Protocol

A Randomized Controlled Trial of Cranberry Capsules for UTI Prevention in Nursing Home Residents

CRANNY (CRANberry capsules for prevention of UTI in Nursing home residents at Yale)

This trial protocol has been provided by the authors to give readers additional information about their work. It has been adapted from the Yale University Human Investigation Committee (HIC) approved study protocol. The initial and final protocols have been submitted for reference. This supplement contains a summary of important changes, original protocol, and final protocol, including the original and final statistical analysis plan.

CRANNY Study Protocol (HIC#1112009472) – Summary of Important Changes

Version 1.0, February 21, 2012 (original)

Version 2.0, April 26, 2012

Version 3.0, June 20, 2012

Version 4.0, August 22, 2012

Version 5.0, October 18, 2012

Version 6.0, January 4, 2013 (Renewal)

Version 7.0, June 10, 2013

Version 8.0, December 3, 2013

Version 9.0, January 28, 2014 (Renewal)

Version 10.0, February 25, 2014

Version 11.0, September 23, 2014

Version 12.0, September 26, 2014

Version 13.0, October 28, 2014

Version 14.0, January 29, 2015 (Renewal)

Version 15.0, August 13, 2015

Version 16.0, November 16, 2015

Version 17.0, January 25, 2016 (Renewal)

Summary of changes from Version 1.0 (February 21, 2012) to Version 2.0 (April 26, 2012)

Added one new nursing home site and provided letter of support. Revised protocol to show change from 16 to 17 sites.

Revised nursing home sites needed "up to 20".

Revision of language from Data Safety Monitoring Board (DSMB) to Data Safety Monitoring Plan (DSMP). In initial discussions with the Yale Human Investigation Committee (HIC), a DSMP had been approved but the funding agency (NIA) initially required a DSMB. After further review by the NIA program officer, the NIA approved a DSMP with an Independent Safety Monitor nominated by the NIA.

Revised the surveillance of adverse events from "once per week" to "on a monthly basis".

Revised interim monitoring by replacing DSMB language with "the Independent Safety Monitor and NIA Program Officer on a quarterly basis."

Indicated that Yale-New Haven Hospital's Investigational Drug Service would prepare and store the cranberry capsules.

Changed the Principal Investigator's address.

Added a recruitment/informational brochure.

Added Health Information To Be Collected: telephone numbers, fax numbers, Email addresses, social security numbers and medical record numbers.

Changes to Adult & Surrogate Consent Forms:

Changed address of principal investigator, language change regarding medical and laboratory records, capitalized "Hospital", added language to bottom of form. This language was added to ensure that hospitals that participants are admitted to allow review of medical records after the stamped date of the HIC consent. "The Surrogate understands that information in connection with the study may be collected beyond the Form Valid Date (listed above) for thirty (30) months."

Summary of changes from Version 2.0 (April 26, 2012) to Version 3.0 (June 20, 2012)

Removed one nursing home site which in turn changed the number of sites participating from 17 to 16.

Added Authorization to Release Protected Health Information for Research form.

Summary of changes from Version 3.0 (June 20, 2012) to Version 4.0 (August 22, 2012)

Added new letters of support signed by new Administrators at two nursing home sites which replaced the old letters of support.

Summary of changes from Version 4.0 (August 22, 2012) to Version 5.0 (October 18, 2012)

Added one new Study Personnel member.

Summary of changes from Version 5.0 (October 18, 2012) to Version 6.0 (January 4, 2013)

Yearly renewal approved.

Summary of changes from Version 6.0 (January 4, 2013) to Version 7.0 (June 10, 2013)

Added four new nursing home sites with letters of support.

Revision to Recruitment Methods of "YCCI Recruitment database".

Revision to Recruitment Procedures by adding a Research Associate to people recruiting subjects.

Revision to Consent Personnel by adding a Research Associate to people obtaining consent.

Summary of changes from Version 7.0 (June 10, 2013) to Version 8.0 (December 3, 2013)

Added one new Study Personnel.

Added five new nursing home sites with letters of support. Deleted two nursing home sites.

Revised "Role" for Research Nurses. One becoming "Field team nurse leader" and one becoming "Field nurse".

Added language to Overview Intervention to show that capsules will be given "for 12 months (30-day blister pack per month equaling 360 days)".

Added language regarding waves of recruitment.

Revised the number of mailings from 3 to 2.

Added language regarding capsule administration and follow-up.

Added an "s" to the word outcome in title of section.

Revised specimen collection from 1 to 2 weeks and at any time of the day, and added Research Associate.

Outcome adjudication. Revised title and nurses.

Surveillance of adverse events. Revised language for Field Nurse Team Leader and nurses.

Surveillance revised language about pill counting from "two weeks" to "month".

Revised recruitment age language.

Data and Safety Monitoring Plan: To be consistent with the Manual of Procedures approved by the funding agency (NIA), the plan has been expanded to include the role of the Independent Safety Monitor.

Interim monitoring. Changed language from quarterly to semi-annual. Added language.

Summary of changes from Version 8.0 (December 3, 2013) to Version 9.0 (January 28, 2014)

Yearly renewal approved.

Summary of changes from Version 9.0 (January 28, 2014) to Version 10.0 (February 25, 2014)

Removed one Study Personnel member.

Summary of changes from Version 10.0 (February 25, 2014) to Version 11.0 (September 23, 2014)

Added six new nursing home sites with letters of support.

Removed eight nursing homes.

Summary of changes from Version 11.0 (September 23, 2014) to Version 12.0 (September 26, 2014)

Revised nursing home sites from 16 to 21.

Revised enrollment number/sample size because of more missing culture data than expected, the new recruitment goal was up to 190 participants (95 per group).

Summary of changes from Version 12.0 (September 26, 2014) to Version 13.0 (October 28, 2014)

Removed two Study Personnel members.

Summary of changes from Version 13.0 (October 28, 2014) to Version 14.0 (January 29, 2014)

Added three Study Personnel as Outcome Adjudication Committee members.

Added a flyer to be used at the presentation thanking the nursing home sites that have completed participation in the study.

Revisions showing that study is closed to enrollment.

Yearly renewal approved.

Summary of changes from Version 14.0 (January 29, 2014) to Version 15.0 (August 13, 2015)

Added two Study Personnel as Outcome Adjudication Committee members.

Added language regarding primary outcome > or = 100,000

Summary of changes from Version 15.0 (August 13, 2015) to Version 16.0 (November 16, 2015)

Revision from Phase II to Phase III under Research Type/Phase.

Revised spelling of last name “Trentalage” to “Trentalange” under Research.

Corrected spelling of words throughout the protocol and changed to past tense.

Changed language from “quarterly” to “semi-annual” under Intervention paragraph.

Changed language from “attending physician” to “home administrator” under Consent and Enrollment procedures.

Summary of changes from Version 16.0 (November 16, 2015) to Version 17.0 (January 25, 2016)

Sandra Ginter was removed from this study because training requirements were not met by the time of this protocol’s re-approval.

The HIC has determined that this protocol currently presents minimal risk to subjects as it is closed to enrollment, all subjects have completed all research interventions, and the research remains open for data analysis only.

The Committee acknowledged the use of cranberry capsules in this study is exempt from the requirements for an IND, per 21 CFR 312.2(b).

Re-approval approved by HIC.

ORIGINAL PROTOCOL (Version 1.0 February 21, 2012)

1. Statement of Purpose:

The **primary aim** of this study is to test the efficacy of two oral cranberry capsules per day for prevention of bacteriuria plus pyuria in female nursing home residents. The **secondary aim** is to compare the occurrence of urinary tract specific symptoms in the cranberry capsule versus placebo groups.

The primary **hypothesis** is that two oral cranberry capsules will be associated with a 33% relative reduction in the occurrence of episodes of bacteriuria plus pyuria over 12 months, compared to placebo.

Supplementary Aims are to determine the:

- safety of administrating oral cranberry capsules over a 12 month surveillance period.
- adherence of nursing home residents and staff to the administration protocol of two oral cranberry capsules daily over 12 months.
- incidence of adverse clinical outcomes (i.e., symptomatic UTI, all cause death, all cause hospitalization, number and duration of all antibiotic prescriptions, all multi-drug antibiotic resistant organisms) in the intervention and control arms over 12 months.

2. Background:

2.1. Importance of urinary tract infection (UTI) in nursing home residents. UTI is the most common bacterial infection in nursing home residents with an incidence of 0.1 to 2.4 cases per 1000 resident-days. UTI is also a common cause of infectious disease hospitalizations and deaths; the National Nursing Home Survey indicated that UTI was an admitting or current diagnosis for hospitalization for 7,111/100,000 female residents. The Urologic Diseases of America determined that UTI was the most costly and resource intensive condition studied among Medicare beneficiaries. Total Medicare expenditures for UTI amounted to over $1.7 billion, exclusive of medication costs in 2006.

2.2. Diagnostic challenges of UTI in nursing home residents. Distinguishing symptomatic UTI (a quantitative count of $\geq 10^5$ colony forming units of bacteria per milliliter cfu/ml in one urine specimen in the presence of urinary tract specific symptoms i.e., dysuria, suprapubic pain or tenderness, new urinary frequency or urgency) from bacteriuria (a quantitative count of $\geq 10^5$ cfu/ml) is problematic in nursing home residents because of the challenges involved with symptom assessment. Bacteriuria is prevalent in 25-50% of female nursing home residents, and pyuria (any white blood cells in the urine) is present in 90% of residents with bacteriuria. Given the high prevalence of bacteriuria in this population, three randomized controlled trials of antibiotic treatment (versus no treatment) of bacteriuria were conducted; none of these trials showed any decrease in

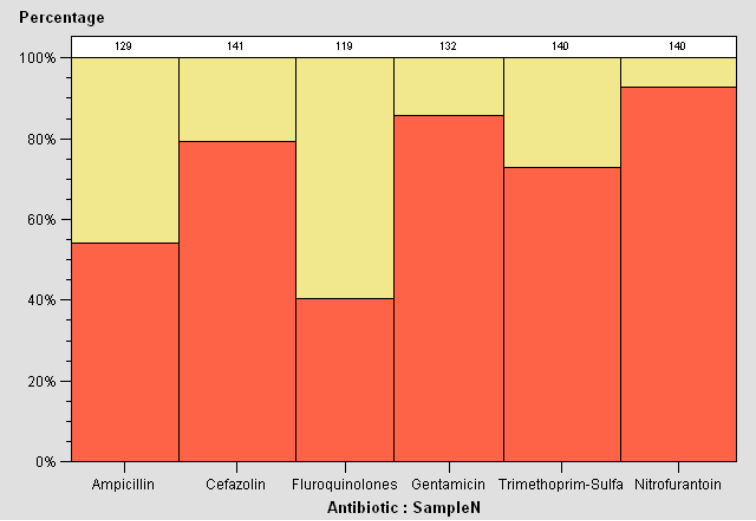

Figure 1: Urinary Isolates UTI Episodes

mortality with treatment. These studies led to the recommendation that bacteriuria should not be treated with antibiotics in older institutionalized adults. Consequently, bacteriuria plus pyuria are necessary but not sufficient conditions to make the diagnosis of UTI in this population. Infectious diseases physicians have distinguished bacteriuria from symptomatic UTI, which requires urinary tract specific symptoms. However, in clinical practice, it is not always clear how to classify a nursing home resident as symptomatic. Recent data from a large cohort in the New Haven area have shown that dysuria plus a change in mental status and/or a change in character of urine are the best combination of symptoms to predict bacteriuria plus pyuria among nursing home residents with suspected UTI. However, change in mental status and change in character of urine are subject to confounding and small numbers of patients meet these clinical criteria. Hence, symptoms have limited utility in clinical decision-making regarding the diagnosis of UTI. Given the current diagnostic uncertainty, antibiotics are commonly prescribed, and UTI accounts for 30% to 56% of all antibiotic prescriptions in the nursing home setting.

2.3. Widespread empiric antimicrobial administration. Although treatment of bacteriuria is not recommended, many nursing home residents are still prescribed antibiotics because of the diagnostic challenges involved in identifying those residents that will benefit most from antibiotic therapy. Only 13% of antibiotic prescriptions for UTI occur prior to results of urine cultures being available. Isolation of resistant organisms is associated with prior antibiotic exposure, and resistant organisms from UTI are more frequent in nursing home residents than in community dwellers. Urinary isolates from nursing home residents are frequently resistant to commonly prescribed oral antibiotics (see **Figure 1**). Use of antibiotics is associated with several risks, including the development of multi-drug antibiotic-resistant organisms, drug-related adverse effects, and significant costs. In order to reduce antibiotic prescriptions, prevention strategies should be targeted to bacteriuria, pyuria, and symptomatic UTI.

2.4. Rationale for prevention of bacteriuria, pyuria, and UTI. Bacteriuria has been shown to be a risk factor for subsequent development of symptomatic UTI among young women and women with diabetes mellitus, and it is hypothesized that bacteriuria precedes the development of symptomatic UTI in nursing home residents (see **Figure 2**). The presence of bacteriuria is the greatest trigger for the initiation of antibiotic therapy. Since nursing home practitioners usually wait to obtain results of urine cultures, reducing bacteriuria could reduce antibiotic prescriptions. Therefore, efforts to prevent bacteriuria, pyuria, and UTI represent the most logical means of reducing antibiotic prescriptions in the nursing home setting.

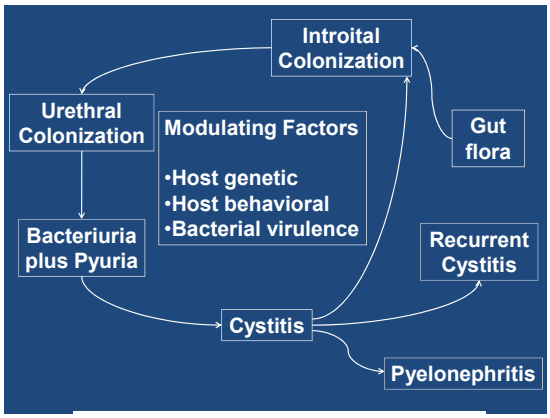

Figure 2: Pathogenesis of UTI

2.5. Cranberry for prevention of UTI.

Many of the identified risk factors for bacteriuria and UTI in nursing home residents (e.g., functional disability, dementia) are largely non-modifiable. Vaginal estrogen therapy, which has been shown to be effective at preventing recurrent UTI in post-menopausal women, has potential risks and side effects which would be undesirable in a nursing home population. With few other feasible intervention strategies to prevent the common and morbid condition of UTI in nursing home residents, cranberry capsules represent a novel intervention warranting investigation. Cranberry products represent an existing, non-antimicrobial method for prevention of UTI. Cranberry proanthocyanidins (PAC) have been shown to inhibit adherence of P-fimbriated *E.coli* to uroepithelial cells. P fimbriae are finger-like projections that the organism uses to attach to bladder cells (see **Figure 3**). In vitro studies have demonstrated that cranberry changes the formation of P fimbriae such that they can no longer attach to the bladder mucosa. Since *E.coli* represents the majority of urinary isolates (54%), this preventive strategy may be an effective method among nursing home residents. Empirical data supporting the potential benefit of cranberry include: 1) in the study by Avorn et al., cranberry juice decreased bacteriuria plus pyuria in older women, even those not caused by *E.coli;* 2) urine from young women that ingested cranberry capsules has been shown in vitro and in vivo to decrease uropathogenic *E.coli* virulence; and 3) limited clinical studies of cranberry juice in elderly women have demonstrated reductions in bacteriuria but have not been of adequate size or quality to result in changes in patient care. The acrid flavor of cranberry juice is challenging for patients to tolerate in large volumes. Nursing home residents in particular are unable to ingest sufficient volumes to maintain hydration because of swallowing disorders, exacerbation of incontinence, and decreased thirst drive. Hence, cranberry capsules represent a prevention strategy that warrants testing in the nursing home population.

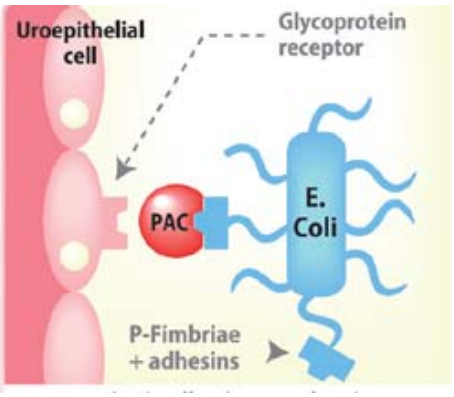

Figure 3: Anti-adhesion of PAC

2.6. Effective dose of cranberry. Previous studies regarding cranberry products for prevention of UTI yielded conflicting results, likely because of variability of PAC dose and clinical populations studied. Initial studies identified PAC to be the active ingredient in cranberry that prevents binding of *E.coli.* In the clinical trial by Avorn et al. of 300ml of cranberry juice beverage daily (36mg PAC), older women (mean age 78.5 years) had a 58% reduction in the odds of having bacteriuria plus pyuria compared to controls, particularly after more than one month of cranberry juice ingestion. Previously, there were at least three different methods of quantifying PAC in the market place, and many products purported effectiveness with variability in dose of PAC. Methods to quantify PAC have now been standardized and can be independently measured. Only one product on the market currently can deliver 36mg PAC as measured by the BL-DMAC method in each capsule and it will be utilized in this proposed project. In vitro data have shown that 36 to 108mg of PAC is effective at inhibiting bacterial adherence to epithelial cells. Since patient adherence to cranberry capsule administration is important and nursing home residents often take multiple medications, the least pill burden and dose of cranberry capsules with the largest effect will be utilized for this efficacy trial.

2.7. Potential adverse effects of cranberry. The only side effect reported with the ingestion of unsweetened cranberry juice is gastro-esophageal reflux; however, this side effect has not been reported with cranberry capsules. Additionally, ingestion of large amounts of liquid is challenging for nursing home residents with demonstrated poor adherence, thereby making cranberry capsules a more preferable intervention option to test in this particularly vulnerable population.

2.8. Investigating the effects of cranberry capsules on women only. The reasons for investigating cranberry capsules in women only include: 1) Avorn et al. investigated cranberry juice among women

only; 2) women represent 75-85% of nursing home residents; 3) there is no evidence to date that cranberry products reduce UTI in men; 4) the predominant risk factor for UTI in men is underlying structural or functional abnormalities of the urinary tract; and 5) the prevalence of bacteriuria plus pyuria in female nursing home residents ranges from 25-50% versus 15-30% for men. Since the prevalence of bacteriuria plus pyuria is lower in men, a study that would detect an effect in men and women would have to be larger. Powering a study to detect a difference in female nursing home residents is an important first step.

2.9. Comparison of this proposal to the landmark cranberry juice study by Avorn et al. The landmark study by Avorn et al. included 153 female subjects, 109 community dwellers living in housing complexes for the elderly and 44 long-term care facility residents, with a mean age of 78.5 years. Participants ingested 300ml of cranberry juice cocktail per day for 6 months. All participants provided self-consent, and most participants were instructed on how to collect an adequate clean-voided specimen themselves. Most participants were enrolled only after a 1-month trial of placebo beverage to ensure that daily intake would be adequate throughout the study. This study informed the development of this proposal by identifying areas where further investigation is needed: 1) only 29% of participants were nursing home residents; 2) the mean age was 10 years lower than the mean age of nursing home residents; 3) most nursing home residents are unable to provide self consent or self collected urine specimens; 4) dehydration is prevalent in up to 90% of nursing home residents because of swallowing difficulty, aspiration risk, increased incontinence with hydration, and decreased olfactory, taste, and thirst sensations. Daily intake of 300ml of juice would not be feasible for most nursing home residents. Since UTI is the most prevalent infection in nursing home residents, a study designed specifically for the nursing home population is warranted.

2.10. Rationale for this study. Given the biological plausibility for its preventive effects and the challenges involved with cranberry juice ingestion by nursing home residents, cranberry capsules represent a promising preventive strategy that should be further explored in this vulnerable population. Because symptomatic UTI is a leading cause of morbidity in nursing home residents, preventing bacteriuria plus pyuria will likely reduce morbidity. Furthermore, a reduction in bacteriuria plus pyuria will result in a reduction in antibiotic use and its attendant adverse effects. Our prior work has demonstrated that 1) cranberry capsule administration is feasible in nursing home residents; 2) an optimal dose of administration has been identified; and 3) there is preliminary evidence that cranberry capsules reduce bacteriuria plus pyuria. This proposal will determine whether cranberry capsules reduce the occurrence of bacteriuria plus pyuria, whether administration of cranberry capsules is safe and adhered to over 12 months, and whether bacteriuria plus pyuria is associated with UTI morbidity. **This study is significant because cranberry capsules are a feasible and low risk intervention that may reduce the morbidity and mortality associated with bacteriuria, pyuria, and UTI in nursing home residents.**

2.11. Preliminary studies.

2.11.1. Previous studies by principal investigator (P.I.) regarding UTI in nursing home residents. Dr. Juthani-Mehta has spent the past eight years investigating diagnostic, management, and prevention strategies of UTI in nursing home residents. She competed for, and was awarded, an R03 Small Research Grant and a K23 Career Development Award funded by the National Institute on Aging on this topic. She has conducted studies involving interviews with nursing staff, observational cohort studies, and pilot intervention studies that have prepared her for conducting the proposed study.

2.11.2. Pilot feasibility and adherence study of cranberry capsules in long-term care residents. In a previous study conducted by the P.I. and funded by the Donaghue Foundation, a cranberry capsule product with 16.25mg PAC per capsule was studied. Fifty-seven participants received none (N=18), one

(N=20), or two (N=19) cranberry capsules per day and were followed for 6 months. The mean age was 86.8 years, 47 (83%) were women, and 100% were white. The baseline bacteriuria rate was 45%. Of 240 urine samples that were scheduled for collection, 207 samples were collected (86.3%). Of 237 doses of cranberry capsules that were prescribed, only 7 (3%) were missed. Six subjects had one or more side effect noted after cranberry administration (i.e., vomiting [N=5], diarrhea [N=3], nausea [N=3]); however, whether another etiology could account for these symptoms was not noted in the medical record. This study demonstrated that 1) cranberry capsules were feasible to administer and adhered to, and 2) clean catch urine specimens could be obtained in this population. Although the study was not designed to evaluate efficacy, trend towards efficacy of cranberry capsules could not be demonstrated, and it is possible that under-dosing of the active components of cranberry was responsible for this finding.

2.11.3. Cranberry capsule dosing study in nursing home residents. Given the findings of the study outlined in **Section C.2.2.**, the P.I. competed for and received funding through the Yale Center for Clinical Investigation (YCCI – the Yale CTSA) to conduct a pilot dosing study of cranberry capsules to identify the optimal dose among nursing home residents. This study was a double-blind, randomized, placebo-controlled trial of 3 cranberry capsules once per day (108mg PAC), 2 cranberry capsules plus one placebo capsule once per day (72mg PAC), 1 cranberry capsule plus two placebo capsules once per day (36mg PAC), and 3 placebo capsules once per day to determine the number of participants with bacteriuria plus pyuria over a one month period. Urine specimens were collected at baseline and then on a weekly basis for 4 weeks (total = 5 specimens). Inclusion criteria were: 1) female residents; 2) history of UTI recorded in the existing medical record; 3) age ≥ 65 years; 4) long term residence; 5) English speaking. Exclusion criteria included: 1) total incontinence; 2) warfarin therapy; 3) residence for < 4 weeks; 4) chronic indwelling bladder catheter; 5) terminal (life expectancy < one month); 6) chronic antibiotic therapy; 7) kidney stones; 8) dialysis; 9) cranberry therapy; 10) allergy to cranberry. Through a HIPAA waiver, chart review was conducted, and eligible residents were identified. Eligible residents or surrogates were approached for written consent.

2.11.3.1. Eligibility and enrollment data. Thirteen nursing homes consented to participate in this study, and 11 were required to reach our target of 80 participants, 20 in each arm of the study. In 11 homes, 1928 residents were screened for participation; 1380 residents did not meet inclusion criteria (see **Table 1**); of 548 remaining residents screened, 308 residents met exclusion criteria and 240 residents were eligible; 90 residents consented (37.5% consent rate), and 80 residents enrolled (10 participants met an exclusion criterion prior to enrollment). The primary reason for lack of inclusion in this study was no history of UTI. This was listed as an inclusion criterion in order to target the group of residents with the highest predicted rate of bacteriuria.

Table 1: Inclusion Criteria

Residents not meeting inclusion criteria	Frequency	Percent
No history of UTI	664	48.1%
Male	479	34.7%
Short term rehabilitation	163	11.8%
Non-English speaking	38	2.8%
Age<65 years	36	2.6%
Total	1380	100%

2.11.3.2. Preliminary feasibility and adherence data. Eighty participants each should have provided 4 urine specimens, one per week during the month of follow up. Of the 320 urine specimens that should have been collected, 293 urinalyses and urine cultures were obtained (92%). Adherence was assessed by the mean number of doses administered in the four arms of the study out of a total of 30 daily doses over the one month study period → placebo 26.8 doses (SD 5.1), one capsule 27.5 doses (SD 6.0), two capsules 29.1 doses (SD 1.7), three capsules 27.9 (SD 4.1). There were no adverse events possibly related to cranberry capsule ingestion (i.e., nausea, vomiting, or gastrointestinal distress) during the one month of follow up. Hence, adherence was best in the two capsule treatment group, although not significantly different from the other groups.

2.11.3.3. Preliminary efficacy data. Preliminary data were obtained from the 80 enrolled participants. Twenty participants were randomized to each of four treatment groups, receiving 0, 1, 2, and 3 active cranberry capsules respectively. Baseline data, including a baseline urine culture and urinalysis, was collected prior to randomization. Four additional urine specimens were obtained at one-week intervals after randomization. The rate of bacteriuria plus pyuria was 52% in the placebo group. Of the 320 anticipated outcome measurements, 27 were missing. Investigation of missing data suggested that the data were missing completely at random. The effect of dose on development of bacteriuria plus pyuria was tested using a Generalized Estimating Equations (GEE) model, adjusted for baseline bacteriuria status (present vs. absent). Results displayed in **Table 2** show that over one month, there was a 37% reduction in the odds of having bacteriuria plus pyuria among the 2 cranberry capsule group as compared to the placebo group, but the confidence intervals were wide. Since Avorn et al. demonstrated no effect at one month of surveillance, these preliminary data showing some effect could become more pronounced with one year of surveillance. The reason for the lack of a dose response for three capsules is not clear. Two possible reasons are 1) the sample size was too small with an unstable estimate of the effect of three capsules; 2) the one month duration of surveillance was too brief to demonstrate a dose response effect.

Table 2: Regression Analysis (N=293)

Predictor Variable	Odds Ratio	95% Confidence Interval
One capsule	0.83	0.28-2.41
Two capsules	0.63	0.21-1.94
Three capsules	1.03	0.34-3.17

3. Research Plan:

3.1. Overview. The **primary aim** of this study is to test the efficacy of two oral cranberry capsules per day in the prevention of bacteriuria plus pyuria in female nursing home residents. The **secondary aim** is to compare the occurrence of urinary tract specific symptoms in the cranberry capsule versus placebo groups. The **primary hypothesis** is that two oral cranberry capsules per day will be associated with a 33% relative reduction in the occurrence of episodes of bacteriuria plus pyuria over 12 months, compared to placebo, in a cohort of female nursing home residents. This aim will be accomplished by conducting a double-blind randomized placebo-controlled efficacy trial of two oral cranberry capsules per day versus placebo in a cohort of Connecticut female nursing home residents.

Trial Setting. The setting will be up to 20 nursing homes within a 50 mile radius of New Haven, licensed by the Connecticut Department of Public Health as "Chronic and Convalescent Nursing Homes", providing skilled care and certified for Medicare or Medicaid. These 20 homes each have at least 90 residents, UTI rates comparable to the national average of 9% annually, and sociodemographic characteristics similar to national averages.

Design. The design will be a double-blind, randomized, placebo-controlled efficacy trial in which all participants will undergo urine sample testing at baseline and every two months over 12 months of prospective surveillance. Training of staff, screening, and enrollment of participants will occur one home at a time. Each home will require 8 weeks from training initiation to the start of the intervention. Each participant will receive treatment and be followed for outcomes for 12 months.

Participants. The participants will be female long-term care nursing home residents, 65 years or older. Assuming a Type 1 error of 5% (2-sided), 80% power, a control group prevalence rate of 45%, a relative reduction of 33% (absolute risk difference of 15%), serial correlation among 6 repeated urine measurements on each participant of 0.35, and a drop-out rate of 20% (e.g.,

death 17%, transfer and/or inability to provide further urine specimens 3%), the sample size required is 90 participants in each group (total N=180).

Intervention. The intervention will be two cranberry capsules per day, compared to two placebo capsules per day. Data entry and management will occur at the Yale Program on Aging. Interim monitoring will include patient accrual, protocol adherence, data quality, safety, efficacy, and futility. A series of monitoring tables will be developed that include the above elements for presentation to a Data and Safety Monitoring Board (DSMB) at periodic intervals. Final analysis will consist of comparability of treatment groups, treatment efficacy, and safety. All primary treatment comparisons will analyze participants as randomized. An Executive Committee will oversee the study design and troubleshoot methodological problems that arise during the course of the study. A Steering Committee will oversee daily issues related to participant enrollment, data collection and management, intervention implementation, and outcome assessment. An Internal Safety and Outcome Adjudication Committee will monitor adverse events, adjudicate outcomes, and interface with the DSMB. The DSMB will be convened with a planned structure and duties for duration of the clinical trial. The P.I., Dr. Juthani-Mehta, has completed one observational cohort study, two pilot intervention studies, and is the Chair of the Internal Safety Committee of another nursing home intervention trial. She has assembled a team that is well equipped to complete this proposed project.

3.2. Trial Setting. This study will take place at up to 20 nursing homes within a 50 mile radius of New Haven**.** The setting will be up to 20 nursing homes within a 50 mile radius of New Haven**,** licensed by the Connecticut Department of Public Health as "Chronic and Convalescent Nursing Homes", providing skilled care and certified for Medicare or Medicaid. These 20 homes each have at least 90 residents, UTI rates comparable to the national average of 9% annually, and sociodemographic characteristics similar to national averages.

3.2.1. Rationale. Residents of nursing homes within the greater New Haven area are reflective of the nursing home population within the United States. Nursing homes chosen to participate in this study represent a mix of urban and suburban, proprietary and nonprofit, private pay and Medicaid homes. Our target minority rate of 12% will be met with the spectrum of homes participating. We recognize the great challenges involved in working with these non-academic nursing homes, but we have established good relationships with many of them, and we have successfully conducted previous observational and interventional studies in this environment. The Yale Program on Aging has vast experience conducting research in challenging but important real world settings with high recruitment, retention, and adherence rates.

3.2.2. Determination of eligible pool of residents. Using information available through Medicare on www.medicare.gov/nhcompare, the national and Connecticut state averages for the percent of residents who had a UTI annually were 9% and 7%, respectively. To improve study efficiency, we selected nursing homes with an average UTI rate at least as high as the CT and national averages within a 50 mile radius of New Haven and with at least 90 beds. Women comprise 75-85% of nursing home residents. In the first cranberry capsule feasibility study, the baseline bacteriuria rate was 45%. In order to increase the baseline rate of bacteriuria, in the pilot dosing study, history of UTI was a required eligibility criterion. However, 664 residents were excluded by requiring this inclusion criterion, and the baseline rate of bacteriuria plus pyuria only increased to 52%. In an effort to increase the baseline bacteriuria rate, a large pool of potentially eligible subjects was lost and the rate only increased from 45% to 52%. Therefore, for this proposed study, history of UTI will not be a required inclusion criterion. In the identified 20 homes, we expect to find at least 700 eligible residents so that with a 30% consent rate, we can enroll 180 participants. In the pilot dosing study, when history of UTI was included as an inclusion criterion and 664 residents were excluded for this reason, 240 eligible residents were

identified in 11 homes. If history of UTI would not have been an inclusion criterion, 904 residents would have been eligible for the pilot dosing study (240+664=904). Although we had a 37.5% consent rate in the pilot dosing study, with a conservative 30% consent rate which is consistent with other nursing home intervention studies, 271 residents could have consented from 11 nursing homes. Therefore, in this proposed study, we anticipate that 10 homes will be sufficient to achieve our sample size of 180. Nevertheless, 6 back-up homes have been recruited in the event that 10 homes will not be sufficient to meet our target sample size.

3.2.3. Identification of participating nursing homes. Based on our sample size estimate of 180 participants, we anticipate the need for up to 20 nursing homes and, at this time, we have 16 participating nursing homes that have already agreed to participate.

3.3. Trial Design. This study will be a double-blind, placebo controlled, randomized, clinical efficacy trial of two cranberry capsules versus placebo. The unit of randomization will be each individual participant.

3.4. Trial Participants. The participants in this trial will be female long-term care nursing home residents.

3.4.1. Screening and eligibility assessment. Screening at each nursing home will occur sequentially. From the date of screening to enrollment, each home will require eight weeks. Once enrollment is completed at one home, screening will begin at the next home. Residents, age >65 years, residing in one of the participating nursing homes will be identified from a computerized log kept by the Director of Nursing Services at the home. Subsequently, study personnel will perform a brief chart review to establish the presence of inclusion and exclusion criteria. A HIPAA waiver will be obtained for recruitment purposes only.

3.4.1.1. Inclusion criteria. All races will be considered for inclusion if they are: 1) female; 2) long-term care residents; 3) English speaking; and 4) 65 years or older. Since surrogate consent is required in most instances and since the participants often have underlying dementia, English speaking participants are required who can be explained the protocol and express their assent to participate not only to study staff but also to nursing home staff over the course of the study.

3.4.1.2. Exclusion criteria. Residents will be excluded if they: 1) are not expected to be in the nursing home for at least one month (i.e., short term rehabilitation, pending discharge, terminal life expectancy < 1 month); 2) are on chronic suppressive antibiotic or anti-infective (i.e., mandelamine) therapy for recurrent UTI; 3) have end stage renal disease on dialysis (they do not regularly produce urine); 4) are unable to produce a baseline clean catch urine specimen for collection; 5) are on warfarin therapy because of a potential interaction of warfarin and cranberry juice; 6) have a history of nephrolithiasis because cranberry may increase the risk of nephrolithiasis; 7) have an indwelling bladder catheter in place; 8) have an allergy to cranberry products; 9) are being treated with cranberry products; 10) residence < 4 weeks.

3.4.2. Consent and enrollment procedures. Permission will be obtained from the potential participant's attending physician before each resident is approached for study recruitment. Informed consent will be obtained by trained study personnel. All potential participants will receive a general description of the study, including the baseline and surveillance evaluations, the intervention, potential risks and benefits. As part of the study protocol, participants will be advised to avoid ingestion of other cranberry products. In addition, participants will be asked to sign a HIPAA authorization form that explains the protected health information that will be used, disclosed, and to whom it will be disclosed as part of this study. For potential participants who are determined to be decisionally impaired by study recruitment personnel, consent will be sought from their designated surrogates along with assent from the participant. Surrogate consent will be sought through a combination of up to three phone calls and three mailings describing the study purpose, intervention, surveillance evaluations, risks and benefits. We have successfully utilized this method of surrogate consent in our observational cohort studies, in

pilot intervention studies, and in the pilot dosing study in which the consent rate was 37.5% from eligible residents or surrogates. Based on our pilot studies, we anticipate that >95% of eligible residents will require surrogate consent because of decisional impairment.

3.4.3. Availability of participants for enrollment. We recognize that in an intervention trial, there will be obstacles to patient enrollment, adherence, and retention. These include ineligibility due to exclusion criteria defined, resident (or surrogate) refusal to participate, drop outs, and loss from competing morbidities. However, among the 10 homes that have agreed to participate, we estimate that we will have ≥600 eligible residents with the average number of eligible residents per home of 50 at the time of the initial two month enrollment period. Given the anticipated replacement of the 20% of residents censored annually, we estimate an additional 200 eligible residents available over the two year enrollment period (100 each year), resulting in 500+200=700 total eligible residents. A consent rate of 30% would yield at least our sample size target of 180 participants (700x30%=210). The consent rate of 30% is feasible because data from our dosing study. revealed a 37.5% consent rate. In the vulnerable nursing home population, consent rates of approximately 30% for an intervention study are well documented. In addition, 6 additional back-up homes have agreed to participate if more homes are required for recruitment.

3.4.4. Expected attrition. We anticipate the following sources of attrition of participants: deaths, transfers out of the nursing home, and functional decline prohibiting continued participation in the study. The total anticipated attrition rate is 20%, 17% for death and 3% for other reasons. These rates are based on observed numbers in our prior studies. We do not expect any drop ins from placebo to treatment. Because we will analyze participants as they are randomized, intervention drop-outs, and non-adherent participants to the assigned treatment arm are not considered losses. Deaths occurring before obtaining outcome data or the end of the 12 month follow-up are unavoidable in a nursing home population and analyses to make use of the existing data on these losses are discussed below. Transfers out of the homes are also expected. Based our prior studies, the transfer rate is expected to be low (i.e., 3%).

3.5. Stratified randomization. Once consent is obtained, a baseline clean catch urine specimen will be obtained from participants prior to initiation of therapy to ensure that subsequent clean catch urine specimen collection will be possible. Then, enrolled participants will be randomized to two placebo or two cranberry capsules within nursing home using a permuted block design with a variable block size and equal allocation. Stratification by nursing home is being proposed to account for potentially different standards of nursing and medical care among nursing homes. The randomization will be double-blind. Neither the personnel (study nurses, P.I., nursing home nurses and CNAs) nor the patient will be aware of the treatment allocation. Only the study biostatistician will have access to the randomization codes.

3.6. Trial Intervention. The intervention is two cranberry capsules versus placebo capsules for the prevention of bacteriuria plus pyuria. This trial serves as an efficacy study in which the reduction of bacteriuria plus pyuria is the primary outcome. The secondary outcome is the occurrence of urinary tract specific symptoms in the cranberry capsule and placebo groups. This study will also determine rates of adverse clinical outcomes (i.e., symptomatic UTI, all cause hospitalization, all cause death, all antibiotic prescriptions, and all multi-drug antibiotic resistant organisms) in the placebo and treatment groups.

3.6.1. Justification for two cranberry capsules. Based on preliminary data, two cranberry capsules had the best adherence and largest effect in reducing bacteriuria plus pyuria. Since nursing home residents often take multiple medications, utilizing a safe dose with the lowest pill burden is warranted. Therefore, this regimen has the greatest likelihood of working in a real-world setting.

3.6.2. Training of nursing home staff. As the study begins in each new home, the Senior Intervention Nurse Educator will collaborate with nursing administration to organize a series of “in-service” didactic

training sessions to orient and mentor the nurses and certified nursing assistants (CNAs) as a group to the methods involved in urine specimen collection and capsule administration. This will occur prior to initiation of the intervention in any participant. Since staff turnover is high in the nursing home setting, we anticipate the need to retrain nurses and CNAs on a quarterly basis over the course of the study. During the first 4 weeks after initiation of the intervention, the team of training nurses will identify barriers to administrating the intervention (e.g., storage location of study capsules) and facilitate solutions. The importance of timely and clean urine specimen collection will be reinforced to all nursing home staff to reduce the number of missing urine specimens. Since clean catch urine specimens are most easily obtained in the first morning void, specimens will be collected by nursing home staff between 5-7AM. Study staff will supervise baseline collections of these specimens in each home, and train nursing home staff for subsequent urine specimen collections. Prior pilot testing has demonstrated that nursing home patients experience more agitation when unfamiliar study personnel perform routine care. Therefore, urine specimens will be collected by nursing home staff members that are well known to the participants. This strategy of urine specimen collection was effective in the pilot dosing study.

3.6.3. Incentives for nursing home facilities, nurses, and CNAs for study participation. Although our pilot dosing study demonstrated high feasibility and adherence to capsule administration and obtaining of urine specimens, the pilot was conducted for only one month. Therefore, we will work with nursing administration and opinion leaders in the various homes to identify and provide relevant incentives for the nursing homes, CNAs, and nurses to maintain the enthusiasm and cooperation of all homes in the study. Planned incentives will include 1) an annual Certificate of Research Participation for all participating nursing home facilities which documents active participation in this Yale University research study for purposes of annual surveys conducted by regulatory bodies; 2) continuing education "in-service" hours that are required by the state of Connecticut for all CNAs; 3) gift certificates to participating nursing home staff. The amount of gift certificates will depend on how often they are given. If a gift certificate is given every other month, then it will be for $20.00. If given only once a year, then the gift certificate will be for $120.00.

3.6.4. Retention events for nursing home facilities, nurses, and CNAs for study participation. We will establish a series of retention events for all the nursing home facilities, and retention events for all the nurses and CNAs to maintain their enthusiasm, cooperation, and interest in maintaining adherence to the study protocol. For nursing home facilities, we will organize an evening meeting session every 12 months between the P.I., the nursing home administrator, the Director of Nursing Services, and the Medical Director. For the nurses and CNAs, we will organize a luncheon meeting session every 6 months between the field staff and the nurses and CNAs of the homes. Specific issues to be discussed will include barriers to implementing the protocol, troubleshooting, and other topics of interest to the nursing home staff that might improve patient care (e.g. nursing home-acquired pneumonia prevention, prevention of decubitus ulcer formation).

3.7. Trial Data: Descriptive, Outcomes, Sample Size Estimate, Data Management, and Analyses

3.7.1. Baseline clinical assessment. Consenting participants will undergo a baseline assessment during which descriptive characteristics will be recorded. Facility, age, race, medications, comorbidities, and history of UTI will be obtained from chart review. The primary nurse and/or CNA will be asked questions adapted from the Minimum Data Set (MDS) regarding cognitive status, behavior, activities of daily living, continence, and degree of mobility. This method was used successfully in our observational cohort study and our pilot dosing study.

3.7.2. Clinical outcome surveillance: primary and secondary outcomes. Urine specimens will be obtained at baseline (prior to randomization) and every two months thereafter via clean catch (7

specimens total). The primary outcome will be the presence or absence of bacteriuria plus pyuria at each time point. Treatment will not be discontinued if urine culture results are positive. This is the primary outcome of the study. All cultures will be recorded over the course of the year and tabulated at the end of the study.

3.7.2.1. Definition of primary outcome: bacteriuria plus pyuria and urinary tract specific symptoms. Presence of bacteriuria will be defined as >100,000 cfu/ml of one or two organisms. Absence of bacteriuria will be defined as a urine culture with no growth, mixed flora (three or more organisms), or less than 100,000 cfu/ml. Pyuria will be defined as any number of white blood cells on urinalysis. Urinary tract specific symptoms (i.e., acute dysuria, new suprapubic pain or tenderness, acute costovertebral angle pain or tenderness, gross hematuria; new or marked increase in: incontinence, urgency, or frequency) will be assessed at the time of each urine specimen collection. In the study by Avorn et al., the rate of urinary tract specific symptoms at monthly intervals was 7% in the placebo group and 4% in the cranberry group.

3.7.2.2. Definition of secondary outcomes for supplementary aims.

3.7.2.2.1. Symptomatic UTI. Symptomatic UTI will be defined as 1) acute dysuria, fever or leukocytosis and (a) at least **one** of the following: acute costovertebral angle pain or tenderness; suprapubic pain; gross hematuria; new or marked increase in: incontinence, urgency, or frequency; OR (b) two or more of new or marked increase in: incontinence, urgency, suprapubic pain, new gross hematuria **AND** 2) a voided urine culture with (a) $\geq 10^5$ cfu/ml of a single predominant organism or two gram negative organisms OR (b) a specimen collected by in and out catheter specimen with $\geq 10^2$ cfu/ml of any number of organisms.

3.7.2.2.2. Hospitalization. All cause hospitalizations, including those related to UTI, and visits to the emergency room will be recorded.

3.7.2.2.3. Death. All cause death, including UTI as a reason, will be recorded.

3.7.2.2.4. Antibiotic prescriptions. Information on all antibiotic therapy prescribed, whether for UTI or other cause, will be recorded. If antibiotic therapy is for UTI, it will be noted in data collection.

3.7.2.2.5. Resistant organisms. All resistant bacterial isolates, either from the urine specimens obtained for study purposes or as recorded from other clinical specimens in the medical record, will be recorded. These isolates will include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococci* (VRE), and multi-drug resistant gram negative rods, with multi-drug resistance defined as resistance to at least 3 of the following antibiotics: ampicillin-sulbactam, cefazolin, ceftriaxone, ceftazidime, fluoroquinolones, piperacillin-tazobactam, meropenem, imipenem, and trimethoprim-sulfamethoxazole.

3.7.2.3. Surveillance of primary outcome: bacteriuria plus pyuria and urinary tract specific symptoms. Surveillance of the primary outcome will occur every two months for a total of six assessments over the 12 months of follow up. The primary nursing home staff (i.e., nurses and CNAs) will be responsible for collecting clean catch urine specimens every two months from 5-7AM on the same day for a given home. Study staff will provide reminders as to when sample collection is due. If the specimen is not collected on the due date, attempts at specimen collection will continue for one additional week prior to noting the specimen as missing. Urinary tract specific symptom assessment will occur on the day of urine specimen collection. Based on our pilot data, we anticipate that 14% of specimens initially will be missing. The research assistant, Luann Bianco, will collect all urine samples that are obtained and deliver to the Yale-New Haven Hospital Hematology and Microbiology Laboratories for processing. Urinalysis processing is automated in the Hematology Laboratory. Performing quantitative urine cultures will require the following steps: 1) mix urine; 2) vertically insert a flamed and cooled calibrated platinum loop that delivers 0.01 ml of urine into the specimen; 3) remove a loopful of urine; 4) inoculate one loopful of urine onto a Sheep blood agar and MacConkey agar plate

by making a straight line down the center and then a series of close perpendicular streaks throughout the first line. Lactobacillus species, alpha-streptococci, and diphtheroids will not have susceptibility testing performed. All other isolates will have antibiotic susceptibility testing performed. When three or more organisms are isolated, the urine culture will not undergo further processing and will be regarded as a mixed culture. We successfully utilized this method of urine collection and processing in our pilot dosing study.

3.7.2.4. Outcome adjudication. If a urine culture reports growth of one or two organisms at least one of which is >100,000 cfu/ml and the urinalysis reveals any number of white blood cells, the primary outcome will be met. The Outcome Adjudication Committee, consisting of the P.I. (Juthani-Mehta), the Senior Research Nurse (Ginter), and the senior infectious diseases specialist (Quagliarello), will meet monthly to adjudicate the primary and secondary outcomes noted above.

3.7.3. Surveillance of adverse events. The Senior Assessment and Recruitment Study Nurse, Ms. Ginter, along with Ms. Bianco will monitor for any potential adverse events once per week for the duration of the 12 month surveillance period per participant, through interviews with nursing staff and report to the Internal Safety Committee. To ensure a rapid and systematic approach to adverse events, the Internal Safety Committee will evaluate all suspected adverse events, however mild or severe. The Chair of the Internal Safety Committee (Quagliarello) will determine which serious adverse events must immediately be reported to the Yale Human Investigation Committee, DSMB, and funding agencies.

3.7.4. Surveillance of adherence to intervention. Adherence will be determined by the number of capsules that were administered to each participant in relation to the targeted number. The medication administration record will be reviewed to determine if the study capsules were documented to be administered. However, in our pilot study, we identified discordance between the numbers of capsules recorded to have been administered versus the numbers of capsules remaining. Therefore, surveillance of the remaining capsules by pill counting every two weeks will be conducted to ensure that they are being administered. Reasons for lack of administration will be noted (e.g., refusal). Since it will not be possible to continue capsule administration during a hospitalization, hospitalization will be noted as the reason for lack of adherence to the missed doses. High adherence will be defined as administration of ≥80% of prescribed capsules and low adherence will be administration of <80% of prescribed capsules. For those homes in which high adherence is maintained for three months, adherence assessments will be reduced to every four weeks.

3.7.5. Sample size estimate. Sample size was determined to detect a difference between the proportion with bacteriuria plus pyuria over time in the placebo group versus the treatment group receiving 2 cranberry capsules using the method of Diggle et al. for repeated binary outcomes. In the study by Avorn et al., the sample size was based on a 40% reduction in bacteriuria plus pyuria (0.50 in placebo to 0.30 in cranberry juice group). The following assumptions were made for this sample size calculation: Type 1 error of 5% (2-sided), 80% power, a serial correlation of 0.35 between 6 urine specimens, a bacteriuria plus pyuria rate of 0.45 in the control group, a 33% reduction with the cranberry intervention (0.30 bacteriuria plus pyuria rate), and 20% inflation for deaths, transfers and missing cultures. Based on these assumptions, the total sample size is 180 participants (90 per group). There are no data to determine power for secondary outcomes.

3.7.6. Data management. All Data management systems will be developed and implemented by the Data Management and Informatics Core (DMIC) of the Program on Aging/Claude D. Pepper Older Americans Independence Center (OAIC) at Yale. Data collection for the eligibility and enrollment protocol, the baseline assessment and outcome assessment will be accomplished using computerized instruments on tablet PCs, or on printed forms. Computerized instruments will be developed using the "Pepper Informatics" (Pi) software developed by Mr. Charpentier (http://pi.med.yale.edu). Instruments designed using Pi support a "point and click" interface suitable for direct data collection, as well as a "heads down" mode optimized for rapid, double-pass data entry from paper forms. In addition to data

collection and data entry, DMIC will provide other critical services, such as between-form error checking and resolution; conduct-of-study reports; performance monitoring reports; randomization; and follow-up contact scheduling.

3.8. Anticipated Timeline of Clinical Trial. Enrollment of each nursing home will occur sequentially (i.e., prevalent recruitment). We anticipate that it will require 8 weeks from receiving the nursing home roster to enrollment of the first participant in a given nursing home. Recruitment staff will return to each nursing home every three months for additional recruitment (i.e., incident recruitment). We anticipate that prevalent recruitment will require one year and additional incident recruitments will require an additional year.

	YEAR 1				YEAR 2				YEAR 3				YEAR 4			
1. Preparing for Trial																
Meet with administrators of all participating homes to reinforce the details of the protocol, surveillance of outcomes, and adverse events	x	x														
Develop Manual of Procedures	x	x														
"In-service" training sessions for nursing staff at participating homes	x	x														
Develop data collection instruments	x	x														
2. Enrollment of Participants																
Determine eligibility of residents			x	x	x	x	x	x	x	x						
Obtain informed consent from eligible residents or proxies			x	x	x	x	x	x	x	x						
Obtain baseline urine specimens			x	x	x	x	x	x	x	x						
Conduct stratified randomization based on nursing home residence			x	x	x	x	x	x	x	x						
3. Intervention Implementation																
Initiate placebo and cranberry capsule administration			x	x	x	x	x	x	x	x						
Obtain urine specimens every two weeks			x	x	x	x	x	x	x	x	x	x	x	x		
Process urine specimens in microbiology and hematology laboratories			x	x	x	x	x	x	x	x	x	x	x	x		
Retrain staff regarding urine specimen collection and capsules			x	x	x	x	x	x	x	x	x	x	x	x		
Surveillance of staff for adherence to capsule administration			x	x	x	x	x	x	x	x	x	x	x	x		
Surveillance for adverse events with reporting to Internal Safety Committee, Medical Safety Monitor, and DSMB			x	x	x	x	x	x	x	x	x	x	x	x		
Conduct retention events for nursing home administrators						x				x				x		
Conduct retention events for nursing home staff				x		x		x		x		x		x		
4. Outcome Surveillance and Assessment																
Surveillance and adjudication of primary outcome → bacteriuria plus pyuria; assessment of urinary tract specific symptoms			x	x	x	x	x	x	x	x	x	x	x	x		
Surveillance and adjudication of secondary outcomes → UTI, death, hospitalization, antibiotic prescriptions, and resistant organisms			x	x	x	x	x	x	x	x	x	x	x	x		
5. Data Management and Analysis																
Data Management			x	x	x	x	x	x	x	x	x	x	x	x	x	x
Preparation of Clinical and Safety Data Summaries to DSMB				x		x		x		x		x				
Final Data Cleaning													x	x		
Lock Dataset and Data analysis															x	x
6. Report Generation															x	x

4. Subject Population:

The participants will be female long-term care nursing home residents, 65 years or older. Assuming a Type 1 error of 5% (2-sided), 80% power, a control group prevalence rate of 45%, a relative reduction of 33% (absolute risk difference of 15%), serial correlation among 6 repeated urine measurements on each participant of 0.35, and a drop-out rate of 20% (e.g., death [17%], transfer and/or inability to provide further urine specimens [3%]), the sample size required is 90 participants in each group (total N=180).

5. Inclusion/Exclusion Criteria:

Inclusion criteria. All races will be considered for inclusion if they: 1) are female; 2) are long-term care residents; 3) are English speaking; and 4) are 65 years or older. Since surrogate consent is required in most instances (95%) and since the participants often have underlying dementia, English speaking participants are required who can be explained the protocol and express their assent to participate not only to study staff but also to nursing home staff over the course of the study. We have utilized this strategy in our previous intervention cohorts and in the current R01 funded clinical trial to reduce pneumonia in nursing home residents.

For this proposed randomized clinical trial, we plan to identify and enroll female participants who are residents of nursing homes within a 50 mile radius of New Haven, CT. We anticipate the characteristics of the study population to be similar to those enrolled in our observational and pilot intervention cohorts with a mean age of approximately 86 and 12% Hispanic or racial minorities. We are estimating a sample size of 180 participants (90 randomized to the treatment arm, 90 randomized to the control arm).

Exclusion criteria. Residents will be excluded if they: 1) are not expected to be in the nursing home for at least one month (i.e., short term rehabilitation, pending discharge, terminal life expectancy < 1 month); 2) are on chronic suppressive antibiotic or anti-infective (i.e., mandelamine) therapy for recurrent UTI; 3) have end stage renal disease on dialysis (they do not regularly produce urine); 4) are unable to produce a baseline clean catch urine specimen for collection; 5) are on warfarin therapy because of a potential interaction of warfarin and cranberry juice; 6) have a history of nephrolithiasis because cranberry may increase the risk of nephrolithiasis; 7) have an indwelling bladder catheter in place; 8) have an allergy to cranberry products; 9) are being treated with cranberry products; 10) residence < 4 weeks.

Women represent the vast majority (75-85%) of nursing home residents and the genitourinary anatomy of men and women differ. The risk factor for UTI in men usually relates to underlying structural or functional abnormalities of the urinary tract, and there is no evidence to date that cranberry products reduce UTI in men. Therefore, only female nursing home residents will be recruited to this study. Participants will be stratified by nursing home and then randomized to receive either placebo or two cranberry capsules per day. There will be up to 20 nursing homes within a 50 mile radius of the greater New Haven, CT area participating in this study.

Screening at each nursing home will occur sequentially. From the date of screening to enrollment, each home will require eight weeks. Once enrollment is completed at one home, screening will begin at the next home. Residents, age >65 years, residing in one of the participating nursing homes will be identified from a computerized log kept by the Director of Nursing Services at the home. Subsequently, trained field staff will perform a brief chart review to establish the presence of inclusion and exclusion criteria. A HIPAA waiver will be obtained for recruitment purposes only.

6. How will **eligibility** be determined, and by whom?

Screening at each nursing home will occur sequentially. From the date of screening to enrollment, each home will require eight weeks. Once enrollment is completed at one home, screening will begin at the next home. Residents, age >65 years, residing in one of the participating nursing homes will be identified from a computerized log kept by the Director of Nursing Services at the home. Subsequently, trained field staff will perform a brief chart review to establish the presence of inclusion and exclusion criteria. A HIPAA waiver will be obtained for recruitment purposes only

7. Risks:

There are no reasonably foreseeable physical, psychological, emotional, social, economic, or legal risks involved in the two arms of the proposed study, or in obtaining a clean catch urine sample, which will be collected by trained nursing home staff if subjects need assistance. In the United States, cranberry capsules are considered to be a dietary supplement, not a drug or medication. As such, their usage is not regulated by the Food and Drug administration (FDA). In previous studies by our group and others, very few incidences of side effects have been noted after cranberry capsule administration. In a study of 57 participants taking a different cranberry capsule from the one used in this study, only six subjects noted symptoms after cranberry capsule administration (vomiting, nausea, and/or diarrhea), but it was unclear whether these symptoms were actually a side effect from the cranberry capsules. These possible protocol-related side effects will be monitored by research staff.

8. Minimizing Risks:

If a subject is unable to swallow the capsules, her nurse will be able to open the capsule and mix its contents into applesauce or yogurt. Subjects with feeding tubes will not be excluded from the study. If a subject has a feeding tube, the cranberry powder can be administered through the tube.

See attached article Brazier AM, et al. "Collecting Clean-Catch Urine in the Nursing Home: Obtaining the Uncontaminated Specimen". *Geriatric Nursing.* September/October 1995; 16(5): 217-224 for a description of the training education that the nursing home staff will receive from the nurse researcher in order to obtain the clean catch urine specimens.

9. Data and Safety Monitoring Plan:

The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews on a monthly basis. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment.

Either the principal investigator or the Human Investigation Committee (HIC) have the authority to stop or suspend the study or require modifications.

This protocol presents minimal risks to the subjects and adverse events or other problems are not anticipated. Adverse events will be recorded by the nursing home staff into the subject's medical record and study staff will perform chart review to retrieve this data. In the unlikely event that such events occur, serious and unanticipated and related adverse events or unanticipated problems involving risks to subjects or others will be reported in writing within 48 hours to the HIC (using the appropriate HIC forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all adverse events that occur during the conduct of this research project through regular study meetings, via email as they are reviewed by the principal investigator. The protocol's research monitor(s), e.g., study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies will be informed of adverse events within 5 days of the event becoming known to the principal investigator.

While adverse effects secondary to cranberry capsule administration are expected to be minimal based on evidence from previous studies, all adverse effects secondary to cranberry capsule administration will be prospectively recorded. A secondary outcome variable will be coded with a 1 for the occurrence

of any adverse event and a 0 for the occurrence of none. Rates of adverse events will be described and calculated for each arm of the study.

10. Statistical Considerations:

10.1 Data analysis plan.

10.1.1. Interim monitoring. Interim monitoring will focus on participant accrual (overall and by nursing home), baseline comparability of treatment groups, protocol adherence, completeness of data retrieval, data quality, safety, and efficacy. A set of interim data monitoring tables will be developed for presentation to a DSMB at periodic intervals. We will carefully monitor participant accrual and adherence to ensure that the study is on target to achieve the required level of statistical power. We will propose to the DSMB one interim look for efficacy at the mid-point of the study using a Haybittle-Peto boundary with p-value of 0.001. This will have a negligible effect on the overall type I error at the end of the trial. Thus, the sample size was not inflated to account for the interim look. Futility will be assessed by calculating conditional power (under both the observed and hypothesized trend) and the feasibility of achieving the target sample size.

10.1.2. Final analyses: primary outcome. Final analyses will address comparability of treatment groups, efficacy and safety. All analyses will be conducted as randomized, i.e., participants will be analyzed according to their original treatment assignment regardless of adherence. A significance level of 0.05 (2-sided) will be used for statistical significance. SAS® 9.2 statistical software will be used for the analyses.

10.1.2.1. Baseline comparability of treatment groups. The adequacy of the randomization will be assessed by comparing the distribution of baseline demographic and clinical characteristics between the treatment groups. Comparability for continuous variables will be examined graphically and by summary statistics (means, medians, quartiles, etc.). Categorical variables will be examined by calculating frequency distributions. Adjustment for significant treatment imbalances in baseline covariates will not be done because this approach can be biased. Instead the following pre-specified covariates will be adjusted for: baseline bacteriuria, age, and number of comorbid conditions.

10.1.2.2. Treatment efficacy for the primary outcome. The primary study outcome is bacteriuria plus pyuria. The difference in the proportion with bacteriuria plus pyuria between the two treatment groups will be estimated using a multivariable logistic regression model that accounts for the serial correlation of repeated measurements, adjusted for the pre-specified covariates (baseline bacteriuria status, age, and number of comorbid conditions) and the randomization (stratification by nursing home). Prior to regression modeling, the potential impact of missing data and deaths on the study outcome will be investigated. If it is reasonable to assume that missing values are missing at random, generalized linear mixed effects modeling[4] will be used. Variables that are predictive of missing values will be included in the model. In a sensitivity analysis we will examine the possibility that data are missing not at random and will consider joint modeling of the longitudinal and survival outcomes.[5] In a sensitivity analysis, facility heterogeneity will be further assessed by using a random effect for nursing home in the regression model to account for the variability among homes. Model fit will be assessed by residual analyses, influence diagnostics, and goodness-of-fit tests. The treatment effect will be estimated as an odds ratio (treatment vs. control) with corresponding 95% confidence intervals. In exploratory analyses the impact of non-adherence on treatment effect will be investigated by methods described by Little, et al.

10.1.2.3. Analysis of safety. The incidence of adverse events will be tabulated and compared between treatment groups using statistics appropriate for categorical or count data, such as

the chi-square or Wilcoxon statistics. We will also examine the timing of the adverse events by calculating cumulative incidence curves.

10.1.3. Final analyses: secondary outcomes. The analysis of symptomatic UTI will be similar to that described for bacteriuria plus pyuria. Cumulative death rates will be estimated by the method of Kaplan-Meier and compared between treatment groups using the log-rank statistic. Frequency of hospitalizations, antibiotic prescriptions, and multi-drug antibiotic resistant organisms will be tabulated and compared between the treatment and control groups using the Wilcoxon statistic.

A. DRUGS, BIOLOGICS and RADIOTRACERS

1. **Identification of Drug, Device or Biologic:**

Cranberry capsules contain a highly concentrated food extract of North American cranberries (*Vaccinium macrocarpon*). North American cranberries are one of the richest natural sources of A-type proanthocyanidins which have been shown to be effective in inhibiting certain uropathogenic strains of *E. coli* from adhering to the lining of the urinary tract. As a dietary supplement, cranberry capsules are not regulated by the FDA.

2. **Background Information:**

Concentrated forms of cranberry extract have been shown in various studies to be safe and well-tolerated. The only possible contraindications include warfarin anticoagulant therapy or persons with a history of nephrolithiasis. Individuals with either of these conditions will be excluded from participation in this study.

3. **Source:**

Cranberry capsules are produced in bulk by an independent manufacturer. The packaging of capsules will be done by YNHH Investigational Drug Services based on the preferences of each nursing home.

4. **Storage, Preparation and Use:**

Study cranberry capsules contain 36mg of proanthocyanidins per capsule. They are stable at room temperature and will be administered as part of enrolled patients' regular daily pill pack at the nursing homes. The two capsules will be administered at 5:00 pm every day. As described, the capsules will be stored at room temperature. These will be locked in a secure place at the Program on Aging.

5. **Use of Placebo:**

As previously stated in the background information, there is no currently accepted prophylactic therapy for asymptomatic bacteriuria. Additionally, none of the trials of antibiotic treatment of asymptomatic bacteriuria showed any decrease in mortality. Use of placebo in this study will simply assist us in determining the baseline rate of bacteriuria in the nursing home populations under study.

The maximum possible duration that a participant may receive placebo is 12 months.

In this study, placebo represents the current state of affairs for prophylactic management of bacteriuria. There is no potential harm in receiving placebo in this study. Participation in the study will end after 12 months. Management of the bacteriuria at this point will then be the responsibility of the patient's primary care provider.

As stated in point c above, there is no potential harm in receiving placebo in this study, and as such, no safeguard procedures are required.

6. **Targeted Enrollment: Give the number of subjects:**

Targeted for enrollment at Yale for this protocol 180.

7. **Recruitment Procedures:**

Participants will be recruited from the nursing units at the 16 New Haven area nursing homes listed in the protocol. Residents, age >65 years, residing in one of the participating nursing homes will be identified from a computerized log kept by the Director of Nursing Services at the home. Subsequently, study personnel will perform a brief chart review to establish the presence of inclusion and exclusion criteria.

After potential subjects have been identified through chart review covered by a HIPAA waiver, subjects, or their legally authorized surrogate, will be approached by the research team to obtain written consent. Individuals will be given sufficient time to read through the consent form, or if this presents difficulty, the form will be read to them by a member of the research team. Surrogates will receive a follow up phone call after receiving a Proxy Authorization letter (see attached) and consent form. A member of the research team will answer any questions that the potential subject or surrogate may have. Permission will be obtained from the potential participant's attending physician before they are approached for study recruitment. Informed consent will be obtained by trained study personnel. All potential participants will receive a general description of the study, including the baseline and surveillance evaluations with a general description of risks and benefits. Participants will receive a full detailed description of the intervention strategy, including potential risks and benefits. In addition, participants will be asked to sign a HIPAA authorization form that explains the protected health information that will be used, disclosed, and to whom it will be disclosed as part of this study. Potential participants or surrogates will sign the consent form and HIPAA authorization forms prior to the baseline assessment. If surrogate consent is obtained, assent from the participant will still be required for participation in the study. The principal investigator will be available to answer any questions.

An experienced research assistant (i.e., Luann Bianco) and nurse researchers (i.e., Andrea Rink, Sandra Ginter) at the Yale Program on Aging.

8. **Consent Personnel:**

Informed consent will be obtained by trained study personnel including an experienced research assistant (i.e., Luann Bianco) and nurse researchers (i.e., Andrea Rink and Sandra Ginter) at the Yale Program on Aging.

9. **Process of Consent/Assent:**

After potential subjects have been identified through chart review covered by a HIPAA waiver, subjects will be approached by the research team to obtain written consent or surrogates will be mailed an introductory letter, compound authorization form, and FAQ pamphlet. Individuals will be given sufficient time to read through the consent form, or if this presents difficulty, the form will be read to them by a member of the research team. All potential participants will receive a general description of the study, including the baseline and surveillance evaluations with a general description of risks and benefits. Participants will receive a full detailed description of the intervention strategy, including potential risks and benefits. In addition, participants will be asked to sign a HIPAA authorization form that explains the protected health information that will be used, disclosed, and to whom it will be disclosed as part of this study. Potential participants or surrogates will sign the consent form and HIPAA authorization forms prior to the baseline assessment. If surrogate consent is obtained, assent of the participant will still be attempted. The principal investigator will be available to answer any questions.

The phone number of the principal investigator will be provided to each participant to contact for any questions or problems.

10. **Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent:**

It is recognized that: 1) there may be a significant proportion of eligible residents who are decisionally impaired (i.e., who have a compromised capacity to understand information and make a reasoned decision about participation in research), and who require additional protections; and 2) the purpose of identifying eligible residents who may be decisionally impaired is not necessarily to exclude them from research, but to seek ways to enable their participation in an ethically appropriate manner that is also compliant with regulatory requirements. Therefore, at the time of approaching any potential participant for consent, our plans are as follows:

- **study personnel obtaining consent will use professional judgment to determine if the potential participant is capable of providing consent.** Members of the Field Staff who are responsible for participant recruitment and consent are all highly trained and experienced personnel in determining capacity to consent in aging populations. This determination will rely on individual observation of, and interaction with, the potential participant as well as the opinion of the caregiver, when available. In general, the assessment of the potential participant's capacity to consent will be based on her/his: 1) ability to communicate a choice; 2) ability to understand relevant information; 3) ability to appreciate the nature of the situation and its likely consequences; and 4) ability to manipulate information rationally.

- **determination of decisional impairment for providing consent.** Potential participants will be considered decisionally impaired for providing consent if they have: 1) an inability to express or communicate a preference or choice; 2) an inability to understand a situation and its potential consequences as well as the impact of study participation on those circumstances (e.g., do not understand that they may be hurt or may not be helped or cannot distinguish research from treatment); 3) an inability to provide a logical rationale for participation/no participation in the study (i.e., cannot address risk/benefit); or 4) have been legally determined to be incompetent and/or have a conservator of person. If there is any uncertainty, we will pursue surrogate consent.

- **plans for surrogate consent when decisional impairment is identified.** For potential participants who are deemed to be decisionally impaired, their identified surrogate will be approached for consent because: 1) the risks of this study are limited and are justified given the potential benefits of the research to the subject and the development of generalizable knowledge that will benefit elderly nursing home residents nationwide; 2) the intervention is commensurate with clinical treatments already available in clinical practice (multiple over-the-counter cranberry capsules and tablets) and 3) a Data and Safety Monitoring Board will be convened to monitor the study. All potential participants deemed decisionally impaired will be notified of that determination before permission is sought from their legally authorized surrogate to enroll in the study. If permission is given to enroll in the study, the potential participant will then be notified and their verbal assent will be obtained (i.e., their active affirmation of a desire to participate).

- **plans for assent for decisionally impaired potential participants.** In all cases in which assent is sought, the assent discussion will include the following: 1) a simplified description of the

purpose of the research, including risks and benefits; 2) a description of the procedures and interventions to which the participant will be exposed; 3) a statement explaining that participation in this study is voluntary only; 3) an explanation of the procedures that may hurt and for how long; 4) a question and answer period in which the participant will be encouraged to ask questions about their participation in the study.

11. **Documentation of Consent/Assent:**
    1) Compound Authorization and Consent [Adult Form]
    2) Compound Authorization and Consent [Legally Authorized Representative/Surrogate Form]

12. **Non-English Speaking Subjects:**

Since surrogate consent is required in most instances (95%) and since the participants often have underlying dementia, English speaking participants are required who can be explained the protocol and express their assent to participate not only to study staff but also to nursing home staff over the course of the study.

Confidentiality & Security of Data:

Name, address of nursing home residence, birth date, dates and details of previous episodes of bacteriuria and/or UTI, and dates and details of prior antibiotic administration will be recorded. Additionally, data on comorbidities, other medications, continence, and functional status will also be recorded. The sources of research data on enrolled participants will be interviews with the nursing staff and administrators at the institution and the participants' medical records. Baseline descriptive data (i.e., facility, age, race, ethnicity, gender, comorbid disease, cognitive status, activities of daily living, degree of mobility, medications, continence, history of UTI) will be recorded. These data will be ascertained from the Minimum Data Set, the medical record, and interview with the primary care provider (i.e., the Certified Nursing Assistant). The hierarchy of data sources will be based on the least burdensome source of data. Data regarding clinical outcomes (i.e., bacteriuria, pyuria, urinary tract specific symptoms, UTI, hospitalization, death, antibiotic prescriptions, resistant organisms), staff adherence to the intervention, and adverse events will be collected by research study personnel. To safeguard confidentiality, each study participant enrolled will be assigned a unique code number and the participant's name will never be attached to any form. A separate file linking the participant's name with study number will be kept in a password-protected data file, and will be used confidentially only by research staff.

Research data will be compiled into a spreadsheet and/or database format and stored on the secure Yale-ITS network which is backed-up nightly. Each subject will be identified by a study number. All data recorded on the data extraction sheet will be identified only by the study number and will be kept in a locked filing cabinet.

All data will be password protected and access limited to those individuals with direct responsibility for the research project. Moveable electronic media used to collect or store the data is equipped with encryption software recommended by the University (PGP). The PI and other members of the research team work with coded or de-identified data when using moveable device(s) to perform data analysis.

To safeguard confidentiality of protected health information, each study participant enrolled will be assigned a unique code number and the participant's name will never be attached to any form. A separate file linking the participant's name with participant ID code will be kept in a password-protected

data file, and will be used confidentially only by research staff. The study investigators will assume full responsibility to maintain confidentiality. All study results will be presented only as statistical aggregates that will neither identify, nor permit identification, of individual research participants. This has been an effective method in our previous studies.

The data systems and procedures at the Data Management and Informatics Core (DMIC) of the Program on Aging/Claude D. Pepper Older Americans Independence Center (OAIC) at Yale conform to Yale's HIPAA security policy (http://www.yale.edu/ppdev/Procedures/its/1610/1610PR.01SystemsNetwrokSecurity.pdf), and all equipment is certified by the Yale Information Security Officer. Since tablet PCs will be used by study staff, they will be configured with mandatory security safeguards that are enforced by Yale Information Technology Services, including "strong" passwords, password-protected standby mode, and whole-disk encryption. At the end of every day on which data are collected, each tablet PC will be synchronized with the master database on the DMIC system over a secure, encrypted mobile broadband connection. Master data will be stored in a Microsoft SQL Server database to which only the data manager will have access. Files prepared for analysis will be in SAS format, and will not include personal identifiers. To remove the possibility of any data value in an analysis file being traced to a specific study subject, files exported for analysis will not include the participant ID codes used by the field and data management staff to file records and questionnaires. An arbitrary code for record linkage will be included, but only the data manager will be able to map these linkage codes to the participant ID codes. The file export subsystem of Pi logs all files created for distribution outside of the master database.

All data will be password protected and access limited to those individuals with direct responsibility for the research project. Moveable electronic media used to collect or store the data is equipped with encryption software recommended by the University (PGP). The PI and other members of the research team work with coded or de-identified data when using moveable device(s) to perform data analysis.

When the research is completed, identifiable data will be destroyed three years after the completion of the study. Paper forms will be shredded and the study computer will be zeroed. The anonymous data will be retained indefinitely.

The principal investigator, research staff, sponsor and Yale Human Investigation Committee will have access to the protected health information.

It is possible that reporting of communicable diseases and elderly abuse will be necessary in this study. The nursing home administrator for the home that the participant resides in will be notified if such a circumstance arises.

Potential Benefits:

The potential benefits for the interventions are significant because we hypothesize that cranberry capsules will reduce the incidence of bacteriuria plus pyuria and morbidity associated with UTI in female nursing home residents. Administration of cranberry capsules has been documented in our pilot feasibility and dosing studies to be feasible and adhered to by staff, and it is designed to be generalizable and easily incorporated into the usual nursing care of nursing home residents. Although implementing the use of cranberry capsules would result in greater initial costs, there is the potential for healthcare savings from decreased antibiotic use, hospitalization, and emergence of resistant organisms. In summary, the anticipated benefits of the intervention to the participants and society far outweigh the

minimal risks. Therefore, the risk-benefit ratio appears to be favorable for proceeding with this clinical trial.

The importance of the knowledge gained in this proposed trial is great, including the following: 1) the identification of a feasible and safe intervention that is effective in reducing bacteriuria in elderly nursing home residents and can be generalized to female nursing home populations nationwide; 2) the determination of whether routine use of cranberry capsules, which are not regulated by the Food and Drug Administration (FDA), should be implemented in the nursing home setting; and 3) the potential for a major reduction in morbidity, mortality, hospitalizations, and healthcare expenditures related to UTI among elderly nursing home residents.

Alternatives:

As described previously in this application, there are currently no other standardized accepted alternatives for prophylactic treatment of asymptomatic bacteriuria in the nursing home population

Payments for Participation (Economic Considerations):

Participants will not be paid for participation in this study. However, since clean catch urine specimens are difficult to collect in this disabled nursing home population, nursing homes will be provided an incentive that is approved of by each nursing home administration. Urine samples will be collected by the nursing home staff nurses and/or aides. Since the collection of these urine specimens is cumbersome, only for study purposes, and essential to the successful completion of this project, individualized incentive programs for each participating nursing home will be designed. Incentive programs will be constructed with the input from the Administrator and Director of Nurses at each nursing home. Incentives may be distributed to a given floor or team. Planned incentives will include 1) an annual Certificate of Research Participation for all participating nursing home facilities which documents active participation in this Yale University research study for purposes of annual surveys conducted by regulatory bodies; 2) continuing education “in-service” hours that are required by the state of Connecticut for all CNAs; 3) gift certificates to participating nursing home staff. The amount of gift certificates will depend on how often they are given. If a gift certificate is given every other month, then it will be for $20.00. If given only once a year, then the gift certificate amount will be $120.00.

Costs for Participation (Economic Considerations):

There are no costs to the subjects associated with participation in this research project. Both the cranberry and placebo capsules will be provided at no cost to the subjects. Additionally, the clean catch urine sample, urinalysis, and culture will be performed at no cost to the subjects.

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1. Statement of Purpose:

The **primary aim** of this study is to test the efficacy of two oral cranberry capsules per day for prevention of bacteriuria plus pyuria in female nursing home residents. The **secondary aim** is to compare the occurrence of urinary tract specific symptoms in the cranberry capsule versus placebo groups.

The primary **hypothesis** is that two oral cranberry capsules will be associated with a 33% relative reduction in the occurrence of episodes of bacteriuria plus pyuria over 12 months, compared to placebo.

Supplementary Aims are to determine the:

- safety of administrating oral cranberry capsules over a 12 month surveillance period.
- adherence of nursing home residents and staff to the administration protocol of two oral cranberry capsules daily over 12 months.
- incidence of adverse clinical outcomes (i.e., symptomatic UTI, all cause death, all cause hospitalization, number and duration of all antibiotic prescriptions, all multi-drug antibiotic resistant organisms) in the intervention and control arms over 12 months.

2. Background:

2.1. Importance of urinary tract infection (UTI) in nursing home residents. UTI is the most common bacterial infection in nursing home residents with an incidence of 0.1 to 2.4 cases per 1000 resident-days. UTI is also a common cause of infectious disease hospitalizations and deaths; the National Nursing Home Survey indicated that UTI was an admitting or current diagnosis for hospitalization for 7,111/100,000 female residents. The Urologic Diseases of America determined that UTI was the most costly and resource intensive condition studied among Medicare beneficiaries. Total Medicare expenditures for UTI amounted to over $1.7 billion, exclusive of medication costs in 2006.

2.2. Diagnostic challenges of UTI in nursing home residents. Distinguishing symptomatic UTI (a quantitative count of $\geq 10^5$ colony forming units of bacteria per milliliter cfu/ml in one urine specimen in the presence of urinary tract specific symptoms i.e., dysuria, suprapubic pain or tenderness, new urinary frequency or urgency) from bacteriuria (a quantitative count of $\geq 10^5$ cfu/ml) is problematic in nursing home residents because of the challenges involved with symptom assessment. Bacteriuria is prevalent in 25-50% of female nursing home residents, and pyuria (any white blood cells in the urine) is present in 90% of residents with bacteriuria. Given the high prevalence of bacteriuria in this population, three randomized controlled trials of antibiotic treatment (versus no treatment) of bacteriuria were conducted; none of these trials showed any decrease in mortality with treatment. These studies led to the recommendation that bacteriuria should not be treated with antibiotics in older institutionalized adults. Consequently, bacteriuria plus pyuria are necessary but not sufficient conditions to make the diagnosis of UTI in this population. Infectious diseases physicians have distinguished bacteriuria from symptomatic UTI, which requires urinary tract specific symptoms. However, in clinical practice, it is not always clear how to classify a nursing home resident as symptomatic. Recent data from a large cohort in the New Haven area have shown that dysuria plus a change in mental status and/or a change in character of urine are the best combination of symptoms to predict bacteriuria plus pyuria among

nursing home residents with suspected UTI. However, change in mental status and change in character of urine are subject to confounding and small numbers of patients meet these clinical criteria. Hence, symptoms have limited utility in clinical decision-making regarding the diagnosis of UTI. Given the current diagnostic uncertainty, antibiotics are commonly prescribed, and UTI accounts for 30% to 56% of all antibiotic prescriptions in the nursing home setting.

2.3. Widespread empiric antimicrobial administration. Although treatment of bacteriuria is not recommended, many nursing home residents are still prescribed antibiotics because of the diagnostic challenges involved in identifying those residents that will benefit most from antibiotic therapy. Only 13% of antibiotic prescriptions for UTI occur prior to results of urine cultures being available. Isolation of resistant organisms is associated with prior antibiotic exposure, and resistant organisms from UTI are more frequent in nursing home residents than in community dwellers. Urinary isolates from nursing home residents are frequently resistant to commonly prescribed oral antibiotics (see **Figure 1**). Use of antibiotics is associated with several risks, including the development of multi-drug antibiotic-resistant organisms, drug-related adverse effects, and significant costs. In order to reduce antibiotic prescriptions, prevention strategies should be targeted to bacteriuria, pyuria, and symptomatic UTI.

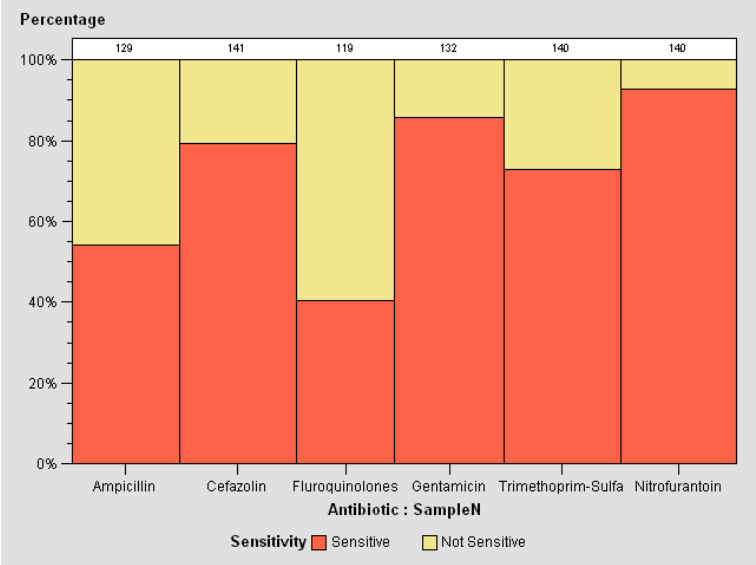
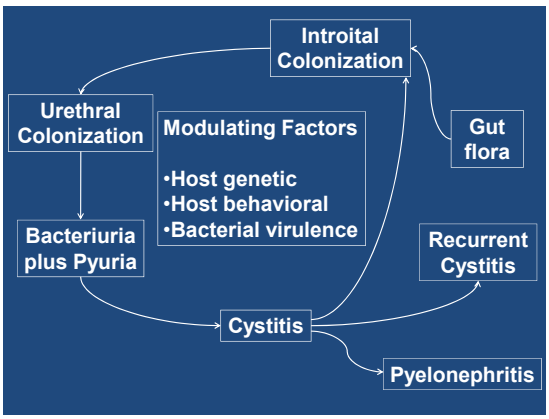


Figure 1: Urinary Isolates UTI Episodes

2.4. Rationale for prevention of bacteriuria, pyuria, and UTI. Bacteriuria has been shown to be a risk factor for subsequent development of symptomatic UTI among young women and women with diabetes mellitus, and it is hypothesized that bacteriuria precedes the development of symptomatic UTI in nursing home residents (see **Figure 2**). The presence of bacteriuria is the greatest trigger for the initiation of antibiotic therapy. Since nursing home practitioners usually wait to obtain results of urine cultures, reducing bacteriuria could reduce antibiotic prescriptions. Therefore, efforts to prevent bacteriuria, pyuria, and UTI represent the most logical means of reducing antibiotic prescriptions in the nursing home setting.

Figure 2: Pathogenesis of UTI



2.5. Cranberry for prevention of UTI.

Many of the identified risk factors for bacteriuria and UTI in nursing home residents (e.g., functional disability, dementia) are largely non-modifiable. Vaginal estrogen therapy, which has been shown to be effective at preventing recurrent UTI in post-menopausal women, has potential risks and side effects which would be undesirable in a nursing home population. With few other feasible intervention strategies to prevent the common and morbid condition of UTI in nursing home residents, cranberry capsules represent a novel intervention warranting investigation. Cranberry products represent an existing, non-antimicrobial method for prevention of UTI. Cranberry proanthocyanidins (PAC) have been shown to inhibit adherence of P-fimbriated *E.coli* to uroepithelial cells. P fimbriae are finger-like projections that the organism uses to attach to bladder cells (see **Figure 3**). In vitro studies have demonstrated that cranberry changes the formation of P fimbriae such that they can no longer attach to the bladder mucosa. Since *E.coli* represents the majority of urinary isolates (54%), this preventive strategy may be an effective method among nursing home residents. Empirical data supporting the potential benefit of cranberry include: 1) in the study by Avorn et al., cranberry juice decreased bacteriuria plus pyuria in older women, even those not caused by *E.coli;* 2) urine from young women that ingested cranberry capsules has been shown in vitro and in vivo to decrease uropathogenic *E.coli* virulence; and 3) limited clinical studies of cranberry juice in elderly women have demonstrated reductions in bacteriuria but have not been of adequate size or quality to result in changes in patient care. The acrid flavor of cranberry juice is challenging for patients to tolerate in large volumes. Nursing home residents in particular are unable to ingest sufficient volumes to maintain hydration because of swallowing disorders, exacerbation of incontinence, and decreased thirst drive. Hence, cranberry capsules represent a prevention strategy that warrants testing in the nursing home population.

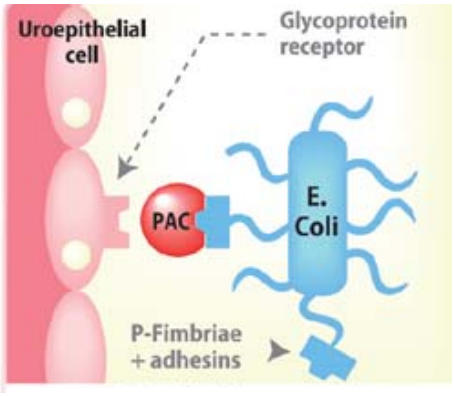


Figure 3: Anti-adhesion of PAC

2.6. Effective dose of cranberry. Previous studies regarding cranberry products for prevention of UTI yielded conflicting results, likely because of variability of PAC dose and clinical populations studied. Initial studies identified PAC to be the active ingredient in cranberry that prevents binding of *E.coli.* In the clinical trial by Avorn et al. of 300ml of cranberry juice beverage daily (36mg PAC), older women (mean age 78.5 years) had a 58% reduction in the odds of having bacteriuria plus pyuria compared to controls, particularly after more than one month of cranberry juice ingestion. Previously, there were at least three different methods of quantifying PAC in the market place, and many products purported effectiveness with variability in dose of PAC. Methods to quantify PAC have now been standardized and can be independently measured. Only one product on the market currently can deliver 36mg PAC as measured by the BL-DMAC method in each capsule and it will be utilized in this proposed project. In vitro data have shown that 36 to 108mg of PAC is effective at inhibiting bacterial adherence to epithelial cells. Since patient adherence to cranberry capsule administration is important and nursing home residents often take multiple medications, the least pill burden and dose of cranberry capsules with the largest effect will be utilized for this efficacy trial.

2.7. Potential adverse effects of cranberry. The only side effect reported with the ingestion of unsweetened cranberry juice is gastro-esophageal reflux; however, this side effect has not been reported with cranberry capsules. Additionally, ingestion of large amounts of liquid is challenging for nursing home residents with demonstrated poor adherence, thereby making cranberry capsules a more preferable intervention option to test in this particularly vulnerable population.

2.8. Investigating the effects of cranberry capsules on women only. The reasons for investigating cranberry capsules in women only include: 1) Avorn et al. investigated cranberry juice among women only; 2) women represent 75-85% of nursing home residents; 3) there is no evidence to date that cranberry products reduce UTI in men; 4) the predominant risk factor for UTI in men is underlying structural or functional abnormalities of the urinary tract; and 5) the prevalence of bacteriuria plus pyuria in female nursing home residents ranges from 25-50% versus 15-30% for men. Since the prevalence of bacteriuria plus pyuria is lower in men, a study that would detect an effect in men and women would have to be larger. Powering a study to detect a difference in female nursing home residents is an important first step.

2.9. Comparison of this proposal to the landmark cranberry juice study by Avorn et al. The landmark study by Avorn et al. included 153 female subjects, 109 community dwellers living in housing complexes for the elderly and 44 long-term care facility residents, with a mean age of 78.5 years. Participants ingested 300ml of cranberry juice cocktail per day for 6 months. All participants provided self-consent, and most participants were instructed on how to collect an adequate clean-voided specimen themselves. Most participants were enrolled only after a 1-month trial of placebo beverage to ensure that daily intake would be adequate throughout the study. This study informed the development of this proposal by identifying areas where further investigation is needed: 1) only 29% of participants were nursing home residents; 2) the mean age was 10 years lower than the mean age of nursing home residents; 3) most nursing home residents are unable to provide self consent or self collected urine specimens; 4) dehydration is prevalent in up to 90% of nursing home residents because of swallowing difficulty, aspiration risk, increased incontinence with hydration, and decreased olfactory, taste, and thirst sensations. Daily intake of 300ml of juice would not be feasible for most nursing home residents. Since UTI is the most prevalent infection in nursing home residents, a study designed specifically for the nursing home population is warranted.

2.10. Rationale for this study. Given the biological plausibility for its preventive effects and the challenges involved with cranberry juice ingestion by nursing home residents, cranberry capsules represent a promising preventive strategy that should be further explored in this vulnerable population. Because symptomatic UTI is a leading cause of morbidity in nursing home residents, preventing bacteriuria plus pyuria will likely reduce morbidity. Furthermore, a reduction in bacteriuria plus pyuria will result in a reduction in antibiotic use and its attendant adverse effects. Our prior work has demonstrated that 1) cranberry capsule administration is feasible in nursing home residents; 2) an optimal dose of administration has been identified; and 3) there is preliminary evidence that cranberry capsules reduce bacteriuria plus pyuria. This proposal will determine whether cranberry capsules reduce the occurrence of bacteriuria plus pyuria, whether administration of cranberry capsules is safe and adhered to over 12 months, and whether bacteriuria plus pyuria is associated with UTI morbidity. **This study is significant because cranberry capsules are a feasible and low risk intervention that may reduce the morbidity and mortality associated with bacteriuria, pyuria, and UTI in nursing home residents.**

2.11. Preliminary studies.

2.11.1. Previous studies by principal investigator (P.I.) regarding UTI in nursing home residents. Dr. Juthani-Mehta has spent the past eight years investigating diagnostic, management, and prevention strategies of UTI in nursing home residents. She competed for, and was awarded, an R03 Small Research Grant and a K23 Career Development Award funded by the National Institute on Aging on this topic. She has conducted studies involving interviews with nursing staff, observational cohort studies, and pilot intervention studies that have prepared her for conducting the proposed study.

2.11.2. Pilot feasibility and adherence study of cranberry capsules in long-term care residents. In a previous study conducted by the P.I. and funded by the Donaghue Foundation, a cranberry capsule product with 16.25mg PAC per capsule was studied. Fifty-seven participants received none (N=18), one (N=20), or two (N=19) cranberry capsules per day and were followed for 6 months. The mean age was 86.8 years, 47 (83%) were women, and 100% were white. The baseline bacteriuria rate was 45%. Of 240 urine samples that were scheduled for collection, 207 samples were collected (86.3%). Of 237 doses of cranberry capsules that were prescribed, only 7 (3%) were missed. Six subjects had one or more side effect noted after cranberry administration (i.e., vomiting [N=5], diarrhea [N=3], nausea [N=3]); however, whether another etiology could account for these symptoms was not noted in the medical record. This study demonstrated that 1) cranberry capsules were feasible to administer and adhered to, and 2) clean catch urine specimens could be obtained in this population. Although the study was not designed to evaluate efficacy, trend towards efficacy of cranberry capsules could not be demonstrated, and it is possible that under-dosing of the active components of cranberry was responsible for this finding.

2.11.3. Cranberry capsule dosing study in nursing home residents. Given the findings of the study outlined in **Section C.2.2.**, the P.I. competed for and received funding through the Yale Center for Clinical Investigation (YCCI – the Yale CTSA) to conduct a pilot dosing study of cranberry capsules to identify the optimal dose among nursing home residents. This study was a double-blind, randomized, placebo-controlled trial of 3 cranberry capsules once per day (108mg PAC), 2 cranberry capsules plus one placebo capsule once per day (72mg PAC), 1 cranberry capsule plus two placebo capsules once per day (36mg PAC), and 3 placebo capsules once per day to determine the number of participants with bacteriuria plus pyuria over a one month period. Urine specimens were collected at baseline and then on a weekly basis for 4 weeks (total = 5 specimens). Inclusion criteria were: 1) female residents; 2) history of UTI recorded in the existing medical record; 3) age ≥ 65 years; 4) long term residence; 5) English speaking. Exclusion criteria included: 1) total incontinence; 2) warfarin therapy; 3) residence for < 4 weeks; 4) chronic indwelling bladder catheter; 5) terminal (life expectancy < one month); 6) chronic antibiotic therapy; 7) kidney stones; 8) dialysis; 9) cranberry therapy; 10) allergy to cranberry. Through a HIPAA waiver, chart review was conducted, and eligible residents were identified. Eligible residents or surrogates were approached for written consent.

2.11.3.1. Eligibility and enrollment data. Thirteen nursing homes consented to participate in this study, and 11 were required to reach our target of 80 participants, 20 in each arm of the study. In 11 homes, 1928 residents were screened for participation; 1380 residents did not meet inclusion criteria (see **Table 1**); of 548 remaining residents screened, 308 residents met exclusion criteria and 240 residents

Table 1: Inclusion Criteria

Residents not meeting inclusion criteria	Frequency	Percent
No history of UTI	664	48.1%
Male	479	34.7%
Short term rehabilitation	163	11.8%
Non-English speaking	38	2.8%
Age<65 years	36	2.6%
Total	1380	100%

were eligible; 90 residents consented (37.5% consent rate), and 80 residents enrolled (10 participants met an exclusion criterion prior to enrollment). The primary reason for lack of inclusion in this study was no history of UTI. This was listed as an inclusion criterion in order to target the group of residents with the highest predicted rate of bacteriuria.

2.11.3.2. Preliminary feasibility and adherence data. Eighty participants each should have provided 4 urine specimens, one per week during the month of follow up. Of the 320 urine specimens that should have been collected, 293 urinalyses and urine cultures were obtained (92%). Adherence was assessed by the mean number of doses administered in the four arms of the study out of a total of 30 daily doses over the one month study period → placebo 26.8 doses (SD 5.1), one capsule 27.5 doses (SD 6.0), two capsules 29.1 doses (SD 1.7), three capsules 27.9 (SD 4.1). There were no adverse events possibly related to cranberry capsule ingestion (i.e., nausea, vomiting, or gastrointestinal distress) during the one month of follow up. Hence, adherence was best in the two capsule treatment group, although not significantly different from the other groups.

2.11.3.3. Preliminary efficacy data. Preliminary data were obtained from the 80 enrolled participants. Twenty participants were randomized to each of four treatment groups, receiving 0, 1, 2, and 3 active cranberry capsules respectively. Baseline data, including a baseline urine culture and urinalysis, was collected prior to randomization. Four additional urine specimens were obtained at one-week intervals after randomization. The rate of bacteriuria plus pyuria was 52% in the placebo group. Of the 320 anticipated outcome measurements, 27 were missing. Investigation of missing data suggested that the data were missing completely at random. The effect of dose on development of bacteriuria plus pyuria was tested using a Generalized Estimating Equations (GEE) model, adjusted for baseline bacteriuria status (present vs. absent). Results displayed in **Table 2** show that over one month, there was a 37% reduction in the odds of having bacteriuria plus pyuria among the 2 cranberry capsule group as compared to the placebo group, but the confidence intervals were wide. Since Avorn et al. demonstrated no effect at one month of surveillance, these preliminary data showing some effect could become more pronounced with one year of surveillance. The reason for the lack of a dose response for three capsules is not clear. Two possible reasons are 1) the sample size was too small with an unstable estimate of the effect of three capsules; 2) the one month duration of surveillance was too brief to demonstrate a dose response effect.

Table 2: Regression Analysis (N=293)

Predictor Variable	Odds Ratio	95% Confidence Interval
One capsule	0.83	0.28-2.41
Two capsules	0.63	0.21-1.94
Three capsules	1.03	0.34-3.17

3. Research Plan:

3.1. Overview. The **primary aim** of this study is to test the efficacy of two oral cranberry capsules per day in the prevention of bacteriuria plus pyuria in female nursing home residents. The **secondary aim** is to compare the occurrence of urinary tract specific symptoms in the cranberry capsule versus placebo groups. The **primary hypothesis** is that two oral cranberry capsules per day will be associated with a 33% relative reduction in the occurrence of episodes of bacteriuria plus pyuria over 12 months, compared to placebo, in a cohort of female nursing home residents. This aim will be accomplished by conducting a double-blind randomized placebo-controlled efficacy trial of two oral cranberry capsules per day versus placebo in a cohort of Connecticut female nursing home residents.

Trial Setting. The setting will be up to 21 nursing homes within a 50 mile radius of New Haven, licensed by the Connecticut Department of Public Health as "Chronic and Convalescent Nursing Homes", providing skilled care and certified for Medicare or Medicaid. These 21 homes each have at least 90 residents, UTI rates comparable to the national average of 9% annually, and sociodemographic characteristics similar to national averages.

Design. The design will be a double-blind, randomized, placebo-controlled efficacy trial in which all participants will undergo urine sample testing at baseline and every two months over 12 months of prospective surveillance. Training of staff, screening, and enrollment of participants will occur one home at a time. We anticipate each home will require 8 weeks from training initiation to the start of the intervention. Each participant will receive treatment and be followed for outcomes for 12 months.

Participants. The participants will be female long-term care nursing home residents, 65 years or older. Assuming a Type 1 error of 5% (2-sided), 80% power, a control group prevalence rate of 45%, a relative reduction of 33% (absolute risk difference of 15%), serial correlation among 6 repeated urine measurements on each participant of 0.35, and a drop-out rate of 20% (e.g., death 17%, transfer and/or inability to provide further urine specimens 3%), the sample size required is 90 participants in each group (total N=180).

Intervention. The intervention will be two cranberry capsules per day, compared to two placebo capsules per day for 12 months (30-day blister pack per month equaling 360 days). Data entry and management will occur at the Yale Program on Aging. Interim monitoring will include patient accrual, protocol adherence, data quality, safety, efficacy, and futility. A series of monitoring tables will be developed that include the above elements for presentation on a semi-annual basis to the Independent Safety Monitor appointed by the NIA. Final analysis will consist of comparability of treatment groups, treatment efficacy, and safety. All primary treatment comparisons will analyze participants as randomized. An Executive Committee will oversee the study design and troubleshoot methodological problems that arise during the course of the study. A Steering Committee will oversee daily issues related to participant enrollment, data collection and management, intervention implementation, and outcome assessment. An Internal Safety and Outcome Adjudication Committee will monitor adverse events, adjudicate outcomes, and interface with the Independent Safety Monitor. The P.I., Dr. Juthani-Mehta, has completed one observational cohort study, two pilot intervention studies, and was the Chair of the Internal Safety Committee of another nursing home intervention trial. She has assembled a team that is well equipped to complete this proposed project.

3.2. Trial Setting. This study will take place at up to 21 nursing homes within a 50 mile radius of New Haven**.** The setting will be up to 21 nursing homes within a 50 mile radius of New Haven**,** licensed by the Connecticut Department of Public Health as "Chronic and Convalescent Nursing Homes", providing skilled care and certified for Medicare or Medicaid. These 21 homes each have at least 90 residents, UTI rates comparable to the national average of 9% annually, and sociodemographic characteristics similar to national averages.

3.2.1. Rationale. Residents of nursing homes within the greater New Haven area are reflective of the nursing home population within the United States. Nursing homes chosen to participate in this study represent a mix of urban and suburban, proprietary and nonprofit, private pay and Medicaid homes. We anticipate our target minority rate of 12% will be met with the spectrum of homes participating. We recognize the great challenges involved in working with these non-academic nursing homes, but we have established good relationships with many of them, and we have successfully conducted previous

observational and interventional studies in this environment. The Yale Program on Aging has vast experience conducting research in challenging but important real world settings with high recruitment, retention, and adherence rates.

3.2.2. Determination of eligible pool of residents. Using information available through Medicare on www.medicare.gov/nhcompare, the national and Connecticut state averages for the percent of residents who had a UTI annually were 9% and 7%, respectively. To improve study efficiency, we selected nursing homes with an average UTI rate at least as high as the CT and national averages within a 50 mile radius of New Haven and with at least 90 beds. Women comprise 75-85% of nursing home residents. In the first cranberry capsule feasibility study, the baseline bacteriuria rate was 45%. In order to increase the baseline rate of bacteriuria, in the pilot dosing study, history of UTI was a required eligibility criterion. However, 664 residents were excluded by requiring this inclusion criterion, and the baseline rate of bacteriuria plus pyuria only increased to 52%. In an effort to increase the baseline bacteriuria rate, a large pool of potentially eligible subjects was lost and the rate only increased from 45% to 52%. Therefore, for this proposed study, history of UTI will not be a required inclusion criterion.

In the initially identified 10 homes, we expected to find at least 700 eligible residents so that with a 30% consent rate, we could enroll 180 participants. In the pilot dosing study, when history of UTI was included as an inclusion criterion and 664 residents were excluded for this reason, 240 eligible residents were identified in 11 homes. If history of UTI would not have been an inclusion criterion, 904 residents would have been eligible for the pilot dosing study (240+664=904). Although we had a 37.5% consent rate in the pilot dosing study, with a conservative 30% consent rate which is consistent with other nursing home intervention studies, 271 residents could have consented from 11 nursing homes. Therefore, in this proposed study, we anticipated that 10 homes would be sufficient to achieve our sample size of 180. Nevertheless, 6 back-up homes were recruited in the event that 10 homes would not be sufficient to meet our target sample size. Over the course of the study, because of a lower eligibility rate, a total of 21 nursing homes were required to achieve the calculated sample size.

3.2.3. Identification of participating nursing homes. Based on our sample size estimate of 180 participants, we anticipate the need for up to 21 nursing homes and, at this time, we have 21 participating nursing homes that have already agreed to participate.

3.3. Trial Design. This study will be a double-blind, placebo controlled, randomized, clinical efficacy trial of two cranberry capsules versus placebo. The unit of randomization will be each individual participant.

3.4. Trial Participants. The participants in this trial will be female long-term care nursing home residents.

3.4.1. Screening and eligibility assessment. Screening at each nursing home will occur sequentially. We anticipate that from the date of screening to enrollment, each home will require eight weeks. Once enrollment is initiated at one home, screening will begin at the next home. Residents, age ≥65 years, residing in one of the participating nursing homes will be identified from a computerized log kept by the Director of Nursing Services at the home. Subsequently, study personnel will perform a brief chart review to establish the presence of inclusion and exclusion criteria. A HIPAA waiver will be obtained for recruitment purposes only. After the initial wave of recruitment ("prevalent participants"), each nursing home will be re-screened approximately every three months for one year. Participants in subsequent waves of recruitment will be "incident participants." Therefore, there will be up to five total waves of recruitment at each participating nursing home.

3.4.1.1. Inclusion criteria. All races will be considered for inclusion if they are: 1) female; 2) long-term care residents; 3) English speaking; and 4) 65 years or older. Since surrogate consent is required in most

instances and since the participants often have underlying dementia, English speaking participants are required who can be explained the protocol and express their assent to participate not only to study staff but also to nursing home staff over the course of the study.

3.4.1.2. Exclusion criteria. Residents will be excluded if they: 1) are not expected to be in the nursing home for at least one month (i.e., short term rehabilitation, pending discharge, terminal life expectancy < 1 month); 2) are on chronic suppressive antibiotic or anti-infective (i.e., mandelamine) therapy for recurrent UTI; 3) have end stage renal disease on dialysis (they do not regularly produce urine); 4) are unable to produce a baseline clean catch urine specimen for collection; 5) are on warfarin therapy because of a potential interaction of warfarin and cranberry juice; 6) have a history of nephrolithiasis because cranberry may increase the risk of nephrolithiasis; 7) have an indwelling bladder catheter in place; 8) have an allergy to cranberry products; 9) are being treated with cranberry products; 10) residence < 4 weeks.

3.4.2. Consent and enrollment procedures. Permission will be obtained from the potential participant's home administrator before each resident is approached for study recruitment. Informed consent will be obtained by trained study personnel. All potential participants will receive a general description of the study, including the baseline and surveillance evaluations, the intervention, potential risks and benefits. As part of the study protocol, participants will be advised to avoid ingestion of other cranberry products. In addition, participants will be asked to sign a HIPAA authorization form that explains the protected health information that will be used, disclosed, and to whom it will be disclosed as part of this study and an Authorization to Release Protected Health Information for Research form. For potential participants who are determined to be decisionally impaired by study recruitment personnel, consent will be sought from their designated surrogates along with assent from the participant. Surrogate consent will be sought through a combination of up to three phone calls and two mailings describing the study purpose, intervention, surveillance evaluations, risks and benefits. We have successfully utilized this method of surrogate consent in our observational cohort studies, in pilot intervention studies, and in the pilot dosing study in which the consent rate was 37.5% from eligible residents or surrogates. Based on our pilot studies, we anticipate that >95% of eligible residents will require surrogate consent because of decisional impairment.

3.4.3. Availability of participants for enrollment. We recognize that in an intervention trial, there will be obstacles to patient enrollment, adherence, and retention. These include ineligibility due to exclusion criteria defined, resident (or surrogate) refusal to participate, drop outs, and loss from competing morbidities. However, among the 10 initial homes that agreed to participate, we estimated that we would have ≥600 eligible residents with the average number of eligible residents per home of 50 at the time of the initial two month enrollment period. Given the anticipated replacement of the 20% of residents censored annually, we estimated an additional 200 eligible residents available over the two year enrollment period (100 each year), resulting in 500+200=700 total eligible residents. A consent rate of 30% would yield at least our sample size target of 180 participants (700x30%=210). The consent rate of 30% is feasible because data from our dosing study revealed a 37.5% consent rate. In the vulnerable nursing home population, consent rates of approximately 30% for an intervention study are well documented. In addition, additional back-up homes agreed to participate if more homes were required for recruitment and all were utilized.

3.4.4. Expected attrition. We anticipate the following sources of attrition of participants: deaths, transfers out of the nursing home, and functional decline prohibiting continued participation in the study. The total anticipated attrition rate is 20%, 17% for death and 3% for other reasons. These rates are based on observed numbers in our prior studies. We do not expect any drop ins from placebo to

treatment. Because we will analyze participants as they are randomized, intervention drop-outs, and non-adherent participants to the assigned treatment arm are not considered losses. Deaths occurring before obtaining outcome data or the end of the 12 month follow-up are unavoidable in a nursing home population and analyses to make use of the existing data on these losses are discussed below. Transfers out of the homes are also expected. Based our prior studies, the transfer rate is expected to be low (i.e., 3%).

3.5. Stratified randomization. Once consent is obtained, a baseline clean catch urine specimen will be obtained from participants prior to initiation of therapy to ensure that subsequent clean catch urine specimen collection will be possible. Then, enrolled participants will be randomized to two placebo or two cranberry capsules within nursing home using a permuted block design with a variable block size and equal allocation. Stratification by nursing home is being proposed to account for potentially different standards of nursing and medical care among nursing homes. The randomization will be double-blind. Neither the personnel (study nurses, P.I., nursing home nurses and CNAs) nor the patient will be aware of the treatment allocation. The senior data manager will implement the randomization scheme, and the Investigational Drug Services pharmacist will make the arm assignment. Only they will have access to the randomization codes during the enrollment process.

3.6. Trial Intervention. The intervention is two cranberry capsules versus placebo capsules for the prevention of bacteriuria plus pyuria. Cranberry capsules will be administered for 360 days and total follow up of each participant will be one year. This trial serves as an efficacy study in which the reduction of bacteriuria plus pyuria is the primary outcome. The secondary outcome is the occurrence of urinary tract specific symptoms in the cranberry capsule and placebo groups. This study will also determine rates of adverse clinical outcomes (i.e., symptomatic UTI, all cause hospitalization, all cause death, all antibiotic prescriptions, and all multi-drug antibiotic resistant organisms) in the placebo and treatment groups.

3.6.1. Justification for two cranberry capsules. Based on preliminary data, two cranberry capsules had the best adherence and largest effect in reducing bacteriuria plus pyuria. Since nursing home residents often take multiple medications, utilizing a safe dose with the lowest pill burden is warranted. Therefore, this regimen has the greatest likelihood of working in a real-world setting.

3.6.2. Training of nursing home staff. As the study begins in each new home, the Senior Intervention Nurse Educator will collaborate with nursing administration to organize a series of “in-service” didactic training sessions to orient and mentor the nurses and certified nursing assistants (CNAs) as a group to the methods involved in urine specimen collection and capsule administration. This will occur prior to initiation of the intervention in any participant. Since staff turnover is high in the nursing home setting, we anticipate the need to retrain nurses and CNAs on a quarterly basis over the course of the study. During the first 4 weeks after initiation of the intervention, the team of training nurses will identify barriers to administrating the intervention (e.g., storage location of study capsules) and facilitate solutions. The importance of timely and clean urine specimen collection will be reinforced to all nursing home staff to reduce the number of missing urine specimens. Since clean catch urine specimens are most easily obtained in the first morning void, specimens will be targeted for collection by nursing home staff between 5-7AM. Study staff will supervise baseline collections of these specimens in each home, and train nursing home staff for subsequent urine specimen collections. Prior pilot testing has demonstrated that nursing home patients experience more agitation when unfamiliar study personnel perform routine care. Therefore, urine specimens will be collected by nursing home staff members that are well known to the participants. This strategy of urine specimen collection was effective in the pilot dosing study.

3.6.3. Incentives for nursing home facilities, nurses, and CNAs for study participation. Although our pilot dosing study demonstrated high feasibility and adherence to capsule administration and obtaining of urine specimens, the pilot was conducted for only one month. Therefore, we will work with nursing administration and opinion leaders in the various homes to identify and provide relevant incentives for the nursing homes, CNAs, and nurses to maintain the enthusiasm and cooperation of all homes in the study. Planned incentives will include 1) an annual Certificate of Research Participation for all participating nursing home facilities which documents active participation in this Yale University research study for purposes of annual surveys conducted by regulatory bodies; 2) continuing education "in-service" hours that are required by the state of Connecticut for all CNAs; 3) gift certificates to participating nursing homes. The amount of gift certificates will depend on how often they are given.

3.6.4. Retention events for nursing home facilities, nurses, and CNAs for study participation. We will establish a series of retention events for all the nursing home facilities, and retention events for all the nurses and CNAs to maintain their enthusiasm, cooperation, and interest in maintaining adherence to the study protocol. For nursing home facilities, the study staff will interface with the nursing home staff periodically to discuss the study. Specific issues to be discussed will include barriers to implementing the protocol, troubleshooting, and other topics of interest to the nursing home staff that might improve patient care (e.g. nursing home-acquired pneumonia prevention, prevention of decubitus ulcer formation).

3.7. Trial Data: Descriptive, Outcomes, Sample Size Estimate, Data Management, and Analyses

3.7.1. Baseline clinical assessment. Consenting participants will undergo a baseline assessment during which descriptive characteristics will be recorded. Facility, age, race, medications, comorbidities, and history of UTI will be obtained from chart review. The primary nurse and/or CNA will be asked questions adapted from the Minimum Data Set (MDS) regarding cognitive status, behavior, activities of daily living, continence, and degree of mobility. This method was used successfully in our observational cohort study and our pilot dosing study.

3.7.2. Clinical outcome surveillance: primary and secondary outcomes. Urine specimens will be obtained at baseline (prior to randomization) and every two months thereafter via clean catch (7 specimens total). The primary outcome will be the presence or absence of bacteriuria plus pyuria at each time point. Treatment will not be discontinued if urine culture results are positive. This is the primary outcome of the study. All cultures will be recorded over the course of the year and tabulated at the end of the study.

3.7.2.1. Definition of primary outcomes: bacteriuria plus pyuria and urinary tract specific symptoms. Presence of bacteriuria will be defined as both >100,000 cfu/ml and ≥100,000 cfu/ml of one or two organisms, based on the highest quantitation of bacteriuria reported by the laboratory. Absence of bacteriuria will be defined as a urine culture with no growth, mixed flora (three or more organisms), or less than the highest quantitation of bacteriuria reported by the laboratory. Pyuria will be defined as any number of white blood cells on urinalysis. Urinary tract specific symptoms (i.e., acute dysuria, new suprapubic pain or tenderness, acute costovertebral angle pain or tenderness, gross hematuria; new or marked increase in: incontinence, urgency, or frequency) will be assessed at the time of each urine specimen collection. In the study by Avorn et al., the rate of urinary tract specific symptoms at monthly intervals was 7% in the placebo group and 4% in the cranberry group.

3.7.2.2. Definition of secondary outcomes for supplementary aims.

3.7.2.2.1. Symptomatic UTI. Symptomatic UTI will be defined as 1) (a) acute dysuria; OR (b) fever or leukocytosis and at least **one** of the following: acute costovertebral angle pain or

tenderness; suprapubic pain; gross hematuria; new or marked increase in: incontinence, urgency, or frequency; OR (c) two or more of new or marked increase in: incontinence, urgency, frequency, suprapubic pain, new gross hematuria **AND** 2) a voided urine culture with (a) >100,000 cfu/ml or $\geq 10^5$ cfu/ml of a single predominant organism or two gram negative organisms OR (b) a specimen collected by in and out catheter specimen with $\geq 10^2$ cfu/ml of any number of organisms.

3.7.2.2.2. Hospitalization. All cause hospitalizations, including those related to UTI, and visits to the emergency room will be recorded.

3.7.2.2.3. Death. All cause death, including UTI as a reason, will be recorded.

3.7.2.2.4. Antibiotic prescriptions. Information on all antibiotic therapy prescribed, whether for UTI or other cause, will be recorded. If antibiotic therapy is for UTI, it will be noted in data collection.

3.7.2.2.5. Resistant organisms. All resistant bacterial isolates, either from the urine specimens obtained for study purposes or as recorded from other clinical specimens in the medical record, will be recorded. These isolates will include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococci* (VRE), and multi-drug resistant gram negative rods, with multi-drug resistance defined as resistance to at least 3 of the following antibiotics: ampicillin-sulbactam, cefazolin, ceftriaxone, ceftazidime, fluoroquinolones, piperacillin-tazobactam, meropenem, imipenem, and trimethoprim-sulfamethoxazole.

3.7.2.3. Surveillance of primary outcome: bacteriuria plus pyuria and urinary tract specific symptoms. Surveillance of the primary outcome will occur every two months for a total of six assessments over the 12 months of follow up. The primary nursing home staff (i.e., nurses and CNAs) will be responsible for collecting clean catch urine specimens every two months, targeted to be collected from 5-7AM on the same day for a given home. Study staff will provide reminders as to when sample collection is due. If the specimen is not collected on the due date, attempts at specimen collection will continue for two additional weeks at any time of the day prior to noting the specimen as missing. Urinary tract specific symptom assessment will occur on the day of urine specimen collection. Based on our pilot data, we anticipate that 14% of specimens initially will be missing. The research assistants, Luann Bianco or Sabina Rubeck, will collect all urine samples that are obtained and deliver to the Yale-New Haven Hospital Hematology and Microbiology Laboratories for processing. Urinalysis processing is automated in the Hematology Laboratory. Performing quantitative urine cultures will require the following steps: 1) mix urine; 2) vertically insert a flamed and cooled calibrated platinum loop that delivers 0.01 ml of urine into the specimen; 3) remove a loopful of urine; 4) inoculate one loopful of urine onto a Sheep blood agar and MacConkey agar plate by making a straight line down the center and then a series of close perpendicular streaks throughout the first line. Lactobacillus species, alpha-streptococci, and diphtheroids will not have susceptibility testing performed. All other isolates will have antibiotic susceptibility testing performed. When three or more organisms are isolated, the urine culture will not undergo further processing and will be regarded as a mixed culture. We successfully utilized this method of urine collection and processing in our pilot dosing study.

3.7.2.4. Outcome adjudication. If a urine culture reports growth of one or two organisms at least one of which is >100,000 cfu/ml or ≥100,000 cfu/ml and the urinalysis reveals any number of white blood cells, the primary outcome will be met. The Outcome Adjudication Committee, consisting of the P.I. (Juthani-Mehta), the Investigator (Datta), the Field Nurse Team Leader (Rink), the Project Manager (Luann Bianco), the Data Manager (Stephanie Argraves), Research Associate (Sabina Rubeck), and the senior infectious diseases specialist (Quagliarello), will participate in the adjudication of outcomes.

3.7.3. Surveillance of adverse events. The Field Nurse Team Leader, Ms. Rink, along with Ms. Ginter will monitor for any potential adverse events on a monthly basis for the duration of the 12 month surveillance period per participant, through interviews with nursing staff and report to the Internal Safety Committee. To ensure a rapid and systematic approach to adverse events, the Internal Safety Committee will evaluate all suspected adverse events, however mild or severe. The Chair of the Internal Safety Committee (Quagliarello) will determine which serious adverse events must immediately be reported to the Yale Human Investigation Committee, Independent Safety Monitor, and the NIA. At the request of the NIA, all deaths, unanticipated problems, and unanticipated/protocol related serious adverse events will be reported to the NIA and Independent Safety Monitor within 48 hours of the PI being notified.

3.7.4. Surveillance of adherence to intervention. Adherence will be determined by the number of capsules that were administered to each participant in relation to the targeted number. The medication administration record will be reviewed to determine if the study capsules were documented to be administered. However, in our pilot study, we identified discordance between the numbers of capsules recorded to have been administered versus the numbers of capsules remaining. Therefore, surveillance of the remaining capsules by pill counting every month will be conducted to ensure that they are being administered. Reasons for lack of administration will be noted (e.g., refusal). Since it will not be possible to continue capsule administration during a hospitalization, hospitalization will be noted as the reason for lack of adherence to the missed doses. High adherence will be defined as administration of ≥80% of prescribed capsules and low adherence will be administration of <80% of prescribed capsules.

3.7.5. Sample size estimate. Sample size was determined to detect a difference between the proportion with bacteriuria plus pyuria over time in the placebo group versus the treatment group receiving 2 cranberry capsules using the method of Diggle et al. for repeated binary outcomes. In the study by Avorn et al., the sample size was based on a 40% reduction in bacteriuria plus pyuria (0.50 in placebo to 0.30 in cranberry juice group). The following assumptions were made for this sample size calculation: Type 1 error of 5% (2-sided), 80% power, a serial correlation of 0.35 between 6 urine specimens, a bacteriuria plus pyuria rate of 0.45 in the control group, a 33% reduction with the cranberry intervention (0.30 bacteriuria plus pyuria rate), and 20% inflation for deaths, transfers and missing cultures. Based on these assumptions, the total sample size is 180 participants (90 per group). However, if additional patients consent to the study during the recruitment period, because of more missing culture data than expected, the new recruitment goal is up to 190 participants (95 per group) if possible. There are no data to determine power for secondary outcomes.

3.7.6. Data management. All Data management systems will be developed and implemented by the Data Management and Informatics Core (DMIC) of the Program on Aging/Claude D. Pepper Older Americans Independence Center (OAIC) at Yale. Data collection for the eligibility and enrollment protocol, the baseline assessment and outcome assessment will be accomplished using computerized instruments on tablet PCs, or on printed forms. Computerized instruments will be developed and deployed using REDCap, a HIPAA-compliant, NIH-supported, web-based tool for data capture (http://project-redcap.org) that at Yale is hosted by DMIC (Harris PA, Taylor R, Theilke R, Payne J, Gonzalez N, Conde JG, Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009 Apr;42(2):377-81). In addition to data collection and data entry, DMIC will provide other critical services, such as between-form error checking and resolution; specialized database programming; conduct-of-study reports; performance monitoring reports; randomization; and follow-up contact scheduling.

3.8. Anticipated Timeline of Clinical Trial. Enrollment of each nursing home will occur sequentially (i.e., prevalent recruitment). We anticipate that it will require 8 weeks from receiving the nursing home roster to enrollment of the first participant in a given nursing home. Recruitment staff will return to each nursing home every three months for additional recruitment (i.e., incident recruitment). We anticipate that prevalent recruitment will require one year and additional incident recruitments will require an additional year.

	YEAR 1				YEAR 2				YEAR 3				YEAR 4			
1. Preparing for Trial																
Meet with administrators of all participating homes to reinforce the details of the protocol, surveillance of outcomes, and adverse events	x	x														
Develop Manual of Procedures	x	x														
"In-service" training sessions for nursing staff at participating homes	x	x														
Develop data collection instruments	x	x														
2. Enrollment of Participants																
Determine eligibility of residents			x	x	x	x	x	x	x	x						
Obtain informed consent from eligible residents or proxies			x	x	x	x	x	x	x	x						
Obtain baseline urine specimens			x	x	x	x	x	x	x	x						
Conduct stratified randomization based on nursing home residence			x	x	x	x	x	x	x	x						
3. Intervention Implementation																
Initiate placebo and cranberry capsule administration			x	x	x	x	x	x	x	x						
Obtain urine specimens every two weeks			x	x	x	x	x	x	x	x	x	x	x	x		
Process urine specimens in microbiology and hematology laboratories			x	x	x	x	x	x	x	x	x	x	x	x		
Retrain staff regarding urine specimen collection and capsules			x	x	x	x	x	x	x	x	x	x	x	x		
Surveillance of staff for adherence to capsule administration			x	x	x	x	x	x	x	x	x	x	x	x		
Surveillance for adverse events with reporting to Internal Safety Committee, Medical Safety Monitor, and DSMB			x	x	x	x	x	x	x	x	x	x	x	x		
Conduct retention events for nursing home administrators						x				x				x		
Conduct retention events for nursing home staff				x		x		x		x		x		x		
4. Outcome Surveillance and Assessment																
Surveillance and adjudication of primary outcome → bacteriuria plus pyuria; assessment of urinary tract specific symptoms			x	x	x	x	x	x	x	x	x	x	x	x		
Surveillance and adjudication of secondary outcomes → UTI, death, hospitalization, antibiotic prescriptions, and resistant organisms			x	x	x	x	x	x	x	x	x	x	x	x		
5. Data Management and Analysis																
Data Management			x	x	x	x	x	x	x	x	x	x	x	x	x	x
Preparation of Clinical and Safety Data Summaries to Independent Safety Monitor and NIA				x		x		x		x		x				
Final Data Cleaning													x	x		
Lock Dataset and Data analysis															x	x
6. Report Generation															x	x

4. Subject Population:

The participants will be female long-term care nursing home residents, 65 years or older. Assuming a Type 1 error of 5% (2-sided), 80% power, a control group prevalence rate of 45%, a relative reduction of 33% (absolute risk difference of 15%), serial correlation among 6 repeated urine measurements on each participant of 0.35, and a drop-out rate of 20% (e.g., death [17%], transfer and/or inability to provide further urine specimens [3%]), the sample size required is 90 participants in each group (total N=180).

However, if additional patients consent to the study during the recruitment period, because of more missing culture data than expected, the new recruitment goal is up to 190 participants (95 per group) if possible.

5. Inclusion/Exclusion Criteria:

Inclusion criteria. All races will be considered for inclusion if they: 1) are female; 2) are long-term care residents; 3) are English speaking; and 4) are 65 years or older. Since surrogate consent is required in most instances (95%) and since the participants often have underlying dementia, English speaking participants are required who can be explained the protocol and express their assent to participate not only to study staff but also to nursing home staff over the course of the study. We have utilized this strategy in our previous intervention cohorts and in the recently completed R01 funded clinical trial to reduce pneumonia in nursing home residents.

For this proposed randomized clinical trial, we plan to identify and enroll female participants who are residents of nursing homes within a 50 mile radius of New Haven, CT. We anticipate the characteristics of the study population to be similar to those enrolled in our observational and pilot intervention cohorts with a mean age of approximately 86 and 12% Hispanic or racial minorities. We are estimating a sample size of 180 participants (90 randomized to the treatment arm, 90 randomized to the control arm).

Exclusion criteria. Residents will be excluded if they: 1) are not expected to be in the nursing home for at least one month (i.e., short term rehabilitation, pending discharge, terminal life expectancy < 1 month); 2) are on chronic suppressive antibiotic or anti-infective (i.e., mandelamine) therapy for recurrent UTI; 3) have end stage renal disease on dialysis (they do not regularly produce urine); 4) are unable to produce a baseline clean catch urine specimen for collection; 5) are on warfarin therapy because of a potential interaction of warfarin and cranberry juice; 6) have a history of nephrolithiasis because cranberry may increase the risk of nephrolithiasis; 7) have an indwelling bladder catheter in place; 8) have an allergy to cranberry products; 9) are being treated with cranberry products; 10) residence < 4 weeks.

Women represent the vast majority (75-85%) of nursing home residents and the genitourinary anatomy of men and women differ. The risk factor for UTI in men usually relates to underlying structural or functional abnormalities of the urinary tract, and there is no evidence to date that cranberry products reduce UTI in men. Therefore, only female nursing home residents will be recruited to this study. Participants will be stratified by nursing home and then randomized to receive either placebo or two cranberry capsules per day. There will be up to 21 nursing homes within a 50 mile radius of the greater New Haven, CT area participating in this study.

6. How will **eligibility** be determined, and by whom?

Screening at each nursing home will occur sequentially. From the date of screening to enrollment, each home will require eight weeks. Once enrollment is initiated at one home, screening will begin at the next home. Residents, age ≥65 years, residing in one of the participating nursing homes will be identified from a computerized log kept by the Director of Nursing Services at the home. Subsequently, trained field staff will perform a brief chart review to establish the presence of inclusion and exclusion criteria. A HIPAA waiver will be obtained for recruitment purposes only.

7. Risks:

There are no reasonably foreseeable physical, psychological, emotional, social, economic, or legal risks involved in the two arms of the proposed study, or in obtaining a clean catch urine sample, which will be

collected by trained nursing home staff if subjects need assistance. In the United States, cranberry capsules are considered to be a dietary supplement, not a drug or medication. As such, their usage is not regulated by the Food and Drug administration (FDA). In previous studies by our group and others, very few incidences of side effects have been noted after cranberry capsule administration. In a study of 57 participants taking a different cranberry capsule from the one used in this study, only six subjects noted symptoms after cranberry capsule administration (vomiting, nausea, and/or diarrhea), but it was unclear whether these symptoms were actually a side effect from the cranberry capsules. These possible protocol-related side effects will be monitored by research staff.

8. Minimizing Risks:

If a subject is unable to swallow the capsules, her nurse will be able to open the capsule and mix its contents into food (e.g., applesauce or yogurt). Subjects with feeding tubes will not be excluded from the study. If a subject has a feeding tube, the cranberry powder can be administered through the tube.

See attached article Brazier AM, et al. "Collecting Clean-Catch Urine in the Nursing Home: Obtaining the Uncontaminated Specimen". *Geriatric Nursing.* September/October 1995; 16(5): 217-224 for a description of the training education that the nursing home staff will receive from the nurse researcher in order to obtain the clean catch urine specimens.

9. Data and Safety Monitoring Plan:

The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews on a monthly basis. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment.

Either the principal investigator or the Human Investigation Committee (HIC) have the authority to stop or suspend the study or require modifications.

This protocol presents minimal risks to the subjects and adverse events or other problems are not anticipated. Adverse events will be recorded by the nursing home staff into the subject's medical record and study staff will perform chart review to retrieve this data. In the unlikely event that such events occur, serious and unanticipated and related adverse events or unanticipated problems involving risks to subjects or others will be reported in writing within 48 hours to the HIC (using the appropriate HIC forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all adverse events that occur during the conduct of this research project through regular study meetings, via email as they are reviewed by the principal investigator. The PI will report all deaths that occur to the NIA Program Officer (Barbara Radziszewska, PhD) within 48 hours of PI notification.

As required by the funding agency (NIA), an Independent Safety Monitor (ISM) has been appointed. The ISM will have a critical function in ensuring that participants receive good clinical care and that safety concerns are quickly identified. The ISM may suggest measures to prevent the occurrence of particular adverse events (e.g., protocol modification). To prevent bias, the ISM will evaluate serious and non-serious adverse events blinded to treatment assignment. The ISM will review semi-annual reports concerning serious adverse events (not segregated and segregated by treatment group). In the event of any unanticipated and treatment related serious adverse events or anticipated non-serious and/or serious adverse events twice as frequent in one treatment group versus the other, the ISM will promptly contact the PI and possibly the IRB representative and the NIA Program Officer, Dr. Barbara Radziszewska. A difference in adverse events of this magnitude may lead to a decision to unblind the ISM, Program Officer and a clinical investigator and biostatistician participating in this study to

determine if the difference may be related to the cranberry capsule treatment. The need for changes to the protocol will be determined at that time by the Principal Investigator.

While adverse effects secondary to cranberry capsule administration are expected to be minimal based on evidence from previous studies, all adverse effects secondary to cranberry capsule administration will be prospectively recorded. A secondary outcome variable will be coded with a 1 for the occurrence of any adverse event and a 0 for the occurrence of none. Rates of adverse events will be described and calculated for each arm of the study.

10. Statistical Considerations:

10.1 Data analysis plan.

10.1.1. Interim monitoring. Interim monitoring will focus on participant accrual (overall and by nursing home), baseline comparability of treatment groups, protocol adherence, completeness of data retrieval, data quality, and safety. A set of interim data monitoring tables will be developed for presentation to the Independent Safety Monitor and NIA Program Officer on a semi-annual basis. We will carefully monitor participant accrual and adherence to ensure that the study is on target to achieve the required level of statistical power. We originally proposed one interim look for efficacy at the mid-point of the study using a Haybittle-Peto boundary with p-value of 0.001. This would have had a negligible effect on the overall type I error at the end of the trial. Thus, the sample size was not inflated to account for the interim look. Futility was planned to be assessed by calculating conditional power (under both the observed and hypothesized trend) and the feasibility of achieving the target sample size. Prior to study initiation, the NIA proposed that a DSMB was not necessary; rather, a DSMP with an Independent Safety Monitor was required. Therefore, it was decided that one interim look for efficacy and futility would not be performed, and this plan was approved by the NIA.

10.1.2. Final analyses: primary outcome. Final analyses will address comparability of treatment groups, efficacy and safety. All analyses will be conducted as randomized, i.e., participants will be analyzed according to their original treatment assignment regardless of adherence. A significance level of 0.05 (2-sided) will be used for statistical significance. SAS® 9.4 statistical software will be used for the analyses.

10.1.2.1. Baseline comparability of treatment groups. The adequacy of the randomization will be assessed by comparing the distribution of baseline demographic and clinical characteristics between the treatment groups. Comparability for continuous variables will be examined graphically and by summary statistics (means, medians, quartiles, etc.). Categorical variables will be examined by calculating frequency distributions. Adjustment for significant treatment imbalances in baseline covariates will not be done because this approach can be biased. Instead the following pre-specified covariates will be adjusted for: baseline bacteriuria, age, and number of comorbid conditions.

10.1.2.2. Treatment efficacy for the primary outcome. The primary study outcome is bacteriuria plus pyuria. The difference in the proportion with bacteriuria plus pyuria between the two treatment groups will be estimated using a multivariable logistic regression model that accounts for the serial correlation of repeated measurements, adjusted for the pre-specified covariates (baseline bacteriuria status, age, incontinence, and number of comorbid conditions). Prior to regression modeling, the potential impact of missing data and deaths on the study outcome will be investigated. If it is reasonable to assume that missing values are missing at random (MAR), generalized linear mixed effects modeling will be used. Facility heterogeneity will be accessed by introducing a random effect for nursing home in the regression model to account for the variability among homes. Variables that are

predictive of missing values will be included in the model. If required by considerations of poor model fit or convergence problems, we will explore other methods for handling MAR data, and we will consider joint modeling of the longitudinal and survival outcomes. Model fit will be assessed by residual analyses, influence diagnostics, and goodness-of-fit tests. The treatment effect will be estimated as an odds ratio (treatment vs. control) with corresponding 95% confidence intervals. In exploratory analyses the impact of non-adherence on treatment effect will be investigated by methods described by Little, et al.

10.1.2.3. Analysis of safety. The incidence of adverse events will be tabulated and compared between treatment groups using statistics appropriate for categorical or count data, such as the chi-square or Wilcoxon statistics. We will also examine the timing of the adverse events by calculating cumulative incidence curves.

10.1.3. Final analyses: secondary outcomes. The analysis of secondary outcomes will be similar to that described for bacteriuria plus pyuria. Cumulative death rates will be estimated by the method of Kaplan-Meier and compared between treatment groups using the log-rank statistic. Frequency of symptomatic UTI, hospitalizations, antibiotic prescriptions, and multi-drug antibiotic resistant organisms will be tabulated and compared between the treatment and control groups using the Wilcoxon statistic.

A. DRUGS, BIOLOGICS and RADIOTRACERS

1. **Identification of Drug, Device or Biologic:**

Cranberry capsules contain a highly concentrated food extract of North American cranberries (*Vaccinium macrocarpon*). North American cranberries are one of the richest natural sources of A-type proanthocyanidins which have been shown to be effective in inhibiting certain uropathogenic strains of *E. coli* from adhering to the lining of the urinary tract. As a dietary supplement, cranberry capsules are not regulated by the FDA.

2. **Background Information:**

Concentrated forms of cranberry extract, such as those found in cranberry capsules, have been shown in various studies to be safe and well-tolerated. The only possible contraindications include warfarin anticoagulant therapy or persons with a history of nephrolithiasis. Individuals with either of these conditions will be excluded from participation in this study.

3. **Source:**

Study cranberry capsules are produced in bulk by an independent manufacturer. The packaging of capsules will be done by YNHH Investigational Drug Services based on the preferences of each nursing home.

4. **Storage, Preparation and Use:**

Cranberry capsules contain 36mg of proanthocyanidins per capsule. They are stable at room temperature and will be administered as part of enrolled patients' regular daily pill pack at the nursing homes. The two capsules will be targeted to be administered at 5:00 pm every day.

5. **Use of Placebo:**

As previously stated in the background information, there is no currently accepted prophylactic therapy for asymptomatic bacteriuria. Additionally, none of the trials of antibiotic treatment of asymptomatic

bacteriuria showed any decrease in mortality. Use of placebo in this study will simply assist us in determining the baseline rate of bacteriuria in the nursing home populations under study.

The maximum possible duration that a participant may receive placebo is 12 months (30-day blister pack per month equaling 360 days).

In this study, placebo represents the current state of affairs for prophylactic management of bacteriuria. There is no potential harm in receiving placebo in this study. Participation in the study will end after 12 months. Management of the bacteriuria at this point will then be the responsibility of the patient's primary care provider.

As stated in point c above, there is no potential harm in receiving placebo in this study, and as such, no safeguard procedures are required.

6. **Targeted Enrollment: Give the number of subjects:**

Targeted for enrollment at Yale for this protocol 180.

7. **Recruitment Procedures:**

Participants will be recruited from the nursing units at the 21 New Haven area nursing homes listed in the protocol. Residents, age ≥65 years, residing in one of the participating nursing homes will be identified from a computerized log kept by the Director of Nursing Services at the home. Subsequently, study personnel will perform a brief chart review to establish the presence of inclusion and exclusion criteria.

After potential subjects have been identified through chart review covered by a HIPAA waiver, subjects, or their legally authorized surrogate, will be approached by the research team to obtain written consent. Individuals will be given sufficient time to read through the consent form, or if this presents difficulty, the form will be read to them by a member of the research team. Surrogates will receive a follow up phone call after receiving a Proxy Authorization letter (see revised letter attached), consent form, and Authorization to Release Protected Health Information for Research form (see attached). A member of the research team will answer any questions that the potential subject or surrogate may have. Permission will be obtained from the potential participant's home administrator before they are approached for study recruitment. Informed consent will be obtained by trained study personnel. All potential participants will receive a general description of the study, including the baseline and surveillance evaluations with a general description of risks and benefits. Participants will receive a full detailed description of the intervention strategy, including potential risks and benefits. In addition, participants will be asked to sign a HIPAA authorization form that explains the protected health information that will be used, disclosed, and to whom it will be disclosed as part of this study. Potential participants or surrogates will sign the consent form and HIPAA authorization forms prior to the baseline assessment. If surrogate consent is obtained, assent from the participant will still be sought for participation in the study. The principal investigator will be available to answer any questions.

Experienced research assistants (i.e., Luann Bianco and Sabina Rubeck) and nurse researchers (i.e., Andrea Rink, Sandra Ginter) at the Yale Program on Aging.

8. **Consent Personnel:**

Informed consent will be obtained by trained study personnel including an experienced research assistant (i.e., Luann Bianco and Sabina Rubeck) and nurse researchers (i.e., Andrea Rink and Sandra Ginter) at the Yale Program on Aging.

9. **Process of Consent/Assent:**

After potential subjects have been identified through chart review covered by a HIPAA waiver, subjects will be approached by the research team to obtain written consent or surrogates will be mailed an introductory letter, compound authorization form, Authorization to Release Protected Health Information for Research, and FAQ pamphlet. Individuals will be given sufficient time to read through the consent form, or if this presents difficulty, the form will be read to them by a member of the research team. All potential participants will receive a general description of the study, including the baseline and surveillance evaluations with a general description of risks and benefits. Participants will receive a full detailed description of the intervention strategy, including potential risks and benefits. In addition, participants will be asked to sign a HIPAA authorization form that explains the protected health information that will be used, disclosed, and to whom it will be disclosed as part of this study. Potential participants or surrogates will sign the consent form and HIPAA authorization forms prior to the baseline assessment. If surrogate consent is obtained, assent of the participant will still be sought. The principal investigator will be available to answer any questions. The phone number of the principal investigator will be provided to each participant to contact for any questions or problems.

10. **Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent:**

It is recognized that: 1) there may be a significant proportion of eligible residents who are decisionally impaired (i.e., who have a compromised capacity to understand information and make a reasoned decision about participation in research), and who require additional protections; and 2) the purpose of identifying eligible residents who may be decisionally impaired is not necessarily to exclude them from research, but to seek ways to enable their participation in an ethically appropriate manner that is also compliant with regulatory requirements. Therefore, at the time of approaching any potential participant for consent, our plans are as follows:

- **study personnel obtaining consent will use professional judgment to determine if the potential participant is capable of providing consent.** Members of the Field Staff who are responsible for participant recruitment and consent are all highly trained and experienced personnel in determining capacity to consent in aging populations. This determination will rely on individual observation of, and interaction with, the potential participant as well as the opinion of the caregiver, when available. In general, the assessment of the potential participant's capacity to consent will be based on her/his: 1) ability to communicate a choice; 2) ability to understand relevant information; 3) ability to appreciate the nature of the situation and its likely consequences; and 4) ability to manipulate information rationally.

- **determination of decisional impairment for providing consent.** Potential participants will be considered decisionally impaired for providing consent if they have: 1) an inability to express or communicate a preference or choice; 2) an inability to understand a situation and its potential consequences as well as the impact of study participation on those circumstances (e.g., do not understand that they may be hurt or may not be helped or cannot distinguish research from treatment); 3) an inability to provide a logical rationale for participation/no participation in the study (i.e., cannot address risk/benefit); or 4) have been legally determined to be incompetent and/or have a conservator of person. If there is any uncertainty, we will pursue surrogate consent.

- **plans for surrogate consent when decisional impairment is identified.** For potential participants who are deemed to be decisionally impaired, their identified surrogate will be approached for consent because: 1) the risks of this study are limited and are justified given the potential benefits of the research to the subject and the development of generalizable knowledge that will benefit elderly nursing home residents nationwide; 2) the intervention is commensurate with clinical treatments already available in clinical practice (multiple over-the-counter cranberry capsules and tablets) and 3) an Independent Safety Monitor and NIA Program Officer will monitor the study. All potential participants deemed decisionally impaired will be notified of that determination before permission is sought from their legally authorized surrogate to enroll in the study. If permission is given to enroll in the study, the potential participant will then be notified and their verbal assent will be sought (i.e., their active affirmation of a desire to participate).

- **plans for assent for decisionally impaired potential participants.** In all cases in which assent is sought, the assent discussion will include the following: 1) a simplified description of the purpose of the research, including risks and benefits; 2) a description of the procedures and interventions to which the participant will be exposed; 3) a statement explaining that participation in this study is voluntary only; 3) an explanation of the procedures that may hurt and for how long; 4) a question and answer period in which the participant will be encouraged to ask questions about their participation in the study.

11. **Documentation of Consent/Assent:** Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects.

1) Compound Authorization and Consent [Adult Form]

2) Compound Authorization and Consent [Legally Authorized Representative/Surrogate Form]

3) Authorization to Release Protected Health Information for Research

12. **Non-English Speaking Subjects:**

Since surrogate consent is required in most instances (95%) and since the participants often have underlying dementia, English speaking participants are required who can be explained the protocol and express their assent to participate not only to study staff but also to nursing home staff over the course of the study.

Confidentiality & Security of Data:

Name, address of nursing home residence, birth date, dates and details of previous episodes of bacteriuria and/or UTI, and dates and details of prior antibiotic administration will be recorded. Additionally, data on comorbidities, other medications, continence, and functional status will also be recorded. The sources of research data on enrolled participants will be interviews with the nursing staff and administrators at the institution and the participants' medical records. Baseline descriptive data (e.g., facility, age, race, ethnicity, gender, comorbid disease, cognitive status, activities of daily living, degree of mobility, medications, continence, history of UTI) will be recorded. These data will be ascertained from the Minimum Data Set, the medical record, and interview with the primary care provider (e.g., the Certified Nursing Assistant). The hierarchy of data sources will be based on the least burdensome source of data. Data regarding clinical outcomes (i.e., bacteriuria, pyuria, urinary tract specific symptoms, UTI, hospitalization, death, antibiotic prescriptions, resistant organisms), staff adherence to the intervention, and adverse events will be collected by research study personnel. To

safeguard confidentiality, the data linking study ID codes and patient names are strictly confined to an electronic data capture system (REDCap) that is accessible only to selected study staff, and which has been approved as HIPAA-secure by the Yale Information Security Office (ISO).

Research data will be stored and managed in a database format (REDCap) and stored on the secure Yale-ITS network which is backed-up nightly. Each subject will be identified by a study number. All data recorded on the data extraction sheet will be identified only by the study number and will be kept in a locked filing cabinet.

All data will be password protected and access limited to those individuals with direct responsibility for the research project. Study data will reside on database and file sharing resources managed by Yale ITS, and will not be permitted on movable electronic media.

To safeguard confidentiality of protected health information, each study participant enrolled will be assigned a unique code number and the participant's name will never be attached to any paper form. Linkage between study ID code and patient name will be limited to a highly secure electronic database, and will be used confidentially only by research staff. The study investigators will assume full responsibility to maintain confidentiality. All study results will be presented only as statistical aggregates that will neither identify, nor permit identification, of individual research participants. This has been an effective method in our previous studies.

The data systems and procedures at the Data Management and Informatics Core (DMIC) of the Program on Aging/Claude D. Pepper Older Americans Independence Center (OAIC) at Yale conform to Yale's HIPAA security policy (http://www.yale.edu/ppdev/Procedures/its/1610/1610PR.01SystemsNetwrokSecurity.pdf), and all equipment is certified by the Yale Information Security Officer. Desktop and portable PCs used by study staff will be configured with mandatory security safeguards that are enforced by Yale Information Technology Services, including "strong" passwords, password-protected standby mode, and whole-disk encryption. Encrypted and password-protected tablet computers (iPads) will be used for data collection but no data will be stored on them. All data will reside in a central REDCap database, and the tablets will access these data through a web browser. REDCap is designed to forbid local storage of cached data. Files prepared for analysis will be in SAS format, and will not include personal identifiers.

All data will be password protected and access limited to those individuals with direct responsibility for the research project. Moveable electronic media used to collect or store the data is equipped with encryption software recommended by the University (**Bitlocker**). The PI and other members of the research team work with coded or de-identified data when using moveable device(s) to perform data analysis.

When the research is completed, identifiable data will be destroyed three years after the completion of the study. Paper forms will be shredded and the study computer will be zeroed. The anonymous data will be retained indefinitely.

The principal investigator, research staff, sponsor and Yale Human Investigation Committee will have access to the protected health information.

It is possible that reporting of communicable diseases and elderly abuse will be necessary in this study. The nursing home administrator for the home that the participant resides in will be notified if such a circumstance arises.

Potential Benefits:

The potential benefits for the interventions are significant because we hypothesize that cranberry capsules will reduce the incidence of bacteriuria plus pyuria and morbidity associated with UTI in female nursing home residents. Administration of cranberry capsules has been documented in our pilot feasibility and dosing studies to be feasible and adhered to by staff, and it is designed to be generalizable and easily incorporated into the usual nursing care of nursing home residents. Although implementing the use of cranberry capsules would result in greater initial costs, there is the potential for healthcare savings from decreased antibiotic use, hospitalization, and emergence of resistant organisms. In summary, the anticipated benefits of the intervention to the participants and society far outweigh the minimal risks. Therefore, the risk-benefit ratio appears to be favorable for proceeding with this clinical trial.

The importance of the knowledge gained in this proposed trial is great, including the following: 1) the identification of a feasible and safe intervention that is effective in reducing bacteriuria in elderly nursing home residents and can be generalized to female nursing home populations nationwide; 2) the determination of whether routine use of cranberry capsules, which are not regulated by the Food and Drug Administration (FDA), should be implemented in the nursing home setting; and 3) the potential for a major reduction in morbidity, mortality, hospitalizations, and healthcare expenditures related to UTI among elderly nursing home residents.

Alternatives:

As described previously in this application, there are currently no other standardized accepted alternatives for prophylactic treatment of asymptomatic bacteriuria in the nursing home population

Payments for Participation (Economic Considerations):

Participants will not be paid for participation in this study. However, since clean catch urine specimens are difficult to collect in this disabled nursing home population, nursing homes will be provided an incentive that is approved of by each nursing home administration. Urine samples will be collected by the nursing home staff nurses and/or aides. Since the collection of these urine specimens is cumbersome, only for study purposes, and essential to the successful completion of this project, individualized incentive programs for each participating nursing home will be designed. Incentive programs will be constructed with the input from the Administrator and Director of Nurses at each nursing home. Incentives may be distributed to a given floor or team. Planned incentives will include 1) an annual Certificate of Research Participation for all participating nursing home facilities which documents active participation in this Yale University research study for purposes of annual surveys conducted by regulatory bodies; 2) continuing education “in-service” hours that are required by the state of Connecticut for all CNAs; 3) gift certificates to participating nursing home staff. The amount of gift certificates will depend on how often they are given.

Costs for Participation (Economic Considerations):

There are no costs to the subjects associated with participation in this research project. Both the cranberry and placebo capsules will be provided at no cost to the subjects. Additionally, the clean catch urine sample, urinalysis, and culture will be performed at no cost to the subjects.

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