Study Protocol and Statistical Analysis Plan

B. SIGNIFICANCE:

B.1 Recurrent urinary tract infections in older women are common, poorly understood, and complicated by confounding symptom overlap.

Urinary tract infection (UTI) is the most common bacterial infection, accounting for more than 8 million office visits and 1 million emergency department visits each year in the United States.[2] Importantly, ~80% of visits for UTI are in women,[32] and the highest rates of UTI recurrence occur in older women[33] who also have more variation and antibiotic resistance in the uropathogens that cause UTIs.[5,34] It is clear that menopause is a predominant risk factor for rUTI and that the pathophysiology of a single, sporadic UTI in premenopausal women is very different than that of rUTI in older women.[8,35] In older women with patient reported UTI, given the symptom overlap between overactive bladder and genitourinary syndrome of menopause, the diagnosis of acute UTI should be made using a combination of symptom assessment and urine diagnostic studies.[14,36] Although dysuria seems to be the most discriminating symptom for a culture-positive UTI,[37] we are still unable to reliably predict other factors that correlate with culture positivity and who will require antibiotics to clear a symptomatic UTI.[38] Prospective investigations are crucial to improve our ability to predict those that may have symptom resolution without antibiotic therapy, but also those that can be safely managed with a urine culture-directed antibiotic strategy.

B.2. Preliminary observational data suggests that a urine culture-directed antibiotic strategy for patient reported UTI in older women is safe, but randomized controlled trials are needed to substantiate broad adoption of such a strategy.

Non-antibiotic treatment and placebo as initial management of UTI symptoms have been evaluated in several randomized controlled trials (RCTs) that enroll a mostly premenopausal population.[16,39–43] An initial non-antibiotic strategy leads to a decrease in overall antibiotic use given either resolution of symptoms,[18] or lack of bacteriuria.[19] The results of these trials suggest that initial non-antibiotic management can be reasonable, but it may not be the method of choice for every woman with uncomplicated UTI. The literature on non-antibiotic treatment as initial management for UTI symptoms in older women is limited as the majority of studies did not enroll participants over the age of 65-70 and had a participant mean age of 30-40 years[16,39–43] even though older women are an especially vulnerable population for drug interactions due to age-related physiologic changes and higher concomitant medication use.[44]

Preliminary data: Recently, we performed a prospective cohort study on 152 women who were seeking care for UTI symptoms with mean age 66.4 (SD 14.9) of which 52.0% had a history of recurrent UTI. Women completed the UTI symptom assessment (UTISA) questionnaire[45] before they submitted a culture and then were either placed on empiric antibiotics or managed expectantly based on provider and/or patient preference. After urine cultures were resulted, participants completed another UTISA questionnaire and the global rating of change (GRC). Our primary outcome was “symptom improvement” defined as reporting symptoms of “better” on the GRC questionnaire.

TABLE 1: Proportion of Culture Positivity in Prospective Cohort of Women with Patient Reported Urinary Tract Infection

		Empiric Antibiotics	
Positive Urine Culture		Yes (n=30)	No (n=122)
	Yes (n=88)	16 (53.3%)	72 (59.0%)
	No (n=64)	14 (46.7%)	50 (41.0%)

Overall, 122 (80.3%) were managed expectantly, 30 (19.7%) were managed with empiric antibiotics. ***The proportion of positive UCx in those treated empirically (53.3%) was similar to those managed expectantly (59%) (Table 1) which highlights the opportunity for antibiotic stewardship that could come from a culture-directed management strategy in older women with UTI symptoms.*** In the expectant management cohort, 78/122 (63.9%) completed the follow-up questionnaires and 20 (25.6%) of those women reported symptom improvement. ***Importantly, 0/152 (0%) women were diagnosed with pyelonephritis or urosepsis in the 30-days following their initial symptoms.***[46] Although this data begins to tell the story of the safety and efficacy of an expectant management approach for older women with UTI symptoms, there was inherent bias given the non-randomized nature of the cohort and no qualitative aims to understand the patient and provider perspective. There is still much we do not know regarding the ideal approach for an older woman presenting

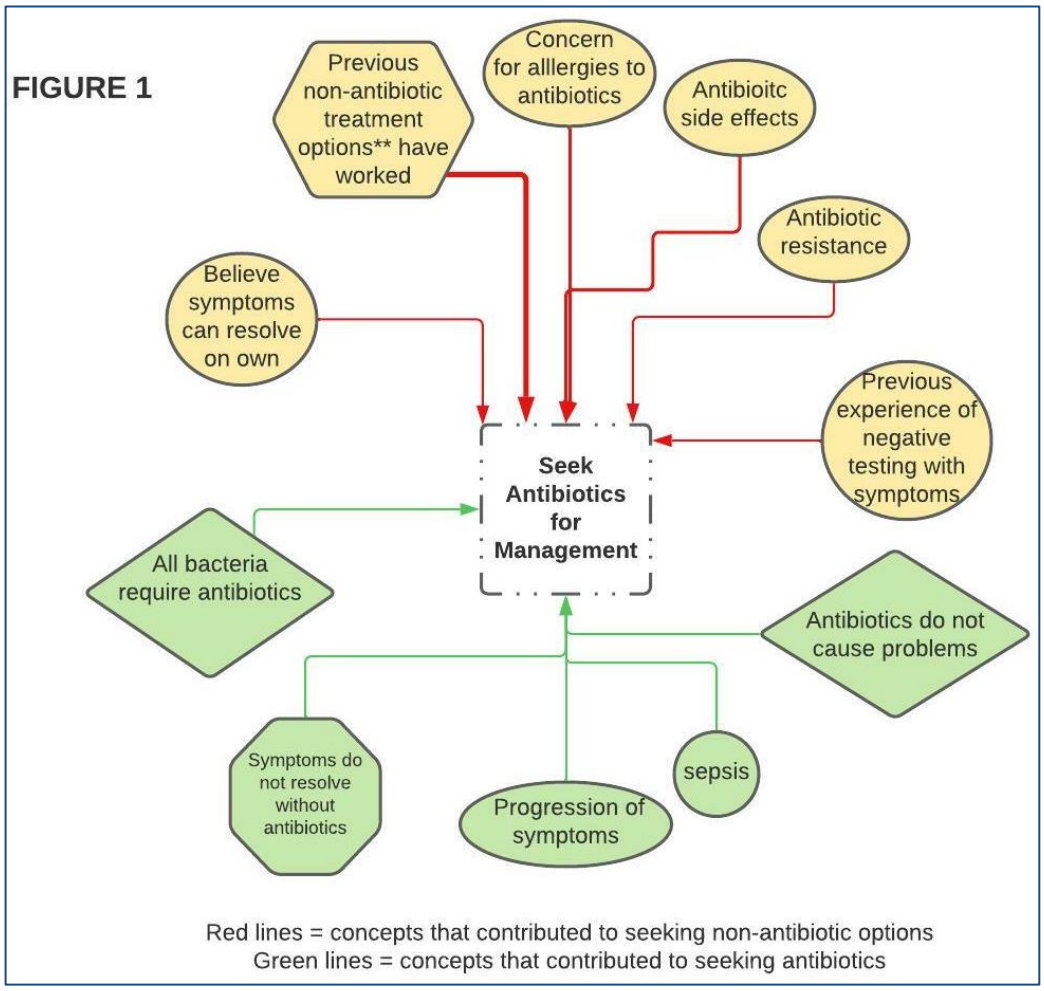
with UTI symptoms. A prospective, randomized trial of a urine culture-directed approach compared to an empiric-antibiotic strategy specifically in older women would be the first step towards an evidence-based algorithm taking subjective and objective factors into account.

B.4. Qualitative studies find large discrepancies among patients regarding preference for management of UTI symptoms and poor understanding of UTI pathophysiology.
Some qualitative studies, completed in younger women, suggest that they are aware and fearful of the adverse effects of antibiotics. They voice a need for physicians to modify management strategies to address these concerns and to devote more research efforts to improving nonantibiotic options for prevention and treatment of rUTIs, as well as management strategies that better empower patients.[47]

Preliminary data (Bradley and Krishnamurti, unpublished). We performed 30 semi-structured interviews with postmenopausal women (mean age 69.4 ±6.4 years) who have been previously treated for a UTI. Participants reported different variables that influenced their symptomatic UTI care-seeking decisions (Figure 1). Two distinct "mental models" of preferred UTI treatment emerged.

- One group reported greater anticipated risks related to antibiotic use (represented as yellow shaded nodes and red lines).
- A separate group of women highly desired antibiotics for any presumed UTI. The desire for antibiotics was largely driven by concern for sequalae from non-treated bacteria (represented as green shaded nodes and green lines) and underweighting of potential side effects of antibiotic use.

Both mental models demonstrate that the way women conceptualize their initial symptoms affect their preferences for antibiotic treatment and subsequent interventions and that we have a lot of work to do in to close the knowledge gap among women suffering with possible UTIs. We concluded that women's cognitive approach to UTI symptoms and care-seeking is complex and influenced by many factors. These factors include both personal and friend/family experience, awareness of non-antibiotic management for presumed UTI and many misconceptions about urinary tract pathophysiology. ***An improved understanding of preconceptions and biases among patient and providers will aid in design of recruitment materials and study consent for a randomized trial of UTI management strategies.***



B.5. Over recent years, qualitative research, drawing on the perspectives of both health-care professionals and patients, has improved our understanding of why clinical trials succeed.
Qualitative research offers insight into the discrepancies between patients' viewpoints and evidence-based managment[48] and can aid in the understanding of why many beneficial innovations diffuse slowly and unevenly, yet widely held superstitions remain immune to evidence.[48] For the complicated issues surrounding bacteriuria in older women, our proposal allows for interviews with both patients, and providers, in order to delineate barriers experienced during recruitment for this pilot, randomized feasibility trial. This qualitative data will be imperative for the design of the definitive, larger trial.

Given that many factors can affect the successful implementation and validity of intervention studies, a primary purpose of feasibility and pilot studies is to assess the potential for successful implementation of the main intervention and to reduce threats to the validity of these studies. The purpose of most feasibility and pilot studies should be to describe information and evidence related to the successful implementation and validity of a planned main trial.[49] Such research has shown how lack of or unstable equipoise regarding trial interventions may affect health-care professionals' engagement.[50] Qualitative research has also highlighted how more pragmatic resource-related concerns (shortfalls) may undermine even committed health-care professionals' support for trials. Research involving patients has provided further insight into the barriers to and facilitators of trial recruitment.[51]

Our qualitative goals seek to determine

- acceptability of the interventions to the users (patients and health-care provider)
- ways to ensure representative recruitment and engagement
- the willingness of patients to be randomized

- the willingness of clinicians to randomize patients and
- variation in use or delivery of the intervention in each setting.[52]

B.3. A pilot and feasibility trial is necessary prior to an adequately powered randomized controlled trial comparing urine culture-directed versus empiric antibiotic treatment of UTI symptoms in older women given the historical concerns of patients and providers.
Regardless of age, the adverse effects of prescribing unindicated antibiotics are undesirable both on the patient level, because of potential side effects and drug interactions, and on the societal level because of its contribution to antimicrobial resistance. Limited data suggests that among women with bacteriuria, great care is needed to explain the rationale behind a delayed antibiotic strategy and to alleviate concerns over complications.[23] Observational studies suggest primary care providers do overprescribe in those with advanced age, a history of recurrent UTIs,[53] worsening urinary incontinence and those with altered mental status[54–56] likely due to provider overcautiousness over concern of UTI sequalae.[57] However, **more recent, claims-based literature suggests that progression to systemic infection after initial uncomplicated UTI is very low in older women (ranging from 0.38-1.7%).[26,58]**

Preliminary data (Bradley and Zyczynski, unpublished). We recently investigated the knowledge, attitudes, and management practices of primary care providers (PCP) when treating older women with symptoms attributed to UTI. Among 142 PCPs, the majority of which were female (60.6%) and practiced in a suburban location (50.7%), only 26.1% felt it was safe to wait for a urine culture before prescribing antibiotics, 62.0% felt delaying antibiotics depended on multiple factors, and 9.2% felt it was never safe to delay antibiotics. We found that 33.1% prescribe empiric antibiotics in ≥50% of encounters, 27.7% of providers were concerned over progression of symptoms and 49.5% of providers were concerned for progression to sepsis. A higher proportion of providers practicing >15 years always felt safe delaying antibiotics compared to those with ≤15 years of experience (33.3% v. 18.3%; p=0.04). **This cross-sectional survey found that providers with more clinical experience have more comfort delaying antibiotics in older women with UTI symptoms, but despite recent literature suggestive of an overall low risk of urosepsis in this population,[26] this sequela remains a significant concern among providers.**

This variability in antibiotic prescribing highlights the pressing need for level 1 evidence of the safety of a culture-directed approach to alleviate concerns among providers caring for older women. To update the current body of literature surrounding the natural progression of patient reported UTIs in ambulatory, community dwelling, older women, an initial randomized, feasibility trial of a urine culture-directed antibiotic approach in older women with patient reported UTI that includes standardized subjective and objective data is imperative. Data acquired from this pilot and feasibility study will provide us with important information regarding patient and provider willingness for enrollment, initial safety data and qualitative information that we can utilize to improve recruitment efficiency in a definitive trial.

B.7. Summary/Strengths of the current proposal:

- **Significance:** This proposal addresses a substantial gap in understanding the acceptability and safety of a urine culture directed antibiotic strategy for symptomatic older women with history of rUTI. The information gained in this feasibility study will lead to successful implementation of a randomized controlled trial and acquisition of Level I evidence – an imperative for the paradigm shift in current care of acute cystitis symptoms in older women with rUTI.

- **Experienced investigator and study team:** Our strong team of investigators are well suited to conduct this clinical study. The PI and Co-Is have extensive experience in design and implementation of clinical trials as well as expertise statistics, qualitative research and in the evaluation and treatment of women with lower urinary tract disorders including rUTI. The Co-I, Dr. Halina Zyczynski, has >20 years' experience as PI in the NICHD Pelvic Floor Disorders Network and the NIDDK Urinary Incontinence Treatment Network. She will provide mentorship for study design, recruitment strategies and outcomes assessments to assure successful completion. The Co-I Dr. Leslie Meyn is well poised to serve as a statistician and Director of the Data Management Center (DMC) given her many years of experience working with basic, translational, and

clinical trial data focused on women's health and reproductive infectious diseases. Dr. Tamar Krishnamurti is an expert in behavioral economics and social psychology, with a focus on decision making around risk and health outcomes. Her research on qualitative and mixed methods approaches to understanding decision making, with a specific focus on mental models related to risk will ensure completion of our qualitative aims. Finally, the PI, Dr. Megan Bradley, has a particular interest and expertise in older women suffering from UTIs with multiple recent publications and grants on this subject matter. Our seasoned clinical research staff have a demonstrated track record of success in patient recruitment and retention for our collaborative interdisciplinary research protocols. Importantly, as a Division, we have been successful in recruitment for studies from multiple locations and our team is well poised to adhere to all study guidelines even with a large patient catchment area.

- **Strong Environment**: The resources available at our institution will increase diversity of participants for both our pilot trial and our qualitative aims to allow for generalizability of results.
    - Our University of Pittsburgh Medical Center **Women's Center for Bladder and Pelvic Health** (WCBPH) faculty are the sole providers of subspecialty FPMRS care in the UPMC Health System where we conduct 3,463 new evaluations for pelvic floor disorders annually. Our clinical program has conducted more new patient evaluations in 2021 than in 2019 due to a 40% increase in number of providers and office locations in the past 4 years. This reflects well on our reliability to enroll women from a large catchment area of north – southwestern PA. Magee-Womens Hospital and the Department of Obstetrics, Gynecology and Reproductive Sciences have made a substantial commitment to providing care to disadvantaged communities at 3 inner city clinics, 7 rural, farming and mining community locations, including 5 that are >100 miles from Pittsburgh. The University of Pittsburgh also has made a commitment to addressing the racial disparities in health outcomes seen in the African American population.
    - The **University of Pittsburgh's Clinical and Translational Science Institute (CTSI) Pitt+Me® Registry** is a recruitment platform that uses ICD-9/10 diagnoses and demographics from the EHR along with participant-reported preferences to algorithmically match registry participants to increase socioeconomic, racial, and geographic representation in our study.
    - The **CTSI Community PARTners Core Stakeholder Engagement Studios** which helps engage community stakeholders in research will broaden the information gained from our qualitative participant aims.
    - Recruitment of providers from the WCBPH, the East POD of PCP offices of UPMC and the East Liberty Family Health Care Center which is a Federally Qualified Health Center (FQHC) with a focus to serve those that are uninsured, underinsured and underserved will increase generalizability of provider feedback.

C. INNOVATION. Our proposed pilot study is innovative in several important ways. For our proposed pilot study, we have many innovative approaches including recruitment from the community through the CTSI Pitt+Me® registry, utilization of electronic consents and completion of research visits/procedures remotely as participants desire. More importantly, the rationale of our pilot trial is to identify barriers to successful implementation, patient and provider concerns, and to develop recruitment material, data collection forms, databases and to establish preliminary safety data which are important for provider and patient engagement in a future RCT. This future trial will be inherently innovative as the first prospective randomized trial of culture-directed versus empiric antibiotic therapy for subjective symptoms of UTI in a population of older women with a history of rUTI. We have developed our aims to assess feasibility and guide methodology. Our proposed mixed methods approach will ascertain both quantitative and qualitative data. Feasibility studies are extremely useful and necessary given the ability to detect unplanned difficulties with for example, the RCT design, recruitment strategies or the acceptability of the intervention.[59] Importantly, our protocol lends itself to future studies in older women with sporadic UTI symptoms as they may be even less likely to have culture-proven disease.[60]

D. APPROACH

D.1. Specific Aim 1: To evaluate A) the feasibility of recruiting eligible participants into a randomized trial of a culture-directed versus empiric antibiotic strategy for patient-reported UTI symptoms in older women and B) the adherence to study procedures. Exploratory Aim: To explore adverse events and clinical success between assigned treatments.

D.1.1 Overview and Design. The proposed pilot study is designed as a culture-directed versus empiric antibiotic strategy for patient-reported UTI symptoms in older women. (Figure 2) Over 12 months, we will recruit 70 women with rUTI. Following enrollment, patients will be randomized in a 1:1 ratio to one of two groups. Patients assigned to the culture-directed arm will await results of urine culture prior to potentially receiving antibiotics and those assigned to the empiric arm will be prescribed immediate antibiotics from an established list of commonly prescribed antibiotics. Participants will be sent electronic questionnaires after urine culture results and then weekly for a total of 4 weeks. The primary outcome is feasibility of trial defined as recruitment of 10% of eligible participants with 70% adherence to study protocol.

D.1.2 Recruitment and Subject Eligibility. Women age ≥65 years[61] with diagnosis of recurrent UTI (rUTI) will be recruited from: 1) UPMC WCBPH faculty practices or 2) CTSI Pitt+Me® Research Registry. Eligibility criteria are listed in Table 2.

Table 2: Detailed Inclusion and Exclusion Criteria

Inclusion Criteria
• Female biologic Sex • Age ≥65 years old • History of recurrent UTI per patient report of greater than 2 UTIs in the last 6 months or 3 UTIs in the last year • Patient reported UTI defined as: ○ Dysuria, increased urinary urgency/frequency and/or suprapubic pain
Exclusion Criteria
• Male biologic sex • Age <65 years old • History of augmentation cystoplasty or cystectomy • Currently performing clean intermittent self-catheterization • Current indwelling foley catheter • Urinary tract instrumentation (i.e., cystourethroscopy, foley catheter placement) in the last 30 days • Undergoing treatment for malignancy • History of either confirmed or patient reported pyelonephritis and/or urosepsis • Cirrhosis and/or end stage liver disease • Chronic kidney disease with most recent estimated glomerular filtration rate <50 ml/min • Dementia and/or currently reside in skilled nursing facility • Current high-dose chronic steroids (>20mg/day of prednisone) • Previous solid organ transplant • Provider concern for pyelonephritis and/or sepsis (i.e., fevers) • Unwilling or unable to comply with study procedures

Rationale for Inclusion Criteria: We will include participants with patient reported recurrent UTI to allow for a pragmatic study design and generalizability. Additionally, our definition of patient reported UTI is like other RCTs evaluating non-antibiotic options as compared to antibiotic strategies for UTI treatment.[43,62] We will exclude participants with features of complicated UTI in the setting of structural or functional abnormalities or instrumentation /catheterization[4,63] Eligibility is limited to female biologic sex given the differential risk profile of males and females who experience recurrent UTIs.

D.1.3 Study procedures (Figure 2).

D.1.3.1 – Screening and Enrollment Procedures. Information on the REDUCTION trial will be broadly disseminated in the University of Pittsburgh faculty practices at the WCBPH, through IRB approved brochures, social media ads, institutional (MWRI) and CTSI websites. Interested women will be encouraged to contact the research staff for more information. Women who meet eligibility criteria after screening will be provided a consent form via their preferred method (electronic or paper).

Importantly, the use of screening tests to assess whether prospective participants are appropriate candidates for inclusion in studies is an appropriate pre-entry activity. Per research guidelines, an investigator may discuss availability of studies and the possibility of entry into a study with a prospective participant without first obtaining consent when no clinical procedures performed solely for the purpose of determining eligibility for research are planned.[64] Importantly, electronic approaches are becoming more widely used to obtain informed consent for research participation. Electronic consent (e-consent) provides an accessible and versatile approach to the consenting process, which can be enhanced with audio-visual and interactive features to improve participant engagement and comprehension of study procedures. E-consent may facilitate remotely conducted research by offering a feasible and robust alternative to face-to-face consenting approaches, however we will offer paper-based options, based on participant preference. [65–67]

D.1.3.2 Enrollment and Randomization (Day 0).

- Upon development of symptoms (Figure 2), interested women will be scheduled for a baseline study visit (either in-person or virtual based on participant preference).

- This visit will first take place with a research coordinator where the participant will be allowed to ask any final questions about their consent which will then be signed either on paper or electronically.
- Final eligibility will be determined by a licensed medical provider on the research team by ensuring the participant is not experiencing any symptoms of pyelonephritis and/or sepsis.
- Consented study participants will then complete baseline questionnaires including the Urinary Tract Infection Symptom Assessment (UTISA)[68] and the pelvic floor distress inventory short form (PFDI-20).[69]
- Participants will submit a urine specimen for urine culture and urinalysis either in-person at one of our Women's Center for Bladder and Pelvic Health faculty practices or a local laboratory

Randomization: Participants will be randomized by the study team to either the "Culture-directed Antibiotic Treatment" or "Empiric (Immediate) Antibiotic Treatment" Group in a 1:1 allocation scheme, with randomization using permuted blocks of 4 or 6.

D.1.3.3 Antibiotic Treatment Strategy. All participants will be allowed to use acetaminophen, non-steroidals, and/or phenazopyridine.
Culture-directed Antibiotic Treatment: Participants will be directed to refrain from taking antibiotics until results of urine culture are reported, which is expected within 48-72h.
Empiric Antibiotic Treatment Participants will be prescribed empiric antibiotics in accordance with our stepwise protocol below.

Antibiotic Protocol. For participants in the empiric Rx arm, we will choose an antibiotic with consideration of patient reported allergies, current medications and current IDSA guidelines.[70] If there is a contraindication to the first antibiotic on the list they will progress to the next option until a suitable selection is achieved.

Antibiotic Protocol:

1. Nitrofurantoin 100 mg PO BID x 5 days
2. Trimethoprim/Sulfamethoxazole 875/125 mg PO BID x 5 days
3. Fosfomycin 3 g once
4. Cephalexin 500 QID x 5 days
5. Ciprofloxacin 500 mg PO BID x 5 days

D.1.3.4 Antibiotic management after urine culture results. All participants will be called with the results of their culture. Participants who register for *MyUPMC*, a no-cost, proprietary secure email service, will also receive the urine culture result by email. Cultures with result of "mixed flora" will be considered contaminated and be managed as negative.[71]

Culture-directed Antibiotic Treatment.

- Those with a negative urine culture will not be prescribed antibiotics and will be followed per protocol.
- Those with a positive urine culture who *report persistent UTI symptoms* will be given antibiotics following the priority list above with consideration to reported antimicrobial sensitivities.
- Those with a positive urine culture who *report resolution of UTI symptoms* will not be given antibiotic

Empiric Antibiotic Treatment.

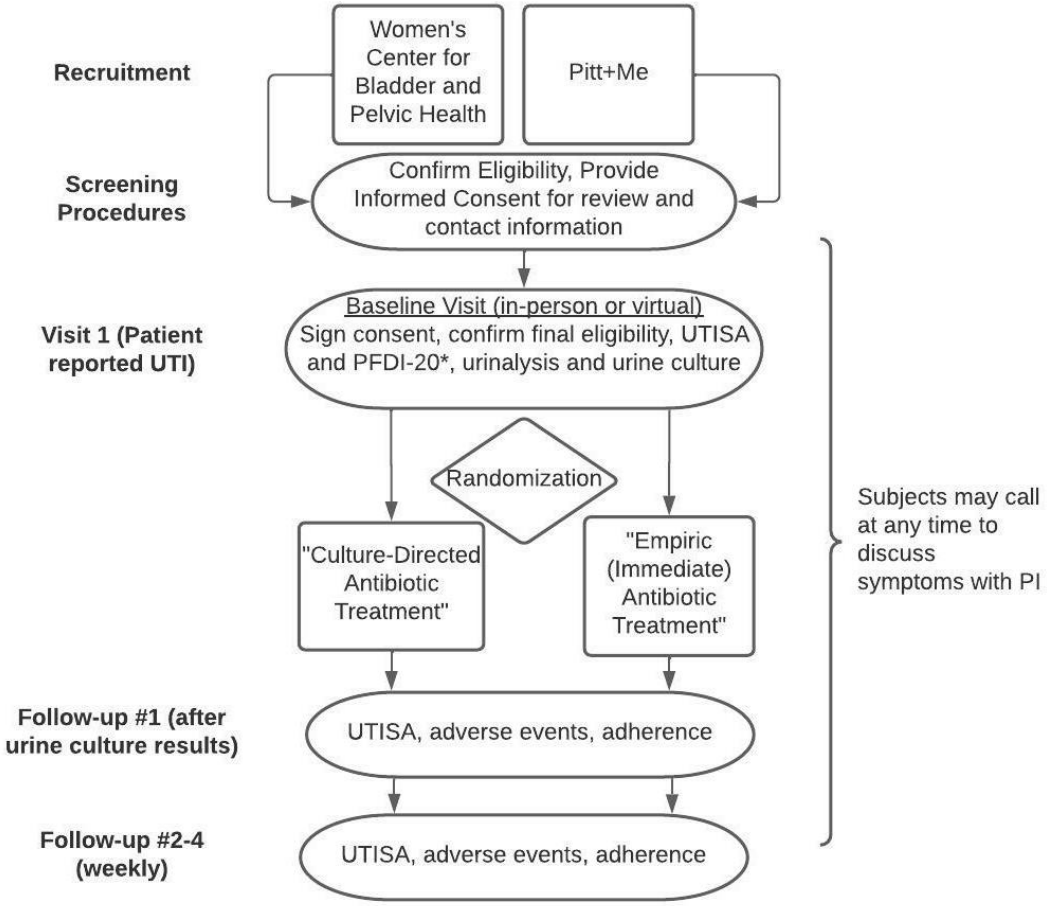
- Those with a negative urine culture will be told to stop antibiotics
- Those with a positive urine culture sensitive to the empiric antibiotic will be instructed to complete the full course of their antibiotics
- Those with a positive culture resistant to empiric antibiotic will be given an alternative antibiotic per antibiotic protocol and will be followed per protocol. If there are no oral antibiotic options with patient-specific and antimicrobial sensitivities, we will engage local infectious disease physicians for management as per standard clinical protocols.

D.1.6. Study follow-up assessments.
All participants will be followed with electronic surveys via Research Electronic Data Capture (REDCap) software, which is a browser-based, metadata-directed EDC software and workflow methodology for designing

clinical and translational research databases,[72] on day 2-3 (after result of urine culture). To avoid limiting enrollment to only those with access to technology, our research coordinator can also call and administer the questionnaire by phone to ensure ability to access and complete electronic materials. Follow-up assessments will be completed weekly for a total of 4 weeks. These will include UTISA questionnaire,[68] antibiotic associated side effects, use of other symptom mitigating remedies, and adherence to assigned study arm.

Participants will be provided with a clinical line to call 24/7 with report of worsening symptoms which will be discussed with the PI, Dr. Bradley for determination of antibiotic prescription and if participants report fevers or chills this will prompt an in-person evaluation in clinic during business hours or the emergency department after hours. If participants call to report new symptoms during the study course, a repeat urine culture will be obtained.[73] Given that these episodes could be considered either a recurrent or incompletely treated infection we plan to manage these per clinical care and not based on the participants initial study arm.

Figure 2: Study Flow Diagram



Pelvic floor distress inventory, PFDI-20; Urinary Tract Infection Symptom Assessment, UTISA
¥ Adverse events will include either antibiotic related side effects, signs/symptoms of pyelonephritis and/or urosepsis or other seriour adverse events

D.1.7. Data analysis.

Specific aim 1A) To evaluate the feasibility of recruiting eligible participants into a randomized trial of a culture-directed versus empiric antibiotic strategy for patient-reported UTI symptoms in older women. All outcomes for the feasibility assessment will be descriptive using numbers and proportions of patients and 95% CIs. We will report the number of patients assessed for eligibility along with the numbers excluded based on not meeting inclusion criteria, participation declined, and other reasons.[74] We will document number and proportion of enrolled participants who were randomized along with the number/proportion who received their

allocated assignment. We will document those lost-to follow-up including potential reasons. These data will provide information on the feasibility of recruiting patients into a future, large randomized, placebo controlled clinical trial. We believe that successfully recruiting 10% of eligible patients (e.g., 6-7 patients per month) will confirm the capacity to recruit for a future trial.

Power calculation:[75,76] The primary outcome is feasibility which we will define as the ability to recruit 10% of eligible patients. As this is a pilot study, the sample size of 70 patients was determined based on clinical and logistical resources rather than statistical requirements for hypothesis testing. We anticipate *screening* approximately 1200 potentially eligible patients (based on known clinical data from our practice and current enrollment of women with recurrent UTI in Pitt+Me®) during the 12 months of recruitment (~100 per month) of which at least 800 will be deemed eligible and have UTI symptoms. (~67 per month) This is based on data from our group on urine cultures sent annually and time between UTI episodes.[35] A 95% confidence interval (CI) for the recruitment rate provides a 2.4% margin of error (MoE) assuming the true rate is 10%.

Specific aim 1B) To evaluate participant adherence to study procedures.
For a larger trial, electronic surveys may significantly reduce research coordinator burden. To evaluate feasibility of this approach we will administer electronic surveys through Research Electronic Data Capture (REDCap) software.[72] Surveys are sent via email and can be accessed through either a laptop, desktop or smart phone. Participants will also be called at day 2-3 (after urine culture results) and then weekly to assess issues with electronic materials. We will evaluate proportion of those with electronic success and investigate demographic variables that may be associated with inability to utilize electronic materials. To assess patient adherence to study procedures, defined as completion of all follow-up questionnaires, we will describe the percentage of enrollees who completed 100% of study procedures, 80% to 100% of study procedures and 50% to 80% of study procedure. A priori, we believe that compliance with 70% of study procedures will demonstrate satisfactory patient adherence to protocol. If the underlying adherence rate is 70%, a sample size of 70 provides a 10.1% MoE.

Exploratory Aim: To explore the safety of a culture-directed UTI treatment strategy and preliminary secondary outcomes of assigned treatments.
Safety Aims[62]

1. Adverse events per group (most likely antibiotic side effects (i.e., gastrointestinal distress, antibiotic related diarrhea, rash) between groups.
2. Serious adverse events per group (defined in line with FDA reporting guidelines as a medical event that does one or more of the following: results in death, is life‐threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.[77]

Analysis. We anticipate that adverse events will be reported relatively infrequent.[78] All outcomes will be described using numbers and proportions of patients. Proportions between groups will be compared with either chi-square or Fischer's exact testing.
Secondary exploratory aims.
Proportion of those with clinical cure (as 2 or less points (slight, very slight, or no problems) on all five components of the UTISA (ref) at day 14 (***future trial primary outcome)***

Analysis. All outcomes will be described using numbers and proportions of patients or means with confidence intervals. Proportions between groups will be compared with either chi-square or Fischer's exact testing and means will be compared with student's t-testing. Exploratory logistic regression modeling will be utilized to investigate the odds of both initial treatment failure and/or recurrent of UTI symptoms between groups and based on baseline characteristics

Power analysis:[76,79] As above, we propose a future trial with a primary outcome to be symptom resolution at day 14 defined as 2 or less points (slight, very slight, or no problems) on all five components of the UTI symptom assessment (UTISA).[43,78] The literature suggests 58-80% of women receiving empiric antibiotics for patient reported UTI will achieve clinical cure by day 3-7 after treatment initiation. [43,78]Given that only women

with a positive urine culture will be given culture-directed antibiotics, and women in the empiric arm may have to have their antibiotics changed or stopped at the time of culture result, we anticipate a higher proportion of those in the culture-directed arm to have symptom resolution at day 7. Assuming 70% symptom resolution in the empiric arm, a future trial of 262 participants, with 131 per arm, would have 80% power to detect a 15-percentage point difference between groups with a 2-sided alpha of 0.05, while a sample size of 300 would be required assuming 65% resolution. Therefore, we believe that successfully recruiting a total of 70 participants at a rate of 6-7 participants/month will confirm the feasibility of future trial completion in <4 years (equivalent to other trials of antibiotic regimens for symptomatic UTI).[17,78]

Statistical methods

Primary Outcomes	***Statistical analysis***
Feasibility: - Number of subjects that were screened for participation - Number and proportion of subjects screened who met inclusion/exclusion criteria - Number and proportion of subjects who either declined participation or were ineligible (including reasons for ineligibility) - Number and proportion of eligible subjects that were enrolled in the study - Number and proportion of subjects enrolled who completed the study - Monthly enrollment rate	Descriptive analysis = counts and proportions or means with standard deviation
Adherence: - Number of those that completed all study procedures - Number of subjects that took alternative agents taken by subjects for management of symptoms - Number of subjects in the culture-directed arm that acquired off-protocol antibiotics for their symptoms - Number of subjects able to complete electronic surveys	Descriptive analysis = counts and proportions
Secondary Outcome	
Proposed primary outcome for future trial (Clinical Success at 14 days UTISA 1-3,5<=1)	Descriptive analysis = counts and proportions Comparative = Chi-square