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Cinnamon as a prophylaxis against UTI in premenopausal women

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Research Proposal:

Cinnamon as a prophylaxis against UTI in premenopausal women

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A. Specific Aims of Proposed Research

This research proposal investigates the potential prophylactic nature of cinnamon against urinary tract infection (UTI) in premenopausal women who suffer from recurrent infection. The purpose of this study is to determine the potential effectiveness of cinnamon intake in reducing the risk of UTI in this population through a double-blind, placebo-controlled randomized clinical trial (RCT) by comparing the effectiveness of interventions. The hypothesis states that if premenopausal women who suffer from recurrent UTIs ingest 36 mg PAC-standardized ground cinnamon product then they will experience a reduced risk of UTI as compared to those ingesting a placebo.

B. Background and Significance

I. Motivation for Research and Relevance to Public Health

This research holds great public health significance. A UTI is a pathogenic invasion of the otherwise sterile urinary tract resulting in inflammation and infection.¹ Diagnosis reflects the signs of clinical symptoms and bacteriuria.¹ The National Center for Health Statistics reports that UTIs account for about 8.1 million visits to health care providers annually in the United States.² UTIs are the second-most common site for infection and, therefore, a critical health concern worthy of research.³

The incidence and prevalence of UTIs is greater in women and has been attributed to female anatomy, hormones, and behavior.¹ UTIs are about 50 times more common in adult women than men.⁴ In the U.S. alone, over 11 million women report ever having a UTI per year.⁵ The Foxman et al. survey show that the overall lifetime risk of developing a UTI is greater than 50% for adult women.⁶ The annual incidence of acute uncomplicated UTI is 7% for all women

with peaks for the age groups of 15-24 and greater than 65 years old.⁷ Unfortunately, women also suffer the greatest from recurrent infection. Recurrent UTI involves experiencing an average of two to three episodes a year.⁸ Among women, up to 25% will experience recurrent infection within six months.⁹ UTIs are considered a chronic health concern because they are often persistent and recur.⁴ After the second recurrence, 30% of these women will have a third occurrence, and 80% of this group will have subsequent recurrences.¹⁰ High recurrences indicate the benefit of a long-term antimicrobial prophylaxis, but rising antimicrobial resistance indicates the need for alternatives.^{11,12}

Infections of the lower urinary tract are common among women due to the female anatomical structure.¹ The length of the urethra is shorter in women, which allows for bacteria's easier ascent. The location of the urethral opening is also near potential bacterial sources, including the anus and vagina.¹⁰ Studies have researched the activity of *Escherichia coli* (*E. coli*), responsible for nearly 95% of UTIs, to determine its ability to cause UTI.¹³ Its ability to adhere to uroepithelial cells is one factor of its infective potential.¹⁴ This bacterial attachment induces the body's immune response and the following cascade of interleukin secretions and leukocyte infiltration, which causes inflammation and the ensuing UTI.¹⁵

The administration of antibiotics is the standard treatment prescribed for UTIs.¹⁶ This, however, is becoming an increasing health concern both biologically and financially. Biologically, the possibility of antibiotic resistance rises as recurrent infections and prescriptions increase. Antibiotic therapy has led to bacterial resistance, evidenced by the increase of clinical failure rates.⁵ Financially, UTIs account for over \$1.6 billion in direct costs.¹⁷ Exploring natural prevention, therefore, is both biologically and financially desirable.

II. Summary of Existing Research and Knowledge

E. coli adheres to cell surfaces by producing two types of adhesins.⁵ In the case of UTI, the *E. coli*'s hair-like fimbria extensions produce adhesins, which attach themselves to receptors on uroepithelial cells.¹⁸ Cranberry consumption has been associated with UTI prevention for nearly 100 years.¹⁹ Clinical research finds that a daily dosage of 250 mL of cranberry juice prevents UTI recurrence about 50% of the time and reduces bacteria and pyuria.²⁰

Research has identified proanthocyanidin (PAC) as a primary chemical compound of cranberry that prevents bacterial adhesion.⁵ PACs are biological compounds in plants found to protect them from harmful microbe invasions and benefit human health.²¹ They are defined chemically based on their structures as oligomers and polymers of monomeric flavanoids linked through specific, or B-type, and double, or A-type, linkage bonds.²¹ Cranberries contain these PACs with A-type linkages.²² Research finds these A-type cranberry PACs to prevent the adhesion of uropathogenic *E. coli* bacteria to uroepithelial cells by inhibiting its P-fimbriated adhesion in both *ex vivo* and *in vivo* studies.²³ Without adhesion, these *E. coli* cells cannot breach the mucosal surface to infect the urinary tract.²⁴ PACs with A-type linkages stop the adherence of uropathogenic bacteria to the uroepithelium by inhibiting its P-fimbriated adhesion and thereby stop infection before it can occur.²⁵

The A-type linkage appears to be the important structural feature for bacterial anti-adhesive activity.⁵ The study by Howell et al. investigated the anti-adhesive properties of PACs by comparing the anti-adhesion activity of cranberry juice, containing A-type PACs, with those of non-cranberry products such as apple juice and dark chocolate, which contain B-type PACs. The results show that only the consumption of cranberry juice prevented bacterial adhesion.²⁵ If the anti-adhesive property was due solely to the presence of fructose or any type of PAC,

regardless of type, then all products should have prevented adhesion. The other food products with type-B linkages, however, did not provide the same benefit as the cranberry product with type-A linkages. The current theory supports that it is the presence of PACs containing A-type linkages, specifically, which provides anti-adhesive properties and thus prevents UTI.²⁶

The results of one meta-analysis on intervention studies investigating cranberry intake and the prevention of UTI show that cranberry products significantly reduce the number of UTIs at 12 months compared to placebo controls and were especially effective in reducing incident UTI cases in women with recurrent UTIs.⁴ While cranberry consumption is effective, the study notes that high withdrawal rates suggest it is an unacceptable therapy that cannot be sustained for certain populations.^{4,26} The low palatability and high sugar content of cranberry juice are cited as causes for withdrawal. The cost of consuming large amounts of sugary, marketed juice products for the preventative benefit may be too great or undesirable for some people. Ocean Spray, a popular brand of cranberry juice, costs an additional 140 calories and 36 grams of sugar per eight ounces and around \$6 per 64-ounce bottle.²⁷ In an American population that already over consumes calories and sugar, an alternative source of prevention is desirable. Thus, finding an alternative source of a dietary inhibitor of bacterial adhesion, which is both more cost and health effective, would provide the benefit of UTI prevention without requiring antibiotics or compromising other areas of life.

This proposed study seeks to further investigate this hypothesized active compound by testing the effectiveness of cinnamon, another food product containing PACs with A-type linkages, as a prophylaxis against UTI. The concentration of PACs in cranberry is measured at 418.8 ± 75.3 mg/100 g and ground cinnamon at 8108.2 ± 424 mg/100 g.²² Costing only 6 calories per teaspoon and about \$2 per 3-ounce jar, cinnamon is a low calorie and price

alternative compared to cranberry juice.²⁸ Cinnamon provides a potent dose of PACs with A-type linkages and is therefore a potentially powerful prophylaxis.

C. Research Design and Methods

I. Study Design

This proposed study has been designed to research the relationship between cinnamon, adult premenopausal women, and UTI. A double-blind, placebo-controlled RCT will test various interventions for their effectiveness in reducing recurrent UTIs in the study population during a 2-year trial period. Both the participant and outcome assessor will be blind to the participant's assigned intervention group. The 2012 Review suggests studying the long-term benefits in future research since most previous studies concluded after only 12 months.

Therefore, the 2-year period has been chosen to test the effectiveness over a longer term.

II. Exposure and Outcome Definition

The primary outcome is defined as the occurrence of a clinically diagnosed UTI during the 2-year trial period. The gold standard for the diagnosis of a UTI is pathogenic detection in the urine with the presence of symptoms.²⁹ The threshold bacterial criteria of 100,000 cfu/mL, the gold standard, will be used to diagnose culture-confirmed UTI.²⁴ Using the study by Stapleton et al. as a model, symptoms include dysuria, frequency, urgency, suprapubic pain, hematuria, and pyuria with a blood cell count of at least 10/ μ L.³⁰ UTI will be defined as cases showing bacteriuria with the onset of urinary symptoms including dysuria plus at least one of the following symptoms: frequency, urgency, suprapubic pain, hematuria, and pyuria.³⁰ As a secondary outcome, women with a urinalysis showing at least 100,000 cfu/mL of bacteria without symptoms will be diagnosed as having asymptomatic bacteriuria. Outcomes will be

evaluated every two weeks by assessing for symptoms and collecting urine samples from the participants.

This study compares the effectiveness of five interventions. The exposures are defined, therefore, according to the type of intervention. While numerous studies show the effectiveness of cranberry, such as consuming 400 mg of cranberry solids or 250 mL of cranberry juice taken three times a day, these do not test equivalent dose concentrations of the active compound.^{31,32} Products contain various PAC concentrations and processing can impact PAC composition.⁵ The specific PAC concentration of a product must be determined, therefore, in a laboratory using a technique such as the dimethylaminocinnamaldehyde (DMAC) method.³³ Since this study tests the effectiveness of PAC as the active compound provided by various sources, the PAC concentration of these sources will be standardized. This ensures equivalent comparisons to test the effectiveness of the exposure, PAC presence, to the outcome, UTI occurrence.

The interventions will be testing the bioactivity of PAC-standardized products containing a dosage of 36 mg PAC. The 2012 Cochrane Review reports that studies show a dosage of at least 36 mg of cranberry PAC equivalents/d taken twice daily effectively inhibits bacterial adhesion.³³ This PAC concentration has been measured, administered, and found to combat UTI in two studies using cranberry in both powder and juice forms.^{24,33} The consistency of results though the form differed, suggests the significance of the PAC component at this dose. Therefore, this study seeks to further test the effectiveness of the PAC, specifically, regardless of its source.

This proposed study is founded on the hypothesis that foods containing 36 mg PAC, provide the anti-adhesive property to protect the uroepithelial cells from infection and thus the

body from UTI. Therefore, this study evaluates the effectiveness of 36 mg PACs by testing different sources, both cranberry and cinnamon, to prevent UTI.

This study will use the DMAC method to quantify and ensure each exposure contains the prescribed 36 mg PAC dose, as advised by the 2012 Cochrane Review.²⁴ The five exposures include: 1) 1 teaspoon of ground cinnamon added to the diet with a placebo juice and placebo tablet, 2) cinnamon tablets containing 400 mg of cinnamon solids with a placebo juice and placebo spice, 3) 300 mL cranberry juice with a placebo tablet and placebo spice, 4) cranberry tablets containing 400 mg cranberry solids with a placebo juice and placebo spice, and 5) placebo tablets, juice, and spice. The placebos will appear, taste, and smell similar to the test products but will not contain any PAC compound. The hypothesis states that if premenopausal women who suffer from recurrent UTIs ingest 36 mg PAC-standardized cinnamon product then they will experience a reduced risk of UTI as compared to those ingesting a placebo.

Each subject will be given two weeks worth of her assigned dosage with directions for self-administration. They will be given recommendations for ways to incorporate the spice into their diet, such as adding it to yogurt, toast, or coffee. She will be responsible for ingesting her daily treatment. She will receive the next supply of treatment each time she reports for data collection.

III. Study Population and Recruitment

The participants in this study will be adult, premenopausal women who suffer from recurrent UTIs. Adult, premenopausal women will be defined as females at least 18 years of age who have menstrual cycles. This population is chosen because female hormones are related to urinary tract health. Estrogen, which is more abundant in menstruating women, helps maintain the normal acidity of vaginal fluid to promote vaginal flora to protect against UTI.¹ There is no

maximum age limit so long as menopause has not occurred. Menopause is defined as having no menstrual cycle in the preceding 12 months.³⁴ By selecting on this criterion, this study attempts to control the baseline risk factor of hormone level among the study population.

The definition of recurrent UTI has varied across previous studies from having two to four UTIs in the past 12 months to simply having a history of recurrent UTI.⁴ In this study, it will be defined as having at least two diagnosed UTIs in the past 12 months. This definition is based on the natural course of UTI, which generally occurs in episodic clusters, and seeks to capture a highly susceptible population.²⁴

Exclusion criteria includes currently having a UTI, taking an antibiotic within the past 6 months, having abnormal urinary tract structures, having catheterization within the past 12 months, pregnancy, or having a cranberry or cinnamon allergy or intolerance. Women must be screened prior to their entry into the study. Women with urine showing at least 100,000 cfu/mL are excluded from the study because they would already meet the threshold for a bacteriuria diagnosis, which is one of the outcome measurements. This screening is critical since women may unknowingly have this condition. Regarding retention, they will also be asked and selected based on if they plan on maintaining residence in the city for the next two years until the study concludes. The criteria of a 6-month lag time since antibiotic use and 12-month lag time since catheterization is validated by previous studies.²⁴ Abnormal anatomy of the urinary tract system and catheterization are factors that greatly increase the risk of UTI.¹ Therefore this study will select for women with similar risk for UTI by excluding those exposed to these identified risks. Pregnant women are excluded from the study because their hormone levels, which are found to affect bacterial adhesion, differ in pregnancy. Lastly, those with a cranberry or cinnamon allergy or intolerance are excluded to protect those whose health would be compensated by participating.

The study population will be recruited from university medical centers and hospitals in a major metropolitan city, such as New York City. New York is an ideal city because there are numerous hospitals and universities within the radius of Manhattan. It is a densely and diversely populated area, which provides for a larger pool from which to recruit. Additionally, the women recruited share a similar urban environment. A variety of races, ethnicities, lifestyle behaviors, and health habits are also represented within an urban population. The study's results, therefore, can potentially speak to a broader audience and can be stratified on specific factors, such as race or behavior.

Student medical centers at universities are ideal recruitment sites since most females seeking health services in this population meet the criteria as adult, premenopausal women. Hospitals are also ideal with their variety of medical specialty departments to meet the needs of such a densely populated city. Therefore, hospitals with departments that specialize in women's health can provide for a large study population. Women will be recruited from general health practitioner offices in addition to patients within the urology and gynecology departments. Urology, specifically, provides for subjects close to the target population since these women are likely seeking help related to their urinary tract health.

Recruitment methods include posting advertisements in local areas, such as on university campuses, and mailing advertisements and interest cards to female student mailboxes. Clinicians will also be asked to refer their patients to the study. Since 12 months are required to have passed since prior UTI, recruitment will be conducted for 18 months. This allows adequate time to recruit potential subjects who have a UTI but can recover before the 12-month critical period for enrollment.

Recruitment of 1,200 women will be planned for this study. On the basis of previous studies from similar populations, this provides for adequate allotment in each intervention group for statistical power while accounting for potential dropout.³⁰ The remaining eligible women, after screening, will be randomly chosen to create a study population of 1,050 subjects for enrollment. Then 210 women, validated by Stapleton et al. for significance, will be randomly assigned to each intervention group.³⁰

Once the women have been recruited and screened, those eligible will complete and sign their informed consent to participate. The women will also agree not to consume any additional cranberry or cinnamon during the study, as this would increase their PAC dosage and exposure. Each subject will be given an identification number to be stored for concealment and used in data analysis. Computer-generated randomization will be used to assign these women to one of the five intervention groups. Randomization theoretically eliminates both known and unknown confounders. Refer to Figure 1 in Appendix for a representative flow chart of this study.

IV. Data Collection

A questionnaire will collect information from the participants at baseline before the study begins (Figure 3). This in-depth, self-reported health history of the subject provides for many variables (Figure 2), which can later be used to stratify the data to compare the effectiveness for subjects. Information including age, weight, height, residence, race, and ethnicity will be reported. The participants will also be asked to report the number of previous UTIs they have experienced throughout life and the corresponding symptoms. They will also complete their first self-reported questionnaire (Figure 4), as described below, which will be completed every two weeks for data collection. An initial urinalysis will be conducted to evaluate their urinary tract health and bacteria concentrations at baseline.

Each participant will report to the research clinic once every two weeks in order to collect her data throughout the study. This frequency is done to capture fluctuating bacterial counts. First, she will be asked to answer a questionnaire that asks about the presence of symptoms since her last visit. She will be asked to report if she has experienced dysuria, frequency, urgency, or suprapubic pain. Second, a “clean catch” urine sample will be collected to test for pyuria, hematuria, and bacteriuria. A sample showing at least 100,000 cfu/mL will be classified as a case of bacteriuria. These cases will then be categorized as culture-confirmed UTI if accompanied by symptoms or asymptomatic bacteriuria if symptoms are absent (Figure 5).

A subject’s participation in the study concludes if she is diagnosed with UTI or asymptomatic bacteriuria. She will be informed about possible treatments and referred to physicians. This is implemented for two reasons. First, since antibiotics are generally administered for treatment and participant eligibility excludes those on antibiotics, a subject cannot both seek antibiotic treatment and participate in the study. Second, it would be unethical to withhold or deny treatment from these women in any way for research purposes. PAC content appears to play a role in UTI prevention but not treatment.²⁴ While an alternative option would be to allow the woman to voluntarily decide to stay in the study, it is unlikely that she will recover without treatment. Additionally, the bacteria from the first incident would likely contribute to causing any subsequent cases. Therefore, this protocol is implemented to protect the study’s ethics and outcome measurements.

Third, she will complete a self-report questionnaire to collect data on behavior patterns. She will be asked questions about her sexual activity regarding type and frequency, indicating a) 0x/week, b) 1-2x/week, or c) $\geq 3x/week$. Sexual activity is identified as a risk factor of UTI since it introduces bacteria near the urinary tract.¹ Therefore, the level of sexual activity would be

helpful for data analysis. This information would allow for the results to be stratified according to sexual activity to determine the relationship, if any, between sexual activity, intervention type, and risk. She will also be asked questions about her smoking behaviors, alcohol consumption, diet, and physical activity. These are general factors related to one's overall health. This data can also be used to stratify and analyze the results, should unforeseen trends arise. She will also report her number of missed doses. Adherence to the dosing regimen can be calculated by dividing the ingested number by the expected number of dosages per two weeks.³⁰ Weighted means can be calculated to account for potential missed dosage treatments, if this occurs.³⁰ Lastly, though she agreed not to ingest either cinnamon or cranberry during the study, this may be difficult and ingestion may occur. Therefore she will be asked to report any such instances. The weighted means and self-reports record and account for unanticipated changes in dosage exposure. They can be used to create compliance groups, for example, if necessary in the data analysis stages.

Fourth, in the interest of its subjects, this study is concerned with adverse effects. They will be asked to report gastrointestinal symptoms, often induced by cranberry consumption.³⁰ Therefore, these can be tracked. To address this issue, women will be informed of their freedom to voluntarily leave the study at any point for any reason at the time of enrollment.

V. Proposed Analysis Strategy and Main Effect Measures of Interest

This study will collect data to determine the following for UTI and asymptomatic bacteriuria cases: 1) incidence, 2) incidence density rate, and 3) time to diagnosed case during the testing period. The time to diagnosis is useful to study the longitudinal effectiveness of each intervention as a potential prophylaxis. The incidence, or risk, is defined as the number of cases that occur during the 2-year study. The incidence density rate is the incidence divided by the

person-time of the population at risk. This is useful because participants may voluntarily leave and those who develop cases are dropped from the study. Therefore, the rate reflects that only those in the study, still at risk for UTI or asymptomatic bacteriuria, contribute to person-time. These risk rates reveal the probabilities of developing UTI and asymptomatic bacteriuria in a given time period. The measurements will be calculated to compare and determine if there is a reduced risk in any of the interventions.

Many analysis tables can be created to study the data. In order to test the hypothesis, a 2x2 table will be constructed to compare the outcomes from each cinnamon group to the placebo group. In the first table, the data from the “Cinnamon Teaspoon” group will be defined as “exposed” while the data from the “Placebo” group will be defined as “unexposed” (Figure 6). The “disease” corresponds to diagnosed UTI and the “no disease” corresponds to no diagnosed UTI. The results, then, reflect an exposure to 36 mg of PAC delivered through ground cinnamon. From this analysis, the risk ratio (RR) can be determined. The RR is calculated by dividing the risk of disease in the exposed by the risk of disease in the unexposed. This indicates that the risk in the exposed group is “x-times” that of the unexposed. The equation $[RR - 1.00 = x(100\%) = x\%]$ can be used to describe the percent increase or decrease in risk with exposure. Theoretically, according to the hypothesis, this study predicts a RR less than one and a negative “x%” to indicate a decreased risk with cinnamon exposure. A reduced risk in the cinnamon group would support the hypothesis. A second table and RR can be calculated comparing the exposed “Cinnamon Tablet” group to the unexposed “Placebo” group (Figure 7). These RRs can then be compared to determine if cinnamon in the ground or tablet form is more effective. This strategy can also be applied to study asymptomatic bacteriuria as the defined “disease” in later analyses. Additional tables and RRs can likewise be created to compare across intervention and

placebo groups, depending on the “exposed” and “disease” definitions and combinations, to compare the effectiveness of the exposures as a prophylaxis (Figure 8).

Further data manipulation will allow for thorough analysis of the results. First, the women will be collapsed into categories based on age to determine biological significance and reveal any trends. This turns the continuous variable of age into a categorical variable of age group. Three categories of women will be created: 18-28, 29-39, and 40+ years old. Age may be implicated as hormone and immune activity change and studies report UTI peaking in age groups.^{1,7} Second, the women will be collapsed into categories based on the averages of their sexual activity. This creates the following three categories of women according to the mean frequency of their sexual activity: 0x/week, 1-2x/week, ≥ 3 x/week. The biological significance of these groups is informed by the studies that show sexual activity as a risk factor. Likewise, stratifying on variables collected in the self-reported health history, such as demographic and lifestyle information, can analyze women with certain characteristics. The effectiveness of the interventions according to race, smoking behavior, or any factor can then be compared.

VI. Potential Biases, Implications, and Points to Consider

There are potential biases in this study. First, the defined diagnosis of UTI is arbitrarily set. While the 2012 Review cites 100,000 cfu/mL as the gold standard, the minimum level of bacteriuria reflecting UTI has not been formally defined in scientific literature or standardized by microbiological laboratories.²⁹ Diagnosis can vary from 10^3 cfu/mL to 10^5 cfu/mL across hospitals, labs, and studies. Each threshold number risks missing relevant case infections.²⁹ Setting a diagnosis threshold unavoidably introduces the potential to miss infections, which could be identified as cases had the criteria been defined otherwise. The incidence and incidence density rate, therefore, may be lower if it misses those below the threshold or higher if it includes

more than another threshold. For purposes of testing, however, the outcome is defined to capture the gold standard most commonly used. UTI is also a broad term and can manifest itself in various cases.¹⁰ Stapleton acknowledges the inconsistency across previous studies in the definition of UTI as the primary outcome.³⁰ This study attempts to address this issue by clearly defining its definition of diagnosis based on the gold standard. The results, therefore, should not be used to suggest the effectiveness against all types of UTIs within all populations.

Second, selection bias is possible. The women who volunteer and enroll to participate may represent a certain population and therefore bias the results. Since participation requires a time commitment and ability to transport oneself to the research clinic twice a month, not all women may be able to commit and enroll. For example, only those women from a higher socioeconomic status may be able to afford the time and cost of travel to participate. One way to address and reduce this bias is by making participation more convenient by holding multiple locations for data collection.

Lastly, there is considerable information bias introduced every time a subject reports information for data collection. This includes the questionnaires used to record past UTIs, experiences of symptoms, and lifestyle behavior. These rely on recall accuracy, which also unavoidably limits this study. Their report of symptoms is especially biased since these are subjective and may easily be influenced by their participation in this type of study, which is focused on UTI. To address this, the subjects will attend a brief orientation at the time of screening which will describe the symptoms. This will help standardize the way the subjects assess and identify the presence of symptoms. A blind clinician will also be present during reporting to help determine a more accurate clinical diagnosis by answering questions to help participants assess their symptoms.

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Appendix

Figure 1: Flow chart of study design and subject counts

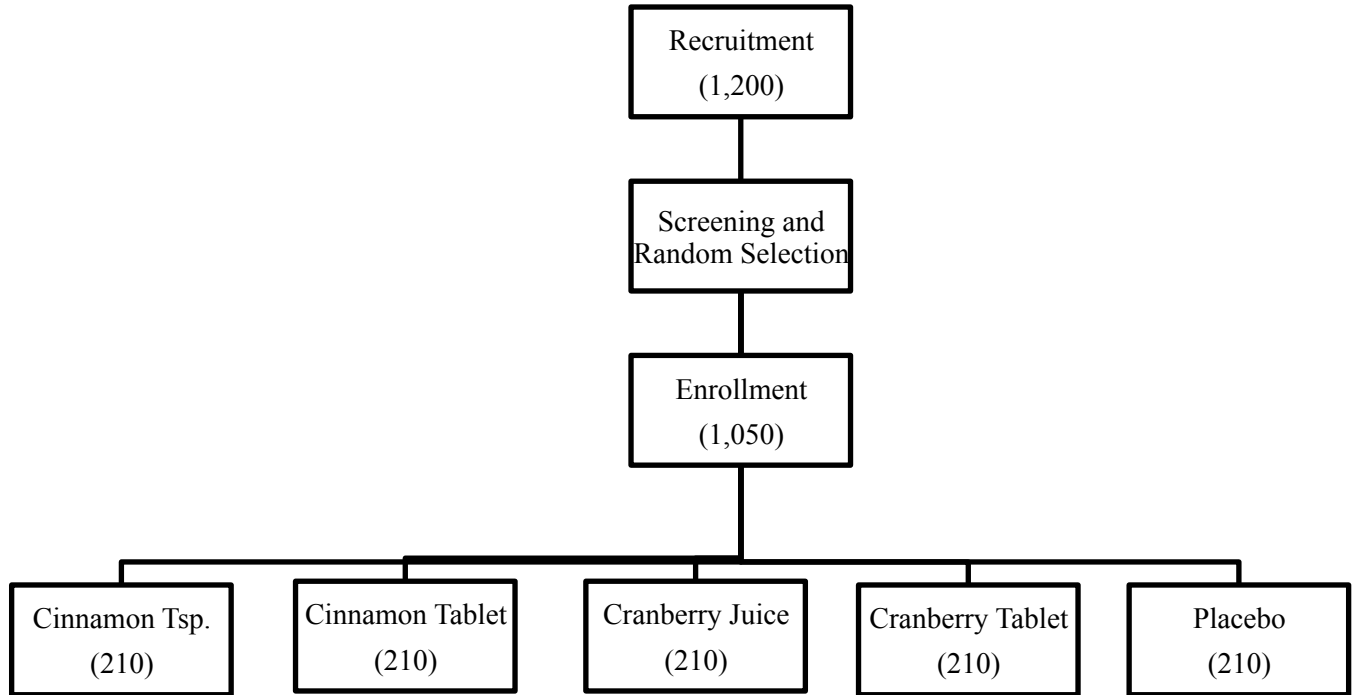


Figure 2: Raw data collected from questionnaire

Variable	Variable Type
Age	Continuous
Height	Continuous
Weight	Continuous
Residence	Categorical
Race	Categorical
Ethnicity	Categorical
# of previous UTIs	Categorical
Sexual activity	Categorical
Physical activity	Categorical
Smoking behavior	Categorical
Alcohol consumption	Categorical

Figure 3: Example of possible questionnaire for baseline data collection prior to start of study

Subject Questionnaire: Baseline

Name: _____ **Date:** _____

Age: _____
Weight: _____
Height: _____
Zip Code: _____

Race: Please indicate by checking the appropriate box below

- African/African-American
- Asian/Asian-American
- Caucasian
- Hispanic/Hispanic-American
- Other: _____

Ethnicity: Please indicate by checking the appropriate box below

- African
- African-American
- Asian
- Asian-American
- Caucasian
- Hispanic
- Hispanic-American
- Other: _____

Number of previous lifetime UTI(s) experienced: Please indicate by checking the appropriate box below

- 2-3
- 4-5
- ≥ 6

Symptoms experienced: Please indicate all that apply by checking the appropriate box(es) below

- Dysuria
- Frequency
- Urgency
- Suprapubic pain
- Culture-confirmed pyuria
- Culture-confirmed hematuria
- Culture-confirmed bacteriuria

BELOW THIS LINE TO BE COMPLETED BY LAB

Bacteriuria content: _____
Hematuria content: _____
Pyuria content: _____

Figure 4: Example of possible questionnaire for data collection conducted and recorded every two weeks throughout study

Subject Questionnaire: # _____ of 49

Name: _____ **Date:** _____

Smoking behavior: Please indicate by checking the appropriate box below

- Never
- Smoked previously but have since stopped
- Currently smoking 1 cigarette/day
- Currently smoking 2-4 cigarettes/day
- Currently smoking ≥ 5 cigarettes/day

Alcohol consumption: Please indicate by checking the appropriate box below

- Never
- Consume 1 drink/week
- Consume 2-4 drinks/week
- Consume ≥ 5 drinks/week

Physical activity: Please indicate by checking the appropriate box below

- 0 min/day
- ≤ 30 min/day
- ≥ 30 min/day

Physical activity frequency: Please indicate by checking the appropriate box below

- 0 days/week
- 1 day/week
- 2-3 days/week
- ≥ 3 days/week

Sexual frequency: Please indicate by checking the appropriate box below

- 0 times/week
- 1-2 times/week
- ≥ 3 times/week

Symptoms experienced: Please indicate all that apply by checking the appropriate box(es) below

- Dysuria
- Frequency
- Urgency
- Suprapubic pain
- None

Number of sexual partners: Please indicate by checking the appropriate box below

- 0
- 1
- ≥ 2

Number of doses missed: Please indicate by checking the appropriate box below

- 0
- 1
- ≥ 2

BELOW THIS LINE TO BE COMPLETED BY LAB

Bacteriuria content: _____ Hematuria content: _____ Pyuria content: _____

Figure 5: Diagnosis

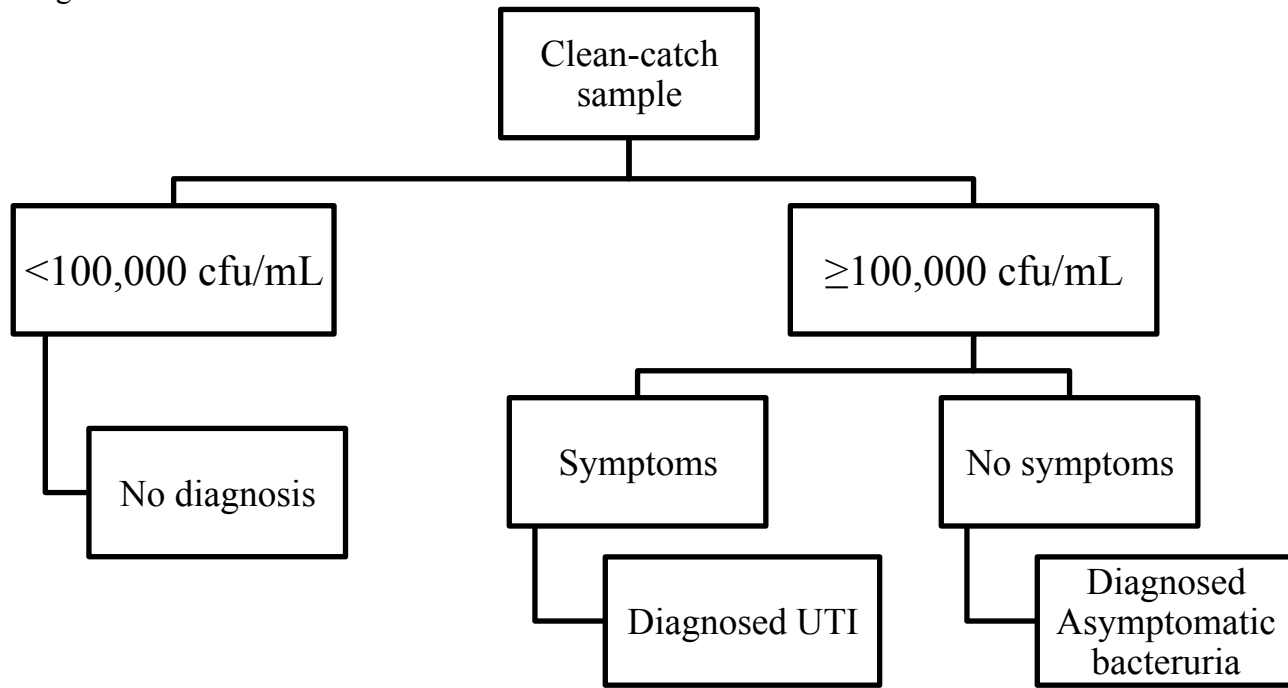


Figure 6

	Cinnamon Teaspoon (Exposed)	Placebo (Unexposed)
Diagnosed UTI (Disease)		
No Diagnosed UTI (No Disease)		

Figure 7

	Cinnamon Tablet (Exposed)	Placebo (Unexposed)
Diagnosed UTI (Disease)		
No Diagnosed UTI (No Disease)		

Figure 8: Each exposure and outcome is categorized. Different combinations can be used to construct various additional 2x2 tables.

Exposed	Unexposed	Disease	No Disease
Cinnamon Teaspoon	Placebo	Diagnosed UTI	No Diagnosed UTI
Cinnamon Tablet		Diagnosed Asymptomatic Bacteruria	No Diagnosed Asymptomatic Bacteruria
Cranberry Juice			
Cranberry Tablet			