Seven vs. 14 Days Treatment for Male Urinary Tract Infection

A randomized placebo-controlled trial of 7 vs. 14 days of antimicrobial treatment for men with UTI

Sponsor: VA Merit Review, award #1I01CX000830-01A2

Intervention: 7 days of antimicrobial treatment (ciprofloxacin or trimethoprim/sulfamethoxazole) followed by 7 days of placebo vs. 14 days of antimicrobial treatment

Principal Investigator: Dimitri Drekonja, MD, MS

Co-Investigator, and Michael E. DeBakey VAMC site investigator: Barbara Trautner, MD, PhD

Protocol version: 9.0

Table of contents Page

1. Introduction 3
   a. Background 3
   b. Preliminary studies and current status 5
2. Research design and methods 8
   a. Study type 8
   b. Summary of study description 8
   c. Details of specific study areas 11
   d. Inclusion and exclusion criteria 14
   e. Method of identifying potential subjects 15
   f. Patient contact and enrollment 16
   g. Sampling of the intestinal microbiota 17
   h. Subject compensation 18
   i. Potential complications during therapy 18
   j. Follow-up and outcome assessment 19
   k. Safety and monitoring 19
   l. Definitions for safety and monitoring 20
   m. Anticipated adverse events 21
   n. Statistical methods 23
   o. Proposed timetable 24
3. Summary 25
4. References 26

1. Introduction

1.a. Background

Urinary tract infection occurring in males (hereafter, male UTI) is a common infection among both hospitalized and ambulatory men. Most patients are treated in the outpatient setting, with only a minority requiring hospitalization[1, 2]. Data from the 2000 National Ambulatory Medical Care Survey demonstrate that male UTI led to 1.8 million annual office visits and 420,000 annual Emergency Department visits in the U.S.[1, 2]. Within the VA health care system, over 33,000 non-hospitalized men have at least one UTI episode in a 12-month period[3]. Treatment is typically with oral antimicrobials, for durations ranging from 3 days to several weeks.

Few data from randomized trials are available to guide treatment duration for male UTI. At one extreme of the treatment duration spectrum, a Scandinavian study found no significant difference in clinical cure or recurrence rates among men with febrile UTI randomized to 14 vs. 28 days of ciprofloxacin[4]. At the other end of the spectrum, in a study of UTI treatment duration among patients with spinal cord injury (85% male), 3 days treatment yielded a higher rate of symptomatic relapse than did 14 days treatment, in both short and long-term follow-up[5]. No other randomized clinical trials are available that directly assess the impact of duration of treatment for male UTI on efficacy; accordingly, the conventional recommendation to treat for 7-14 days is based largely on expert opinion[6-8]. Currently, 7, 10, and 14-day antimicrobial courses are commonly used to treat UTI in male veterans UTI[3].

In addition to the lack of evidence regarding optimal treatment duration, two well-documented trends are making management of male UTI progressively more challenging. First, Gram-negative bacilli, the causative microorganisms for most UTIs, are becoming increasingly resistant to most relevant antimicrobials; consequently, few reliably active oral agents are available for UTI therapy, which is often initiated empirically, before culture results are known. Second, *Clostridium difficile* infection, which is almost invariably precipitated by antimicrobial use, is increasingly frequent and severe[9, 10].

Increasing antimicrobial resistance among Gram-negative bacilli. Antimicrobial resistance among Gram-negative bacilli, a major public health threat, has attracted considerable attention from governmental organizations, professional societies, and leaders in the field of infectious diseases[11]. Perversely, as resistance among Gram-negative bacilli has increased, the development of new antimicrobials that target these organisms has decreased[11].

The problem of Gram-negative resistance is particularly relevant for treating UTI, because the vast majority of UTIs are caused by enteric Gram-negative bacilli, in particular *Escherichia coli*, but also *Klebsiella* species, *Enterobacter* species, and others[8, 12]. Guidelines recommend that when the local prevalence of susceptibility to a particular drug among uropathogens falls below 80%, that drug should no longer be used as empiric therapy for UTI[13, 14]. Currently, many locations, including the MVAMC, have *E. coli* susceptibility rates of only 65-70% for both ciprofloxacin and trimethoprim-sulfamethoxazole (TMP-SMZ) (MVAMC antibiogram, January 2012 through June 2012). These drugs are traditional cornerstones of UTI treatment in the ambulatory setting because of their excellent oral

bioavailability and their track record of tolerability and effectiveness across most types of UTI, including febrile UTI and pyelonephritis[15, 16]. In contrast, alternative oral agents, including β-lactams, nitrofurantoin, and fosfomycin, have inferior efficacy (β-lactams, fosfomycin)[17, 18] and/or achieve low tissue drug levels (nitrofurantoin, fosfomycin)[13, 18], limiting their appeal for UTI therapy, especially for patients with fever or clinical manifestations suggesting pyelonephritis[13, 18].

The rising prevalence of resistance to ciprofloxacin and TMP-SMZ has led providers to use broader-spectrum empirical therapy, such as a parenteral dose of a more predictably active agent combined with empiric oral ciprofloxacin or TMP-SMZ. This practice adds to the selective pressure for the development of antimicrobial resistance, thereby causing future infections to be even more difficult to treat.

Increased incidence and severity of *Clostridium difficile* infection. Beginning in the early 2000's, an increasing incidence and severity of *C. difficile* infection was observed, first in Canada and subsequently worldwide[9, 10, 19, 20]. Multiple factors have been proposed to explain these increases, including increased antimicrobial use, emergence of a new fluoroquinolone-resistant strain of *C. difficile* during a time of increased fluoroquinolone use, increased sporulation and toxin production by this epidemic strain, and better recognition and diagnosis of *C. difficile* infection on the part of clinicians[9, 10]. Whatever the explanation, *C. difficile* now rivals methicillin-resistant *Staphylococcus aureus* as the leading cause of nosocomial infections[21], and is also increasingly prevalent in the community[22]. Thus, efforts to decrease its incidence, including through reduced antimicrobial use, are urgently needed.

Relationship between antimicrobial use, antimicrobial resistance, and *C. difficile* infection. The relationship between antimicrobial use and subsequent antimicrobial resistance is complicated. First, although some patient-level studies have demonstrated the development of resistance during or after receipt of antimicrobial therapy[23-25], in clinical practice the link between past antimicrobial use and subsequent infection with a drug-resistant organism is difficult to prove. Additionally, most patients in whom a resistant organism emerges do not develop a subsequent drug-resistant infection, but rather become carriers of resistant organisms as part of their normal bacterial microbiota. Because carriage of resistant microorganisms is a clinically silent phenomenon, this is an under-recognized harm of antimicrobial use. However, the fecal microbiota serves as the source of many infections, including UTIs. In addition, microorganisms can spread easily among household contacts, thus increasing the population at risk for infection with a resistant organism[26, 27]. Countries with high levels of antimicrobial use typically have correspondingly high rates of antimicrobial resistance among clinical isolates, as compared with countries with lower levels of use[28, 29]. Similarly, individual centers have documented a temporal relationship between antimicrobial use and antimicrobial resistance, with increased use being followed shortly thereafter by a corresponding increase in resistance[30].

Antimicrobial use is also closely linked to *C. difficile* infection, almost all cases of which are preceded by antimicrobial therapy. Increased antimicrobial use is associated with increased *C. difficile* infection[31, 32], and reduced antimicrobial use has been used successfully to combat outbreaks of *C. difficile* infection[33-35]. Accordingly, a joint Clinical Practice Guideline for *C. difficile* infection from the Society for Healthcare Epidemiology of America and the

Infectious Disease Society of America recommends limiting the duration of antimicrobial therapy a way to decrease the incidence of *C. difficile* infection[36].

In summary, antimicrobial use is associated with increases in antimicrobial resistance and *C. difficile* infection; therefore, effective strategies to minimize unnecessary antimicrobial use are urgently needed. One potential method to decrease unnecessary antimicrobial use is to define the minimal effective treatment duration for various diseases, and to use this minimal duration routinely. This approach has been successfully applied to other infectious diseases, including ventilator-associated tracheitis[23], ventilator-associated pneumonia[24], and cellulitis[37]. For these disorders, shorter-duration treatment performed as well as longer-duration treatment, and in the respiratory infections was associated with less colonization and infection with drug-resistant microorganisms, with or without a trend toward lower mortality--without any reduction in efficacy. For male UTI, if 14 days of therapy yields no clinically relevant benefit to that observed with 7 days of therapy, but induces greater resistance in a similar manner as seen in the studies of ventilator-associated pneumonia and tracheitis, then patients treated longer are exposed to potential harms without any benefit. Alternatively, if longer-duration treatment does provide benefits, then a substantial proportion of men with a UTI are being treated for an inappropriately short duration, and may be experiencing worse symptom control and increased rates of recurrence. Accordingly, we propose to conduct a randomized clinical trial to investigate whether 7 days of antimicrobial treatment is non-inferior to 14 days of antimicrobial treatment for men with a UTI.

1.b. Preliminary studies and current status

Historically, UTIs in both males and females were treated with longer courses of antimicrobials than are commonly used today, ranging from 7 days for simple cystitis (i.e., bladder infection or lower-tract disease), to up to 6 weeks for pyelonephritis (i.e., kidney infection or upper-tract disease), which is more serious but also comparatively uncommon[38]. UTI treatment has been studied much more extensively in women than in men; consequently, optimal treatment durations are more clearly defined for women than for men[13]. In women, cystitis can be treated effectively with 3 days of a fluoroquinolone or TMP-SMZ, 5 days of nitrofurantoin, or a single dose of fosfomycin tromethamine; likewise, pyelonephritis can be treated effectively with 5 days of high-dose levofloxacin, 7 days of standard-dose ciprofloxacin, or 14 days of TMP-SMZ[13, 39].

In contrast, little is known regarding the optimal treatment duration for male UTI. This is due in part to the paucity of randomized trials, as compared to UTI in women. It also relates to the additional structures present in the male genitourinary tract, including the prostate gland, epididymis, and seminal vesicles, involvement of which is hypothesized to necessitate longer-duration therapy, since they may serve as sanctuaries or reservoirs from which residual bacteria can emerge and cause a recurrent infection[6]. Also complicating efforts to identify the optimal treatment duration in men is the broader range of entities that constitute the full spectrum of male UTI. Such syndromes range from simple cystitis (manifested as voiding symptoms in the absence of constitutional manifestations, including fever), to febrile UTI (voiding symptoms with documented fever), to pyelonephritis (fever with flank pain,

with or without voiding symptoms). Finally, UTIs can be categorized as complicated vs. uncomplicated. Although consensus is lacking as to which specific conditions define a UTI as being "complicated," the accepted underlying principle is that these are factors that, when present, make UTI more likely to occur, more difficult to treat successfully, and less predictable as to microbiological etiology[7, 8, 40]. Published reviews have recommended longer-duration treatment for complicated male UTI, but because these recommendations are based largely on expert opinion, and because of disagreement as to what constitutes a complicated UTI, they confuse more than clarify the issue of optimal treatment duration.

Previous clinical trials. The most robust evidence for treatment duration in the field of male UTI comes from a non-blinded Scandinavian trial of 114 men with febrile UTI who were randomized to receive 14 vs. 28 days of ciprofloxacin[4]. All patients experienced resolution of signs and symptoms of infection during therapy, and cure rates (defined as remaining symptom-free for two weeks after treatment cessation) were not significantly different between groups (92% vs. 97%, respectively)[4]. Notably, however, treatment durations less than 14 days were not investigated, and this trial included only men with febrile UTI, a syndrome that although clinically important is relatively uncommon.

Most men diagnosed with UTI are afebrile, but instead experience new onset of dysuria, frequency, and/or supra-pubic tenderness[41]. The presence of fever is thought to represent some component of invasive disease, which presumably can be localized within the prostate, kidney, or other tissues, although in practice the actual primary focus is rarely sought or defined, since such knowledge confers no known clinical benefit. Thus, the finding that 14 days of therapy for febrile male UTI performed as well as did 28 days suggests that for men with the less severe UTI syndrome of cystitis extending the duration of treatment beyond 14 days is unlikely to be beneficial.

At the other end of the treatment duration spectrum, in a trial of UTI treatment among spinal cord injury patients, the 60 subjects (85% male, all without fever) were randomized to receive 3 vs. 14 days of ciprofloxacin [5]. Although clinical cure (defined as resolution of symptoms by 19-23 days after treatment initiation) was not significantly different between the 3 and 14-day treatment groups (63% vs. 53%, respectively), relapse was significantly more common in the 3-day group (33% vs. 0%; P = .001)[5]. This suggests that 3 days of treatment may be insufficient for UTI in men with spinal cord injuries, and perhaps also-- although this has not been specifically studied-- in other men.

Previous observational studies. Observational data indicate that in practice the treatment duration used for male UTI varies significantly, and may influence the likelihood of both recurrence and adverse events. At the MVAMC, we retrospectively examined the records of 225 patients (90% male) diagnosed with UTI in 2007-8 for (i) appropriateness of the diagnosis and the associated treatment duration and (ii) clinical outcome[42]. Treatment durations ranged from 3 to 14 days among men and women alike. Notably, among the 152 men with complicated UTI, recurrence was significantly more common among those treated for only 3-7 days, compared with 10-14 days (35% vs. 17%; P = .02)[42]. This indicates that for men with complicated UTI (75% of the study population), shorter-duration therapy may predispose to recurrent infection.

In a separate study using VA administrative data for FY2009, we identified 33,336 unique male veterans treated for UTI, defined as having a diagnostic code for UTI combined with a prescription for an antimicrobial typically used for UTI [3]. Of these men, 35% received 7 or fewer days of treatment, whereas the remaining 65% received more than 7 days of treatment. Recurrence rates were not appreciably different between patients receiving shorter- vs. longer-duration treatment (3.9% vs. 4.2%, respectively, P = .16). However, subsequent *C. difficile* infection was significantly more common among patients receiving longer-duration treatment. That is, whereas in the total population *C. difficile* infection occurred in 144 (0.4%) of the 33,336 UTI patients, it occurred in only 0.3% of patients receiving shorter-duration (≤ 7d) treatment, compared to 0.5% of those receiving longer-duration (> 7d) treatment (P = .02). With multivariable adjustment for age, Charlson comorbidity score, and UTI-specific comorbidities (prostatic hypertrophy, urinary calculi, etc), a borderline significant trend persisted toward increased *C. difficile* infection with treatment durations greater than 7 days (odds ratio 1.42, 95% confidence interval 0.97 to 2.07). Thus, longer-duration therapy was not associated with a reduction in recurrence, but may be associated with increased *C. difficile* infection.

Adverse drug events. Adverse drug events are an increasingly recognized consequence of antimicrobial use. Using active surveillance, the percentage of antimicrobial-treated subjects who report adverse events has been as high as 30%[15-17]. Commonly reported adverse events are generally mild, and include nausea, diarrhea, headache, and dizziness. However, more serious adverse drug events, including allergy, *C. difficile* infection, and interactions with other medications also occur with antimicrobial use, and are frequent enough such that antimicrobials are the cause of up to 20% of adverse drug events diagnosed in emergency departments[43]. Although some adverse drug events, such as anaphylaxis, are unlikely to be affected by treatment duration, many others, including nausea, diarrhea, *C. difficile* infection, headache, and dizziness, conceivably could be reduced or avoided by use of shorter-duration therapy. The issue of adverse drug events has become more important given the recent warning by the US Food and Drug Administration that use of fluoroquinolone antimicrobials is associated with musculoskeletal and nervous system adverse events (http://www.fda.gov/Drugs/DrugSafety/ucm500143.htm). Thus, determining the shortest possible treatment duration for male UTI, a common cause of fluoroquinolone use, is increasingly important.

In summary, the available observational and clinical trial evidence indicates that for male UTI 28 days therapy offers no demonstrable clinical benefit over 14 days, even within the febrile UTI subset, whereas a much shorter treatment duration, e.g., 3 days, may increase the risk of recurrent UTI, even among men with less severe UTI syndromes. This suggests that the optimal treatment duration should be longer than 3 days, but not longer than 14 days, which comports with current recommendations for 7-14 days of treatment. However, *C. difficile* infection may be more frequent among patients treated for more than 7 days, compared to 7 days or fewer. Minor adverse drug events are common with UTI treatment, but whether their frequency is influenced by treatment duration is unknown. Additionally, although the effect of treatment duration on intestinal carriage of antimicrobial-resistant organisms is unknown for UTI, in other infectious diseases longer treatment durations have been associated with increased colonization and infection with drug-resistant organisms, compared with shorter treatment durations. Thus, since longer treatment may have

demonstrable harms, apart from the obvious cost and convenience issues, for longer-duration treatment to be justified it should confer demonstrable clinical benefit. Accordingly, a randomized trial of shorter vs. longer-duration treatment for male UTI is needed, to determine whether 7 days of treatment is non-inferior to 14 days of treatment.

2. Research design and methods

2.a. Study type

We propose to conduct a randomized, double-blind, placebo-controlled trial to determine whether, among men with UTI, 7 days of antimicrobial treatment is non-inferior to 14 days of treatment for resolution of UTI symptoms. The proposed trial will randomize 290 men with UTI to 7 vs. 14 days of treatment. Antimicrobial selection will be at the discretion of the treating clinician. The primary endpoint will be resolution of pre-therapy UTI symptoms, as assessed 14 days after the last dose of active antimicrobial. Secondary outcomes will include intestinal carriage of antimicrobial-resistant Gram-negative bacilli, recurrence of symptomatic UTI, and adverse drug events.

2.b. Summary of study description

The study was initially proposed as a single site study, conducted at the Minneapolis VA Health Care System, which includes the Minneapolis VA Medical Center and the affiliated Community Based Outpatient Clinics(CBOCs). To address slow enrollment, a second site (the Michael E. DeBakey Veterans Affairs Medical Center [MEDVAMC] and their affiliated CBOCs) has been approved by the VA Merit Review Program. Any changes to the protocol and consent will be initiated by the PI, and MEDVAMC IRB approval must be sought prior to implementing changes at that site, except when necessary to eliminate apparent immediate hazards to the subject. To minimize the possibility that the decision to participate is influenced by the initial duration of therapy prescribed, every effort will be made to enroll patients prior to their being prescribed antimicrobial treatment. This will be done by close collaboration with nurse-managers in the clinics and by having the study coordinator screen for eligible patients. Additionally, because we are intervening only on treatment duration, and all enrolled patients will receive at least 7 days of antimicrobial treatment, we will be able to identify and enroll patients seen during off-hours, or those who were missed during regular hours, several days after their initial clinical presentation, but before they have completed 7 days of treatment. Thus, although we plan to enroll the majority of patients at the time of initiating therapy, we will be able to recruit sufficient numbers of subjects without needing to maintain the multiple shifts of study personnel typically needed to enroll patients presenting during evening, night, or weekend tours.

Potential subjects will be identified by the chief complaint elicited by the intake nurses in the outpatient clinics and urgent care, and by notifications/reports from the pharmacy service regarding new UTI prescriptions (if such reports are able to be generated). Nurse managers or physicians will add study coordinator as a signer on CPRS record and give patient an “opt out” flyer when patients with symptoms of dysuria, urinary frequency, urgency, hematuria,

perineal pain, supra-pubic pain, costovertebral angle tenderness, or flank pain come into hospital. The nurse managers of the involved clinics have indicated that this would not overly burden their staff or resources. Patients presenting with UTI during evening, night, weekends, or holidays will be identified by searching recent outpatient clinic encounters for the specific diagnostic codes relevant to UTI. Each day, study staff will review the list of patients newly assigned any of these codes, i.e., the potential subjects, and their medical records to determine (i) the validity of the UTI diagnosis and (ii) whether the patient meets eligibility criteria, as detailed below.

Patients who pass this screen will be contacted, will receive a brief study description, and will be invited to a study visit at which study participation will be further discussed. The visit must occur before the patient completes 7 days of treatment and will be conducted in person at the participating study site or via mail. Patients will be asked to bring their current antimicrobial with them, if they meet with study staff in person. At the visit, inclusion/exclusion criteria will be verified, any questions will be answered, and written informed consent will be obtained. Patients at the MVAMC (and possibly later at the MEDVAMC) will also be invited to participate in a sub-study that investigates the effect of treatment duration on the intestinal carriage of antimicrobial-resistant Gram-negative bacilli (hereafter, resistance sub-study). After providing consent, subjects will be randomized to 7 vs. 14 days of antimicrobial treatment (of the same agent their provider prescribed for them), and will exchange days 8-14 of their current medication for a special medication supply provided by the study. All medications provided by the patients will be collected and returned to the study site's research pharmacy for disposal when possible. Patients who complete study visit via mail, will be instructed to dispose of days 8-14 of their original prescription and use only the study medication. Subjects will be provided with a notebook and will be instructed to record in it their UTI symptoms and any potential adverse drug events, to facilitate accurate recall during follow-up.

The special medication supply to be given to the subjects will be a 7-day pill container loaded with a sufficient supply of medication to complete a 14-day course of treatment when combined with the clinically prescribed medication, which will be used for days 1-7. For example, a patient with a study visit that falls on day 4 of treatment will take their clinically prescribed antimicrobials through day 7, and will complete treatment using the 7-day supply of study medication for days 8-14. We will enroll only patients treated initially with ciprofloxacin and TMP-SMZ, which are used to treat over 90% of male VA patients with UTI [3]. In addition to being the most frequently used medications for male UTI, both agents are highly bioavailable with oral administration, and achieve excellent penetration into the male genitourinary tract (6, 8). Study medications (both active antimicrobial and placebo) will be different in appearance from clinically prescribed medication. Both subjects and investigators will be blinded to duration of active antimicrobial therapy. Patients who cannot attend the study visit in person will have the medication for days 8-14 mailed to them using overnight delivery after the research pharmacist receives the signed consent and HIPAA authorization forms.

After enrollment, subjects will be contacted by telephone on or about the scheduled day of medication completion, and again at days 7, 14, and 28 (± 2) after medication completion. On the day of medication cessation, study staff will verify medication adherence (by patient

report) and will inquire regarding the presence of (i) UTI symptoms, (ii) signs or symptoms of *C. difficile* infection, (iii) other adverse drug events, and (iv) possible infectious complications (retreatment, receipt of care outside the VA system, etc.). Adverse drug events will be elicited first via an open-ended question, then by inquiring specifically regarding a list of typical antimicrobial-related adverse drug events symptoms such as nausea, vomiting, diarrhea, dizziness, rash, thrush, and headache. Similar assessments (excluding medication adherence) will be performed at 7, 14, and 28 days after stopping study medication.

Resolution of UTI symptoms, the primary outcome, will be assessed 7 and 14 (± 2) days after completing medication. However, after study completion and unblinding of treatment allocation, the outcome assessment corresponding to 14 days after last receipt of active antimicrobial will be used for analysis. That is, for subjects in the shorter-duration group, the 7 day assessment will be used, whereas for subjects in the longer-duration group, the 14 day assessment will be used, such that all subjects are assessed 14 days after their last dose of active antimicrobial. Additionally, with the 7 days post-treatment call, subjects in the resistance sub-study will be reminded to obtain a stool swab and to return it using the provided mailer. After the final (28d) follow-up call, subjects will have completed their participation in this study. If at any time subjects report new or unresolved UTI symptoms, or symptoms consistent with *C. difficile* infection or other adverse drug events, they will be directed to seek medical care from their primary care provider or the MVAMC or MEDVAMC Emergency Department.

A 3-member data safety monitoring board (DSMB) will be formed to oversee the safety of this trial, assisted by a biostatistician with experience in clinical trials. Under the direction of the DSMB, the biostatistician will conduct 2 interim analyses, when approximately 33% and 66% of the planned 290 subjects have been evaluated for the primary endpoint. An alpha-spending function approach as described by Lan & DeMets is proposed[44], testing for both non-inferiority and futility. Additionally, rates of adverse events in the treatment groups will be monitored by the DSMB, and reported to the MVAMC institutional review board.

After enrollment and follow-up are concluded, and laboratory testing complete, results will be analyzed using a per-protocol analysis, with subjects analyzed according to which treatment they received. An intention-to-treat analysis will be performed as a secondary analysis. We will test our primary hypothesis that 7 days of antimicrobial treatment is non-inferior to 14 days of treatment for the resolution of UTI symptoms by comparing the proportion of subjects in each group reporting resolution of pre-therapy UTI symptoms at 14 days after completing active antimicrobial therapy. For the purposes of statistical power calculation, treatment inferiority is defined as >10% efficacy between treatment groups. A sample size of 290 subjects (145/group) was calculated, using a one-sided alpha level of 0.025 and power of 85%, to allow detection of a minimum clinically significant absolute difference of 10% (e.g., 90% for 14-day treatment, vs. 80% for 7-day treatment). To adjust for potential loss of subjects to follow-up, we initially increased our enrollment goal by 10% (29 subjects), for a total sample size of 319, but have since opted to remove this 10% margin as there has been no loss to follow-up to date.

Both treatment groups will be assumed to be superior to no treatment, based on prior studies of UTI demonstrating that spontaneous cure occurs in a minority (7-28%) of subjects[45, 46]. Accordingly, it would be unethical to include a placebo-only treatment group.

2.c. Details of specific study areas

Selection of treatment duration. Our decision to compare 7 vs. 14 days treatment duration was based on prior studies[4, 5, 15], the range of current expert recommendations[7, 8, 47], and current practice within the VA system (unpublished data)[4]. The choice of 14 days for the longer-duration treatment arm was relatively straightforward. As outlined in the "prior clinical trials" section above, 14 days was the shorter duration arm in the Swedish study that found no significant efficacy difference between 14 vs. 28 days of treatment[4]. Also, 14 days frequently appears in reviews as the upper-limit of recommended treatment duration for male UTI[7, 8, 40, 47]. Finally, among 33,000 male UTI episodes treated in the VA system in fiscal year 2009, only a small minority (8%) received more than 14 days of therapy[3].

In contrast, the choice of 7 days for the shorter-duration treatment arm was more difficult, since no prior clinical trial of male UTI has used this duration. However, since the 3 vs. 14-day study by Dow et al. among spinal cord injury patients showed a statistically significant increased risk of symptomatic recurrence among subjects receiving 3 days of treatment, we believe that there is not clinical equipoise between 3 and 14 days treatment duration. This belief is reinforced by our own observational data from the MVAMC showing an increase in recurrence among subjects receiving shorter-duration treatment (as discussed above), and the fact that experts typically offer only guarded endorsement for the possibility of using 3-day therapy (which is widely accepted as appropriate for women with uncomplicated cystitis) for treating male UTI, and even then only in young, otherwise healthy men with no complicating conditions[40].

Although 7 days is a widely recommended lower-limit of treatment duration for male UTI[7, 8, 40], in our VA administrative data of male UTI treatment, we observed that 10 days of treatment was actually more common than 7 days, which might suggest that a 10-day duration should be studied. However, if we were to compare 10 vs. 14-day therapy, a between-arm treatment duration difference of only 4 days would make our groups prone to crossover contamination, with those allocated to 14 days of treatment needing to miss only a few doses of antimicrobials to merge with the 10-day group. Additionally, the favorable impact on resistance selection, *C. difficile* infection, and other adverse drug events of a 4-day (29%) reduction in treatment duration is likely to be less than with a 7-day (50%) reduction. Therefore, we selected 7 days for the shorter-duration treatment arm.

Blinding. Because our primary outcome is subjective (i.e., patient symptom reports), we are planning to blind participants, investigators, and clinicians to the duration of active treatment, to minimize potential bias that could be introduced if patients knew that they were receiving shorter-duration treatment. There are difficulties inherent to this approach. First, since we are proposing to randomize subjects only to different treatment durations (not to different antimicrobials), we are not in control over which antimicrobials will be prescribed. Fortunately, 90% of diagnosed outpatient male UTIs in the VA system, both nationally and at the MVAMC, are treated with ciprofloxacin (65%) or TMP-SMZ (25%)[3]. The remaining 10% are treated with a wide variety of agents, including nitrofurantoin, cephalexin, amoxicillin, amoxicillin/clavulanate, etc. We opted to include only patients receiving ciprofloxacin and TMP-SMZ, since the other antimicrobials are used so infrequently that no

valid outcome comparisons could be made, and some are dosed more than the twice-daily ciprofloxacin and TMP-SMZ, increasing the burden on our research pharmacy.

To achieve double-blinding, all patients will take their clinically prescribed medications on days 1-7. However, all patients will receive study medication for days 8-14. Specifically, all patients will be given a supply of medication that is different in appearance from their clinically prescribed medication for days 8-14. This different-appearing medication will be either:

1) active antibiotic (ciprofloxacin or TMP/SMZ, based on what they were initially prescribed) from an alternate manufacturer, different in both color and imprint from the clinically prescribed drug, or

2) a placebo tablet, similar in size to both the antimicrobials (approximately 1 gram), that will be provided by the VA Cooperative Study Pharmacy in Albuquerque, New Mexico.

Thus, all subjects will receive pills that are different in appearance from the initial antibiotic for days 8-14, effectively blinding their allocation. Because there is a possibility of subjects unblinding themselves by using pill-identifier websites, an assessment of blinding will be performed, using a validated blinding index. Of note, similar trials have used overencapsulation to blind participants[15], a method that can be foiled by patients simply removing the gelatin capsule. Research pharmacy staff will prepare 4 different types of containers with these tablets. The containers for the longer-duration subjects will contain ciprofloxacin or TMP-SMZ for days 8-14, and the study coordinator will instruct the patient to use their clinically supplied drug for days 1-7. Those for the shorter-duration subjects will contain placebo for days 8-14, with again the clinically supplied drug used for days 1-7.

The logistics of blinding are as follows: at enrollment, the study coordinator will notify the pharmacy that a patient has been enrolled, and whether ciprofloxacin or TMP-SMZ is being used. Since we are stratifying based on catheter use (see below), the coordinator will inform the pharmacy to use the randomization schedule appropriate to the patient's catheter status and antimicrobial received. Working from this randomization schedule, the pharmacy will send a prepared container with study drug for days 8-14 to the appropriate location, with neither the study coordinator nor the patient knowing whether the tablets are antimicrobial or placebo. The research pharmacies at the MVAMC and MEDVAMC will be charged with tracking and dispensing study medications, a function that they routinely provide for other double-blinded studies. The research pharmacy staff can also unblind the patient in the event of a clinical emergency for which unblinding is deemed necessary. Criteria for unblinding will be admission to the hospital for suspected urosepsis or severe drug reaction, or any other scenario as directed by the local institutional review board, which reviews all study-related serious adverse events. The effectiveness of blinding will be assessed by asking patients which treatment they think they received 7 days after completing the study medication.

Randomization. Randomization will be used to ensure that baseline characteristics, including any potential confounders, are equally distributed between the 2 treatment groups. To ensure relatively equal sample size between the shorter and longer therapy duration groups, block randomization will be used. However, since the proposed sample size is 290 subjects, it is possible that uncommon factors may be unevenly distributed with a simple 1:1

randomization plan. Accordingly, we plan to stratify our randomization by presence of urinary catheter use, a potential confounder that occurs in approximately 10% of male UTI patients at the MVAMC (unpublished data). This will create 2 strata, each of which will have its own randomization schedule, using permuted blocks of 4. Separate randomization tables will be used at the MVAMC and MEDVAMC to avoid any confusion with multiple randomizations occurring in a short time, and to obviate the need to wait for a randomization slot from the MVAMC. Urinary catheter use is relatively uncommon, but is hypothesized by some authorities to require longer-duration therapy[40, 48]. Thus, by allocating this factor in a relatively equal distribution we will ensure that outcomes are not affected by an imbalance in this potentially more difficult-to-treat form of male UTI. Although we initially planned to enroll patients with febrile UTI, because of reviewer concerns, and an ongoing Dutch study specifically addressing treatment duration in men with febrile UTI[49], we have opted to forego including patients with febrile UTI. Since less than 2% of subjects treated in the outpatient setting for male UTI are febrile (unpublished data), this should not significantly affect our enrollment.

Sample size calculations. To determine an appropriate sample size, we first established the minimum significant difference in the primary outcome (resolution of UTI symptoms) that would be clinically relevant. Literature review identified UTI studies that used absolute differences of 10% to 20% for the minimum significant difference[4, 15, 49]. Separately, we queried four international UTI experts as to what difference in treatment success they would view as clinically significant. The range of their responses was also 10-20%, with a mean of 12.5%. Using the conservative lower-limit (10%) as the minimum significant difference the proposed study should be able to detect, and a percentage of subjects experiencing resolution of symptoms with 14 days therapy of 90%[4], we then calculated a total sample size of 290 subjects needed to detect such a difference with 85% power, using a one-sided alpha of 0.025. Accordingly, a group size of 145 subjects (290 total) would provide 85% power to detect a 10% absolute between-group difference in the primary outcome (i.e., 90% vs. 80%). As mentioned, the additional 10% of patients originally built in to account for loss to follow-up is considered unnecessary, as there have been no losses to follow-up at the first interim analysis.

The above calculation assumes a conservative 90% for the outcome of resolution of UTI symptoms. However, in the trial of men with febrile UTI, resolution occurred in 92% (14d) and 97% (28d) of subjects. If we were to assume that 95% of subjects will have resolution of symptoms, instead of the more conservative 90%, then the total number of subjects needed to achieve 85% power to detect a 10% absolute between-group difference in the primary outcome would decrease. However, this may be an overly optimistic projection. Accordingly, we have planned our study using the more conservative assumption of a 90% symptom resolution rate, to minimize the risk of conducting an under-powered trial.

For the resistance sub-study, based on anecdotal data we estimated that 40% of subjects receiving 14 days of treatment would acquire intestinal carriage of a drug-resistant Gram-negative bacillus, compared to 20% of subjects receiving 7 days of treatment. Using a two-sided alpha of 0.05, and 80% power, 91 subjects in each group (182 subjects total) will be needed. This is 57% of the planned total enrollment, which we believe is feasible based on our pre-trial planning. To simplify the logistics of adding a second site, the MEDVAMC will

not enroll patients into the sub-study, unless this is changed via an amendment to the protocol after study activities have commenced.

2.d. Inclusion and exclusion criteria

Inclusion criteria (must have all). With the addition of the MEDVAMC as a second site, there will be significant efforts to ensure that enrollment there is consistent with enrollment at the MVAMC. This will include communication between study coordinators, investigator oversight, and weekly calls during the study roll-out phase at the MEDVAMC. These are deemed necessary since there is some degree of judgement needed as to determining whether documented symptoms meet inclusion criteria (for instance, whether "pain in the lower back and side" qualifies as "flank pain".

1- Male gender

2- New-onset (within 7 days) of at least one of the following symptoms/findings: dysuria, urinary frequency, urgency, hematuria, perineal pain, supra-pubic pain, costovertebral angle tenderness, or flank pain

3- Treated as an outpatient (Primary Care Center or Emergency Department), with < 24 hours observation in the hospital or Emergency Department following the time of initial diagnosis

4- Prescribed treatment with at least 7 days, but not more than 14 days, of either ciprofloxacin or TMP-SMZ

Exclusion criteria (must have none)

1- Admission to the hospital (for > 24h) at the time of diagnosis

2- Documented fever at time of initial evaluation (≥ 38.0 Celsius)

3- Previous enrollment in the study

4- Treatment for UTI in past 14 days

5- Not able to give informed consent

6- Unwilling to either:

   a. return for study visit

   b. participate in a home visit

   c. participate via mail

7- Symptoms thought more likely to be caused by a non-UTI diagnosis (e.g., urinary calculus, sexually transmitted infection, etc.)

8- Other antimicrobial therapy (new or ongoing) prescribed for a non-UTI diagnosis (e.g., cellulitis, pneumonia, etc.)

9- Treatment initiated with an empiric antimicrobial to which the organism isolated in the urine culture is non-susceptible based on standard laboratory criteria

10- Treatment initiated with an empiric antimicrobial regimen that is underdosed, based on current guidelines and reviews

Inclusion criteria were selected to identify male patients with a symptomatic UTI, treated without hospitalization. Identifying patients with a symptomatic UTI (vs. asymptomatic bacteriuria) is crucial, since patients with asymptomatic bacteriuria cannot be expected to improve with antimicrobials, and thus their inclusion would bias the study towards finding no significant difference according to treatment duration. Although we anticipate that most subjects will have a urinalysis and urine culture performed, we have found that over 20% of subjects treated for UTI at the MVAMC are treated without one or the other test being obtained[42]. Accordingly, although we will record the results of any urine testing obtained, performance of urinalysis or culture will not be required for inclusion, although the study coordinator will work closely to increase the rates of urine culture ordering as part of enrolling patients through the involved clinics. Since UTI is largely a clinical diagnosis, with the culture being obtained mainly to help providers identify the causative pathogen and potentially adjust antimicrobial treatment, we believe that including patients without such urine testing (which reflects everyday practice) is appropriate.

Exclusion criteria were selected both to ensure patient safety and for statistical and practical reasons. Specifically, hospitalized patients are excluded because of their severity of illness, including a higher likelihood of bacteremia, which may require longer treatment duration and/or parenteral therapy. Patients previously enrolled in the study were excluded to ensure statistical independence. Patients prescribed less than 7 days of antimicrobial therapy are excluded since they will be difficult to identify before their treatment has ended. Patients prescribed more than 14 days of antimicrobial therapy are excluded because this generally indicates a patient being treated for suspected concomitant prostatitis, for which longer-duration therapy is beneficial[6].

2.e. Method of identifying potential subjects

Patients with UTI symptoms will be identified at the time of their initial clinic nursing visit, and the study coordinator will be notified and patient given the “opt out” flyer. The outpatient clinic areas of the MVAMC and MEDVAMC have been used for study recruitment in the past, with good results. The study coordinators will regularly meet with clinic staff to remind them of the UTI trial, and the principal investigator at the MVAMC and the co-investigator at the MEDVAMC will ask for cooperation form primary care clinicians through several methods, including emails, announcements at staff meetings, and other meetings.

For patients presenting in off-tour hours (evenings, nights, weekends, and holidays), we have established and piloted a system for rapidly identifying patients at the MVAMC who have recently been diagnosed with UTI. Using Vista, diagnostic codes relevant to UTI will be searched to identify potential participants. This is essential, since success of the trial will depend on identifying potential subjects, reviewing their eligibility status, contacting them, and enrolling them before they have completed 7 days of treatment. Using an "Outpatient Diagnosis/Procedure Code Search" function, we were able to electronically search for these ICD-10 codes among all outpatient encounters at the MVAMC, and can limit our searches to specific dates and clinics. In our pre-trial planning, we asked a sample of patients about participation in a hypothetical study. Over 50% indicated that they would be willing to participate, in principle, and over 1/3 were reasonably certain that they would participate.

Finally, we will ask the pharmacy service to generate a daily electronic report of prescriptions for 7-14 days of ciprofloxacin or trimethoprim/sulfamethoxazole. This list will be used as an additional method for identifying potential subjects that are not found via the ICD-10 codes or direct referral.

Currently, recruitment at the MVAMC is at 4.6 subjects/month. Assuming a 30% higher rate at the MEDVAMC, based on 33% more male UTI episodes annually and approximately 30% larger population served, we anticipate a recruitment rate at the MEDVAMC of 6/month. With a combined rate of 10.6/month, we anticipate 16.8 months to enroll the additional 179 subjects needed. With funding approved through December 2018, there is sufficient time to both enroll and follow the required number of subjects.

2.f. Patient contact and enrollment

After being identified as a potential subject (i.e., a man presenting with urinary symptoms) patients will be contacted by the study coordinator, either by phone or a letter sent to them if unable to reach by phone, and the study will be explained to them in detail. Eligible subjects willing to participate in the study will be consented and randomized to shorter vs. longer duration therapy, presuming that their provider subsequently ordered either ciprofloxacin or TMP-SMZ for 7 to 14 days. As mentioned above, eligible subjects can enroll by returning to the Minneapolis VAMC or the MEDVAMC for a study visit, via a home visit, or by mail. Home visits and mail enrollment are being offered as preliminary enrollment has been slower than anticipated, with the single largest reason for not enrolling being time constraints of scheduling a visit at the MVAMC or difficulty arranging transportation.

Home visits will be conducted in the greater Minneapolis/St. Paul or Houston metropolitan area by the study coordinator after review of the medical record for any safety issues, using methods used by Home and Community Care nurses at the Minneapolis VA. Any patient with a behavioral flag, history of inappropriate behavior, or other indications of a possible safety issue will NOT be eligible for home enrollment. The study coordinator will be reimbursed for mileage driven based on the current allowable federal reimbursement rate per local facility policy.

Mail enrollment will be offered to eligible subjects who live outside of the greater Minneapolis/St. Paul or Houston metropolitan area, or who prefer to not have an in-person study visit. Such subjects will be identified by the study coordinator, have the study explained to them in detail via telephone, and then have an informed consent and HIPAA authorization form sent to them. Subjects that were unable to be reached by phone will have a letter sent to them explaining that they may be eligible for a study. Study staff contact information will be included in that letter so they may call staff if interested in participating. To ensure there is no unnecessary time delay, the subject will also be sent the mail enrollment forms with the letter. Study staff will attempt to reach subject via telephone after sending the letter and mail enrollment forms. After receiving the signed forms from the subject, the research pharmacist will release the study medication to the subject. All shipments will be by overnight delivery, with the study coordinator remaining in contact as needed via telephone to answer any questions and to ensure that the subject understands when to begin the study medication.

Subjects not seen and evaluated on the day of treatment initiation will be contacted using the contact information listed in CPRS. In order to avoid "cold-calling" patients, all men presenting to the involved outpatient clinics with urinary symptoms will be provided an informational sheet regarding the study, and informing them that they may be contacted via telephone. A number to call to opt-out of such contact will be included.

2.g. Sampling of the intestinal microbiota (currently only offered at the MVAMC)

Subjects in the resistance sub-study will provide 2 samples of their intestinal microbiota, the first obtained via rectal swab performed by study staff at the time of enrollment at the MVAMC (or self-collected at home for mail enrollment), the second collected and submitted by mail 1 week after completion of study medication. Subjects enrolled via home visit can enroll in the sub-study using self-collected swabs. Although obtaining a rectal swab is mildly invasive and may cause slight discomfort, it has been performed in numerous research studies and is part of routine clinical activity in many U.S. hospitals[50]. We anticipated that only a minority of subjects would agree to this sampling; however, during our mock-enrollment exercise we were surprised to find that 95% of the 19 patients who agreed in principle to participate in the main trial also indicated willingness to participate in the resistance sub-study. Since it is unlikely that patients will feel confident in their ability to collect their own rectal swabs, for the second sample we will ask them to swab a stool specimen and return the swab in a provided mailer, similar to the well-established practice of screening for colon cancer using home-collected fecal occult blood cards.

Swabs will be delivered to and processed in the research laboratory of Dr. James Johnson, which has extensive experience in the isolation, characterization, and storage of enteric bacteria, especially *E. coli*. For this study, the required microbiological techniques are relatively straightforward, and the number of samples per week modest, such that the time and space required for this sub-study will not be onerous. Swabs will be entered into a registry as they are received, with a study number used to link clinical and laboratory information. Swabs will be plated onto plain and antimicrobial-supplemented modified Mueller-Hinton agar plates (i.e., Mueller-Hinton agar containing bile salts and neutral red), to

selectively recover and detect the lactose-fermentation characteristic of any Gram-negative bacilli in the specimen, both generically and specifically those resistant to the included antimicrobials (i.e., ciprofloxacin and TMP-SMZ).

From plates yielding growth of Gram-negative bacilli, 1 representative of up to 3 of the most-numerous colony morphologies per plate will be identified to the species level using the API-20E system (BioMerieux, Durham, NC). Susceptibility to 22 antimicrobial agents will be determined by disk diffusion, using methods, control strains, and interpretive criteria as specific by the Clinical and Laboratory Standards Institute. For each Gram-negative bacillus isolated, a semi-quantitative measure of growth will be recorded. Specimens will be scored for presence of resistant organisms using four different endpoints: (1) any detectable Gram-negative bacilli, (2) any Gram-negative bacilli resistant to ciprofloxacin (or TMP-SMZ), (3) density of ciprofloxacin (or TMP-SMZ)-resistant Gram-negative bacilli, and (4) a Gram-negative bacilli resistance score, which will be the sum of all unique resistance markers detected among the various Gram-negative bacilli isolated from the specimen.

2.h. Subject compensation

Subjects will receive $40 at the time of enrollment in the parent trial to compensate them for their travel and time commitment, regardless of whether they choose to participate in the resistance sub-study. Subjects enrolling in the resistance sub-study will receive $20 for the first fecal swab (obtained at the study visit/after mail enrollment), and an additional $30 for the second fecal swab. The higher compensation for the second swab reflects the extra effort and inconvenience subjects may experience with collecting and mailing the sample. This yields a maximum possible compensation of $90. Finally, patients who received their initial antibiotics through the VA pharmacy and were charged a co-pay will have this co-pay waived or refunded to them in accordance with VA policy.

2.i. Potential complications during therapy

During treatment for their UTI episode, subjects may experience a number of possible unexpected events, some of which could represent complications of the antimicrobials they are receiving. It is unknown whether treatment duration will affect the frequency or severity of any of these events. The most common adverse drug events associated with antimicrobial therapy include nausea, vomiting, diarrhea, dizziness, and headache. Less frequently encountered adverse drug events include allergic reactions (including rash, renal injury, and anaphylaxis), *C. difficile* infection, and increased or decreased effect of other medications, including warfarin. Because subjects are not being assigned to specific antimicrobials by study personnel, extensive discussion regarding the potential harms of the antimicrobial their provider prescribed is beyond the scope of the study. Instead, at the time of enrollment study personnel will briefly review potential generic harms of antimicrobials, will inform patients that treatment duration may or may not influence the probability of experiencing any harms, and will remind subjects to report any adverse events to their primary care provider or the

MVAMC or MEDVAMC Emergency Department. A further assessment of adverse drug events will be conducted during each study contact, with the details of any reported potential harms being recorded.

2.j. Follow-up and outcome assessment

Follow-up telephone contacts will occur at four time points, i.e., (i) on or about the time of medication cessation, (ii) 7 (± 2) days after medication cessation, (iii) 14 (± 2) days after medication cessation and (iv) 28 (± 2) days after medication cessation.

(i) The first contact is primarily to assess for medication adherence and any adverse drug effects. Study personnel will inquire regarding adherence and will screen for adverse drug events, both via an open-ended question and by specifically inquiring regarding the common symptoms of nausea, vomiting, diarrhea, dizziness, headache, and drug allergy. Subjects will be encouraged to refer to their symptom diary to ensure accurate recall.

(ii) At the second contact (7 days after medication cessation, either 7 or 14 days after the last dose of active antimicrobial), **resolution of UTI symptoms (the primary outcome)** will be assessed. Additionally, adverse events will again be assessed, subjects will be asked whether there has been interval retreatment for UTI, and which treatment (active or placebo) they think they received. Subjects in the resistance sub-study will be reminded during this call to obtain and return a stool swab in the provided mailer.

(iii) At the third contact (14 days after medication cessation, either 14 or 21 days after the last dose of active antimicrobial), resolution of UTI symptoms will again be assessed, and subjects will again be asked about adverse events and interval retreatment for UTI. After unblinding, the assessment occurring 14 days after the last dose of active antimicrobial will be used for analysis.

(iv) The fourth contact (28 days after medication cessation) will again include an assessment of adverse drug events and an inquiry as to any retreatment for UTI. All subjects having reported initial resolution of their UTI symptoms will be assessed for the secondary outcome of recurrent UTI, defined as recurrence of UTI symptoms and receipt of antimicrobial treatment.

If at any time subjects report new or unresolved UTI symptoms, symptoms consistent with *C. difficile* infection, or any other potential complication of antimicrobial therapy, they will be directed to seek medical care from their primary provider or the MVAMC or MEDVAMC Emergency Department. Severity of reported adverse events will be assessed and recorded (see section 2.m)

2.k. Safety and monitoring

Subject-specific safety monitoring will be performed via symptom review during the telephone contacts. Additionally, subjects will be given contact information for the primary

investigator and the study coordinator, and will be encouraged to contact study personnel if any suspected adverse events occur between scheduled study calls, in addition to contacting their primary care provider or the MVAMC or MEDVAMC Emergency Department. Serious adverse events will be reported by study personnel to the local Institutional Review Board (IRB) per MVAMC and MEDVAMC policy, and each such event will be reviewed by the IRB to determine whether it was potentially study-related. Monitoring to detect an excess of clinical outcomes or adverse events in either arm (including treatment failure for the initial UTI, recurrence of UTI, and adverse drug events, including *C. difficile* infection) will be performed by an independent DSMB that will include at least one biostatistician with clinical trial experience.

Study records will be maintained within the MVAMC and MEDVAMC on secure research drives, accessible only to the research team. Any paper records will be stored in a locked file cabinet in the principal investigator's locked office (3B-126) at the MVAMC, and in the office of the co-investigator at the MEDVAMC.

2.l. Definitions for safety and monitoring.

Adverse event: an adverse event (AE) is any untoward medical occurrence associated with the antimicrobial treatment, whether or not the event is considered related to the antimicrobial.

Adverse reaction: any adverse event caused by antimicrobial treatment.

Suspected adverse reaction (SAR): any adverse event for which there is a reasonable possibility that the antimicrobial treatment caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the antimicrobial treatment and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction," which means any adverse event caused by the antimicrobial treatment.

Serious adverse event (SAE) or *serious suspected adverse reaction*: An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator, or the IRB, it results in any of the following outcomes:

-Death
-Life-threatening adverse event
-Inpatient hospitalization for ≥ 24 hours or prolongation of an existing hospitalization
-Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Unexpected adverse event or *unexpected suspected adverse reaction*: an adverse event or suspected adverse reaction is considered unexpected or unanticipated if it is not listed in the protocol.

Life-threatening: An adverse event or suspected adverse reaction that places the subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.

2.m. Anticipated adverse events

The following lists anticipated adverse events, including some that are rare but serious:

-Diarrhea
-Nausea
-Vomiting
-Headache
-Drug allergy
-Pain at tendon insertions
-Blood sugar fluctuations among diabetic patients, including severe decreases leading to coma
-Psychiatric side effects such as disturbance in attention, memory impairment, and delirium
-Abdominal aortic aneurysm rupture

Note that failure to resolve UTI symptoms (i.e., not meeting the primary outcome), is not considered an adverse event, but rather will be recorded in the assessment of the primary outcome. Severity of adverse events will be determined using a severity scale (grade 0-5) adapted from the Common Terminology Criteria for Adverse Events, version 4.0, as listed below.

Adverse event	Grade				
	1	2	3	4	5
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated, intensive care unit utilization	Death
C. difficile infection (diarrhea	Increase of <4 stools per day over baseline;	Increase of 4 - 6 stools per day over	Increase of >=7 stools per day over baseline;	Life-threatening consequences;	Death

with a positive assay for *C. difficile*)	mild increase in ostomy output compared to baseline	baseline; moderate increase in ostomy output compared to baseline	incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	urgent intervention indicated, intensive care unit utilization, colectomy	
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	NA	NA
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	NA	NA
Drug allergy	Mild rash, no alteration of daily activities	Moderate rash, treated with topical or oral medications	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death

Hypoglycemia (among diabetic patients)	< lower limit of normal – 55 mg/dL	<55 – 40 mg/dL	<40 – 30 mg/dL	<30 mg/dL; life-threatening consequences, seizures, coma	Death
Hyperglycemia (among diabetic patients)	>ULN - 160 mg/dL	>160 - 250 mg/dL	>250 - 500 mg/dL	>500 mg/dL, life-threatening consequences	Death
Pain at tendon insertion	Mild pain	Moderate pain, limiting Instrumental ADL	Severe pain, limiting self care ADL	Complete tendon rupture, need for surgery	NA
Abdominal aortic aneurysm rupture	NA	NA	NA	Eminent or emergent rupture necessitating surgery	Death

2.n. Statistical methods

Primary outcome: resolution of UTI symptoms 14 days after completing active antimicrobial therapy. This outcome will be assessed in a binary manner. **Subjects with persistent UTI symptoms or having received further antimicrobials because of UTI symptoms will be considered to have not met the primary outcome, whereas those without persistent UTI symptoms and not having received further antimicrobials will be considered to have met the primary outcome**. The proportion of subjects meeting the primary outcome will be compared between the 2 treatment groups using a per-protocol analysis, with subjects analyzed according to which treatment they received. An intention-to-treat analysis will be performed as a secondary analysis. Subjects reporting taking 7 or fewer days of study medication will be analyzed as having received shorter-duration therapy, whereas subjects reporting taking 8 or more days of study medication will be analyzed as having received longer-duration therapy. Non-inferiority testing of the differences in the group proportions of symptom resolution will be done using a z-statistic derived by the adaptive percentage non-inferiority margin approach described by Laster and Johnson[51, 52]. Exploratory sub-group analysis using multiple logistic regression will be performed to assess outcomes stratified by the following putatively clinically relevant characteristics: catheter-associated UTI, functional or mechanical urinary tract obstruction, and diabetes. We anticipate that the proposed study will be under-powered for these analyses, and thus they will primarily be used as pilot data to identify potential specialized populations for future study.

Secondary outcome (1): recurrence rates at 28 days after completing study medication.
The proportion of subjects reporting recurrence of symptomatic UTI (defined as for the study entry criteria, but occurring after the primary outcome assessment) in each group will be calculated, along with corresponding 95% confidence intervals. Between-group comparisons will be made using the Chi-square test.

Secondary outcome (2): incidence of any adverse drug events in the 28 days after completing study medication.
The incidence of adverse drug events, including nausea, vomiting, diarrhea, dizziness, headache, drug allergy, and *C. difficile* infection, both individually and in aggregate, will be compared between treatment groups. For subjective symptoms, subjects will be asked to use their symptom diary to quantify the number of days they experienced each adverse event. Severity will be determined using a severity scale (grade 0-5) adapted from the Common Terminology Criteria for Adverse Events, version 4.0. Adverse events will be analyzed first as whether a subject experienced any adverse drug event vs. none (Chi-square test), and then by comparing the number of days on which each subjective event was experienced (Mann-Whitney U-test). Cases of suspected drug allergy will be reviewed by 2 Infectious Disease staff physicians (who are blinded to study group assignment) to assess: certainty of allergy diagnosis, relatedness to the prescribed antimicrobial, and clinical severity, based on information collected by study personnel and contained in the medical record. Subjects having a history of prior *C. difficile* infection will be recorded, but will not be excluded from analysis since these patients are a small but important subgroup, for which guidance regarding therapy duration is of particular interest. The randomization process should help ensure that there is no imbalance in such patients between treatment groups.

Secondary outcome (3): intestinal carriage of antimicrobial-resistant Gram-negative bacilli after completing study medication, as compared to a baseline sample taken early in treatment.
For the resistance sub-study, the outcomes of interest are (i) the proportion of subjects who develop newly detected intestinal carriage of antimicrobial-resistant Gram-negative bacilli between the baseline sample during treatment and the sample obtained 7 days after completing study medication (Chi-square test), (ii) the density of antimicrobial-resistant Gram-negative bacilli among samples with any growth (t-test or Mann-Whitney U-test, depending on the frequency distributions), and (iii) the overall resistance score, defined as the total number of antimicrobials which at least one of the isolated Gram-negative bacilli is resistant to (t-test or Mann-Whitney U-test).

2.o. Proposed timetable

Pre-study	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
IRB approval Create database and case-report	Purchase supplies Hire personnel	Patient enrollment Process rectal/stool	Patient enrollment Process rectal/stool	Patient enrollment Process rectal/stool	Complete enrollment Data analysis Presentation/

forms Educate and coordinate with clinic staff and providers	Patient enrollment Process rectal/stool swabs Assess rate of subject accrual	swabs	swabs	swabs	publication of results

3. Summary

We propose a single-center, randomized, double-blind, placebo-controlled trial of treatment duration for male UTI, which is a common but relatively understudied infectious disease in the VA population. The results of this study will allow clinicians to make an evidence-based treatment decision regarding an extremely common clinical condition among male veterans and non-veterans. This could help preserve the efficacy of valuable antimicrobials during a time of steadily increasing antimicrobial resistance and protect future male patients from insufficient or excessive antimicrobial therapy for their UTI.

4. References

1. Griebling TL. Urinary Tract Infection in Men. In: Litwin MS, Saigal CS, eds. *Urologic Diseases in America*. Washington, DC: US Government Printing Office; 2007:623- 645.

2. Griebling TL. Urologic diseases in america project: trends in resource use for urinary tract infections in men. *J Urol.*2005;173(4):1288-1294.

3. Drekonja DM, Rector TS, Cutting A, Johnson JR. Urinary Tract Infection in Male Veterans: Treatment Patterns and Outcomes. *Arch Intern Med.*2012:1-7.

4. Ulleryd P, Sandberg T. Ciprofloxacin for 2 or 4 weeks in the treatment of febrile urinary tract infection in men: a randomized trial with a 1 year follow-up. *Scand J Infect Dis.*2003;35(1):34-39.

5. Dow G, Rao P, Harding G, et al. A prospective, randomized trial of 3 or 14 days of ciprofloxacin treatment for acute urinary tract infection in patients with spinal cord injury. *Clin Infect Dis.*2004;39(5):658-664.

6. Lipsky BA. Prostatitis and urinary tract infection in men: what's new; what's true? *Am J Med.*1999;106(3):327-334.

7. Nicolle LE. A practical guide to antimicrobial management of complicated urinary tract infection. *Drugs Aging.*2001;18(4):243-254.

8. Drekonja DM, Johnson JR. Urinary tract infections. *Prim Care.*2008;35(2):345-367, vii.

9. Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. *N Engl J Med.*2005;353(23):2442-2449.

10. Kelly CP, Pothoulakis C, LaMont JT. *Clostridium difficile* colitis. *N Engl J Med.*1994;330(4):257-262.

11. Boucher HW, Talbot GH, Bradley JS, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis.*2009;48(1):1-12.

12. Gupta K, Hooton TM, Roberts PL, Stamm WE. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. *Arch Intern Med.*2007;167(20):2207-2212.

13. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis.*2011;52(5):e103-120.

14. Raz R, Chazan B, Kennes Y, et al. Empiric use of trimethoprim-sulfamethoxazole (TMP-SMX) in the treatment of women with uncomplicated urinary tract infections, in a geographical area with a high prevalence of TMP-SMX-resistant uropathogens. *Clin Infect Dis.*2002;34(9):1165-1169.

15. Talan DA, Stamm WE, Hooton TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis pyelonephritis in women: a randomized trial. *JAMA.*2000;283(12):1583-1590.

16. Peterson J, Kaul S, Khashab M, Fisher AC, Kahn JB. A double-blind, randomized comparison of levofloxacin 750 mg once-daily for five days with ciprofloxacin 400/500 mg twice-daily for 10 days for the treatment of complicated urinary tract infections and acute pyelonephritis. *Urology.*2008;71(1):17-22.

17. Hooton TM, Roberts PL, Stapleton AE. Cefpodoxime vs ciprofloxacin for short-course treatment of acute uncomplicated cystitis: a randomized trial. *JAMA.*2012;307(6):583-589.

18. Fosfomycin for urinary tract infections. *Med Lett Drugs Ther.*1997;39(1005):66-68.

19. Redelings MD, Sorvillo F, Mascola L. Increase in *Clostridium difficile*-related mortality rates, United States, 1999-2004. *Emerg Infect Dis.*2007;13(9):1417-1419.

20. McFarland LV. Update on the changing epidemiology of *Clostridium difficile*-associated disease. *Nat Clin Pract Gastroenterol Hepatol.*2008;5(1):40-48.

21. McDonald LC, Owings M, Jernigan DB. *Clostridium difficile* infection in patients discharged from US short-stay hospitals, 1996-2003. *Emerg Infect Dis.*2006;12(3):409-415.

22. Severe *Clostridium difficile*-associated disease in populations previously at low risk--four states, 2005. *MMWR Morb Mortal Wkly Rep.*2005;54(47):1201-1205.

23. Tamma PD, Turnbull AE, Milstone AM, Lehmann CU, Sydnor ER, Cosgrove SE. Ventilator-associated tracheitis in children: does antibiotic duration matter? *Clin Infect Dis.*2011;52(11):1324-1331.

24. Chastre J, Wolff M, Fagon JY, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA.*2003;290(19):2588-2598.

25. Nordenstam GR, Brandberg CA, Oden AS, Svanborg Eden CM, Svanborg A. Bacteriuria and mortality in an elderly population. *N Engl J Med.*1986;314(18):1152-1156.

26. Johnson JR, Clabots C, Kuskowski MA. Multiple-host sharing, long-term persistence, and virulence of *Escherichia coli* clones from human and animal household members. *J Clin Microbiol.*2008;46(12):4078-4082.

27. Johnson JR, Owens K, Gajewski A, Clabots C. *Escherichia coli* colonization patterns among human household members and pets, with attention to acute urinary tract infection. *J Infect Dis.*2008;197(2):218-224.

28. van de Sande-Bruinsma N, Grundmann H, Verloo D, et al. Antimicrobial drug use and resistance in Europe. *Emerg Infect Dis.*2008;14(11):1722-1730.

29. Barbosa TM, Levy SB. The impact of antibiotic use on resistance development and persistence. *Drug Resist Updat.*2000;3(5):303-311.

30. Johnson L, Sabel A, Burman WJ, et al. Emergence of fluoroquinolone resistance in outpatient urinary *Escherichia coli* isolates. *Am J Med.*2008;121(10):876-884.

31. Gerding DN, Johnson S, Peterson LR, Mulligan ME, Silva J, Jr. *Clostridium difficile*-associated diarrhea and colitis. *Infect Control Hosp Epidemiol.*1995;16(8):459-477.

32. Drekonja DM, Amundson WH, Decarolis DD, Kuskowski MA, Lederle FA, Johnson JR. Antimicrobial use and risk for recurrent *Clostridium difficile* infection. *Am J Med.*2011;124(11):1081 e1081-1087.

33. Fowler S, Webber A, Cooper BS, et al. Successful use of feedback to improve antibiotic prescribing and reduce *Clostridium difficile* infection: a controlled interrupted time series. *J Antimicrob Chemother.*2007;59(5):990-995.

34. O'Connor KA, Kingston M, O'Donovan M, Cryan B, Twomey C, O'Mahony D. Antibiotic prescribing policy and *Clostridium difficile* diarrhoea. *QJM.*2004;97(7):423-429.

35. Ludlam H, Brown N, Sule O, Redpath C, Coni N, Owen G. An antibiotic policy associated with reduced risk of *Clostridium difficile*-associated diarrhoea. *Age Ageing.*1999;28(6):578-580.

36. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the society for healthcare epidemiology of

America (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol.*2010;31(5):431-455.

37. Hepburn MJ, Dooley DP, Skidmore PJ, Ellis MW, Starnes WF, Hasewinkle WC. Comparison of short-course (5 days) and standard (10 days) treatment for uncomplicated cellulitis. *Arch Intern Med.*2004;164(15):1669-1674.

38. Stamm WE, McKevitt M, Counts GW. Acute renal infection in women: treatment with trimethoprim-sulfamethoxazole or ampicillin for two or six weeks. A randomized trial. *Ann Intern Med.*1987;106(3):341-345.

39. Sandberg T, Skoog G, Hermansson AB, et al. Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomised, open-label and double-blind, placebo-controlled, non-inferiority trial. *Lancet.*2012;380(9840):484-490.

40. Hooton TM. The current management strategies for community-acquired urinary tract infection. *Infect Dis Clin North Am.*2003;17(2):303-332.

41. Hooton TM, Stamm WE. Diagnosis and treatment of uncomplicated urinary tract infection. *Infect Dis Clin North Am.*1997;11(3):551-581.

42. Drekonja DM, Okoye NC, Kuskowski MA, Johnson JR. Appropriateness of urinary tract infection diagnosis and treatment duration. *Arch Intern Med.*2010;170(5):489-490.

43. Shehab N, Patel PR, Srinivasan A, Budnitz DS. Emergency department visits for antibiotic-associated adverse events. *Clin Infect Dis.*2008;47(6):735-743.

44. DeMets DL, Lan KK. Interim analysis: the alpha spending function approach. *Stat Med.*1994;13(13-14):1341-1352; discussion 1353-1346.

45. Arav-Boger R, Leibovici L, Danon YL. Urinary tract infections with low and high colony counts in young women. Spontaneous remission and single-dose vs multiple-day treatment. *Arch Intern Med.*1994;154(3):300-304.

46. Ferry SA, Holm SE, Stenlund H, Lundholm R, Monsen TJ. The natural course of uncomplicated lower urinary tract infection in women illustrated by a randomized placebo controlled study. *Scand J Infect Dis.*2004;36(4):296-301.

47. Ronald AR, Harding GK. Complicated urinary tract infections. *Infect Dis Clin North Am.*1997;11(3):583-592.

48. Ulleryd P. Febrile urinary tract infection in men. *Int J Antimicrob Agents.*2003;22 Suppl 2:89-93.

49. van Nieuwkoop C, van't Wout JW, Assendelft WJ, et al. Treatment duration of febrile urinary tract infection (FUTIRST trial): a randomized placebo-controlled multicenter trial comparing short (7 days) antibiotic treatment with conventional treatment (14 days). *BMC Infect Dis.*2009;9:131.

50. Johnson JR, Delavari P. Concurrent fecal colonization with extraintestinal pathogenic *Escherichia coli* in a homosexual man with recurrent urinary tract infection and in his male sex partner. *Clin Infect Dis.*2002;35(6):E65-68.

51. Laster LL, Johnson MF, Kotler ML. Non-inferiority trials: the 'at least as good as' criterion with dichotomous data. *Stat Med.*2006;25(7):1115-1130.

52. Laster LL, Johnson MF. Non-inferiority trials: the 'at least as good as' criterion. *Stat Med.*2003;22(2):187-200.