichia coli* resistance is <10%.⁷ However, since the guideline's publication, *E. coli* FQ-resistance rates now exceed 20% in many US locations.^{8,9} Additionally, FQs are increasingly associated with serious AEs (SAEs) as well as collateral damage through the promotion of bacterial resistance.^{7,10} The U.S. FDA added new "Boxed Warnings" describing risks of peripheral neuropathy and central nervous system effects while strengthening previous warnings regarding tendinopathy and hypoglycemia.^{11,12} Additionally, FQs are associated with increased rates of *Clostridioides difficile* infection (CDI), accounting for >50% of all cases.^{13,14} Trimethoprim-sulfamethoxazole (TMP-SMX) has been used for decades for the treatment of AUP, however, *E. coli* resistance rates have exceeded 20% in most US communities for many years and IDSA guidelines recommend against its use.⁷ Due to the increasing prevalence of FQ resistance, which now exceed thresholds recommended for abandoning an antibiotic class, IDSA guidelines stress the need to evaluate alternative regimens.⁷

The optimal antibiotic for AUP

The preferred antibiotic for treatment of AUP should have the following characteristics: 1) high rate of in vitro activity against Enterobacterales, 2) pharmacokinetics (PK) allowing for infrequent dosing while still achieving adequate tissue and urinary concentration, 3) low incidence of AEs, and 4) low incidence of acquired pathogen resistance. Oral cephalosporins have been used extensively and successfully for the treatment of numerous infectious diseases, including pneumonia and skin and soft tissue infections.¹⁵ Additionally, cephalosporins represent an alternative treatment for UTI based on their activity against the primary pathogens involved and their pharmacokinetic/pharmacodynamic features.¹⁵

Cephalexin is an orally administered 1st generation cephalosporin antimicrobial agent and is used to treat mild-moderate bacterial infections. Cephalexin is primarily eliminated by renal excretion of unchanged drug and has high oral bioavailability when compared to other cephalosporins (e.g., cefdinir, cefpodoxime).¹⁶ Cephalexin is highly active in vitro active against

E. coli and *K. pneumoniae* and exhibits low rates of in vitro inactivity against common uropathogens.^{15,17,18} Table 2 below outlines the pharmacokinetics of several cephalosporins and their clinical cure rates from previous randomized trials (against a variety of comparators) for uncomplicated cystitis and AUP.¹⁹⁻²⁵

Table 2.				
Drug	Bioavailability (%) ^{19,20}	24- hour Urine Excretion (%) ^{19,20}	Clinical cure rates for uncomplicated cystitis (%) ²¹⁻²³	Clinical cure rates for AUP (%) ^{24,25}
Cephalexin	90-100	88	78, 86	NS
Cefaclor	52-95	54	93	83
Cefpodoxime	29-53	32*	82	NS
Cefdinir	21-25	23	91.3	99

NS: Not Studied

*Fasted participants

Longer antimicrobial durations lead to collateral damage and AEs

As opposed to short-course FQ treatment for AUP (5-7 days), for cephalosporin regimens, IDSA recommends a 10-14 day treatment duration for AUP due to some acute cystitis trials showing lower initial cure rates and higher recurrence rates compared with FQ regimens.^{23,26,27} More recent trials among patients with AUP have demonstrated effectiveness of 7-10 days of cefdinir and cefixime (some with an initial IV dose of ceftriaxone), with similar cure rates as achieved with FQs.^{24,28,29}

However, longer treatment durations are associated with antibiotic-associated AEs and selection of multi-drug resistant pathogens.³⁰ The risk of antibiotic-related AEs is cumulative with increasing exposure.³¹ Each extra day of treatment is associated with a 5% increase in odds of antibiotic-related AEs.³² Additionally, the risk of carrying a resistant organism has been shown to increase with each additional day of β -lactam antibiotic use. Clinical trials of AUP support that shorter durations (e.g., 5-7 days with FQs) are just as effective as longer durations of antibiotics of other classes (e.g., 2-6 weeks). For most patients, symptoms fully resolve in fewer than 7 days for both FQ- and β -lactam-based regimens (Figures 1 and 2).^{33,34}

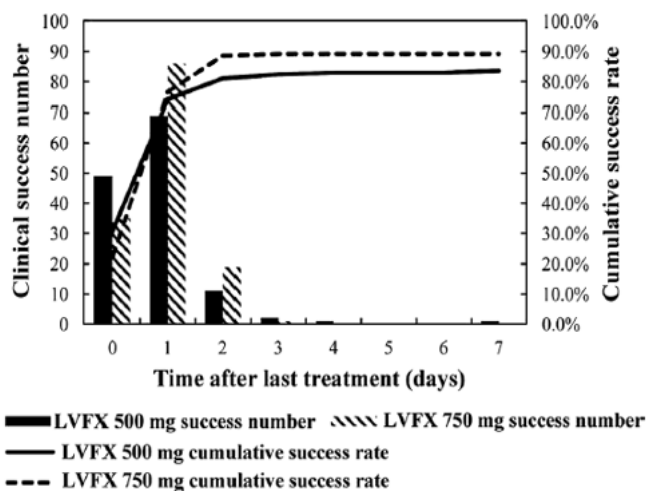


Figure 2. Time course of clinical success after last treatment for patients. LVFX = levofloxacin

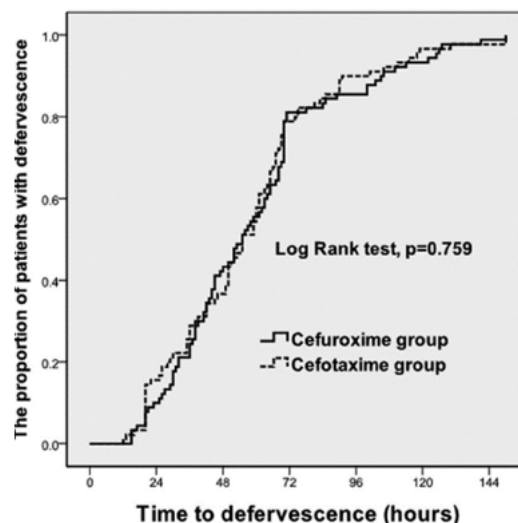


Figure 3. Time to defervescence from the time of administration of 1st dose of cephalosporin.

The one-size-fits all versus precision/personalized medicine approach for antibiotic treatment of infections

Completing the full course has become antimicrobial treatment dogma and is supported by healthcare agencies across the world.^{35,36} It is thought that treating beyond resolution of symptoms helps prevent relapse of infection and development of antimicrobial resistance, however, evidence supporting this practice is lacking.^{37,38} Notably, longer durations of therapy are associated with a greater risk of emergence of antimicrobial resistance and an increased rate of AEs.^{39,40} Further, recurrent infections have been found to most often be due to reinfection following a subsequent negative culture rather than a relapse.⁴¹

A one-size-fits all approach to antimicrobial duration ignores unique host and pathogen characteristics and the specific antimicrobial's effects on an individual's rate of response to the treatment of their infection. Precision or personalized medicine allows for the evaluation of the right dose of the right drug for the right patient at the right time, and now possibly, for the right duration.⁴² The definition of precision medicine aligns with how antimicrobial therapy should be optimized; a patient with an infectious process must receive the right dose/duration of the right antimicrobial agent to optimize the chance of clinical cure and minimize the chance of AEs. Patient-directed antimicrobial durations (PDAD) represent a potentially important new avenue for precision medicine. A longer duration β -lactam regimen for AUP allows a greater opportunity to explore PDAD to minimize collateral antibiotic damage. If PDAD is proven to lead to non-inferior sustained clinical cure rates and fewer AEs compared to those associated with fixed indication-directed duration, a paradigm shift would occur in how clinicians and patients view treatment of many infectious diseases. Instead of the standard one-size-fits all

approach, the new patient-centered approach will be, “Take your antibiotics until you feel all better and then stop.”

2.2 Scientific Rationale

2.2.1 Purpose of Study

The rationale for this study is that advising patients to discontinue antimicrobial therapy upon symptom resolution may be an effective, patient-centered approach that will take into account the patient’s individual response to antibiotics and reduce the antibiotic AE rate. However, since this is a new approach, a preliminary study is needed to assure its feasibility and safety before conducting a large, multi-center trial. If our hypothesis that PDAD is non-inferior to standard care (e.g., completing the standard full course therapy) based on sustained clinical cure is correct, then decreasing antimicrobial therapy exposure could lead to a significant decrease in antibiotic-associated AEs and antimicrobial resistance associated with prolonged treatment.

Participants will be randomized to standard duration (to complete a 10-day course of antimicrobial treatment) or PDAD treatment (must complete a minimum of 3 days of treatment before discontinuation after symptom resolution). Per clinician discretion, patients can receive a single IV dose of guideline-endorsed long-acting parenteral antibiotic (e.g., ceftriaxone or ertapenem) followed by an oral regimen of cephalexin 1000 mg three times a day upon ED discharge.

Study Population

Females ≥ 18 to < 65 years of age who meet criteria for AUP (with negative ED bedside ultrasound for obstructive nephropathy) and can be discharged home from the ED on oral antimicrobial therapy will be eligible for study enrollment. The inclusion criteria have been adapted from FDA recommendations for conducting clinical trials in patients with UTIs and our group’s previous clinical trial evaluating women diagnosed with AUP in the ED, which showed a high degree of specificity for the diagnosis.⁸

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

To enroll patients in our study we will need access to patient identifying and protected health information. Common patient identifiers are necessary for matching medical records and outcomes. Risks to participants whose data are accessed are a breach of privacy and loss of confidentiality. Participants assigned to the PDAD group may be at risk for recurrence of symptoms potentially leading to more serious infection. Based on previous AUP studies, it is not expected that these complications will be greater in patients assigned to the PDAD group, but that is not known for certain. Participants in both groups will receive standard antimicrobial

therapy that can lead to rare SAEs. The standard antimicrobial therapy (i.e., long-acting parenteral antibiotic, cephalexin) can cause side effects (e.g., nausea/vomiting), severe allergic reactions, or antibiotic-associated *Clostridioides difficile*. The alternative to participation in the clinical trial is standard care (i.e., complete full course of antimicrobial therapy). Patients will be informed of alternatives to participation in the informed consent process.

2.3.2 Potential Benefits

There is no direct or immediate benefit to patients who are enrolled in the study. The study findings may ultimately identify a more effective treatment strategy for AUP. Patients enrolled in the study will get medications dispensed to them directly in the ED, and much closer follow-up and access to a clinician than patients who are not enrolled in the study. Patients in the trial will be provided with antibiotics to treat their infection. They will not need to procure or pay for their treatments.

3 STUDY DESIGN, OBJECTIVES AND ENDPOINTS OR OUTCOME MEASURES

3.1 Study Design Description

This will be a two-site double-blind randomized controlled trial (RCT) in women with AUP who are assigned to one of two initial treatment strategies, PDAD or fixed-duration antibiotic treatment. The objectives of the pilot trial are to determine the feasibility and safety of conducting a full-scale multi-center RCT. The primary objective of the larger study will be to test the hypotheses that, among women with AUP who are discharged home from the ED, PDAD is no worse than fixed-duration/standard care in terms of sustained symptom resolution, bacterial elimination, and patient-related outcomes (e.g., time to return to normal activities). An additional objective of the full-scale trial will be to ascertain whether antibiotic usage decreases among the PDAD subject. This will be assessed by comparing the actual number of antibiotic doses among patients in the treatment group and control groups using a superiority design.

After informed consent, participants will be randomized to routine fixed-duration antibiotic treatment (10 days), or to PDAD (discontinue antibiotics upon symptom resolution). Randomization will be 1:1 and treatment will be pre-assigned in each enrollment packet based on a random number sequence with nearly equal assignments to both treatment strategies to ensure that clinicians cannot predict the last treatment strategies based on the need for equal distribution among antibiotic therapy arms.

Participants will be evaluated at enrollment Day 1 (in-person), then daily, with use of a mobile cellphone application (or daily telephone calls from the study team) through the completion of antibiotic therapy (standard care with fixed treatment duration group, Day 10) or until resolution of symptoms (PDAD), at Day 15-21 (in-person), Day 28-37 (in-person), and Day 90 (via telephone). Urine specimens will be collected at each in-person visit (Day 1, 15-21, and 28-37) to identify isolates, determine their antimicrobial susceptibility, and calculate cure rates. While daily follow-up is more intense compared to other studies evaluating antibiotics, it is necessary to capture the specific time/day that the participant has symptom resolution and to further ensure patient safety.

Participants assigned to the PDAD group will be informed to stop therapy once their symptoms reported at their initial visit, including fever, flank/abdominal pain, and dysuria, have completely resolved (and no new symptoms of AUP have developed). For safety purposes, participants assigned to the PDAD group will be required to complete a minimum of 3-days of therapy even if they report their symptoms have resolved before that time. Past studies of patient response times for AUP indicate that almost all patients continue to have symptoms through 3 days, after which increasing proportions have resolution through 10 days.^{33,34} Once symptom resolution is achieved, a research coordinator will contact the participant 24 and 48 hours after their last dose of antibiotics to ensure they have remained symptom-free. Additionally, the participant will be reminded that a study coordinator is available 7 days a week and to contact them if they

experience any worsening of symptoms or have questions. If the participant reports that their symptoms persist or have returned, then their care will be reviewed with a clinician to determine if they should return for re-evaluation or have their treatment changed.

For the pilot clinical trial, Olive View-UCLA IRB will serve as the single Institutional Review Board (sIRB) and will be responsible for safety oversight for study participants enrolled at their site. Serious adverse events (SAEs) will be reported to the IRB per their requirements. For additional safety oversight, we will have an Independent Safety Monitor (ISM) at each site.

3.2 Study Objectives

3.2.1 Primary

The primary objective of this pilot trial is to evaluate trial feasibility of conducting a large-scale, multi-center clinical trial. Feasibility will be assessed based on achieving threshold proportions for the following performance indicators in 40 participants:

- 1) >90% of patients with AUP are identified,
- 2) >30% of eligible patients provide consent to participate,
- 3) >80% of participants are followed through EOT visit, and
- 4) >80% of participants are followed through 30 days.

3.2.2 Secondary

The secondary objective of our study is to conduct a preliminary evaluation of trial safety by:

- 1) Determining whether the upper bound of the 95% CI around the 30-day sustained clinical cure rate for the PDAD group exceeds the lower bound of the 95% CI for that of the standard treatment duration group.

3.2.3 Exploratory

Analysis of Microbiological Failure Strain Types by Next Generation Sequencing

Microbiological failure after UTI treatment is associated with increased risk of late clinical recurrence.⁴³ Past studies have found that recurrent cystitis following initial clinical resolution most often occurs with the same strain (based on pulsed field gel electrophoresis [PFGE]) after an initial negative follow-up culture.⁴³ Thus, recurrent infections appear to primarily be reinfections not relapses.. To the best of our knowledge, strain analysis has not been conducted for recurrent UTI following treatment of AUP. Next generation sequencing (NGS) more accurately types the strain compared to PFGE. Therefore, we will use NGS to characterize infecting strains, including those associated with microbiocidal failure and clinical reoccurrence.

3.3 Study Endpoints or Outcome Measures

3.3.1 Primary

Primary feasibility performance thresholds and safety outcomes are shown in the table below.

Feasibility		Safety	
Indicator	Threshold	Indicator	Threshold
Patients with AUP are identified	>90%	Between group sustained clinical cure with and without recurrence at 30 days (i.e., no additional antibiotic treatment received)	The upper bound of the 95% CI around the 30-day sustained clinical cure rate for the PDAD group exceeds the lower bound of the 95% CI for that of the standard treatment duration group.
Eligible patients who provide consent to participate	>30%		
Participants who have follow-up through Day 21	>80%		
Participants who have follow-up through Day 30	>80%		
Participants who have follow-up through Day 90	>80%		

3.3.2 Secondary

Secondary outcomes of the pilot study will model specific outcomes and related hypotheses to be tested in the large-scale trial. Secondary outcomes will include the following:

- 1) Sustained clinical cure through the 30-day visit defined as no additional antimicrobial treatment for clinical failure (i.e., deterioration at any time, or no improvement of symptoms and signs of the initial infection after 3 days of treatment, or recurrence of symptoms and signs after initial clinical improvement, such that a clinician determines they need a change or additional antibiotics),
- 2) Sustained microbiological cure through the 30-day visit defined as the bacterial pathogen found at trial entry is reduced to fewer than 10^3 cfu/mL and no new pathogen $>10^3$ cfu/mL,

- 3) Clinical and microbiological cure rates after the end of treatment (Day 15-21, as recommended by the FDA),
- 4) AE and SAE rates, and
- 5) Healthcare visits not required by the study.

4 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

4.1 Study Product Description

Cephalexin is an orally administered antibiotic of the cephalosporin class. It is commonly referred to as a 1st generation cephalosporin.

4.1.1 Formulation, Packaging, and Labeling

Cephalexin capsules were approved by the FDA in 1971 as a registered trademark, brand name Keflex®. It is currently available as an FDA approved generic equivalent that is manufactured by Lupin Pharmaceuticals.

The study product will be labeled according to manufacturer or regulatory specifications and include the statement “Caution: New Drug – Limited by Federal Law to Investigational Use.”

Product 1 Name: Active Product(s) and Components

Cephalexin

4.1.2 Product Storage and Stability

Cephalexin 500 mg capsules must be stored between 20°C to 25°C (68°F to 77°F).

Placebo capsules must be stored between 20°C to 25°C (68°F to 77°F).

4.2 Acquisition/Distribution

Cephalexin is available for purchase from major drug wholesalers (e.g., McKesson, Cardinal Health) across the United States.

Product 1 Name: Active Product(s)

Cephalexin 500 mg capsules

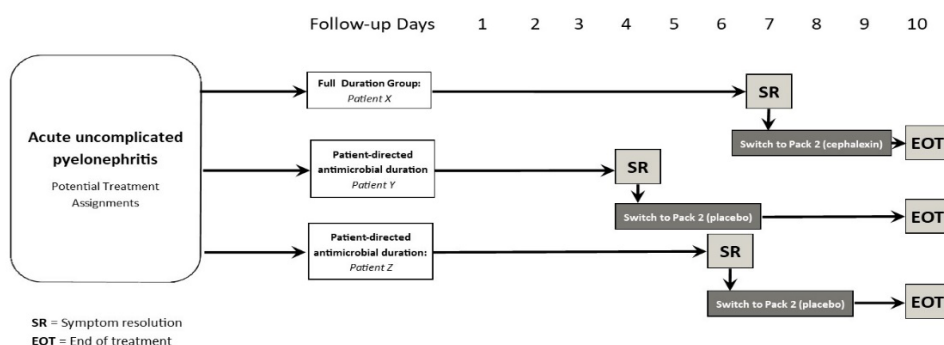
Product 2 Name: Inactive product

Placebo capsules

4.3 Dosage/Regimen, Preparation, Dispensing and Administration of Study Intervention/Investigational Product

Patients who agree to participate in the study will be randomized to fixed indication-directed antimicrobial duration (i.e., complete the full course of therapy regardless of symptom resolution) of oral cephalexin 500 mg capsules, take two capsules by mouth three times daily for 10 days, or PDAD of oral cephalexin 500 mg capsules, take two capsules by mouth three times daily and stop treatment upon symptom resolution for 24 hours after completion of a minimum of 3 days of cephalexin.

To ensure blinding, each participant will receive a study kit that consists of two identical blister packs (Pack A and Pack B) that will not indicate whether they contain cephalexin or placebo. For participants in the PDAD group, Pack A will have a 10-day course of cephalexin 500 mg capsules (i.e., to be taken TID, 60 capsules total) and Pack B will have placebo. For participants in the fixed-duration-assigned group, both Packs A and B will contain cephalexin. Participants in both groups will be instructed to start taking capsules for Pack B after their symptoms have resolved for 24 hours and until all capsules are consumed according to schedule. Figure 3 represents potential treatment algorithms based on randomization assignment.



All supplies packed and labeled will be formally released in accordance with both Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines.

4.4 Accountability Procedures for the Study Intervention/Investigational Product(s)

Cephalexin 500 mg capsules and placebo capsules will be stored and shipped from the University of Iowa to the Clinical Sites. Once received, cephalexin capsules and placebo will be stored in and dispensed by the Investigational Pharmacy. Unused product may be destroyed.

The Food and Drug Administration (FDA) requires accounting for the disposition of all investigational products. The Investigator is responsible for ensuring that a current record of product disposition is maintained, and product is dispensed only at an official study site by authorized personnel as required by applicable regulations and guidelines. Records of product disposition, as required by federal law, consist of the date received, date administered, quantity administered, and the participant number to whom the drug was administered.

The Investigational Pharmacist will be responsible for maintaining accurate records of the shipment and dispensing of the investigational product. The pharmacy records must be available

for inspection by a regulatory agency (e.g., FDA) at any time. An assigned Study Monitor will review the pharmacy records.

At study termination, all unused investigational product will be disposed following complete drug accountability and monitoring.

5 SELECTION OF PARTICIPANTS AND STUDY ENROLLMENT AND WITHDRAWAL

Women and minorities will be included in the study population. University of Iowa Hospitals and Clinics is an academic, tertiary referral center with approximately 10% of the patient participant population being under-represented minorities. The center also serves for statewide referral of people in underserved rural areas. Olive View-UCLA Medical Center serves a medically underserved population in which diverse racial and ethnic groups are well represented. Approximately 70% of the patient population is Hispanic or Latino. Because the proposed study population will include a large number of Spanish-speaking patients, all consent documents and materials will be translated to Spanish by a certified translation service. Women of childbearing potential will not be excluded, but will have a negative pregnancy test documented prior to enrollment. We will not exclude any minorities and we don't expect that clinically important differences will be observed based on sex or minority status.

Children will not be included in this study because acute uncomplicated pyelonephritis (AUP) in children has different diagnostic criteria and treatment recommendations.

AUP is an infectious disease state that is commonly treated in EDs. Study site ED clinicians will identify potential patients with AUP and will notify the research coordinator at their site. Additionally, the research coordinator at each site will conduct daily screening of all patients who were diagnosed with AUP. The research coordinator will maintain a medical record log of all patients screened for eligibility in the study and all patients who were diagnosed with AUP. This log will only include minimal patient information (i.e., patient name, medical record number, date of screening, and whether they are eligible for the study). After the diagnosis of AUP is made by the ED clinician and the research coordinator has deemed the patient eligible for the study based on the predefined exclusion criteria, the ED clinician will ensure that the patient has the mental capacity to discuss the study. Upon approaching the patient, the patient will be provided informational material about the study and the different treatment options in either Spanish or English, as appropriate. Additionally, the research coordinator will review the informed consent document with the patient and will describe all study procedures, risks, and benefits of the study and alternatives to study participation. The informed consent will also include emergency contact information in the case of a study-related problem. If the patient agrees to participate in the RCT, they will be asked to sign the informed consent and a Health Insurance Portability and Accountability Act (HIPAA) Authorization forms.

5.1 Eligibility Criteria

Participant Inclusion and Exclusion Criteria will be confirmed by a study clinician licensed to make medical diagnoses.

5.1.1 Participant Inclusion Criteria

All participants must meet the following criteria:

- 1) Female ≥ 18 to < 65 years of age,
- 2) Diagnosis of AUP,
- 3) Can be discharged home on oral antimicrobial treatment, and
- 4) Able to provide written informed consent in English or Spanish

5.1.2 Participant Exclusion Criteria

All participants must not meet any of the following criteria:

- 1) Took antibiotics in the prior 48 hours before this ED visit,
- 2) Insulin-dependent diabetes,
- 3) End stage liver disease (Note: For patients with serious liver disease, this will be determined by a MELD score ≥ 15),
- 4) If the patient reports a penicillin allergy and is deemed to be high-risk using the PEN-FAST decision rule (score of 4 or 5),⁴⁴
- 5) Serious allergy (e.g., angioedema, anaphylaxis) to the study medication or a similarly reported allergy to a cephalosporin,
- 6) Known or identified hydronephrosis, obstruction, or abscess by ED ultrasound or CT scan,
- 7) Presence of a ureteral stone.
- 8) Pregnancy,
- 9) Renal dysfunction (defined as a creatinine clearance of less than 30 mL/minute)
- 10) Renal transplantation,
- 11) Complicated pyelonephritis (defined anatomical or functional abnormality of the urinary tract that predisposes to infection),
- 12) Need for additional antimicrobial therapy for a coexisting infection,
- 13) Human immunodeficiency virus (HIV) infection, with either a recent (in the past 6 months) acquired immune deficiency syndrome-defining condition or a CD4+ T lymphocyte count $< 200/\text{mm}^3$,
- 14) Systemic or hematological malignancy requiring chemotherapeutic or radiation/immunologic interventions within 6 weeks prior to randomization or anticipated to begin prior to completion of study,
- 15) Immunosuppressive therapy, including maintenance corticosteroid therapy (> 40 mg/day equivalent prednisolone for 5 days or more in the 30 days prior to randomization),
- 16) Currently taking anti-inflammatory monoclonal antibodies,
- 17) Urologic procedures and/or instrumentation within the last 30 days,
- 18) Neutropenia (absolute neutrophil count < 1000 cells/ μL),
- 19) Long-term care residence within 90 days,
- 20) Chronic indwelling foley catheter,

-
- 21) Ureteral stent(s) in place,
 - 22) Previously enrolled in the trial,
 - 23) Lack of telephone, or another barrier that would prevent follow-up visits, or
 - 24) ESBL infection found in urine or blood in the prior year.

5.2 **Withdrawal from the Study, Discontinuation of Study Product, or Study Termination**

5.2.1 Withdrawal from the Study or Discontinuation of the Study Product

A participant may voluntarily withdraw their consent for study participation at any time without penalty or loss of benefits to which they are otherwise entitled. An investigator may also withdraw a participant from receiving the study product for any reason. Follow-up safety evaluations will be conducted, if the participant agrees. If a participant withdraws or is withdrawn prior to completion of the study, the reason for this decision will be recorded in the case report forms (CRFs).

The reasons, might include, but are not limited to the following:

- Participant no longer meets eligibility criteria
- Medical disease or condition, or new clinical finding(s) for which continued participation, in the opinion of the investigator might compromise the safety of the participant, interfere with the participant's successful completion of this study, or interfere with the evaluation of responses
- Participant lost to follow-up (e.g., does not respond to research coordinator after the 10-day treatment course)
- Determined by a physician's discretion to require additional therapy not indicated in the protocol to ensure participant's health and well-being (or treatment failure, if applicable)

The investigator will be explicit regarding study follow-up (e.g., safety follow-up) that might be carried out despite the fact the participant will not receive further study product. If the participant consents, every attempt will be made to follow all SAEs through resolution.

The investigator will inform the participant that already collected data will be retained and analyzed even if the participant withdraws from this study.

5.2.2 Participant Replacement

Participants who withdraw, or are withdrawn from this study, or are lost to follow-up after signing the informed consent form (ICF) and administration of the study product will not be replaced. Participants who withdraw, or are withdrawn from this study, or are lost to follow-up after signing the ICF but before administration of the study product may be replaced.

5.2.3 Study Termination

If the study is prematurely terminated by the sponsor, any regulatory authority, or the investigator for any reason, the investigator will promptly inform the study participants and assure appropriate therapy or follow-up for the participants, as necessary. The investigator will provide a detailed written explanation of the termination to the IRB.

6 STUDY PROCEDURES

6.1 Screening

The study team will orient the ED staff at the University of Iowa Hospitals and Clinics and Olive View-UCLA Medical Center to the study objectives and procedures. Study eligibility information will be posted in the ED with instructions for providers on how to contact the study team. Additionally, each hospital has on-site study coordinators who will screen the ED tracking board for patients with the presumptive diagnosis of AUP. The study coordinators will review with the treating provider if the patient meets inclusion and exclusion criteria. Patients with a diagnosis of AUP who meet the study inclusion criteria and do not meet any study exclusion criteria will be approached by the study coordinator to ask if they are willing to participate in the study. If the patient is willing to participate, then the study team will initiate the informed consent process. If the patient provides informed consent, they will be enrolled in the study and the study coordinator will confirm that a urine specimen was collected for culture and antimicrobial susceptibility testing.

After informed consent is obtained for the research protocol, participants will be asked if they would like to use a novel research app for daily follow-up activities. Using the research app is not a requirement for required study procedures and the participant can opt out of using the research app and use traditional methods for daily follow-up (e.g., telephone). The research app uses a secure, HIPAA compliant database that can only be accessed by research team members and support staff. The app will not collect any geographic location information or video recording of participants.

If the participant agrees to use the research app, they will be assigned a unique identifier in the app. The unique identifier allows for de-identified daily symptom data to be collected. The unique identifier will be linked with the study participant ID in the REDCap database. The data collected in the research app will be securely uploaded into the REDCap database and linked with the enrolled participant. Only research team members will have access to the research data in the REDCap database. All data collected in the research app will be only used for study purposes and destroyed at the completion of the study.

Participants who agree to use the research app and have a smartphone capable of supporting the research app to collect follow-up data will be asked to download the research app with the assistance of the study coordinator. If the study participant does not have a smartphone or the ability to use an app, then they will still participate in the study without using the app and be contacted by traditional methods (e.g., daily telephone call). If the participant is able to utilize the research app for follow-up procedures, then the research coordinator will download the app at enrollment and provide a quick tutorial on how to answer the survey questions. The participant will complete the Day 1 survey on the research app with the research coordinator present to help

demonstrate if necessary. The research app will send a notification to the participant on the scheduled follow-up days and prompt them to complete the relevant surveys. Survey questions will include the following: 1) signs and symptoms of AUP; 2) antibiotic adherence; 3) use of pain medications (NSAIDs, acetaminophen, phenazopyridine); and 4) general health. There will be no open-ended questions in the daily app surveys, but participants will be able to write their comments or concerns in an open text field.

6.2 Enrollment

Baseline/Enrollment Visit (Day 1)

- 1) Patients will be consented to participate in the study.
- 2) Patient medical/surgical history, demographics, vital signs, pain severity, medication use, general health quality, and symptoms related to AUP will be recorded.
- 3) Blood will be drawn and a clean-catch midstream urine specimen will be collected if not already performed/done as part of routine care, all enrolled participants will have urinalysis and urine culture and susceptibility ordered.
- 4) Patients will receive the first dose of cephalexin 500 mg capsule in the ED to ensure they can tolerate the study medication. The participant will be observed for a minimum of 30 minutes after the dose is administered. If the participant has any signs of an allergic reaction, they will be discontinued from the trial.
- 5) If patient consents to use the daily app, the app will be downloaded onto their smartphone and they will complete their day 1 survey with study coordinator help.

As part of standard of care and treating clinician discretion, participants may receive a dose of once-a-day IV/IM antibiotic (e.g., ceftriaxone, ertapenem) in the ED prior to discharge.

6.3 Planned Study Visits

6.3.1 Follow-up Visits

Participants will be evaluated at enrollment Day 1 (in person), then daily through 10 days (via mobile app or telephone). Additional follow-up visits include:

- 1) Day 15-21, end of treatment (EOT) clinical and microbiological cure visit (in person);
- 2) Day 28-37, sustained clinical and microbiological cure visit (in person); and
- 3) Day 90, long-term follow-up (telephone).

Day 2-10, Daily Follow-up Visits Via Mobile App or Telephone

The study coordinator will record the following: 1) signs and symptoms of AUP, 2) medication adherence, 3) pain medication use, and 4) general health quality. During the daily follow-up

visits, if the participant indicates that their symptoms reported at their initial visit have completely resolved, specifically any and all of fever, flank pain, and dysuria (and no new symptoms of AUP have developed), they will be informed by the study coordinator to stop taking blister Pack A and start taking blister Pack B. For safety purposes, the PDAD-assigned participants will be required to complete a minimum of 3-days of blister Pack A (containing active treatment) even if they report their symptoms have resolved. Once symptom resolution has occurred, the study team will monitor their daily symptom responses to ensure they remain symptom free. Additionally, they will be reminded that a study coordinator is available 7 days a week and to contact them if they experience any worsening of symptoms or have questions. If the participant reports that their symptoms persist or have returned, then their care will be reviewed with a clinician to determine if they should return for re-evaluation and/or have their treatment changed.

Switching Treatment Based on Urine Microbiological Susceptibilities

The study coordinator will review urine cultures daily for pathogen resistance to cephalixin. Switching treatment may be required based on the microbiological susceptibilities. Currently, there are no commercially available microbiological susceptibility testing mechanisms for cephalixin; resistance will be based on cefazolin (intravenous 1st generation cephalosporin) susceptibility. If the susceptibility results show resistance to cefazolin, then the participant will be contacted by a research coordinator. The participant will be instructed to stop taking their study medication and will be provided with a new oral course of treatment based on the culture and susceptibility report, patient-reported allergies, and potential drug interactions. Oral options include one of the following antibiotics:

- 1) Ciprofloxacin 500 mg one tablet by mouth twice a day for 7 days, OR
- 2) TMP/SMX 1 double-strength tablet by mouth twice a day for 10 days.

If the culture and susceptibility report shows ceftriaxone-resistance/presumed extended spectrum β -lactamase-producing, then the participant will be provided amoxicillin/clavulanate 875 mg/125 mg, one tablet by mouth twice a day for 7-days to be taken in conjunction with cephalixin, or will be hospitalized for parenteral ertapenem treatment.

If the participant's antibiotic treatment was changed due to in-vitro resistance, the participant will not be deemed a clinical failure and will remain in the study and complete follow-up assessments. At the time of this change, the clinical response of the participant will be assessed. These participants will not be issued new blister packs with the new antibiotic and placebos and, thus, will not be blinded to their treatment. Participants in the fixed-duration group will be instructed to complete 10 days of treatment with the new antibiotic regimen. Participants in the PDAD group will be instructed to stop the new treatment after 24 hours of symptom resolution. For the purpose of ITT analysis, the participant will remain in their assigned group. Those who

remain treated with cephalexin and blinded to their treatment assignment will be analyzed as a modified ITT group (mITT). Those who switched to a new antibiotic will be analyzed as a separate subgroup.

The study coordinator will record the following at each of the assigned follow-up visits:

Day 15-21, End of Treatment in person visit

- 1) Signs and symptoms of AUP,
- 2) Assess antimicrobial compliance,
- 3) Healthcare utilization or return visits,
- 4) Number of days not engaging in normal activities,
- 5) General health quality,
- 6) Urine specimen for culture and in vitro antibiotic susceptibility,
- 7) Any additional antimicrobial treatment required, and
- 8) Any AE or SAEs.

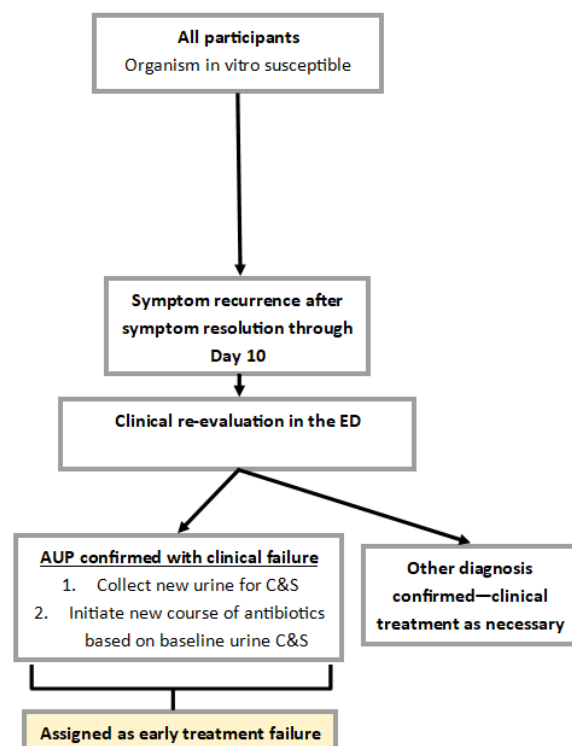
Day 28-37, Sustained clinical and microbiological cure in person visit

- 1) Signs and symptoms of AUP,
- 2) Healthcare utilization or return visits,
- 3) Number of days not engaging in normal activities,
- 4) General health quality,
- 5) Urine specimen for culture and in vitro antibiotic susceptibility,
- 6) Any additional antimicrobial treatment required, and
- 7) Any AEs or SAEs.

Symptom Recurrence After Symptom Resolution Through Day 30

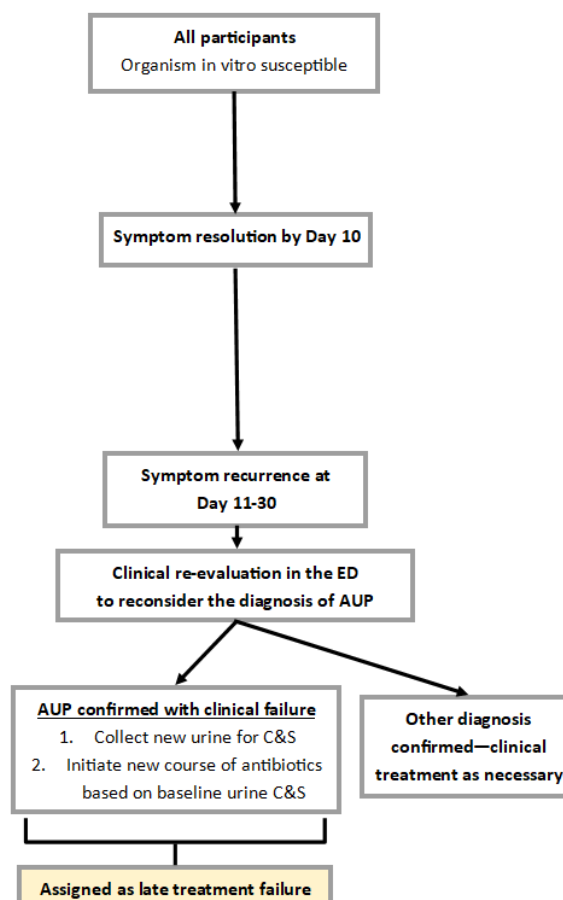
Participants randomized to the PDAD group may experience symptom recurrence after reporting symptom resolution during their daily follow-up visits through Day 10. In addition, all participants may experience symptom recurrence after they have finished their antibiotic treatment through their Day 30 visit. Figures 4 and 5 outline the follow-up and analysis plan for a participant who reports symptom recurrence during the Day 10 and Day 30 follow-up period.

Figure 4.



PDAD—patient directed antimicrobial duration
ED—emergency department
AUP—acute uncomplicated pyelonephritis
C&S—culture and susceptibility

Figure 5.



Additional Follow-up Details.

In order to be eligible to be enrolled, patients must be willing to be followed closely over a 30-day evaluation period. They will be required to provide detailed contact information, including address, telephone/cell phone numbers, and alternative sources for contact including email addresses. Study coordinators will be responsible for scheduling, reminding and meeting participants for their in-person follow-up visits, and contacting participants for their daily follow-up symptom surveys. For follow-up evaluations, in accordance with local IRB guidelines and with prior approval, participant will be provided reasonable funds for the transportation and/or time away from work/school/home costs for visits, which will occur in the ED or Clinical Research Unit at the University of Iowa Hospitals and Clinics (UIHC) and Olive View-UCLA

Medical Center. Patients will also be asked for consent to obtain medical records from outside facilities for any visits or hospitalizations related to AUP or study treatment that occur during the follow-up period.

With IRB approval, participants will be compensated for their time and travel, \$25 at the enrollment visit, \$5/day for each of the daily follow-up surveys they complete, \$20 for returning their medication pack, \$30 for the Day 15-21 visit and \$100 for the Day 28-37 visit. We have prior experience with many clinical trials enrolling patients in our ED and have found that this approach leads to high retention rates for follow-up visits.

Participants will also be reminded that, for in-person visits, they will not have to wait long in the ED waiting room or Clinical Research Unit and will be seen promptly at the time of their scheduled follow-up for evaluation. Each participant will receive a courtesy reminder phone call (and email if they have an email address) one day prior to their follow-up visit to prevent missed visits and lost follow-ups. If for some reason the participant is unable to come in for the visit within the specified time frame, a telephone follow-up will be initiated. Participants will also be given the study coordinators' telephone and pager number and will be encouraged to page/call them with any questions or concerns at any time. It is anticipated that this type of personalized service will be highly valued by participants and will lead to greater cooperation with study requirements and higher retention rates.

Participants will be instructed at enrollment to return to the ED immediately if they experience any adverse symptoms and will be evaluated by a physician if they present to the ED for an unscheduled visit at any time during the study period with a complaint related to AUP.

In addition to these scheduled and unscheduled follow-up assessments, participants will be given the number of the study coordinator team who will be available 7 days a week to answer any questions or concerns, and who will direct any questions or concerns that he/she cannot address with an on-call emergency physician. During non-study coordinator coverage hours the caller will get a message instructing them to call the on-duty emergency physician at a specific number or to return to the ED immediately if there is an immediate concern, or leave a message to be contacted in the morning.

6.3.2 Final Study Visit

Day 90 (+ or – 7 days), Long-term follow-up visit – via telephone

- 1) Recurrence of AUP,
- 2) Healthcare utilization or return visits,
- 3) Any additional antimicrobial treatment required, and
- 4) Any AEs or SAEs.

6.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or protocol-specific MOP requirements. The noncompliance may be either on the part of the participant, the site principal investigator, or the site personnel. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, Section 5.1.1
- 5.20 Noncompliance, Sections 5.20.1, and 5.20.2.

It is the responsibility of the site principal investigator and personnel to use continuous vigilance to identify and report deviations per their IRB requirements.

7 DESCRIPTION OF CLINICAL AND LABORATORY EVALUATIONS

7.1 Clinical Evaluations

1. Demographics
 - a. Demographics will include the participant's sex, date of birth, and racial/ethnic origin (and will be entered on the electronic database).
2. Medical History
 - a. A medical history will be recorded on case report forms. The medical history will include a thorough review of body systems, including but not limited to cardiovascular disease, metabolic disease, allergies, and drug reactions. The review will include all medical history that is significant in relation to AUP, including medication allergies and reactions.
3. Physical examination: A complete physical examination will be performed at the Baseline/Enrollment visit.
4. Temperature
5. Signs and symptoms of AUP will be recorded at each visit.

7.1.1 Assessment of Participant Compliance with the Study Visit Schedule

Participants will receive a phone-call reminder about their upcoming follow-up visits. During enrollment, the study coordinator will ensure that they have accurate follow-up information, and a back-up means of communication with each participant. The study coordinator will document any missed follow-up visits and attempt to contact the participant about their next follow-up visit.

7.1.2 Assessment of Participant Compliance with Study Intervention/Investigational Product/Investigational Device

The study staff will maintain records documenting all medication administered to each participant for the entire study period on case report forms. Participants may receive a single dose of long-acting parenteral antibiotic before being discharged home from the ED. Participants in both arms will receive enough cephalexin in Pack A to complete a 10-day course of treatment. Study medication adherence will also be obtained daily during the daily participant follow-up questionnaires.

7.2 Laboratory Evaluations

7.2.1 Clinical Laboratory Evaluations

All clinical laboratory evaluations will be performed locally at the Olive View-UCLA and University of Iowa Hospitals and Clinics laboratories, which meets Federal safety regulations and guidelines as defined by College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) licensing.

The following laboratory tests will be performed at the specified visits:

- Baseline/Enrollment:
 - 1) Urinalysis,
 - 2) Urine microscopy,
 - 3) Urine culture and susceptibilities (urine will be collected as a clean-catch midstream specimen), and
 - 4) If applicable, pregnancy test will be done in all women of childbearing potential who have not been surgically sterilized prior to study intervention and results must be available prior to study interventions.
- EOT and Sustained Clinical Cure Visit – Urine culture and susceptibilities.

8 ASSESSMENT OF SAFETY

8.1 Assessing and Recording Safety Parameters

Safety will be evaluated by the collection and analysis of data on AEs, clinical laboratory tests, physical examination, vital signs, and concomitant medications. Study staff are responsible for reporting all AEs that are observed or reported up through the Day 28-37 visit, regardless of their relationship to study product.

8.1.1 Adverse Events (AEs)

International Conference on Harmonization (ICH) E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits or interviews of a study recipient presenting for medical care.

Any medical condition that is present at the time that the patient is screened will be considered as baseline and not reported as an AE. However, if it deteriorates at any time up through the sustained clinical cure visit, it will be recorded as an AE.

All AEs will be graded for severity and relationship to study treatment.

Severity of AEs: All AEs will be assessed by the clinician using a protocol-defined grading system. For events not included in the protocol-defined grading system, the following guidelines will be used to quantify intensity.

- 1) None (Grade 0): No AE reported.
- 2) Mild (Grade 1): Events require minimal or no treatment and do not interfere with the participant's daily activities.
- 3) Moderate (Grade 2): Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- 4) Severe (Grade 3): Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- 5) Life-threatening (Grade 4): Any adverse drug experience that places the participant, in the view of the investigator, at immediate risk of death. It does not include a reaction that had it occurred in a more severe form, might have caused death.

8.1.1.1 Adverse Events Grading

All AEs (laboratory and clinical symptoms) will be graded for severity and assessed for relationship to study product (see definitions). AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop date of each reported AE will be recorded on the appropriate data collection form and eCRF. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity.

Severity of Event:

AEs will be assessed by the investigator using a protocol-defined grading system. For events not included in the protocol-defined grading system, the following guidelines will be used to quantify severity:

- Mild (Grade 1): Events that are usually transient and may require only minimal or no treatment or therapeutic intervention and generally do not interfere with the participant's usual activities of daily living.
- Moderate (Grade 2): Events that are usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe (Grade 3): Events interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.

Relationship to Study Product: The assessment of the AE's relationship to study product will be done by the licensed study physician indicated on the Form FDA 1572 and the assessment will be part of the documentation process. Whether the AE is related or not, is not a factor in determining what is or is not reported in this trial. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

In a clinical trial, the study product must always be suspect. The relationship to study product will be assessed for AEs using the terms related or not related:

- Related – There is a reasonable possibility that the study product caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the AE.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.1.2 Serious Adverse Events (SAEs)

An AE or suspected adverse reaction is considered a serious adverse event (SAE) if, in the view of either the site principal investigator or sponsor, it results in any of the following outcomes:

-
- Death,
 - a life-threatening AE¹,
 - inpatient hospitalization or prolongation of existing hospitalization,
 - a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
 - a congenital anomaly/birth defect.
 - Important medical events that may not result in death, be life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

¹ Life-threatening adverse event. An AE is considered “life-threatening” if, in the view of either the site principal investigator or sponsor, its occurrence places the patient or participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by the Institution as the site Principal Investigator or Sub-Investigator.
- Recorded on the appropriate SAE data collection form.
- Followed through resolution by a licensed study physician.
- Reviewed and evaluated by an ISM and the IRB.

8.2 Specification of Safety Parameters

Abnormal assessments (e.g., vital signs, etc.) and abnormal laboratory findings (e.g., clinical chemistry, hematology) which the study investigators believe are clinically significant, if obtained, will be recorded as AEs (up through the Day 28-37 Visit) or SAEs if they meet the definition of an AE or SAE. Abnormal laboratory findings (if obtained) or other abnormal assessments that are detected through the Day 28-37 visit or are present at baseline and significantly worsen up through the Day 28-37 visit will be reported as AEs or SAEs.

8.2.1 Solicited Events

Solicited events are AEs that are common and known to occur following administration of study product. At each follow-up visit, the participant will be asked if they have experienced any of the common AEs that are associated with cephalexin (e.g., nausea, diarrhea). Additionally, because recurrent infections are one of the safety outcomes, the participant will be asked at each visit through the 90-day final visit if they have been diagnosed with a new UTI.

8.2.2 Unsolicited Events

Participants will be encouraged to self-report AEs after the initiation of the study medication. Each enrolling site has study coordinators or investigators available 7 days a week and can be contacted by the participant if they believe they are experiencing an AE. All reported unsolicited events will be documented in a similar fashion to solicited events.

8.3 Reporting Procedures

AEs including local and systemic reactions not meeting the criteria for “SAEs” should be captured on the appropriate source document. Information to be collected includes event description, time of onset, investigator assessment of severity, relationship to study treatment, time of resolution of the event, seriousness, and outcome. All AEs occurring during the study will be documented appropriately regardless of relationship. All AEs and SAEs that occur up through the Day 28-37 visit and SAEs deemed related to study treatment or their AUP after the Day 28-37 visit will be followed to adequate resolution.

For AEs that occur through the Day 28-37 visit, the date of resolution (or when the event is deemed stable/chronic) will be noted on an Adverse Event case report form.

Any medical condition that is present at the time that the patient is screened should be considered as baseline and not reported as an AE. However, if it deteriorates through the Day 28-37 visit it should be recorded as an AE.

8.3.1 Reporting of Pregnancy

Pregnancy is not an AE but is a collectable event. Participants will be required to report a new pregnancy during the period that they are taking the study medication. Because cephalexin is safe in pregnancy (and beta-lactams are recommended for the treatment of UTIs during pregnancy), the participant will continue the study medication. The participant will be removed from the study protocol and will be required to complete the full-course of treatment per current standard of care guidelines.

8.4 **Safety Oversight (ISM)**

8.4.1 Independent Safety Monitor (ISM)

An ISM will be appointed at each participating site. An ISM is a physician with relevant expertise who is not a member of the study team and whose primary responsibility is to provide an independent safety assessment in a timely fashion. The ISM will review SAEs in real time and other AEs as needed and provide an independent assessment to the PIs and NIAID project officer.

9 HUMAN SUBJECTS PROTECTION

9.1 Institutional Review Board/Independent Ethics Committee

A single IRB of record, Olive View-UCLA Education and Research Institute, will be accountable for compliance with regulatory requirements for this multi-centered study, at participating sites. Olive View-UCLA Education and Research Institute has a Federal wide Assurance FWA # 00000495 with the Department of Health and Human Services Office for Human Research Protection (OHRP). The reliance agreements will set forth the specific responsibilities of the IRB and each participating site. Participating sites will then rely on the IRB of record to satisfy the regulatory requirements relevant to the IRB review. The participating sites will maintain essential required documentation of IRB reviews, approvals, and correspondence, and must provide copies of any agreements and essential documentation to the regulatory authorities upon request.

Any amendments to the protocol or consent materials will be approved by the IRB before they are implemented. IRB review and approval will occur at least annually throughout the enrollment and follow-up of participants and may cease if annual review is no longer required by applicable regulations and the IRB. The investigator will notify the IRB of deviations from the protocol and reportable SAEs, as applicable to the IRB policy. Each institution engaged in this research will hold a current Federal wide Assurance (FWA) issued by the Office of Human Research Protection (OHRP) for federally funded research.

9.2 Informed Consent Process

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Before any study procedures are performed, informed consent will be obtained and documented. Patients will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. The explanation will be organized and presented in lay terminology and language that facilitates understanding why one might or might not want to participate.

Clinicians in the ED will notify research coordinators of suspected or confirmed AUP patients. In addition, under waivers of Health Insurance Portability and Accountability Act (HIPAA) and informed consent, the research coordinator will screen the board and review the patient's medical record to confirm the patient's study eligibility. Patients will be approached for informed consent by a research coordinator. Additionally, the research coordinator at each site will conduct daily screening of all patients who were diagnosed with AUP in the ED. The research coordinator will maintain a screening log of all patients screened for eligibility in the study. This log will only include minimal patient information (patient name, medical record number, date of screening, whether they are eligible for the study, reason why they were not eligible if applicable) and will be approved by the IRB.

After the diagnosis of AUP is made by the ED provider and the research coordinator has deemed the patient eligible for the study based on the predefined exclusion criteria, the research coordinator and ED provider will ensure that the patient has the mental capacity to discuss the study.

Upon approaching the patient, the patient will be provided informational material about the study and the different treatment options in either Spanish or English, as appropriate. Additionally, the research coordinator will review the informed consent form with the patient and will describe all study procedures, risk and benefits of the study and alternatives to study participation.

Information will also include the foreseeable circumstances and/or reasons under which their participation in the trial may be terminated. They will be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time without penalty or loss of benefits to which the patient is otherwise entitled.

The extent of the confidentiality of the patient's records will be defined, and they will be informed that applicable data protection legislation will be followed. Patients will be informed that the monitor(s), auditors(s), IRB, NIAID, and regulatory authority(ies) will be granted direct access to the participant's original medical records for verification of clinical trial procedures and/or data without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations, and that, by signing a written informed consent form, the patient is authorizing such access.

Patients will be informed that records identifying them will be kept confidential, and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available and, if the results of the trial are published, their identity will remain confidential. Patients will be informed whether private information collected from this research and/or specimens will be used for additional research, even if identifiers are removed.

Patients will be allowed sufficient time to consider participation in this research trial, and have the opportunity to discuss this trial with their family, friends or legally authorized representative, or think about it prior to agreeing to participate. The rights and welfare of the participant(s) will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Informed consent forms will be IRB-approved, and patients will be asked to read and review the consent form. Patients must sign the informed consent form prior to starting any study procedures being done specifically for this trial. Once signed, a copy of the informed consent form will be given to the participant(s) for their records. The participant(s) may withdraw consent at any time throughout the course of the trial.

Study personnel may employ recruitment efforts prior to obtaining study consent if the IRB has agreed that chart review is allowed. Site clinical staff may pre-screen via chart review and refer

potential eligible patients to the research staff. New information will be communicated by the site principal investigator to participants who consent to participate in this trial in accordance with IRB requirements. The informed consent document will be updated, and participants will be re-consented per IRB requirements, if necessary. Participants will be given a copy of all informed consent forms that they sign.

9.3 Exclusion of Women, Minorities, and Children (Special Populations)

Children will not be included in this study because acute uncomplicated pyelonephritis (AUP) in children has different diagnostic criteria and treatment recommendations.

Urinary tract infection is among the most common diagnoses for women presenting to the ED, with the highest incidence occurring in women ages 20-59 years. As women age, they are at increased risk of undiagnosed co-morbidities and urinary complicating features (e.g., diabetes, urological abnormalities), so we will exclude women ≥ 65 years of age.

9.4 Participant Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality includes documentation, investigation data, participant's clinical information, and all other information generated during participation in the study, including participant data collected via the smart phone app (if they choose this option to use). No information concerning the study or the data generated from the study will be released to any unauthorized third party without prior written approval of the participant. Participant confidentiality will be maintained when study results are published or discussed in conferences. The study monitor or other authorized representatives of the sponsor or governmental regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

All records will be kept locked and all computer entry and networking programs will be carried out with coded numbers only and with password protected systems. All non-clinical specimens, evaluation forms, reports, and other records that leave the site will be identified only by a coded number. At the end of the study after all data are cleaned and analyzed, all identifiers will be removed from all documents and databases.

9.5 Costs, Participant Compensation, and Research Related Injuries

There is no cost to participants for the research tests, procedures, and study product while taking part in this trial. Procedures and treatment for clinical care may be billed to the participant, participant's insurance or third party. Participants may be compensated for their participation in

this trial. Compensation will be in accordance with the local IRB's policies and procedures, and subject to IRB approval.

If it is determined by the site principal investigator that an injury occurred to a participant as a direct result of the tests or treatments that are done for this trial, then referrals to appropriate health care facilities will be provided to the participant. Study personnel will try to reduce, control, and treat any complications from this trial. Immediate medical treatment may be provided by the participating site. No financial compensation will be provided to the participant by the NIAID, NIH to the participant, or by the participating site for any injury suffered due to participation in this trial.

10 STATISTICAL CONSIDERATIONS

10.1 Study Hypotheses

Our study will ultimately focus on addressing the hypothesis that patient-directed antimicrobial duration produces 30-day clinical cure rates that are non-inferior to standard full-course treatment for the treatment of outpatient acute uncomplicated pyelonephritis (safety outcome).

10.2 Sample Size Considerations

The sample size for the pilot study is based on the sample size calculation for our planned larger study addressing safety. For the sample size calculation of 30-day clinical cure rates for the larger trial, we will use a traditional non-inferiority study design. To calculate the sample size needed to detect non-inferiority of patient-directed antimicrobial duration (PDAD) to standard of care fixed durations, we conducted a simulation study based on the following assumptions. Based on the FDA Guidance for Industry, we set the non-inferiority margin to 10%.

With: $\alpha = 0.025$, Power = 80% ($\beta = 0.20$)

P0 = The rate of sustained clinical and microbiological cure at Day 30 in the standard of care group (complete full course of antimicrobial therapy)

P1 = The rate of sustained clinical and microbiological cure at Day 30 in the PDAD group

Non-inferiority limit, $\Delta = 10\%$

The sample size calculation was performed using a simulation-based technique. With a 1:1 randomization ratio, a total sample size of 342 participants (171 per treatment arm) provides 85% power for the analysis in the mITT set to evaluate the noninferiority of PDAD compared with fixed duration, using a noninferiority margin of 10% and a one-sided significance level of 2.5%. This sample size reflects a balanced design between the minimum evaluable threshold (80% power with 150 participants per treatment arm) and the upper range considered for maximal power (90% power with 200 participants per treatment arm), while maintaining robust operating characteristics across a range of plausible event proportions observed in prior data. To account for an anticipated exclusion of up to 18% of randomized participants from the mITT population due to loss to follow-up or baseline urine pathogens not susceptible to the treatment interventions, the total planned enrollment will be increased to 414 participants. It has been suggested that pilot studies should include at least 3% of the sample size for the actual trial. Under this principle our estimated sample size for the pilot study is 40 patients ($40/414 = \sim 10\%$ of the project sample).

The main objectives of this pilot study are to assess the feasibility and safety of conducting a larger multi-center trial; thus, the primary outcomes are related to our ability to identify patients who qualify for the study, consent them to participate, ensure they comply with the study protocol and stay in their assigned treatment arm, retain them through the 90 day follow-up period, and assess them for relapse or recurrence at the 90 day follow-up period. The primary outcomes and their corresponding parameters that will confirm the feasibility and safety of the planned larger randomized controlled trial are as follows:

- 1) >90% of patients who present to the emergency department with acute uncomplicated pyelonephritis will be identified;
- 2) >30% of eligible patients will provide consent to participate in the study;
- 3) >80% of the participants enrolled in the study will remain in their assigned study arm;
- 4) >80% of the participants will have follow-up through day 30; and
- 5) >80% of the participants will have follow-up through day 90.

We will also collect the number of doses of antibiotic consumed by each patient and assess the variability of dosing among both the treatment and control groups. This additional data will serve to support our secondary goal of assessing the efficacy of patient directed therapy in reducing overall antibiotic use. We plan to complete this secondary efficacy analysis using a simple one-sided superiority assessment.

10.3 Assignment Procedures

10.3.1 Randomization Procedures

After informed consent, participants will be randomized to standard full course treatment, or to PDAD.

Randomization will be 1:1 and treatment will be pre-assigned in each enrollment packet contained in an opaque envelope. Pre-assigned treatments will be based on a random number sequence with nearly equal assignments to both treatment strategies.

10.3.2 Masking Procedures

Participants and the research team will be blinded to study arm is assignment. The study analysis team will be masked to all treatment assignments.

10.4 Final Analysis Plan

Categorical variables will be compared using differences in proportions and 95% confidence intervals and continuous variables will be compared using non-parametric tests comparing median scores or values.

Initial assessment of safety

- 1) We will perform a preliminary assessment of safety by measuring the upper bound of the 95% CI around the 30-day sustained clinical cure rate for the PDAD group and determining whether it exceeds the lower bound of the 95% CI for that of the standard treatment duration group. While this measure is not sufficient to assess non-inferiority, failure to meet this low safety threshold in the pilot study would indicate the experimental treatment is associated with significant treatment failures, and that there is no need for a larger trial.
- 2) We will make assessments of other trial feasibility markers by using direct counts to calculate the proportions of eligible patients that satisfy each criterion. Feasibility will be confirmed if these measured proportions satisfy the following limits:
 - a. >90% of patients who present to the emergency department with acute uncomplicated pyelonephritis will be identified;
 - b. >30% of eligible patients will provide consent to participate in the study;
 - c. >80% of the participants enrolled in the study will remain in their assigned study arm;
 - d. >80% of the participants will have follow-up through day 30; and
 - e. >80% of the participants will have follow-up through day 90.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of participants. Each site will permit authorized representatives of appropriate regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data and source documents, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' memory aid or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

All data will be collected on case report forms and entered by study coordinators onto a secure web-based data entry system (REDCap), created and tested by the project director and study statistician. All case report forms and source documents will be stored in locked file cabinets only accessible to study staff. All electronic documents will be stored on password-protected computers on secure drives accessible only to study staff. All data analyses will be conducted by the project director and study statistician.

12 QUALITY CONTROL AND QUALITY ASSURANCE

The site principal investigator will provide direct access to all study-related sites, source data/data collection forms, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The site principal investigator will ensure all study personnel are appropriately trained and applicable documentations are maintained on site.

The study site may be subject to review by the institutional review board (IRB), and/or to quality assurance audits performed by the co-PIs.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process. The DCC will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the participating site(s) for clarification and resolution.

13 DATA HANDLING AND RECORD KEEPING

13.1 Data Management Responsibilities

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study. A CRF is required and should be completed for each included patient.

The investigator has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all clinical, safety, laboratory data entered on the CRFs and any other data collection forms. Any corrections to entries made in the CRFs and source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. **DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.**

13.2 Data Coordinating Center/Biostatistician Responsibilities

Data collection is the responsibility of the study personnel at the participating clinical study site under the supervision of the site principal investigator. During the study, the site principal investigator must maintain complete and accurate documentation for the study. The data coordinating center for this study will be responsible for data management, quality review, analysis, and reporting of the study data.

13.3 Data Capture Methods

Clinical (including, but not limited to, AE/SAEs, concomitant medications, medical history, physical assessments, and clinical laboratory values) will be collected on data collection forms by study personnel then entered into REDCap. If the participant chooses to use the smart phone app for day 1-10 follow-up, we will collect daily symptom, medication adherence, and health care utilization data. This data will be sent securely to the study team and linked by the participant's study ID (not their name or other identifying information) to the main REDCap database. The REDCap data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

13.4 Types of Data

Data for this trial will include clinical, safety, and outcome measures (e.g., clinical laboratory values).

13.5 Study Records Retention

Study records and reports including, but not limited to, eCRFs, source documents, ICFs, laboratory test results, and study drug disposition records will be retained for 2 years after the investigation is discontinued. These documents will be retained for a longer period, however, if required by local regulations. After data analysis and report writing, all personal identifying information will be removed from all data (both paper and electronic).

No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the site principal investigator when these documents no longer need to be retained.

14 CLINICAL MONITORING

Site monitoring is conducted to ensure that the human subjects' protections, study and laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, ICH/GCP guidelines and applicable regulations, and that this trial is conducted in accordance with the protocol, protocol-specific MOP and applicable sponsor standard operating procedures.

15 PUBLICATION POLICY

Following completion of the study, the lead Principal Investigator is expected to publish the results of this research in a scientific journal. All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central (<http://www.ncbi.nlm.nih.gov/pmc/>) an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH funded research. It requires investigators to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. Further, the policy stipulates that these papers must be accessible to the public on PubMed Central no later than 12 months after publication.

Refer to:

- NIH Public Access Policy, <http://publicaccess.nih.gov/>
- NIH Office of Extramural Research (OER) Grants and Funding, <http://grants.nih.gov/grants/oer.htm>

As of January 2018, all clinical trials supported by the NIH must be registered on ClinicalTrials.gov, no later than 21 days after the enrollment of the first participant. Results of all clinical trials supported by the NIH, generally, need to be submitted no later than 12 months following the primary completion date. A delay of up to 2 years is available for trials that meet certain criteria and have applied for certification of delayed posting.

As part of the result posting a copy of this protocol (and its amendments) and a copy of the Statistical Analysis Plan will be posted on ClinicalTrials.gov.

For this trial the responsible party is the lead research coordinator at UCLA Olive-View which will register the trial and post results.

The responsible party does not plan to request certification of delayed posting.

Refer to:

- Public Law 110-85, Section 801, Clinical Trial Databases
- 42CFR11
- NIH NOT-OD-16-149

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17 APPENDICES

Appendix A. Schedule of Events

Evaluation	Screening/ Enrollment Visit 1 Day 1	Daily Visits (via app or telephone, Day 1-10)	End of Treatment (In person, Day 15-21)	Sustained Clinical and Microbiological (In person, Day 28-37)	Long-term follow-up visit (via telephone, Day 90)
Signed consent form	X				
Confirmation of eligibility criteria	X				
Past medical history	X				
Vitals	X	X	X	X	
Signs/symptoms	X	X	X	X	X
Current home medications	X				
Rapid urine pregnancy test	X				
Urine specimen culture and in vitro antibiotic susceptibility	X		X	X	
Urinalysis	X				
Healthcare utilization or return visits		X	X	X	X
Any additional antimicrobial treatment required		X	X	X	X
Number of days not engaging in normal activities		X	X		
AEs or SAEs		X	X	X	
Recurrence of AUP			X	X	X