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CANCER CENTER

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List of abbreviations:

CBC $\overline{c}$ diff	Complete blood count with differential
CMP	Complete metabolic profile
PSA	Prostate specific antigen
MRI	Magnetic resonance imaging
ECOG	Eastern cooperative oncology group
DHEA	Dehydroepiandrosterone
GPS	Genomic Prostate Score
LUTS	Lower urinary tract symptoms
QoL	Quality of life
EGF	Epidermal growth factor
LFT	Liver function test
AE	Adverse event
SAE	Serious adverse event
HPLC-EC	High pressure liquid chromatography/electrochemical detection
UHCC	University of Hawaii Cancer Center
HDPE	High Density Polyethylene
H&E	Hematoxylin and eosin
DSMC	Data and Safety Monitoring Committee
CTCAE	Common Terminology Criteria for AEs
eCRF	Electronic case report forms
PT/PTT	Prothrombin time / Partial Prothrombin Time

Phase II Clinical Study of Noni Extract in Men with Very Low Risk or Low Risk Prostate Cancer

Eligibility:	**Initial Laboratory/Radiologic Results must be within normal range for age:**
• Men with a diagnosis of very low risk (<5% risk of disease relapse after primary treatment, criteria; cT1c, Gleason ≤6, PSA < 10 ng/mL, fewer than 3 positive biopsy cores ≤ 50% cancer in any core, PSA density < 0.15 ng/mL/g); low risk (10% risk of disease relapse after primary treatment, criteria; cT1-2a, Gleason ≤6, PSA < 10 ng/mL) prostate cancer confirmed by Oncotype DX prostate cancer test • No prior treatment of prostate cancer with surgical, radiation, hormonal therapies • 55 years of age and older (≥ 55 years) at the time of informed consent • No evidence of extraprostatic disease on pelvic MRI • ECOG performance status 0−2 • No medications, supplements which can affect PSA within 30 days prior to informed consent including toremifene citrate, finasteride, testosterone, dehydroepiandrosterone (DHEA) or other testosterone-like supplements. No dutasteride within 90 days of first noni dose. • No baseline PT/PTT abnormalities, coagulopathies or anticoagulant drug use, such as heparin, or warfarin (Coumadin) • Consumption of any concomitant nutritional, herbal supplements, and antioxidants should be taken under the discretion of the investigator. • No current use of Noni or noni-containing products	• Complete blood count (CBC $\overline{c}$ diff) • Complete metabolic profile including liver function tests (CMP + LFT) • PT/PTT • MRI of the pelvis with contrast • Very low or low risk classification confirmed by Oncotype DX Prostate Test.

SCHEMA

Screening/Pre-Enrollment:
↓
Baseline/Enrollment:
↓
Intervention:
Self-administration of Noni capsules
6,000 mg/day in divided doses x 12 months
with
Clinic Visits at Months 1, 3, 6, 9
↓
End of Intervention: (Month 12)
↓
Post-intervention Follow-up: (7+- 3 days post-treatment)

Sample size:

The estimated sample size is a total of 30 subjects with paired biopsies (initial diagnosis and 12 months)

Endpoints:
Efficacy (Primary):

- Induction of favorable gene expression changes on Oncotype Dx Prostate Cancer Test after 12 months of intervention with Noni extract (6,000 mg daily)
- Incidence of tumor progression after 12 months of intervention with Noni extract
- Serum PSA doubling time

Safety:

- Primary: Incidence and severity of AEs
- Secondary: Effects on angiogenesis (CD34), cell proliferation (Ki-67) and apoptosis (TUNEL) in prostate tissue biopsy samples from month 12

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OBJECTIVES

Primary

To evaluate the Genomic Prostate Score (GPS, and associated gene expression changes) in prostatic tumors in men treated with Noni extract (6,000 mg/day) for one year following the diagnosis of very low risk or low risk prostate cancer.

To assess the rate of disease progression of prostate cancer at one year in men treated with Noni extract following the diagnosis of very low risk or low risk prostate cancer.

Secondary

Evaluate effects of Noni extract on serum PSA (*i.e.,* serum PSA doubling time) in men diagnosed with very low risk or low risk prostate cancer.

Evaluate the tolerability of Noni extract in men diagnosed with very low risk or low risk prostate cancer.

Explore the fundamental molecular pathways contributing to the activities associated with Noni extract in the prostate cancer (*e.g.,* angiogenesis (CD34), cell proliferation (Ki-67) and apoptosis (TUNEL) in prostate tissue biopsy samples).

Evaluate the effect of Noni extract on lower urinary tract symptoms (LUTS) and quality of life (QoL) in men diagnosed with very low risk or low risk prostate cancer.

Create a specimen repository (serum and prostate biopsies) to assess other genetic or environmental factors that may influence incidence and progression of prostate cancer, and to test future hypotheses related to prostate cancer.

BACKGROUND

Disease Background

Prostate cancer is the most common malignancy affecting men with an estimated 232,090 cases per year in the United States [*Siegal, 2015*]. Despite the high incidence, disease related mortality statistics are quite favorable compared to other cancers. Less than one third of men diagnosed with prostate cancer will die of disease making it considerably less lethal than lung and colorectal cancer which rank first and second in terms of cancer related deaths [*Siegal, 2015*]. The high proportion of PSA-detected cancers in current clinical practice is largely responsible for this phenomenon since patients with early prostate cancer are now diagnosed at a lower tumor stage and grade compared to in previous years. While this may allow for earlier curative therapy of potentially life threatening disease, it also identifies a large group of patients with a relatively low risk of disease relapse in whom radical therapy may be unnecessary and harmful due to its associated morbidity and costs.

The optimal treatment strategy for these patients with early prostate cancer (*i.e.,* very low risk and low risk disease) is the focus of this proposal and will be addressed in the following paragraphs.

Identification of the ideal patient population is fundamental to the development of appropriate treatment strategy. For patients with prostate cancer, outcome after therapy has been shown to be dependent on tumor stage, serum PSA and Gleason score (grade) [*D'Amico 1998, Freedland 2004, Kattan 1998*]. Because of this association, prostate cancer can be stratified as: very low risk (<5% risk of disease relapse after primary therapy, criteria; cT1c, Gleason $\leq$6, PSA < 10 ng/mL, fewer than 3 positive biopsy cores $\leq$ 50% cancer in any core, PSA density < 0.15 ng/mL/g); low risk (10% risk of disease relapse after primary therapy, criteria; cT1-2, Gleason $\leq$6, PSA < 10 ng/mL); intermediate risk (25% risk of disease relapse after primary therapy, criteria; cT2b-2c, Gleason 7, PSA 10-20 ng/mL) and high risk (>50% risk of disease relapse after primary therapy, criteria; cT3a, Gleason 8-10, PSA $\geq$ 20 ng/mL) [*NCCN guidelines 2014*]. Thus a consistent observation that long-term survival is possible in patients with very low risk and low risk prostate cancer managed in a conservative fashion (*i.e.,* active surveillance) is an important aspect when counseling patients. Despite this information, many patients with very low risk or low risk prostate cancer are reluctant to only surveil their prostate cancer. Thus a unique opportunity exist to incorporate a therapeutic option, with minimal side effects, into the armamentarium of physicians caring for patients with very low risk and low risk prostate cancer.

The optimal treatment strategy for very low risk and low risk prostate cancer must be one that is endorsed by patients and physicians, and results in little or no compromise in long term, disease specific survival. The rare progression of very low risk and low risk prostate cancer along with its high prevalence, long latency, significant morbidity associated with radical therapy, provide the most opportunistic and promising approach for evaluating nutritional agents for their cancer inhibition properties. A promising strategy, which will be the focus of this proposal, will be the administration of fruit extracts of Noni (Morinda citrifolia).

STUDY DRUG

Noni Extract

Noni (Morinda citrifolia) is included in the listings of traditional medicines of Native Hawaiians, other Pacific Islanders, and Asian populations, and has been used to treat various diseases for centuries [*McClatchey, 2002*]. Morinda citrifolia has been found previously to have a significant antioxidant activity. Present-day commercially available Noni is reported to be composed of over 140 chemical components, including flavonoids, coumadins, anthraquinones, and iridoid glycosides. Three compounds: asperulosidic acid (an iridoid glycoside), damnacanthal (an anthraquinone) and scopoletin (a coumadin), have

in vitro cellular/molecular effects possibly relevant to the inhibition of cancer development and progression. Asperuloside is reported to suppress tumor-promoting phorbal ester (TPA) - or epidermal growth factor (EGF)-induced cell transformation and associated activating protein-1 (AP-1) transcription factor activity [*Liu & Bode et al., 2001*]. Damnacanthal, which has strong tyrosine kinase-inhibitory effects, stimulates ultraviolet-induced apoptosis in ultraviolet-resistant human UVr-1 cells and has been shown to induce normal phenotypes in ras-transformed cells [*Hiwasa, Arase, Chen, Kita, Umezawa, Ito, & Suzuki, 1999*]. Scopoletin has antiproliferative effects and can induce apoptosis of human androgen-independent prostate cancer, PC-3 cells [*Liu & Zhang et al., 2001*].

Clinical Experience: Noni Extracts and Cancer
In a phase I study involving 51 patients with advanced cancers enrolled at seven dose levels of Noni extract, the maximum tolerated dose was six capsules four times daily (12 g). Although no dose-limiting adverse events were found, seven of eight patients at the next level (14 g), withdrew due to the challenges of ingesting so many capsules. Furthermore, there was no evidence to indicate an optimal therapeutic dose or dosing interval [*Issell, 2008*]. In a study in which ~6-8,000 mg of Noni extract was consumed daily, a significant reduction in systemic inflammatory markers were noted [*Akihisha, 2007*]. Evidence from these clinical trials, as well as the preclinical data on Noni, attest to the safety (*i.e.,* there was no known toxicity) and efficacy of modulating key cellular and molecular pathways that could be involved in prostate cancer progression, thus a confirmatory Phase II clinical trial using Noni extract (6,000 mg/day) is the logical next step. Note - there was no evidence that Noni could accelerate tumor growth.

PATIENT ENROLLMENT CRITERIA

The criteria for inclusion or exclusion of study participants.

Inclusion Criteria

1. Men with a diagnosis of very low risk (<5% risk of disease relapse after primary treatment, criteria; cT1c, Gleason $\leq$6, PSA < 10 ng/mL, fewer than 3 positive biopsy cores $\leq$ 50% cancer in any core, PSA density < 0.15 ng/mL/g); low risk (10% risk of disease relapse after primary treatment, criteria; cT1-2a, Gleason $\leq$6, PSA < 10 ng/mL) prostate cancer

2. Very low risk and low risk groups will be confirmed by Oncotype DX prostate cancer test and provided a Genomic Prostate Score (GPS)

3. 55 years of age and older ($\geq$ 55 years) at the time of informed consent

4. No evidence of extraprostatic disease on pelvic MRI

5. No baseline PT/PTT abnormalities, coagulopathies, or who are on any blood thinners.

6. ECOG performance status 0−2 (**Appendix A**)

7. Participants must have normal organ and marrow function as demonstrated by the following parameters being:
   a. complete blood count with differential (CBC $\overline{c}$ diff) - no clinically significant findings
   b. complete metabolic profile (CMP) - no clinically significant findings

8. Willing to comply with proposed visit and treatment schedule

9. Able to understand and willing to sign a written informed consent document

Exclusion Criteria

1. Prior history of treated prostate cancer

2. Concomitant use of medications that are known CYP3A4 substrates

3. Use of medications or supplements that are known to affect PSA within 30 days prior to informed consent, including toremifene citrate, finasteride, testosterone, dehydroepiandrosterone (DHEA) or other testosterone-like supplements. No dutasteride within 90 days prior to first noni dose (**Appendix B**)

4. Consumption of any concomitant nutritional, herbal supplements, and antioxidants should be taken under the discretion of the investigator. The following foods/supplements are prohibited at least 7 days prior to initiation of and during study treatment:
   – St. John's wort or hyperforin (potent CYP3A4 enzyme inducer)
   – Grapefruit juice (potent cytochrome P450 CYP3A4 enzyme inhibitor)

5. Use of any blood thinners.

6. Consumption or use of any Noni or Noni-containing products

7. History of renal or hepatic disease, including history of hepatitis B or C. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac

arrhythmia, or any psychological, familial, sociological or other concomitant condition that would not allow adequate compliance with the study protocol

8. History of allergic reactions attributed to Noni or other compounds of similar chemical or biologic composition to Noni, or the inactive components present in Noni capsules.

9. Participation in any other interventional study or use of any other investigational agents within 30 days prior to study entry

Inclusion of Women and Minorities
Members of all races and ethnic groups are eligible for this trial. Since this is an investigation targeting men with prostate cancer, women are not eligible for the study.

Recruitment Plan
Men who were diagnosed with very low risk or low risk prostate cancer, confirmed by Oncotype Dx Prostate Cancer Test, within the past12 months will be invited to participate in this trial. After signing an informed consent form patients will be screened for eligibility. UHCC will advertise in local newspapers and community organizations to widen the recruitment/catchment areas. Working with community physicians and oncologists is the most direct and effective approach, and we will target the primary care physicians and urologists as our primary source to recruit subjects, including racial/ethnic minorities, for this clinical trial.

TREATMENT PLAN

Dose Regimen and Dose Groups
This is a phase II study of Noni extract in prostate cancer. Intervention will be administered on an outpatient basis. Drug will be dispensed by clinical research staff at each of the participating investigational sites and self-administered by the participants. Subjects participating in the study will be receiving a total daily dose of 6,000 mg/day (4 capsules with breakfast, 4 capsules with lunch and 4 capsules with dinner). Six bottles each containing 60 capsules will be dispensed to each participant upon enrollment. Then 12 bottles (at 30-day visit) and 18 bottles (at 3, 6 and 9 month visits) will be dispensed to each participant. Timing of next study visit schedule will be taken into consideration when drug is dispensed to ensure an adequate supply of drug until next visit. On the day of a study visit, capsules should be taken within 4 hours of visit and blood draw for required lab work. If the patient is scheduled to come in the afternoon, dose should be taken with lunch.

Study drug administration will continue from the time of enrollment until the time of repeat biopsy (12 month), disease progression or until off study (see *CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION*). The planned/maximum duration of

treatment is one year. A total of 72 bottles of study drug (4,320 capsules) will be distributed per subject over the 12-month treatment period.

Contraindications
Noni is contraindicated in subjects who are hypersensitive to Noni products or any of the inactive ingredients found in the drug product capsules.

Concomitant Medications
During study participation, subjects may not consume any additional Noni extract. Subjects consuming the equivalent of an additional 1,000 mg of Noni extract will be considered noncompliant, and will have the study requirements re-explained to them up to two separate visits. Persistent non-compliance for 6 months may result in removing the subject from study.

Participants may not take anticoagulants, such as heparin, or Coumadin or steroid hormones or medications, which have known impact on PSA. If a subject begins taking these medications after being enrolled, they will be withdrawn, taken off study drug and replaced.

A list of supplements and medications to avoid is provided in **Appendix B**.

All medications (prescription and over-the-counter), vitamin and mineral supplements, nutritional supplements and/or tea consumption by the participant following signing of the informed consent will be documented on the concomitant medication CRF and will include: start and stop date, dose and route of administration, and indication. Medications taken for a procedure (*e.g.*, biopsy) will also be documented.

Dose Modifications
Subjects will be assessed clinically for adverse events during screening, prior to enrollment, at one month during intervention, quarterly during intervention, and at the end of intervention. Blood will be drawn at each of these study visits to assess for any adverse events. Any adverse events occurring during the investigation will be managed according to standard medical practice.

AEs requiring dose suspension or permanent discontinuation of Noni extract are listed in the table below. Following any LFT elevation or INR increase, study drug will be withheld (grade 1) or permanently discontinued (grade ≥2), and liver function and PT/PTT monitored weekly until resolution to normal. Study drug may be resumed when laboratory values return to within reference range and will continue to be monitored weekly for 4 consecutive weeks. Study drug will also be permanently discontinued for grade 3 and 4 AEs, unless clearly not related to therapy. For grade 3-4 AEs not related to Noni extract,

we will suspend the study drug, and notify the site investigator and study PI. Noni extract may be reintroduced if AE resolves within 3 weeks.

Adverse events affecting LFT and/or PT/PTT levels will be monitored weekly until AE resolves. There are no reductions in the Noni extract dose; if AEs occur that require suspension of drug administration, the dose will remain the same once treatment resumes. Subjects who have had an interruption of intake of more than 30 calendar days may be withdrawn from the study at the discretion of the investigator. Subjects who have an unresolved AE at the time of withdrawal from study treatment will continue to be followed until resolution of the event, if possible. If an AE persists for more than 30 days after a subject goes off study, the subject will be referred to his personal physician.

Rules for Dose Suspension and Discontinuation

Event[1]	Action
Grade 1 LFT[2] elevation	Suspend study drug; notify site investigator and study PI. Perform at least weekly LFTs until recovery to normal; study drug may be reintroduced if recovery occurs ≤2 weeks after drug discontinuation, with approval of the study PI and site investigator. After reintroducing drug, perform at least weekly LFTs. Any elevation of LFTs after drug discontinuation will results in permanent discontinuation of drug.
Grade ≥2 LFT elevation	Permanently discontinue study drug; notify site investigator and study PI. Monitor at least weekly until recovery to normal.
Grade 1 Prothrombin Time prolongation or INR increase	Suspend study drug; notify site investigator and study PI. Perform at least weekly PT/PTTs until recovery to normal; study drug may be reintroduced if recovery occurs ≤2 weeks after drug discontinuation, with approval of the study PI and site investigator. After reintroducing drug, perform at least weekly PT/PTTs. Any prolongation of PT/PTTs after drug discontinuation will results in permanent discontinuation of drug.
Grade ≥2 PT prolongation or Grade ≥2 INR increase	Permanently discontinue study drug; notify site investigator and study PI. Monitor at least weekly until recovery to normal.
Bleeding of the mouth and gums, easy bleeding or bruising, frequent nosebleeds	Suspend study agent until event resolves. If study drug is reintroduced and AE returns, permanently discontinue study drug.
Grade 1 AE not related to liver function AND lasting less than four weeks, regardless of drug attribution	No suspension required; capture AE information according to standard procedures.
Grade 2 AE not related to liver function AND not related to therapy	No suspension required; capture AE information according to standard procedures.
Grade 1 AE that persist for greater than 4 weeks AND related to therapy	Suspend study agent until event resolves. If study drug is reintroduced and AE returns, permanently discontinue study drug.
Grade 2 AE AND related to therapy	Suspend study drug; notify site investigator and study PI. Study drug may be reintroduces if AE resolves within 2 weeks. If study drug is reintroduced and AE returns, permanently discontinue study drug.
Grade 3 or 4 AE AND not related to therapy	Suspend study drug; notify site investigator and study PI. Noni extract may be reintroduced if AE resolves within 3 weeks and with approval of the site investigator.
Grade 3 or 4 AE AND related to therapy	Permanently discontinue study drug; notify site investigator and study PI.
Development of clinical evidence of disease progression	Permanently discontinue study drug; notify site investigator and study PI.

[1]AEs classified as unlikely, possibly, probably or definitely related to drug are to be considered related to therapy when assessing drug attribution for dose modification.

[2]Tests used to monitor liver function include: albumin, total and direct bilirubin, alkaline phosphatase, AST, ALT, total protein and PT/PTT

Replacement
All participants that meet the following criteria will be replaced:
• Patients who discontinue treatment before completing 12 months of the study treatment for reasons other than progression of disease.
• Patients that are enrolled but do not receive any study treatment.
• Patients who were unable or unwilling to be in compliance with study requirements or were discontinued from study treatment in the judgment of the Principal Investigator.
• Patients for whom paired biopsies are not available for evaluation and endpoint assessments.

Adherence/Compliance
During study participation, subjects will be asked to: self-administer the study medication; avoid consumption of additional Noni and complete daily drug logs to record study agent intake. Subjects are expected to: maintain ≥85% compliance with study agent intake; comply with dietary, medication and supplement restrictions; and complete drug logs to the best of their ability. Subjects will be interviewed at the quarterly clinic visits, and pill counts will be performed to verify compliance with study requirements. Subjects discovered not to be complying with study requirements will have the requirements re-explained to them up to two separate visits. Persistent non-compliance for 6 months could result in removing the subject from study.

Plasma scopoletin, by will be measured with HPLC-EC at baseline, months 6, 9, and at the end of intervention as an objective marker of compliance and to correlate changes in plasma scopoletin levels to changes in clinical, biochemical and molecular targets.

PHARMACEUTICAL INFORMATION

Noni
Noni study drug is supplied through an agreement with Healing Noni (Hilo, HI). The Noni plant is a small evergreen tree that grows along Hawaii's beaches and in forest areas up to 1,300 feet. The plant has a straight trunk, large, bright green and elliptical leaves, white tubular flowers and distinct, ovid, "grenade-like" yellow fruit. The fruit can grow to 12 cm or more and has a lumpy surface covered by polygonal-shaped sections. Its seeds are triangular shaped and reddish brown. To manufacture Noni extract, a proprietary technique to dehydrate and concentrate the Noni fruit into powder was developed. Once dried, the final product contains of over 140 chemical components, including flavonoids, coumadins, anthraquinones, and iridoid glycosides. It has been used for centuries by the Hawaiians to treat heart problems, diabetes, high blood pressure, arthritis, and other degenerative ailments.

The investigational product to be used in the proposed clinical investigation is a white, opaque, size 1 hard capsule containing 500 mg of Noni extract per capsule. Noni capsules are manufactured, stored, distributed, and evaluated for stability. Inactive excipients in capsules include microcrystalline cellulose NF, croscarmellose sodium NF, colloidal silicon dioxide NF, and magnesium stearate NF. Capsules are packaged in high-density polyethylene (HDPE) containers with child-resistant closures, and stored under controlled room temperature conditions.

Rationale for Dose Selection and Administration
Although no dose-limiting adverse events were found in the phase I clinical trial previously performed at UH Cancer Center, seven of eight patients at the next level (14 g), withdrew due to the challenges of ingesting so many capsules. Furthermore, there was no evidence to indicate an optimal therapeutic dose or dosing interval. In a study in which ~6-8,000 mg of Noni extract was consumed daily, a significant reduction in systemic inflammatory markers were noted. Evidence from these clinical trials, as well as the preclinical data on Noni, attest to the safety and efficacy of modulating key cellular and molecular pathways that could be involved in prostate cancer progression, thus we propose to administer 6,000 mg/day of Noni.

Availability
Noni capsule (500 mg) is an investigational agent supplied by agreement with Healing Noni.

Drug Accountability
The UHCC Central Drug Storage department is responsible for supplying the investigator(s)/institution(s) with the investigational product. The PI, or a responsible party designated by the investigator, will maintain a careful record of receipt, disposition, and return of all study drugs on the Investigational Agent Accountability Record. All study drug supplies will be kept in a locked, limited access area. The study drug will not be used outside the context of the protocol. Under no circumstances will the investigator or other site personnel supply study drug to other investigators, patients, or clinics, or allow supplies to be used other than directed by this protocol. Study agent will not be transferred from one patient to another, from one participating center to another participating center, or from one protocol to another. All other transfers (*i.e.* patient or PI moves) must be approved in advance by the study PI at UH Cancer Center.

The investigator will maintain records documenting the receipt, use, loss or other disposition of the investigational product, including batch or code numbers, and account for the drug disposition on a subject-by-subject basis, including specific dates and quantities. Documentation of the subject's participation in this clinical trial and drug and dosage given, must be documented in the medical and research records. Destruction of investigational product will be documented in accordance with UHCC SOPs.

Packaging and Labels
Noni extract (500 mg) capsules are packaged with 60 capsules per bottle in 150 cc white HDPE bottles. Bottle labels include agent name, protocol number, dosing and storage instructions, required warnings for restricted, investigational use, and spaces for recording the subject registration.

Storage
Noni capsules will be stored in a secure location at room temperature [between 59˚F and 86˚F (15–30˚C)].

Agent Destruction/Disposal
At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to destruction of unused study drug. Drug destroyed on site will be documented in the study files.

REGISTRATION/ENROLLMENT/STUDY DURATION

Potential subjects will be screened by the research coordinator using an Initial Assessment Form (***Appendix C***). Subjects will be provided with information about the nature of their current medical condition and must be willing to give consent after being informed of the experimental nature of therapy, alternatives, potential benefits, side-effects, risks and discomforts. Interested subjects who appear eligible based on information available at the screening will be given the opportunity to sign an Informed Consent document

All subjects who sign an Informed Consent document will be assigned a registration number by the PI. This number will consist of a seven-digit alpha-numeric code comprised of: a two-digit institution code; the subject's first and last initials; and a three digit sequential number assigned by the clinic site (*i.e.,* Subject 01AZ001 would be the first subject registered at UH Cancer Center, 01, with initials AZ). As subjects are registered, demographic information and registration information will be entered into a computerized system for tracking purposes.

After signing the informed consent and being assigned a registration number, participating subjects will have blood drawn for confirmation of eligibility and the original biopsy specimens (slides) will be collected (**mandatory**). If a subject is later found ineligible for the study based on screening blood tests or Oncotype DX analysis, the samples collected during screening for banking and pathology slides will be destroyed.

Only men meeting all inclusion and exclusion criteria, and returning for the

baseline/enrollment visit will partake in the treatment phase of the study.

A total of 30 men will be enrolled. Patients will receive Noni capsules (6,000 mg/day) for 12 months of treatment intervention The accrual rate is expected to be approximately 1 to 2 patients / month and it is expected to take about 15-30 months to accrue the 30 patients.

CLINICAL EVALUATIONS AND PROCEDURES

Schedule of Events

Evaluation/ Procedure	Screening - 4 weeks	Enrollment 0 week	1 month ±7 days	3 months ±7 days	6 months ±7 days	9 months ±7 days	12 months (±7 days) or early termination	Post-Tx Day 7 Phone Contact
Informed Consent Signed/Registration Number Assigned	■							
Demographic Questionnaire		■						
Physical Exam (weight, height and vital signs)	■	■					■	
AEs (Signs and Symptoms)		■	■	■	■	■	■	■
Concomitant Medications	■	■	■	■	■	■	■	■
PSA	■[1]			■	■	■	■	
DRE	■[2]						■	
Serum Chemistry and Hematology (CMP, CBC c̄diff)	■			■	■	■	■	
PT/PTT	■		■	■	■	■	■	
Pathology – Biopsy (12 core biopsies)	■[3]						■[3]	
Oncotype DX Prostate Test	■[3]						■[3]	
Pelvic MRI with contrast	■[6]							
Compliance Check (review log and perform pill count)			■	■	■	■	■	
Collect Serum for Banking		■			■		■	
Plasma scopoletin Levels		■		■	■	■	■	
LUTS[4]		■		■	■	■	■	
QoL[5]		■		■	■	■	■	
Dispense Study Agent		■	■	■	■	■		

[1]PSA is not required at the screening visit if results are available from testing performed prior to the diagnostic biopsy, and within three months of enrollment.
[2]DRE does not need to be performed at the screening/ visit if performed by participating study sub-investigator at time of TRUS or within six months of enrollment.
[3]Original slides will be reviewed for presence of prostate cancer by a pathologist affiliated with the UHCC consortium. Paraffin blocks will be sent to Genomic Health to undergo Oncotype DX Prostate Cancer Test.
[4]Assessed using the AUA BPH Symptom score
[5]UCLA QoL questionnaire
[6]Baseline MRI repeated if >12 months

Screening visit Evaluation
Procedures that will be performed as part of the screening/pre-enrollment process are described below.

- Very low risk or low risk prostate cancer must be present in at least one of 8 cores from the diagnostic biopsy. Representative slides and biopsy paraffin blocks from the initial biopsy are required for Oncotype DX analysis (**mandatory**) and review by pathologists affiliated with the UHCC consortium.
- All subjects will have the study fully explained to them and will sign an informed consent document prior to having any invasive procedures performed.
- A limited physical exam will be performed, including anthropometric measurements (height and weight) and vital signs (blood pressure).
- Epidemiological Data: The research staff will obtain personal and physical characteristics, family history, history of environmental and personal exposures, alcohol intake, dietary and physical activity, cancer screening, medication use including nutritional supplements and disease outcomes as detailed in the Excel workbook CRF.
- Pelvic MRI with contrast will be performed to ensure there is no extraprostatic disease. *(Please note, MRI is not required at the screening visit if results are available from testing performed within twelve months of enrollment.)*
- Blood will be drawn for serum PSA, CMP, PT/PTT and CBC$\overline{c}$ diff. *(Please note, measurement of PSA is not required at the screening visit if results are available from testing performed prior to the diagnostic biopsy, and within three months of enrollment.)*
- A DRE will be performed. *(Please note, this test is not required at the screening visit if performed by participating study sub-investigator within six months of enrollment.)*

Enrollment
Procedures followed during the enrollment visit are described below. Enrollment should take place within 4 weeks of the screening visit.

- All components of eligibility will be confirmed (inclusion criteria, exclusion criteria).
- Results from PSA, CMP, PT/PTT and CBC $\overline{c}$ diff tests should be available prior to enrollment.
- Subjects will be interviewed for baseline symptoms and concomitant medications.
- LUTS score will be assessed using the AUA BPH Symptom Score Questionnaire (**Appendix D**).
- Subjects will complete the UCLA QoL questionnaire (**Appendix E**).
- Blood will be collected for baseline scopoletin measurement and banking.

- Six bottles (60 capsules per bottle) of study agent will be dispensed. The Study drug will be dispensed only to eligible patients under the supervision of the investigator or identified sub investigator(s).
- The appropriate study personnel will maintain records of study drug receipt and dispensing. The subject will be provided with logs for recording study agent during the subsequent month of treatment (**Appendix F**).

Evaluations during Study Intervention
Months 1, 3, 6, 9:
Procedures followed during the visits while on study intervention are described below. Visits should take place within ±7 days of the noted 1, 3, 6 and 9 month visits.

- At each clinic visit the research staff will assess compliance (pill count) review and collect the study agent log (**Appendix F*)***. All symptoms experienced by the patient and any concomitant medications taken will be recorded on the appropriate CRF and clinic notes and study logs will be entered into the subject's folder as source documents.
- Serum PSA will be drawn at 3, 6 and 9 months. Note - a 30% increase in serum PSA over baseline PSA would trigger counseling to the patient regarding the need of a repeat biopsy sooner than 12 months.
- CBC$\overline{c}$ diff and CMP will be performed at screening, 3, 6, and 9 months. PT/PTT will also be monitored at each study visit. If medically indicated, blood will be drawn for hepatic function panel.
- Study blood will be collected at 6 and 9 months for banking and 3, 6, 9 months for scopoletin levels.
- LUTS score will be assessed using the AUA BPH Symptom Score Questionnaire and all patients will complete the UCLA QoL questionnaire.
- Study requirements will be reviewed with the subject.
- Counted medication will be returned to study participants and study drug will be dispensed as needed, to ensure adequate supply until the next clinic visit.
- The patient will be provided with new logs for recording study agent intake and reminded to note any signs and symptoms and concomitant medications.

Evaluations at Completion of Study Intervention (12 months)
The following procedures will be performed at the completion of the planned intervention period (12 months) or, when possible, upon early discontinuation of study agent or early study termination.

- A limited physical exam will be performed (weight, vital signs, anthropometric measurements).

- Blood will be drawn for serum PSA, PT/PTT, CBC, CMP, plasma scopoletin analysis and serum banking.
- A DRE will be performed.
- The research staff will collect the investigational agent intake log, review signs and symptoms, and concomitant medications. All symptoms and concomitant medications will be recorded on the appropriate CRF and clinic notes and study logs will be entered into the subject's folder as source documents.
- A repeat prostate biopsy will be performed (12 core biopsy) and tissue / slides sent for assessment by Oncotype DX Prostate Cancer Test.
- Finally LUTS score will be assessed using the AUA BPH Symptom Score Questionnaire and all patients will complete the UCLA QoL questionnaire..
- Remaining study medication will be collected, counted, and appropriately stored while awaiting destruction.

Post-intervention Follow-up Period
Subjects will be contacted by telephone 7+/-3 days after discontinuing study agent to capture any signs and symptoms occurring since stopping the study drug and changes to concomitant medications. The subject is considered off study after the repeat biopsy, other end-of-intervention procedures, and final telephone contact are completed.

METHODS FOR CLINICAL PROCEDURES

Prostate Biopsy
Prostate tissue will be obtained and evaluated by a pathologist affiliated with the UHCC. Representative slides from the initial biopsy and from the biopsies obtained after treatment are required for analysis. At least eight (8) core biopsies will be obtained. Formalin-fixed paraffin-embedded prostate biopsy specimens from all patients included in this study will be performed at each site, where original slides will be stained with hematoxylin and eosin (H & E). The H&E stained sections will be evaluated by light microscopy for presence of prostate cancer by a pathologist with genitourinary experiences. Then if not previously performed, the biopsy paraffin blocks will be sent to Genomic Health to undergo Oncotype DX Prostate Cancer Test.

Blood Draw
Non-fasting blood samples will be drawn following standard institutional procedures. The amount of blood to be collected and the types of tubes is listed under section BLOOD COLLECTION SCHEDULE AND PURPOSE.

Anthropometric Measurements
Anthropometric measurements such as participant's height and weight will be performed at screening/pre-enrollment and post-intervention.

Collection of AE and Concomitant Medications Information
All subjects on study will be asked to keep a record of any signs or symptoms and concomitant medications/supplements they experience once the informed consent document is signed. The research staff will collect the logs and review with the subject at each clinic visit. All signs and symptoms and concomitant medications will be recorded on the appropriate CRF; clinic notes and study logs will be entered into the subject's folder as source documents. AEs will also be documented for abnormal results obtained during scheduled blood tests. All signs and symptoms and concomitant medication will be captured until the date the subject is terminated from the study.

Demographics
Epidemiological data as required to complete the CRF will be collected by the research staff and may include personal and physical characteristics, family history, history of environmental and personal exposures, alcohol intake, dietary and physical activity, cancer screening, medication use including nutritional supplements and disease.

LUTS Score Assessment (AUA BPH Symptom Score questionnaire)
LUTS will be measured at baseline, 3, 6, 9 and 12 months. LUTS represent a common conglomeration of symptoms (increased urinary frequency, increased urgency, hesitancy, reduced stream and nocturia), and have a debilitating effect on quality of life. Studies have demonstrated their prevalence to be as high as 90% in men aged 50−80 years old, including 31% for moderate to severe LUTS and 59% for mild LUTS. The American Urological Association Symptom Score (**Appendix D**) for the evaluation LUTS will be used in this patient population.

Quality of Life Assessment
Quality of life will be measured at baseline, 3, 6, 9 and 12 months from start of intervention using the UCLA Prostate Cancer Index (**Appendix E**).

CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

Since obtaining sufficient tissue from biopsies in this study will present a challenge, as the amount of tissue available may not be sufficient to conduct all the tissue biomarker studies, parameters for evaluation are prioritized as follows: (a) Oncotype DX Prostate Cancer Test**,** (b) angiogenesis (CD34), (c) apoptotic index, (d) Ki-67, (e) tissue procurement for banking.

Primary Endpoint
The primary efficacy endpoint is evaluation of the Genomic Prostate Score (GPS) after intervention with Noni extract. All subjects who meet eligibility criteria, have taken at least one dose of study medication, and have a post-treatment biopsy will be considered

evaluable for the primary efficacy endpoint. Tissue from prostate biopsies will be evaluated by a pathologist affiliated with the UHCC at screening and post-intervention with study agent. Representative slides from the diagnostic biopsy (at least 8 cores) and from biopsy specimens at 12 months post-intervention (at least 8 cores) are required for analysis. Biopsies will be obtained, and formalin-fixed. Paraffin-embedded prostate biopsy specimens from all patients included in this study will be prepared at each site, where original slides will be stained with H&E. Then biopsy samples will be shipped to Genomic Health to undergo Oncotype DX Prostate Cancer Test with the assessment of Genomic Prostate Score (GPS). The H&E-stained sections will be evaluated by light microscopy for presence of cancer, extent of cancer, grade of cancer by a centralized pathologist affiliated with UHCC, using uniform established standards.

Progression of Disease
PSA progression:
a) PSA doubling time (DT) < 2 years, based on at least 3 separate measurements over a minimum of 6 months

Histological progression:
a) > 3 cores positive for prostate cancer;
b) Gleason pattern predominant 4 or higher (*i.e.* Gleason 7 (4+3) or higher) in the re-biopsy specimen of the prostate performed at 12 months as per protocol

Clinical progression:
a) more than twice increase in the product of the maximum perpendicular diameters of the primary lesion as measured radiographically
b) local progression of prostate cancer requiring transurethral resection of the prostate
c) development of ureteric obstruction
d) radiological and/or clinical evidence of distant metastasis

Secondary Endpoints
The effects of Noni extract on serum PSA during the course of the study will be noted.

The incidence and severity of AEs occurring during intervention will be noted. All AEs that are reported by the subject, detected during a visit, physical examination, or laboratory work-up will be recorded in the participant's medical record and recorded on the CRF. All AEs that occur after study enrollment will be recorded on the AE CRF whether or not related to study agent. The following information will be captured for each AE: date reported; CTCAE Term (v 4.0); onset and resolution date; severity grade; attribution to study agent; whether or not the event was reported as an SAE; action taken; whether or not the subject dropped due to the AE; outcome; and comments.

Treatment related changes in angiogenesis (CD34), proliferation (Ki-67) and apoptosis (TUNEL) will be reported comparing initial diagnostic prostate biopsy and 12 month prostate biopsy provided sufficient tissue is available.

QoL and LUTS will be noted during the course of the study.

OFF DRUG CRITERIA

Participants may stop taking study agent for the following reasons:

- after completing the protocol-prescribed intervention
- at the discretion of the investigator
- AE or SAE requiring dose interruption
- inadequate agent supply
- noncompliance with study requirements
- medical contraindication

Off Study Criteria

If the subject never took study medication (*e.g.*, does not meet eligibility criteria or withdraws consent prior to enrollment) the only activity required to remove the subject from the study is to complete the Off Study CRF. If the subject was enrolled and received study medication, post-intervention procedures according to the schedule of events should be completed to the extent possible.

Off-study criteria include:

- not meeting enrollment (eligibility) criteria
- the protocol intervention and any protocol-required follow-up period is completed
- experiencing an AE or SAE
- lost to follow-up
- taking a concomitant medication
- medical contraindication prohibiting further study participation
- discovery of a pre-existing condition not observed at baseline eligibility
- withdrawal of consent
- disease progression
- protocol non-compliance *(i.e.,* visit schedule, dose administration, *etc*.)
- at the discretion of the investigator
- death

Study Termination

The study sponsor has the right to discontinue the study at any time.

SPECIMEN MANAGEMENT

Laboratories

Pathology: Confirmation of very low risk or low risk prostate cancer in prostate biopsy samples initially analyzed outside of a Hawaii Cancer Consortium institute will be confirmed by a pathologists associated with the Hawaii Cancer Consortium as standard practice.

Genomic Prostate Score: Prostatic tissue (paraffin block) will be sent to Genomic Health and subjected to Oncotype DX Prostate Cancer Test.

Serum PSA, PT/PTT, CBC and CMP: assessed by CLIA/CAP approved clinical laboratories

Plasma scopoletin Levels: measured by Dr. Adrian Franke UH Cancer Center

Collection and Handling Procedures

Tissue Samples

Prostate Cancer Pathology

Prostate tissue will be obtained by the site surgeons. Representative slides from the initial biopsy and a post-intervention biopsy are required for analysis. At least eight (8) cores for initial diagnostic and 12 month biopsies will be obtained. Formalin-fixed, paraffin-embedded prostate biopsy specimens from all patients included in this study will be prepared at each site, where original slides will be stained with H&E. The H&E stained sections will be evaluated by light microscopy for presence of cancer by the pathologist, using the uniform established standards.

Paraffin embedded tissue (initial diagnosis and 12 months) will be sent to Genomic Health and the tissue subjected to Oncotype DX Prostate cancer Test in which a Genomic Prostate Score (GPS) will be rendered.

Unstained slides from the above paraffin embedded blocks will be made available to Dr. Charles J. Rosser molecular laboratory to perform immunohistochemical staining for CD34 (angiogenesis), Ki-67 (proliferation) and TUNEL (apoptosis).

Blood Samples

Non-fasting blood will be collected according to the schedule shown in the table below. Information on processing and handling requirements for the various samples is provided in the sections following the table.

Blood Collection Schedule and Purpose:

Tube Type:	**Speckled SST tube**	**EDTA**	**EDTA**	**Speckled SST tube**	**Sodium Citrate**	
Amount of Blood Collected:	**~ 10 ml**	**~ 5 ml**	**~ 5 ml**	**~5 ml**	**~5 ml**	
Processing Requirements:	**Serum**	**Blood**	**Plasma**	**Serum**		
Purpose:	**CMP[1], PSA**	**CBC**	**Scopoletin levels**	**Banking**	PT/PTT	**Total**
Screening	■	■			■	20 ml
Enrollment			■	■		10 ml
Month 1					■	5 ml
Month 3	■	■	■		■	25 ml
Month 6	■	■	■	■	■	30 ml
Month 9	■	■	■		■	25 ml
Month 12	■	■	■	■	■	30 ml

[1]The CMP panel includes all required tests from the hepatic function panel including direct bilirubin.

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PSA (Screening, Months 3, 6, 9 and 12): Approximately 5 ml of blood will be collected in a speckled red-top SST tube. *(Please note, measurement of PSA is not required at the screening/pre-enrollment visit if results are available from testing performed prior to the diagnostic biopsy and within three months of enrollment)*

Comprehensive Metabolic Panel (CMP) (Screening, Months 3, 6, 9 and 12): Approximately 5 ml of blood will be collected in a speckled red-top SST tube. CMP includes glucose, BUN, creatinine, sodium, potassium, chloride, CO2, calcium, SGOT, SGPT, alkaline phosphatase, total bilirubin, direct bilirubin, total protein and albumin.

CBC (Screening and Month 3, 6, 9 and 12): Approximately 5 ml of blood collected in lavender top EDTA-containing tubes will be used for CBC. Tests performed as part of the CBC panel include the following: WBC; RBC; HgB; HCT; MCV; MCH; MCHC; RDW; PLT; MPV; absolute neutrophils; absolute bands; absolute lymphs; absolute monocytes; absolute eosinophils; and absolute basophils.

PT/PTT (Screening, Months 1, 3, 6, 9, and 12): Approximately 5 ml of blood will be collected in a blue-top sodium citrate containing tube to be used for PT/PTT analysis.

Plasma for Scopoletin Level Analysis (Enrollment, Months 3, 6 9, and 12): Approximately 5 ml of blood will be collected in a lavender-top EDTA-containing tube to

be used for plasma scopoletin analysis. Blood will be delivered immediately to the Bioanalytical Core (UH Cancer Center) for assessment.

Serum Banking for Future Mechanistic Studies (Enrollment, Months 6 and 12): Approximately 5 ml of blood will be collected in a speckled red-top SST tube and processed at the clinic site by standing for 20–60 minutes to clot, then spinning for 20 minutes at 3200 rpm. The serum will be collected in separate tubes for banking at the serum archiving facility for future mechanistic studies with patient consent and approval from Institutional Review Boards. All tubes of serum will be frozen to –70ºC.

Shipping Instructions
Study samples (plasma for scopoletin and serum for banking) will be processed and packaged at the UHCC. All study samples (tissue slides, paraffin blocks, plasma for scopoletin analysis, serum for banking) will be shipped to Dr. Rosser's attention at UH Cancer Center. All samples collected will be labeled with a tough tag using a unique specimen number to include the (a) site number, (b) subject registration number, (c) visit number, (d) and specimen ID to permit computerized tracking of master and daughter specimens. All blood and tissue sample shipped to the UH Cancer Center for storage and banking will be addressed as follows:

Charles Rosser, M.D., M.B.A., F.A.C.S.
University of Hawaii Cancer Center
701 Ilalo St.
Rm 327
Honolulu, HI 96813
Contact: Janos Molnar, Ph.D.

Sample Banking
A human tissue repository consisting of prostate tissue biopsies from very low risk and low risk prostate cancer obtained from all subjects at baseline screening and 12 months, to permit the testing of hypotheses anticipated in future research for which external NIH funds will be sought. Serum samples will be similarly stored for future research.

Sample Tracking
All samples collected will be labeled with a unique specimen number. This information will be entered into an existing, customized software program for tracking. The master log, maintained at the UH Cancer Center, will indicate the location of each sample by storage box, freezer shelf, and freezer.

Plasma Scopoletin Analysis
Will be performed by HPLC-EC completed at enrollment, 3, 6, 9 and 12 months

DATA AND SAFETY MONITORING

Adverse events will be monitored continuously through the trial. In this Phase II clinical trial, the local Data and Safety Monitoring Committee (DSMC) ensures that the progress of this protocol is monitored and that appropriate and adequate measures to monitor patient safety are in place. The local Data and Safety Monitoring Committee (DSMC) will monitor for safety and recommendations to discontinue this clinical trial. If no early stopping occurs, the study will end 12 months after enrollment of the final patient. The DSMC will meet semi-annually. In addition, serious AEs, as identified by PI will trigger the DSMC to immediately review any data prior to each semi-annual review. At each meeting of the DSMC for data monitoring, data are presented on AEs and on study outcome variables by the Biostatistics team. The DSMC reviews data on incidence of AEs and can recommend early termination if a serious imbalance were to occur and the estimated risk of harm appeared to warrant such action. The plan assures compliance with AE reporting and follow-up requirements and appropriate reporting. Data are reviewed by the DSMC every six months. These data include current participant accrual in the trial, baseline characteristics of participants, outcome data, study dropouts, and ongoing adverse event monitoring (tabulations of AEs). The Biostatistics team prepares the reports and then leads the meetings of the DSMC. Some tabulations are presented in open session; any results separated by intervention group are presented in closed session only to DSMC members. Data will be reported yearly (in closed session) to the DSMC on rates of outcome events. Analyses can be performed that account for varying periods of follow-up across participants. The DSMC will review the accumulating outcome data and evaluate the results in the context of results of any other trials that might be reported in the interval.

REPORTING ADVERSE EVENTS (AEs)

Definition: An AE is any untoward medical occurrence in a study participant. An AE does not necessarily have a causal relationship with the treatment or study participant. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with participation in a study, whether or not related to that participation. This includes all deaths that occur while a participant is on a study.

Reportable AEs

All AEs that are reported by the subject, detected during a visit, physical examination, or laboratory work-up must be recorded in the participant's medical record and recorded on the CRF. All AEs that occur after the informed consent is signed must be recorded on the AE CRF whether or not related to study agent.

Data Elements

- AE reported date
- AE Verbatim Term

- CTCAE Term (v 4.0)
- Event onset date and event ended date
- Severity grade
- Attribution to study agent (relatedness)
- Whether or not the event was reported as a Serious AE (SAE)
- Action taken with the study agent
- Whether or not the subject dropped due to the event
- Outcome of the event
- Comments

Severity of AEs
Identify the AE using the NCI Common Terminology Criteria for AEs (CTCAE) version 4.0. The CTCAE provides descriptive terminology and a grading scale for each AE listed. A copy of the CTCAE can be found at http://ctep.cancer.gov.

AEs will be assessed according to the CTCAE grade associated with the AE term. AEs that do not have a corresponding CTCAE term will be assessed according to their impact on the participant's ability to perform daily activities as follows:

Grade	Severity	Description
1	Mild	• Barely noticeable, does not influence functioning • Causing no limitations of usual activities
2	Moderate	• Makes participant uncomfortable, influences functioning • Causing some limitations of usual activities
3	Severe	• Severe discomfort, treatment needed • Severe and undesirable, causing inability to carry out usual activities
4	Life threatening	• Immediate risk of death • Life threatening or disabling
5	Fatal	• Causes death of the participant

Assessment of relationship of AE to treatment
Relationship of the AE to study drug will be classified as one of the following: not related, unlikely, possibly, probably, definitely. All AEs will be considered due to drug (AEs classified as unlikely, possibly, probably or definitely) unless clearly not related to therapy. The severity and seriousness of each AE will be assessed by the site investigator.

Follow-up of AEs
All AEs, including lab abnormalities that in the opinion of the investigator are clinically significant, will be followed until resolution, if possible. If an AE persists more than 30 days after the subject goes off study, the subject will be referred to his personal physician.

SERIOUS ADVERSE EVENTS (SAEs)

Definition: As those events, occurring at any dose, which meet any of the following criteria:

- Results in death
- Is life threatening (*Note: the term life-threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)*
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Events that may not meet these criteria, but which the investigator finds very unusual and/or potentially serious, will also be reported in the same manner

The PI is responsible for the reporting any unexpected fatal or life-threatening suspected adverse reactions to the FDA no later than 7 calendar days after initial receipt of the information by facsimile or email. Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to the FDA and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting.

UH Cancer Center and all participating organizations will report SAEs to the local Data Safety Monitoring Committee (DSMC) according to the GCP, clinical trial regulations (21 CFR 312.32, 312.33, and 312.64), and safety reporting guidelines.

PI will contact DSMC by phone or e-mail within 24 hours of knowledge of the event. A SAE regardless of relatedness or expectedness will be reported to DSMC by telephone within 24 hours of the PI/study team becoming aware of the event. An SAE form will be completed by the investigator and faxed to DSMC (808-586-2984) within 48 hours. The investigator will keep a copy of this SAE form on file at the study site.

IRB Notification by Investigator: Reports of all SAEs (including follow-up information) will be submitted to the all IRBs per state and federal guidelines. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's binder.

UH Cancer Center and all participating organizations will comply with applicable regulatory requirements at the participating institution related to reporting SAEs to the IRB.

Follow-up of SAE

Site staff should send follow-up reports as requested when additional information is available or to resolve queries. Additional information should be entered on the SAE form in the appropriate format. SAEs will be followed until resolved or stable, especially for those related to the study agent. SAEs still ongoing at the end of the study period will be followed up to determine the final outcome.

STUDY MONITORING, AUDITING, AND INSPECTION

Data Management

The Data Management team will consist of the PI, biostatistician and Data Entry Assistant at UH Cancer Center. The collected data will be inputted into case report forms which will be uploaded into OnCore. Once the case report forms are complete, they will be transmitted electronically to the study biostatistician who will convert it to a SAS© (V. 9.1 or later, SAS® Institute, Inc., Cary, NC) database.

The investigator will permit study-related monitoring, auditing, and inspection by the IRB and government regulatory bodies of all study-related documents (*e.g.*, source documents, regulatory documents, laboratory data, data collection instruments, *etc*.). The investigator will ensure the capability for inspection of all applicable study-related facilities (*e.g.*, pharmacy, diagnostic laboratory, *etc*.).

Case Report Forms

Participant data will be collected using protocol-specific case report forms (CRFs) that will be uploaded into OnCore.

Source Documents

Original documents (*i.e.,* informed consent forms), patient diaries, evaluation checklists, laboratory reports, pharmacy dispensing records, diagnostic reports, data recorded from automated instruments or any clinical observation recorded in a medical record, clinic or physician note, or hospital record will be treated as source documentation for this clinical trial. Photocopies of completed case report forms are not valid source documents for this

clinical trial. Any data captured on the e-CRF and entered into OnCore will be supported by a notation in the subject's source file.

Record Retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, *etc.*), as well as IRB records and other regulatory documentation will be retained by the each site investigator in a secure storage facility in compliance with HIPAA, OHRP, FDA regulations, and ICH requirements unless the standard at the site is more stringent for a minimum of two years. The sponsor will be notified prior to the planned destruction of any materials. The records should be accessible for inspection and copying by authorized persons of the Food and Drug Administration.

STATISTICAL CONSIDERATIONS

Sample Size

A number of methods have been developed to extract useful and robust information from genomic data sets. However, attention also has to be paid to the experimental design before the investigator completes the experiment. One of the principal limitations of previous molecular profiling studies is the relatively low numbers of samples analyzed. We needed to estimate the sample size requirements necessary to satisfy a specified false discovery rate and power given various biological and experimental variations. We estimated variance based on previous biomarker work. Sample size for this study was estimated according to equation

$$n = \frac{\sigma^2\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2}{\left(\mu_1 - \mu_0\right)^2}$$

where σ^2 is the variance of the gene expression, $Z_{1-\alpha/2}$, $Z_{1-\beta}$ are the (1-α/2)th, (1-β)th quantile of the standard normal distribution respectively, with α being the type I error and β being the type II error. All signal values were log2 transformed. Variance was calculated for each protein. The 90th percentile variance value (3.94) was chosen be the σ^2 in equation. In order to detect a 2-fold change in the expression level, $(\mu_1 - \mu_0)^2$ in equation will be 1. We used 0.05 as the significance level. The estimated sample size is 30 for 80% power. Each patient will have 2 sets of genomic data (baseline and 12 months) collected over the course of the study to monitor a unique genomic signature associated with Noni extract in very low risk or low risk prostate cancer. The accrual rate is expected to be approximately 1 to 2 patients / month. Thus, it is expected to take about 15-30 months to accrue the 30 patients.

Study Design/Endpoints

The proposed clinical study is a Phase II, single arm, open label trial in men $\geq$ 55 years of age with biopsy proven (minimum of 8 cores) very low risk or low risk prostate cancer (confirmed by Oncotype DX Prostate Cancer Test); a total of 30 men will be enrolled. Subjects will receive Noni capsules (6,000 mg/day) for 12 months. After the planned 12-

month intervention is complete (or if a biopsy is indicated earlier), a repeat prostate biopsy will be performed for post-intervention endpoint measurements. The primary endpoint of the study is a comparison of the Genomic Prostate Score (GPS) after treatment with Noni extract. Furthermore, pelvic MRI with contrast will be performed and the size of any lesion calculated. Radiologic report of the MRI should be collected as it is a source document. Other endpoints include: investigating progression of prostate cancer after treatment with Noni extract, investigating modulation of serum PSA after treatment with Noni extract, reporting the tolerability of Noni extract in men with very low risk and low risk prostate cancer, investigating key molecular changes associated with angiogenesis, proliferation or apoptosis and reporting quality of life elements.

ETHICAL AND REGULATORY CONSIDERATIONS

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

Informed Consent

All potential study participants will be given a copy of the IRB-approved Informed Consent to review. The investigator or qualified study staff will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he will be asked to sign the Informed Consent document. The subject is considered enrolled in the study from the time the informed consent document is signed. Any and all AEs and concomitant medication taken by the study participant must be captured up to the time of termination from the study. The study agent(s) will not be released to a participant who has not signed the Informed Consent document. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

Participants must be provided the option to allow the use of blood samples, other body fluids, and tissues obtained during testing, operative procedures, or other standard medical practices for further research purposes. A separate signature area is required to allow participants to opt out of allowing tissue to be used for further research.

The informed consent document must be reviewed and approved by WIRB at each organization at which the protocol will be implemented prior to study initiation. Any subsequent changes to the informed consent must be approved by WIRB prior to initiation.

Confidentiality

Information about the study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Additionally, subject will not be identified by name, only subject identification numbers, on specimens and questionnaires.

Publication Plan
Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

Resource Sharing Plan
As required by NIH rules, we will make the data collected as part of this protocol available to outside investigators. In order to maintain compliance with HIPAA regulations, our preferred method will be to execute a data sharing agreement with the requestor for a limited use dataset as defined by the US Department of Health and Human Services.

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Appendix A: Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Appendix B: List of Foods, Medications, and Supplements to Avoid

Supplements to Avoid

- Consumption or use of any Noni or Noni-containing products
- The following foods/supplements are prohibited at least 7 days prior to initiation of and during study treatment:
  - St. John's wort or hyperforin (potent CYP3A4 enzyme inducer)
  - Grapefruit juice (potent cytochrome P450 CYP3A4 enzyme inhibitor)
- All other herbs, vitamins, minerals, and herbal, dietary and nutritional supplements (except the multi-vitamin/mineral supplement provided as part of the study) should be taken under the discretion of the investigator.

Medications to Avoid

- Medications, which have known impact on PSA, should not be taken while on study. These include: Toremifene Citrate, Finasteride, Dutasteride, Testosterone and Testosterone-like Supplements, Dehydroepiandrosterone (DHEA)

If you have any questions about a food, supplement or medication that you are taking now or may be taking in the future, please do not hesitate to ask your study doctor for more information. All supplement and medication use should be reported to your study doctor.

Appendix C:

Phase II Clinical Study of Noni Extract in Men with Very Low Risk or Low Risk Prostate Cancer

Initial Assessment Form

Date___/___/___ Subject Initials: ___/___ Year of Birth:

YES	NO	QUESTION	ACTION
		Does the subject have pathology confirmed very low risk or low risk prostate cancer?	If No, STOP
		Has these biopsies been evaluated by Oncotype DX Prostate Cancer test or is there paraffin blocks of these biopsies available for the test?	
		Did the subject have recent (within 6 months) prostate biopsy (with a minimum of 8 cores) that shows cancer?	If No, STOP

YES	NO	If the answer is "no" to any of the following questions, STOP; subject is not eligible for further screening at this time. (See also protocol §4.1)
		Is subject between the ages of 30-80?
		Does the subject have a PSA ≤ 10 ng/ml?
		Does the subject eat an omnivorous diet?
		Is the subject's ECOG performance status between 0-2?
		Does the subject have normal organ and marrow function? (Per protocol §4.1)
		Is there an absence of consumption of any nutritional or herbals supplements and high dose antioxidants?
		Is the subject willing to not consume Noni extract?
		Is the subject willing to comply with proposed visit treatment schedule?
		Is the subject able to understand and willing to sign a written informed consent?

YES	NO	STOP if response is "yes" to any of these questions; subject is not eligible for further screening at this time.
		Is there a prior history of prostate cancer?
		Is there a history of renal or hepatic disease including hepatitis B or C?
		Has the subject participated in any other investigational study or used any other investigational agents within 30 days of study entry?
		Does the subject have a history of allergic reactions attributed to Noni or other compounds of similar chemical?
		Has the subject taken toremifene citrate, finasteride, testosterone, dehydroepiandrosterone (DHEA) or other testosterone supplements within past 30 days, or dutasteride within the past 90 days?
		Is the subject aware of having any other uncontrolled intercurrent illness (e.g., ongoing or active infection, symptomatic congestive heart failure, unstable angina, cardiac arrhythmia)?

Is subject eligible to continue screening?: ___YES___NO If no, specify

Signature of Interviewer _____Date

AUA BPH Symptom Score Questionnaire

Patient Name: _____ Date of birth: _____ Date completed _____

	Not at All	Less than 1 in 5 Times	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always	Your score
1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5	
2. Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
3. Over the past month, how often have you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
	None	**1 Time**	**2 Times**	**3 Times**	**4 Times**	**5 or More**	
7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5+	
Total Symptom Score							

Score: 1-7: *Mild* 8-19: *Moderate* 20-35: *Severe*

The possible total runs from 0 to 35 points with higher scores indicating more severe symptoms. Scores less than seven are considered mild and generally do not warrant treatment.

Disclaimer: This material is provided for information purposes only and is not a substitute for a consultation. You should consult with a urologist regarding your specific symptoms or medical condition.

APPENDIX E: QOL

1. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(Circle 1,2, or 3 on each line)	Yes, Limited A Lot	Yes, Limited A little	No, Not Limited At All
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports……	1	2	3
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf……..	1	2	3
c. Lifting or carrying groceries…….	1	2	3
d. Climbing **several** flights of stairs……	1	2	3
e. Climbing **one** flight of stairs……	1	2	3
f. Bending, kneeling, or stooping……..……	1	2	3
g. Walking **more than a mile**…….....	1	2	3
h. Walking **several blocks**……..…	1	2	3
i. Walking **one block**……..….	1	2	3
j. Bathing or dressing yourself……...…	1	2	3

2. During the **PAST 4 WEEKS**, have you had any of the following problems with your work or other regular daily activities as a result of your **PHYSICAL HEALTH**?

(Please answer YES or NO for each question by circling 1·or 2 on each line)

	Yes	No
a. Cut down the **amount of time** you spent on work or other activities……...	1	2
b. **Accomplished less** than you would like…….……	1	2
c. Were limited in the **kind** of work or other activities…….	1	2
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)……...	1	2

3. During the **PAST 4 WEEKS**, have you had any of the following problems with your work or other regulat daily activites as a result of any **EMOTIONAL PROBLEMS**, such as feeling depressed or anxious?

(Please answer YES or NO for each question by circling 1 or 2 on each line)

		Yes	No
a.	Cut down the **amount of time** you spent on work or other activities.....	1	2
b.	**Accomplished less** than you would like……..	1	2
c.	Didn't do work or other activities as **carefully** as usual……..	1	2

4. These questions are about how you feel and how things have been with you **during the PAST 4 WEEKS**. For each question, please give the one answer that comes closest to the way you have been feeling
How much of the time **during the past 4 weeks…**

(Circle one number on each line)

		All of the Time	Most of the Time	A good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a.	Did you feel full of pep?.....	1	2	3	4	5	6
b.	Have you been a very nervous person?.....	1	2	3	4	5	6
c.	Have you felt so down in the dumps that nothing could cheer you up?.....	1	2	3	4	5	6
d.	Have you felt calm and peaceful?..	1	2	3	4	5	6
e.	Did you have a lot of energy?.....	1	2	3	4	5	6
f.	Have you felt downhearted and blue?.....	1	2	3	4	5	6
g.	Did you feel worn out?.....	1	2	3	4	5	6
h.	Have you been a happy person?...	1	2	3	4	5	6
i.	Did you feel tired?.....	1	2	3	4	5	6

5. During **the past 4 weeks**, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc)?

All of the time…….	1	
Most of the time…….	2	
Some of the time…….	3	(Circle one number)
A little of the time…….	4	
None of the time…….	5	

6. During **the past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all…….	1	
Slightly…….	2	
Moderately…….	3	(Circle one number)
Quite a bit…….	4	
Extremely…….	5	

7. How much **bodily** pain have you had during the **past 4 weeks**?

None…….	1	
Very mild……	2	
Mild…….	3	(Circle one number)
Moderate…….	4	
Severe…….	5	
Very severe…….	6	

8. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

Not at all…….	1	
Slightly…….	2	
Moderately…….	3	(Circle one number)
Quite a bit…….	4	
Extremely…….	5	

9. Please choose the answer that best describes how true or false each of the following statements is for you.

(Circle one number on each line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
I seem to get sick a little easier than other people……..…	1	2	3	4	5
I am as healthy as anyone I know…….	1	2	3	4	5
I expect my health to get worse…….	1	2	3	4	5
My health is excellent……	1	2	3	4	5

10. In general, would you say your health is:

Excellent……..	1	
Very Good……	2	
Good…….	3	(Circle one number)
Fair……	4	
Poor……..	5	

11. **Compared to one year ago**, how would you rate your health in general **now**?

Much better now than one year ago…….	1	
Somewhat better now than one year ago…….	2	
About the same…….	3	(Circle one number)
Somewhat worse now than one year ago…….	4	
Much worse now than one year ago.....	5	

12. Below is a list of Problem Statements that describe different situations and experiences. Read each statement and circle the number that best describes **HOW MUCH EACH STATEMENT APPLIES TO YOU** during the **PAST 4 WEEKS**.

(Circle one number on each line) HOW MUCH DOES IT APPLY TO YOU?

		Not At All	A Little	A Fair Amount	Much	Very Much
a.	I have difficulty bending or lifting……	0	1	2	3	4
b.	I do not have the energy I used to……..	0	1	2	3	4
c.	I have difficulty doing household chores……	0	1	2	3	4
d.	I have difficulty bathing, brushing my teeth, or grooming myself……	0	1	2	3	4
e.	I have difficulty planning activities because of the cancer or its treatments……	0	1	2	3	4
f.	I cannot gain weight……..	0	1	2	3	4
g.	I find food unappealing……	0	1	2	3	4
h.	I find that cancer or its treatments interfere with my ability to work……	0	1	2	3	4
i.	I frequently have pain……...	0	1	2	3	4
j.	I find that my clothes do not fit……	0	1	2	3	4
k.	I find that doctors don't explain what they are doing to me……	0	1	2	3	4
l.	I have difficulty asking doctors questions……..	0	1	2	3	4
m.	I have difficulty understanding what the doctors tell me about the cancer or its treatments……..	0	1	2	3	4
n.	I would like to have more control over what the doctors do to me……..	0	1	2	3	4
o.	I am uncomfortable with the changes in my body……	0	1	2	3	4
p.	I frequently feel anxious……...	0	1	2	3	4
q.	I have difficulty sleeping……...	0	1	2	3	4
r.	I have difficulty concentrating……..	0	1	2	3	4
s.	I have difficulty asking friends or relatives to do things for me……..	0	1	2	3	4
t.	I have difficulty telling my friends or relatives about the cancer…….	0	1	2	3	4

u. I find that my friends or relatives tell me I'm looking well when I'm not……..	0	1	2	3	4
v. I find that my friends or relatives do not visit often enough……	0	1	2	3	4
w. I find that friends or relatives have difficulty talking with me about my ill ness……	0	1	2	3	4
x. I become nervous when I am waiting to see the doctor..	0	1	2	3	4
y. I become nervous when I get my blood drawn…….	0	1	2	3	4
z. I worry about whether the cancer is progressing……..…	0	1	2	3	4
aa. I worry about not being able to care for myself……..	0	1	2	3	4
bb. I do not feel sexually attractive……	0	1	2	3	4
cc. I am not interested in having sex……	0	1	2	3	4
dd. I sometimes don't follow my doctor's instructions……	0	1	2	3	4
ee. I have financial problems…….	0	1	2	3	4
ff. I have insurance problems……..	0	1	2	3	4
gg. I would like to have more control over what the doctors do to me……..	0	1	2	3	4
hh. I am gaining too much weight…….	0	1	2	3	4
ii. I have frequent episodes of diarrhea…….	0	1	2	3	4
jj. I have times when I do not have control of my bladder..	0	1	2	3	4

13. If you have children, answer the question in this box. Otherwise, check here: ____

(Circle one number)	HOW MUCH DOES IT APPLY TO YOU?				
	Not at All	A Little	A Fair Amount	Much	Very Much
I have difficulty helping my children cope with my illness…….	0	1	2	3	4

14. If you are **MARRIED** or in a **SIGNIFICANT RELATIONSHIP**, answer the questions in this box:

(Circle one number on each line)	HOW MUCH DOES IT APPLY TO YOU?				
	Not at All	A Little	A Fair Amount	Much	Very Much
a. My partner and I have difficulty talking about our feelings……	0	1	2	3	4
b. My partner and I have difficulty talking about wills and financial arrangements……..	0	1	2	3	4
c. I do not feel like embracing, kissing, or caressing my partner…….	0	1	2	3	4
d. My partner and I are not getting along as well as we usually do……	0	1	2	3	4
e. My partner spends too much time taking care of me…..……..	0	1	2	3	4
f. I have difficulty asking my partner to take care of me….	0	1	2	3	4

15. If you are **SINGLE** or **NOT IN A SIGNIFICANT RELATIONSHIP**, answer the questions in this box:

(Circle one number on each line)	HOW MUCH DOES IT APPLY TO YOU?				
	Not at All	A Little	A Fair Amount	Much	Very Much
a. I have difficulty initiating contact with potential dates…..	0	1	2	3	4
b. I have difficulty telling a date about the cancer or its treatments……..	0	1	2	3	4

URINARY FUNCTION

This section is about your urinary habits. Please consider **ONLY THE LAST 4 WEEKS**.

16. Over the past 4 weeks, how often have you leaked urine?

Every day…….	1	
About once a week…….	2	
Less than once a week……..	3	(Circle one number)
Not at all……..	4	

17. Which of the following best describes your urinary control **during the last 4 weeks**?

No control whatsoever…….	1	
Frequent dribbling……...	2	(Circle one number)
Occasional dribbling……...	3	
Total control…….	4	

18. How many pads or adult diapers per day did you usually use to .control leakage **during the last 4 weeks**?

3 or more pads per day……..	1
1-2 pads per day…….	2
No pads……	3

19. How big a problem, if any, has each of the following been for you?

(Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Dripping urine or wetting your pants	0	1	2	3	4
b. Urine leakage interfering with your sexual activity	0	1	2	3	4

20. Overall, how big a problem has you urinary function been for you **during the last 4 weeks?**

No problem……..	1	
Very small problem……	2	
Small problem……..	3	(Circle one number)
Moderate problem……	4	
Big problem…….	5	

BOWEL HABITS

The next section is about your bowel habits and abdominal pain.

Please consider **ONLY THE LAST 4 WEEKS**

21. How often have you had rectal urgency (felt like I had to pass stool, but did not) during the last 4 weeks?

More than once a day……	1	
About once a day……..	2	
More than once a week…….	3	(Circle one number)
About once a week……	4	
Rarely or never……..	5	

22. How often have you had stools (bowel movements) that were loose or liquid (no form, watery, mushy) during the last 4 weeks?

Never……	1	
Rarely…….	2	
About half the time…….	3	(Circle one number)
Usually …….	4	
Always……..	5	

23. How much distress have your bowel movements caused you **during the last 4 weeks**?

Severe distress……..	1	
Moderate distress…….....	2	(Circle one number)
Little distress……	3	
No distress……..	4	

24. How often have you had crampy pain in your abdomen or pelvis during the last 4 weeks?

Several times a day……	1	
About once a day……	2	
Several times a week…….	3	(Circle one number)
About once a week…….	4	
About once this month……	5	
Rarely or never……	6	

25. Overall, how big a problem have your bowel habits been for you during the last 4 weeks?

Big problem……..	1	
Moderate problem……..	2	
Small problem…….	3	(Circle one number)
Very small problem…….	4	
No problem……..	5	

SEXUAL FUNCTION

The next section is about your sexual function and sexual satisfaction. Many of the questions are very personal, but they will help us understand the important issues that you face every day. Remember, YOU NAME DOES NOT APPEAR ANYWHERE ON THIS SURVEY. Please answer honestly about **THE LAST 4 WEEKS ONLY**.

26. How would you rate each of the following during the last 4 weeks? (Circle one number on each line)

		Very Poor	Poor	Fair	Good	Very Good
a.	Your level of sexual desire? …….	1	2	3	4	5
b.	Your ability to have an erection? …….	1	2	3	4	5
c.	Your ability to reach orgasm (climax)? ……..	1	2	3	4	5

27. How would you describe the usual QUALITY of your erections?

None at all……	1	
Not firm enough for any sexual activity…….....	2	
Firm enough for masturbation and foreplay only……..	3	(Circle one number)
Firm enough for intercourse……..	4	

28. How would you describe the FREQUENCY of your erections?

I NEVER had an erection when I wanted one……...…	1	
I had an erection LESS THAN HALF the time I wanted one…	2	
I had an erection ABOUT HALF the time I wanted one……	3	(Circle one number)
I had an erection MORE THAN HALF the time I wanted one..	4	
I had an erection WHENEVER I wanted one…….....	5	

29. How often have you awakened in the morning or night with an erection?

Never……	1	
Seldom (less than 25% of the time)……	2	
Not often (less than half the time)……	3	(Circle one number)
Often (more than half the time)……	4	
Very often (more than 75% of the time)…..	5	

30. During the **last 4 weeks** did you have vaginal or anal intercourse?

No……	1	
Yes, Once ……	2	(Circle one number)
Yes, More than Once ……..	3	

31. Overall, how would you rate your ability to function sexually during the last 4 weeks?

Very poor……	1	
Poor ……	2	
Fair ……..	3	(Circle one number)
Good ……	4	
Very good ……...	5	

32. Overall, how big a problem has your sexual function been for you during the last 4 weeks?

No problem……..	1	
Very small problem……	2	
Small problem…….	3	(Circle one number)
Moderate problem……..	4	
Big problem…….	5	

33. Overall, how satisfied are you with the treatment you received for your prostate cancer?

Extremely dissatisfied……	1	
Dissatisfied……..	2	
Uncertain…….	3	(Circle one number)
Satisfied……..	4	
Extremely satisfied ……	5	

THANK YOU VERY MUCH!!

APPENDIX F MEDICATION LOG

Name
Date of Birth
Address

SSN

Doctor
Doctor Phone #
Pharmacy
Pharmacy Phone #

Medication	Dosage	Date	Time	Remark