Nutrition and Prostate Cancer

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Amendment History

Version	Date
v.1.0	29 March 2018
v.2.0	26 September 2018
v.3.0	18 September 2018

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (45 CFR 46), the Yale University Human Research Protection Program (HRPP) and the Yale Institutional Review Board. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and FDA GCP Training.

The protocol, informed consent form, recruitment materials, and all participant materials have been submitted to the IRB for review and approval. Approval of both the protocol and the consent form will be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: ***Nutrition and Prostate Cancer: Assessing the Clinical Response of Prostate Cancer to Fermented Soy***

Study Description: This is a parallel group, double blind, randomized, controlled trial to assess the efficacy of a fermented soy product (Q-CAN® Plus or "QC") vs. placebo, in 72 adults with localized prostate cancer prior to prostatectomy. We propose a line of inquiry to assess the effects of QC in humans, assessing immunological and clinical parameters.

Objectives: ***Primary Objective:*** To assess the efficacy of QC vs. placebo in 72 adults with localized prostate cancer prior to radical prostatectomy.

Secondary Objectives: To assess the efficacy of QC on disease progression, prostate cancer biomarkers, and quality of life.

Endpoints: *Primary Endpoint:* Serum PSA (prostate specific antigen)

Secondary Endpoints:

1. Volume of prostate gland
2. Volume of biopsy-proven, index prostate cancer (PCa) lesion
3. Gleason score compared to preoperative biopsies
4. PCa tissue telomeric DNA length
5. Cancer of the Prostate Risk Assessment (CAPRA-S) post-surgical score

6. Cell cycle progression score assessment of PCa mRNA
7. Specific marker changes on PCa tissue microarrays using automated quantitative analysis (AQUA)
8. Functional Assessment of Cancer Therapy – Prostate (FACT-P 4©)

Study Population: The study population (N=72) will consist of men with histologically verified prostate cancer (at any stage) aged 18 years and older, scheduled for radical prostatectomy within 4-10 weeks at Yale New Haven Hospital in New Haven, CT, or Lawrence+Memorial Hospital in New London, CT, or South County Hospital in Wakefield, RI.

Phase: Phase 3 trial

Description of Sites/Facilities Enrolling Participants: This is a multi-site study being conducted at Yale University School of Medicine, New Haven, CT, Lawrence+Memorial Hospital in New London, CT, and South County Hospital in Wakefield, RI, USA. The Yale New Haven Health System (YNHHS) is a non-profit healthcare system with corporate headquarters in New Haven, CT. Yale New Haven Health operates five delivery networks, one of which is Lawrence+Memorial Hospital (LMH). South County Hospital (SCH) is an independent, non-profit acute care hospital serving southern Rhode Island. All study urologists/Co-Investigators have appointments in Yale University School of Medicine.

Description of Study Intervention: We will assess the efficacy of a fermented soy extract in a placebo-controlled study of 72 adult males with localized prostate cancer. Over the course of 4-10 weeks (between baseline and prostatectomy), subjects will consume two 12.5-gram packets of soy or matched dose placebo per day.

Study Duration: 36 months

Participant Duration: The time it will take for each individual participant to complete all participant visits will vary (4-10 weeks), depending on the surgery date of each individual's prostatectomy.

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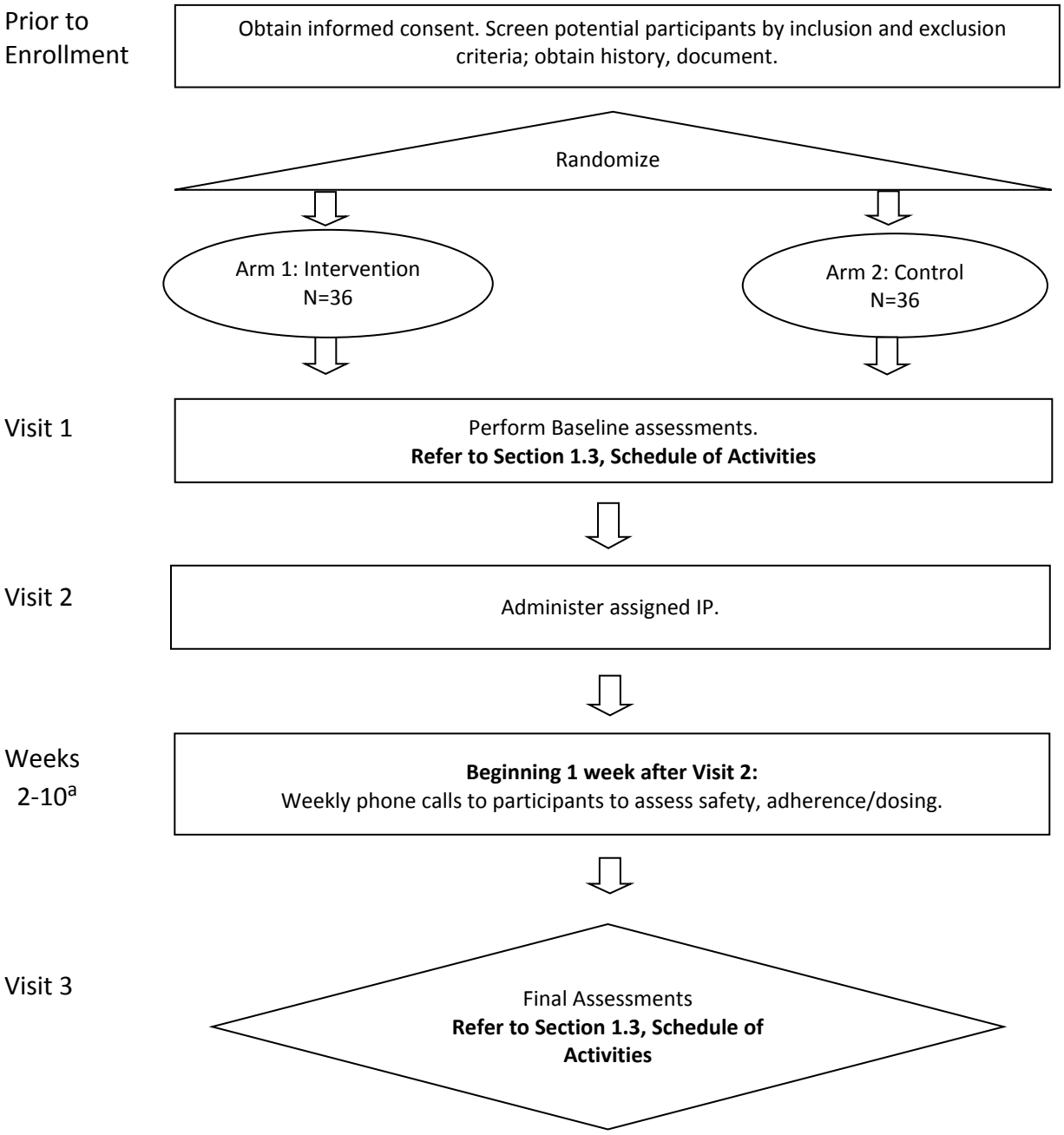
1.2 SCHEMA

Flow diagram of Study Schema



[a] Duration in the study varies (between 4-10 weeks), and is dependent upon each subject's date for surgery.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	**Screening/Baseline** Day -7 to -1	**Study Visit 1** Day 1 +/-3 days	Phone Assessment 1 Day 7 +/- 1 day	Phone Assessment 2 Day 14 +/-1 day	Phone Assessment 3 Day 21 +/-1 day	Phone Assessment 4 Day 28 +/-1 day	Phone Assessment 5 Day 35 +/-1 day	Phone Assessment 6 Day 42 +/-1 day	Phone Assessment 7 Day 49 +/-1 day	Phone Assessment 8 Day 56 +/-1 day	Phone Assessment 9 Day 63 +/- 1 day	Phone Assessment 10 Day 70 +/-1 day	**Final Study Visit 2** Day 77 +/- 1 day
Informed consent	X												
Demographics	X												
Medical history	X												
Anthropometrics (height, weight)	X												
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X
Soy consumption inventory	X												
FACT-P QoL questionnaire	X												X
Serology †	X												X
Randomization/Enrollment	X												
IP dispensed		X											X
IP consumed ††		X	X	X	X	X	X	X	X	X	X	X	X
Weekly telephone calls †† assessing adherence/IP accountability, safety			X	X	X	X	X	X	X	X	X	X	X
Adverse event review and evaluation			X	X	X	X	X	X	X	X	X	X	X
Other laboratory assessments ††† (Telomere assay, CCP, AQUA)													

† Amylase, CBC with diff, CMP, CRP, estrogen, ESR, IGF-1, IGFBP-1, IGFBP-2, IGFBP-3, lipase, lipid panel, PHI (prostate health index - includes PSA), testosterone (total, bioavailable and free), and TSH.

†† Duration in the study varies (between 4-10 weeks), and is dependent upon each subject's date for surgery.

††† Biopsied prostate tissue (pre-enrollment) and the excised prostate are biobanked by pathology outside the clinical trial's schedule of activities, regardless of participation. At Screening/Baseline, participants are consented for analysis of their frozen prostate tissue (to conduct the telomere assay, CCP, and AQUA laboratory assessments) after the study has concluded enrollment.

2 INTRODUCTION

2.1 STUDY RATIONALE

Prostate cancer is the most commonly diagnosed non-cutaneous cancer in men in the Western world. Prostate cancer is often localized and grows slowly, so men may live for many years with the disease. However, some forms of prostate cancer may behave more aggressively and is an important cause of morbidity and mortality. Given the protracted, yet potentially fatal, natural history of the disease, there is growing interest in low-toxicity interventions in the tertiary prevention of morbidity and mortality due to prostate cancer.[1]

2.2 BACKGROUND

Soy Isoflavones and Prostate Cancer

Genistin is an isoflavone found in a number of dietary plants such as soy. Genistin is also converted to a more familiar *genistein*, thus, the biological activities including anti-atherosclerotic, estrogenic and anticancer effects are analogous.

Genistin, genistein and other isoflavones have been identified as angiogenesis inhibitors, and found to inhibit the uncontrolled cell growth of cancer, most likely by inhibiting the activity of substances in the body that regulate cell division and cell survival (growth factors). Various studies have found that moderate doses of genistein have inhibitory effects on cancers of the prostate, cervix, brain, breast, and colon.[2,3]

Studies on rodents have found genistein to be useful in the treatment of leukemia, and that it can be used in combination with certain other anti-leukemic drugs to improve their efficacy.[4]

A recent systematic review assessed the role of genistein in prostate cancer, where the effect of genistein supplementation was investigated in two studies. In men randomized to 30 mg genistein daily for three to six weeks prior to prostatectomy, differences in favor of the experimental, versus control, group were reported for percentage change in PSA ($p = 0.051$), cellular response ($p = 0.033$), and cell proliferation ($p < 0.001$). However, the trial was assessed as having high or unclear risk of bias on four of the seven criteria, and it was assessed to have low risk of bias for sequence generation and blinding of participants, as well as selective outcome reporting.[5] Comparably, in a trial with relatively low risk of bias, in men undergoing watchful waiting, randomization to 60 mg genistein daily versus an isocaloric placebo for 12 weeks had no impact on mean change in PSA.[1]

Q-CAN® Plus and Fermented Soy

There is an emerging literature demonstrating bioactive effects of ZhenHua 851 (Q-CAN® Plus or "QC"), a fermented soy food in humans. Uncontrolled studies and case reports support benefits in cancer progression and changes in activation markers in humans' immune cells including changes in expression of CD3, CD4, and CD8 markers, as well increased NK cell activity. These are generic changes in immune activation and are associated with increased anti-cancer activity. Case reports associate consumption of QC with reduced prostate specific antigen (PSA) velocity in men with prostate cancer. Fermented soy products are reported to have increased isoflavone concentration[6] compared to standard soy foods, and may contain a rich mixture of probiotic species.

Yang et al. reported that 13-methyltetradecanoic acid (13-MTD), a possible active ingredient in QC, inhibited growth of various cancer cell lines through the induction of apoptosis without adverse effects.[7] Furthermore, Lin et al. found induction of mitochondrial-mediated apoptosis through regulation of the AKT and MAPK pathways.[8] Most recently, Cai et al. reported that 13-MTD inhibits proliferation and induces apoptosis through the down-regulation of AKT phosphorylation followed by caspase activation.[9]

Identifying the anti-cancer profile of QC in human cancer cell lines

13-MTD has been demonstrated to induce apoptosis of a range of human cancer cell lines (HT-29-colon, MCF7-breast [estrogen sensitive], MDA-MB-231-breast [estrogen insensitive], LNCaP-prostate [androgen sensitive], DU 145-prostate [androgen insensitive], NCI-SNU-1-stomach, SNU-423-liver, NCI-H1688-lung, BxPC3-pancreas) in a concentration range of 10-25µg/ml.[7] The reductionist approach of testing a single metabolite in QC is helpful as it can provide mechanistic insight into the biological actions. It also has disadvantages, and primary among these is that beneficial effects of QC may be due to the combinations of effects of the QC metabolites, and such effects will be missed when only single metabolites such as 13-MTD are investigated.

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Preliminary Studies Conducted at the Yale School of Medicine

We have recently produced data showing that 13-MTD can reduce IL-6 production from activated macrophages. As IL-6 contributes to the development of cachexia, this may result in a beneficial clinical response in addition to any direct anti-tumor effects.

Our team recently completed a comprehensive independent analysis of QC.[10] In order to validate the Certificate of Analysis, the soy test agent (QC) underwent quarantine and independent third party laboratory analysis (product characterization) for: total soy isoflavones and essential fatty acids, aflatoxins, authenticity (GMO status), microbial contamination, heavy metals, residual solvents and herbicides, pesticides and fungicides. Selected, individual methods are referenced in the results section under their corresponding tables. Q-CAN® Plus contained 290.12 mg of total soy isoflavones and 5.48 g of total fatty acids per 240 ml. Qualitative PCR assays for CaMV 35s promoter and MON89788 RR2 soybean were negative, indicating that no soy genetically modified organisms were present. Aflatoxins were not detected. *Enterobacteriaceae*, *E. coli*, *Salmonella* (spp), *S. aureus*, *Pseudomonas aeruginosa*, mold and yeast were absent, demonstrating a sterile product. A profile of 300 herbicides, pesticides and fungicides was negative and none of the 52 chemical residual solvents tested above the limit of quantification. Lead, mercury, arsenic, and cadmium were all below the detectable limit (5-10 ppb). Among the isoflavones isolated in significant quantities were genistein and genestin. In this independent evaluation, the manufacturer's Certificate of Analysis was validated.

We are currently assessing data from the consumption of QC in 10 lean and 10 obese, otherwise healthy adults (Yale HIC/IRB #1507016139). During the 14-week study, participants consumed 16oz of QC daily for 4 weeks (week 3 through week 7). The oral and fecal microbiome of each participant was assayed starting at baseline, from saliva and stool samples. Samples were collected once a week, for the first 7 weeks of the study, then every other week for the remainder of the study. This sampling regimen is intended to reveal any changes in the microbiome due to consumption of QC and the persistence of any changes for 7 weeks after cessation of QC. Blood was also collected at 8 time points throughout the study to assay activation of the inflammasome machinery in peripheral blood cells. Results from these microbiome and blood assays are being compared between the lean and obese groups. Other measures of the study included BMI and a 24-hour dietary recall. The study closed to enrollment when targeted accrual was met in August 2017. We are performing ongoing correlative laboratory testing of specimens obtained in blood and stool.

Based on participant reports in the preliminary study, QC was both palatable and tolerable (only one participant withdrew), with no adverse effects besides some reports of mild gastrointestinal symptoms. Thus, the palatability and tolerability of the product dosing in the preliminary study (two 8-oz. bottles/day) serves, in part, as the basis for dosage in the proposed study. The product characterization (noted above) further justifies dosing for the proposed study, as the laboratory analysis demonstrated that this dose contains 141 mg of genistin and 26 mg of genistein per 8 oz. (240 ml) bottle.

We propose a line of inquiry to assess the effects of QC fermented soy consumption in humans, assessing immunological and clinical parameters.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Immediate risks: There is a risk of allergic reaction to any soy product, such as hives, itching, abdominal discomfort, aversion and anaphylaxis. Persons allergic or sensitive to soy are excluded from the study. Participants in this study will be asked to consume GRAS foods - a brown rice-based placebo or fermented soy.

Preliminary testing indicated that Q-CAN® Plus oral liquid had no toxic effects, even when large doses were taken acutely. In our preliminary safety/tolerability study with healthy volunteers (N=20), some participants reported mild, short-lasting gastrointestinal symptoms with the daily intake of the fermented soy beverage: nausea (3), stomach pain (1), diarrhea (1), and bloating (4).

There is a small risk that when blood is drawn, participants may experience pain at the venipuncture site, bruising, or fainting, and in rare instances infection. This is very unlikely to occur, as all phlebotomists where subject visits will occur are trained, certified, and experienced in standard phlebotomy procedures.

Long-range risks: As with any trial, there is potential risk of loss of confidentiality; however, every effort will be made to keep participant information confidential, including study team training in GCP and HIPAA Privacy and Security, and limiting access to any related health information to only the small number of individuals who require access to carry out their role in the study.

2.3.2 KNOWN POTENTIAL BENEFITS

Immediate potential benefits: We anticipate beneficial changes in prostate condition in association with fermented soy consumption.

Long-range potential benefits: We hope that the results of the study will help researchers better understand the role of fermented soy in relation to its anti-tumor effects, signaling pathways in tumor cells, which will add to scientific knowledge in prostate cancer.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

This is a minimal risk study; refer to Section 2.3.1, Known Potential Risks.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To assess the efficacy of QC fermented soy vs. placebo in 72 adults with localized prostate cancer (PCa) prior to radical prostatectomy.	The primary assessment will be a comparison between participants in the QC arm vs. the placebo arm, in mean **serum PSA (prostate-specific antigen)** level changes, from baseline and time of admission for surgery.	Fermented soy supplementation/soy isoflavones are known to decrease serum PSA, the levels of which are used to indicate prostate health.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Secondary		
To assess the efficacy of QC on disease progression (**1**, **2**, **3**, **4, 5**), PCa biomarkers (**6, 7**), and quality of life (**8**).	**1**. Volume of prostate gland **2.** Volume of biopsy-proven, index PCa lesion **3.** Gleason score compared to preoperative biopsies	**1, 2, 3:** Pathological investigation of the removed prostate gland, to analyze any modulation of PCa grade (Gleason score) compared to preoperative biopsies, volume of gland and of biopsy-proven, index prostate cancer lesion, and extent (involvement of surgical margins and extraprostatic extension) of clinical and pathological tumor stage and degree of tumor focality.
	4. PCa tissue telomeric DNA length	**4.** Analysis of telomere length in research samples of human peripheral blood mononuclear cells reveals that telomere length decreases with increased replication of cells, reflecting the replicative history of those cells.
	5. Cancer of the Prostate Risk Assessment (CAPRA-S) score	**5.** Post surgical/post intervention CAPRA score for comparison with baseline
	6. Cell cycle progression score assessment of prostate cancer mRNA from PCa tissue	**6.** Cell cycle progression score assessment of PCa mRNA (from PCa tissue before and after treatment and between treatment arms) is a novel RNA expression-based assay that directly measures tumor cell growth characteristics in order to stratify patients with localized PCa according to disease aggressiveness.
	7. Specific marker changes on PCa tissue microarrays (TMAs) using AQUA - automated quantitative analysis	**7**. AQUA can assess TMAs using fluorescent tags to define tumors, localize sub-cellular compartments, and grade intensity of specific markers on a continuous scale.
	8. Functional Assessment of Cancer Therapy – Prostate (FACT-P v4©)	**8.** Quality of life assessment for men with PCa

4 STUDY DESIGN

4.1 OVERALL DESIGN

We hypothesize that QC fermented soy is beneficial in adults with prostate cancer on the basis of prior anti-cancer activity in human prostate cancer cell lines.

This is a parallel group, double-blind, randomized, phase III clinical trial. The primary aim is to assess the efficacy of Q-CAN (QC) fermented soy vs. placebo in 72 adults with prostate cancer. Subjects will be randomized to one of two arms (n=72; 36 per arm), and stratified (low/high) based on Cancer of the Prostate Risk Assessment[11] (CAPRA) score: 0-4=low/intermediate risk, 5-10=high risk). The two arms are:

1. **Intervention:** Daily QC (two 12.5g packets/day) (~1 ounce/day) taken between the time of enrollment and radical prostatectomy.
2. **Control:** Daily (matched dose) placebo, taken between the time of enrollment and radical prostatectomy.

This is a multi-site trial. Clinical assessments (3 study visits) will take place either in the Yale Center for Clinical Investigation's Research Outpatient Unit, or in LMH's urology clinic space, or South County Hospital (SCH) urology clinic space (as determined by the referring physician's location), at: 1) screening/baseline, 2) enrollment (~1-3 days after BL), and 3) just prior to prostatectomy, *estimated* at between 4 and 10 weeks from baseline/enrollment (see section 1.3 SOA). Length of time in the study will vary for each subject, depending on how far out their prostatectomy will occur; all prostatectomies will be scheduled to occur between 4-10 weeks post-baseline.

To minimize bias, the Medical Informatics Group will handle randomization through Yale's Clinical Trial Management System, OnCore® (Forte Research Systems, Inc., Madison, WI). The blinded study coordinator will access the OnCore® system to indicate eligibility status based on inclusion/exclusion criteria. The assignment will then be retrieved by a blinded OnCore® Statistician, who will perform randomization. Once the participant has been successfully randomized to a treatment arm, the statistician will send confirmation to the pharmacy for dispensing, and also inform the study coordinator. Once made, the assignment is final and the participant will be analyzed in that group regardless of future events or information, in accordance with the intent-to-treat principle.

For interim analysis details, refer to Section 9.4.6, Planned Interim Analysis.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The design and rationale for this study are informed by and based on the work of Lazarevic et al.[5]

4.3 JUSTIFICATION FOR DOSE

Based on participant reports in the preliminary study, QC was both palatable and tolerable (only one participant withdrew), with no adverse effects besides some reports of mild gastrointestinal symptoms. Thus, the palatability and tolerability of the product dosing in the preliminary study (two 8-oz.

bottles/day) serves, in part, as the basis for dosage in the proposed study. The product characterization (as described in Section 2.2, Background) further justifies dosing for the proposed study, as the laboratory analysis demonstrated that this dose contains 141 mg of genistin and 26 mg of genistein per 8 oz. (240 ml) bottle.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he has completed all study visits (including participation in the weekly phone calls to assess daily IP intake), as shown in Section 1.3, Schedule of Activities. The end of the study is defined as completion of the last subject's final study visit.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to enter this study, an individual must meet all of the following criteria:

1) Histologically verified Prostate Cancer (at any stage)
2) Age ≥18 years
3) Scheduled to be treated by radical prostatectomy within the next 4-10 weeks
4) Understanding and willingness to provide consent

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria[5] will be excluded from participation in this study:

1) Previous (within 6 months of enrollment) or concurrent hormonal therapy or chemotherapy; specifically, treatment with 5-alpha reductase inhibitors (finasteride and dutasteride).
2) History of hormone dependent malignancies
3) Concomitant thyroid disease or currently taking thyroid hormone replacement medication
4) Current high-dose soy consumption, micronutrient, or herbal supplements, on soy or vegetarian nutrition, or any other extreme dietary habits
5) Current or past history of any liver or pancreas disease
6) History of hypersensitivity to soy-containing products
7) Malabsorption conditions that might interfere with absorption of the investigational product

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants may maintain their current diet and level of physical activity to which they are accustomed, i.e., they will not be asked to abstain from small amounts of soy in their diet. (At time of phone screening, individuals who reported current high-dose soy consumption, use of herbal supplements, or soy or vegetarian nutrition, or any other extreme dietary habits would have been excluded from participation.)

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of indecision about surgical treatment or temporary use of NSAIDS may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment for this multi-site trial will take place in southern and southeastern Connecticut in the catchment areas of Yale University and Lawrence+Memorial Hospital (LMH), respectively, and in southern Rhode Island, South County Hospital's service area. Primarily, Principal Investigator Dr. Michael Leapman and Site Principal Investigator Dr. Joseph Renzulli II will be drawing from their and fellow Yale School of Medicine urologic oncologist's patient base meeting study eligibility criteria. Eligible patients of all ethnicities and races will be recruited without preference.

Positive post-biopsy prostate cancer patients of Drs. Leapman and Renzulli and the urologist Co-Investigators will be identified to the Clinical Trials Manger, who will invite patients awaiting prostatectomy to meet in person for clinical screening in Yale Center for Clinical Investigation's Church Street Research Unit (CSRU), or in LMH's or SCH's urology clinic (as determined by referring physician's location). The Clinical Trials Manger will thoroughly telephone screen interested persons to ensure eligibility (i.e., they meet no exclusion criteria) before inviting and scheduling them for a face-to-face informed consent and clinical screening at the CSRU or LMH, or SCH.

If needed, the investigators may employ the services of the Yale Center for Clinical Investigation/Clinical and Translational Science Award (CTSA) for recruitment, including dedicated recruitment staff, community outreach personnel, as well as the use of the www.yalestudies.org website with targeted recruitment information.

The targeted enrollment (n=72) over the 3-year recruitment period will be met with an estimated accrual rate of 24 participants enrolled per year.

As a thank you for their time, participants will be remunerated a total of $300 using the Bank of America reloadable card ePayment system through OnCore®, for consuming the study drink, providing blood samples, answering the questionnaire, and being available for phone check-in on a weekly basis. $100 will be given at Visit 1 and $200 will be given at Visit 2.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The investigational product is Q-CAN® Plus ("QC"), a fermented soybean-derived phytochemical food supplement in liquid form. QC is a commercially available GRAS beverage; the active ingredient is soybean (22%). The product's primary constituents are the isoflavones genistin and daidzin (and respective metabolites genistein and daidzein). This trial will assess the efficacy of QC fermented soy in freeze-dried powdered form vs. placebo, in 72 adults with prostate cancer during the interim between biopsy and prostatectomy (4-10 weeks). The placebo is a brown rice-based powder matching in color and consistency with the (active) soy intervention, and is flavored with the same natural chocolate flavor and sweetener, *Siraitia grosvenorii* (monk fruit) as the soy intervention powder.

6.1.2 DOSING AND ADMINISTRATION

At Visit 1, participants will be given their allotment of assigned study drink. One week of study drink equals 14 single dose packets. (Dose escalation or dose-ranging is not applicable to this trial.) Each participant will be dispensed 10 weeks' worth of IP (referred to as a "kit"), a box containing 140 foil pouch packets.

Participants randomized to the Intervention arm will orally consume two 12.5 g packets/day (~1 ounce/day) of the fermented soy powder, reconstituted with 8 oz. of water or juice (per packet), taken between the time of enrollment and their final study visit (Visit 2), approximately 24-48 hours prior to prostatectomy. Participants randomized to the Control arm will orally consume a matched daily dose of the placebo, reconstituted with 8 oz. of water or juice (per packet), taken between the time of enrollment and their final study visit (Visit 2), approximately 24-48 hours prior to prostatectomy.

Participants will be instructed they may drink each daily portion all at once or throughout the day, as preferred. However, once the study drink has been prepared with liquid, any portion remaining requires refrigeration until consumed. Ideally, the study drink is to be taken with food.

Participants will keep a daily account ("Daily Log for IP Intake") of when they consumed (or did not consume) their assigned study drink. If they miss a dose, they will be instructed to record "0" on their daily log for any dose missed, and resume the following day with dosing as usual (i.e., they will not be instructed to "make up" the dose by consuming extra packets).

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

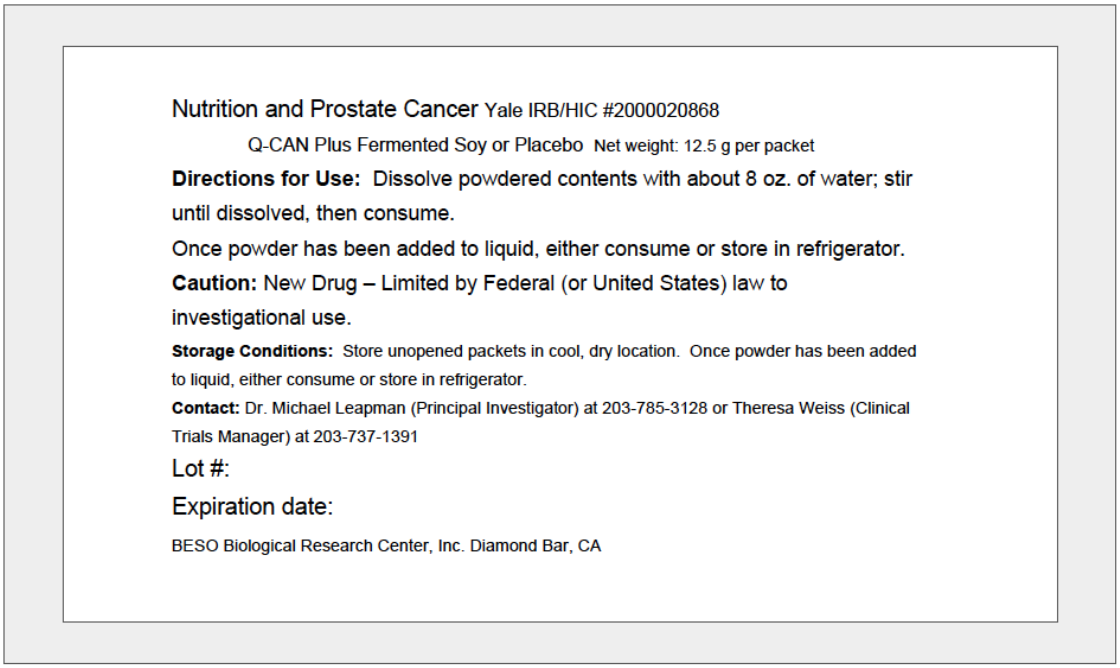
Kits of packets containing the study intervention and control will be shipped from the manufacturer directly to the YNHH pharmacy and the SCH pharmacy. Once the OnCore® statistician has informed the pharmacy of the participant's randomization event and surgery date for prostatectomy, a member of the pharmacy team will generate the "prescription order". The applicable pharmacy will dispense the appropriate kit to the clinical trials manager, who will then meet with the participant during Visit 1 to dispense it. Participants will be instructed to return all packets for reconciliation count/compliance at Visit 2 (whether used or unused). The clinical trials manager or designee will deliver the packets to the applicable pharmacy for final documentation and final disposition/destruction.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The intervention product is Q-CAN® Plus, a fermented soybean-derived phytochemical liquid food supplement in a freeze-dried version. Q-CAN® is a commercially available GRAS beverage that has been marketed in China since 1985 and in the United States since 1991. In the US, it is marketed as a food, under Fujian Yang Zhenhua 851 Bio-Science Co., Ltd., registration number 17334630796. The active ingredient is soybean (22%), and primary constituents of the formulation are isoflavones genistin, daidzin genistein, and daidzein. The freeze-dried powder consists of fermented soy (78.2%), soy extract (1.8%), natural chocolate flavor (18%), and *Siraitia grosvenorii* (2%).

The placebo product for this trial will be a brown rice flour-based powder, matching in color and consistency with the intervention product. The placebo will contain the same flavoring (natural chocolate flavor, 18%) and sweetener (*Siraitia grosvenorii*, 2%) as the intervention, for dual purposes of matching taste (to the greatest degree possible) and masking the difference in flavor between fermented soy and brown rice powders.

Fujian Yang Zhenhua 851 Bio-Science Co., Ltd./BESO Biological Research Center, Inc., will manufacture the intervention and placebo products. The immediate packaging for both will be a sealed foil pouch, as shown below:



6.2.3 PRODUCT STORAGE AND STABILITY

From an environmental standpoint, using an intervention product and placebo in powdered form imposes minimum storage requirements. To prevent moisture and contaminants from degrading the products, seal integrity of the foil packaging (primary container) for both products will be assessed at stability testing. Cardboard packaging (secondary container) will enclose both products.

The foil packets containing the intervention product and placebo product will be stored in a dedicated space at the YNHH pharmacy and at the SCH pharmacy in a temperature- and humidity-controlled room. For participants being seen in LMH, the YNHH pharmacy will currier the kits of IP to LMH pharmacy the day of or the day prior the scheduled IP dispensing visit.

6.2.4 PREPARATION

Participants will be instructed to reconstitute contents of 2 packets per day by pouring the powder into 8 oz. of water or juice (per packet) and mixing well before drinking. Also refer to section 6.1.2, Dosing and Administration.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Description of randomization and blinding procedures: A single randomization scheme for the study will be generated. This scheme will be written and validated by a system programmer in the Medical Informatics Group, Yale Center for Clinical Investigation (YCCI)/NIH CTSA, and will be incorporated into Yale's Clinical Trial Management System, OnCore®. Participants will be randomized to one of two arms, intervention or placebo control (n = 72; allocated in a 1:1 ratio to 36 per arm). Allocation will be concealed through restrictions within the OnCore® system, where neither the block nor block size can be revealed to study personnel. The randomization scheme is stratified by risk level (0-4 = low/intermediate risk, 5-10 = high risk), which is based on the Cancer of the Prostate Risk Assessment (CAPRA) score. Once made, the assignment is final and the participant will be analyzed in that group regardless of future events or information, in accordance with the intent-to-treat principle.

Plans for the maintenance of trial randomization codes and appropriate blinding: After review of eligibility criteria, the blinded clinical trials manager will access the OnCore® system to enter the participant's screening/baseline data and indicate study eligibility status, thus initiating randomization. Once a participant's study status is updated to "Eligible", this indication will then be retrieved by a blinded, specified OnCore® statistician who will perform the randomization assignment through OnCore®. The statistician will also serve as liaison to the dispensing pharmacy by sending confirmation via email to either the Yale-New Haven Hospital pharmacists or the South County Hospital pharmacist, informing them of the randomization event, in order for them to release the order for preparing the assigned IP for dispensing. The statistician will also inform the clinical trials manager when a participant has been randomized, giving an indication when the IP may be obtained from the pharmacy. The YNHH and SCH pharmacists will be necessarily unblinded to participant's randomization status. LMH pharmacists, however, will remain blinded; YNHH pharmacy will simply currier the kits needed for subject visits at LMH.

Circumstances in which the blind would be broken for an individual would be in the event of an SAE. Unblinding of all participants would occur only by the PI, with concern for a suspected or substantiated SAE associated with the intervention or placebo.

Problems anticipated: Compared to brown rice, the odor of fermented soy is distinctive and strong. The potential for unblinding of study personnel would exist in handling participants' used/opened pouches. For this reason, participants will be asked to return their packets for accountability and reconciliation in a large, re-sealable plastic bag, which will be supplied for each kit.

Intervention and control/placebo are as indistinguishable as possible: Foil pouch labeling for intervention and placebo will be identical, with the exception of lot number. The manufacturer will communicate directly with the pharmacy to ensure the dispensing pharmacists can distinguish between active and control packets.

Measures to prevent unblinding by laboratory measurements: Unblinding by laboratory measurements is highly improbable as participants with CAPRA scores at low- and high-risk levels (stratification scheme) will be randomized into each of the study's two arms.

Plans for managing and reporting inadvertent unblinding: All inadvertent unblinding will be reported to the PI. Unblinded patients would be censored from analysis and excluded from participation.

6.4 STUDY INTERVENTION COMPLIANCE

Using the paper form, "Daily Log for IP Intake", participants will keep a daily record of their assigned study drink intake, to both facilitate reconciliation and reduce recall bias when queried each week during phone assessment. The Clinical Trials Manger or a member of the study team will call participants on a weekly basis to assess, log, and track safety, tolerance and adherence to study drink consumption. An eCRF in the OnCore® system will be used to document and manage weekly data on each participant, regarding the number of doses missed per week and the reason(s) why. Compliance with study procedures will be assessed weekly for every participant. Participants will be in compliance if they if they receive at least one dose per day for an average of greater than 50% of study days.

6.5 CONCOMITANT THERAPY

Immediately prior to screening/baseline, participants' concomitant prescription medications, over-the-counter medications, and supplements are reviewed by the Clinical Trials Manager in Epic EMR (electronic medical record, Epic Systems Corporation) to verify exclusion criteria. Thereafter, at all visits and weekly telephone calls, participants are asked whether there have been any changes in their medications since their previous encounter with the Clinical Trials Manager or designee.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

A participant's elective discontinuation from soy or placebo intake means discontinuation from active participation in the study. Study personnel will attempt to collect any remaining study procedure data as the participant's (final) post-consumption data.

If a clinically significant finding is identified (including, but not limited to change in eligibility criteria from baseline) after enrollment, the Principal Investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

Data to be collected at the time of study intervention discontinuation will include data collected at date of study initiation (date of first participant enrollment) through to the date of last participant follow-up. Participants who withdraw prior to study termination will be discussed in the clinical study report. The trial database will be closed/frozen and be considered ready for final analysis after all queries and edits have been reviewed and applied.

No new health information will be gathered after the date of participant withdrawal/discontinuation. Information that has already been gathered may still be used until the end of the study, as necessary to insure the integrity of the study and/or study oversight.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

Compliance with study requirements will be assessed throughout the study. Participants may be withdrawn from the study if they do not agree or adhere to study requirements listed in section 1.3, Schedule of Activities.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- Any clinical adverse event (AE), intercurrent illness, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- Development of any exclusion criteria (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to consume fermented soy or placebo for 15 days.

The reason for participant discontinuation or withdrawal from the study will be recorded in the OnCore® electronic data capture system. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Participants who sign the informed consent form, are randomized, and receive the study intervention, but either subsequently withdraw, or are withdrawn/discontinued from the study, will be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he fails to return for Visit 1 or Visit 2 and is unable to be contacted by study staff.

The following actions will be taken if a participant fails to return to the clinic for a required study visit:

- Study staff will attempt to contact the participant the day the appointment was missed to reschedule the missed visit as soon as possible, and will counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or clinical trials manager will make every effort to regain contact with the participant (where possible, 3 telephone calls and email attempts). These contact attempts will be documented in the participant's study file.
- Should the participant continue to be unreachable, he will be considered to have withdrawn from the study with a primary reason noted and date of lost to follow-up recorded in the participant's study file and in OnCore®.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Sequence of events to occur during the screening process and any decision points regarding participant eligibility: Positive post-biopsy prostate cancer patients of the PI and other Yale School of Medicine referring urologists will be invited to participate in the study. The patients will be identified to the clinical trials manager, who will invite them to meet in person for clinical screening at the Yale Center for Clinical Investigation's outpatient research clinic, the CSRU (Church Street Research Unit), or LMH's or SCH's urology clinic area (determined by referring physician's location), as they await prostatectomy. An initial phone screening will take place to first, to assess the patient's interest in participating, discuss study details, and determine whether any unknown exclusion criteria exist before scheduling the screening visit. The referring urologist determines their patients' eligibility for study entry at time of referral.

Time frame prior to enrollment within which screening procedures/evaluations must be performed: The Screening/Baseline Visit will take place as soon after the patient's prostatic biopsy as possible. Ideally, study enrollment will occur within 3-4 days after the Screening/Baseline Visit, as patients will have been given their date for prostatectomy, and the interim between biopsy and surgery is the period of the intervention.

In the event a randomized patient's prostatectomy is postponed (whether by patient preference or otherwise) beyond 180 days from the initial Screening/Baseline visit, the patient must be re-screened to have new baseline laboratory values established if he wishes to resume participation in the study.

*Procedures and evaluations to be done as part of the study to support the determination of **efficacy** include:*

- ***Biological specimen collection and laboratory evaluations –*** Screening/baseline and end-of-study serology *(final study visit, Visit 2 - time of admission for surgery, 24 hours after ingestion of the last study dose)* includes:

  PHI (prostate health index, which gives total and % free PSA - prostate-specific antigen), ESR (erythrocyte sedimentation rate), CBC with Diff (complete blood count with differential), CMP (comprehensive metabolic panel), testosterone (total, bioavailable and free), CRP (C-reactive protein), lipase, lipid panel, amylase, TSH (thyroid stimulating hormone), estrogen, IGF-1 (insulin-like growth factor), IGFBP-1, IGFBP-2, and IGFBP-3 (insulin-like growth factor binding proteins).
  - Nursing staff and phlebotomists at all sites are trained and certified in standard phlebotomy techniques.
  - Total volume of blood to be drawn per subject visit is approximately 20-30 cc.

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- A single, central processing laboratory (YNHH) will be used for all sites, to decrease variability in test results for the primary outcome, PSA.

- ***Special assays or procedures required –*** The following pathological analyses and assays will be performed after the study has closed to enrollment:
  - Pathological investigation of the removed prostate gland, analyzing any modulation of prostate cancer grade (Gleason score) and disease progression (CAPRA-S) compared to preoperative biopsies, volume of gland and of biopsy-proven, index prostate cancer lesion, and extent (involvement of surgical margins and extraprostatic extension) of clinical and pathological tumor stage and degree of tumor focality.
  - Telomere length (*T*elo*TAGGG*™ Telomere Length Assay) will be used to estimate telomeric DNA length from prostate cancer tissue.
  - Automated quantitative (AQUA) immunofluorescence analysis of markers of prostate cancer aggressiveness on a tissue microarray, using fluorescent tags to define tumors, localize sub-cellular compartments, and grade intensity of specific markers.

- ***Instances when curative treatment plan changes –*** Should an enrolled participant's course of treatment change in that he would not undergo prostatectomy (such as undergoing radiation therapy instead), with the treating urologist's approval, the participant may elect to remain in the study, continue daily IP dosing and attend his final subject visit as scheduled. The primary outcome of the study is prostate-specific antigen (PSA), which can be obtained post-IP consumption regardless. It is accepted that the secondary outcomes (AQUA, CCP and telomere assay) comparing biopsied tissue with tissue from the resectioned prostate would be lost in these rare instances when individuals do not undergo surgical removal of their prostate.

- ***Administration of questionnaires, instruments and patient-reported outcomes -*** Participants will be asked to complete:
  - An inventory of soy-containing foods they have consumed within the past month at Screening/Baseline.
  - Pre/post FACT-P (Functional Assessment of Cancer Therapy - Prostate), a validated, 39-item questionnaire that measures health-related quality of life specific to men with prostate cancer, and assesses well-being in four domains (physical, social/family, emotional, and functional).
  - Participants will be given thorough dosing instructions for consuming the study drink, and will be asked to complete a daily dosing diary.

Follow-up procedures after administration: The final participant assessments will occur at Visit 2, approximately 24-48 hours prior to prostatectomy. No further follow-up by research personnel is planned at this time; patients will be followed by their treating urologist for clinical care.

8.2 SAFETY AND OTHER ASSESSMENTS

Sequence of events to occur during the screening process and any decision points regarding participant eligibility: refer to Section 8.1, Efficacy Assessments

Time frame prior to enrollment within which screening procedures/evaluations must be performed: refer to Section 8.1, Efficacy Assessments

*Procedures and evaluations to be done as part of the study to support the determination of **safety** include:*

- ***Biological specimen collection and laboratory evaluations -***
  - *Screening/Baseline Serology (*to ensure patients' laboratory results are within acceptable range for study participation): CRP (C-reactive protein), lipase, lipid panel, amylase, TSH (thyroid stimulating hormone), ESR (erythrocyte sedimentation rate), CBC with Diff (complete blood count with differential), and CMP (comprehensive metabolic panel). These tests will be repeated at Visit 2 to ensure deleterious changes have not occurred and that patients' laboratory results are within acceptable range prior to prostatectomy (refer to Section 1.3, SOA for complete serology list).
  - Nursing staff and phlebotomists at all sites are trained and certified in standard phlebotomy techniques.
  - Total volume of blood to be drawn at Screening/Baseline and at Visit 2 is approximately 20-30 cc.

- ***Administration of questionnaires, instruments and patient-reported outcomes*** – refer to Section 8.1, Efficacy Assessments

- ***Counseling procedures, including any dietary or activity considerations*** - During this study, participants may maintain their current diet and level of physical activity to which they are accustomed, i.e., they will not be asked to abstain from small amounts of soy in their diet. (At time of phone screening, individuals who reported current high-dose soy consumption, use of herbal supplements, or soy or vegetarian nutrition, or any other extreme dietary habits – or soy allergy or sensitivity – would have been excluded from participation.) Participants will be given thorough dosing instructions for consuming the study drink, and will be asked to complete a daily dosing diary.

- ***Assessment of study intervention adherence*** - Safety, tolerability and adherence to IP intake will be assessed through participant self-report since baseline, via weekly phone calls to participants until they complete the study (Visit 2). If any AEs are noted during the phone assessments or study visits, they will also be recorded in OnCore® using an Adverse Events eCRF, including actions taken to resolve the AE.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). Further, an AE is any unfavorable and unintended or abnormal laboratory finding, symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

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An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32 (a)).

For this trial, adverse events meeting the definition of serious will be collected on all participants, regardless of their association with the study treatment, from the time of randomization to the end of a participant's follow-up.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

The principal investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. As with our preliminary safety/tolerability study of fermented soy consumption in healthy volunteers (N=20) we would expect that mild, intermittent gastrointestinal (GI) symptoms (nausea, stomach pain, diarrhea, and/or distension) could occur in a minority of participants, and would more likely become known after the first few doses, at the beginning of the study. While subjects will be screened for known allergy to soy, there is a risk of allergic reaction. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with symptoms as described here.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate eCRF in OnCore®. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The clinical trials manager will record all reportable events (AEs and SAEs) with start dates occurring any time after informed consent is obtained until the last day of study participation. At each study visit, the clinical trials manager will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

An assessment of treatment relatedness is required for each event reported. The project's clinical team will generate tabulations of any AEs in the OnCore® system. A summary of all AEs believed to be related to the study intervention will be reviewed by the PI, who will then coordinate reporting of these events to the DSMC.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

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An assessment of treatment relatedness is required for each event reported. The project's clinical team will generate tabulations of SAEs in the OnCore® system. A summary of all SAEs believed to be related to the study intervention will be reviewed by the PI and co-investigators.

Unexpected SAEs that occur during the conduct of the trial will be expeditiously reported (within 24 hours of becoming known) by the Clinical Trials Manager to the study sponsor. The Sponsor-Investigator will report to the FDA (if deemed appropriate), as specified in the protocol.

Data on fatal or life-threatening SAEs will be reported by the Sponsor-Investigator, if required, to regulatory authorities as per 21 CFR 312.32(c)(2) as soon as possible but in no case later than 7 calendar days after initial receipt of the information (treatment assignment blinded) and will be tabulated and presented to the DSMC (treatment assignment blinded or unblinded as per DSMC decision).

In addition, the Sponsor-Investigator will notify FDA in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the Sponsor-Investigator determines that the information qualifies for reporting.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Participants in this RCT will be informed should any SAEs develop during the course of the study, which would affect their willingness to participate. SAEs (and any significant new findings) will require urgent contact with current participants. Depending on the circumstances of the SAE, this may be extended to include informing previous and potential participants. Communications with each participant will be documented in their research record and in the Adverse Event eCRF in OnCore®. AEs will be evaluated individually as to whether they are product/study-related. If so, communications with each individual affected will be documented in the same manner.

Frequent opportunities will exist for an assessment of safety/tolerability, as participants will be called on a weekly basis throughout the intervention period of the study. Management (corrective action) of incidental findings will follow according to those outlined in Section 8.4.1, Definition of Unanticipated Problems (UP) and Section 8.4.2, Unanticipated Problem Reporting.

A description of this clinical trial and study-related results on an aggregate level will be will be available on the ClinicalTrials.gov clinical trial registry website.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets *all* of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and

informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This protocol presents minimal risks to the participants. Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including adverse events, are not anticipated. However, corrective actions or changes that may be considered in response to an Unanticipated Problem include:

- Modification of inclusion or exclusion criteria to mitigate the newly identified risks
- Implementation of additional safety monitoring procedures
- Suspension of enrollment of new participants or halting of study procedures for enrolled participants
- Modification of informed consent documents to include a description of newly recognized risks
- Provision of additional information about newly recognized risks to previously enrolled participants.

8.4.2 UNANTICIPATED PROBLEM REPORTING

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including adverse events, are not anticipated in this study, as it presents minimal risks to participants. In the unlikely event that such events occur, "reportable events" (events that are serious or life-threatening and unanticipated) or events that are anticipated but may be occurring with a greater frequency than expected (whether they are possibly, probably, or definitely related), or any UPIRSOs that may require a temporary or permanent interruption of study activities, will be reported immediately (if possible), followed by a written report to the IRB, using the appropriate forms from the Yale Human Research Protection Program website as per their written policies and procedures. The appropriate funding and regulatory agencies will also be notified. The principal investigator will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project via email, as the PI would review them all.

The UP report will include the following information:

- Protocol title, IRB/Human Investigation Committee protocol number, and name of PI
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an unanticipated problem
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB as per their written policies and procedures and to the study sponsor immediately (within 24 hours) upon the principal investigator becoming aware of the event.

- Any other UPs will be reported to the IRB as per their written policies and procedures and to the study sponsor within 5 calendar days of the investigator becoming aware of the problem.

The protocol's research monitor(s), e.g. Cancer Center Protocol Review Committee (PRC), Yale Cancer Center Data and Safety Monitoring Committee (DSMC) reviews entries of unanticipated problems in OnCore® at each meeting.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

The principal investigator or study personnel will inform participants about UPs which may affect them on an individual basis via preferred their means of contact, whether by phone, email or in person.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s): Serum prostate-specific antigen (PSA)

The study is designed as a superiority trial; the primary comparison will be the main effects of QC vs. Placebo. This comparison will be made by assessing the change in serum PSA values (Time of admission for surgery – Baseline) of participants in the two study arms. A two-tailed p-value will be used with a Type I error of 0.05 as the level of statistical significance.

- Secondary Efficacy Endpoint(s):

Variables assessed pre and post-surgery are classified as secondary endpoints:

1. Volume of prostate gland
2. Volume of biopsy-proven, index prostate cancer lesion
3. Prostate cancer tissue telomeric DNA length
4. Cell cycle progression (CCP) score assessment of prostate cancer mRNA from prostate cancer tissue
5. Specific marker changes on PCa tissue microarrays (TMAs) using automated quantitative analysis (AQUA)
6. Gleason score compared to preoperative biopsies
7. Quality of life (FACT-P)
8. CAPRA-S (post-surgical CAPRA score)

9.2 SAMPLE SIZE DETERMINATION

The sample size calculation was based on the following assumptions:

PSA difference*= 15 units
Standard Deviation = 20.3
Power (Type II error) = 0.8
Type I error (two-sided) = 0.05

Repeated measures analysis design

Estimate of difference informed by results from Lazarevic et al.[5]

Interim Monitoring:
The use of the Peto method for the interim analysis (alpha level=0.001) would not necessitate any consideration for sample size adjustment.

9.3 POPULATIONS FOR ANALYSES

Intention-to-treat ('as randomized') analyses will be performed on all randomized participants. Duration of treatment will be taken into account in the analysis.

Per-protocol ('as-treated') analysis will also be carried out; assessment of treatment adherence will be based on self-reported reporting during phone follow-up calls.

The Safety Analysis dataset will include participants who took at least one dose of study medication.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Categorical data will be presented as counts and percentages. Continuous variables will be presented using mean with standard deviation and median with IQR. Graphical presentations will also be made as appropriate.

Two-tailed, Type I error of 0.05 and 95% Confidence intervals will be used in analyses.

The CAPRA score level (low/medium vs high) will be used to run a stratified primary outcome analysis. Other variables will be considered later in the SAP for use as covariates in subsequent analyses.
Normality of distributions of continuous variables will be assessed and transformations (e.g. log, square root) will be considered, as appropriate, to normalize not normal distributions. In the event that normality cannot be achieved, nonparametric tests will be employed.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary outcome is change in serum PSA. This is the difference between the PSA value at baseline and the value at the time of admission for surgery (prostatectomy).

'Baseline' is defined as the date that an eligible participant enrolls in the trial; randomization will occur within 3 days of baseline assessment. If no measurement is available in this 3-day window, the first measurement after randomization BUT before the date of treatment initiation and up to day 7, will be defined as baseline.

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Repeated measures analysis or linear mixed models analysis will be used to assess whether the mean change in PSA from pre to post-treatment differs in the two groups. This can be achieved by measuring the (time by group) interaction term in a repeated measures ANOVA.

In secondary analysis of the primary outcome, the difference in PSA mean level at post-intervention/pre-surgery between the two groups will be assessed using ANCOVA and adjusting for pre-intervention/baseline values. This analytical approach will test whether the QC group has a higher PSA mean level following treatment. Adjusting for pre-treatment/baseline PSA level ensures that any post-treatment differences are a consequence of treatment, and not a result of some random effect from the pre-treatment differences between the groups. In addition, variation in the post-treatment means stemming from the variation introduced from the pre-treatment participant starting point.

Stratified analysis (low/medium vs. high CAPRA score) will also be carried out.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

A number of secondary outcomes will be compared between the two trial arms.

A. Assessed pre and post-surgery

Continuous variables:

1. Volume of gland
2. Volume of biopsy-proven, index prostate cancer lesion
3. Prostate cancer tissue telomeric DNA length
4. Cell cycle progression score assessment of prostate cancer mRNA from prostate cancer tissue

Analysis will be carried out using linear mixed models to assess whether mean changes (pre to post-surgery) differs between the two groups.

Ordinal variables:

1. Gleason score compared to preoperative biopsies
2. Quality of life (FACT-P)

The Wilcoxon Signed Rank test will be used to analyze these variables.

B. Assessed post-surgery

Continuous variables

1. Automated quantitative (AQUA) immunofluorescence analysis of markers of prostate cancer aggressiveness on a tissue microarray
2. CAPRA-S[11] post-surgical score (a validated risk stratification tool incorporating PSA, pathologic Gleason score, surgical margin status, extracapsular extension, seminal vesicle extension, lymph node status (0-12 points)

Post-surgery comparisons of continuous secondary outcomes between the two study groups will be carried out using parametric (t-test) or non-parametric (Wilcoxon Rank Sum) as deemed appropriate (based on normality of distribution).

Categorical variables

1. Degree of tumor focality

Chi-square methods will be used to analyze this variable.

C. Assessed weekly for the duration of the study

1. Adverse events

The percentage and rate of adverse events will be compared between the two groups.

2. Adherence: Number of doses missed (assessed weekly from baseline to final visit)

Repeated measures/longitudinal analysis will be used to analyze adherence to QC.

9.4.4 SAFETY ANALYSES

Safety data will be collected as per definitions established in Section 8.3.2, Definition of Adverse Event (AE) and Section 8.3.2, Definition of Serious Adverse Event (SAE).

For this trial, adverse events meeting the definition of serious will be collected on all participants, regardless of their association with the study treatment, from the time of randomization to the end of a participant's follow-up. Attribution of the AE/SAE will also be presented in the Safety tables. In addition, those AE/SAE that led to study discontinuation will be presented in a separate table.

Safety tables will be generated for AE and SAE, overall and by treatment arm. Data will be presented at the event level as well as the patient level, i.e., AE/SAE and number of participants with AE/SAE.

The OnCore® clinical trial management system uses the Common Terminology Criteria for Adverse Events (CTCAE, v4.0) to grade AE/SAE. Since CTCAE Version 4.0 in May 2009, all CTCAE terms are MedDRA lowest level terms.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

In order to assess the adequacy of randomization, participant baseline characteristics among the treatment groups (demographics, laboratory measurements) will be tabulated and evaluated using descriptive statistics (mean, median, IQR) and graphs. Baseline characteristics that are determined as not equally distributed between the treatment groups will be considered for covariate adjustment in order to determine their impact on treatment comparisons.

9.4.6 PLANNED INTERIM ANALYSES

An interim analysis will be carried out when 50% of the information on the primary outcome has been collected i.e. after post-prostatectomy PSA has been assessed for 36 participants. The interim analysis will be carried out using the conservative Peto method ($p=0.0001$). The interim monitoring analysis will be for efficacy and will be provided to the DSMC by the unblinded trial biostatistician. After consultation with the DSMC, outcome data will be presented either with a different labeling notation for the treatment arm (e.g. A/B) or with clear indication of treatment group assignment. If statistical superiority is achieved ($p<0.0001$) the DSMC would be requested to provide a recommendation of premature termination of the trial due to efficacy. In addition, the DSMC would be at liberty to request conditional

power estimates in the event effect size assumptions used in the initial sample size estimation are not met.

The investigators (on an on-going basis), the Study Monitor (see 10.1.7, Clinical Monitoring), and the DSMC (at its regular meetings) will closely monitor study progress, and individual patients will be closely monitored for signs and reports of adverse reactions. The investigators will conduct safety reviews at monthly intervals. During the review process the PI and investigators will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment. Either the PI, or the Yale Human Research Protection Program (IRB), following consultation and recommendation from the DSMC, have the authority to stop or suspend the study or require modifications.

9.4.7 SUB-GROUP ANALYSES

Currently, sub-group (using demographic and/or baseline variables) analyses of primary or secondary endpoints are not planned. This will be re-assessed, as necessary, in the SAP and sub-group analyses will be defined a prior to database lock.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

For analytical purposes, participants will be counted in the group to which they were randomized, i.e. intent-to-treat analysis.

Individual participant level data will be presented only in the case of safety data monitoring and as requested by the DSMC and/or IRB.

9.4.9 EXPLORATORY ANALYSES

The association of certain baseline variables with changes in serum PSA will be explored. Such analyses will evaluate change in PSA from baseline (at each time point and over the whole study period).

Additional exploratory analysis will be carried out to compare the two trial arms in terms of the proportion of participants who achieve a 15% reduction in PSA.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

A consent form, describing in detail the study intervention, study procedures, and risks will be given to the participant as written documentation of informed consent, required prior to administering any study

procedures. The "Compound Authorization and Consent for Participation in a Research Project" is submitted with this protocol.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. The consent form will be Yale IRB-approved and the participant will be asked to read and review the document. The principal investigator or clinical trials manager will explain the research study to the individual and answer any questions that may arise. A verbal explanation will be provided in terms suited to the individual's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Investigators will determine the ability and capacity of individuals to give consent by questioning during the process of consent. Potential participants will be asked, "Could you explain to me what we are going to ask you to do in this study? This will help me to be sure that you understand the research," as well as, "What more would you like to know about this study?"

Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants will be informed that their participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to each participant for his records. The informed consent process will be documented in the Clinical Trial Management System, OnCore® (including the date and protocol version number), and the paper consent form signed, before the participant undergoes any study-specific procedures. A PDF of each signed consent form will be uploaded to OnCore® in the study's 'Documents' tab. An electronic screening log in OnCore® will be used to document study eligibility status/reasons for ineligibility. Reasons for non-participation of eligible candidates is kept electronically in a password-protected Excel file on an encrypted server. All participants will be informed that their participation is voluntary and they have the option of not participating, or of stopping at any time during the study.

The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

As needed, the consent document will be translated into Spanish versions for Spanish-speaking individuals. Spanish version consent documents will be submitted to the HIC for review and approval before administration. And, as needed, we will utilize bilingual translators for the informed consent process.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants and the Institutional Review Board (IRB), and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Overview: The PI, Co-Investigators, and entire clinical research team adhere to stringent practices according to Yale HIC and HIPAA regulations to ensure participant confidentiality and privacy at all times. This confidentiality is extended to cover testing of participant samples, clinical data, genetic tests, and all other information generated or obtained during the study. All documents and participant information will be strictly maintained; only the PI, co-investigators and research team will have access to PHI, which will be limited to a "need to know" basis. Data will be coded to maintain confidentiality. Only those investigators with appropriate Human Subjects training will have access to subject data. All health care providers subject to HIPAA are required to protect the privacy of participant information. Research staffs at both the Yale School of Medicine and Yale-New Haven Hospital are required to comply with HIPAA and to ensure the confidentiality of patient/participant information. All research activities will be conducted in as private a setting as possible; the CSRU and urology clinic space at both hospitals have individual patient rooms where subject visits will occur.

Electronic records: All electronic files are encrypted, password protected, and stored on a secure server. Storing research data in OnCore®, Yale's encrypted electronic clinical trials management system, will minimize the risk of a breach of confidentiality.

Paper records: Minimal paper data will be kept in a locked file cabinet, in a locked office, in a locked suite at the Yale School of Medicine. Only the PI and immediate study staff will have access to the participant's study records. Study forms will be coded with subject number to ensure that no personally identifiable information will be associated with these forms. The master list linking the code to participant/patient identifiers will be kept in a separate location than research data. Participant contact information will be securely stored for internal use during the study. At the end of the study, all paper records will continue to be kept in a secure location no longer than five years.

Limited data sharing: Information about participants and their health which might identify them may be used by or given to the following individuals/entities, which are required to keep all information confidential:

- Yale Human Investigation Committee
- Medical personnel who provide services to participants in connection with this study (CSRU, YNHH, LMH, SCH)
- Those providers who are participants in the Electronic Medical Record (EMR) system
- Co-Investigators and other investigators (clinical trial consultant)
- Other members of the research team (laboratory investigators, statisticians)
- Data and Safety Monitoring Committee and others authorized to monitor study conduct

Laboratory security measures: All blood samples provided in this study will be analyzed in a de-identified manner. Upon receipt, participant samples will be coded without PHI, before transfer to the Co-Investigator lab-based team. The link between the participant's code/ID # and PHI will be kept in the Clinical Trials Manager's locked file cabinet. Members of the laboratory-based study team will also examine biopsied prostate cancer tissue. No results of any genetic testing will appear in the participant's medical record. The genetic testing is for research purposes only. The results will not be made available to the participant, their physician, or any treating physicians outside this study, or to any other clinical staff. These samples will be stored in Co-Investigator's labs, which are locked when not in use. The samples will be used until they are exhausted.

Record retention: Participant data will be kept for five years after the study ends. Data will be de-identified using a "Safe Harbor" (45CFR164.514(b)(2)) approach consistent with the HIPAA Privacy rule. The principal investigator is responsible for the implementation of data de-identification. The link to coded information will be destroyed and the data will become anonymous. The data will be kept in this anonymous form indefinitely.

Certificate of Confidentiality: A *COC* is not needed, and therefore has not been requested.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Digital data collected for this study will be stored in OnCore and analyzed using an encrypted, password-protected server at the Yale School of Medicine. After the study is completed, the de-identified, archived data will be stored as described in Section 10.1.3, Confidentiality and Privacy.

The consent form for this study contains a section describing "Optional Specimens for Future Storage/Testing", and allows the individual being consented the option to allow or not allow their samples and information to be stored and used for future research. With the participant's indication of approval on the form, the samples will be used to research the role of soy isoflavones on inhibiting disease progression or controlling prostate cancer cell growth. This may help researchers in the future learn more about signaling pathways in tumor cells, treatment of prostate cancer, inflammatory diseases and other health conditions. Participants' stored material will not be shared beyond the investigative team of this study.

During the conduct of the study, even after agreeing to allow banking of their specimens, a participant may choose to withdraw consent to have their biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Sponsor-Investigator
Michael S. Leapman, MD *Assistant Professor of Urology*
Yale University *School of Medicine*
Urology

APPROVED BY THE YALE UNIVERSITY IRB 12/13/2019

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As described below in sections 10.1.6 and 10.1.7, the Yale Center for Clinical Investigation (YCCI), the Yale Cancer Center (YCC) Data and Safety Monitoring Committee (DSMC) will provide data and safety monitoring of this multi-site trial.

Under the direction of the Sponsor-Investigator, the clinical trials manager will oversee daily operations of the study, with ongoing quality assurance and evaluation of all aspects of the clinical trial (e.g., recruitment, enrollment, randomization, study visits and data collection, IRB reporting, queries, and team communication), and will both apprise and consult the PI, co-investigators, and other team members as needed. Aspects of (ancillary) laboratory tissue data analysis and blood chemistry data analysis are delegated to co-investigators and statisticians, under the direction of the Sponsor-Investigator.

10.1.6 SAFETY OVERSIGHT

The Yale Cancer Center (YCC) Data and Safety Monitoring Committee (DSMC) will provide the primary oversight of data and safety monitoring. The Yale DSMC will review and monitor compliance, toxicity and deviations from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator.

The DSMC will review this protocol bi-annually, at a minimum. Information to be provided to the committee includes: a study narrative by the PI, a summary DSMC report produced by OnCore® (which includes participant accrual, response, trial status history, SAEs, adverse events, deviations and survival); audit results, and monitoring reports, as applicable. Other information (e.g., scans, laboratory values, etc.) will be provided upon request. Upon completing the review, the DSMC will approve whether the study should continue as planned, require modification/ amendment, or be placed on administrative hold with accrual temporarily suspended.

Trials being monitored by the YCC DSMC will remain under the YCC DSMC purview until a DSMC review has occurred that includes the research activity of the last subject who completed the intervention, or until the DSMC feels there are no patient safety concerns that require further monitoring. The DSMC will determine the length of continued DSMC review.

The DSMC has authority to intervene in the conduct of these studies as necessary to ensure the safety of the participants and to maintain the highest quality in the clinical research performed at YCC. The DSMC has the authority to require additional monitoring and/ or more frequent reporting on study progress and serious adverse events.

10.1.7 CLINICAL MONITORING

YCCI's assigned Study Monitor (Clinical Research Associate) will monitor all essential documents and data for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring

will begin at the time of participant registration and will continue during protocol performance until study completion.

The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews, formally at a quarterly basis. Safety data, however, is communicated to the investigators in real time. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

The principal investigator, the Yale University IRB, or the Yale Cancer Center Data and Safety Monitoring Committee have the authority to stop or suspend the study or require modifications.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Under the direction of the Sponsor-Investigator the clinical trials manager will be responsible for addressing QA and QC issues and will oversee all activities related to study conduct according to the Yale IRB-approved application (HIC# 2000020868), and as stipulated in this protocol. The Yale Center for Clinical Investigation monitors participant accrual and status on study through OnCore®. All data changes to records are strictly audited. Examples of audit trail information available from the application include changes to subject demographics, changes to protocol status, and eCRF changes.

The laboratory-based study team will perform pathological investigations and assays required for the secondary endpoint analyses according to GLPs. All clinical and laboratory personnel on the study are current in GCP training.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Ongoing processing and data collection is the responsibility of the clinical trials manager and research staff under the supervision of the principal investigator. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the electronic medical record data reported (Epic Systems Corporation) regarding pre-biopsy serology and any recent imaging of the prostate. The clinical trials manager is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the study visit data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. The FACT-P questionnaire will be administered in paper form, for data entry into the OnCore® data management system. All paper forms will be coded with subject number; no personally identifiable information will be associated with these forms, kept in each study participant's record and stored in a locked file cabinet. All other clinical trial data (adherence, safety, anthropometrics, demographics) will be collected in real-time using OnCore®. The OnCore® system is encrypted, includes password protection and internal quality checks, such as automatic range checks to identify data that appear inconsistent, incomplete, or inaccurate.

Only the PI and study staff at the study's data coordinating center (Yale School of Medicine/New Haven) site will have access to the participant's study records. Additionally, all specimens collected will be coded with subject number so that no personally identifiable information will be associated with the

specimens. Upon receipt of the samples for laboratory analysis of secondary endpoints telomere length, cell cycle progression of PCa mRNA, and markers of PCa tissue microarrays, the samples will be coded with the subject number (without PHI) before transfer to the laboratory on the Yale campus of co-investigators responsible for these analyses. The link between the participant's code/ID # and PHI will be kept in the clinical trial manager's locked file cabinet.

In order for the PI and/or Clinical Trials Manager to receive surgical pathology reports of Dr. Renzulli's patients at SCH (*biopsy report*: to obtain CAPRA score variables – needed for randomization, and *prostatectomy report*: to obtain CAPRA-S post-surgical score variables – a secondary outcome measure), Dr. Renzulli will utilize Yale's Secure File Transfer. Access to the Yale Secure File Transfer system ("Filelocker") is gained though Yale's Central Authentication Service. Filelocker allows Yale NetId users to share files with other people both inside and outside of Yale University. It is a temporary and secure storage system for sharing files and data.

10.1.9.2 STUDY RECORDS RETENTION

All documents and subject information will be strictly maintained according to the Yale IRB and HIPAA regulations to ensure confidentiality at all times. Access to subject information will be limited to a "need to know" basis and all data will be coded to maintain confidentiality. Only those investigators with appropriate Human Subjects training will have access to subject data. All data will be managed to assure strict confidentiality of participants at all times. Data will be kept for five years after the study ends. Data will then be de-identified using a "Safe Harbor" (45CFR164.514(b)(2)) approach consistent with the HIPAA Privacy rule. No records will be destroyed without the written consent of the principal investigator.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the Yale University IRB-approved clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or study staff. As a result of deviations, corrective and preventive actions will be developed by the principal investigator and relevant study team members and implemented promptly.

It is the responsibility of the clinical trials manager to use continuous vigilance to identify and report deviations to the principal investigator as soon as the deviation becomes known. Protocol deviations will be reported to the Yale IRB (per Yale's HRPP Procedure 700 PR.1), if the deviation is determined major (using Yale's HRPP Decision Tree 700 GD.1). All investigators and study staff are responsible for knowing and adhering to protocol and IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by an industry sponsor, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. Yale University has established policies and procedures to disclose all conflicts of interest, and has a mechanism in place for the management of all reported dualities of interest by requiring conflict of interest disclosure reporting prior to protocol approval (and annually), for every individual listed on the protocol.

10.2 ADDITIONAL CONSIDERATIONS

In addition to the Yale University IRB, approval for the clinical trial protocol was received from the Yale Cancer Center Protocol Review Committee, on March 20, 2017.

10.3 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CAPRA	Cancer of the Prostate Risk Assessment
CAPRA-S	Cancer of the Prostate Risk Assessment Post-Surgical
CFR	Code of Federal Regulations
CMC	Chemistry, Manufacturing and Controls
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTSA	Clinical and Translational Science Award
DHHS	Department of Health and Human Services
DSMC	Data Safety Monitoring Committee
eCRF	Electronic Case Report Form
FACT-P	Functional Assessment of Cancer Therapy – Prostate
FDA	Food and Drug Administration
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GRAS	Generally Recognized as Safe
GWAS	Genome-Wide Association Studies
HIC	Human Investigation Committee

HIPAA	Health Insurance Portability and Accountability Act
HRPP	Human Research Protection Program
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
IP	Investigational Product
IQR	Interquartile Range
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
LMH	Lawrence+Memorial Hospital
MedDRA	Medical Dictionary for Regulatory Activities
NCT	National Clinical Trial
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PCa	Prostate Cancer
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCH	South County Hospital
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UP	Unanticipated Problem
YNHH	Yale-New Haven Hospital

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