

1 **Protocol**

2

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

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

5

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

11

12

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

14

15 Version 1.0, February 21, 2012 (original)

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17 Version 2.0, April 26, 2012

18

19 Version 3.0, June 20, 2012

20

21 Version 4.0, August 22, 2012

22

23 Version 5.0, October 18, 2012

24

25 Version 6.0, January 4, 2013 (Renewal)

26

27 Version 7.0, June 10, 2013

28

29 Version 8.0, December 3, 2013

30

31 Version 9.0, January 28, 2014 (Renewal)

32

33 Version 10.0, February 25, 2014

34

35 Version 11.0, September 23, 2014

36

37 Version 12.0, September 26, 2014

38

39 Version 13.0, October 28, 2014

40

41 Version 14.0, January 29, 2015 (Renewal)

42

43 Version 15.0, August 13, 2015  
44  
45 Version 16.0, November 16, 2015  
46  
47 Version 17.0, January 25, 2016 (Renewal)  
48

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

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

52 Revised nursing home sites needed “up to 20”.

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

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

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

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

62 Changed the Principal Investigator’s address.

63 Added a recruitment/informational brochure.

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

66 **Changes to Adult & Surrogate Consent Forms:**

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

72

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

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

75 Added Authorization to Release Protected Health Information for Research form.

76

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

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

80

81

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

83 Added one new Study Personnel member.

84

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

86 Yearly renewal approved.

87

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

89 Added four new nursing home sites with letters of support.

90 Revision to Recruitment Methods of “YCCI Recruitment database”.

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

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

93

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

95 Added one new Study Personnel.

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

97 Revised “Role” for Research Nurses. One becoming “Field team nurse leader” and one becoming “Field  
98 nurse”.

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

101 Added language regarding waves of recruitment.

102 Revised the number of mailings from 3 to 2.

103 Added language regarding capsule administration and follow-up.

104 Added an “s” to the word outcome in title of section.

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

107 Outcome adjudication. Revised title and nurses.

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

109 Surveillance revised language about pill counting from “two weeks” to “month”.

110 Revised recruitment age language.

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

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

115

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

117 Yearly renewal approved.

118

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

120 Removed one Study Personnel member.

121

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

123 Added six new nursing home sites with letters of support.

124 Removed eight nursing homes.

125

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

127 Revised nursing home sites from 16 to 21.

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

130

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

132

133 Removed two Study Personnel members.

134

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

136

137 Added three Study Personnel as Outcome Adjudication Committee members.

138

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

141

142 Revisions showing that study is closed to enrollment.

143

144 Yearly renewal approved.

145

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

147

148 Added two Study Personnel as Outcome Adjudication Committee members.

149

150 Added language regarding primary outcome > or = 100,000

151

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

153

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

155

156 Revised spelling of last name "Trentalage" to "Trentalange" under Research.

157

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

159

160 Changed language from "quarterly" to "semi-annual" under Intervention paragraph.

161

162 Changed language from "attending physician" to "home administrator" under Consent and Enrollment procedures.

163

164

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

166

167 Sandra Ginter was removed from this study because training requirements were not met by the time of

168 this protocol's re-approval.

169

170 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.

171

172 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).

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174 Re-approval approved by HIC.

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181 **1. Statement of Purpose:**

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

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

188 **Supplementary Aims** are to determine the:

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

196 **2. Background:**

197

198 **2.1. Importance of urinary tract infection (UTI) in nursing home residents.** UTI is the most common  
 199 bacterial infection in nursing home residents with an incidence of 0.1 to 2.4 cases per 1000 resident-  
 200 days. UTI is also a common cause of infectious disease hospitalizations and deaths; the National Nursing  
 201 Home Survey indicated that UTI was an admitting or current diagnosis for hospitalization for  
 202 7,111/100,000 female residents. The Urologic Diseases of America determined that UTI was the most  
 203 costly and resource intensive condition studied among Medicare beneficiaries. Total Medicare  
 204 expenditures for UTI amounted to over \$1.7 billion, exclusive of medication costs in 2006.

205 **2.2. Diagnostic challenges of UTI in nursing home residents.** Distinguishing symptomatic UTI (a  
 206 quantitative count of  $\geq 10^5$  colony forming units of bacteria per milliliter cfu/ml in one urine specimen in  
 207 the presence of urinary tract specific symptoms i.e., dysuria, suprapubic pain or tenderness, new urinary  
 208 frequency or urgency) from bacteriuria (a  
 209 quantitative count of  $\geq 10^5$  cfu/ml) is  
 210 problematic in nursing home residents  
 211 because of the challenges involved with  
 212 symptom assessment. Bacteriuria is  
 213 prevalent in 25-50% of female nursing  
 214 home residents, and pyuria (any white  
 215 blood cells in the urine) is present in 90% of  
 216 residents with bacteriuria. Given the high  
 217 prevalence of bacteriuria in this population,  
 218 three randomized controlled trials of  
 219 antibiotic treatment (versus no treatment)  
 220 of bacteriuria were conducted; none of  
 221 these trials showed any decrease in

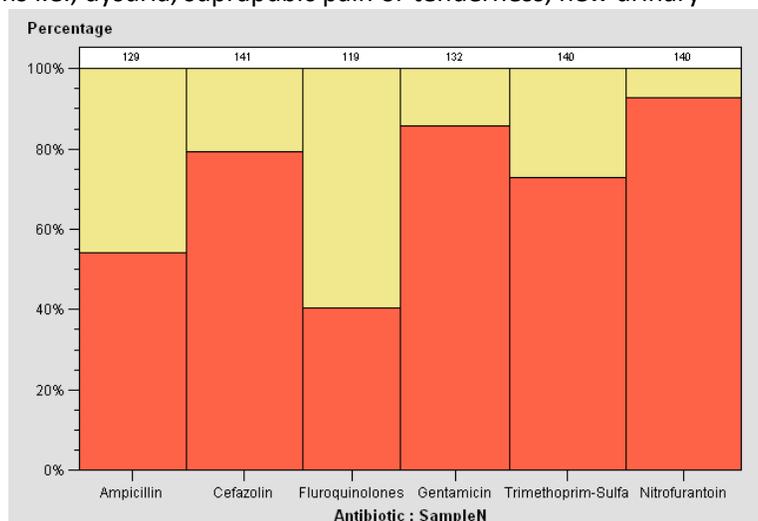
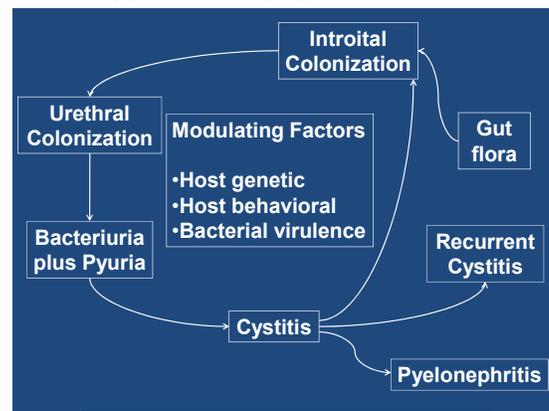


Figure 1: Urinary Isolates UTI Episodes

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

235 **2.3. Widespread empiric antimicrobial administration.** Although treatment of bacteriuria is not  
 236 recommended, many nursing home residents are still prescribed antibiotics because of the diagnostic  
 237 challenges involved in identifying those residents that will benefit most from antibiotic therapy. Only  
 238 13% of antibiotic prescriptions for UTI occur prior to results of urine cultures being available. Isolation of  
 239 resistant organisms is associated with prior antibiotic exposure, and resistant organisms from UTI are  
 240 more frequent in nursing home residents than in community dwellers. Urinary isolates from  
 241 nursing home residents are frequently resistant to commonly prescribed oral antibiotics (see **Figure 1**).  
 242 Use of antibiotics is associated with several risks, including the development of multi-drug antibiotic-  
 243 resistant organisms, drug-related adverse effects, and significant costs. In order to reduce antibiotic  
 244 prescriptions, prevention strategies should be targeted to bacteriuria, pyuria, and symptomatic UTI.

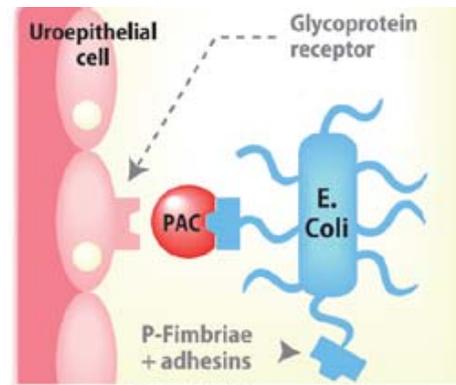
245 **2.4. Rationale for prevention of bacteriuria, pyuria, and**  
 246 **UTI.** Bacteriuria has been shown to be a risk factor for  
 247 subsequent development of symptomatic UTI among  
 248 young women and women with diabetes mellitus, and it is  
 249 hypothesized that bacteriuria precedes the development of  
 250 symptomatic UTI in nursing home residents (see **Figure 2**).  
 251 The presence of bacteriuria is the greatest trigger for the  
 252 initiation of antibiotic therapy. Since nursing home  
 253 practitioners usually wait to obtain results of urine  
 254 cultures, reducing bacteriuria could reduce antibiotic  
 255 prescriptions. Therefore, efforts to prevent bacteriuria,



256 pyuria, and UTI represent the most logical means of reducing  
 257 antibiotic prescriptions in the nursing home setting.  
 258 **2.5. Cranberry for prevention of UTI.**

**Figure 2: Pathogenesis of UTI**

259 Many of the identified risk factors for bacteriuria and UTI in  
260 nursing home residents (e.g., functional disability, dementia) are  
261 largely non-modifiable. Vaginal estrogen therapy, which has been  
262 shown to be effective at preventing recurrent UTI in post-  
263 menopausal women, has potential risks and side effects which  
264 would be undesirable in a nursing home population. With few  
265 other feasible intervention strategies to prevent the common and  
266 morbid condition of UTI in nursing home residents, cranberry  
267 capsules represent a novel intervention warranting investigation.  
268 Cranberry products represent an existing, non-antimicrobial



**Figure 3: Anti-adhesion of PAC**

269 method for prevention of UTI. Cranberry proanthocyanidins (PAC)  
270 have been shown to inhibit adherence of P-fimbriated *E.coli* to  
271 uroepithelial cells. P fimbriae are finger-like projections that the organism uses to attach to bladder  
272 cells (see **Figure 3**). In vitro studies have demonstrated that cranberry changes the formation of P  
273 fimbriae such that they can no longer attach to the bladder mucosa. Since *E.coli* represents the majority  
274 of urinary isolates (54%), this preventive strategy may be an effective method among nursing home  
275 residents. Empirical data supporting the potential benefit of cranberry include: 1) in the study by Avorn  
276 et al., cranberry juice decreased bacteriuria plus pyuria in older women, even those not caused by *E.coli*;  
277 2) urine from young women that ingested cranberry capsules has been shown in vitro and in vivo to  
278 decrease uropathogenic *E.coli* virulence; and 3) limited clinical studies of cranberry juice in elderly  
279 women have demonstrated reductions in bacteriuria but have not been of adequate size or quality to  
280 result in changes in patient care. The acrid flavor of cranberry juice is challenging for patients to tolerate  
281 in large volumes. Nursing home residents in particular are unable to ingest sufficient volumes to  
282 maintain hydration because of swallowing disorders, exacerbation of incontinence, and decreased thirst  
283 drive. Hence, cranberry capsules represent a prevention strategy that warrants testing in the nursing  
284 home population.

285 **2.6. Effective dose of cranberry.** Previous studies regarding cranberry products for prevention of UTI  
286 yielded conflicting results, likely because of variability of PAC dose and clinical populations studied.  
287 Initial studies identified PAC to be the active ingredient in cranberry that prevents binding of *E.coli*. In  
288 the clinical trial by Avorn et al. of 300ml of cranberry juice beverage daily (36mg PAC), older women  
289 (mean age 78.5 years) had a 58% reduction in the odds of having bacteriuria plus pyuria compared to  
290 controls, particularly after more than one month of cranberry juice ingestion. Previously, there were at  
291 least three different methods of quantifying PAC in the market place, and many products purported  
292 effectiveness with variability in dose of PAC. Methods to quantify PAC have now been standardized and  
293 can be independently measured. Only one product on the market currently can deliver 36mg PAC as  
294 measured by the BL-DMAC method in each capsule and it will be utilized in this proposed project. In  
295 vitro data have shown that 36 to 108mg of PAC is effective at inhibiting bacterial adherence to epithelial  
296 cells. Since patient adherence to cranberry capsule administration is important and nursing home  
297 residents often take multiple medications, the least pill burden and dose of cranberry capsules with the  
298 largest effect will be utilized for this efficacy trial.

299 **2.7. Potential adverse effects of cranberry.** The only side effect reported with the ingestion of  
300 unsweetened cranberry juice is gastro-esophageal reflux; however, this side effect has not been  
301 reported with cranberry capsules. Additionally, ingestion of large amounts of liquid is challenging for  
302 nursing home residents with demonstrated poor adherence, thereby making cranberry capsules a more  
303 preferable intervention option to test in this particularly vulnerable population.

304 **2.8. Investigating the effects of cranberry capsules on women only.** The reasons for investigating  
305 cranberry capsules in women only include: 1) Avorn et al. investigated cranberry juice among women

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

313 **2.9. Comparison of this proposal to the landmark cranberry juice study by Avorn et al.** The landmark  
314 study by Avorn et al. included 153 female subjects, 109 community dwellers living in housing complexes  
315 for the elderly and 44 long-term care facility residents, with a mean age of 78.5 years. Participants  
316 ingested 300ml of cranberry juice cocktail per day for 6 months. All participants provided self-consent,  
317 and most participants were instructed on how to collect an adequate clean-voided specimen  
318 themselves. Most participants were enrolled only after a 1-month trial of placebo beverage to ensure  
319 that daily intake would be adequate throughout the study. This study informed the development of this  
320 proposal by identifying areas where further investigation is needed: 1) only 29% of participants were  
321 nursing home residents; 2) the mean age was 10 years lower than the mean age of nursing home  
322 residents; 3) most nursing home residents are unable to provide self consent or self collected urine  
323 specimens; 4) dehydration is prevalent in up to 90% of nursing home residents because of swallowing  
324 difficulty, aspiration risk, increased incontinence with hydration, and decreased olfactory, taste, and  
325 thirst sensations. Daily intake of 300ml of juice would not be feasible for most nursing home residents.  
326 Since UTI is the most prevalent infection in nursing home residents, a study designed specifically for the  
327 nursing home population is warranted.

328 **2.10. Rationale for this study.** Given the biological plausibility for its preventive effects and the  
329 challenges involved with cranberry juice ingestion by nursing home residents, cranberry capsules  
330 represent a promising preventive strategy that should be further explored in this vulnerable population.  
331 Because symptomatic UTI is a leading cause of morbidity in nursing home residents, preventing  
332 bacteriuria plus pyuria will likely reduce morbidity. Furthermore, a reduction in bacteriuria plus pyuria  
333 will result in a reduction in antibiotic use and its attendant adverse effects. Our prior work has  
334 demonstrated that 1) cranberry capsule administration is feasible in nursing home residents; 2) an  
335 optimal dose of administration has been identified; and 3) there is preliminary evidence that cranberry  
336 capsules reduce bacteriuria plus pyuria. This proposal will determine whether cranberry capsules reduce  
337 the occurrence of bacteriuria plus pyuria, whether administration of cranberry capsules is safe and  
338 adhered to over 12 months, and whether bacteriuria plus pyuria is associated with UTI morbidity. **This  
339 study is significant because cranberry capsules are a feasible and low risk intervention that may  
340 reduce the morbidity and mortality associated with bacteriuria, pyuria, and UTI in nursing home  
341 residents.**

342 **2.11. Preliminary studies.**

343 **2.11.1. Previous studies by principal investigator (P.I.) regarding UTI in nursing home residents.** Dr.  
344 Juthani-Mehta has spent the past eight years investigating diagnostic, management, and prevention  
345 strategies of UTI in nursing home residents. She competed for, and was awarded, an R03 Small  
346 Research Grant and a K23 Career Development Award funded by the National Institute on Aging on this  
347 topic. She has conducted studies involving interviews with nursing staff, observational cohort studies,  
348 and pilot intervention studies that have prepared her for conducting the proposed study.

349 **2.11.2. Pilot feasibility and adherence study of cranberry capsules in long-term care residents.** In a  
350 previous study conducted by the P.I. and funded by the Donaghue Foundation, a cranberry capsule  
351 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.

**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.

**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%

400 **2.11.3.3. Preliminary efficacy data.** Preliminary data were obtained from the 80 enrolled participants.  
 401 Twenty participants were randomized to each of four treatment groups, receiving 0, 1, 2, and 3 active  
 402 cranberry capsules respectively. Baseline data, including a baseline urine culture and urinalysis, was  
 403 collected prior to randomization. Four additional urine specimens were obtained at one-week intervals  
 404 after randomization. The rate of bacteriuria plus pyuria was 52% in the placebo group. Of the 320  
 405 anticipated outcome measurements, 27 were missing. Investigation of missing data suggested that the  
 406 data were missing completely at random. The effect of dose on development of bacteriuria plus pyuria  
 407 was tested using a Generalized Estimating Equations (GEE) model, adjusted for baseline bacteriuria  
 408 status (present vs. absent). Results displayed in **Table 2** show that over one month, there was a 37%  
 409 reduction in the odds of having bacteriuria plus pyuria among the 2 cranberry capsule group as  
 410 compared to the placebo group, but the confidence intervals were wide. Since Avorn et al.  
 411 demonstrated no effect at one month of surveillance, these preliminary data showing some effect could  
 412 become more pronounced with one year of surveillance. The reason for the lack of a dose response for  
 413 three capsules is not clear. Two possible reasons are 1) the sample size was too small with an unstable  
 414 estimate of the effect of three capsules; 2) the one month duration of surveillance was too brief to  
 415 demonstrate a dose response effect.

416 **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

417  
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422 **3. Research Plan:**

423 **3.1. Overview.** The **primary aim** of this study is to test the efficacy of two oral cranberry capsules per  
 424 day in the prevention of bacteriuria plus pyuria in female nursing home residents. The **secondary aim** is  
 425 to compare the occurrence of urinary tract specific symptoms in the cranberry capsule versus placebo  
 426 groups. The **primary hypothesis** is that two oral cranberry capsules per day will be associated with a  
 427 33% relative reduction in the occurrence of episodes of bacteriuria plus pyuria over 12 months,  
 428 compared to placebo, in a cohort of female nursing home residents. This aim will be accomplished by  
 429 conducting a double-blind randomized placebo-controlled efficacy trial of two oral cranberry capsules  
 430 per day versus placebo in a cohort of Connecticut female nursing home residents.

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

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

442 **Participants.** The participants will be female long-term care nursing home residents, 65 years or  
 443 older. Assuming a Type 1 error of 5% (2-sided), 80% power, a control group prevalence rate of  
 444 45%, a relative reduction of 33% (absolute risk difference of 15%), serial correlation among 6  
 445 repeated urine measurements on each participant of 0.35, and a drop-out rate of 20% (e.g.,

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

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

464 **3.2. Trial Setting.** This study will take place at up to 20 nursing homes within a 50 mile radius of New  
465 Haven. The setting will be up to 20 nursing homes within a 50 mile radius of New Haven, licensed by the  
466 Connecticut Department of Public Health as “Chronic and Convalescent Nursing Homes”, providing  
467 skilled care and certified for Medicare or Medicaid. These 20 homes each have at least 90 residents, UTI  
468 rates comparable to the national average of 9% annually, and sociodemographic characteristics similar  
469 to national averages.

470 **3.2.1. Rationale.** Residents of nursing homes within the greater New Haven area are reflective of the  
471 nursing home population within the United States. Nursing homes chosen to participate in this study  
472 represent a mix of urban and suburban, proprietary and nonprofit, private pay and Medicaid homes.  
473 Our target minority rate of 12% will be met with the spectrum of homes participating. We recognize the  
474 great challenges involved in working with these non-academic nursing homes, but we have established  
475 good relationships with many of them, and we have successfully conducted previous observational and  
476 interventional studies in this environment. The Yale Program on Aging has vast experience conducting  
477 research in challenging but important real world settings with high recruitment, retention, and  
478 adherence rates.

479 **3.2.2. Determination of eligible pool of residents.** Using information available through Medicare on  
480 [www.medicare.gov/nhcompare](http://www.medicare.gov/nhcompare), the national and Connecticut state averages for the percent of  
481 residents who had a UTI annually were 9% and 7%, respectively. To improve study efficiency, we  
482 selected nursing homes with an average UTI rate at least as high as the CT and national averages within  
483 a 50 mile radius of New Haven and with at least 90 beds. Women comprise 75-85% of nursing home  
484 residents. In the first cranberry capsule feasibility study, the baseline bacteriuria rate was 45%. In order  
485 to increase the baseline rate of bacteriuria, in the pilot dosing study, history of UTI was a required  
486 eligibility criterion. However, 664 residents were excluded by requiring this inclusion criterion, and the  
487 baseline rate of bacteriuria plus pyuria only increased to 52%. In an effort to increase the baseline  
488 bacteriuria rate, a large pool of potentially eligible subjects was lost and the rate only increased from  
489 45% to 52%. Therefore, for this proposed study, history of UTI will not be a required inclusion criterion.  
490 In the identified 20 homes, we expect to find at least 700 eligible residents so that with a 30% consent  
491 rate, we can enroll 180 participants. In the pilot dosing study, when history of UTI was included as an  
492 inclusion criterion and 664 residents were excluded for this reason, 240 eligible residents were

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

500 **3.2.3. Identification of participating nursing homes.** Based on our sample size estimate of 180  
501 participants, we anticipate the need for up to 20 nursing homes and, at this time, we have 16  
502 participating nursing homes that have already agreed to participate.

503 **3.3. Trial Design.** This study will be a double-blind, placebo controlled, randomized, clinical efficacy trial  
504 of two cranberry capsules versus placebo. The unit of randomization will be each individual participant.

505 **3.4. Trial Participants.** The participants in this trial will be female long-term care nursing home  
506 residents.

507 **3.4.1. Screening and eligibility assessment.** Screening at each nursing home will occur sequentially.  
508 From the date of screening to enrollment, each home will require eight weeks. Once enrollment is  
509 completed at one home, screening will begin at the next home. Residents, age >65 years, residing in  
510 one of the participating nursing homes will be identified from a computerized log kept by the Director of  
511 Nursing Services at the home. Subsequently, study personnel will perform a brief chart review to  
512 establish the presence of inclusion and exclusion criteria. A HIPAA waiver will be obtained for  
513 recruitment purposes only.

514 **3.4.1.1. Inclusion criteria.** All races will be considered for inclusion if they are: 1) female; 2) long-term  
515 care residents; 3) English speaking; and 4) 65 years or older. Since surrogate consent is required in most  
516 instances and since the participants often have underlying dementia, English speaking participants are  
517 required who can be explained the protocol and express their assent to participate not only to study  
518 staff but also to nursing home staff over the course of the study.

519 **3.4.1.2. Exclusion criteria.** Residents will be excluded if they: 1) are not expected to be in the nursing  
520 home for at least one month (i.e., short term rehabilitation, pending discharge, terminal life expectancy  
521 < 1 month); 2) are on chronic suppressive antibiotic or anti-infective (i.e., mandelamine) therapy for  
522 recurrent UTI; 3) have end stage renal disease on dialysis (they do not regularly produce urine); 4) are  
523 unable to produce a baseline clean catch urine specimen for collection; 5) are on warfarin therapy  
524 because of a potential interaction of warfarin and cranberry juice; 6) have a history of nephrolithiasis  
525 because cranberry may increase the risk of nephrolithiasis; 7) have an indwelling bladder catheter in  
526 place; 8) have an allergy to cranberry products; 9) are being treated with cranberry products; 10)  
527 residence < 4 weeks.

528 **3.4.2. Consent and enrollment procedures.** Permission will be obtained from the potential  
529 participant's attending physician before each resident is approached for study recruitment. Informed  
530 consent will be obtained by trained study personnel. All potential participants will receive a general  
531 description of the study, including the baseline and surveillance evaluations, the intervention, potential  
532 risks and benefits. As part of the study protocol, participants will be advised to avoid ingestion of other  
533 cranberry products. In addition, participants will be asked to sign a HIPAA authorization form that  
534 explains the protected health information that will be used, disclosed, and to whom it will be disclosed  
535 as part of this study. For potential participants who are determined to be decisionally impaired by study  
536 recruitment personnel, consent will be sought from their designated surrogates along with assent from  
537 the participant. Surrogate consent will be sought through a combination of up to three phone calls and  
538 three mailings describing the study purpose, intervention, surveillance evaluations, risks and benefits.  
539 We have successfully utilized this method of surrogate consent in our observational cohort studies, in

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

543 **3.4.3. Availability of participants for enrollment.** We recognize that in an intervention trial, there will  
544 be obstacles to patient enrollment, adherence, and retention. These include ineligibility due to exclusion  
545 criteria defined, resident (or surrogate) refusal to participate, drop outs, and loss from competing  
546 morbidities. However, among the 10 homes that have agreed to participate, we estimate that we will  
547 have ≥600 eligible residents with the average number of eligible residents per home of 50 at the time of  
548 the initial two month enrollment period. Given the anticipated replacement of the 20% of residents  
549 censored annually, we estimate an additional 200 eligible residents available over the two year  
550 enrollment period (100 each year), resulting in 500+200=700 total eligible residents. A consent rate of  
551 30% would yield at least our sample size target of 180 participants (700x30%=210). The consent rate of  
552 30% is feasible because data from our dosing study. revealed a 37.5% consent rate. In the vulnerable  
553 nursing home population, consent rates of approximately 30% for an intervention study are well  
554 documented. In addition, 6 additional back-up homes have agreed to participate if more homes are  
555 required for recruitment.

556 **3.4.4. Expected attrition.** We anticipate the following sources of attrition of participants: deaths,  
557 transfers out of the nursing home, and functional decline prohibiting continued participation in the  
558 study. The total anticipated attrition rate is 20%, 17% for death and 3% for other reasons. These rates  
559 are based on observed numbers in our prior studies. We do not expect any drop ins from placebo to  
560 treatment. Because we will analyze participants as they are randomized, intervention drop-outs, and  
561 non-adherent participants to the assigned treatment arm are not considered losses. Deaths occurring  
562 before obtaining outcome data or the end of the 12 month follow-up are unavoidable in a nursing home  
563 population and analyses to make use of the existing data on these losses are discussed below. Transfers  
564 out of the homes are also expected. Based our prior studies, the transfer rate is expected to be low (i.e.,  
565 3%).

566 **3.5. Stratified randomization.** Once consent is obtained, a baseline clean catch urine specimen will be  
567 obtained from participants prior to initiation of therapy to ensure that subsequent clean catch urine  
568 specimen collection will be possible. Then, enrolled participants will be randomized to two placebo or  
569 two cranberry capsules within nursing home using a permuted block design with a variable block size  
570 and equal allocation. Stratification by nursing home is being proposed to account for potentially  
571 different standards of nursing and medical care among nursing homes. The randomization will be  
572 double-blind. Neither the personnel (study nurses, P.I., nursing home nurses and CNAs) nor the patient  
573 will be aware of the treatment allocation. Only the study biostatistician will have access to the  
574 randomization codes.

575 **3.6. Trial Intervention.** The intervention is two cranberry capsules versus placebo capsules for the  
576 prevention of bacteriuria plus pyuria. This trial serves as an efficacy study in which the reduction of  
577 bacteriuria plus pyuria is the primary outcome. The secondary outcome is the occurrence of urinary  
578 tract specific symptoms in the cranberry capsule and placebo groups. This study will also determine  
579 rates of adverse clinical outcomes (i.e., symptomatic UTI, all cause hospitalization, all cause death, all  
580 antibiotic prescriptions, and all multi-drug antibiotic resistant organisms) in the placebo and treatment  
581 groups.

582 **3.6.1. Justification for two cranberry capsules.** Based on preliminary data, two cranberry capsules had  
583 the best adherence and largest effect in reducing bacteriuria plus pyuria. Since nursing home residents  
584 often take multiple medications, utilizing a safe dose with the lowest pill burden is warranted.  
585 Therefore, this regimen has the greatest likelihood of working in a real-world setting.

586 **3.6.2. Training of nursing home staff.** As the study begins in each new home, the Senior Intervention  
587 Nurse Educator will collaborate with nursing administration to organize a series of “in-service” didactic

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

603 **3.6.3. Incentives for nursing home facilities, nurses, and CNAs for study participation.** Although our  
604 pilot dosing study demonstrated high feasibility and adherence to capsule administration and obtaining  
605 of urine specimens, the pilot was conducted for only one month. Therefore, we will work with nursing  
606 administration and opinion leaders in the various homes to identify and provide relevant incentives for  
607 the nursing homes, CNAs, and nurses to maintain the enthusiasm and cooperation of all homes in the  
608 study. Planned incentives will include 1) an annual Certificate of Research Participation for all  
609 participating nursing home facilities which documents active participation in this Yale University  
610 research study for purposes of annual surveys conducted by regulatory bodies; 2) continuing education  
611 “in-service” hours that are required by the state of Connecticut for all CNAs; 3) gift certificates to  
612 participating nursing home staff. The amount of gift certificates will depend on how often they are  
613 given. If a gift certificate is given every other month, then it will be for \$20.00. If given only once a year,  
614 then the gift certificate will be for \$120.00.

615 **3.6.4. Retention events for nursing home facilities, nurses, and CNAs for study participation.** We will  
616 establish a series of retention events for all the nursing home facilities, and retention events for all the  
617 nurses and CNAs to maintain their enthusiasm, cooperation, and interest in maintaining adherence to  
618 the study protocol. For nursing home facilities, we will organize an evening meeting session every 12  
619 months between the P.I., the nursing home administrator, the Director of Nursing Services, and the  
620 Medical Director. For the nurses and CNAs, we will organize a luncheon meeting session every 6 months  
621 between the field staff and the nurses and CNAs of the homes. Specific issues to be discussed will  
622 include barriers to implementing the protocol, troubleshooting, and other topics of interest to the  
623 nursing home staff that might improve patient care (e.g. nursing home-acquired pneumonia prevention,  
624 prevention of decubitus ulcer formation).

### 625 626 **3.7. Trial Data: Descriptive, Outcomes, Sample Size Estimate, Data Management, and Analyses**

627 **3.7.1. Baseline clinical assessment.** Consenting participants will undergo a baseline assessment during  
628 which descriptive characteristics will be recorded. Facility, age, race, medications, comorbidities, and  
629 history of UTI will be obtained from chart review. The primary nurse and/or CNA will be asked questions  
630 adapted from the Minimum Data Set (MDS) regarding cognitive status, behavior, activities of daily living,  
631 continence, and degree of mobility. This method was used successfully in our observational cohort  
632 study and our pilot dosing study.

633 **3.7.2. Clinical outcome surveillance: primary and secondary outcomes.** Urine specimens will be  
634 obtained at baseline (prior to randomization) and every two months thereafter via clean catch (7

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

639 **3.7.2.1. Definition of primary outcome: bacteriuria plus pyuria and urinary tract specific**  
640 **symptoms.** Presence of bacteriuria will be defined as >100,000 cfu/ml of one or two organisms.  
641 Absence of bacteriuria will be defined as a urine culture with no growth, mixed flora (three or more  
642 organisms), or less than 100,000 cfu/ml. Pyuria will be defined as any number of white blood cells on  
643 urinalysis. Urinary tract specific symptoms (i.e., acute dysuria, new suprapubic pain or tenderness,  
644 acute costovertebral angle pain or tenderness, gross hematuria; new or marked increase in:  
645 incontinence, urgency, or frequency) will be assessed at the time of each urine specimen collection. In  
646 the study by Avorn et al., the rate of urinary tract specific symptoms at monthly intervals was 7% in the  
647 placebo group and 4% in the cranberry group.

648 **3.7.2.2. Definition of secondary outcomes for supplementary aims.**

649 **3.7.2.2.1. Symptomatic UTI.** Symptomatic UTI will be defined as 1) acute dysuria, fever  
650 or leukocytosis and (a) at least **one** of the following: acute costovertebral angle pain or tenderness;  
651 suprapubic pain; gross hematuria; new or marked increase in: incontinence, urgency, or frequency; OR  
652 (b) two or more of new or marked increase in: incontinence, urgency, suprapubic pain, new gross  
653 hematuria **AND** 2) a voided urine culture with (a)  $\geq 10^5$  cfu/ml of a single predominant organism or two  
654 gram negative organisms OR (b) a specimen collected by in and out catheter specimen with  $\geq 10^2$  cfu/ml  
655 of any number of organisms.

656 **3.7.2.2.2. Hospitalization.** All cause hospitalizations, including those related to UTI, and  
657 visits to the emergency room will be recorded.

658 **3.7.2.2.3. Death.** All cause death, including UTI as a reason, will be recorded.

659 **3.7.2.2.4. Antibiotic prescriptions.** Information on all antibiotic therapy prescribed,  
660 whether for UTI or other cause, will be recorded. If antibiotic therapy is for UTI, it will be noted in data  
661 collection.

662 **3.7.2.2.5. Resistant organisms.** All resistant bacterial isolates, either from the urine  
663 specimens obtained for study purposes or as recorded from other clinical specimens in the medical  
664 record, will be recorded. These isolates will include methicillin-resistant *Staphylococcus aureus* (MRSA),  
665 vancomycin-resistant *Enterococci* (VRE), and multi-drug resistant gram negative rods, with multi-drug  
666 resistance defined as resistance to at least 3 of the following antibiotics: ampicillin-sulbactam, cefazolin,  
667 ceftriaxone, ceftazidime, fluoroquinolones, piperacillin-tazobactam, meropenem, imipenem, and  
668 trimethoprim-sulfamethoxazole.

669 **3.7.2.3. Surveillance of primary outcome: bacteriuria plus pyuria and urinary tract specific**  
670 **symptoms.** Surveillance of the primary outcome will occur every two months for a total of six  
671 assessments over the 12 months of follow up. The primary nursing home staff (i.e., nurses and CNAs)  
672 will be responsible for collecting clean catch urine specimens every two months from 5-7AM on the  
673 same day for a given home. Study staff will provide reminders as to when sample collection is due. If  
674 the specimen is not collected on the due date, attempts at specimen collection will continue for one  
675 additional week prior to noting the specimen as missing. Urinary tract specific symptom assessment will  
676 occur on the day of urine specimen collection. Based on our pilot data, we anticipate that 14% of  
677 specimens initially will be missing. The research assistant, Luann Bianco, will collect all urine samples  
678 that are obtained and deliver to the Yale-New Haven Hospital Hematology and Microbiology  
679 Laboratories for processing. Urinalysis processing is automated in the Hematology Laboratory.  
680 Performing quantitative urine cultures will require the following steps: 1) mix urine; 2) vertically insert a  
681 flamed and cooled calibrated platinum loop that delivers 0.01 ml of urine into the specimen; 3) remove  
682 a loopful of urine; 4) inoculate one loopful of urine onto a Sheep blood agar and MacConkey agar plate

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

689 **3.7.2.4. Outcome adjudication.** If a urine culture reports growth of one or two organisms at least  
690 one of which is >100,000 cfu/ml and the urinalysis reveals any number of white blood cells, the primary  
691 outcome will be met. The Outcome Adjudication Committee, consisting of the P.I. (Juthani-Mehta), the  
692 Senior Research Nurse (Ginter), and the senior infectious diseases specialist (Quagliarello), will meet  
693 monthly to adjudicate the primary and secondary outcomes noted above.

694 **3.7.3. Surveillance of adverse events.** The Senior Assessment and Recruitment Study Nurse, Ms.  
695 Ginter, along with Ms. Bianco will monitor for any potential adverse events once per week for the  
696 duration of the 12 month surveillance period per participant, through interviews with nursing staff and  
697 report to the Internal Safety Committee. To ensure a rapid and systematic approach to adverse events,  
698 the Internal Safety Committee will evaluate all suspected adverse events, however mild or severe. The  
699 Chair of the Internal Safety Committee (Quagliarello) will determine which serious adverse events must  
700 immediately be reported to the Yale Human Investigation Committee, DSMB, and funding agencies.

701 **3.7.4. Surveillance of adherence to intervention.** Adherence will be determined by the number of  
702 capsules that were administered to each participant in relation to the targeted number. The medication  
703 administration record will be reviewed to determine if the study capsules were documented to be  
704 administered. However, in our pilot study, we identified discordance between the numbers of capsules  
705 recorded to have been administered versus the numbers of capsules remaining. Therefore, surveillance  
706 of the remaining capsules by pill counting every two weeks will be conducted to ensure that they are  
707 being administered. Reasons for lack of administration will be noted (e.g., refusal). Since it will not be  
708 possible to continue capsule administration during a hospitalization, hospitalization will be noted as the  
709 reason for lack of adherence to the missed doses. High adherence will be defined as administration of  
710  $\geq 80\%$  of prescribed capsules and low adherence will be administration of  $< 80\%$  of prescribed capsules.  
711 For those homes in which high adherence is maintained for three months, adherence assessments will  
712 be reduced to every four weeks.

713 **3.7.5. Sample size estimate.** Sample size was determined to detect a difference between the  
714 proportion with bacteriuria plus pyuria over time in the placebo group versus the treatment group  
715 receiving 2 cranberry capsules using the method of Diggle et al. for repeated binary outcomes. In the  
716 study by Avorn et al., the sample size was based on a 40% reduction in bacteriuria plus pyuria (0.50 in  
717 placebo to 0.30 in cranberry juice group). The following assumptions were made for this sample size  
718 calculation: Type 1 error of 5% (2-sided), 80% power, a serial correlation of 0.35 between 6 urine  
719 specimens, a bacteriuria plus pyuria rate of 0.45 in the control group, a 33% reduction with the  
720 cranberry intervention (0.30 bacteriuria plus pyuria rate), and 20% inflation for deaths, transfers and  
721 missing cultures. Based on these assumptions, the total sample size is 180 participants (90 per group).  
722 There are no data to determine power for secondary outcomes.

723 **3.7.6. Data management.** All Data management systems will be developed and implemented by the  
724 Data Management and Informatics Core (DMIC) of the Program on Aging/Claude D. Pepper Older  
725 Americans Independence Center (OAIC) at Yale. Data collection for the eligibility and enrollment  
726 protocol, the baseline assessment and outcome assessment will be accomplished using computerized  
727 instruments on tablet PCs, or on printed forms. Computerized instruments will be developed using the  
728 "Pepper Informatics" (Pi) software developed by Mr. Charpentier (<http://pi.med.yale.edu>). Instruments  
729 designed using Pi support a "point and click" interface suitable for direct data collection, as well as a  
730 "heads down" mode optimized for rapid, double-pass data entry from paper forms. In addition to data

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

734 **3.8. Anticipated Timeline of Clinical Trial.** Enrollment of each nursing home will occur sequentially (i.e.,  
 735 prevalent recruitment). We anticipate that it will require 8 weeks from receiving the nursing home  
 736 roster to enrollment of the first participant in a given nursing home. Recruitment staff will return to  
 737 each nursing home every three months for additional recruitment (i.e., incident recruitment). We  
 738 anticipate that prevalent recruitment will require one year and additional incident recruitments will  
 739 require an additional year.

	YEAR 1				YEAR 2				YEAR 3				YEAR 4			
<b>1. Preparing for Trial</b>																
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														
<b>2. Enrollment of Participants</b>																
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						
<b>3. Intervention Implementation</b>																
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		
<b>4. Outcome Surveillance and Assessment</b>																
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		
<b>5. Data Management and Analysis</b>																
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
<b>6. Report Generation</b>															x	x

741  
 742 **4. Subject Population:**  
 743 The participants will be female long-term care nursing home residents, 65 years or older. Assuming a  
 744 Type 1 error of 5% (2-sided), 80% power, a control group prevalence rate of 45%, a relative reduction of  
 745 33% (absolute risk difference of 15%), serial correlation among 6 repeated urine measurements on each  
 746 participant of 0.35, and a drop-out rate of 20% (e.g., death [17%], transfer and/or inability to provide  
 747 further urine specimens [3%]), the sample size required is 90 participants in each group (total N=180).

748

749 **5. Inclusion/Exclusion Criteria:**

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

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

763

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

773

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

781

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

788

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

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

796

797 **7. Risks:**

798 There are no reasonably foreseeable physical, psychological, emotional, social, economic, or legal risks  
799 involved in the two arms of the proposed study, or in obtaining a clean catch urine sample, which will be  
800 collected by trained nursing home staff if subjects need assistance. In the United States, cranberry  
801 capsules are considered to be a dietary supplement, not a drug or medication. As such, their usage is  
802 not regulated by the Food and Drug administration (FDA). In previous studies by our group and others,  
803 very few incidences of side effects have been noted after cranberry capsule administration. In a study of  
804 57 participants taking a different cranberry capsule from the one used in this study, only six subjects  
805 noted symptoms after cranberry capsule administration (vomiting, nausea, and/or diarrhea), but it was  
806 unclear whether these symptoms were actually a side effect from the cranberry capsules. These  
807 possible protocol-related side effects will be monitored by research staff.

808

809 **8. Minimizing Risks:**

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

813

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

818

819 **9. Data and Safety Monitoring Plan:**

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

824

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

827

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

839

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

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

845

## 846 **10. Statistical Considerations:**

### 847 **10.1 Data analysis plan.**

848 **10.1.1. Interim monitoring.** Interim monitoring will focus on participant accrual (overall  
849 and by nursing home), baseline comparability of treatment groups, protocol adherence, completeness  
850 of data retrieval, data quality, safety, and efficacy. A set of interim data monitoring tables will be  
851 developed for presentation to a DSMB at periodic intervals. We will carefully monitor participant  
852 accrual and adherence to ensure that the study is on target to achieve the required level of statistical  
853 power. We will propose to the DSMB one interim look for efficacy at the mid-point of the study using a  
854 Haybittle-Peto boundary with p-value of 0.001. This will have a negligible effect on the overall type I  
855 error at the end of the trial. Thus, the sample size was not inflated to account for the interim look.  
856 Futility will be assessed by calculating conditional power (under both the observed and hypothesized  
857 trend) and the feasibility of achieving the target sample size.

858 **10.1.2. Final analyses: primary outcome.** Final analyses will address comparability of  
859 treatment groups, efficacy and safety. All analyses will be conducted as randomized, i.e., participants  
860 will be analyzed according to their original treatment assignment regardless of adherence. A  
861 significance level of 0.05 (2-sided) will be used for statistical significance. SAS<sup>®</sup> 9.2 statistical software  
862 will be used for the analyses.

863 **10.1.2.1. Baseline comparability of treatment groups.** The adequacy of the  
864 randomization will be assessed by comparing the distribution of baseline demographic and  
865 clinical characteristics between the treatment groups. Comparability for continuous variables  
866 will be examined graphically and by summary statistics (means, medians, quartiles, etc.).  
867 Categorical variables will be examined by calculating frequency distributions. Adjustment for  
868 significant treatment imbalances in baseline covariates will not be done because this approach  
869 can be biased. Instead the following pre-specified covariates will be adjusted for: baseline  
870 bacteriuria, age, and number of comorbid conditions.

871 **10.1.2.2. Treatment efficacy for the primary outcome.** The primary study outcome is  
872 bacteriuria plus pyuria. The difference in the proportion with bacteriuria plus pyuria between the two  
873 treatment groups will be estimated using a multivariable logistic regression model that accounts for the  
874 serial correlation of repeated measurements, adjusted for the pre-specified covariates (baseline  
875 bacteriuria status, age, and number of comorbid conditions) and the randomization (stratification by  
876 nursing home). Prior to regression modeling, the potential impact of missing data and deaths on the  
877 study outcome will be investigated. If it is reasonable to assume that missing values are missing at  
878 random, generalized linear mixed effects modeling<sup>4</sup> will be used. Variables that are predictive of missing  
879 values will be included in the model. In a sensitivity analysis we will examine the possibility that data are  
880 missing not at random and will consider joint modeling of the longitudinal and survival outcomes.<sup>5</sup> In a  
881 sensitivity analysis, facility heterogeneity will be further assessed by using a random effect for nursing  
882 home in the regression model to account for the variability among homes. Model fit will be assessed by  
883 residual analyses, influence diagnostics, and goodness-of-fit tests. The treatment effect will be  
884 estimated as an odds ratio (treatment vs. control) with corresponding 95% confidence intervals. In  
885 exploratory analyses the impact of non-adherence on treatment effect will be investigated by methods  
886 described by Little, et al.

887 **10.1.2.3. Analysis of safety.** The incidence of adverse events will be tabulated and  
888 compared between treatment groups using statistics appropriate for categorical or count data, such as

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

891 **10.1.3. Final analyses: secondary outcomes.** The analysis of symptomatic UTI will be similar  
892 to that described for bacteriuria plus pyuria. Cumulative death rates will be estimated by the method of  
893 Kaplan-Meier and compared between treatment groups using the log-rank statistic. Frequency of  
894 hospitalizations, antibiotic prescriptions, and multi-drug antibiotic resistant organisms will be tabulated  
895 and compared between the treatment and control groups using the Wilcoxon statistic.

896

#### 897 **A. DRUGS, BIOLOGICS and RADIOTRACERS**

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

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

904

##### 905 **2. Background Information:**

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

910

##### 911 **3. Source:**

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

914

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

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

920

##### 921 **5. Use of Placebo:**

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

926

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

928

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

933

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

936

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

938 Targeted for enrollment at Yale for this protocol 180.

939

940 **7. Recruitment Procedures:**

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

946

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

963

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

966

967 **8. Consent Personnel:**

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

971

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

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

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

987

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

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

996 • **study personnel obtaining consent will use professional judgment to determine if the**  
997 **potential participant is capable of providing consent.** Members of the Field Staff who are responsible  
998 for participant recruitment and consent are all highly trained and experienced personnel in determining  
999 capacity to consent in aging populations. This determination will rely on individual observation of, and  
1000 interaction with, the potential participant as well as the opinion of the caregiver, when available. In  
1001 general, the assessment of the potential participant's capacity to consent will be based on her/his: 1)  
1002 ability to communicate a choice; 2) ability to understand relevant information; 3) ability to appreciate  
1003 the nature of the situation and its likely consequences; and 4) ability to manipulate information  
1004 rationally.

1005 • **determination of decisional impairment for providing consent.** Potential participants will  
1006 be considered decisionally impaired for providing consent if they have: 1) an inability to express or  
1007 communicate a preference or choice; 2) an inability to understand a situation and its potential  
1008 consequences as well as the impact of study participation on those circumstances (e.g., do not  
1009 understand that they may be hurt or may not be helped or cannot distinguish research from treatment);  
1010 3) an inability to provide a logical rationale for participation/no participation in the study (i.e., cannot  
1011 address risk/benefit); or 4) have been legally determined to be incompetent and/or have a conservator  
1012 of person. If there is any uncertainty, we will pursue surrogate consent.

1013 • **plans for surrogate consent when decisional impairment is identified.** For potential  
1014 participants who are deemed to be decisionally impaired, their identified surrogate will be approached  
1015 for consent because: 1) the risks of this study are limited and are justified given the potential benefits of  
1016 the research to the subject and the development of generalizable knowledge that will benefit elderly  
1017 nursing home residents nationwide; 2) the intervention is commensurate with clinical treatments  
1018 already available in clinical practice (multiple over-the-counter cranberry capsules and tablets) and 3) a  
1019 Data and Safety Monitoring Board will be convened to monitor the study. All potential participants  
1020 deemed decisionally impaired will be notified of that determination before permission is sought from  
1021 their legally authorized surrogate to enroll in the study. If permission is given to enroll in the study, the  
1022 potential participant will then be notified and their verbal assent will be obtained (i.e., their active  
1023 affirmation of a desire to participate).

1024 • **plans for assent for decisionally impaired potential participants.** In all cases in which  
1025 assent is sought, the assent discussion will include the following: 1) a simplified description of the

1026 purpose of the research, including risks and benefits; 2) a description of the procedures and  
1027 interventions to which the participant will be exposed; 3) a statement explaining that participation in  
1028 this study is voluntary only; 3) an explanation of the procedures that may hurt and for how long; 4) a  
1029 question and answer period in which the participant will be encouraged to ask questions about their  
1030 participation in the study.

1031 **11. Documentation of Consent/Assent:**

- 1032 1) Compound Authorization and Consent [Adult Form]
- 1033 2) Compound Authorization and Consent [Legally Authorized Representative/Surrogate Form]

1034

1035 **12. Non-English Speaking Subjects:**

1036 Since surrogate consent is required in most instances (95%) and since the participants often have  
1037 underlying dementia, English speaking participants are required who can be explained the protocol and  
1038 express their assent to participate not only to study staff but also to nursing home staff over the course  
1039 of the study.

1040

1041 **Confidentiality & Security of Data:**

1042 Name, address of nursing home residence, birth date, dates and details of previous episodes of  
1043 bacteriuria and/or UTI, and dates and details of prior antibiotic administration will be recorded.  
1044 Additionally, data on comorbidities, other medications, continence, and functional status will also be  
1045 recorded. The sources of research data on enrolled participants will be interviews with the nursing staff  
1046 and administrators at the institution and the participants' medical records. Baseline descriptive data  
1047 (i.e., facility, age, race, ethnicity, gender, comorbid disease, cognitive status, activities of daily living,  
1048 degree of mobility, medications, continence, history of UTI) will be recorded. These data will be  
1049 ascertained from the Minimum Data Set, the medical record, and interview with the primary care  
1050 provider (i.e., the Certified Nursing Assistant). The hierarchy of data sources will be based on the least  
1051 burdensome source of data. Data regarding clinical outcomes (i.e., bacteriuria, pyuria, urinary tract  
1052 specific symptoms, UTI, hospitalization, death, antibiotic prescriptions, resistant organisms), staff  
1053 adherence to the intervention, and adverse events will be collected by research study personnel. To  
1054 safeguard confidentiality, each study participant enrolled will be assigned a unique code number and  
1055 the participant's name will never be attached to any form. A separate file linking the participant's name  
1056 with study number will be kept in a password-protected data file, and will be used confidentially only by  
1057 research staff.

1058

1059 Research data will be compiled into a spreadsheet and/or database format and stored on the secure  
1060 Yale-ITS network which is backed-up nightly. Each subject will be identified by a study number. All data  
1061 recorded on the data extraction sheet will be identified only by the study number and will be kept in a  
1062 locked filing cabinet.

1063

1064 All data will be password protected and access limited to those individuals with direct responsibility for  
1065 the research project. Moveable electronic media used to collect or store the data is equipped with  
1066 encryption software recommended by the University (PGP). The PI and other members of the research  
1067 team work with coded or de-identified data when using moveable device(s) to perform data analysis.

1068

1069 To safeguard confidentiality of protected health information, each study participant enrolled will be  
1070 assigned a unique code number and the participant's name will never be attached to any form. A  
1071 separate file linking the participant's name with participant ID code will be kept in a password-protected

1072 data file, and will be used confidentially only by research staff. The study investigators will assume full  
1073 responsibility to maintain confidentiality. All study results will be presented only as statistical  
1074 aggregates that will neither identify, nor permit identification, of individual research participants. This  
1075 has been an effective method in our previous studies.

1076  
1077 The data systems and procedures at the Data Management and Informatics Core (DMIC) of the Program  
1078 on Aging/Claude D. Pepper Older Americans Independence Center (OAIC) at Yale conform to Yale's  
1079 HIPAA security policy  
1080 (<http://www.yale.edu/ppdev/Procedures/its/1610/1610PR.01SystemsNetwrokSecurity.pdf>), and all  
1081 equipment is certified by the Yale Information Security Officer. Since tablet PCs will be used by study  
1082 staff, they will be configured with mandatory security safeguards that are enforced by Yale Information  
1083 Technology Services, including "strong" passwords, password-protected standby mode, and whole-disk  
1084 encryption. At the end of every day on which data are collected, each tablet PC will be synchronized  
1085 with the master database on the DMIC system over a secure, encrypted mobile broadband connection.  
1086 Master data will be stored in a Microsoft SQL Server database to which only the data manager will have  
1087 access. Files prepared for analysis will be in SAS format, and will not include personal identifiers. To  
1088 remove the possibility of any data value in an analysis file being traced to a specific study subject, files  
1089 exported for analysis will not include the participant ID codes used by the field and data management  
1090 staff to file records and questionnaires. An arbitrary code for record linkage will be included, but only  
1091 the data manager will be able to map these linkage codes to the participant ID codes. The file export  
1092 subsystem of Pi logs all files created for distribution outside of the master database.

1093  
1094 All data will be password protected and access limited to those individuals with direct responsibility for  
1095 the research project. Moveable electronic media used to collect or store the data is equipped with  
1096 encryption software recommended by the University (PGP). The PI and other members of the research  
1097 team work with coded or de-identified data when using moveable device(s) to perform data analysis.

1098  
1099 When the research is completed, identifiable data will be destroyed three years after the completion of  
1100 the study. Paper forms will be shredded and the study computer will be zeroed. The anonymous data  
1101 will be retained indefinitely.

1102  
1103 The principal investigator, research staff, sponsor and Yale Human Investigation Committee will have  
1104 access to the protected health information.

1105  
1106 It is possible that reporting of communicable diseases and elderly abuse will be necessary in this study.  
1107 The nursing home administrator for the home that the participant resides in will be notified if such a  
1108 circumstance arises.

1109  
1110 **Potential Benefits:**  
1111 The potential benefits for the interventions are significant because we hypothesize that cranberry  
1112 capsules will reduce the incidence of bacteriuria plus pyuria and morbidity associated with UTI in female  
1113 nursing home residents. Administration of cranberry capsules has been documented in our pilot  
1114 feasibility and dosing studies to be feasible and adhered to by staff, and it is designed to be  
1115 generalizable and easily incorporated into the usual nursing care of nursing home residents. Although  
1116 implementing the use of cranberry capsules would result in greater initial costs, there is the potential for  
1117 healthcare savings from decreased antibiotic use, hospitalization, and emergence of resistant organisms.  
1118 In summary, the anticipated benefits of the intervention to the participants and society far outweigh the

1119 minimal risks. Therefore, the risk-benefit ratio appears to be favorable for proceeding with this clinical  
1120 trial.

1121 The importance of the knowledge gained in this proposed trial is great, including the following: 1) the  
1122 identification of a feasible and safe intervention that is effective in reducing bacteriuria in elderly  
1123 nursing home residents and can be generalized to female nursing home populations nationwide; 2) the  
1124 determination of whether routine use of cranberry capsules, which are not regulated by the Food and  
1125 Drug Administration (FDA), should be implemented in the nursing home setting; and 3) the potential for  
1126 a major reduction in morbidity, mortality, hospitalizations, and healthcare expenditures related to UTI  
1127 among elderly nursing home residents.

1128

1129 **Alternatives:**

1130 As described previously in this application, there are currently no other standardized accepted  
1131 alternatives for prophylactic treatment of asymptomatic bacteriuria in the nursing home population  
1132

1133

1133 **Payments for Participation (Economic Considerations):**

1134 Participants will not be paid for participation in this study. However, since clean catch urine  
1135 specimens are difficult to collect in this disabled nursing home population, nursing homes will be  
1136 provided an incentive that is approved of by each nursing home administration. Urine samples will be  
1137 collected by the nursing home staff nurses and/or aides. Since the collection of these urine specimens is  
1138 cumbersome, only for study purposes, and essential to the successful completion of this project,  
1139 individualized incentive programs for each participating nursing home will be designed. Incentive  
1140 programs will be constructed with the input from the Administrator and Director of Nurses at each  
1141 nursing home. Incentives may be distributed to a given floor or team. Planned incentives will include 1)  
1142 an annual Certificate of Research Participation for all participating nursing home facilities which  
1143 documents active participation in this Yale University research study for purposes of annual surveys  
1144 conducted by regulatory bodies; 2) continuing education “in-service” hours that are required by the  
1145 state of Connecticut for all CNAs; 3) gift certificates to participating nursing home staff. The amount of  
1146 gift certificates will depend on how often they are given. If a gift certificate is given every other month,  
1147 then it will be for \$20.00. If given only once a year, then the gift certificate amount will be \$120.00.

1148

1149 **Costs for Participation (Economic Considerations):**

1150 There are no costs to the subjects associated with participation in this research project. Both  
1151 the cranberry and placebo capsules will be provided at no cost to the subjects. Additionally, the clean  
1152 catch urine sample, urinalysis, and culture will be performed at no cost to the subjects.

1153

1154

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**1. Statement of Purpose:**

1318 The **primary aim** of this study is to test the efficacy of two oral cranberry capsules per day for  
1319 prevention of bacteriuria plus pyuria in female nursing home residents. The **secondary aim** is to  
1320 compare the occurrence of urinary tract specific symptoms in the cranberry capsule versus placebo  
1321 groups.

1322 The primary **hypothesis** is that two oral cranberry capsules will be associated with a 33% relative  
1323 reduction in the occurrence of episodes of bacteriuria plus pyuria over 12 months, compared to placebo.

1324 **Supplementary Aims** are to determine the:

- 1325 • safety of administering oral cranberry capsules over a 12 month surveillance period.
- 1326 • adherence of nursing home residents and staff to the administration protocol of two oral  
1327 cranberry capsules daily over 12 months.
- 1328 • incidence of adverse clinical outcomes (i.e., symptomatic UTI, all cause death, all cause  
1329 hospitalization, number and duration of all antibiotic prescriptions, all multi-drug antibiotic  
1330 resistant organisms) in the intervention and control arms over 12 months.

1331

1332 **2. Background:**

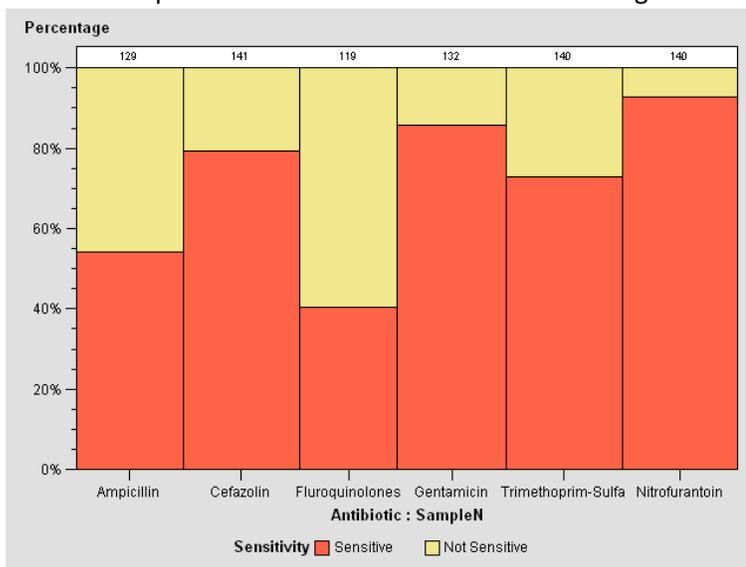
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1334 **2.1. Importance of urinary tract infection (UTI) in nursing home residents.** UTI is the most common  
1335 bacterial infection in nursing home residents with an incidence of 0.1 to 2.4 cases per 1000 resident-  
1336 days. UTI is also a common cause of infectious disease hospitalizations and deaths; the National Nursing  
1337 Home Survey indicated that UTI was an admitting or current diagnosis for hospitalization for  
1338 7,111/100,000 female residents. The Urologic Diseases of America determined that UTI was the most  
1339 costly and resource intensive condition studied among Medicare beneficiaries. Total Medicare  
1340 expenditures for UTI amounted to over \$1.7 billion, exclusive of medication costs in 2006.

1341 **2.2. Diagnostic challenges of UTI in nursing home residents.** Distinguishing symptomatic UTI (a  
1342 quantitative count of  $\geq 10^5$  colony forming units of bacteria per milliliter cfu/ml in one urine specimen in  
1343 the presence of urinary tract specific symptoms i.e., dysuria, suprapubic pain or tenderness, new urinary  
1344 frequency or urgency) from bacteriuria (a quantitative count of  $\geq 10^5$  cfu/ml) is problematic in nursing  
1345 home residents because of the challenges involved with symptom assessment. Bacteriuria is prevalent  
1346 in 25-50% of female nursing home residents, and pyuria (any white blood cells in the urine) is present in  
1347 90% of residents with bacteriuria. Given the high prevalence of bacteriuria in this population, three  
1348 randomized controlled trials of antibiotic treatment (versus no treatment) of bacteriuria were  
1349 conducted; none of these trials showed any decrease in mortality with treatment. These studies led to  
1350 the recommendation that bacteriuria should not be treated with antibiotics in older institutionalized  
1351 adults. Consequently, bacteriuria plus pyuria are necessary but not sufficient conditions to make the  
1352 diagnosis of UTI in this population. Infectious diseases physicians have distinguished bacteriuria from  
1353 symptomatic UTI, which requires urinary tract specific symptoms. However, in clinical practice, it is not  
1354 always clear how to classify a nursing home resident as symptomatic. Recent data from a large cohort in  
1355 the New Haven area have shown that dysuria plus a change in mental status and/or a change in  
1356 character of urine are the best combination of symptoms to predict bacteriuria plus pyuria among

1357 nursing home residents with suspected UTI. However, change in mental status and change in character  
 1358 of urine are subject to confounding and small numbers of patients meet these clinical criteria. Hence,  
 1359 symptoms have limited utility in clinical decision-making regarding the diagnosis of UTI. Given the  
 1360 current diagnostic uncertainty, antibiotics are commonly prescribed, and UTI accounts for 30% to 56% of  
 1361 all antibiotic prescriptions in the nursing home setting.

1362 **2.3. Widespread empiric antimicrobial administration.** Although treatment of bacteriuria is not  
 1363 recommended, many nursing home residents are still prescribed antibiotics because of the diagnostic  
 1364 challenges involved in identifying  
 1365 those residents that will benefit most  
 1366 from antibiotic therapy. Only 13% of  
 1367 antibiotic prescriptions for UTI occur  
 1368 prior to results of urine cultures being  
 1369 available. Isolation of resistant  
 1370 organisms is associated with prior  
 1371 antibiotic exposure, and resistant  
 1372 organisms from UTI are more frequent  
 1373 in nursing home residents than in  
 1374 community dwellers. Urinary isolates  
 1375 from nursing home residents are  
 1376 frequently resistant to commonly  
 1377 prescribed oral antibiotics (see **Figure**  
 1378 **1**). Use of antibiotics is associated with  
 1379 several risks, including the  
 1380 development of multi-drug antibiotic-  
 1381 resistant organisms, drug-related  
 1382 adverse effects, and significant costs. In order to reduce antibiotic prescriptions, prevention strategies  
 1383 should be targeted to bacteriuria, pyuria, and symptomatic UTI.



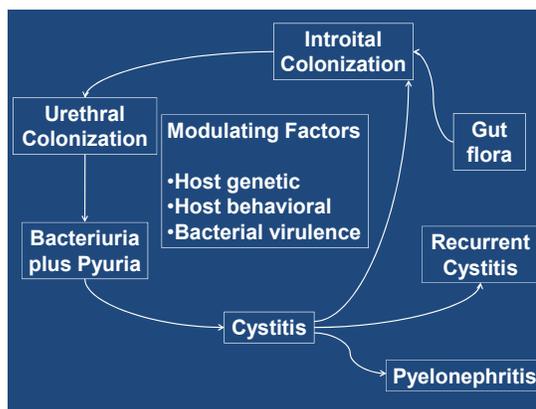
**Figure 1: Urinary Isolates UTI Episodes**

1384 **2.4. Rationale for prevention of bacteriuria, pyuria, and UTI.**

1385 Bacteriuria has been shown to be a risk factor for subsequent

1386 development of symptomatic UTI among young women  
 1387 and women with diabetes mellitus, and it is  
 1388 hypothesized that bacteriuria precedes the development  
 1389 of symptomatic UTI in nursing home residents (see  
 1390 **Figure 2**). The presence of bacteriuria is the greatest  
 1391 trigger for the initiation of antibiotic therapy. Since  
 1392 nursing home practitioners usually wait to obtain results  
 1393 of urine cultures, reducing bacteriuria could reduce  
 1394 antibiotic prescriptions. Therefore, efforts to prevent  
 1395 bacteriuria, pyuria, and UTI represent the most logical  
 1396 means of reducing antibiotic prescriptions in the nursing  
 1397 home setting.

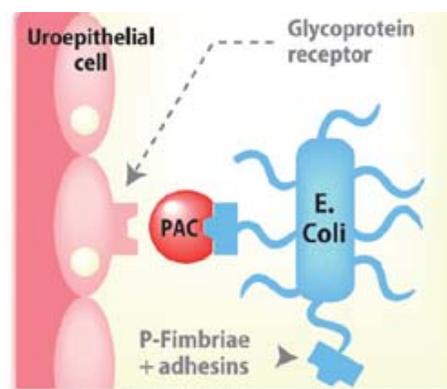
**Figure 2: Pathogenesis of UTI**



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1399 **2.5. Cranberry for prevention of UTI.**

1400 Many of the identified risk factors for bacteriuria and UTI in nursing home residents (e.g., functional  
1401 disability, dementia) are largely non-modifiable. Vaginal estrogen therapy, which has been shown to be  
1402 effective at preventing recurrent UTI in post-menopausal women, has potential risks and side effects  
1403 which would be undesirable in a nursing home population. With few other feasible intervention  
1404 strategies to prevent the common and morbid condition of UTI in nursing home residents, cranberry  
1405 capsules represent a novel intervention warranting investigation. Cranberry products represent an  
1406 existing, non-antimicrobial method for prevention of UTI. Cranberry proanthocyanidins (PAC) have been  
1407 shown to inhibit adherence of P-fimbriated *E.coli* to uroepithelial cells. P fimbriae are finger-like  
1408 projections that the organism uses to attach to bladder cells (see **Figure 3**). In vitro studies have  
1409 demonstrated that cranberry changes the formation of P fimbriae such that they can no longer attach to  
1410 the bladder mucosa. Since *E.coli* represents the majority of urinary isolates (54%), this preventive  
1411 strategy may be an effective method among nursing home residents. Empirical data supporting the  
1412 potential benefit of cranberry include: 1) in the study by Avorn  
1413 et al., cranberry juice decreased bacteriuria plus pyuria in older  
1414 women, even those not caused by *E.coli*; 2) urine from young  
1415 women that ingested cranberry capsules has been shown in  
1416 vitro and in vivo to decrease uropathogenic *E.coli* virulence; and  
1417 3) limited clinical studies of cranberry juice in elderly women  
1418 have demonstrated reductions in bacteriuria but have not been  
1419 of adequate size or quality to result in changes in patient care.  
1420 The acrid flavor of cranberry juice is challenging for patients to  
1421 tolerate in large volumes. Nursing home residents in particular  
1422 are unable to ingest sufficient volumes to maintain hydration  
1423 because of swallowing disorders, exacerbation of incontinence,  
1424 and decreased thirst drive. Hence, cranberry capsules represent  
1425 a prevention strategy that warrants testing in the nursing home population.



**Figure 3: Anti-adhesion of PAC**

1426 **2.6. Effective dose of cranberry.** Previous studies regarding cranberry products for prevention of UTI  
1427 yielded conflicting results, likely because of variability of PAC dose and clinical populations studied.  
1428 Initial studies identified PAC to be the active ingredient in cranberry that prevents binding of *E.coli*. In  
1429 the clinical trial by Avorn et al. of 300ml of cranberry juice beverage daily (36mg PAC), older women  
1430 (mean age 78.5 years) had a 58% reduction in the odds of having bacteriuria plus pyuria compared to  
1431 controls, particularly after more than one month of cranberry juice ingestion. Previously, there were at  
1432 least three different methods of quantifying PAC in the market place, and many products purported  
1433 effectiveness with variability in dose of PAC. Methods to quantify PAC have now been standardized and  
1434 can be independently measured. Only one product on the market currently can deliver 36mg PAC as  
1435 measured by the BL-DMAC method in each capsule and it will be utilized in this proposed project. In  
1436 vitro data have shown that 36 to 108mg of PAC is effective at inhibiting bacterial adherence to epithelial  
1437 cells. Since patient adherence to cranberry capsule administration is important and nursing home  
1438 residents often take multiple medications, the least pill burden and dose of cranberry capsules with the  
1439 largest effect will be utilized for this efficacy trial.

1440

1441 **2.7. Potential adverse effects of cranberry.** The only side effect reported with the ingestion of  
1442 unsweetened cranberry juice is gastro-esophageal reflux; however, this side effect has not been  
1443 reported with cranberry capsules. Additionally, ingestion of large amounts of liquid is challenging for  
1444 nursing home residents with demonstrated poor adherence, thereby making cranberry capsules a more  
1445 preferable intervention option to test in this particularly vulnerable population.

1446 **2.8. Investigating the effects of cranberry capsules on women only.** The reasons for investigating  
1447 cranberry capsules in women only include: 1) Avorn et al. investigated cranberry juice among women  
1448 only; 2) women represent 75-85% of nursing home residents; 3) there is no evidence to date that  
1449 cranberry products reduce UTI in men; 4) the predominant risk factor for UTI in men is underlying  
1450 structural or functional abnormalities of the urinary tract; and 5) the prevalence of bacteriuria plus  
1451 pyuria in female nursing home residents ranges from 25-50% versus 15-30% for men. Since the  
1452 prevalence of bacteriuria plus pyuria is lower in men, a study that would detect an effect in men and  
1453 women would have to be larger. Powering a study to detect a difference in female nursing home  
1454 residents is an important first step.

1455 **2.9. Comparison of this proposal to the landmark cranberry juice study by Avorn et al.** The landmark  
1456 study by Avorn et al. included 153 female subjects, 109 community dwellers living in housing complexes  
1457 for the elderly and 44 long-term care facility residents, with a mean age of 78.5 years. Participants  
1458 ingested 300ml of cranberry juice cocktail per day for 6 months. All participants provided self-consent,  
1459 and most participants were instructed on how to collect an adequate clean-voided specimen  
1460 themselves. Most participants were enrolled only after a 1-month trial of placebo beverage to ensure  
1461 that daily intake would be adequate throughout the study. This study informed the development of this  
1462 proposal by identifying areas where further investigation is needed: 1) only 29% of participants were  
1463 nursing home residents; 2) the mean age was 10 years lower than the mean age of nursing home  
1464 residents; 3) most nursing home residents are unable to provide self consent or self collected urine  
1465 specimens; 4) dehydration is prevalent in up to 90% of nursing home residents because of swallowing  
1466 difficulty, aspiration risk, increased incontinence with hydration, and decreased olfactory, taste, and  
1467 thirst sensations. Daily intake of 300ml of juice would not be feasible for most nursing home residents.  
1468 Since UTI is the most prevalent infection in nursing home residents, a study designed specifically for the  
1469 nursing home population is warranted.

1470 **2.10. Rationale for this study.** Given the biological plausibility for its preventive effects and the  
1471 challenges involved with cranberry juice ingestion by nursing home residents, cranberry capsules  
1472 represent a promising preventive strategy that should be further explored in this vulnerable population.  
1473 Because symptomatic UTI is a leading cause of morbidity in nursing home residents, preventing  
1474 bacteriuria plus pyuria will likely reduce morbidity. Furthermore, a reduction in bacteriuria plus pyuria  
1475 will result in a reduction in antibiotic use and its attendant adverse effects. Our prior work has  
1476 demonstrated that 1) cranberry capsule administration is feasible in nursing home residents; 2) an  
1477 optimal dose of administration has been identified; and 3) there is preliminary evidence that cranberry  
1478 capsules reduce bacteriuria plus pyuria. This proposal will determine whether cranberry capsules reduce  
1479 the occurrence of bacteriuria plus pyuria, whether administration of cranberry capsules is safe and  
1480 adhered to over 12 months, and whether bacteriuria plus pyuria is associated with UTI morbidity. **This  
1481 study is significant because cranberry capsules are a feasible and low risk intervention that may  
1482 reduce the morbidity and mortality associated with bacteriuria, pyuria, and UTI in nursing home  
1483 residents.**

1484

1485

1486 **2.11. Preliminary studies.**

1487 **2.11.1. Previous studies by principal investigator (P.I.) regarding UTI in nursing home residents.** Dr.  
1488 Juthani-Mehta has spent the past eight years investigating diagnostic, management, and prevention  
1489 strategies of UTI in nursing home residents. She competed for, and was awarded, an R03 Small  
1490 Research Grant and a K23 Career Development Award funded by the National Institute on Aging on this  
1491 topic. She has conducted studies involving interviews with nursing staff, observational cohort studies,  
1492 and pilot intervention studies that have prepared her for conducting the proposed study.

1493 **2.11.2. Pilot feasibility and adherence study of cranberry capsules in long-term care residents.** In a  
1494 previous study conducted by the P.I. and funded by the Donaghue Foundation, a cranberry capsule  
1495 product with 16.25mg PAC per capsule was studied. Fifty-seven participants received none (N=18), one  
1496 (N=20), or two (N=19) cranberry capsules per day and were followed for 6 months. The mean age was  
1497 86.8 years, 47 (83%) were women, and 100% were white. The baseline bacteriuria rate was 45%. Of  
1498 240 urine samples that were scheduled for collection, 207 samples were collected (86.3%). Of 237  
1499 doses of cranberry capsules that were prescribed, only 7 (3%) were missed. Six subjects had one or  
1500 more side effect noted after cranberry administration (i.e., vomiting [N=5], diarrhea [N=3], nausea  
1501 [N=3]); however, whether another etiology could account for these symptoms was not noted in the  
1502 medical record. This study demonstrated that 1) cranberry capsules were feasible to administer and  
1503 adhered to, and 2) clean catch urine specimens could be obtained in this population. Although the study  
1504 was not designed to evaluate efficacy, trend towards efficacy of cranberry capsules could not be  
1505 demonstrated, and it is possible that under-dosing of the active components of cranberry was  
1506 responsible for this finding.

1507 **2.11.3. Cranberry capsule dosing study in nursing home residents.** Given the findings of the study  
1508 outlined in **Section C.2.2.**, the P.I. competed for and received funding through the Yale Center for  
1509 Clinical Investigation (YCCI – the Yale CTSA) to conduct a pilot dosing study of cranberry capsules to  
1510 identify the optimal dose among nursing home residents. This study was a double-blind, randomized,  
1511 placebo-controlled trial of 3 cranberry capsules once per day (108mg PAC), 2 cranberry capsules plus  
1512 one placebo capsule once per day (72mg PAC), 1 cranberry capsule plus two placebo capsules once per  
1513 day (36mg PAC), and 3 placebo capsules once per day to determine the number of participants with  
1514 bacteriuria plus pyuria over a one month period. Urine specimens were collected at baseline and then  
1515 on a weekly basis for 4 weeks (total = 5 specimens). Inclusion criteria were: 1) female residents; 2)  
1516 history of UTI recorded in the existing medical record; 3) age ≥ 65 years; 4) long term residence; 5)  
1517 English speaking. Exclusion criteria included: 1) total incontinence; 2) warfarin therapy; 3) residence for  
1518 < 4 weeks; 4) chronic indwelling bladder catheter; 5) terminal (life expectancy < one month); 6) chronic  
1519 antibiotic therapy; 7) kidney stones; 8) dialysis; 9) cranberry therapy; 10) allergy to cranberry. Through a  
1520 HIPAA waiver, chart review was conducted, and eligible residents were identified. Eligible residents or  
1521 surrogates were approached for written consent.

1522 **2.11.3.1. Eligibility and enrollment data.** Thirteen nursing

1523 homes consented to participate in this study, and 11  
1524 were required to reach our target of 80 participants,  
1525 20 in each arm of the study. In 11 homes, 1928  
1526 residents were screened for participation; 1380  
1527 residents did not meet inclusion criteria (see **Table**  
1528 **1**); of 548 remaining residents screened, 308  
1529 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%

1530 were eligible; 90 residents consented (37.5% consent rate), and 80 residents enrolled (10 participants  
1531 met an exclusion criterion prior to enrollment). The primary reason for lack of inclusion in this study  
1532 was no history of UTI. This was listed as an inclusion criterion in order to target the group of residents  
1533 with the highest predicted rate of bacteriuria.

1534 **2.11.3.2. Preliminary feasibility and adherence data.** Eighty participants each should have provided 4  
1535 urine specimens, one per week during the month of follow up. Of the 320 urine specimens that should  
1536 have been collected, 293 urinalyses and urine cultures were obtained (92%). Adherence was assessed by  
1537 the mean number of doses administered in the four arms of the study out of a total of 30 daily doses  
1538 over the one month study period → placebo 26.8 doses (SD 5.1), one capsule 27.5 doses (SD 6.0), two  
1539 capsules 29.1 doses (SD 1.7), three capsules 27.9 (SD 4.1). There were no adverse events possibly  
1540 related to cranberry capsule ingestion (i.e., nausea, vomiting, or gastrointestinal distress) during the one  
1541 month of follow up. Hence, adherence was best in the two capsule treatment group, although not  
1542 significantly different from the other groups.

1543 **2.11.3.3. Preliminary efficacy data.** Preliminary data were obtained from the 80 enrolled participants.  
1544 Twenty participants were randomized to each of four treatment groups, receiving 0, 1, 2, and 3 active  
1545 cranberry capsules respectively. Baseline data, including a baseline urine culture and urinalysis, was  
1546 collected prior to randomization. Four additional urine specimens were obtained at one-week intervals  
1547 after randomization. The rate of bacteriuria plus pyuria was 52% in the placebo group. Of the 320  
1548 anticipated outcome measurements, 27 were missing. Investigation of missing data suggested that the  
1549 data were missing completely at random. The effect of dose on development of bacteriuria plus pyuria  
1550 was tested using a Generalized Estimating Equations (GEE) model, adjusted for baseline bacteriuria  
1551 status (present vs. absent). Results displayed in **Table 2** show that over one month, there was a 37%  
1552 reduction in the odds of having bacteriuria plus pyuria among the 2 cranberry capsule group as  
1553 compared to the placebo group, but the confidence intervals were wide. Since Avorn et al.  
1554 demonstrated no effect at one month of surveillance, these preliminary data showing some effect could  
1555 become more pronounced with one year of surveillance. The reason for the lack of a dose response for  
1556 three capsules is not clear. Two possible reasons are 1) the sample size was too small with an unstable  
1557 estimate of the effect of three capsules; 2) the one month duration of surveillance was too brief to  
1558 demonstrate a dose response effect.

1559 **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

1563

### 1564 **3. Research Plan:**

1565 **3.1. Overview.** The **primary aim** of this study is to test the efficacy of two oral cranberry capsules per  
1566 day in the prevention of bacteriuria plus pyuria in female nursing home residents. The **secondary aim** is  
1567 to compare the occurrence of urinary tract specific symptoms in the cranberry capsule versus placebo  
1568 groups. The **primary hypothesis** is that two oral cranberry capsules per day will be associated with a  
1569 33% relative reduction in the occurrence of episodes of bacteriuria plus pyuria over 12 months,  
1570 compared to placebo, in a cohort of female nursing home residents. This aim will be accomplished by  
1571 conducting a double-blind randomized placebo-controlled efficacy trial of two oral cranberry capsules  
1572 per day versus placebo in a cohort of Connecticut female nursing home residents.

1573 **Trial Setting.** The setting will be up to 21 nursing homes within a 50 mile radius of New Haven,  
1574 licensed by the Connecticut Department of Public Health as “Chronic and Convalescent Nursing  
1575 Homes”, providing skilled care and certified for Medicare or Medicaid. These 21 homes each  
1576 have at least 90 residents, UTI rates comparable to the national average of 9% annually, and  
1577 sociodemographic characteristics similar to national averages.

1578 **Design.** The design will be a double-blind, randomized, placebo-controlled efficacy trial in which  
1579 all participants will undergo urine sample testing at baseline and every two months over 12  
1580 months of prospective surveillance. Training of staff, screening, and enrollment of participants  
1581 will occur one home at a time. We anticipate each home will require 8 weeks from training  
1582 initiation to the start of the intervention. Each participant will receive treatment and be  
1583 followed for outcomes for 12 months.

1584 **Participants.** The participants will be female long-term care nursing home residents, 65 years or  
1585 older. Assuming a Type 1 error of 5% (2-sided), 80% power, a control group prevalence rate of  
1586 45%, a relative reduction of 33% (absolute risk difference of 15%), serial correlation among 6  
1587 repeated urine measurements on each participant of 0.35, and a drop-out rate of 20% (e.g.,  
1588 death 17%, transfer and/or inability to provide further urine specimens 3%), the sample size  
1589 required is 90 participants in each group (total N=180).

1590 **Intervention.** The intervention will be two cranberry capsules per day, compared to two  
1591 placebo capsules per day for 12 months (30-day blister pack per month equaling 360 days).  
1592 Data entry and management will occur at the Yale Program on Aging. Interim monitoring will  
1593 include patient accrual, protocol adherence, data quality, safety, efficacy, and futility. A series  
1594 of monitoring tables will be developed that include the above elements for presentation on a  
1595 semi-annual basis to the Independent Safety Monitor appointed by the NIA. Final analysis will  
1596 consist of comparability of treatment groups, treatment efficacy, and safety. All primary  
1597 treatment comparisons will analyze participants as randomized. An Executive Committee will  
1598 oversee the study design and troubleshoot methodological problems that arise during the  
1599 course of the study. A Steering Committee will oversee daily issues related to participant  
1600 enrollment, data collection and management, intervention implementation, and outcome  
1601 assessment. An Internal Safety and Outcome Adjudication Committee will monitor adverse  
1602 events, adjudicate outcomes, and interface with the Independent Safety Monitor. The P.I., Dr.  
1603 Juthani-Mehta, has completed one observational cohort study, two pilot intervention studies,  
1604 and was the Chair of the Internal Safety Committee of another nursing home intervention trial.  
1605 She has assembled a team that is well equipped to complete this proposed project.

1606 **3.2. Trial Setting.** This study will take place at up to 21 nursing homes within a 50 mile radius of New  
1607 Haven. The setting will be up to 21 nursing homes within a 50 mile radius of New Haven, licensed by the  
1608 Connecticut Department of Public Health as “Chronic and Convalescent Nursing Homes”, providing  
1609 skilled care and certified for Medicare or Medicaid. These 21 homes each have at least 90 residents, UTI  
1610 rates comparable to the national average of 9% annually, and sociodemographic characteristics similar  
1611 to national averages.

1612 **3.2.1. Rationale.** Residents of nursing homes within the greater New Haven area are reflective of the  
1613 nursing home population within the United States. Nursing homes chosen to participate in this study  
1614 represent a mix of urban and suburban, proprietary and nonprofit, private pay and Medicaid homes.  
1615 We anticipate our target minority rate of 12% will be met with the spectrum of homes participating. We  
1616 recognize the great challenges involved in working with these non-academic nursing homes, but we  
1617 have established good relationships with many of them, and we have successfully conducted previous

1618 observational and interventional studies in this environment. The Yale Program on Aging has vast  
1619 experience conducting research in challenging but important real world settings with high recruitment,  
1620 retention, and adherence rates.

1621 **3.2.2. Determination of eligible pool of residents.** Using information available through Medicare on  
1622 [www.medicare.gov/nhcompare](http://www.medicare.gov/nhcompare), the national and Connecticut state averages for the percent of  
1623 residents who had a UTI annually were 9% and 7%, respectively. To improve study efficiency, we  
1624 selected nursing homes with an average UTI rate at least as high as the CT and national averages within  
1625 a 50 mile radius of New Haven and with at least 90 beds. Women comprise 75-85% of nursing home  
1626 residents. In the first cranberry capsule feasibility study, the baseline bacteriuria rate was 45%. In order  
1627 to increase the baseline rate of bacteriuria, in the pilot dosing study, history of UTI was a required  
1628 eligibility criterion. However, 664 residents were excluded by requiring this inclusion criterion, and the  
1629 baseline rate of bacteriuria plus pyuria only increased to 52%. In an effort to increase the baseline  
1630 bacteriuria rate, a large pool of potentially eligible subjects was lost and the rate only increased from  
1631 45% to 52%. Therefore, for this proposed study, history of UTI will not be a required inclusion criterion.

1632 In the initially identified 10 homes, we expected to find at least 700 eligible residents so that with a 30%  
1633 consent rate, we could enroll 180 participants. In the pilot dosing study, when history of UTI was  
1634 included as an inclusion criterion and 664 residents were excluded for this reason, 240 eligible residents  
1635 were identified in 11 homes. If history of UTI would not have been an inclusion criterion, 904 residents  
1636 would have been eligible for the pilot dosing study (240+664=904). Although we had a 37.5% consent  
1637 rate in the pilot dosing study, with a conservative 30% consent rate which is consistent with other  
1638 nursing home intervention studies, 271 residents could have consented from 11 nursing homes.  
1639 Therefore, in this proposed study, we anticipated that 10 homes would be sufficient to achieve our  
1640 sample size of 180. Nevertheless, 6 back-up homes were recruited in the event that 10 homes would not  
1641 be sufficient to meet our target sample size. Over the course of the study, because of a lower eligibility  
1642 rate, a total of 21 nursing homes were required to achieve the calculated sample size.

1643 **3.2.3. Identification of participating nursing homes.** Based on our sample size estimate of 180  
1644 participants, we anticipate the need for up to 21 nursing homes and, at this time, we have 21  
1645 participating nursing homes that have already agreed to participate.

1646 **3.3. Trial Design.** This study will be a double-blind, placebo controlled, randomized, clinical efficacy trial  
1647 of two cranberry capsules versus placebo. The unit of randomization will be each individual participant.

1648 **3.4. Trial Participants.** The participants in this trial will be female long-term care nursing home  
1649 residents.

1650 **3.4.1. Screening and eligibility assessment.** Screening at each nursing home will occur sequentially.  
1651 We anticipate that from the date of screening to enrollment, each home will require eight weeks. Once  
1652 enrollment is initiated at one home, screening will begin at the next home. Residents, age  $\geq 65$  years,  
1653 residing in one of the participating nursing homes will be identified from a computerized log kept by the  
1654 Director of Nursing Services at the home. Subsequently, study personnel will perform a brief chart  
1655 review to establish the presence of inclusion and exclusion criteria. A HIPAA waiver will be obtained for  
1656 recruitment purposes only. After the initial wave of recruitment (“prevalent participants”), each nursing  
1657 home will be re-screened approximately every three months for one year. Participants in subsequent  
1658 waves of recruitment will be “incident participants.” Therefore, there will be up to five total waves of  
1659 recruitment at each participating nursing home.

1660 **3.4.1.1. Inclusion criteria.** All races will be considered for inclusion if they are: 1) female; 2) long-term  
1661 care residents; 3) English speaking; and 4) 65 years or older. Since surrogate consent is required in most

1662 instances and since the participants often have underlying dementia, English speaking participants are  
1663 required who can be explained the protocol and express their assent to participate not only to study  
1664 staff but also to nursing home staff over the course of the study.

1665 **3.4.1.2. Exclusion criteria.** Residents will be excluded if they: 1) are not expected to be in the nursing  
1666 home for at least one month (i.e., short term rehabilitation, pending discharge, terminal life expectancy  
1667 < 1 month); 2) are on chronic suppressive antibiotic or anti-infective (i.e., mandelamine) therapy for  
1668 recurrent UTI; 3) have end stage renal disease on dialysis (they do not regularly produce urine); 4) are  
1669 unable to produce a baseline clean catch urine specimen for collection; 5) are on warfarin therapy  
1670 because of a potential interaction of warfarin and cranberry juice; 6) have a history of nephrolithiasis  
1671 because cranberry may increase the risk of nephrolithiasis; 7) have an indwelling bladder catheter in  
1672 place; 8) have an allergy to cranberry products; 9) are being treated with cranberry products; 10)  
1673 residence < 4 weeks.

1674 **3.4.2. Consent and enrollment procedures.** Permission will be obtained from the potential  
1675 participant's home administrator before each resident is approached for study recruitment. Informed  
1676 consent will be obtained by trained study personnel. All potential participants will receive a general  
1677 description of the study, including the baseline and surveillance evaluations, the intervention, potential  
1678 risks and benefits. As part of the study protocol, participants will be advised to avoid ingestion of other  
1679 cranberry products. In addition, participants will be asked to sign a HIPAA authorization form that  
1680 explains the protected health information that will be used, disclosed, and to whom it will be disclosed  
1681 as part of this study and an Authorization to Release Protected Health Information for Research form.  
1682 For potential participants who are determined to be decisionally impaired by study recruitment  
1683 personnel, consent will be sought from their designated surrogates along with assent from the  
1684 participant. Surrogate consent will be sought through a combination of up to three phone calls and two  
1685 mailings describing the study purpose, intervention, surveillance evaluations, risks and benefits. We  
1686 have successfully utilized this method of surrogate consent in our observational cohort studies, in pilot  
1687 intervention studies, and in the pilot dosing study in which the consent rate was 37.5% from eligible  
1688 residents or surrogates. Based on our pilot studies, we anticipate that >95% of eligible residents will  
1689 require surrogate consent because of decisional impairment.

1690 **3.4.3. Availability of participants for enrollment.** We recognize that in an intervention trial, there will  
1691 be obstacles to patient enrollment, adherence, and retention. These include ineligibility due to exclusion  
1692 criteria defined, resident (or surrogate) refusal to participate, drop outs, and loss from competing  
1693 morbidities. However, among the 10 initial homes that agreed to participate, we estimated that we  
1694 would have  $\geq 600$  eligible residents with the average number of eligible residents per home of 50 at the  
1695 time of the initial two month enrollment period. Given the anticipated replacement of the 20% of  
1696 residents censored annually, we estimated an additional 200 eligible residents available over the two  
1697 year enrollment period (100 each year), resulting in  $500+200=700$  total eligible residents. A consent  
1698 rate of 30% would yield at least our sample size target of 180 participants ( $700 \times 30\% = 210$ ). The consent  
1699 rate of 30% is feasible because data from our dosing study revealed a 37.5% consent rate. In the  
1700 vulnerable nursing home population, consent rates of approximately 30% for an intervention study are  
1701 well documented. In addition, additional back-up homes agreed to participate if more homes were  
1702 required for recruitment and all were utilized.

1703 **3.4.4. Expected attrition.** We anticipate the following sources of attrition of participants: deaths,  
1704 transfers out of the nursing home, and functional decline prohibiting continued participation in the  
1705 study. The total anticipated attrition rate is 20%, 17% for death and 3% for other reasons. These rates  
1706 are based on observed numbers in our prior studies. We do not expect any drop ins from placebo to

1707 treatment. Because we will analyze participants as they are randomized, intervention drop-outs, and  
1708 non-adherent participants to the assigned treatment arm are not considered losses. Deaths occurring  
1709 before obtaining outcome data or the end of the 12 month follow-up are unavoidable in a nursing home  
1710 population and analyses to make use of the existing data on these losses are discussed below. Transfers  
1711 out of the homes are also expected. Based our prior studies, the transfer rate is expected to be low (i.e.,  
1712 3%).

1713 **3.5. Stratified randomization.** Once consent is obtained, a baseline clean catch urine specimen will be  
1714 obtained from participants prior to initiation of therapy to ensure that subsequent clean catch urine  
1715 specimen collection will be possible. Then, enrolled participants will be randomized to two placebo or  
1716 two cranberry capsules within nursing home using a permuted block design with a variable block size  
1717 and equal allocation. Stratification by nursing home is being proposed to account for potentially  
1718 different standards of nursing and medical care among nursing homes. The randomization will be  
1719 double-blind. Neither the personnel (study nurses, P.I., nursing home nurses and CNAs) nor the patient  
1720 will be aware of the treatment allocation. The senior data manager will implement the randomization  
1721 scheme, and the Investigational Drug Services pharmacist will make the arm assignment. Only they will  
1722 have access to the randomization codes during the enrollment process.

1723 **3.6. Trial Intervention.** The intervention is two cranberry capsules versus placebo capsules for the  
1724 prevention of bacteriuria plus pyuria. Cranberry capsules will be administered for 360 days and total  
1725 follow up of each participant will be one year. This trial serves as an efficacy study in which the  
1726 reduction of bacteriuria plus pyuria is the primary outcome. The secondary outcome is the occurrence  
1727 of urinary tract specific symptoms in the cranberry capsule and placebo groups. This study will also  
1728 determine rates of adverse clinical outcomes (i.e., symptomatic UTI, all cause hospitalization, all cause  
1729 death, all antibiotic prescriptions, and all multi-drug antibiotic resistant organisms) in the placebo and  
1730 treatment groups.

1731 **3.6.1. Justification for two cranberry capsules.** Based on preliminary data, two cranberry capsules had  
1732 the best adherence and largest effect in reducing bacteriuria plus pyuria. Since nursing home residents  
1733 often take multiple medications, utilizing a safe dose with the lowest pill burden is warranted.  
1734 Therefore, this regimen has the greatest likelihood of working in a real-world setting.

1735 **3.6.2. Training of nursing home staff.** As the study begins in each new home, the Senior Intervention  
1736 Nurse Educator will collaborate with nursing administration to organize a series of “in-service” didactic  
1737 training sessions to orient and mentor the nurses and certified nursing assistants (CNAs) as a group to  
1738 the methods involved in urine specimen collection and capsule administration. This will occur prior to  
1739 initiation of the intervention in any participant. Since staff turnover is high in the nursing home setting,  
1740 we anticipate the need to retrain nurses and CNAs on a quarterly basis over the course of the study.  
1741 During the first 4 weeks after initiation of the intervention, the team of training nurses will identify  
1742 barriers to administrating the intervention (e.g., storage location of study capsules) and facilitate  
1743 solutions. The importance of timely and clean urine specimen collection will be reinforced to all nursing  
1744 home staff to reduce the number of missing urine specimens. Since clean catch urine specimens are  
1745 most easily obtained in the first morning void, specimens will be targeted for collection by nursing home  
1746 staff between 5-7AM. Study staff will supervise baseline collections of these specimens in each home,  
1747 and train nursing home staff for subsequent urine specimen collections. Prior pilot testing has  
1748 demonstrated that nursing home patients experience more agitation when unfamiliar study personnel  
1749 perform routine care. Therefore, urine specimens will be collected by nursing home staff members that  
1750 are well known to the participants. This strategy of urine specimen collection was effective in the pilot  
1751 dosing study.

1752 **3.6.3. Incentives for nursing home facilities, nurses, and CNAs for study participation.** Although our  
1753 pilot dosing study demonstrated high feasibility and adherence to capsule administration and obtaining  
1754 of urine specimens, the pilot was conducted for only one month. Therefore, we will work with nursing  
1755 administration and opinion leaders in the various homes to identify and provide relevant incentives for  
1756 the nursing homes, CNAs, and nurses to maintain the enthusiasm and cooperation of all homes in the  
1757 study. Planned incentives will include 1) an annual Certificate of Research Participation for all  
1758 participating nursing home facilities which documents active participation in this Yale University  
1759 research study for purposes of annual surveys conducted by regulatory bodies; 2) continuing education  
1760 “in-service” hours that are required by the state of Connecticut for all CNAs; 3) gift certificates to  
1761 participating nursing homes. The amount of gift certificates will depend on how often they are given.

1762 **3.6.4. Retention events for nursing home facilities, nurses, and CNAs for study participation.** We will  
1763 establish a series of retention events for all the nursing home facilities, and retention events for all the  
1764 nurses and CNAs to maintain their enthusiasm, cooperation, and interest in maintaining adherence to  
1765 the study protocol. For nursing home facilities, the study staff will interface with the nursing home staff  
1766 periodically to discuss the study. Specific issues to be discussed will include barriers to implementing the  
1767 protocol, troubleshooting, and other topics of interest to the nursing home staff that might improve  
1768 patient care (e.g. nursing home-acquired pneumonia prevention, prevention of decubitus ulcer  
1769 formation).

### 1770 **3.7. Trial Data: Descriptive, Outcomes, Sample Size Estimate, Data Management, and Analyses**

1771 **3.7.1. Baseline clinical assessment.** Consenting participants will undergo a baseline assessment during  
1772 which descriptive characteristics will be recorded. Facility, age, race, medications, comorbidities, and  
1773 history of UTI will be obtained from chart review. The primary nurse and/or CNA will be asked questions  
1774 adapted from the Minimum Data Set (MDS) regarding cognitive status, behavior, activities of daily living,  
1775 continence, and degree of mobility. This method was used successfully in our observational cohort  
1776 study and our pilot dosing study.

1777 **3.7.2. Clinical outcome surveillance: primary and secondary outcomes.** Urine specimens will be  
1778 obtained at baseline (prior to randomization) and every two months thereafter via clean catch (7  
1779 specimens total). The primary outcome will be the presence or absence of bacteriuria plus pyuria at  
1780 each time point. Treatment will not be discontinued if urine culture results are positive. This is the  
1781 primary outcome of the study. All cultures will be recorded over the course of the year and tabulated at  
1782 the end of the study.

1783 **3.7.2.1. Definition of primary outcomes: bacteriuria plus pyuria and urinary tract specific**  
1784 **symptoms.** Presence of bacteriuria will be defined as both >100,000 cfu/ml and ≥100,000 cfu/ml of one  
1785 or two organisms, based on the highest quantitation of bacteriuria reported by the laboratory. Absence  
1786 of bacteriuria will be defined as a urine culture with no growth, mixed flora (three or more organisms),  
1787 or less than the highest quantitation of bacteriuria reported by the laboratory. Pyuria will be defined as  
1788 any number of white blood cells on urinalysis. Urinary tract specific symptoms (i.e., acute dysuria, new  
1789 suprapubic pain or tenderness, acute costovertebral angle pain or tenderness, gross hematuria; new or  
1790 marked increase in: incontinence, urgency, or frequency) will be assessed at the time of each urine  
1791 specimen collection. In the study by Avorn et al., the rate of urinary tract specific symptoms at monthly  
1792 intervals was 7% in the placebo group and 4% in the cranberry group.

1793 **3.7.2.2. Definition of secondary outcomes for supplementary aims.**

1794 **3.7.2.2.1. Symptomatic UTI.** Symptomatic UTI will be defined as 1) (a) acute dysuria;  
1795 OR (b) fever or leukocytosis and at least **one** of the following: acute costovertebral angle pain or

1796 tenderness; suprapubic pain; gross hematuria; new or marked increase in: incontinence, urgency, or  
1797 frequency; OR (c) two or more of new or marked increase in: incontinence, urgency, frequency,  
1798 suprapubic pain, new gross hematuria **AND 2)** a voided urine culture with (a) >100,000 cfu/ml or  $\geq 10^5$   
1799 cfu/ml of a single predominant organism or two gram negative organisms OR (b) a specimen collected  
1800 by in and out catheter specimen with  $\geq 10^2$  cfu/ml of any number of organisms.

1801 **3.7.2.2.2. Hospitalization.** All cause hospitalizations, including those related to UTI, and  
1802 visits to the emergency room will be recorded.

1803 **3.7.2.2.3. Death.** All cause death, including UTI as a reason, will be recorded.

1804 **3.7.2.2.4. Antibiotic prescriptions.** Information on all antibiotic therapy prescribed,  
1805 whether for UTI or other cause, will be recorded. If antibiotic therapy is for UTI, it will be noted in data  
1806 collection.

1807 **3.7.2.2.5. Resistant organisms.** All resistant bacterial isolates, either from the urine  
1808 specimens obtained for study purposes or as recorded from other clinical specimens in the medical  
1809 record, will be recorded. These isolates will include methicillin-resistant *Staphylococcus aureus* (MRSA),  
1810 vancomycin-resistant *Enterococci* (VRE), and multi-drug resistant gram negative rods, with multi-drug  
1811 resistance defined as resistance to at least 3 of the following antibiotics: ampicillin-sulbactam, cefazolin,  
1812 ceftriaxone, ceftazidime, fluoroquinolones, piperacillin-tazobactam, meropenem, imipenem, and  
1813 trimethoprim-sulfamethoxazole.

1814 **3.7.2.3. Surveillance of primary outcome: bacteriuria plus pyuria and urinary tract specific**  
1815 **symptoms.** Surveillance of the primary outcome will occur every two months for a total of six  
1816 assessments over the 12 months of follow up. The primary nursing home staff (i.e., nurses and CNAs)  
1817 will be responsible for collecting clean catch urine specimens every two months, targeted to be  
1818 collected from 5-7AM on the same day for a given home. Study staff will provide reminders as to when  
1819 sample collection is due. If the specimen is not collected on the due date, attempts at specimen  
1820 collection will continue for two additional weeks at any time of the day prior to noting the specimen as  
1821 missing. Urinary tract specific symptom assessment will occur on the day of urine specimen collection.  
1822 Based on our pilot data, we anticipate that 14% of specimens initially will be missing. The research  
1823 assistants, Luann Bianco or Sabina Rubeck, will collect all urine samples that are obtained and deliver to  
1824 the Yale-New Haven Hospital Hematology and Microbiology Laboratories for processing. Urinalysis  
1825 processing is automated in the Hematology Laboratory. Performing quantitative urine cultures will  
1826 require the following steps: 1) mix urine; 2) vertically insert a flamed and cooled calibrated platinum  
1827 loop that delivers 0.01 ml of urine into the specimen; 3) remove a loopful of urine; 4) inoculate one  
1828 loopful of urine onto a Sheep blood agar and MacConkey agar plate by making a straight line down the  
1829 center and then a series of close perpendicular streaks throughout the first line. Lactobacillus species,  
1830 alpha-streptococci, and diphtheroids will not have susceptibility testing performed. All other isolates  
1831 will have antibiotic susceptibility testing performed. When three or more organisms are isolated, the  
1832 urine culture will not undergo further processing and will be regarded as a mixed culture. We  
1833 successfully utilized this method of urine collection and processing in our pilot dosing study.

1834 **3.7.2.4. Outcome adjudication.** If a urine culture reports growth of one or two organisms at  
1835 least one of which is >100,000 cfu/ml or  $\geq 100,000$  cfu/ml and the urinalysis reveals any number of white  
1836 blood cells, the primary outcome will be met. The Outcome Adjudication Committee, consisting of the  
1837 P.I. (Juthani-Mehta), the Investigator (Datta), the Field Nurse Team Leader (Rink), the Project Manager  
1838 (Luann Bianco), the Data Manager (Stephanie Argraves), Research Associate (Sabina Rubeck), and the  
1839 senior infectious diseases specialist (Quagliarello), will participate in the adjudication of outcomes.

1840 **3.7.3. Surveillance of adverse events.** The Field Nurse Team Leader, Ms. Rink, along with Ms. Ginter  
1841 will monitor for any potential adverse events on a monthly basis for the duration of the 12 month  
1842 surveillance period per participant, through interviews with nursing staff and report to the Internal  
1843 Safety Committee. To ensure a rapid and systematic approach to adverse events, the Internal Safety  
1844 Committee will evaluate all suspected adverse events, however mild or severe. The Chair of the Internal  
1845 Safety Committee (Quagliarello) will determine which serious adverse events must immediately be  
1846 reported to the Yale Human Investigation Committee, Independent Safety Monitor, and the NIA. At the  
1847 request of the NIA, all deaths, unanticipated problems, and unanticipated/protocol related serious  
1848 adverse events will be reported to the NIA and Independent Safety Monitor within 48 hours of the PI  
1849 being notified.

1850 **3.7.4. Surveillance of adherence to intervention.** Adherence will be determined by the number of  
1851 capsules that were administered to each participant in relation to the targeted number. The medication  
1852 administration record will be reviewed to determine if the study capsules were documented to be  
1853 administered. However, in our pilot study, we identified discordance between the numbers of capsules  
1854 recorded to have been administered versus the numbers of capsules remaining. Therefore, surveillance  
1855 of the remaining capsules by pill counting every month will be conducted to ensure that they are being  
1856 administered. Reasons for lack of administration will be noted (e.g., refusal). Since it will not be  
1857 possible to continue capsule administration during a hospitalization, hospitalization will be noted as the  
1858 reason for lack of adherence to the missed doses. High adherence will be defined as administration of  
1859  $\geq 80\%$  of prescribed capsules and low adherence will be administration of  $< 80\%$  of prescribed capsules.

1860 **3.7.5. Sample size estimate.** Sample size was determined to detect a difference between the  
1861 proportion with bacteriuria plus pyuria over time in the placebo group versus the treatment group  
1862 receiving 2 cranberry capsules using the method of Diggle et al. for repeated binary outcomes. In the  
1863 study by Avorn et al., the sample size was based on a 40% reduction in bacteriuria plus pyuria (0.50 in  
1864 placebo to 0.30 in cranberry juice group). The following assumptions were made for this sample size  
1865 calculation: Type 1 error of 5% (2-sided), 80% power, a serial correlation of 0.35 between 6 urine  
1866 specimens, a bacteriuria plus pyuria rate of 0.45 in the control group, a 33% reduction with the  
1867 cranberry intervention (0.30 bacteriuria plus pyuria rate), and 20% inflation for deaths, transfers and  
1868 missing cultures. Based on these assumptions, the total sample size is 180 participants (90 per group).  
1869 However, if additional patients consent to the study during the recruitment period, because of more  
1870 missing culture data than expected, the new recruitment goal is up to 190 participants (95 per group) if  
1871 possible. There are no data to determine power for secondary outcomes.

1872 **3.7.6. Data management.** All Data management systems will be developed and implemented by the  
1873 Data Management and Informatics Core (DMIC) of the Program on Aging/Claude D. Pepper Older  
1874 Americans Independence Center (OAIC) at Yale. Data collection for the eligibility and enrollment  
1875 protocol, the baseline assessment and outcome assessment will be accomplished using computerized  
1876 instruments on tablet PCs, or on printed forms. Computerized instruments will be developed and  
1877 deployed using REDCap, a HIPAA-compliant, NIH-supported, web-based tool for data capture  
1878 (<http://project-redcap.org>) that at Yale is hosted by DMIC (Harris PA, Taylor R, Theilke R, Payne J,  
1879 Gonzalez N, Conde JG, Research electronic data capture (REDCap) – A metadata-driven methodology  
1880 and workflow process for providing translational research informatics support. J Biomed Inform. 2009  
1881 Apr;42(2):377-81). In addition to data collection and data entry, DMIC will provide other critical services,  
1882 such as between-form error checking and resolution; specialized database programming; conduct-of-  
1883 study reports; performance monitoring reports; randomization; and follow-up contact scheduling.

1884 **3.8. Anticipated Timeline of Clinical Trial.** Enrollment of each nursing home will occur sequentially (i.e.,  
 1885 prevalent recruitment). We anticipate that it will require 8 weeks from receiving the nursing home  
 1886 roster to enrollment of the first participant in a given nursing home. Recruitment staff will return to  
 1887 each nursing home every three months for additional recruitment (i.e., incident recruitment). We  
 1888 anticipate that prevalent recruitment will require one year and additional incident recruitments will  
 1889 require an additional year.

	YEAR 1				YEAR 2				YEAR 3				YEAR 4			
<b>1. Preparing for Trial</b>																
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														
<b>2. Enrollment of Participants</b>																
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						
<b>3. Intervention Implementation</b>																
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		
<b>4. Outcome Surveillance and Assessment</b>																
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		
<b>5. Data Management and Analysis</b>																
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				
Final Data Cleaning														x	x	
Lock Dataset and Data analysis															x	x
<b>6. Report Generation</b>															x	x

1891

1892 **4. Subject Population:**

1893 The participants will be female long-term care nursing home residents, 65 years or older. Assuming a  
 1894 Type 1 error of 5% (2-sided), 80% power, a control group prevalence rate of 45%, a relative reduction of  
 1895 33% (absolute risk difference of 15%), serial correlation among 6 repeated urine measurements on each  
 1896 participant of 0.35, and a drop-out rate of 20% (e.g., death [17%], transfer and/or inability to provide  
 1897 further urine specimens [3%]), the sample size required is 90 participants in each group (total N=180).

1898 However, if additional patients consent to the study during the recruitment period, because of more  
1899 missing culture data than expected, the new recruitment goal is up to 190 participants (95 per group) if  
1900 possible.  
1901

## 1902 **5. Inclusion/Exclusion Criteria:**

1903 **Inclusion criteria.** All races will be considered for inclusion if they: 1) are female; 2) are long-term care  
1904 residents; 3) are English speaking; and 4) are 65 years or older. Since surrogate consent is required in  
1905 most instances (95%) and since the participants often have underlying dementia, English speaking  
1906 participants are required who can be explained the protocol and express their assent to participate not  
1907 only to study staff but also to nursing home staff over the course of the study. We have utilized this  
1908 strategy in our previous intervention cohorts and in the recently completed R01 funded clinical trial to  
1909 reduce pneumonia in nursing home residents.

1910 For this proposed randomized clinical trial, we plan to identify and enroll female participants who are  
1911 residents of nursing homes within a 50 mile radius of New Haven, CT. We anticipate the characteristics  
1912 of the study population to be similar to those enrolled in our observational and pilot intervention  
1913 cohorts with a mean age of approximately 86 and 12% Hispanic or racial minorities. We are estimating a  
1914 sample size of 180 participants (90 randomized to the treatment arm, 90 randomized to the control  
1915 arm).

1916 **Exclusion criteria.** Residents will be excluded if they: 1) are not expected to be in the nursing home for  
1917 at least one month (i.e., short term rehabilitation, pending discharge, terminal life expectancy < 1  
1918 month); 2) are on chronic suppressive antibiotic or anti-infective (i.e., mandelamine) therapy for  
1919 recurrent UTI; 3) have end stage renal disease on dialysis (they do not regularly produce urine); 4) are  
1920 unable to produce a baseline clean catch urine specimen for collection; 5) are on warfarin therapy  
1921 because of a potential interaction of warfarin and cranberry juice; 6) have a history of nephrolithiasis  
1922 because cranberry may increase the risk of nephrolithiasis; 7) have an indwelling bladder catheter in  
1923 place; 8) have an allergy to cranberry products; 9) are being treated with cranberry products; 10)  
1924 residence < 4 weeks.

1925 Women represent the vast majority (75-85%) of nursing home residents and the genitourinary anatomy  
1926 of men and women differ. The risk factor for UTI in men usually relates to underlying structural or  
1927 functional abnormalities of the urinary tract, and there is no evidence to date that cranberry products  
1928 reduce UTI in men. Therefore, only female nursing home residents will be recruited to this study.  
1929 Participants will be stratified by nursing home and then randomized to receive either placebo or two  
1930 cranberry capsules per day. There will be up to 21 nursing homes within a 50 mile radius of the greater  
1931 New Haven, CT area participating in this study.

## 1932 **6. How will eligibility be determined, and by whom?**

1933 Screening at each nursing home will occur sequentially. From the date of screening to enrollment, each  
1934 home will require eight weeks. Once enrollment is initiated at one home, screening will begin at the  
1935 next home. Residents, age  $\geq 65$  years, residing in one of the participating nursing homes will be  
1936 identified from a computerized log kept by the Director of Nursing Services at the home. Subsequently,  
1937 trained field staff will perform a brief chart review to establish the presence of inclusion and exclusion  
1938 criteria. A HIPAA waiver will be obtained for recruitment purposes only.

## 1939 **7. Risks:**

1940 There are no reasonably foreseeable physical, psychological, emotional, social, economic, or legal risks  
1941 involved in the two arms of the proposed study, or in obtaining a clean catch urine sample, which will be

1942 collected by trained nursing home staff if subjects need assistance. In the United States, cranberry  
1943 capsules are considered to be a dietary supplement, not a drug or medication. As such, their usage is  
1944 not regulated by the Food and Drug administration (FDA). In previous studies by our group and others,  
1945 very few incidences of side effects have been noted after cranberry capsule administration. In a study of  
1946 57 participants taking a different cranberry capsule from the one used in this study, only six subjects  
1947 noted symptoms after cranberry capsule administration (vomiting, nausea, and/or diarrhea), but it was  
1948 unclear whether these symptoms were actually a side effect from the cranberry capsules. These  
1949 possible protocol-related side effects will be monitored by research staff.

#### 1950 **8. Minimizing Risks:**

1951 If a subject is unable to swallow the capsules, her nurse will be able to open the capsule and mix its  
1952 contents into food (e.g., applesauce or yogurt). Subjects with feeding tubes will not be excluded from  
1953 the study. If a subject has a feeding tube, the cranberry powder can be administered through the tube.

1954 See attached article Brazier AM, et al. "Collecting Clean-Catch Urine in the Nursing Home: Obtaining  
1955 the Uncontaminated Specimen". *Geriatric Nursing*. September/October 1995; 16(5): 217-224 for a  
1956 description of the training education that the nursing home staff will receive from the nurse researcher  
1957 in order to obtain the clean catch urine specimens.

#### 1958 **9. Data and Safety Monitoring Plan:**

1959 The principal investigator is responsible for monitoring the data, assuring protocol compliance, and  
1960 conducting the safety reviews on a monthly basis. During the review process the principal investigator  
1961 will evaluate whether the study should continue unchanged, require modification/amendment,  
1962 continue or close to enrollment.

1963 Either the principal investigator or the Human Investigation Committee (HIC) have the authority to stop  
1964 or suspend the study or require modifications.

1965 This protocol presents minimal risks to the subjects and adverse events or other problems are not  
1966 anticipated. Adverse events will be recorded by the nursing home staff into the subject's medical record  
1967 and study staff will perform chart review to retrieve this data. In the unlikely event that such events  
1968 occur, serious and unanticipated and related adverse events or unanticipated problems involving risks to  
1969 subjects or others will be reported in writing within 48 hours to the HIC (using the appropriate HIC forms  
1970 from the website) and any appropriate funding and regulatory agencies. The investigator will apprise  
1971 fellow investigators and study personnel of all adverse events that occur during the conduct of this  
1972 research project through regular study meetings, via email as they are reviewed by the principal  
1973 investigator. The PI will report all deaths that occur to the NIA Program Officer (Barbara Radziszewska,  
1974 PhD) within 48 hours of PI notification.

1975 As required by the funding agency (NIA), an Independent Safety Monitor (ISM) has been appointed. The  
1976 ISM will have a critical function in ensuring that participants receive good clinical care and that safety  
1977 concerns are quickly identified. The ISM may suggest measures to prevent the occurrence of particular  
1978 adverse events (e.g., protocol modification). To prevent bias, the ISM will evaluate serious and non-  
1979 serious adverse events blinded to treatment assignment. The ISM will review semi-annual reports  
1980 concerning serious adverse events (not segregated and segregated by treatment group). In the event of  
1981 any unanticipated and treatment related serious adverse events or anticipated non-serious and/or  
1982 serious adverse events twice as frequent in one treatment group versus the other, the ISM will promptly  
1983 contact the PI and possibly the IRB representative and the NIA Program Officer, Dr. Barbara  
1984 Radziszewska. A difference in adverse events of this magnitude may lead to a decision to unblind the  
1985 ISM, Program Officer and a clinical investigator and biostatistician participating in this study to

1986 determine if the difference may be related to the cranberry capsule treatment. The need for changes to  
1987 the protocol will be determined at that time by the Principal Investigator.

1988 While adverse effects secondary to cranberry capsule administration are expected to be minimal based  
1989 on evidence from previous studies, all adverse effects secondary to cranberry capsule administration  
1990 will be prospectively recorded. A secondary outcome variable will be coded with a 1 for the occurrence  
1991 of any adverse event and a 0 for the occurrence of none. Rates of adverse events will be described and  
1992 calculated for each arm of the study.

## 1993 **10. Statistical Considerations:**

### 1994 **10.1 Data analysis plan.**

1995 **10.1.1. Interim monitoring.** Interim monitoring will focus on participant accrual (overall  
1996 and by nursing home), baseline comparability of treatment groups, protocol adherence, completeness  
1997 of data retrieval, data quality, and safety. A set of interim data monitoring tables will be developed for  
1998 presentation to the Independent Safety Monitor and NIA Program Officer on a semi-annual basis. We  
1999 will carefully monitor participant accrual and adherence to ensure that the study is on target to achieve  
2000 the required level of statistical power. We originally proposed one interim look for efficacy at the mid-  
2001 point of the study using a Haybittle-Peto boundary with p-value of 0.001. This would have had a  
2002 negligible effect on the overall type I error at the end of the trial. Thus, the sample size was not inflated  
2003 to account for the interim look. Futility was planned to be assessed by calculating conditional power  
2004 (under both the observed and hypothesized trend) and the feasibility of achieving the target sample  
2005 size. Prior to study initiation, the NIA proposed that a DSMB was not necessary; rather, a DSMP with an  
2006 Independent Safety Monitor was required. Therefore, it was decided that one interim look for efficacy  
2007 and futility would not be performed, and this plan was approved by the NIA.

2008 **10.1.2. Final analyses: primary outcome.** Final analyses will address comparability of  
2009 treatment groups, efficacy and safety. All analyses will be conducted as randomized, i.e., participants  
2010 will be analyzed according to their original treatment assignment regardless of adherence. A  
2011 significance level of 0.05 (2-sided) will be used for statistical significance. SAS<sup>®</sup> 9.4 statistical software  
2012 will be used for the analyses.

2013 **10.1.2.1. Baseline comparability of treatment groups.** The adequacy of the  
2014 randomization will be assessed by comparing the distribution of baseline demographic and  
2015 clinical characteristics between the treatment groups. Comparability for continuous variables  
2016 will be examined graphically and by summary statistics (means, medians, quartiles, etc.).  
2017 Categorical variables will be examined by calculating frequency distributions. Adjustment for  
2018 significant treatment imbalances in baseline covariates will not be done because this approach  
2019 can be biased. Instead the following pre-specified covariates will be adjusted for: baseline  
2020 bacteriuria, age, and number of comorbid conditions.

2021 **10.1.2.2. Treatment efficacy for the primary outcome.** The primary study outcome is  
2022 bacteriuria plus pyuria. The difference in the proportion with bacteriuria plus pyuria between the two  
2023 treatment groups will be estimated using a multivariable logistic regression model that accounts for the  
2024 serial correlation of repeated measurements, adjusted for the pre-specified covariates (baseline  
2025 bacteriuria status, age, incontinence, and number of comorbid conditions). Prior to regression  
2026 modeling, the potential impact of missing data and deaths on the study outcome will be investigated. If  
2027 it is reasonable to assume that missing values are missing at random (MAR), generalized linear mixed  
2028 effects modeling will be used. Facility heterogeneity will be accessed by introducing a random effect for  
2029 nursing home in the regression model to account for the variability among homes. Variables that are

2030 predictive of missing values will be included in the model. If required by considerations of poor model  
2031 fit or convergence problems, we will explore other methods for handling MAR data, and we will consider  
2032 joint modeling of the longitudinal and survival outcomes. Model fit will be assessed by residual analyses,  
2033 influence diagnostics, and goodness-of-fit tests. The treatment effect will be estimated as an odds ratio  
2034 (treatment vs. control) with corresponding 95% confidence intervals. In exploratory analyses the impact  
2035 of non-adherence on treatment effect will be investigated by methods described by Little, et al.

2036 **10.1.2.3. Analysis of safety.** The incidence of adverse events will be tabulated and  
2037 compared between treatment groups using statistics appropriate for categorical or count data, such as  
2038 the chi-square or Wilcoxon statistics. We will also examine the timing of the adverse events by  
2039 calculating cumulative incidence curves.

2040 **10.1.3. Final analyses: secondary outcomes.** The analysis of secondary outcomes will be  
2041 similar to that described for bacteriuria plus pyuria. Cumulative death rates will be estimated by the  
2042 method of Kaplan-Meier and compared between treatment groups using the log-rank statistic.  
2043 Frequency of symptomatic UTI, hospitalizations, antibiotic prescriptions, and multi-drug antibiotic  
2044 resistant organisms will be tabulated and compared between the treatment and control groups using  
2045 the Wilcoxon statistic.

2046

## 2047 **A. DRUGS, BIOLOGICS and RADIOTRACERS**

### 2048 **1. Identification of Drug, Device or Biologic:**

2049 Cranberry capsules contain a highly concentrated food extract of North American cranberries  
2050 (*Vaccinium macrocarpon*). North American cranberries are one of the richest natural sources of A-type  
2051 proanthocyanidins which have been shown to be effective in inhibiting certain uropathogenic strains of  
2052 *E. coli* from adhering to the lining of the urinary tract. As a dietary supplement, cranberry capsules are  
2053 not regulated by the FDA.

### 2054 **2. Background Information:**

2055 Concentrated forms of cranberry extract, such as those found in cranberry capsules, have been shown in  
2056 various studies to be safe and well-tolerated. The only possible contraindications include warfarin  
2057 anticoagulant therapy or persons with a history of nephrolithiasis. Individuals with either of these  
2058 conditions will be excluded from participation in this study.

### 2059 **3. Source:**

2060 Study cranberry capsules are produced in bulk by an independent manufacturer. The packaging of  
2061 capsules will be done by YNHH Investigational Drug Services based on the preferences of each nursing  
2062 home.

### 2063 **4. Storage, Preparation and Use:**

2064 Cranberry capsules contain 36mg of proanthocyanidins per capsule. They are stable at room  
2065 temperature and will be administered as part of enrolled patients' regular daily pill pack at the nursing  
2066 homes. The two capsules will be targeted to be administered at 5:00 pm every day.

### 2067 **5. Use of Placebo:**

2068 As previously stated in the background information, there is no currently accepted prophylactic therapy  
2069 for asymptomatic bacteriuria. Additionally, none of the trials of antibiotic treatment of asymptomatic

2070 bacteriuria showed any decrease in mortality. Use of placebo in this study will simply assist us in  
2071 determining the baseline rate of bacteriuria in the nursing home populations under study.

2072 The maximum possible duration that a participant may receive placebo is 12 months (30-day blister pack  
2073 per month equaling 360 days).

2074 In this study, placebo represents the current state of affairs for prophylactic management of bacteriuria.  
2075 There is no potential harm in receiving placebo in this study. Participation in the study will end after 12  
2076 months. Management of the bacteriuria at this point will then be the responsibility of the patient's  
2077 primary care provider.

2078 As stated in point c above, there is no potential harm in receiving placebo in this study, and as such, no  
2079 safeguard procedures are required.

2080 **6. Targeted Enrollment: Give the number of subjects:**

2081  
2082 Targeted for enrollment at Yale for this protocol 180.  
2083

2084 **7. Recruitment Procedures:**

2085  
2086 Participants will be recruited from the nursing units at the 21 New Haven area nursing homes listed in  
2087 the protocol. Residents, age  $\geq 65$  years, residing in one of the participating nursing homes will be  
2088 identified from a computerized log kept by the Director of Nursing Services at the home. Subsequently,  
2089 study personnel will perform a brief chart review to establish the presence of inclusion and exclusion  
2090 criteria.

2091 After potential subjects have been identified through chart review covered by a HIPAA waiver, subjects,  
2092 or their legally authorized surrogate, will be approached by the research team to obtain written consent.  
2093 Individuals will be given sufficient time to read through the consent form, or if this presents difficulty,  
2094 the form will be read to them by a member of the research team. Surrogates will receive a follow up  
2095 phone call after receiving a Proxy Authorization letter (see revised letter attached), consent form, and  
2096 Authorization to Release Protected Health Information for Research form (see attached). A member of  
2097 the research team will answer any questions that the potential subject or surrogate may have.  
2098 Permission will be obtained from the potential participant's home administrator before they are  
2099 approached for study recruitment. Informed consent will be obtained by trained study personnel. All  
2100 potential participants will receive a general description of the study, including the baseline and  
2101 surveillance evaluations with a general description of risks and benefits. Participants will receive a full  
2102 detailed description of the intervention strategy, including potential risks and benefits. In addition,  
2103 participants will be asked to sign a HIPAA authorization form that explains the protected health  
2104 information that will be used, disclosed, and to whom it will be disclosed as part of this study. Potential  
2105 participants or surrogates will sign the consent form and HIPAA authorization forms prior to the baseline  
2106 assessment. If surrogate consent is obtained, assent from the participant will still be sought for  
2107 participation in the study. The principal investigator will be available to answer any questions.

2108 Experienced research assistants (i.e., Luann Bianco and Sabina Rubeck) and nurse researchers (i.e.,  
2109 Andrea Rink, Sandra Ginter) at the Yale Program on Aging.

2110

2111

2112 8. **Consent Personnel:**  
2113 Informed consent will be obtained by trained study personnel including an experienced research  
2114 assistant (i.e., Luann Bianco and Sabina Rubeck) and nurse researchers (i.e., Andrea Rink and Sandra  
2115 Ginter) at the Yale Program on Aging.

2116 9. **Process of Consent/Assent:**  
2117 After potential subjects have been identified through chart review covered by a HIPAA waiver, subjects  
2118 will be approached by the research team to obtain written consent or surrogates will be mailed an  
2119 introductory letter, compound authorization form, Authorization to Release Protected Health  
2120 Information for Research, and FAQ pamphlet. Individuals will be given sufficient time to read through  
2121 the consent form, or if this presents difficulty, the form will be read to them by a member of the  
2122 research team. All potential participants will receive a general description of the study, including the  
2123 baseline and surveillance evaluations with a general description of risks and benefits. Participants will  
2124 receive a full detailed description of the intervention strategy, including potential risks and benefits. In  
2125 addition, participants will be asked to sign a HIPAA authorization form that explains the protected health  
2126 information that will be used, disclosed, and to whom it will be disclosed as part of this study. Potential  
2127 participants or surrogates will sign the consent form and HIPAA authorization forms prior to the baseline  
2128 assessment. If surrogate consent is obtained, assent of the participant will still be sought. The principal  
2129 investigator will be available to answer any questions. The phone number of the principal investigator  
2130 will be provided to each participant to contact for any questions or problems.

2131 10. **Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent:**  
2132 It is recognized that: 1) there may be a significant proportion of eligible residents who are decisionally  
2133 impaired (i.e., who have a compromised capacity to understand information and make a reasoned  
2134 decision about participation in research), and who require additional protections; and 2) the purpose of  
2135 identifying eligible residents who may be decisionally impaired is not necessarily to exclude them from  
2136 research, but to seek ways to enable their participation in an ethically appropriate manner that is also  
2137 compliant with regulatory requirements. Therefore, at the time of approaching any potential  
2138 participant for consent, our plans are as follows:

2139 • **study personnel obtaining consent will use professional judgment to determine if the**  
2140 **potential participant is capable of providing consent.** Members of the Field Staff who are responsible  
2141 for participant recruitment and consent are all highly trained and experienced personnel in determining  
2142 capacity to consent in aging populations. This determination will rely on individual observation of, and  
2143 interaction with, the potential participant as well as the opinion of the caregiver, when available. In  
2144 general, the assessment of the potential participant's capacity to consent will be based on her/his: 1)  
2145 ability to communicate a choice; 2) ability to understand relevant information; 3) ability to appreciate  
2146 the nature of the situation and its likely consequences; and 4) ability to manipulate information  
2147 rationally.

2148 • **determination of decisional impairment for providing consent.** Potential participants will  
2149 be considered decisionally impaired for providing consent if they have: 1) an inability to express or  
2150 communicate a preference or choice; 2) an inability to understand a situation and its potential  
2151 consequences as well as the impact of study participation on those circumstances (e.g., do not  
2152 understand that they may be hurt or may not be helped or cannot distinguish research from treatment);  
2153 3) an inability to provide a logical rationale for participation/no participation in the study (i.e., cannot  
2154 address risk/benefit); or 4) have been legally determined to be incompetent and/or have a conservator  
2155 of person. If there is any uncertainty, we will pursue surrogate consent.

2156 • **plans for surrogate consent when decisional impairment is identified.** For potential  
2157 participants who are deemed to be decisionally impaired, their identified surrogate will be approached  
2158 for consent because: 1) the risks of this study are limited and are justified given the potential benefits of  
2159 the research to the subject and the development of generalizable knowledge that will benefit elderly  
2160 nursing home residents nationwide; 2) the intervention is commensurate with clinical treatments  
2161 already available in clinical practice (multiple over-the-counter cranberry capsules and tablets) and 3) an  
2162 Independent Safety Monitor and NIA Program Officer will monitor the study. All potential participants  
2163 deemed decisionally impaired will be notified of that determination before permission is sought from  
2164 their legally authorized surrogate to enroll in the study. If permission is given to enroll in the study, the  
2165 potential participant will then be notified and their verbal assent will be sought (i.e., their active  
2166 affirmation of a desire to participate).

2167 • **plans for assent for decisionally impaired potential participants.** In all cases in which  
2168 assent is sought, the assent discussion will include the following: 1) a simplified description of the  
2169 purpose of the research, including risks and benefits; 2) a description of the procedures and  
2170 interventions to which the participant will be exposed; 3) a statement explaining that participation in  
2171 this study is voluntary only; 3) an explanation of the procedures that may hurt and for how long; 4) a  
2172 question and answer period in which the participant will be encouraged to ask questions about their  
2173 participation in the study.

2174 11. **Documentation of Consent/Assent:** Specify the documents that will be used during the  
2175 consent/assent process. Copies of all documents should be appended to the protocol, in the same  
2176 format that they will be given to subjects.

2177 1) Compound Authorization and Consent [Adult Form]

2178 2) Compound Authorization and Consent [Legally Authorized Representative/Surrogate Form]

2179 3) Authorization to Release Protected Health Information for Research

2180 12. **Non-English Speaking Subjects:**

2181 Since surrogate consent is required in most instances (95%) and since the participants often have  
2182 underlying dementia, English speaking participants are required who can be explained the protocol and  
2183 express their assent to participate not only to study staff but also to nursing home staff over the course  
2184 of the study.

2185

2186 **Confidentiality & Security of Data:**

2187 Name, address of nursing home residence, birth date, dates and details of previous episodes of  
2188 bacteriuria and/or UTI, and dates and details of prior antibiotic administration will be recorded.  
2189 Additionally, data on comorbidities, other medications, continence, and functional status will also be  
2190 recorded. The sources of research data on enrolled participants will be interviews with the nursing staff  
2191 and administrators at the institution and the participants' medical records. Baseline descriptive data  
2192 (e.g., facility, age, race, ethnicity, gender, comorbid disease, cognitive status, activities of daily living,  
2193 degree of mobility, medications, continence, history of UTI) will be recorded. These data will be  
2194 ascertained from the Minimum Data Set, the medical record, and interview with the primary care  
2195 provider (e.g., the Certified Nursing Assistant). The hierarchy of data sources will be based on the least  
2196 burdensome source of data. Data regarding clinical outcomes (i.e., bacteriuria, pyuria, urinary tract  
2197 specific symptoms, UTI, hospitalization, death, antibiotic prescriptions, resistant organisms), staff  
2198 adherence to the intervention, and adverse events will be collected by research study personnel. To

2199 safeguard confidentiality, the data linking study ID codes and patient names are strictly confined to an  
2200 electronic data capture system (REDCap) that is accessible only to selected study staff, and which has  
2201 been approved as HIPAA-secure by the Yale Information Security Office (ISO).

2202 Research data will be stored and managed in a database format (REDCap) and stored on the secure Yale-  
2203 ITS network which is backed-up nightly. Each subject will be identified by a study number. All data  
2204 recorded on the data extraction sheet will be identified only by the study number and will be kept in a  
2205 locked filing cabinet.

2206 All data will be password protected and access limited to those individuals with direct responsibility for  
2207 the research project. Study data will reside on database and file sharing resources managed by Yale ITS,  
2208 and will not be permitted on movable electronic media.

2209 To safeguard confidentiality of protected health information, each study participant enrolled will be  
2210 assigned a unique code number and the participant's name will never be attached to any paper form.  
2211 Linkage between study ID code and patient name will be limited to a highly secure electronic database,  
2212 and will be used confidentially only by research staff. The study investigators will assume full  
2213 responsibility to maintain confidentiality. All study results will be presented only as statistical  
2214 aggregates that will neither identify, nor permit identification, of individual research participants. This  
2215 has been an effective method in our previous studies.

2216 The data systems and procedures at the Data Management and Informatics Core (DMIC) of the Program  
2217 on Aging/Claude D. Pepper Older Americans Independence Center (OAIC) at Yale conform to Yale's  
2218 HIPAA security policy  
2219 (<http://www.yale.edu/ppdev/Procedures/its/1610/1610PR.01SystemsNetwrokSecurity.pdf>), and all  
2220 equipment is certified by the Yale Information Security Officer. Desktop and portable PCs used by study  
2221 staff will be configured with mandatory security safeguards that are enforced by Yale Information  
2222 Technology Services, including "strong" passwords, password-protected standby mode, and whole-disk  
2223 encryption. Encrypted and password-protected tablet computers (iPads) will be used for data collection  
2224 but no data will be stored on them. All data will reside in a central REDCap database, and the tablets will  
2225 access these data through a web browser. REDCap is designed to forbid local storage of cached data.  
2226 Files prepared for analysis will be in SAS format, and will not include personal identifiers.

2227 All data will be password protected and access limited to those individuals with direct responsibility for  
2228 the research project. Moveable electronic media used to collect or store the data is equipped with  
2229 encryption software recommended by the University (**Bitlocker**). The PI and other members of the  
2230 research team work with coded or de-identified data when using moveable device(s) to perform data  
2231 analysis.

2232 When the research is completed, identifiable data will be destroyed three years after the completion of  
2233 the study. Paper forms will be shredded and the study computer will be zeroed. The anonymous data  
2234 will be retained indefinitely.

2235 The principal investigator, research staff, sponsor and Yale Human Investigation Committee will have  
2236 access to the protected health information.

2237 It is possible that reporting of communicable diseases and elderly abuse will be necessary in this study.  
2238 The nursing home administrator for the home that the participant resides in will be notified if such a  
2239 circumstance arises.

2240

2241 **Potential Benefits:**

2242 The potential benefits for the interventions are significant because we hypothesize that cranberry  
2243 capsules will reduce the incidence of bacteriuria plus pyuria and morbidity associated with UTI in female  
2244 nursing home residents. Administration of cranberry capsules has been documented in our pilot  
2245 feasibility and dosing studies to be feasible and adhered to by staff, and it is designed to be  
2246 generalizable and easily incorporated into the usual nursing care of nursing home residents. Although  
2247 implementing the use of cranberry capsules would result in greater initial costs, there is the potential for  
2248 healthcare savings from decreased antibiotic use, hospitalization, and emergence of resistant organisms.  
2249 In summary, the anticipated benefits of the intervention to the participants and society far outweigh the  
2250 minimal risks. Therefore, the risk-benefit ratio appears to be favorable for proceeding with this clinical  
2251 trial.

2252 The importance of the knowledge gained in this proposed trial is great, including the following: 1) the  
2253 identification of a feasible and safe intervention that is effective in reducing bacteriuria in elderly  
2254 nursing home residents and can be generalized to female nursing home populations nationwide; 2) the  
2255 determination of whether routine use of cranberry capsules, which are not regulated by the Food and  
2256 Drug Administration (FDA), should be implemented in the nursing home setting; and 3) the potential for  
2257 a major reduction in morbidity, mortality, hospitalizations, and healthcare expenditures related to UTI  
2258 among elderly nursing home residents.

2259 **Alternatives:**

2260 As described previously in this application, there are currently no other standardized accepted  
2261 alternatives for prophylactic treatment of asymptomatic bacteriuria in the nursing home population

2262 **Payments for Participation (Economic Considerations):**

2263 Participants will not be paid for participation in this study. However, since clean catch urine specimens  
2264 are difficult to collect in this disabled nursing home population, nursing homes will be provided an  
2265 incentive that is approved of by each nursing home administration. Urine samples will be collected by  
2266 the nursing home staff nurses and/or aides. Since the collection of these urine specimens is  
2267 cumbersome, only for study purposes, and essential to the successful completion of this project,  
2268 individualized incentive programs for each participating nursing home will be designed. Incentive  
2269 programs will be constructed with the input from the Administrator and Director of Nurses at each  
2270 nursing home. Incentives may be distributed to a given floor or team. Planned incentives will include 1)  
2271 an annual Certificate of Research Participation for all participating nursing home facilities which  
2272 documents active participation in this Yale University research study for purposes of annual surveys  
2273 conducted by regulatory bodies; 2) continuing education "in-service" hours that are required by the  
2274 state of Connecticut for all CNAs; 3) gift certificates to participating nursing home staff. The amount of  
2275 gift certificates will depend on how often they are given.

2276 **Costs for Participation (Economic Considerations):**

2277 There are no costs to the subjects associated with participation in this research project. Both the  
2278 cranberry and placebo capsules will be provided at no cost to the subjects. Additionally, the clean catch  
2279 urine sample, urinalysis, and culture will be performed at no cost to the subjects.

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