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Randomized, controlled trial to determine the efficacy of nutraceutical vs control as non-antibiotic prophylaxis for recurrent urinary tract infection in postmenopausal women using vaginal estrogen therapy

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A Introduction

A1 Study Abstract

The objective of this study is to determine the efficacy of D-mannose as a non-antibiotic prophylaxis for postmenopausal women on vaginal estrogen therapy (VET) with a history of symptomatic, culture-proven recurrent urinary tract infection (rUTI) by means of a randomized, controlled trial. Recurrent urinary tract infections have a significant impact on patient health, quality of life, and finances (personal and societal).

The most common uropathogen for both acute and recurrent UTIs is *Escherichia coli*.

Historically, patients with rUTI have been placed on long-term prophylactic antibiotics to prevent recurrence. Long term antibiotic use can lead to antibiotic resistance, collateral damage to normal flora, and organ damage, such as pulmonary and hepatic toxicity with long-term nitrofurantoin use. There is an increasing prevalence of antibiotic resistance of uropathogenic *E. coli* and other uropathogens. Antibiotic resistance and its consequences have resulted in a need for non-antibiotic prophylaxis regimens.

A growing body of literature supports the use of vaginal estrogen therapy as a first-line non-antibiotic UTI prevention strategy in postmenopausal women. While VET has been shown to significantly reduce the risk of rUTIs, some women continue to have rUTIs. Other non-antibiotic strategies have been utilized including D-mannose, a nutraceutical. Three prior studies examined D-mannose as an isolated therapy with promising results, but in our experience, a multimodal approach has often been needed. Therefore, additional studies, such as this proposed research, are needed to determine the potential additive effect of D-mannose as a non-antibiotic prophylaxis for postmenopausal women using vaginal estrogen therapy.

We plan to calculate the cumulative incidence of symptomatic, culture-proven urinary tract infections in a study population of postmenopausal women using vaginal estrogen therapy and randomized to additional prophylactic D-mannose treatment verses vaginal estrogen therapy alone. We will also compare the incidence of symptomatic, culture-proven urinary tract infections caused by uropathogens susceptible to D-mannose between the treatment and control groups. In addition to the randomized, controlled trial, we will enroll and follow an observational arm of women who meet the same inclusion and exclusion criteria of the RCT except are not able or willing to use vaginal estrogen therapy. We will also describe side effects of D-mannose and determine the discontinuation rate of therapy due to D-mannose side effects. This information will be imperative in establishing a multimodal non-antibiotic treatment regimen for recurrent urinary tract infection in postmenopausal women.

A2 Primary Hypothesis

The central hypothesis of the proposed research is D-mannose will be an effective and tolerable prophylactic treatment that helps further reduce rUTIs, especially those caused by *Escherichia coli*, in women using VET compared to VET alone. This hypothesis was formulated based on the existing D-mannose (and mannosides) literature and anecdotal clinical experience. However, this study is needed to provide the scientific evidence for D-mannose as part of a multimodal rUTI non-antibiotic treatment strategy.

A3 Purpose of the Study Protocol

The purpose of this study protocol is to describe how the clinical trial will be conducted and to ensure the safety of study participants and integrity of the data collected.

B Background

B1 Prior Literature and Studies

Recurrent urinary tract infections (rUTI) are a common and serious health problem for postmenopausal women. A woman's lifetime probability of experiencing a urinary tract infection (UTI) is 60% [1]. Approximately 11% of women in the United States report having a physician-diagnosed UTI each year [1]. The estimated annual societal cost in the United States to treat UTI in all patients is between $2.4 to over $2.6 billion [2, 3]. Up to 50% of women will have an additional UTI within the first year of initial infection [1, 4]. In a primary care setting, women 55 years and older who have a UTI have been shown to have a recurrence rate of 53% within one year [5]. Recurrent urinary tract infections have a significant impact on patients' quality of life and have a significant personal and societal financial burden. Office, urgent care, and emergency room visits for UTI both have a financial cost to the patient in addition to a negative impact on work productivity, time away from work, and personal and family responsibilities. The impact of rUTI is significant as well on a woman's quality of life. In a retrospective 2013 study of patients with a history of UTI, 78% of participants reported that their history of UTI impacted their sex life and 17% reported UTIs interrupted their sex lives [6]. **Recurrent UTIs have significant health, quality of life, and resource utilization implications. Treatment strategies to maximize prevention of UTI recurrences should be highly prioritized**.

The increasing prevalence of antibiotic resistance of uropathogenic E. coli supports the need for studies comparing non-antibiotic approaches to treating and preventing bacterial infections [7]. The efficacy of antibiotics to prevent rUTI in non-pregnant women was well established by a Cochrane review [8]. Currently, the American Congress of Obstetricians and Gynecologists (ACOG) recommends once daily treatment with one of a variety of antibiotics (nitrofurantoin, norfloxacin, ciprofloxacin, trimethoprim, trimethoprim-sulfamethoxazole, or another agent) for 6-12 months to decrease the recurrent risk of UTI by 95% [1]. While antibiotics are effective, they have significant side effects and the risk of antibiotic resistance. Vaginal and oral candidiasis and gastrointestinal upset are common among patients taking antibiotics. In one study, 27.2% of women taking nitrofurantoin for rUTI prophylaxis experienced side effects such as diarrhea, nausea, headache, skin rash, and vaginal burning [9]. In addition, some patients can experience dangerous allergic reactions such as severe anaphylaxis. Use of long-term antibiotic prophylaxis not only results in antibiotic resistance to the particular prophylactic agent, it can lead to higher rates of resistance to other antibiotics as well. In a 2012 study, trimethoprim-sulfamethoxazole prophylaxis resulted in increased resistance to trimethoprim-sulfamethoxazole, amoxicillin, and fluoroquinolones among *E. coli* isolated from commensal fecal flora and among uropathogenic *E. coli* [10]. **Due to concern for antibiotic resistance with long-term antibiotic use, there is a critical need to find non-antibiotic regimens that are safe and effective at preventing rUTI.**

Past studies evaluating alternatives to antibiotic therapy, such as cranberry and vitamin C, for rUTI have been met with mixed results. Cranberry juice and tablets have been studied by many different researchers with mixed results. The most recent Cochrane review on cranberry products and UTI in 2012 concluded cranberry products did not significantly reduce symptomatic UTI occurrence in women with recurrent UTI [11]. This is a different conclusion

than the 2008 Cochrane review on the same subject after two additional trials were added to the analysis. Similarly, ascorbic acid (vitamin C) is often recommended after in vitro studies suggested it had a bacteriostatic urinary effect with acidification of the urine [5]. Clinical evidence to support these in vitro studies is lacking based on few trials with contradictory results [4]. Vaginal estrogen has been well established to help decrease the rate of rUTI in postmenopausal women but recurrences still occur [5, 12]. **The results of these studies leave providers with a need for other alternatives to antibiotic therapy that are evidence-based.**

D-mannose shows promise as an alternative to antibiotic therapy. D-mannose is a sugar normally present in human metabolism. There are *in vitro* and *in vivo* studies to support the use of D-mannose to prevent UTI. D-mannose works as a FimH antagonist by saturating the tip of Type 1 fimbria of enteric bacteria to prevent adhesion to D-mannose moieties present on urothelial cells. *E. coli* is the most common enteric uropathogen and has evolved a Type 1 fimbria with high specificity to D-mannose [4, 5, 9, 13]. Type 1 fimbriae have been documented on certain *Enterobacteriaceae* family members including *Escherichia coli, Klebsiella pneumoniae*, *Shigella flexneri*, *Salmonella typhimurium*, *Serratia marcescens*, and *Enterobacter cloacae [14]*. *In vitro* studies have demonstrated the effectiveness of D-mannose on uropathogenic *E. coli*. Only one clinical study of sixty women using D-mannose from 22 to 54 years old has documented the number of urine cultures from various uropathogens [15]. **No clinical study has documented the frequency and resistance patterns of recurrent UTI in postmenopausal women on D-mannose. Obtaining and tracking this information would help better inform clinicians regarding the overall efficacy of D-mannose**. To date, there have been three studies published on D-mannose for rUTI prevention. In a 3-arm RCT comparing D-mannose as a single therapy, antibiotic prophylaxis with nitrofurantoin, and no prophylaxis for rUTI prevention, D-mannose was found to have the lowest recurrence rate (14.6%) [9]. This study evaluated 308 women >18 years old with acute and recurrent UTI and found a 14.6% recurrent UTI rate in subjects on D-mannose versus 20.4% in subjects on nitrofurantoin and 60% in subjects who did not receive prophylaxis. While there was not a statistical difference between reduction in recurrence rates between D-mannose and nitrofurantoin groups, there was a dramatic reduction between subjects receiving D-mannose versus those not receiving prophylaxis. Porru et al published a randomized cross-over trial assessing D-mannose versus trimethoprim/sulfamethoxazole in 60 participants between the ages of 22-54 years old, with an average age of 42 years old [15]. This study also demonstrated a benefit of D-mannose over antibiotics within the age range of their cohort. In the third published study, a pilot study was performed to evaluate D-mannose in combination with sodium bicarbonate, sorbitol, and silicon dioxide as a prevention strategy in comparison to an untreated group [16]. The overall UTI recurrence incidence was 4.5% in the D-mannose group versus 33.3% in the untreated group. Although these small trials have demonstrated promising benefits, **additional studies of D-mannose as part of a multimodal non-antibiotic treatment strategy are needed to confirm these findings before D-mannose can be routinely adopted in practice**.

Ideal non-antibiotic methods to prevent recurrent UTI should be better tolerated than long-term antibiotic prophylaxis. In one of the previously mentioned RCTs of D-mannose as an isolated therapy, patients taking D-mannose prophylaxis had a significantly lower risk of side effects than patients on nitrofurantoin prophylaxis (RR 0.276, 95% CI 0.132-0.574, p<0.0001) [9]. Another study found the frequency of mannose adverse effects was dose dependent, with doses >0.2 g mannose/kg body weight causing gastrointestinal disturbances and bloating in nearly half the participants [17]. Only 10% of study participants experienced similar symptoms at 0.15 g mannose/kg body weight. **Further studies are needed to assess the side effects and subsequent discontinuation rates of D-mannose before it can be recommended as a**

standard treatment. This study would provide the necessary information to address these knowledge gaps.

B2 Rationale for this Study

Currently, the mainstay of prophylactic treatment for rUTI is long term antibiotic therapy. Increased antibiotic use has led to increased antibiotic resistance. Long term use of antibiotics is associated with serious side effects, collateral damage to normal flora, and antibiotic resistance. At the time of literature review, there were three published studies examining D-mannose alone to prevent rUTI. The two randomized, controlled trials evaluated D-mannose as an isolated therapy, and in one of the randomized, controlled trials, the average patient age was 42 years old, with the oldest enrolled patient being 54 years old. The study populations reported on so far may be very different than the postmenopausal cohort in the proposed study. Postmenopausal women are at the highest cumulative risk for rUTIs. In the third study, D-mannose was combined with sodium bicarbonate, sorbitol, and silicone dioxide (none of these have been shown to reduce the risk of UTI/rUTI). In clinical practice, a multimodal approach to rUTI prevention is typically utilized when non-antibiotic agents are not; D-mannose is not typically used alone. Vaginal estrogen therapy (VET) is considered by many as a standard first line prevention for rUTI in postmenopausal women when there is not a contraindication. Our study would help determine the potential additive effect of D-mannose as adjunct therapy with VET. This study seeks to further our knowledge towards precision rUTI prevention and the goal of using non-antibiotic regimens as the mainstay of prophylactic treatment for rUTI.

C Study Objectives

C1 Primary Aim

To compare the cumulative incidence of symptomatic, culture-proven urinary tract infections in postmenopausal women with a history of rUTI on vaginal estrogen therapy randomized to receive prophylactic D-mannose versus women using vaginal estrogen therapy alone (control).

C2 Secondary Aims

There are multiple secondary aims of this study:

- To compare the incidence of symptomatic, culture-proven urinary tract infections caused by all uropathogens potentially susceptible to D-mannose therapy in women receiving D-mannose and the control group. We will also compare these findings to the incidence of symptomatic, culture-proven urinary tract infections caused by uropathogens susceptible to D-mannose therapy in the absence of vaginal estrogen therapy (observational arm).
- To describe the side effects of D-mannose and determine the incidence of discontinuation of therapy due to side effects.
- To compare the cumulative incidence of symptomatic, culture-proven urinary tract infections between women receiving prophylactic D-mannose treatment alongside vaginal estrogen therapy verses women receiving prophylactic D-mannose treatment whom are not on vaginal estrogen therapy (observational arm).
- To gain information to use in designing future rUTI studies.

C3 Rationale for the Selection of Outcome Measures

The proposed RCT examining D-mannose efficacy in postmenopausal women with a history of rUTI on vaginal estrogen therapy is innovative. To date, no study has examined D-mannose in the context of use with other therapies. The primary and secondary outcomes of this study are

expected to add greatly to the understanding of non-antibiotic regimens as the mainstay of prophylactic treatment for rUTI in postmenopausal women. In addition to the randomized, controlled trial, the observational arm of the study will help track and verify outcomes in participants with rUTI who either have a contraindication to vaginal estrogen use or chose to not use vaginal estrogen therapy. Use of other agents (cranberry extract, Vitamin C, etc.) will be recorded and controlled for.

D Investigational Agent

D1 Preclinical Data

Our study will evaluate the impact of D-mannose in patients already using or willing to start VET for the prevention of rUTI. Since use of VET as an accepted and proven strategy to reduce rUTI in postmenopausal women is part of the inclusion criteria for the RCT portion of this study, D-mannose is the only "study drug" being evaluated in this study. Vaginal estrogen therapy (VET) has been well established to help decrease the rate of rUTI in postmenopausal women [5, 12]. VET provides hormone in a low dose to local vaginal tissue with minimal systemic absorption [18]. Studies have shown that low dose VET, as used with rUTI therapy, does not cause sustained serum estrogen levels outside the normal menopausal range [18]. For these reasons, as a non-antibiotic treatment, vaginal estrogen should be included as a standard treatment in any study analyzing rate of recurrent UTI in postmenopausal women without contraindications. The prior small trials evaluating D-mannose did not include VET in all patients as a standard of care.

The female pelvic medicine and reconstructive surgery (FPMRS) division has a strong track record of recruiting patients into clinical research and into studies for rUTI. In the eight weeks prior to submission of this research protocol, our division has seen an average of four new and/or referral patients for rUTI per week. This number does not include preexisting patients with a new diagnosis of rUTI. In the previous rUTI studies in our division, patients with rUTI have been very willing to participate in research for rUTI therapy, with very few declining participation. Taking into consideration exclusion criteria the feasible enrollment is estimated to be ten patients a month in this study, achieving enrollment of one hundred twenty study patients in the randomized, controlled trial within twelve months of initiating study enrollment.

D2 Dose Rationale and Risk/Benefits

The RCT treatment arm of this study will use 2 grams of D-mannose powder dissolved in water once daily. The observational arm of this study will use either the same 2 grams of D-mannose powder daily as used in the RCT treatment arm or two 500 mg D-mannose capsules every 12 hours (for a total of 2 grams every day).

The prior studies previously mentioned evaluating D-mannose each used a different dose. The first RCT used 2 grams of D-mannose dissolved in 200 ml water [9]. In the other RCT, participants were started on D-mannose 1 gram three times daily for two weeks (as treatment for acute urinary tract infection) followed by 1 gram twice daily [15].

To date the FPMRS division clinical practice has been to recommend either two 500 mg capsules of D-mannose twice daily or 2 grams (1 teaspoon of powder) dissolved in water once daily. The powdered D-mannose will be used for the randomized, controlled trial as pure D-mannose can be dissolved in water and administered without the additional additives required to encapsulate D-mannose. Using the powdered D-mannose limits the possible additional side effects due to additives. For the observational arm, the powdered D-mannose will be strongly recommended, but patients will be allowed to purchase either the powder or capsules and formulation will be tracked.

Alton et al found the frequency of mannose adverse effects is dose dependent, with only 10% of their study subjects experiencing gastrointestinal disturbances and bloating at 0.15 g mannose/kg body weight [17]. Using the numbers from Alton's study, if a study participant weighs 100 pounds then the participant would have a 10% chance of experiencing gastrointestinal side effects if a mannose dose of 6.8 grams were used, which is a much larger dose than the 2 grams per day in this study protocol. This same study also found that regardless of the mannose dose used in their study (which ranged from 0.1-0.25 g mannose/kg body weight), participants' blood glucose levels were stable and within the normal physiologic range. This study protocol uses a smaller dose of D-mannose that Alton's study: for a 100 pound study participant, the 2 grams/day total dose would equal 0.044 g D-mannose/kg body weight. In order to exceed the maximum D-manose dose in Alton's study (where the blood glucose level was still not affected), a participant in our study would have to weigh less than 18 pounds, which is considerably less than the weight of a post menopausal woman.

E Study Design

E1 Overview or Design Summary

In the RCT portion of the study, we will enroll 120 postmenopausal female patients with rUTI (either new patients or existing patients with a new diagnosis of rUTI) as defined by ≥ 2 culture-proven UTI episodes in the last six months or ≥ 3 culture-proven UTI episodes in the last twelve months. Each subject must have at minimum a documented culture-proven UTI with a D-mannose susceptible microbe. Subjects will be randomized to vaginal estrogen therapy (VET) plus D-mannose versus VET alone and will be followed for 90 days. All RCT participants will have a minimum four-week run-in period with VET prior to study day 1. Subjects previously on VET will not require a run-in period as long as the four-week minimum on VET has been met. According to the North American Menopause Society, the effect of vaginal estrogen therapy is rapid and can generally be observed within four weeks of treatment onset with cream, ring, or tablet forms of vaginal estrogen therapy [19]. Subjects randomized to treatment with D-mannose will receive their D-mannose as part of the study so that D-mannose treatment is controlled for the use of pure D-mannose powder. A study period of 90 days was determined as an adequate study period as prior publications have demonstrated that UTI recurrence most commonly occurs within two months [9, 20, 21].

In the observation arm of the study, we will enroll 60 postmenopausal women with rUTI (either new patients or existing patients with a new diagnosis of rUTI) as defined by ≥ 2 culture-proven UTI episodes in the last six months or ≥ 3 culture-proven UTI episodes in the last twelve months. Each study participant must have at minimum a documented culture-proven UTI with a D-mannose susceptible microbe. These patients must meet all of the same inclusion and exclusion criteria as the randomized, controlled trial subjects with the exception of not using VET due to a contraindication or preference not to use VET. Participants in this arm of the study will be followed for three months after starting D-mannose. For the observational arm, the powdered D-mannose will be strongly recommended, but patients will be allowed to purchase either the powder or capsules and formulation will be tracked.

E2 Subject Selection and Withdrawal

2.a Inclusion Criteria

For the RCT arms of the study, the following inclusion criteria will apply:

a. Postmenopausal women with recurrent UTI
    i. Recurrent UTI defined as:

1. ≥ 2 symptomatic, culture-proven UTI in 6 months *OR*
2. ≥ 3 symptomatic, culture-proven UTI in 12 months

ii. Postmenopausal defined as no menses for at least 12 months or surgical menopause

b. At least one documented prior uropathogen susceptible to D-mannose
c. Using VET for a minimum of two weeks at enrollment (with plan for four weeks prior to study day 1)

Inclusion criteria for the Observational arm of the study are the same with the exception of item 'c.' above (using VET) as participants will not be on vaginal estrogen therapy.

2.b Exclusion Criteria

For the RCT arms of the study, the exclusion criteria are as follows:

a. Not postmenopausal
b. Currently on daily antibiotic UTI prophylaxis
    i. If this is the only exclusion criteria met, a woman could be cleared for inclusion in study/enrollment after a 2 week washout period occurs prior to inclusion in the study (RCT or Observational arm)
c. Complicated UTIs
    i. known renal tract anomaly
    ii. inability to empty bladder due to neurologic causes
    iii. performs self-catheterization or has an indwelling catheter
d. Patients with incomplete bladder emptying (defined as PVR > 150 cc when minimal voided volume is >150 cc)
e. Known contraindication to VET unless approved by patient's oncologist, oncologic surgeon, or primary care physician
    i. History of or current endometrial cancer without approval of patient, patient's oncologist, oncologic surgeon, or primary care physician to use vaginal estrogen after counseling
    ii. History of estrogen sensitive breast cancer without approval of patient, patient's oncologist, oncologic surgeon, or primary care physician to use vaginal estrogen after counseling
f. History of interstitial cystitis/painful bladder syndrome
g. Urothelial cancer
h. Non-English speaking
i. Enrolled in other clinical trials for UTIs
j. Currently using D-mannose or Methenamine for UTI prevention

Exclusion criteria for the Observational arm of the study are the same with the exception of item 'e.' above (known contraindication to VET) as participants will not be on vaginal estrogen therapy.

2.c Ethical Considerations

Inclusion of Women and Minorities

The patient sample for this study is limited to women as rUTI is most common in postmenopausal women. Men with UTI are by definition complicated and would not meet the inclusion criteria. In addition, men do not go through menopause and do not have a vagina and would thus not be treated with VET. All four locations of the Washington University Physicians

Women's Center for Bladder and Pelvic Health are located in the St. Louis Metropolitan area, which is the 20th largest metropolitan statistical area in the nation [22]. As of 2015, of the 2.8 million people in the St Louis Metropolitan Area, approximately 510,000 individuals identify as Black and an additional 81,000 identify as Hispanic [22]. The main office location for the Women's Center for Bladder and Pelvic Health is located in St. Louis City where approximately 50% of residents are Black or African American [23]. Six percent of the citizens of the St. Louis Missouri and Illinois Metropolitan area are non-English language speakers, which is considerably lower than the national average of 21.5% [22]. For this reason, even though this study is limited to English speaking patients, we do not anticipate this will negatively impacting the racial/ethnic minority representation in our study.

Inclusion of Children

We will not include children younger than 18 years old in our study. Our criteria require postmenopausal status for inclusion into this study.

2.d Subject Recruitment Plans and Consent Process

All new or newly diagnosed women with rUTIs receiving care at the Washington University Physicians Women's Center for Bladder and Pelvic Health who meet screening criteria will be approached. Existing rUTI patients that are not currently using D-mannose may also be approached. Enrollment may occur at any of the practice's four outpatient locations (Washington University Physicians' offices at: Center for Outpatient Health, Missouri Baptist Medical Center Women's Wellness Center, Center for Advanced Medicine - South County, and Barnes Jewish West County Medical Building). This study will involve only adult, postmenopausal women as rUTI predominantly affect this population. Recurrent UTI in men would be considered complicated and would not be addressed with a prophylactic treatment like d-mannose. In addition, men do not go through menopause and do not have a vagina and would thus not be treated with VET. Women meeting study criteria will be approached by a member of the research team for consent at the conclusion of the clinical visit during which the patient is screened eligible for the study. Women who meet RCT eligibility criteria except for a minimum of four weeks of VET use but are being started on VET for clinical indications will followup in approximately four weeks for a routine follow up clinical visit. These patients will be offered enrollment in the study at that time if they have been using VET for a couple weeks even if they aren't at the four week mark yet. However, their study day one cannot occur until they have been using VET for four weeks.

Eligible women interested in the study will have the study explained to them, the consent reviewed, and questions reviewed in a confidential manner in a private room. If the potential research participant would like to take the consent home with them to review before their next office appointment that will be allowed.

The following methods may be used to inform the public about our research study: letter and/or email to local and/or referring providers, Twitter, study flyers, news story or segment. Inclusion in this list does not guarantee that the method will be used, but instead allows for the method to be used. All of the methods would require a potential research participant to be referred to the office for care of their rUTI. A "Dear Doctor" letter and/or email to local and/or referring providers can be sent to referring providers to inform them of ongoing recurrent UTI research at the Washington University Physicians Women's Center for Bladder and Pelvic Health. Twitter posts will be limited to IRB-approved tweets and images. The Twitter posts will be able to link to the Washington University Physicians Women's Center for Bladder and Pelvic Health website (at urogyn.wustl.edu) to find out more about the Washington University Physicians Women's Center for Bladder and Pelvic Health. A study flyer would provide the Washington University Physicians Women's Center for Bladder and Pelvic Health name and phone number with information describing rUTI and that our research team is trying to

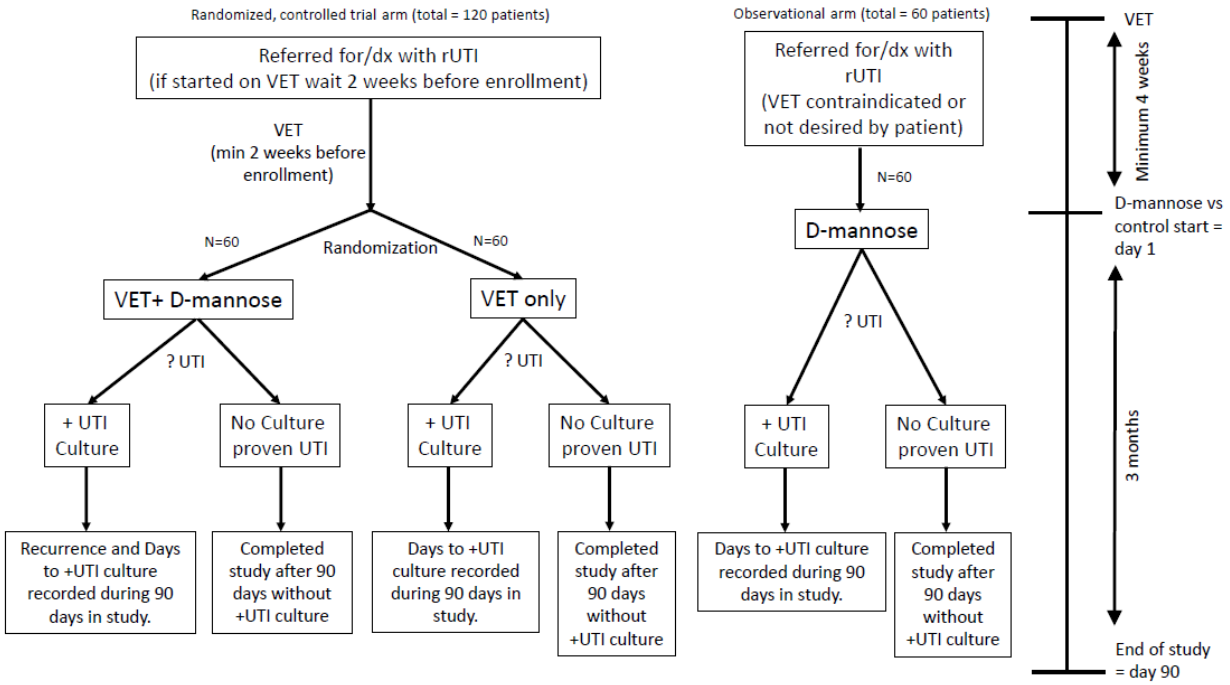
determine the beneft of non-antibiotic treatments to prevent recurrent urinary tract infections in menopausal women. These flyers could be distributed to local and/or referring providers with the “Dear Doctor” letter to display in their waiting room or offices. The flyer could also be displayed in break rooms at Barnes Jewish Hospital, Center for Outpatient Health, Center for Advanced Medicine, St. Louis Children’s Hospital, and St. Louis College of Pharmacy. The research team would like the opportunity to work with the Washington University School of Medicine Medical Public Affairs office to spread word about this study via a local television or radio as part of a news story or segment. The principal investigator would work with the Medical Public Affairs office to contact specific local reporters and pitch the story to them. There will not be an official news release. If any current subjects would like to share their experiences in the trial with the media for a news story or segment then all HIPAA protocol will be complied with. Subjects would be made aware that their care and participation in the trial would not be affected by their voluntary decision to share their experience, and that they do not have to share their story if they do not wish to.

2.e Randomization Method and Blinding

For the randomized, controlled trial portion of the study:
Allocation concealment will be in place to ensure the individual enrolling the subject into the study has no a priori knowledge of group assignment. Block randomization will occur with randomly mixed block sizes of 2, 4, and 6. The allocator will hide block size from the executer in order to prevent the executor from predicting the next assignment. Randomization will be carried out by having a piece of paper that has the phrase “Intervention (Nutraceutical + VET)” or “Control (VET only)” placed inside an envelope. The outside of the envelopes will be labeled with the sequence number. After a patient has been enrolled into the study and consented, the next sequence numbered envelope on the stack will be opened to determine the study group that the subject will enter.

For the observational portion of the study, no randomization or blinding will occur.

The diagram below outlines randomization details:



2.f Risks and Benefits

D-mannose is a nutraceutical sold over the counter solely for the prevention of UTI. It falls under the category of dietary supplements regulated by FDA under the Dietary Supplement Health and Education Act of 1994 (DSHEA) [24]. This is a different set of regulations than the regulations used for conventional food and drug products [24]. Risks associated with D-mannose use are believed to be mainly related to gastrointestinal side effects (bloating, loose stool, and diarrhea). Other possible side effects can include but are not limited to hypersensitivity or allergic reactions (acute skin or pulmonary changes). These side effects would be the same for subjects enrolled in this study as for patients not enrolled in this study that we recommend D-mannose prophylaxis to on a daily basis. Other potential risks of the study include participants may feel uncomfortable or be inconvenienced by filling out study related papers. They may prefer to obtain treatment for UTI-like symptoms from an urgent care or other outside provider. However, all rUTI patients in our office (no matter if enrolled in the study or not) are instructed to call our office when they experience UTI-like symptoms since our clinical practice is to obtain (when possible) urine cultures prior to initiating treatment and to have our patients followed primarily through our office for their urinary tract infections.

A potential benefit is the decreased incidence of rUTI among patients randomized to D-mannose in the randomized, controlled trial portion of the study or patients in the observational arm of the study. Otherwise, benefits for the participant are no different than if they were recommended D-mannose as part of their routine clinical care as a patient without being enrolled in the study. There is a global benefit of increased knowledge surrounding the utility of non-antibiotic prophylaxis for rUTI.

2.g Early Withdrawal of Subjects

At the time of consent, participants will be informed that their participation in this research is voluntary and that they may discontinue participation without penalty at any time.

2.h When and How to Withdraw Subjects

Withdrawal of subject as the result of subject decision:

- A subject enrolled in the study may decide to withdraw from the research at any time by notifying the principle investigator and/or another member of the research team by calling the office at 314-747-1402 and letting the office staff know she needs to speak to the principle investigator and/or member of the research team. The investigator speaking with the subject will clarify whether the subject wishes to withdraw from all components of the trial or only from a particular component of the trial. If the latter is desired, then follow-up data collection activities, for which the subject perviously gave consent may continue.
- If a subject withdraws from the study then a member of the research team will ask the subject if she is willing to complete an study exit survey and/or the information that would have been gathered at the originally planned 3 month follow up appointment. This exit survey and 3 month follow up visit information may be obtained by appointment, by phone, or by mail.

Withdrawal of subject as the result of investigator decision:

- If an investigator terminates a subject's participation in the trial, the investigator should explain to the subject the reasons for this action and, as appropriate, other treatment options.
- If subjects were to have a serious adverse reaction to the medication, the investigator would recommend discontinuation of medication.

- An investigator may terminate a subject's participation in the study to protect a participant from excessive risk or risk with demonstrated lack of benefits or to maintain integrity of the data (for instance if a participant is not following study procedures or may be deliberately providing false information).
- If a subject is treated for an acute UTI during the 90 day study period without having an urine culture performed then data will be assessed both as if she did and did not have an acute UTI. She does not need to be withdrawn from the study as of the date of treatment of subjective UTI.. Antibiotics used for reasons other than UTI do not require subject withdrawal. Data obtained for any subject to the point of study withdrawal may be used in the study.
- If a subject is withdrawn from the study then a member of the research team will ask the subject if she is willing to complete an study exit survey and/or the information that would have been gathered at the originally planned 3 month follow up appointment. This exit survey and 3 month follow up visit information may be obtained by appointment, by phone, or by mail.
- Subjects lost to follow up will be presumed to not have an acute urinary tract infection from the time of last contact.

2.i Data Collection and Follow-up for Withdrawn Subjects

Data collected prior to participant withdrawal may be retained and used including Protected Personally Identifiable Information (PPII) in a manner that is consistent with the study purpose and procedures as noted in this protocol and supplemental documents, unless the study participant notifies the primary investigator that all participant information must be removed from the study. All subjects that withdraw or are withdrawn from the study will be asked if they would be willing to complete an exit survey or the questions from the 3 month follow up visit form. The purpose of the exit survey would be to obtain information such as the "spot checks" that are built into the 3 month follow up/end of study form and to find out more information about why the subject decided to withdraw. This exit survey would be completed in clinic (at their next scheduled appt), by phone, or by mail.

E3 Study Drug

3.a Description

D-mannose is a nutraceutical available over the counter at pharmacies, supermarkets, and supplement stores and for purchase online. D-mannose is a sugar normally present in human metabolism. It falls under the category of dietary supplements that is regulated by FDA under the Dietary Supplement Health and Education Act of 1994 (DSHEA) [24]. This is a different set of regulations than the regulations used for conventional food and drug products [24]. Studies have shown that D-mannose saturates FimH adhesin located at the end of type 1 fimbria of enteric bacteria on the epithelium of the urinary tract [5, 7, 25, 26].

3.b Treatment Regimen

To date the FPMRS division clinical practice has been to recommend either two 500 mg capsules of D-mannose every 12 hours or 2 grams (1 teaspoon of power) dissolved in water once daily. The RCT treatment arm of this study will use 2 grams of D-mannose powder dissolved in water once daily. The observational arm of this study will use either the same 2 grams of D-mannose powder daily as used in the RCT treatment arm or two 500 mg D-mannose capsules every 12 hours (for a total of 2 grams every day). The instructions to patients on their patient information handout will be as follows:

- "Powder specific instructions: Dissolve one (1) teaspoon of the nutraceutical powder in at least 200 ml of water one time a day. (200 ml of water = 6.7 fluid ounces). Please attempt to take doses of the nutraceutical powder dissolved in water approximately 24 (twenty-four) hours apart. It is ok if you use a larger volume of water to dissolve the powder, but do not use any less than 200 ml of water. You MUST drink all of the water that the powder is dissolved in."
- "Capsule specific instructions: Take two 500 mg capsules (total of 1000 mg dose) every 12 hours."

The powdered D-mannose will be used for the RCT as pure D-mannose can be dissolved in water and administered without the additional additives required to encapsulate D-mannose. Using the powdered D-mannose limits the possible additional side effects due to additives. For the Observational arm, the powdered D-mannose will be strongly recommended, but patients will be allowed to purchase either the powder or capsules and formulation will be tracked.

3.c Method for Assigning Subjects to Treatment Groups

If a participant is using VET and therefore eligible for the RCT portion of the study, they will be randomized according to the preset randomization allocation to determine if she is in the treatment arm of the randomized control trial (D-mannose plus vaginal estrogen therapy) or the control arm of the randomized controlled trial (vaginal estrogen therapy only).

If a patient is not using VET but meets all other study requirement then she would be eligible only for the Observational arm of the study.

3.d Preparation and Administration of Study Drug

For the treatment arm of the RCT, the D-mannose powder will be ordered and distributed by the research team. The study team has selected NOW D-mannose pure powder as the D-mannose to be used in the RCT. The manufacturer label will be covered up/removed and a study label stating contents of a nutraceutical will be used to maintain patient blinding to which nutraceutical is being used.

For both arms of the RCT, the VET may be renewed or prescribed by a physician on the research team per routine clinical care. The patient will then pick up their prescription (vaginal cream, ring, or tablet) from their pharmacy of choice for continued use.

For the Observational arm of the study we will recommend the powdered D-mannose, but since participants will be purchasing their own D-mannose in the Observational arm they will be instructed to purchase either NOW D-mannose pure powder or NOW D-mannose 500 mg capsules. NOW will be the only brand patients are instructed to purchase, and example labels will be available for viewing by participants in the Observational arm to confirm they purchase the recommended D-mannose. We will communicate with the participants after they purchase their D-mannose of choice to record if powder or tablet and brand/manufacturer.

Medication (D-mannose, VET) will be self-administered by the patient. For patients using VET they will continue to use their VET as previously prescribed prior to enrollment in this study. On study day 1, if the patient is in an arm using D-mannose they will begin self administering D-mannose according to the instructions on the patient information handout. These instructions are as follows:

- "Powder specific instructions: Dissolve one (1) teaspoon of the nutraceutical powder in at least 200 ml of water one time a day. (200 ml of water = 6.7 fluid ounces). Please attempt to take doses of the nutraceutical powder dissolved in water approximately 24 (twenty-four) hours apart. It is ok if you use a larger volume of water to dissolve the powder, but do not use any less than 200 ml of water. You MUST drink all of the water that the powder is dissolved in."

- "Capsule specific instructions: Take two 500 mg capsules (total of 1000 mg dose) every 12 hours."

3.e Subject Compliance Monitoring

All participants will be asked to complete a simple weekly study diary. The 90 days of the study will be divided into 12 full weeks and 1 partial week for a total of 13 weeks of the diary. In the diary, one of the questions asked for each week of the study is number of doses missed each week. This study will use a text message service through the REDCap (Research Electronic Data Capture) database. During the 90 day study period, all study participants in both the RCT and Observational arms will receive text message reminders to complete their study diary for the week on study days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, and 90. This same text message will ask patients if any new symptoms were experienced in the past week and request a "Yes" or "No" response via text message. Study participant responses will automatically be entered in the REDCap (Research Electronic Data Capture) database for this study. If the study participant sends a "Yes" response by text message a member of the research team will contact the patient to follow up for more information about the symptoms. If they declined text messaging when enrolling in the study, the study participant will receive periodic phone calls with reminders to complete their study diary. The subject will be instructed to bring their study diary to each appointment.

Six weeks into the study, each study participant will receive a phone call from a member of the research team. During this phone call questions referencing compliance with completing the study diary, taking study medications as prescribed, if they have been treated for a UTI by anyone outside of our office during the study period, side effects noted, and if they have any questions to be answered will all be addressed.

All participants will be seen by a physician and research staff after 3 months in the study (when they have completed their 90 days in the study). At this visit, participants will be asked to bring their study diary and any unused D-mannose to their appointment (including empty bottles if more than one bottle was provided to a patient in order for a patient to have a 90 day supply of D-mannose). A 3 month follow up survey and exit survey will be given to the participant to fill out at the 3 month follow up appointment. Depending on participant convenience, this 3 month follow up survey can be completed at their appointment, by phone, or by mail. The survey will include questions on medication adherence. The study team will review the chart for any adverse events or UTIs not previously reported. Participants will fill out a questionnaire at this appointment to confirm the same. If a participant does not show for their 3 month follow up appointment then a member of the research team will attempt to contact the participant to reschedule this appointment. If a participant does not bring their study drug to their 3 month follow up, or if the participant is lost to follow up, then a reasonable attempt will be made to contact the patient and ask her to bring the study drug to the office. If a participant is lost to follow up then a reasonable attempt will be made to see if the participant is willing to complete a 3 month follow up survey and/or exit survey over the phone or by mail. If the participant does not complete all 90 days of the study, or if they forget to bring their study diary to their 3 month follow up appointment, then she will be offered the alternative of mailing or faxing her study diary to the office. If a participant completed the study early then she will be asked if she is willing to complete the 3 month follow up appointment information and exit survey at their next office visit, by phone, or by mail.

3.f Packaging

D-mannose is the only study drug and will be in its original container from the manufacturer. The study team has selected NOW D-mannose pure powder as the D-mannose to be used in the

RCT. The patient label for the treatment arm of the randomized, controlled portion of the study will be updated to maintain blinding of the patient to which nutraceutical is being studied.

Planned label for the treatment arm of the randomized, controlled trial is as follows:

Study Name: Nutraceutical efficacy in rUTI
IRB Number: XXXXX
Principal Investigator: Jerry Lowder, MD, M.Sc.
Office Phone: (314)747-1402

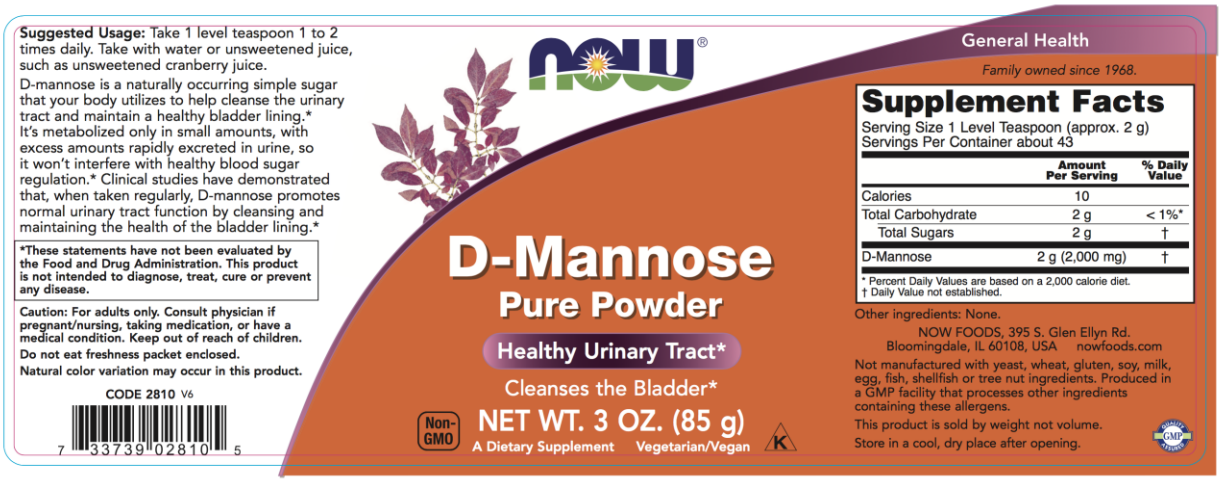
Participant Name: XXXX XXXXX

Dose and Frequency: Dissolve one (1) level teaspoon of the nutraceutical powder in at least 200 ml of water one time a day. (200 ml of water = 6.7 fluid ounces). Please attempt to take doses of the nutraceutical powder dissolved in water approximately 24 (twenty-four) hours apart. You may use a larger volume of water to dissolve the powder, but do not use any less than 200 ml of water. You MUST drink all of the water that the powder is dissolved in.

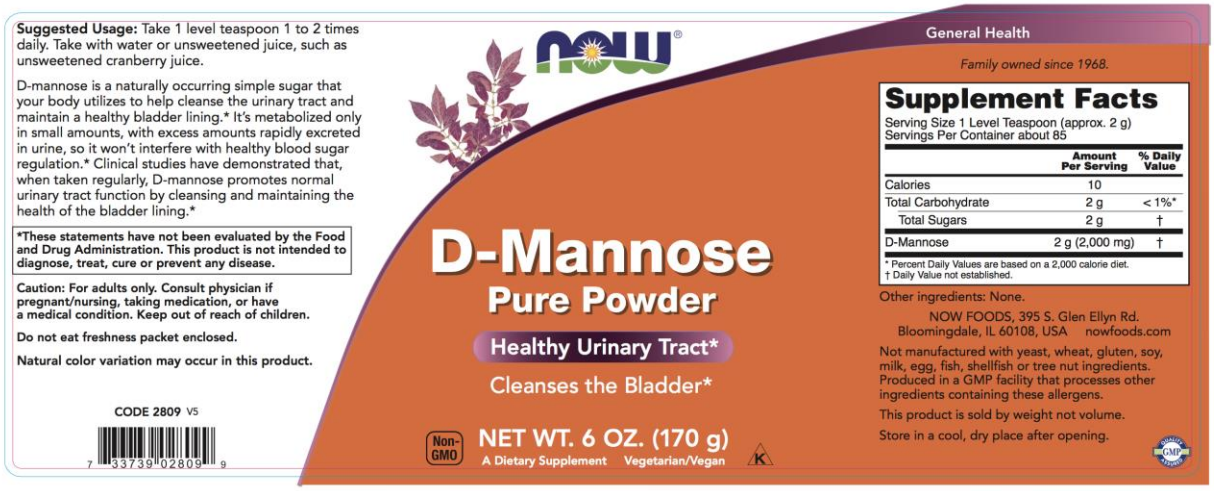
Caution: New Drug – Limited by United States law to investigational use.

Participants in the Observational arm will be instructed to purchase either NOW D-mannose pure powder or NOW D-mannose 500 mg capsules.

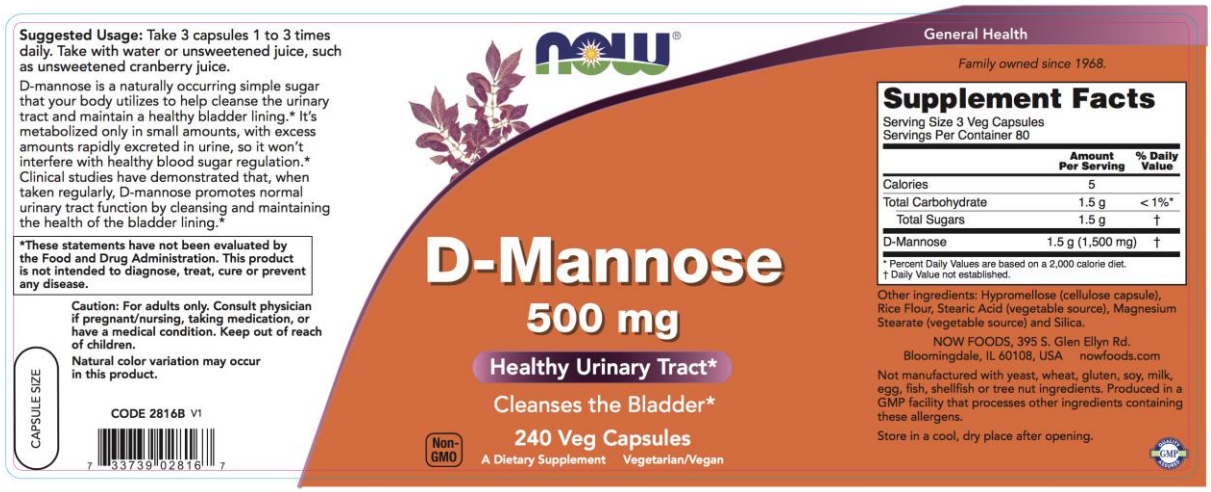
The following are examples of the D-mannose labels from NOW. NOW does not have a separate instruction for use from the label.



example 3 ounce powder label size: 2 3/4" x 7 3/8"



example 6 ounce powder label size: 3 1/2 ” x 9”



example capsule label size: 3 1/2” x 9”

3.g Blinding of Study Drug

For the treatment arm of the RCT, the D-mannose powder will be ordered and distributed by the research team. The manufacturer label will be covered up/removed and a study label stating contents of a nutraceutical will be used to maintain patient blinding to which nutraceutical is being used. The research team will not be blinded to the study drug. There are no placebos being used in this study.

3.h Receiving, Storage, Dispensing and Return

After receiving the purchased D-mannose, it will be stored in a secure area for each of the four outpatient locations for the Washington University Physicians Women’s Center for Bladder and Pelvic Health and in a secure area in the academic offices for the Washington University Division of Female Pelvic Medicine and Reconstructive Surgery. D-mannose should be stored in a cool place where the container is kept dry and tightly closed. It should be stored away from extreme heat.

The only medication that will be dispensed to study participants during the course of this study will be D-mannose to patients in the treatment arm of the RCT. Once a subject is randomized to the treatment arm, they will receive D-mannose in its original packaging but

relabeled as Nutraceutical to maintain patient blinding to which nutraceutical is being tested in the smallest quantity available to meet the amount required for a 90 day supply. For example, many manufacturers only distribute powder D-mannose in 42 day or 80 day supply bottles. In this situation, one 80 day and one 42 day bottle of D-mannose will be given to the patient in order to meet the 90 day required supply for the study. The medication that is not used will be brought to the patient's 3 month follow up appointment to be weighed.

F Study Procedures

F1 Screening for Eligibility

Prior to a new patient appointment, all patients referred for or with a chief complaint of frequent or recurrent urinary tract infections will be prescreened by a member of the research team. Items from the patient's chart or clinical records that may be used to identify potential participants for recruitment include: name, date of birth, date of appointment, reason for appointment, history of UTI, medication history, menopausal status, if patient has a known renal tract anomaly, neurogenic bladder, performs self-catheterization of has indwelling catheter, history of incomplete bladder emptying, history of contraindication to vaginal estrogen therapy including but not limited to current endometrial cancer or breast cancer without approval of patient's oncologist, surgical oncologist, or primary care physician, history of interstitial cystitis/painful bladder syndrome, history of urothelial cancer, and primary language spoken.

For patients that are existing patients of FPMRS division but with a new diagnosis of rUTI, the member of the research team that diagnoses the patient with rUTI will notify the members of the research team performing screening that the existing patient will be coming to the office for a new diagnosis of rUTI. Prior to the patient's appointment, she will be prescreened by a member of the research team. If the patient appears eligible from screening then any missing information will be obtained during routine clinical care during the patient's appointment to complete the screening process. If a patient is an existing patient of the FPMRS division with rUTI and not already using D-mannose, then they may be screened when they attend a routine clinical appointment with a member of the research team.

If a patient is noted to be eligible during an office visit (i.e. the new diagnosis of recurrent urinary tract infection was made during an appointment) and therefore the patient was not prescreened prior to the appointment, then a member of the research team will be notified as soon as possible to complete the screening process to see if a patient is eligible for study participation.

F2 Schedule of Measurements

During the clinical visit where the participant is enrolled, she will be asked to complete a form with study-related questions. A urine specimen or other labs may be ordered as part of routine clinical practice at this visit. No additional specimens will be collected for this study except for those clinically indicated.

If a participant is in the Observational arm, then they will receive a phone call approximately one week after study enrollment to confirm if D-mannose powder or capsules were purchased. They will also be asked what brand was purchased and confirm they were able to start the D-mannose on the planned study day 1. If there are delays in the participant's purchasing and receiving of their D-mannose then the date of study day 1 will be adjusted accordingly.

Participants will be expected to complete a weekly paper study diary. All participants that agree to receive text messages will receive a weekly text message reminder to complete their weekly study diary. Text messages will be sent at a standardized time on study days 7, 14, 21,

28, 35, 42, 49, 56, 63, 70, 77, 84, and 90. This same text message will ask patients if any new symptoms were experienced in the past week and request a “Yes” or “No” response via text message. Study participant responses will automatically be entered in the REDCap (Research Electronic Data Capture) database for this study. If the study participant sends a “Yes” response by text message a member of the research team will contact the patient to follow up for more information about the symptoms. If they declined text messaging when enrolling in the study, the study participant will receive periodic phone calls with reminders to complete their study diary. The subject will bring their study diary to each appointment.

Six weeks into the study, each study participant will receive a phone call from a member of the research team. During this phone call questions referencing compliance with completing the study diary, taking study medications as prescribed, if they have been treated for a UTI by anyone outside of our office during the study period, side effects noted, and if they have any questions to be answered will all be addressed.

In addition to the clinical visit in which the patient was enrolled, there will be a routine clinical 3 month follow up visit scheduled where the 3 month follow up form for the subject’s arm of the study will be completed. A 3 month follow up visit is standard protocol in our office for all rUTI patients that are started on a new medication. No additional specimens will be collected other than those indicated for routine clinical care at this appointment. If a participant missed a scheduled follow-up clinical visit, we will attempt to reach the participant by phone and reschedule their visit as soon as possible.

If any of the measures planned for 3 month follow up are not completed by the participant at this appointment, then it can alternatively be completed by phone or by mail, depending on participant convenience. If the participant does not complete all 90 days of the study, or if they forget to bring their study diary to their 3 month follow up appointment, then she will be offered the alternative of mailing or faxing her study diary to the office. If a participant completes the study early due to culture proven UTI then she will be asked to complete the 3 month follow up appointment information at their next office visit, by phone, or by mail.

If a participant does not bring their study drug to their 3 month follow up, or if the participant is lost to follow up, then a reasonable attempt will be made to contact the patient and ask her to bring the study drug to the office. If a participant is lost to follow up then a reasonable attempt will be made to see if the participant is willing to complete a 3 month follow up survey and/or exit survey over the phone or by mail. If the participant does not complete all 90 days of the study, or if they forget to bring their study diary to their 3 month follow up appointment, then she will be offered the alternative of mailing or faxing her study diary to the office. If a participant ended the study early then she will be asked if she is willing to complete the 3 month follow up appointment information and exit survey at their next office visit, by phone, or by mail.

F3 Safety and Adverse Events

3.a Safety and Compliance Monitoring

All women will be asked to complete a simple weekly study diary. The 90 days of the study will be divided into 12 full weeks and 1 partial week for a total of 13 weeks of the diary. In the diary, one of the questions asked for each week of the study is number of doses missed each week. This study will use a text message service through the REDCap (Research Electronic Data Capture) database. If agreed to by the participant, during the 90 day study period, a text message will be received by the participant as a reminder to complete their study diary for the week on study days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, and 90. This same text message will ask patients if any new symptoms were experienced in the past week and request a “Yes” or “No” response via text message. Study participant responses will automatically be entered in the REDCap (Research Electronic Data Capture) database for this study. If the study

participant sends a “Yes” response by text message a member of the research team will contact the patient to follow up for more information about the symptoms. If they declined text messaging when enrolling in the study, the study participant will receive periodic phone calls with reminders to complete their study diary. The subject will be instructed to bring their study diary to each appointment.

Six weeks into the study, each study participant will receive a phone call from a member of the research team. During this phone call questions referencing compliance with completing the study diary, taking study medications as prescribed, if they have been treated for a UTI by anyone outside of our office during the study period, side effects noted, and if they have any questions to be answered will all be addressed.

All subjects will be seen by a physician and research staff after 3 months in the study (when they have completed their 90 days in the study). At this visit, subjects will bring their study diary and any unused D-mannose to their appointment (including empty bottles if more than one bottle was provided to a patient in order for a patient to have a 90 day supply of D-mannose). A survey will be given to the patient to fill out at the 3 month follow up appointment. The survey will include questions on medication adherence. The study team will review the chart for any adverse events or UTIs not previously reported. Patients will fill out a questionnaire at this appointment to confirm the same. If a subject does not show for their 3 month follow up appointment then a member of the research team will attempt to contact the patient to reschedule this appointment. If any of the measures planned for 3 month follow up are not completed by the participant at this appointment, or if a participant does not show and does not reschedule this appointment, then it can alternatively be completed by phone or by mail, depending on participant convenience. If the participant does not complete all 90 days of the study, or if they forget to bring their study diary to their 3 month follow up appointment, then she will be offered the alternative of mailing or faxing her study diary to the office. If a participant completes the study early then she will be asked if she is willing to complete the 3 month follow up appointment information and exit survey at their next office visit, by phone, or by mail.

For confidentiality, only research team members will have access to the study information and the information entered into the database. Subjects will be assigned a unique study ID that will be used on all case report forms and database reporting. The database that will be used is REDCap which is HIPPA (Health Insurance Portability and Accountability Act of 1996) compliant, encrypted, and password protected. Any hard copies will be maintained in a locked cabinet in a locked office by a member of the research team. Data collection will occur on participants’ private devices (and sent to a locked phone) and/or on paper and placed in a locked cabinet in a locked office by a member of the research team. For text messaging, we will be using a SMS service that does not collect protected health information (PHI).

3.b Medical Monitoring

i Investigator only

Data will be collected via the weekly text message, possible phone call to follow up on text message response, the six week follow up phone call, and the three month follow up office visit with regard to any side effects experienced during the study period. All of this data will be reviewed weekly.

ii Institutional Data and Safety Monitoring Board

After the first ten participants have completed the study, review of adverse events experienced by the first ten participants will be compiled and assessed. The data and compiled information will be made available to an institutional data and safety monitoring board (DSMB) for

independent analysis. A similar sequence of events will occur after half of the participants in the study have completed the study and again at completion of all participants in the study.

The DSMB will include an individual with expertise and experience with conducting randomized controlled trials in the field of obstetrics and gynecology, an individual with expertise in urology and experience with recurrent UTI, and a biostatistician.

3.c Definitions of Adverse Events

Adverse events will include medication side effects including gastrointestinal upset symptoms such as nausea, vomiting, flatulence, diarrhea, dyspepsia, and abdominal pain. Other medication side effects may include rash or itching.

3.d Classification of Events

i Severity

All expected adverse events are of mild severity.

For this study, the following standard adverse event (AE) definitions are used:

Adverse event: Any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure.

Serious Adverse Event (SAE): Any AE related to the study drug that results in any of the following circumstances: death, life-threatening, event requiring inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity

AEs are graded according to the following scale:

Mild: An experience that is transient and requires no special treatment or intervention. The experience does not generally interfere with usual daily activities.

Moderate: An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities.

Severe: An experience that require therapeutic intervention. The experience interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment of something related to the study drug, it becomes a SAE.

The study uses the follow AE attribution scale:

Not related: The AE is clearly not related to the study procedure (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).

Possibly related: An event that follows a reasonable temporal sequence from the initation of study procedures, but that could readily have been produced by a number of other factors.

Related: The AE is clearly related to the study procedures.

ii Expectedness

Less common: gastrointestinal upset symptoms (such as nausea, vomiting, flatulence, diarrhea, constipation, dyspepsia, and abdominal pain)

Rare: Rash or itching with medication.

3.e Data Collection Procedures for Adverse Events

Adverse events will be noted in each subject's file. Their text message response to the weekly question about new symptoms related to study medication will be reviewed in a timely fashion. If symptoms were noted by text message response, then a follow up phone call to the patient will be made.

F4 Study Outcome Measurements and Ascertainment

Outcomes will be measured by a weekly study diary with follow up as indicated and by the patient notifying the office if UTI like symptoms are experienced. Control checks to make sure a UTI was not missed are built into a six week follow up phone call and the three month follow up appointment.

G Statistical Plan

G1 Sample Size Determination and Power

We based our sample size estimate on assumptions for our primary aim, as this is the most important aim for providing information to support future recommendations and studies aimed at individualized patient care. The first published study on D-mannose was a RCT that showed 14.6% of rUTI patients develop another UTI while on treatment [9]. To be conservative in our sample size calculations, we assume 20% of patient on D-mannose will develop a UTI during the three-month treatment period. Very few studies have stated the percent of rUTI patients that develop another UTI while on vaginal estrogen therapy [27-29]. Due to the range of the published values, an average of these numbers was taken to arrive at an assumption that 45% of patients on only vaginal estrogen therapy will develop another UTI during the treatment period. We also accounted for a 10% dropout rate during the study period. Using these numbers to determine sample size, we calculated 60 patients would be needed per RCT arm for a total of 120 patients in the RCT. We recognize that our power for secondary aims is lower; however, we included these to begin to explore these other areas that are fundamental for understanding the underlying mechanism of D-mannose and how it works with rUTI. We have decided to also enroll 60 patients in the Observational arm of the study.

G2 Interim Monitoring and Early Stopping

In late 2019/early 2020 an interim analysis will be performed on the study data with all data to date serving as a "pilot" of the study. This will allow for interim analysis of safety and efficacy of the nutraceutical. The Haybittle-Peto rule will be followed for early stopping. Due to a slower recruitment rate than expected, an additional feasibility manuscript has been planned to inform the scientific community of these aspects of the trial. We would like to include a preliminary estimate of effect size and variability from interim analysis. The interim analysis rule is being used to avoid inflating type 1 error, but we expect to finish the trial as originally planned irrespective of the preliminary estimate, so no bias in study conduct should be introduced. The investigators will remain blinded to participants' assignment.

G3 Analysis Plan and Statistical Methods

We are studying D-mannose in postmenopausal women with a history of rUTI on VET. We will plan for an intent to treat analysis with an additional per protocol analysis likely.

For our primary outcome of the RCT, we will calculate the cumulative incidence of symptomatic culture-proven UTIs. If we have loss to follow-up, we will use the Kaplan-Meier method to calculate the cumulative incidence by arm (i.e., 1.0 - survival). We will compare the cumulative incidence between arms by chi-squared tests, Fisher's exact tests, or log-rank tests, as appropriate. Although women will be randomized into the two arms, we will compare their distributions of potential confounding variables by calculating group-specific means and proportions, as appropriate. If these differ by an appreciable degree, we will calculate adjusted associations, using logistic or Cox proportional hazards regression, as appropriate.

We will calculate the incidence of side effects and discontinuation as the number of women in the D-mannose +VET arm who experience these events during follow-up divided by the number of women in the D-mannose +VET arm. 95% confidence limits will be calculated by normal approximation or the Clopper-Pearson exact method, as appropriate.

G4 Missing Outcome Data

Missing data and patterns will be assessed monthly by the data manager. Remedial measures, including retraining of staff, will be used as needed to minimize missing data.

We plan for an intent to treat analysis. In doing this, study participants that are lost to followup will be presumed to not have an acute urinary tract infection from the time of last contact with the study participant.

We will additionally have a per protocol analysis.

G5 Unblinding Procedures

Every attempt will be made to ensure that the patients enrolled in the RCT under the knowledge that a nutraceutical is being studied will continue to be blinded to which nutraceutical is being studied. If a patient is in the treatment arm of the RCT, and they are unblinded then this will be documented and reported to the research team for recording purposes.

H Data Handling and Record Keeping

H1 Confidentiality and Security

Confidential and informed consent will occur in a private counseling room. Every precaution will be taken to ensure data confidentiality. Only research team members will have access to both the paper and electronic data. Subjects will be assigned a unique study ID that will be used on all case report forms and database reporting. The database that will be used is REDCap which is HIPPA compliant, encrypted, and password protected. Electronic data files will be accessible only on password protected computers. Any hard copies will be maintained in a locked cabinet in a locked office by a member of the research team. Data collection will occur on participants' private devices (and sent to a locked phone) and/or on paper and placed in a locked cabinet in a locked office by a member of the research team. For text messaging, we will be using a SMS service that does not collect PHI. There will be strict adherence to data management protocols.

H2 Training

All members of the research team will be educated on the study protocol at a division meeting or meeting set up for training purposes. All members of the research team will be able to ask questions at this education session and after the education session to ensure they are comfortable with all aspects of the study protocol. Members of the research staff that will be using REDCap (Research Electronic Data Capture) will be trained on how to use this database.

H3 Records Retention

Subjects will be assigned a unique study ID that will be used on all case report forms and database reporting.

Any hard copies will be maintained in a locked cabinet in a locked office by a member of the research team.

Weekly study diary reminder response will be collected via text message. Data will be stored in REDCap which is HIPPA compliant, encrypted, and password protected. Work will only be done on password protected computers. Only members of the research team will have study information access.

I Study Administration

I1 Organization and Participating Centers

The location of this study will be the four outpatient office locations of the Division of Female Pelvic Medicine and Reconstructive Surgery in the Department of Obstetrics and Gynecology at Washington University in St. Louis School of Medicine.

I2 Funding Source and Conflicts of Interest

Funding for this project will be supplied by the division of Female Pelvic Medicine and Reconstructive Surgery. This is a division of the Department of Obstetrics and Gynecology in the Washington University in St. Louis School of Medicine.

I3 Subject Stipends or Payments

Subjects will not be reimbursed for their participation in this research study. Patients in the treatment arm of the RCT portion of the study will received their D-mannose as part of the study.

I4 Study Timetable

Study Measure (mo = months) [Month 0 = January 2018]	0-4 mo	4-8 mo	8-12 mo	12-16 mo	16-20 mo	20-24 mo
Patient enrollment						
3 mo of D-mannose treatment vs control treatment with patient follow up and re-examination						
Data analysis						
Manuscript preparation and submission						

J Publication Plan

We plan use the data from this study to write a manuscript for publication in a respected peer-reviewed journal in a timely fashion. Journal choice will be dependent on study findings, but will likely be relating to the fields of female pelvic medicine and reconstructive surgery, gynecology, or urology.

K Attachments

K1 Informed consent documents

The following documents are attached in the myIRB application:

- Informed consent – RTC arm
- Informed consent – Observational arm

K2 Patient education brochures

- Participant instructions – RCT arm
- Participant instructions – Observational arm

K3 Questionnaires or surveys

The following documents are attached in the myIRB application:

- Nutraceutical efficacy in rUTI screening log
- Enrollment visit form – complete with participant
- Study Diary – RCT Arm
- Study Diary – Observational Arm
- Follow up call for Yes text response form
- 1 week confirmation of D-mannose in Observational Arm
- 6 week follow up phone call – RCT Arm
- 6 week follow up phone call – Observational Arm
- 3 month followup appointment form – RCT Arm
- 3 month followup appointment form – Observational Arm
- Exit survey (completed less than 90 days of study)
- Exit survey (completed 90 days of study)

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