Washington University in St. Louis

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INFORMED CONSENT DOCUMENT – RCT ARM

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

Principal Investigator: Jerry Lowder

Research Team Contact: Jerry Lowder, M.D., M.Sc., 314-747-1402

This consent form describes the research study and helps you decide if you want to participate. It provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights and responsibilities as a research participant. By signing this form you are agreeing to participate in this study.

- You should read and understand the information in this document including the procedures, risks and potential benefits.
- If you have questions about anything in this form, you should ask the research team for more information before you agree to participate.
- You may also wish to talk to your family or friends about your participation in this study.
- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We invite you to participate in this research study because you are a postmenopausal woman with recurrent urinary tract infections. Recurrent urinary tract infection (rUTI) means you have had multiple recent infections in your urinary tract: at least two infections in the last six months or at least three infections in the last twelve months. Since you are using either vaginal estrogen cream, tablet, or ring (meaning you are using vaginal estrogen therapy) you are invited to participate in the randomized clinical trial (RCT) portion of this study.

The purpose of this research study is to evaluate a nutraceutical as a non-antibiotic treatment to prevent rUTI in women that have completed menopause. In this study, the nutraceutical is a specific dietary supplement that is available at health food stores and without a prescription. Previous small studies have looked at this same nutraceutical to prevent rUTI, but none of these studies evaluated the nutraceutical in patients that were using vaginal estrogen therapy. Many times when women with rUTI are treated a combination of treatments may be considered, which is why this study is being performed to look at the nutraceutical as a non-antibiotic treatment in women like yourself who are on vaginal estrogen.

The nutraceutical is considered investigational, which means that it has not been approved by the U.S. Food and Drug Administration.

WHAT WILL HAPPEN DURING THIS STUDY?

You will be randomly assigned to receive one of the two study treatments; either you will be given the nutraceutical to take in addition to the vaginal estrogen (cream, tablet, or ring) that you are already taking or you will continue with only using the vaginal estrogen (cream, tablet, or ring). This means that the study treatment you will receive will be determined purely by chance, like flipping a coin. You will have a 50% chance of receiving either of the study treatments.

The study team will know the specific name of the nutraceutical that is being studied, but patients in the study will not be informed of the specific name of the nutraceutical until after the study is completed. This is done because we want to get unbiased information from participants in the study.

If you are assigned to receive the nutraceutical, you will take it once daily as a powder that is dissolved in water that you will drink.

If you decide to participate in this study, the following health information will be gathered as part of the study: your UTI history, medical and surgical history, pregnancy history, social history, medication history, race, and menopausal status; history of pelvic pain; history of prior pelvic floor physical therapy; presence of vaginal discharge; symptoms you experience if you get a UTI during the study; side effects experienced in the study; urinalysis or urine culture results collected during the study. Routine clinical information from today's office visit including your height, weight, physical exam findings, and urine culture may also be included.

This study is 90 (ninety) days long from the date that we tell you is day 1 (one). Most likely study day 1 will be 5 (five) days after you enroll in the study. You have to wait this period of time before study day 1 to make sure that the urine culture that was sent as part of your normal office visit is negative. If your urine culture was not negative, the research team will recommend you having your UTI treated with antibiotics like you normally would be whether if you were in the study or not. After you finish the antibiotics you would to have another urine culture test. After that urine culture is negative, then you will be told the day for your study day 1 (one).

There will not be any additional office visits just for research purposes. All research will be conducted during normal clinic follow up appointments for patients with rUTI or by contact with you by text message, mail, or phone between your appointments.

If you decide to participate in the study today, you will be asked to complete study related questions before leaving your appointment. You are free to skip any questions you would prefer not to answer.

During your 90 (ninety) days in the study, you will be asked to fill out a study diary at the end of each 7 (seven) day period. If you agree to receive text messages as part of this study, you will receive a text message reminding you to fill out your study diary every 7 (seven) days until study day 90 (ninety) when your study participation is complete. The same text message will ask you to reply 'yes' or 'no' to whether you have had any new symptoms from the study medications in the past week. A 'yes' response will prompt a phone call from a member of the study team. If you do not wish to receive text messages as part of this study you will receive a phone call no more than once a week reminding you to fill out your study diary.
You will also receive a phone call from a member of the research team approximately 6 (six) weeks into the study. The purpose of this phone call is to check if you have any questions about your medications,

how often you are taking your medication, and if you have been treated for a urinary tract infection by anyone outside of our office during the study period.

After you complete your 90 (ninety) days in the study, you will return to the office for a 3 (three) month follow up appointment. A three month follow up appointment is normal for all patients with rUTI being cared for at the Washington University Physicians Women's Center for Bladder and Pelvic Health. You should bring your completed study diary to this appointment. If you are in the treatment arm taking the nutraceutical, you should bring any remaining study medication with you to this appointment. You will be asked to answer questionnaires related to the study while at your appointment. You are free to skip any questions you would prefer not to answer.

If at any point you forget to complete any of the questionnaires in the office or if you forget to bring your study diary with you to your follow up appointment, we may ask you to complete these forms over the phone or have them mailed to you for completion and return to a member of the research team. If you stop the study early we may ask that you complete an exit survey or follow up questionnaire either over the phone, via mail, or at your next appointment.

If you develop UTI like symptoms during the study you will be instructed to call the office just like you would if you were not in the study. This means that if you are having burning or painful urination, increased urinary frequency, and/or increased urinary urgency, you should call the office to leave a message for one of the nurses. If you are having nausea, vomiting, chills, and/or one-sided pain near the bottom of your rib cage on your back in addition to burning or painful urination, increased urinary frequency, and/or increased urinary urgency then you should call the office to speak with one of the nurses during the day or the after-hours emergency number for the office if it is at night or on the weekend. An order for a urine culture will be sent to a lab of your choice so a urine sample can be cultured to see if there are any bacteria growing in your urine.

If you have a urinary tract infection diagnosed by a urine culture that grows bacteria during the study period, you will be treated with an antibiotic like you normally would be whether if you were in the study or not. Even if you have a positive urine culture you will continue in the study for 90 days, unless you decide you want to withdraw from the study.

Will you save my samples or research data to use in future research studies?

As part of this study, we are obtaining data from you. We would like to use these data for studies going on right now as well as studies that are conducted in the future. These studies may provide additional information that will be helpful in understanding recurrent urinary tract infections, or other diseases or conditions, including research to develop investigational tests, treatments, drugs or devices that are not yet approved by the U.S. Food and Drug Administration. It is unlikely that what we learn from these studies will have a direct benefit to you. There are no plans to provide financial compensation to you should this occur. By allowing us to use your data you give up any property rights you may have in the data.

We will share your data with other researchers. They may be doing research in areas similar to this research or in other unrelated areas. These researchers may be at Washington University, at other research centers and institutions, or industry sponsors of research. We may also share your research data with large data repositories (a repository is a database of information) for broad sharing with the

research community. If your individual research data is placed in one of these repositories, only qualified researchers, who have received prior approval from individuals that monitor the use of the data, will be able to look at your information.

If you change your mind and do not want us to store and use your data for future research, you should contact the research team member identified at the top of this document. The data will no longer be used for research purposes. However, if some research with your data has already been completed, the information from that research may still be used. Also, if the data has been shared with other researchers it might not be possible to withdraw the data to the extent it has been shared.

Please place your initials in the blank next to Yes or No for each of the questions below:

My data may be stored and used for future research as described above.

_____ Yes **_____ No**
Initials **Initials**

My data may be shared with other researchers and used by these researchers for the future research as described above.

_____ Yes **_____ No**
Initials **Initials**

HOW MANY PEOPLE WILL PARTICIPATE?

Approximately 180 people will take part in this study conducted by investigators at Washington University. There will be 120 patients in this randomized, controlled trial portion of the study and an additional 60 patients in an observational arm of the study.

HOW LONG WILL I BE IN THIS STUDY?

If you agree to take part in this study, your involvement will last for 90 (ninety) days after your study day 1 is determined as described earlier under "What will happen in this study?". In addition to today's visit the only office visit will be your routine 3 month follow up visit. This visit would be expected to range from 30 minutes to 1 hour in length. During the study you will also be asked to fill out your weekly study diary and answer a text. We estimate the total weekly time for the diary and text to be no more than 5 (five) minutes. We estimate that your six week follow up phone call will take approximately 5 (five) minutes as well.

WHAT ARE THE RISKS OF THIS STUDY?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

Nutraceutical
Overall the nutraceutical used in this study is thought to be generally well tolerated in people since it is

found in many natural foods. Risks associated with the nutraceutical are believed to be mainly related to gastrointestinal side effects. You may prefer to obtain treatment for UTI like symptoms from an emergency room or other outside provider.

Less Likely / Less Common

Mild

- Nausea
- Vomiting
- Flatulence (gas)
- Diarrhea (loose stool)
- Indigestion
- Abdominal pain
- Bloating

Rare

Mild

- Rash
- Itching
- Allergic reaction

Questionnaires

You may feel uncomfortable or be inconvenienced by filling out study related papers.

Breach of Confidentiality

One risk of participating in this study is that confidential information about you may be accidentally disclosed. We will use our best efforts to keep the information about you secure. Please see the section in this consent form titled *"How will you keep my information confidential?"* for more information.

WHAT ARE THE BENEFITS OF THIS STUDY?

You may or may not benefit from being in this study.

However, we hope that, in the future, other people might benefit from this study because of increased knowledge surrounding the use of non-antibiotic prophylaxis (giving something to try to prevent the UTI from occurring before it occurs) for rUTI.

WHAT OTHER TREATMENT OPTIONS ARE THERE?

Before you decide whether or not to be in this study, your doctor will discuss the other options that are available to you. The historical treatment to prevent further UTIs when a patient is diagnosed with rUTI is a preventative antibiotic. With increasing concern about antibiotic resistance and side effects from antibiotics, treatment options other than preventative antibiotics are preferred by some healthcare providers. Vaginal estrogen therapy, like you are currently using, has been shown to help prevent rUTI in women that have completed menopause. Sometimes when vaginal estrogen is not enough by itself, your doctor may suggest additional nutraceuticals or medications to be added in addition to using

vaginal estrogen. These additional nutraceuticals and medications are vitamin C, cranberry, D-mannose, and methenamine. There is not a current consensus on the recommended treatment order and/or best combination of the additional non-antibiotic treatments. If you were not in the study you could receive the same nutraceutical that is being studied. However, if you decide to be in the study then we ask that you don't take any additional vitamin C, cranberry, D-mannose, and methenamine as it could change study outcomes.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?

As part of this study you will receive tests and procedures that are similar to what you would receive during routine clinical care of your condition. Your health plan/insurance company will be billed for some or all of these costs, and you will be responsible for any co-pays and deductibles that are normally required by your health plan/insurance. Not all insurance plans cover the costs associated with being in a study. Even if they do, you may be responsible for more out-of-pocket expenses, such as co-pays and deductibles, when there are more tests and procedures or more expensive tests and procedures involved in the study than if you were to receive routine clinical care outside the study.

If you wish to know whether there are more tests and procedures or more expensive tests and procedures in the study, you should ask your study doctor.

If you wish to know whether your insurance will pay, you should contact them directly, or speak with the study team about obtaining a financial pre-certification prior to enrolling in the study.

If you are randomly assigned to receive the nutraceutical then it will be provided at no cost to you.

WILL I BE PAID FOR PARTICIPATING?

You will not be paid for being in this research study.

WHO IS FUNDING THIS STUDY?

The University and the research team are not receiving payment from other agencies, organizations, or companies to conduct this research study.

WHAT IF I AM INJURED AS A RESULT OF THIS STUDY?

Washington University investigators and staff will try to reduce, control, and treat any complications from this research. If you feel you are injured because of the study, please contact the investigator at (314)747-1402 and/or the Human Research Protection Office at 1-(800)-438-0445.

Decisions about whether payment for medical treatment for injuries relating to your participation in research will be made by Washington University. If you need to seek medical care for a research-related injury, please notify the investigator as soon as possible.

HOW WILL YOU KEEP MY INFORMATION CONFIDENTIAL?

Other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you. We will keep your participation in this research study confidential to the extent permitted by law.

- Government representatives (including the Office for Human Research Protections) to complete federal or state responsibilities
- The U.S. Food and Drug Administration
- Your primary care physician if a medical condition that needs urgent attention is discovered
- Hospital or University representatives to complete Hospital or University responsibilities
- Information about your participation in this study may be documented in your health care records and will be available to anyone with access to your health care record, including your health insurance company. This information may also be released as part of a release of information request.
- The last four digits of your social security number may be used in hospital or University systems to track billing information for research procedures.
- Washington University's Institutional Review Board (a committee that oversees the conduct of research involving human participants) and the Human Research Protection Office. The Institutional Review Board has reviewed and approved this study.

To help protect your confidentiality, only research team members will have access to both the paper and electronic data. You will be assigned a unique study ID that will be used on all forms and database reporting. The database that will be used 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. For text messaging, we will be using a short message service (SMS) that does not collect any identifying information. Urine samples are not stored after testing.

Any report or article that we write will not include information that can directly identify you. The journals that publish these reports or articles require that we share your information that was collected for this study with others. Sharing this information will allow others to make sure the results of this study are correct and help develop new ideas for research. Your information will be shared in a way that cannot directly identify you.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Are there additional protections for my health information?

Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, you must give the research team permission to use and disclose (share) your PHI for the study as explained in this consent form. The research team will follow state and federal laws and may share your health information with the agencies and people listed under the previous section titled, "How will you keep my information confidential?"

Once your health information is shared with someone outside of the research team, it may no longer be protected by HIPAA.

The research team will only use and share your information as talked about in this form or as permitted or required by law. When possible, the research team will make sure information cannot be linked to you (de-identified). Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form. If you have questions or concerns about your privacy and the use of your PHI, please contact the University's Privacy Officer at 866-747-4975.

Although you will not be allowed to see the study information, you may be given access to your health care records by contacting your health care provider.

If you decide not to sign this form, it will not affect

- your treatment or the care given by your health provider.
- your insurance payment or enrollment in any health plans.
- any benefits to which you are entitled.

However, it will not be possible for you to take part in the study.

If you sign this form:

- You authorize the use of your PHI for this research
- This authorization does not expire.
- You may later change your mind and not let the research team use or share your information (you may revoke your authorization).
    - To revoke your authorization, complete the withdrawal letter, found in the Participant section of the Human Research Protection Office website at https://hrpo.wustl.edu/participants/withdrawing-from-a-study/ or you may request that the investigator send you a copy of the letter.
        - **If you revoke your authorization:**
            - The research team may only use and share information already collected for the study.
            - Your information may still be used and shared as necessary to maintain the integrity of the research, for example, to account for a participant's withdrawal from the research study or for safety reasons.
            - You will not be allowed to continue to participate in the study.

Can we contact you by text?

We would like to contact you by text message for the purposes listed below. Some of these texts may contain health information that identifies you.

- To remind you to complete your diary
- To ask you if you have had any new symptoms

Only the research team will have access to your texting communications. We will only communicate by text to send you the information listed above. If you have any questions or need to contact us for an

urgent or emergent situation, please contact the research team member identified at the top of this document. Only the immediate response you send to a text message will be seen by a research team member. Other text messages sent to the study number will not be read or accessible by the research team. Message and Data rates may apply. You will receive a maximum of six messages a month. You can text STOP or contact the research team member identified at the top of the document to opt-out of receiving these messages.

You should be aware that there are risks associated with allowing us to text you for the purposes of this study.

- There is always a risk that the text message could be intercepted or sent to the wrong telephone number. To avoid sending messages to the wrong number, the first text we send you will be a test message to ensure we have the correct telephone number.

Do you agree to allow us to send you a test message at the beginning of the study, reminders to complete your diary, and questions about new symptoms via text?

_____ Yes **_____ No**
Initials **Initials**

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all. If you decide to be in this study, you may stop participating at any time. Any data that was collected as part of your participation in the study will remain as part of the study records and cannot be removed.

If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

What if I decide to withdraw from the study?

You may withdraw by telling the study team you are no longer interested in participating in the study or you may send in a withdrawal letter. A sample withdrawal letter can be found at https://hrpo.wustl.edu/participants/withdrawing-from-a-study/ under Withdrawing from a Research Study.

If you decide to leave the study early, we will ask you to return any unused nutraceutical to the Washington University Physicians Women's Center for Bladder and Pelvic Health.

Will I receive new information about the study while participating?

If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

Can someone else end my participation in this study?

Under certain circumstances, the investigator might decide to end your participation in this research study earlier than planned. This might happen for no reason or because in our judgment it would not be safe for you to continue, if you receive an antibiotic for UTI like symptoms without having bacteria found on urine culture, or if funding for the research study has ended.

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself, please contact: Jerry Lowder, M.D. or another member of the research team at (314)747-1402. If you experience a research-related injury, please contact: Jerry Lowder, M.D. or another member of the research team at (314)747-1402.

If you have questions, concerns, or complaints about your rights as a research participant, please contact the Human Research Protection Office at 660 South Euclid Avenue, Campus Box 8089, St. Louis, MO 63110, 1-(800)-438-0445, or email hrpo@wustl.edu. General information about being a research participant can be found on the Human Research Protection Office web site, http://hrpo.wustl.edu. To offer input about your experiences as a research participant or to speak to someone other than the research staff, call the Human Research Protection Office at the number above.

This consent form is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by agreeing to participate in this study. As a participant you have rights and responsibilities as described in this document and including:

- To be given enough time before signing below to weigh the risks and potential benefits and decide if you want to participate without any pressure from the research team or others.
- To understand all of the information included in the document, have your questions answered, and receive an explanation of anything you do not understand.
- To follow the procedures described in this document and the instructions of the research team to the best of your ability unless you choose to stop your participation in the research study.
- To give the research team accurate and complete information.
- To tell the research team promptly about any problems you have related to your participation, or if you are unable to continue and wish to stop participating in the research study.

Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a signed and dated copy of this form.

Do not sign this form if today's date is after EXPIRATION DATE: 11/12/21.

_____ _____
(Signature of Participant) (Date)

_____
(Participant's name – printed)

Statement of Person Who Obtained Consent

The information in this document has been discussed with the participant or, where appropriate, with the participant's legally authorized representative. The participant has indicated that they understand the risks, benefits, and procedures involved with participation in this research study.

_____ _____
(Signature of Person who Obtained Consent) (Date)

_____
(Name of Person who Obtained Consent - printed)

Washington University in St. Louis

INFORMED CONSENT DOCUMENT – OBSERVATIONAL ARM

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

Principal Investigator: Jerry Lowder

Research Team Contact: Jerry Lowder, M.D., M.Sc., 314-747-1402

This consent form describes the research study and helps you decide if you want to participate. It provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights and responsibilities as a research participant. By signing this form you are agreeing to participate in this study.

- You should read and understand the information in this document including the procedures, risks and potential benefits.
- If you have questions about anything in this form, you should ask the research team for more information before you agree to participate.
- You may also wish to talk to your family or friends about your participation in this study.
- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We invite you to participate in this research study because you are a postmenopausal woman with recurrent urinary tract infections. Recurrent urinary tract infection (rUTI) means you have had multiple recent infections in your urinary tract: at least two infections in the last six months or at least three infections in the last twelve months. Since you are not using vaginal estrogen you are invited to participate in the observational portion of this study.

The purpose of this research study is to evaluate the nutraceutical D-mannose as a non-antibiotic treatment to prevent rUTI in women that have completed menopause. D-mannose is a dietary supplement that is available at health food stores and without a prescription. Previous small studies have looked at D-mannose to prevent rUTI, but none of these studies evaluated the nutraceutical in patients that were using vaginal estrogen therapy. Many times when women with rUTI are treated a combination of treatments may be considered, which is why this study is being performed to look at D-mannose as a non-antibiotic treatment in postmenopausal women. Since you are not using vaginal estrogen like the women in the other part of our study, your information in this study will be used to compare to the women using vaginal estrogen that are in the other part of our study. The observation portion of this study is for our patients, like yourself, that we would recommend D-mannose for as part of their normal treatment in our office.

The use of D-mannose is considered investigational, which means that it has not been approved by the U.S. Food and Drug Administration.

WHAT WILL HAPPEN DURING THIS STUDY?

As part of the observational arm of our study, you are a patient that we would recommend D-mannose for as part of your normal treatment in our office. We would provide you with the necessary dose information to purchase D-mannose from a supplement store, just like we would if you were not in the study.

You will take 2 grams of D-mannose per day as either a powder that is dissolved in water that you will drink once daily or as two capsules that you will swallow every 12 hours. The brand you will be required to purchase is called NOW (and you will purchase either the NOW D-mannose pure powder or the NOW D-mannose 500mg capsules). You will receive an instruction sheet explaining how to take the D-mannose.

If you decide to participate in this study, the following health information will be gathered as part of the study: your UTI history, medical and surgical history, pregnancy history, social history, medication history, race, and menopausal status; history of pelvic pain; history of prior pelvic floor physical therapy; presence of vaginal discharge; symptoms you experience if you get a UTI during the study; side effects experienced in the study; urinalysis or urine culture results collected during the study. Routine clinical information from today's office visit including your height, weight, physical exam findings, and urine culture may also be included.

This study is 90 (ninety) days long from the date that we tell you is day 1 (one). Most likely study day 1 will be 5 (five) days after you enroll in the study. You have to wait this period of time before study day 1 to make sure that the urine culture that was sent as part of your normal office visit is negative. If your urine culture was not negative, the research team will recommend you having your UTI treated with antibiotics like you normally would be whether if you were in the study or not. After you finish the antibiotics you would to have another urine culture test. After that urine culture is negative then you will be told the day for your study day 1 (one).

There will not be any additional office visits just for research purposes. All research will be conducted during normal clinic follow up appointments for patients with rUTI or by contact with you by text message, mail, or phone between your appointments.

You will receive a phone call from a member of the research team approximately 1 week after you enroll in the study to find out which type of D-mannose you purchased (powder of capsules) and what the first day was that you started taking the D-mannose.

During your 90 (ninety) days in the study, you will be asked to fill out a study diary at the end of each 7 (seven) day period. If you agree to receive text messages as part of this study, you will receive a text message reminding you to fill out your study diary every 7 (seven) days until study day 90 (ninety) when your study participation is complete. The same text message will ask you to reply 'yes' or 'no' to whether you have had any new symptoms from the study medications in the past week. A 'yes' response will prompt a phone call from a member of the study team. If you do not wish to receive text messages as part of this study you will receive a phone call no more than once a week reminding you to fill out your study diary.

You will also receive a phone call from a member of the research team approximately 6 (six) weeks into the study. The purpose of this phone call is check if you have any questions about your medications, how often you are taking your medication, and if you have been treated for a urinary tract infection by anyone outside of our office during the study period.

After you complete your 90 (ninety) days in the study, you will return to the office for a 3 (three) month follow up appointment. A three month follow up appointment is normal for all patients with rUTI being cared for at the Washington University Physicians Women's Center for Bladder and Pelvic Health. You should bring your completed study diary to this appointment. You will be asked to answer questionnaires related to the study while at your appointment. You are free to skip any questions you would prefer not to answer.

If at any point you forget to complete any of the questionnaires in the office or if you forget to bring your study diary with you to your follow up appointment, we may ask you to complete these forms over the phone or have them mailed to you for completion and return to a member of the research team. If you stop the study early we may ask that you complete an exit survey or follow up questionnaire either over the phone, via mail, or at your next appointment.

If you develop UTI-like symptoms during the study you will be instructed to call the office just like you would if you were not in the study. This means that if you are having burning or painful urination, increased urinary frequency, and/or increased urinary urgency, then you should call the office to leave a message for one of the nurses. If you are having nausea, vomiting, chills, and/or one-sided pain near the bottom of your rib cage on your back in addition to burning or painful urination, increased urinary frequency, and/or increased urinary urgency then you should call the office to speak with one of the nurses during the day or the after-hours emergency number for the office if it is at night or on the weekend. An order for a urine culture will be sent to a lab of your choice so a urine sample can be cultured to see if there are any bacteria growing in your urine.

If you have a urinary tract infection diagnosed by a urine culture that grows bacteria during the study period, you will be treated with an antibiotic like you normally would be whether if you were in the study or not. Even if you have a positive urine culture you will continue in the study for 90 days, unless you decide you want to withdraw from the study.

Will you save my samples or research data to use in future research studies?

As part of this study, we are obtaining data from you. We would like to use this and data for studies going on right now as well as studies that are conducted in the future. These studies may provide additional information that will be helpful in understanding recurrent urinary tract infections, or other diseases or conditions, including research to develop investigational tests, treatments, drugs or devices that are not yet approved by the U.S. Food and Drug Administration. It is unlikely that what we learn from these studies will have a direct benefit to you. There are no plans to provide financial compensation to you should this occur. By allowing us to use your data you give up any property rights you may have in the data.

We will share your data with other researchers. They may be doing research in areas similar to this

research or in other unrelated areas. These researchers may be at Washington University, at other research centers and institutions, or industry sponsors of research. We may also share your research data with large data repositories (a repository is a database of information) for broad sharing with the research community. If your individual research data is placed in one of these repositories only qualified researchers, who have received prior approval from individuals that monitor the use of the data, will be able to look at your information.

If you change your mind and do not want us to store and use your data for future research you should contact the research team member identified at the top of this document. The data will no longer be used for research purposes. However, if some research with your data has already been completed, the information from that research may still be used. Also, if the data has been shared with other researchers it might not be possible to withdraw the data to the extent it has been shared.

Please place your initials in the blank next to Yes or No for each of the questions below:

My data may be stored and used for future research as described above.

_____ Yes **_____ No**
Initials **Initials**

My data may be shared with other researchers and used by these researchers for the future research as described above.

_____ Yes **_____ No**
Initials **Initials**

HOW MANY PEOPLE WILL PARTICIPATE?

Approximately 180 people will take part in this study conducted by investigators at Washington University. There will be 120 patients in the randomized, controlled trial portion of the study and an additional 60 patients in this observational arm of the study.

HOW LONG WILL I BE IN THIS STUDY?

If you agree to take part in this study, your involvement will last for 90 (ninety) days after your study day 1 is determined as described earlier under "What will happen in this study?". In addition to today's visit the only office visit will be your routine 3 month follow up visit. This visit would be expected to range from 30 minutes to 1 hour in length. During the study you will also be asked to fill out your weekly study diary and answer a text. We estimate the total weekly time for the diary and text to be no more than 5 (five) minutes. We estimate that your six week follow up phone call will take approximately 5 (five) minutes as well.

WHAT ARE THE RISKS OF THIS STUDY?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

D-mannose
Overall D-mannose is thought to be generally well tolerated in people since it is found in many natural foods. Risks associated with the nutraceutical are believed to be mainly related to gastrointestinal side effects . You may prefer to obtain treatment for UTI like symptoms from an emergency room or other outside provider.

Less Likely / Less Common
Mild

- Nausea
- Vomiting
- Flatulence (gas)
- Diarrhea (loose stool)
- Indigestion
- Abdominal pain
- Bloating

Rare
Mild

- Rash
- Itching
- Allergic Reaction

Questionnaires
You may feel uncomfortable or be inconvenienced by filling out study related papers.

Breach of Confidentiality
One risk of participating in this study is that confidential information about you may be accidentally disclosed. We will use our best efforts to keep the information about you secure. Please see the section in this consent form titled *"How will you keep my information confidential?"* for more information.

WHAT ARE THE BENEFITS OF THIS STUDY?

You may or may not benefit from being in this study.

However, we hope that, in the future, other people might benefit from this study because of increased knowledge surrounding the use of non-antibiotic prophylaxis (giving something to try to prevent the UTI from occurring before it occurs) for rUTI.

WHAT OTHER TREATMENT OPTIONS ARE THERE?

Before you decide whether or not to be in this study, your doctor will discuss the other options that are available to you. The historical treatment to prevent further UTIs when a patient is diagnosed with rUTI is a preventative antibiotic. With increasing concern about antibiotic resistance and side effects from antibiotics, treatment options other than preventative antibiotics are preferred by some healthcare providers. Vaginal estrogen therapy has been shown to help prevent rUTI in women that have

completed menopause. Sometimes when vaginal estrogen can't be used by a patient or is not enough by itself, your doctor may suggest additional nutraceuticals or medications to be added in addition to using vaginal estrogen. These additional nutraceuticals and medications are vitamin C, cranberry, D-mannose, and methenamine. There is not a current consensus on the recommended treatment order and/or best combination of the additional non-antibiotic treatments. If you were not in the study you could still receive the treatment (D-mannose) that is being studied. However, if you decide to be in the study then we ask that you don't take any additional vitamin C, cranberry, D-mannose, and methenamine as it could change study outcomes.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?

As part of this study you will receive tests and procedures that are similar to what you would receive during routine clinical care of your condition. Your health plan/insurance company will be billed for some or all of these costs, and you will be responsible for any co-pays and deductibles that are normally required by your health plan/insurance. Not all insurance plans cover the costs associated with being in a study. Even if they do, you may be responsible for more out-of-pocket expenses, such as co-pays and deductibles, when there are more tests and procedures or more expensive tests and procedures involved in the study than if you were to receive routine clinical care outside the study.

If you wish to know whether there are more tests and procedures or more expensive tests and procedures in the study, you should ask your study doctor.

If you wish to know whether your insurance will pay, you should contact them directly, or speak with the study team about obtaining a financial pre-certification prior to enrolling in the study.

D-mannose is not prescription and you would be responsible for the cost and purchasing it from store that sells supplements.

WILL I BE PAID FOR PARTICIPATING?

You will not be paid for being in this research study.

WHO IS FUNDING THIS STUDY?

The University and the research team are not receiving payment from other agencies, organizations, or companies to conduct this research study.

WHAT IF I AM INJURED AS A RESULT OF THIS STUDY?

Washington University investigators and staff will try to reduce, control, and treat any complications from this research. If you feel you are injured because of the study, please contact the investigator at (314)747-1402 and/or the Human Research Protection Office at 1-(800)-438-0445.

Decisions about whether payment for medical treatment for injuries relating to your participation in research will be made by Washington University. If you need to seek medical care for a research-related injury, please notify the investigator as soon as possible.

HOW WILL YOU KEEP MY INFORMATION CONFIDENTIAL?

Other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you. We will keep your participation in this research study confidential to the extent permitted by law.

- Government representatives (including the Office for Human Research Protections) to complete federal or state responsibilities
- The U.S. Food and Drug Administration
- Your primary care physician if a medical condition that needs urgent attention is discovered
- Hospital or University representatives to complete Hospital or University responsibilities
- Information about your participation in this study may be documented in your health care records and will be available to anyone with access to your health care record, including your health insurance company. This information may also be released as part of a release of information request.
- The last four digits of your social security number may be used in hospital or University systems to track billing information for research procedures.
- Washington University's Institutional Review Board (a committee that oversees the conduct of research involving human participants) and the Human Research Protection Office. The Institutional Review Board has reviewed and approved this study.

To help protect your confidentiality, only research team members will have access to both the paper and electronic data. You will be assigned a unique study ID that will be used on all forms and database reporting. The database that will be used 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. For text messaging, we will be using a short message service (SMS) service that does not collect any identifying information. Urine samples are not stored after testing.

Any report or article that we write will not include information that can directly identify you. The journals that publish these reports or articles require that we share your information that was collected for this study with others. Sharing this information will allow others to make sure the results of this study are correct and help develop new ideas for research. Your information will be shared in a way that cannot directly identify you.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Are there additional protections for my health information?

Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, you must give the research team permission to use and disclose (share) your PHI for the study as explained in this consent form. The research team will follow state and federal laws and may share

your health information with the agencies and people listed under the previous section titled, "How will you keep my information confidential?"

Once your health information is shared with someone outside of the research team, it may no longer be protected by HIPAA.

The research team will only use and share your information as talked about in this form or as permitted or required by law. When possible, the research team will make sure information cannot be linked to you (de-identified). Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form. If you have questions or concerns about your privacy and the use of your PHI, please contact the University's Privacy Officer at 866-747-4975.

Although you will not be allowed to see the study information, you may be given access to your health care records by contacting your health care provider.

If you decide not to sign this form, it will not affect

- your treatment or the care given by your health provider.
- your insurance payment or enrollment in any health plans.
- any benefits to which you are entitled.

However, it will not be possible for you to take part in the study.

If you sign this form:

- You authorize the use of your PHI for this research
- This authorization does not expire.
- You may later change your mind and not let the research team use or share your information (you may revoke your authorization).
    - To revoke your authorization, complete the withdrawal letter, found in the Participant section of the Human Research Protection Office website at https://hrpo.wustl.edu/participants/withdrawing-from-a-study/ or you may request that the investigator send you a copy of the letter.
        - **If you revoke your authorization:**
            - The research team may only use and share information already collected for the study.
            - Your information may still be used and shared as necessary to maintain the integrity of the research, for example, to account for a participant's withdrawal from the research study or for safety reasons.
            - You will not be allowed to continue to participate in the study.

Can we contact you by text?

We would like to contact you by text message for the purposes listed below. Some of these texts may contain health information that identifies you.

- To remind you to complete your diary
- To ask you if you have had any new symptoms

Only the research team will have access to your texting communications. We will only communicate by text to send you the information listed above. If you have any questions or need to contact us for an urgent or emergent situation, please contact the research team member identified at the top of this document. Only the immediate response you send to a text message will be seen by a research team member. Other text messages sent to the study number will not be read or accessible by the research team. Message and Data rates may apply. You will receive a maximum of six messages a month. You can text STOP or contact the research team member identified at the top of the document to opt-out of receiving these messages.

You should be aware that there are risks associated with allowing us to text you for the purposes of this study.

- There is always a risk that the text message could be intercepted or sent to the wrong telephone number. To avoid sending messages to the wrong number, the first text we send you will be a test message to ensure we have the correct telephone number.

Do you agree to allow us to send you a test message at the beginning of the study, reminders to complete your diary, and questions about new symptoms via text?

_____ Yes **_____ No**
Initials **Initials**

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all. If you decide to be in this study, you may stop participating at any time. Any data that was collected as part of your participation in the study will remain as part of the study records and cannot be removed.

If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

What if I decide to withdraw from the study?

You may withdraw by telling the study team you are no longer interested in participating in the study or you may send in a withdrawal letter. A sample withdrawal letter can be found at https://hrpo.wustl.edu/participants/withdrawing-from-a-study/ under Withdrawing from a Research Study.

Will I receive new information about the study while participating?

If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

Can someone else end my participation in this study?

Under certain circumstances, the investigator might decide to end your participation in this research study earlier than planned. This might happen for no reason or because in our judgment it would not be

safe for you to continue, if you receive an antibiotic for UTI like symptoms without having bacteria found on urine culture, or if funding for the research study has ended.

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself, please contact: Jerry Lowder, M.D. or another member of the research team at (314)747-1402**.** If you experience a research-related injury, please contact: Jerry Lowder, M.D. or another member of the research team at (314)747-1402.

If you have questions, concerns, or complaints about your rights as a research participant, please contact the Human Research Protection Office at 660 South Euclid Avenue, Campus Box 8089, St. Louis, MO 63110, 1-(800)-438-0445, or email hrpo@wustl.edu. General information about being a research participant can be found on the Human Research Protection Office web site, http://hrpo.wustl.edu. To offer input about your experiences as a research participant or to speak to someone other than the research staff, call the Human Research Protection Office at the number above.

This consent form is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by agreeing to participate in this study. As a participant you have rights and responsibilities as described in this document and including:

- To be given enough time before signing below to weigh the risks and potential benefits and decide if you want to participate without any pressure from the research team or others.
- To understand all of the information included in the document, have your questions answered, and receive an explanation of anything you do not understand.
- To follow the procedures described in this document and the instructions of the research team to the best of your ability unless you choose to stop your participation in the research study.
- To give the research team accurate and complete information.
- To tell the research team promptly about any problems you have related to your participation, or if you are unable to continue and wish to stop participating in the research study.

Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a signed and dated copy of this form.

Do not sign this form if today's date is after EXPIRATION DATE: 11/12/21.

_____ _____
(Signature of Participant) (Date)

_____
(Participant's name – printed)

Statement of Person Who Obtained Consent

The information in this document has been discussed with the participant or, where appropriate, with the participant's legally authorized representative. The participant has indicated that they understand the risks, benefits, and procedures involved with participation in this research study.

_____ _____
(Signature of Person who Obtained Consent) (Date)

_____
(Name of Person who Obtained Consent - printed)