

Comprehensive Cancer Center of Wake Forest University
 CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

Title: Randomized Study of Soy Protein and Effexor on Vasomotor Symptoms of Men with Prostate Cancer

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Approval Dates: **PRC:** 11-06-05 **NCI:** 06-02-06
FDA: N/A **IRB:** 12-01-05

Activation Date: **WFU:** 02-15-07
Sites: 02-15-07

Renewal Date: 10-25-06
 10-02-07
 10-07-08

NCI Version Date: 08-03-09

Amendment #: 1 08-23-06
 2 09-26-06
 3 11-10-06
 4 04-25-07
 5 10-25-07
 6 12-16-08
 7 07-07-09
 8 08-19-09

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This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Institutions not aligned with the Comprehensive Cancer Center of Wake Forest University (CCCWFU) CCOP Research Base (or its non-CCOP centers) will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix N.

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at <https://members.ctsu.org>
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by the CCCWFU CCOP Research Base Data Management Center (DMC). **Case report forms** (with the exception of patient enrollment forms), **signed consents, clinical reports, symptom and medication diaries, and transmittals** must be sent via mail or fax to the CCCWFU CCOP Research Base DMC unless otherwise directed by the protocol. Your institutions standard fax transmittal cover sheet should accompany all data submissions. Do not send study data or case report forms to CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by CCCWFU CCOP Research Base DMC. Please send query responses and delinquent data to CCCWFU CCOP Research Base DMC and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP IAM account contact information current. This will ensure timely communication between the clinical site and the CCCWFU CCOP Research Base DMC.

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

| To submit site registration documents: | For patient enrollments: | To submit study data: |
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| <u>For patient eligibility or treatment-related questions</u> contact the Research Nurse listed on the protocol cover page | | |
| <u>For clinical data questions</u> contact the Data Manager listed on the protocol cover page. | | |
| <u>For questions unrelated to patient eligibility, treatment, or data submission</u> contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com . All calls and correspondence will be triaged to the appropriate CTSU representative. | | |
| The CTSU Public Web site is located at: www.ctsu.org | | |
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CTSU logistical information is located in Appendix N

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Comprehensive Cancer Center of Wake Forest University
CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

TABLE OF CONTENTS

| | Page |
|---|------|
| TITLE PAGE | i |
| TABLE OF CONTENTS | vii |
| SCHEMA | xi |
| 1. BACKGROUND | |
| 1.1 Study Disease..... | 1 |
| 1.2 Study Agent(s)..... | 1 |
| 1.3 Rationale..... | 2 |
| 2. OBJECTIVES | |
| 2.1 Primary Protocol Objectives..... | 3 |
| 2.2 Secondary Protocol Objectives | 3 |
| 3. PATIENT SELECTION | |
| 3.1 Eligibility Criteria..... | 3 |
| 3.2 Exclusion Criteria..... | 3 |
| 4. DRUG AND SUPPLEMENT THERAPY | |
| 4.1 Drug Information..... | 4 |
| 4.2 Study Supplement Information..... | 6 |
| 4.3 Dose Modification..... | 7 |
| 4.4 Treatment Schedule | 7 |
| 4.5 Pre-medication..... | 10 |
| 4.6 Treatment Duration..... | 10 |
| 4.7 Concomitant Treatment..... | 10 |
| 4.8 Supportive Care Guidelines..... | 10 |
| 4.9 Patient Refuses Further Active Treatment | 10 |
| 5. RADIATION THERAPY – N/A | |
| 6. SURGERY- N/A | |
| 7. OTHER THERAPY- N/A | |
| 8. PATHOLOGY/TISSUE BANK – N/A | |
| 9. PROTOCOL SPECIFIC TRAINING REQUIREMENTS – N/A | |
| 10. CORRELATIVE/SPECIAL STUDIES - N/A | |
| 11. STUDY PARAMETERS | 11 |
| 12. REGISTRATION PROCEDURES | |
| Online Registration..... | 11 |
| 13. DATA SUBMISSION PROCEDURES | 12 |

Comprehensive Cancer Center of Wake Forest University
 CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

14. ADVERSE EVENT REPORTING

| | | |
|------|---|----|
| 14.1 | Definitions and Terminology..... | 13 |
| 14.2 | Grading of Adverse Events | 13 |
| 14.3 | General Guidelines | 13 |
| 14.4 | Cancer Prevention Agents Not Supplied by NCI..... | 15 |
| 14.5 | Unblinding Guidelines..... | 17 |
| 14.6 | CDUS Reporting | 18 |

15. STATISTICAL CONSIDERATIONS

| | | |
|------|---|----|
| 15.1 | Objectives..... | 18 |
| 15.2 | Study Design..... | 18 |
| 15.3 | Monitoring Rules..... | 19 |
| 15.4 | Accrual Feasibility | 20 |
| 15.5 | Inclusion of Women and Minorities | 21 |
| 15.6 | Recruitment/Retention Plan..... | 21 |
| 15.7 | Analysis | 22 |

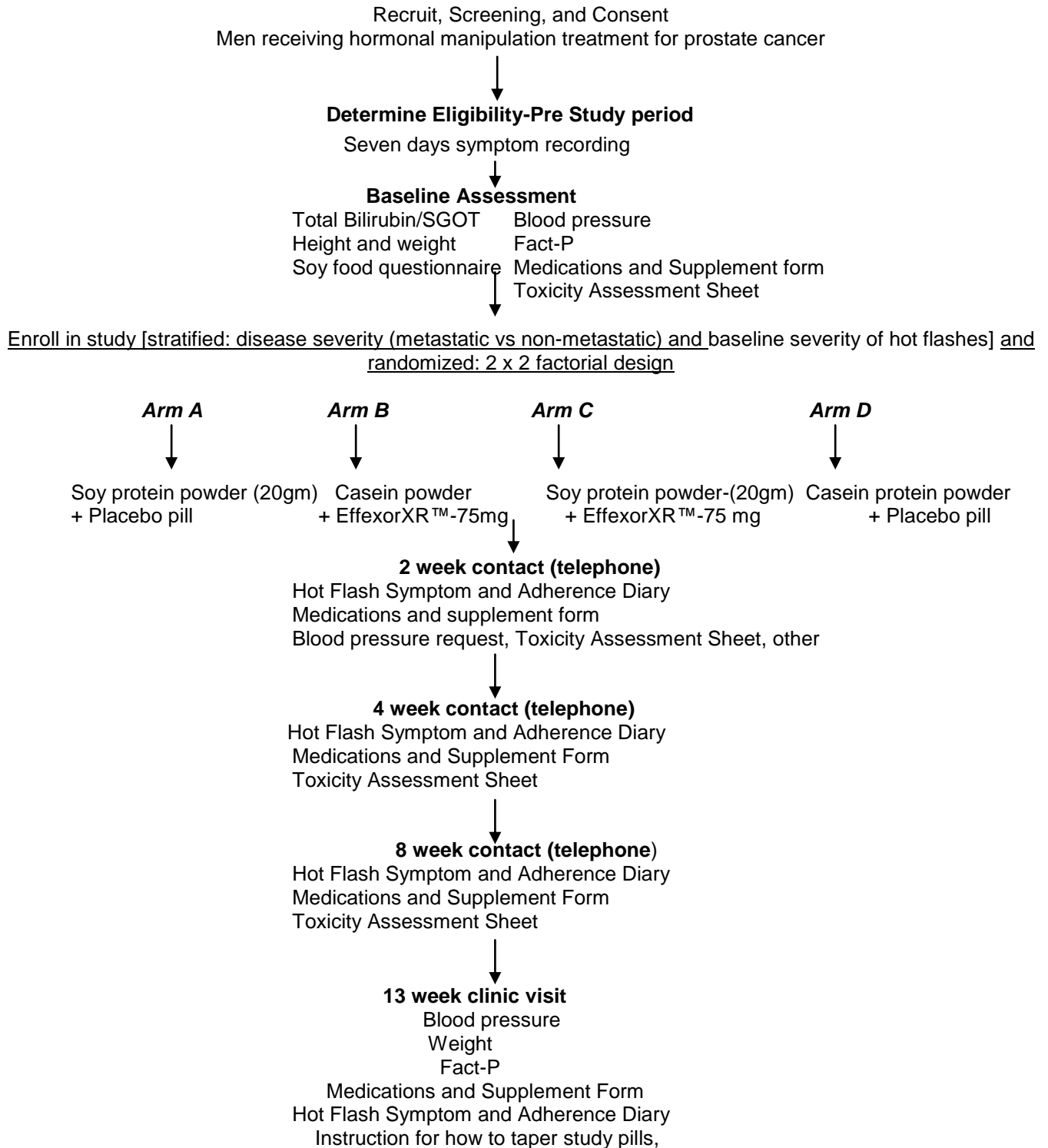
16. REFERENCES..... 23

17. Appendices

- a. Hot Flash Symptom Diary- Pre-Study
- b. Hot Flash Symptom Diary- Baseline through Week 13
- c. Soy Food Questionnaire
- d. Eligibility Checklist/Registration Form
- e. Medication and Supplement Form
- f. FACT-P (Version 4)
- g. Study Flyer
- h. Flow sheet
- i. Study Powder Information
- j. Flavor Packet Recipes
- k. Toxicity Assessment Sheet
- l. Telephone Contact Sheet
- m. Supplement Facts
- n. CTSU Logistics

Comprehensive Cancer Center of Wake Forest University
CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

Randomized Study of Soy Protein and Effexor™ on Vasomotor Symptoms of Men with Prostate Cancer



Sample Size: A maximum of 176 men

Time on study: 7 day pre-screening symptom recording and 12 weeks on “treatment”

Comprehensive Cancer Center of Wake Forest University
CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

1. BACKGROUND

1.1 STUDY DISEASE

Hormonal manipulation is an effective and frequently used intervention for the management and control of prostate cancer. Hormone therapy is useful as adjuvant therapy in early stage disease as well as being the foundation for disease and symptom management in advanced disease. In late stage prostate cancer, some men may select orchiectomy as a permanent ablative approach, while others undergo chemical castration using Leutinizing Hormone Releasing Hormone (LHRH) agonists. The addition of antiandrogens is a frequently used approach to managing patients who become refractory to primary androgen ablation.

Hot flashes occur in up to two thirds of men who undergo hormone manipulation (Stempkowski, 2000, Schow et al, 1998). They may continue for years during chronic therapy and for months after adjuvant therapy is completed (Schow et al, 1998). These vasomotor symptoms have been shown to greatly affect the quality of life of men who have undergone androgen deprivation therapy (Charig et al, 1989). Although men who undergo orchiectomy may have fewer symptoms of hot flashes than men who receive LHRH agonists, those men who experience severe and frequent hot flashes suffer equally, regardless of the castration method.

With regards to vasomotor symptoms, some men report having physical sensations of feeling warm or hot, others report emotional responses such as mild to marked anxiety and irritability (Quella et al, 1994). Some men experience severe vasomotor symptoms that result in drenching sweats that occur seven or more times a day on a routine basis.

1.2 STUDY AGENT(S)

Management of hot flashes in men receiving hormone therapy has been challenging and relatively ineffective. Megestrol acetate has been found to be helpful for long term survivors of both prostate cancer and breast cancer (Quella, 1998). However megestrol acetate withdrawal complicates its use in prostate cancer patients (Dawson et al., 2000, Sartor & Eastham, 1999 Dawson & McLeod, 1995). A study comparing standard versus moderately high dose megestrol acetate in patients with advanced prostate cancer, demonstrated that seven percent of participants experienced an acute pain flair within a week of starting the medication (Dawson et al, 2000). Although megestrol acetate may be commonly used in an attempt to control hot flashes, it may be harmful to some patients. Estrogens have been utilized with caution due to their potential adverse cardiovascular effects in men. (Gerber et al, 2000). Clonidine has been useful in some men, but hypotension is sometimes an unacceptable side effect. Unpublished and anecdotal reports have also suggested effective control following the administration of medroxyprogesterone (Stempkowski, 2000). Most recently attention has turned to new classes of drugs for their effectiveness in managing hot flashes, based on work with women receiving hormone therapy for treatment of breast cancer. Paroxetine, a selective serotonin uptake inhibitor (SSRI), provided a reduction in hot flash frequency and severity in a small pilot trial of twenty-seven perimenopausal women with a history of breast cancer. (Stearns et al, 2000). Roth & Scher (1998) suggested that sertraline, an SSRI, relieved hot flashes over the course of 1-2 months in the case studies of five men receiving hormone therapy for prostate cancer. Venlafaxine, a mixed neurotransmitter reuptake inhibitor, also provided significant relief at the dose of 75mg/day in a randomized pilot study of 180 women with a history of breast cancer (Loprinzi et al, 2000). Some pilot work has been done in men with prostate cancer. In a pilot study of 16 evaluable men on hormones for treatment of prostate cancer, more than half reported that venlafaxine at a dose of 12.5mg twice a day, reduced the severity of the hot flashes by at least 50% (Quella et al, 1999).

Comprehensive Cancer Center of Wake Forest University
CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

Another intervention of interest in relieving vasomotor symptoms is soy protein. Cross cultural comparisons show that women who live in countries where substantial amounts of soy are consumed have fewer adverse menopausal symptoms than women in countries where people consume low levels of soy (Messina 1991, Messina, 1994). Isoflavones, naturally occurring plant substances found in many foods, are structurally similar to estradiol but have both estrogenic and antiestrogenic properties. As weak estrogen agonists, they may protect against menopausal symptoms, osteoporosis, and cardiovascular disease (Rose 1992, Adlercreutz 1990, Setchell et al 1984, Knight and Eden 1996). Studies utilizing soy pills have been mixed. Quella et al (2000) reported that isoflavone pills did not alleviate hot flashes in breast cancer survivors. However, data from a study conducted by Greaves et al (1999) may explain these negative results. Greaves found that when semipurified extracted soy rich in isoflavones was added to casein-lactalbumin protein it did not have the same cholesterol lowering effect as intact soy protein did on plasma lipids and lipoproteins. Therefore, it may be necessary to keep the soy protein intact to produce favorable effects on cholesterol and perhaps to achieve vasomotor symptom relief as well. For this study we will use a study powder containing soy protein and its naturally occurring isoflavones. In a small clinical trial, healthy postmenopausal women treated with soy flour had a 40% decrease in hot flushes within a six week period which persisted for the 12 weeks of the study (Murkies et al, 1995). Another study, conducted by Albertazzi et al (1998), found soy protein isolate powder to be superior to placebo powder for reducing the mean number of hot flushes per 24 hours after 4, 8, and 12 weeks of treatment. In a recent review of 13 trials evaluating the efficacy of both soy foods and isoflavone supplement pills on hot flash relief, the reviewers identified a statistically significant relationship between hot flash frequency at baseline and treatment efficacy (Messina and Hughes, 2003). Forty-six percent of the effect of the soy treatment for decreasing hot flashes was explained by baseline hot flash frequency. For study participants who reported experiencing 5 or more hot flashes a day, hot flash frequency was lowered by approximately 5% over placebo/control effects for every additional hot flash reported at baseline. It may be possible, in men with prostate carcinoma, to reduce the risk of disabling vasomotor symptoms (hot flashes) by consuming soy products.

1.3 RATIONALE

Treatments:

Evidence suggests that men on hormones for treatment of prostate cancer experienced a reduction in the severity of the hot flashes by at least half when given venlafaxine (Quella et al, 1999). Unfortunately, no studies have been conducted to evaluate the ability of soy intake to reduce vasomotor symptoms in men on hormone ablation therapy. This type of study seems warranted as soy products are generally well tolerated and inexpensive. Cultures whose diets are rich in soy products (Japan and the Pacific Rim) have less prostate cancer, less atherosclerosis, and generally better health than those countries where intake of soy products is low (the United States and Western Europe) (Messina et al, 1991, Messina et al, 1994). Both soy and venlafaxine represent exciting possibilities as interventions for hot flashes in men who have undergone androgen-deprivation therapy for metastatic prostate cancer.

The beneficial action of symptom reduction by venlafaxine has been attributed to the ability of this medication to inhibit serotonin reuptake (Sterns et al 2002). One of the physiologic mechanisms proposed for the beneficial effects soy protein consumption on vasomotor symptoms is that isoflavones bind to estrogen receptors as previously discussed. Although the individual effects of venlafaxine and soy protein may not be as powerful as the effects reported for estrogen replacement therapy perhaps taking both therapies concomitantly will provide additional symptom relief. Since these two treatments impact different aspects of the physiological vasomotor symptom mechanisms the two taken together may provide more relief than either alone and warrants investigation.

Comprehensive Cancer Center of Wake Forest University
CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

Quality of life:

In recent years there has been a growing concern among health practitioners and the public about whether treatments are helping extend the quality, as well as the quantity, of patients' lives. Thus, the concept of health-related quality of life (HRQL) is recognized by many researchers and clinicians as an important component to fully understanding the impact of treatments on individuals. The use of HRQL to augment the more traditional measures of morbidity and mortality has increased substantially, and is particularly important in symptom relief studies such as this where it is critical to demonstrate that the benefits of treatment outweigh any potential adverse effects with respect to the day-to-day functional status of the participants.

The inclusion of HRQL measures in clinical research provides three important functions. First, it allows characterization of the impact of treatment in terms of "clinically relevant human attributes," such as anxiety, depression, and ability to function. Second, HRQL data can tell us how HRQL relates, prospectively, to the progression of disease. That is, HRQL dimensions may be independent predictors of important clinical outcomes such as adherence. Finally, HRQL provides data on how treatment affects the daily functioning of the individual. Currently, there are limited data available on HRQL in men with prostate cancer who are receiving hormone ablation therapy. Thus, the proposed study offers a unique opportunity to provide a detailed characterization of the HRQL as well as to assess the effects of treatments on men's HRQL.

In summary, elucidating the effects soy protein with its intact isoflavones, venlafaxine, and the combination of these two treatments have on the vasomotor symptoms (hot flashes) and health related quality of life of men receiving hormonal manipulation for prostate cancer treatment seems highly desirable.

2. OBJECTIVES**2.1 Primary Protocol Objective**

- 1) Assess the effect of soy and Venlafaxine (EffexorXR™) on the hot flash symptom severity score in men receiving hormonal manipulation treatment for prostate cancer

2.2 Secondary Protocol Objective

- 1) Assess the effect of soy and EffexorXR™ on quality of life in men receiving hormonal manipulation treatment for prostate cancer
- 2) Monitor and assess participant drop out rate

3. PATIENT SELECTION**3.1 Eligibility Criteria**

3.1.1 Histologic documentation of prostate cancer, any stage

3.1.2 Life expectancy of \geq nine months

3.1.3 Prior or current androgen deprivation for treatment or control of prostate cancer to include:

- Bilateral Orchiectomy
- LHRH agonist (with or without antiandrogen therapy) ie: leuprolide (Lupron), goserelin (Zoladex), bicalutamide (Casodex), flutamide (Eulexin), or similar agents
- Chemotherapy
- Radiation (Patients may undergo concurrent radiation therapy to the prostate , prostate + seminal vesicles, and/or pelvis).

Comprehensive Cancer Center of Wake Forest University
CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

- 3.1.4. Participant report of hot flash frequency of an average of four or more per day, as defined by sweating, flushing, sensation of warmth, night sweats (Average of 28 per week)
- 3.1.5 Hot flashes must be moderate or severe
- 3.1.6 Age ≥ 21
- 3.1.7 No allergies to soy or dairy products
- 3.1.8 No current use of SSRIs, SNRI's, MAOIs
- 3.1.9 No uncontrolled hypertension (160/90) or greater than Class I American Heart Association functional capacity
- 3.1.10 No history of mania, hypomania, bipolar disorder, or anorexia nervosa
- 3.1.11 No history of seizures
- 3.1.12 Adequate hepatic function (total bilirubin ≤ 2 ; AST (SGOT) ≤ 2 x institutional ULN)
- 3.1.13 Must have a telephone
- 3.1.14 Signed protocol-specific Informed Consent
- 3.1.15 Participant must be willing to discontinue and/or avoid consuming soy foods or soy based supplements during study participation
- 3.1.16 Patients should maintain same treatment and medications for prostate cancer throughout entire study.

3.2 Exclusion Criteria

- 3.2.1 Anticipated changes in prostate cancer treatment plan (i.e., hormonal manipulation, changes in chemotherapy)
- 3.2.2 Concurrent antidepressant therapy
- 3.2.3 History of intolerance to venlafaxine
- 3.2.4 Recent (within 14 days) use of venlafaxine (EffexorTM), monoamine oxidase inhibitor, SSRI (selective serotonin reuptake inhibitor), or SNRI (selective norepinephrine reuptake inhibitor)
- 3.2.5 History of seizure disorder
- 3.2.6 Current use of medication to relieve hot flashes.

4. DRUG AND STUDY SUPPLEMENT

4.1 Drug Information

Effexor XR Therapy

Venlafaxine Extended Release Capsules Effexor XRTM will contain venlafaxine hydrochloride extended release equivalent to 75 mg of Effexor XRTM. Effexor XRTM is an oral antidepressant agent that inhibits serotonin and norepinephrine.

Comprehensive Cancer Center of Wake Forest University
CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

4.1.1 **Availability**

Effexor XR™: funding for the purchase of the EffexorXR™ capsules and placebo pills has been obtained through NCAM funding (U10 CA081851-06S2 PI: SHAW, EDWARD G)

Effexor XR™ will be purchased from Cardinal Health. Biologics, Inc. will procure, store and distribute the Effexor XR™ following the completion of an acceptable run-in period.

4.1.2 **Agent Ordering and Distribution**

Following patient registration, Biologics, Inc will be notified through the On-line registration process. Biologics will contact the site directly to obtain specific shipping information. All treatment required for the participant to complete the study will be delivered to the site in one shipment.

4.1.3 **Storage and Stability**

EFFEXOR XR™ should be stored at room temperature (68° to 77°F, or 20° to 25°C). At the end of the 12 week treatment period, all participants will be instructed to bring their unused pills and powder packets with them to their 12 week clinic visit (closeout). Participants will be given a 1 week taper of the Effexor/Placebo. The remaining powders and pills will be destroyed on site following site institution's policies and procedures.

4.1.4 **Preparation – N/A**

4.1.5 **Toxicities**

Side effects will be monitored by clinic contact. Participants will be encouraged to contact the Study Manager during the study if they feel they are experiencing side effects related to the study interventions.

Effexor XR: The most commonly observed adverse effects associated with the use of Effexor XR™ (reported in at least 10% of patients and at least twice as often as with placebo) were:

- | | |
|------------------------|---------------------|
| • Constipation | • weakness |
| • Dizziness | • sleeplessness |
| • dry mouth | • bruising |
| • insomnia | • shakiness |
| • loss of appetite | • gas |
| • nausea/stomach upset | • bloating |
| • nervousness | • yawning |
| • sexual side effects | • allergic reaction |
| • sleepiness | • agitation |
| • sweating | |

Rare but serious side effects include:

- hypertension
- seizures
- confusion
- increased heart rate

As a safety measure blood will be drawn at baseline to evaluate the candidate's liver function.

Comprehensive Cancer Center of Wake Forest University
CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

4.1.6 Administration

Effexor XR is a tablet to be taken by mouth every morning through week 12.
Effexor/Placebo will be tapered to one pill every other day for week 13.

4.2 Study Supplement Information

Soy/Casein Therapy

Study supplements will consist of protein powder containing 20 gm of soy protein and approximately 160 mg of total isoflavones or an isocaloric supplement of casein protein.

4.2.1 Availability

The study supplement powders soy and casein (20 gm protein), will be provided free of charge by Physicians Pharmaceuticals, Inc., the maker of Revival Soy products. The soy and casein powders will be obtained from a single batch. Revival Soy is manufactured in an USDA-inspected food facility and undergoes rigorous quality-control testing above and beyond what is required by law. Each production batch undergoes rigorous testing for taste, purity and protein quality. Industry-standard laboratory analysis is performed during and after manufacturing for E. Coli, Staph Aureus, Yeast, Mold and Salmonella before approval for release for patient consumption. Revival Soy is not chemically-processed in any way. Revival Soy protein isolate is made via a water extraction, thus preserving the natural soy isoflavones and other potentially beneficial soy phytochemicals. All ingredients are in dry powder form which are then blended and packaged in individual serving packets. Ingredients are obtained reputable food-grade suppliers (eg. cocoa is acquired from Archer Daniels Midland). Quality and purity testing is performed on each individual ingredient before delivery to manufacturing facilities. Biologics, Inc. will store and distribute the study powders directly to the sites in a single mailing, following the completion of an acceptable run-in period.

4.2.2 Agent Ordering and Distribution

Following patient registration, Biologics, Inc will be notified through the On-line registration process. Biologics will contact the site directly to obtain specific shipping information. All treatment required for the participant to complete the study will be delivered to the site in one shipment.

4.2.3 Storage & Stability

The soy/casein powder should be stored in a cool dry place, such as a cabinet, closet or cupboard.

At the end of the week 12 treatment period, all participants will be instructed to bring their unused pills and powder packets with them to their week 13 clinic visit (closeout). Participants will be given a 1 week taper (week 13) of the Effexor/Placebo. The remaining powders and pills will be destroyed on site following site institution's policies and procedures.

4.2.4 Preparation – N/A

4.2.5 Toxicities

Side effects will be monitored by clinic contact. Participants will be encouraged to contact the Study Manager during the study if they feel they are experiencing side effects related to the study interventions.

Comprehensive Cancer Center of Wake Forest University
CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

Soy Supplement: Soy is generally recognized as safe. The doses to be given in this study are within the range of soy doses consumed by Asian populations as part of their everyday diet. Some concerns have recently been raised in the Honolulu Heart Study by an observation of a greater frequency of cognitive decline in men regularly consuming tofu and other soy foods for many years (White et al). However, it is unclear whether this association is causative or whether soy consumption merely serves as a marker of acculturation or lack thereof. We believe it is highly unlikely that any adverse effect will result from the short intervention proposed herein.

Casein Supplement: Casein is generally recognized as safe. It is a naturally occurring milk-based protein. The potential side effects of the supplement include:

- Nausea/Stomach upset
- Bloating
- Constipation
- Diarrhea

4.2.6 Administration

Study supplements will consist of protein powder containing 20 gm of soy protein and approximately 160 mg of total isoflavones or an isocaloric supplement of casein protein. Participants will be instructed to consume one packet of study powder each day. The powder will be vanilla flavored, and can be mixed with milk, juice, fruit (to create a smoothie) or water or added to foods such as oatmeal.

4.3 Dose Modification

4.3.1 Toxicity Management – Side effects will be monitored by telephone contact. Participants will be encouraged to contact the Study Manager during the study if they feel they are experiencing side effects related to the study interventions.

4.3.2 Withdraw from study treatment: Any side effects experienced by the participant may or may not be due to the study supplement or study drug. If side effects become intolerant for the patient, he may be withdrawn from the study at the discretion of the physician.

4.4 Treatment Schedule

After the 7 day baseline record of hot flashes, participants are randomly assigned, in a blinded fashion, to (A) placebo pill po qAM and soy protein powder (20 gms with 160 mg isoflavones) 1 packet/day; or (B) Effexor XR™ 75mg po qAM and casein powder (20 gms) 1 packet/day or (C) Effexor XR™ 75mg po qAM and soy protein powder(20 gms with 160 mg isoflavones) 1 packet/day; or (D) placebo pill po qAM and casein powder placebo (20 gms) 1 packet/day.

The participant will be issued a supply of study powder and pills and vasomotor symptom diaries at the participating sites discretion. During the study period, participants will take one pill and consume one packet of study powder each day. Participants will be instructed to begin their study treatments on a **Sunday**, in order to make it easier to complete the symptom diaries. Participants will be instructed to document symptoms in the diary each day and to indicate if they took their pill and study powder each day.

At week 2, the participant will be contacted by telephone to complete forms and check compliance. Patients should be advised to have blood pressure checked and report result to research personnel. Study coordinators will evaluate how he is doing in completing the

Comprehensive Cancer Center of Wake Forest University
CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

diaries, to see if he has any questions about the study powder and pills, and to encourage compliance.

At week 4, the participant will be contacted by telephone to complete forms and check compliance. Patients will also be asked to return their 4 week Hot Flash Symptom and Adherence Diaries to the study coordinators.

At week 8 the participant will be contacted by telephone to complete forms and check compliance. Participants will also be asked to return their 8 week Hot Flash symptom and Adherence Diaries to the study coordinators. During the phone contact, patients will be instructed to taper their pills to one every other day at the beginning of week 13.

At the week 13 visit, patients will come to the clinic to be weighed and have their blood pressure measures. They will be asked to return their remaining powders, pill bottle, and pills, and all of their remaining symptom diaries.

Participants who fail to return study materials at the designated intervals will be called by the study staff to determine if the study materials were received and to address any problems or concerns.

Study forms will be reviewed by the study coordinators and participants will be called, if necessary, to complete any missing information.

Candidates who are screened during a clinic visit and are eligible and willing to participate in the study, will be asked to complete the informed consent form at that visit, if possible. Patients signing the informed consent form will be asked to complete a vasomotor symptom diary for the next 7 days to document their baseline level of hot flashes. This week long period will also enable study personnel to determine if the patient is able to comply with completing the diary correctly during the entire 7 day period. Candidates experiencing difficulty in completing the diary correctly and/or completely will be counseled again in correct diary completion, and will be asked to complete a second 7 day vasomotor symptom diary to see if their recording of vasomotor symptoms improves. At the end of the second 7 day period, if the patient still has not completed the diary correctly and/or completely, the candidate will not progress to the study intervention phase of the study and will be dropped.

The **pre-study** hot flash symptom diary does not have to start on a Sunday.

Additionally, the candidate must have an average of four or more hot flashes per day (i.e., 28 or more hot flashes for the week) and must report that his symptoms were moderate to severe. Candidates reporting fewer flushes will be deemed ineligible.

Adherence to Study Strategies: Several strategies will be used to assure that study participants remain in the study and that study participants adhere to their treatment regimen. We will provide written instructions to the participants to help them integrate study pill and powder consumption into daily schedules as well as provide recipes and suggestions for improving the palatability and flavor of the study powder. Participants will be encouraged to contact study staff should problems arise.

4.4.1 **Intervention assessments**

- **Vasomotor Symptom and Adherence Diary:**

Comprehensive Cancer Center of Wake Forest University
CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

Hot flush assessment will be performed daily using a modification of a form validated by Loprinzi et al.(1994) The weekly patient diary will assess the following:

- number of hot flushes/night sweats in 24-hour period
- severity of hot flushes
- amount of powders and pills consumed

- **Quality of life:** The Functional Assessment of Cancer Therapy- Prostate (FACT-P) is a multidimensional measure of quality of life in prostate cancer patients. It consists of 39 items which assess an individual's current status in five subscales: physical well-being, social/family well-being, emotional well-being, functional well-being, and additional concerns specific to prostate cancer. The FACT-P is a commonly used instrument for quality of life in prostate cancer patients and has established validity, reliability, and sensitivity to detect change over time.
- **Soy food questionnaire/dietary screener:** To screen for dietary consumption of soy foods. Participants will be instructed to consume their usual diet throughout the study and to avoid consuming soy foods or soy-based supplements.
- **Medication Form/assessment of antibiotic use** - Since gastrointestinal integrity affects isoflavone absorption, recent antibiotic and medication use will be carefully monitored throughout the study.
- **Height and weight;** it has been reported that compared to normal weight women, very obese women had significantly higher odds of hot flashes. Therefore, we will collect height and weight to calculate BMI.
- **Blood draw-** Included as a participant safety measure. Bilirubin and SGOT will be checked to evaluate liver function at the baseline visit.
- **Two Week telephone contact:** This follow-up telephone contact will be conducted to record blood pressure as reported per participant and compliance to the study protocol.
- **Four week telephone Contact and Maintenance of Cohort:** Follow-up telephone contact will be used to monitor participants for study adherence and side effects at 4 weeks on study. During the phone call, participants will be invited to ask any questions and to discuss any problems with the study, specifically their adherence to the study supplement or pills. Participants' medication supplement and medication diary history will be reviewed. Participants will be instructed to return their diaries.
- **Eight week (telephone):** Follow-up telephone contact will be used to monitor participants for study adherence and side effects at 8 weeks on study. During the phone call, participants will be invited to ask any questions and to discuss any problems with the study, specifically their adherence to the study supplement or pills. Participants' medication supplement and medication diary history will be reviewed. Participants will be instructed to return their diaries.
- **Thirteen week - Close Out Clinic Visit:**
 - Collection of Hot Flash Symptoms and Adherence Diary - Change in hot flashes frequency and severity
 - FACT-P

Comprehensive Cancer Center of Wake Forest University
CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

- Medication and Supplement Form
- Weight
- Blood pressure
- Toxicity Assessment
- Instruction in tapering study medication

4.5 **Pre-Medication - N/A**

4.6 **Treatment Duration**

The time a patient will participate on this study is as follows: a 7 day pre-screening symptom recording and 12 weeks on “treatment”, and one week taper for a total of 13 weeks.

4.7 **Concomitant Treatment**

Patients should receive full concomitant care including: transfusions of blood and blood products, antibiotics, antiemetics, etc. as appropriate – Record reasons and treatment on the flow sheets.

4.8 **Supportive Care Guidelines**

Patients should receive full supportive care including: transfusions of blood and blood products, antibiotics, antiemetics, etc. as appropriate – Record reasons and treatment on the flow sheets

4.9 **Patient Refuses Further Active Treatment**

Refusing active treatment may not necessarily mean the patient withdraws consent. If a patient refuses active protocol treatment after therapy begins, the data collection may continue according to protocol unless the patient also withdraws the consent in writing (to the site PI) which would then discontinue follow-up.

If patient discontinues protocol treatment, clearly indicate this on the flow sheet. Also, continue to follow patient on study and submit all patient completed data management forms. Contact DMC at (336) 713-3172 for any questions.

5. RADIATION THERAPY – N/A

6. SURGERY – N/A

7. OTHER THERAPY – N/A

8. PATHOLOGY/TISSUE BANK – N/A

9. PROTOCOL SPECIFIC TRAINING REQUIREMENTS – N/A

10. CORRELATIVE/SPECIAL STUDIES – N/A

11. STUDY PARAMETERS

Physical exam and lab tests required within 3 months of registration.

| Study Measure | Pre-study Period | Baseline | Week 2 Telephone contact | Week 4 Telephone contact | Week 8 Telephone contact | Week 13 Clinic contact |
|--|------------------|----------|--------------------------|--------------------------|--------------------------|------------------------|
| Physical Exam | X ^A | | | | | |
| Hot Flash Symptom Diary (Appendix A) | X ^B | | | | | |
| Hot Flash Symptom and Adherence Diary (Appendix B) | | X | X | X | X | X |
| Soy Food Questionnaire (Appendix C) | | X | | | | |
| Toxicity Assessment Sheet (Appendix K) | | X | X | X | X | X |
| Fact-P (Appendix F) | | X | | | | X |
| Medications & Supplement Form (Appendix E) | | X | X | X | X | X |
| Total Bilirubin (Appendix H) | X ^A | | | | | |
| SGOT (AST) (Appendix H) | X ^A | | | | | |
| Height (Appendix H) | | X | | | | |
| Weight (Appendix H) | | X | | | | X |
| Blood Pressure (Appendix H) | | X | X ^C | | | X |

(A) Must be completed within the last 3 months.

(B) Must be completed in a 7 day time period.

(C) Patient needs to have blood pressure monitored and results reported to research personnel.

12. REGISTRATION PROCEDURES

A form 310 or IRB letter of approval and an IRB approved consent form must be received by the Research Base Protocol Information Office – Attn: Site Coordinator prior to patient registration. Fax: (336)716-6275. **CTSU Participants: Refer to the CTSU Logistical Appendix N for site registration and patient enrollment instructions.**

Fill out Appendix D, “Eligibility Checklist / Registration Form”. Use this to complete the on-line registration.

Log on to the CCCWFU Research Base registration web site at <<http://www.phsapps.wfubmc.edu/CCRBIS/Login/defaultlogin.cfm>>. Enter your user name and

Comprehensive Cancer Center of Wake Forest University
CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

password (which may be obtained by contacting Ping Tan at ptan@wfubmc.edu or June Fletcher-Steede at jsteede@wfubmc.edu.) *In the 'Patient Registration and Protocol Information' table, click the 'Register Patient/Patient Info', with the corresponding protocol number found in the drop down box to the right. Fill in the eligibility criteria forms using the drop down boxes.* If further information is needed by Biologics or Data Management, they will contact you. Once the patient information has been entered online print a copy of the eligibility checklist/registration form for your records. Press the submit button, a confirmation page will appear. **Print this confirmation sheet for your records.** The CCCWFU On-line Protocol Registration/Eligibility form, the initial flow sheet, signed consent, histology reports, scan reports and lab reports (as required in protocol) should be faxed to 336-713-6476 or mailed to Data Management:

Data Management Center
Department of Radiation Oncology
WFUBMC
Medical Center Boulevard
Winston-Salem, NC 27157

These forms should be retained in the patient's study file. These forms will be evaluated during an institutional NCI/CCCWFU CCOP Research Base site member audit.

If you have questions related to the registration process or require assistance with registration, please contact the CCCWFU CCOP Research Base DMC between 8:30am and 4:00pm EST, Monday through Friday at (336) 713-6507.

13. DATA SUBMISSION PROCEDURES

Data forms will be submitted to the CCCWFU CCOP Research Base, Attn: Data Management Center, Outpatient Comprehensive Cancer Center, Medical Center Boulevard, Winston-Salem, NC 27157-1030 according to the timetable below:

| Form | Submission Schedule |
|--|-----------------------------|
| Hot Flash Symptom – Pre-study | ≤ 1 week from registration |
| Signed, Protocol Specific Consent Form | ≤ 1 week from registration |
| Eligibility Checklist | Baseline |
| Soy Food Questionnaire | Baseline |
| Hot Flash Symptom Adherence Diary | Baseline, 2, 4, 8, 13 weeks |
| Medications & Supplement Form | Baseline, 2, 4, 8, 13 weeks |
| Lab reports | ≤ 1 week from registration |
| Histology Report | ≤ 1 week from registration |
| Flow sheet | Baseline, 2, 4, 8, 13 weeks |
| Phone Contact Sheet | 2 weeks, 4 weeks, 8 weeks |
| Toxicity Sheet | Baseline, 2, 4, 8, 13 weeks |
| FACT-P | Baseline, 13 weeks |

14. ADVERSE EVENT REPORTING

Federal regulations require that investigators report adverse events and reactions in a timely manner.

Comprehensive Cancer Center of Wake Forest University
CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

Toxicity Criteria- Toxicity will be determined using the revised NCI Common Toxicity Criteria (CTC) version 3.0 for Toxicity and Adverse Event Reporting. A copy of the CTC Version 3.0 can be downloaded from CTEP homepage (<http://ctep.info.nin.gov>) and is included as an Appendix.

14.1 Definitions and Terminology

An adverse event is defined as an undesirable, unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure. This may be a new event that was not pre-existing at the beginning of treatment, a pre-existing event that recurs with increased intensity or frequency subsequent to the beginning of treatment or an event though present at the beginning of treatment becomes more severe following initiation of treatment. These undesirable effects may be classified as “known or expected” or “unknown or unexpected”.

Known/expected events are those that have been previously identified as having resulted from administration of the agent or treatment. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

Unknown/unexpected events are those thought to have resulted from the agent, e.g. temporal relationship but not previously identified as a known effect.

Assessment of Attribution

In evaluating whether an adverse event is related to a procedure or treatment, the following attribution categories are utilized:

- Definite - The adverse event *is clearly related* to the treatment/procedure.
- Probable - The adverse event *is likely related* to the treatment /procedure.
- Possible - The adverse event *may be related* to the treatment/procedure.
- Unlikely - The adverse event *is doubtfully related* to the treatment/procedure.
- Unrelated - The adverse event *is clearly NOT related* to the treatment/procedure.

14.2 Grading Of Adverse Events

Unless specified otherwise, the NCI Common toxicity Criteria (CTC) v3.0 is used to grade severity of adverse events for this protocol.

- Grade 1 - Mild AE
- Grade 2 - Moderate AE
- Grade 3 - Severe AE
- Grade 4 - Life-Threatening or disabling AE
- Grade 5 - Death related to AE

14.3 General Guidelines

In order to assure complete and timely reporting of adverse events and toxicity, the following general guidelines are to be observed. When protocol-specific guidelines indicate more intense monitoring than the standard guidelines, the study-specific reporting procedures supersede the General Guidelines. A protocol may stipulate that specific grade 4 events attributable to treatment

Comprehensive Cancer Center of Wake Forest University
CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

are expected and may not require the standard reporting, however, exceptions to standard reporting must be specified in the text of the protocol.

Adverse Event reporting begins after the patient is registered to the study drug (or begins the run-in period of the study or begins the wash out period of the study). Adverse Events occurring within 30 days of study completion must be reported via FDA form 3500 (Medwatch).

1. The protocol Principal Investigator will report to the RB Data Management Staff within 24 hours of discovering the details of all unexpected severe, life-threatening (grade 4) and fatal adverse events (grade 5) if there is reasonable suspicion that the event was definitely, probably, or possibly related to protocol treatment.
2. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of attribution require notification within 24 hours of discovery.
3. Any medical event requiring hospitalization or prolongation of existing hospitalization must be reported regardless of attribution or whether the adverse event is expected or unexpected.
4. A written report, including all relevant clinical information and all data collection forms due up to and including the date of the event will be sent by mail or FAX to the RB DMC within 10 calendar days unless specified otherwise within the protocol. The material must be labeled: "Attention: Adverse Event Reporting".
5. The Research Base Grant PI, Clinical Research Oversight Committee and/or Study Chair will take appropriate action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures, if this warranted.
6. Serious adverse events will be communicated by phone and MedWatch as soon as identified to the CCCWFU Research Base Data Management Center (DMC) at (336) 713-4390. The DMC is responsible for communicating with the FDA, the drug sponsor, WFU IRB, and other regulatory agencies, as well as reporting all SAE's grade 4 or 5 to the Clinical Research Oversight Committee (CROC).
7. For events that require telephone reporting to the NCI, Investigational Drug Branch, the FDA or study sponsor, the investigator may first call the Research Base DMC unless this will unduly delay the required notification process.
8. A copy of all correspondences sent recipients of the notification, e.g. NCI, IDB, FDA must be submitted to the Research Base DMC. Copies must include the RB study and case (PID #).
9. Institutions must comply with their individual Institutional Review Board (IRB) policy regarding submission of documentation of adverse events. All MedWatch reports should be sent to the local IRB in accordance with the local IRB policies.
10. When submitting AE, SAE reports and supporting documentation, the study number and the case number (PID #) must be recorded on the FDA Form 3500 (MedWatch) so that the case may be associated with the appropriate study file.

Comprehensive Cancer Center of Wake Forest University
CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

14.4 **Cancer Prevention Agents Commercially Available**

Cancer Prevention agents may or may not be commercially available, may or may not be sponsored by a third party and may or may not be under an IND.. The Adverse Event Reporting for all commercially available drugs should be reported via the FDA Form 3500 (MedWatch).

Table A: Reporting requirements for Adverse Events (AEs) and Serious Adverse Events (SAEs).

| | MILD | | | | MODERATE | | | | SEVERE | | | |
|---|----------------------|-------------------------|----------------------|-------------------------|----------------------|-------------------------|----------------------|-------------------------|----------------------|-------------------------|----------------------|-------------------------|
| | 1 | | 1 | | 2 | | 2 | | 3 | | 3 | |
| | Unexpected | | Expected | | Unexpected | | Expected | | Unexpected | | Expected | |
| | With Hospitalization | Without Hospitalization | With Hospitalization | Without Hospitalization | With Hospitalization | Without Hospitalization | With Hospitalization | Without Hospitalization | With Hospitalization | Without Hospitalization | With Hospitalization | Without Hospitalization |
| Unrelated Unlikely | 10 Calendar Days | Not Required | 10 Calendar Days | Not Required | 10 Calendar Days | Not Required | 10 Calendar Days | Not Required | 10 Calendar Days | 10 Calendar Days | 10 Calendar Days | 10 Calendar Days |
| Possible Probable Definite | 10 Calendar Days | Not Required | 10 Calendar Days | Not Required | 10 Calendar Days | 10 Calendar Days | 10 Calendar Days | 10 Calendar Days | 10 Calendar Days | 10 Calendar Days | 10 Calendar Days | 10 Calendar Days |

| | LIFE-THREATENING/DISABLING | | | | DEATH | | | |
|---|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| | 4 | | 4 | | 5 | | 5 | |
| | Unexpected | | Expected | | Unexpected | | Expected | |
| | With Hospitalization | Without Hospitalization | With Hospitalization | Without Hospitalization | With Hospitalization | Without Hospitalization | With Hospitalization | Without Hospitalization |
| Unrelated Unlikely | 10 Calendar Days | 10 Calendar Days | 10 Calendar Days | 10 Calendar Days | 24-hour; 5 Calendar Days | 24-hour; 5 Calendar Days | 24-hour; 5 Calendar Days | 24-hour; 5 Calendar Days |
| Possible Probable Definite | 24-hour; 5 Calendar Days | 24-hour; 5 Calendar Days | 24-hour; 5 Calendar Days | 24-hour; 5 Calendar Days | 24-hour; 5 Calendar Days | 24-hour; 5 Calendar Days | 24-hour; 5 Calendar Days | 24-hour; 5 Calendar Days |

CTEP, NCI Guidelines

Comprehensive Cancer Center of Wake Forest University
CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

14.5 **Unblinding Guidelines**

In the event a patient on this study develops a life-threatening toxicity or serious adverse event for which the patient's physician or other health care professional feels that it is in the patient's best interest to know what drug they are taking (active study drug(s) or placebo), the following procedure should be followed:

- Step 1: the patient's physician or a designated health care professional should call the Wake Forest University Baptist Medical Center Physician Access Line (336-716-7654) and ask that Dr. Ed Shaw, Principal Investigator of the CCCWFU CCOP Research Base, be contacted immediately either in his office, by pager, or at home. In the event Dr. Shaw cannot be reached, the PAL operator should contact Dr. Glenn Lesser, Chair, Cancer Treatment Protocols in his office, by pager, or at home. If neither Dr. Shaw nor Dr. Lesser can be reached, the PAL operator should contact Gina Enevold, Research Base Administrator, either in her office, by pager, or at home.
- Step 2: Once contact has been made; the patient's physician or health care professional should explain the reason for the request to unblind the treatment arm that the patient is on. If the Research Base representative feels that the toxicity (AE/SAE) is possibly, probably or definitely related to the study drug, then the next step will be followed.
- Step 3: The responsible Research Base representative will call the pharmacist @ Biologics, Inc.(phone: 1-800-850-4306). There is an "on-call" service provided 24 hours a day, seven days a week for the Chemical Drug Trials unblinding service. The Biologics pharmacist may contact the patients' physician and/or health care professional directly with the unblinding information. Written documentations of the unblinding process will be sent to the Research Base Principal Investigator by Biologics, Inc.

OR-

The responsible Research Base representative will locate the envelope which contains the code for all CCCWFU CCOP Research Base clinical trials which are double-blind. It is located in the Outpatient Comprehensive Cancer Center, Department of Radiation Oncology (first floor)in the Research Base Clinical Trials Office (phone: 336-713-6519), in a locked file cabinet drawer which bares the label "Unblinding Code". Only Dr. Shaw, Dr. Lesser, Ms. Enevold, and the Research Base Biostatistician (who maintains the unblinding code envelope for the appropriate Research Base trials) have a copy of the key.

- Step 4: In the event that the patient's treatment is unblinded, that patient will be taken off study with no further study follow-up. Appropriate procedures for grading toxicities, assigning causality, and reporting severe adverse events (if applicable), should be followed for each protocol for all Phase III Clinical Trials. The event will be reviewed by the CCCWFU Clinical Research Oversight Committee. All Phase III Clinical Trials will be reviewed by the CCOP Research Base Data Safety and Monitoring Board.

Comprehensive Cancer Center of Wake Forest University
CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

14.6 CDUS Reporting

The CCCWFU CCOP Research Base Data Management Center will submit quarterly reports to DCP/CTEP by electronic means using the Clinical Data Update System (CDUS)

15.0 STATISTICAL CONSIDERATIONS

15.1 Objectives

The primary objective of this randomized trial is to assess the effect of soy and Effexor on the hot flash symptom severity score in men undergoing hormonal manipulation for treatment of prostate cancer. Secondary objectives are to assess the effect of these two treatments on quality of life in men and to evaluate adherence to each treatment regimen and to assess participant drop out rate. Hot flash severity will be quantitated using the symptom diary. The daily symptom severity score will be calculated as the product of the frequency and the average severity (1=mild, 2=moderate, and 3=severe) of the symptoms, and these daily scores will be averaged weekly. The primary end point is the percentage change in the hot flash score from baseline to 12 weeks relative to the baseline value (i.e., $100 \times (12 \text{ week score} - \text{baseline score}) / \text{baseline score}$). Quality of life will be quantitated using the FACT-P instrument. For adherence, we will estimate the proportion of men who complete the study, the average number of weeks of participation, the proportion of men who take 80% of their prescribed pills and supplement, and the average amount of pills and supplement taken.

15.2 Study Design

Participants will be stratified by severity of disease (metastatic, not metastatic) and baseline severity of hot flashes and randomized to receive no treatment (soy and Effexor placebos), soy only, Effexor only, or the combination of soy and Effexor with equal probability, using blocked randomization to ensure approximately equal accrual to each treatment throughout the study. Block sizes of varying length will be determined randomly to make it difficult to predict future assignments from past assignments. Treatment assignments will be generated using Proc Plan in SAS and incorporated into the randomization table in our registration facility. Various codes will be assigned to each treatment so that unblinding of a single participant will not unblind the entire arm.

A 2 x 2 factorial study design will be used to assess the activity of each treatment regimen. For design purposes we will base our sample size on data provided by Sloan et al (2001) on the percentage reduction in the hot flash severity score. They state that the standard deviation of the hot flash score percentage reduction is 25%. We will power the study to detect a 12.5% marginal difference in the percentage reduction in the hot flash score during the 12th week compared to baseline between those who receive soy and those who do not and between those who receive Effexor and those who do not, assuming 1) each treatment, given alone, would increase the % reduction in hot flash score by 15%, and 2) the effects of soy and Effexor are partially (though not completely) additive (so that the two treatments, in combination, will increase the % reduction by 25%). Quella et al (1999) indicate that a placebo treatment will typically reduce hot flash activity by approximately 20% - 30%. Thus assuming the patients randomized to the control arm (no soy & no Effexor) have a

Comprehensive Cancer Center of Wake Forest University
 CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

25% reduction in the hot flash score, we expect those patients who receive soy but no Effexor and those patients who receive Effexor but no soy to have reductions in the hot flash score of 40%, while those patients who receive both soy and Effexor to have a reduction of 50% (Table 10.2.1).

Table 10.2.1. Anticipated reductions in the hot flash score for the various treatments

| | No Soy | Soy | Overall |
|------------|--------|-----|---------|
| No Effexor | 25% | 40% | 32.5% |
| Effexor | 40% | 50% | 45% |
| Overall | 32.5% | 45% | |

Based on a two-sample t-test, a fixed sample size of 128 men (32 per cell) is needed to provide 90% power for detecting a 12.5% treatment effect due either to soy or Effexor at the 5% overall one-sided level of significance (i.e., each treatment hypothesis will be tested at the Bonferroni corrected .025 level of significance (.05/2), and we use that corrected significance level in the sample size calculation).

15.3 Monitoring Rules

The primary outcome for this study, hot flash severity score, will be monitored according to a two-stage group sequential design that is intermediate between Pocock and O'Brien-Fleming designs in its degree of conservativeness. This design will be applied to both the soy arm and the Effexor arm. Should one arm (e.g., soy) be stopped early, the study will continue and subsequent patients would be randomized to receive either Effexor or the placebo. The stopping boundaries are shown in Table 16.3.1, both in terms of the actual mean difference in hot flash severity reduction between the two groups and the p-value for the group comparison. The maximum sample size for this two-stage design, should both stages be necessary, is 132 and is slightly higher than that of a fixed sample design. The interim analysis will be conducted after 66 analyzable patients (i.e., patients with twelve week outcome measures) are accrued to the study (which we anticipate will be after 88 actual accruals assuming a 25% dropout rate). At the first stage, the study will be terminated and H_0 rejected if the difference (treatment arm – placebo arm) in mean hot flash reduction is greater than .1451. The study will be terminated and we will fail to reject H_0 if the difference in hot flash severity reduction is less than .0044. Otherwise the study will continue and another 66 analyzable patients accrued. At that point, H_0 will be rejected if the difference in mean hot flash reduction is greater than .0893. (a difference for rejection corresponding to a one-sided p-value of .0199).

Table 16.3.1. Interim monitoring plan allowing early termination for efficacy and lack of an effect

| Stage | N (analyzable) | Total N* | Stop – Reject H_0 | | Stop – Fail to Reject H_0 | |
|-------|----------------|----------|---------------------|-----------|-----------------------------|-----------|
| | | | Difference > | p-value < | Difference < | p-value > |
| 1 | 62 | 83 | .1528 | .0081 | .0289 | .3245 |
| 2 | 124 | 166 | .0909 | .0216 | .0909 | .0216 |

* Allowing for 25% dropout

Comprehensive Cancer Center of Wake Forest University
CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

Operating characteristics for the group sequential design presented in Table 16.3.1 are shown in Table 16.3.2. Under the null hypothesis, the probability of stopping early and rejecting H_0 is .009 while the probability of stopping early and failing to reject H_0 is .528. The expected sample size under H_0 is 96.8. Under the alternative hypothesis, the probability of stopping early and rejecting H_0 is .372 while the probability of stopping early and failing to reject H_0 is .025. The expected sample size under H_1 is 106.1.

Table 16.3.2. Operating Characteristics for Interim monitoring plan allowing early termination for efficacy and lack of an effect

| True Difference | <i>Probability of stopping and failing to reject H_0</i> | | <i>Probability of stopping and rejecting H_0</i> | | ESS |
|-----------------|---|---------|---|---------|-------|
| | Stage 1 | Stage 2 | Stage 1 | Stage 2 | |
| 0 | .528 | .447 | .009 | .016 | 96.8 |
| .15 | .025 | .175 | .372 | .428 | 106.1 |

Assuming the dropout rate is approximately 25% (similar to that seen in the Quella et al (1999) study), we will need to accrue a maximum of 176 men. The actual sample size will be either 88 or 176 (66 or 132 analyzable patients), depending on whether the second stage is necessary.

15.4 Feasibility

The CCCWFU CCOP Research Base includes the Comprehensive Cancer Center of Wake Forest University, as well as 25 community cancer centers in 8 CCOP's and 4 non-CCOP aligned community cancer centers for a total of 30 participating sites. At the September 2004 Annual Meeting of the Research Base, ten sites expressed an interest in participating. Primary and metastatic prostate cancer is the most common solid tumor diagnosed/treated in the Research Base. Since androgen deprivation is used in men with high risk, locally advanced, and metastatic disease, the majority of these patients will be potentially eligible. Wake Forest University alone will enter 2 patients per month. Conservatively assuming that the 3 top-accruing Research Base sites enroll 1 patient per month and all the other sites combined enter 2 patients per month, accrual will then be approximately 7 per month, or 88 per year, for a total accrual period of 2.1 years.

Comprehensive Cancer Center of Wake Forest University
 CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

15.5 Inclusion of Women and Minorities

Only men and members of all ethnic groups are eligible for this trial. The proposed study population is illustrated in the table below.

| Gender | Race/Ethnicity | | | | | Total |
|--------|-------------------------------|-------------------------------|----------|---------------------------|-----------------|-------|
| | White, not of Hispanic Origin | Black, not of Hispanic Origin | Hispanic | Asian or Pacific Islander | American Indian | |
| Male | 137 | 19 | 13 | 3 | 4 | 176 |
| Female | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 137 | 19 | 13 | 3 | 4 | 176 |

Full text of the Policies, Guidelines, and Procedures pertinent to this section is available on the NIH web site
http://grants.nih.gov/grants/funding/women_min/guidelines_update.htm

15.6 Recruitment/Retention Plan

The research PI or designee at each WFU Research Base CCOP, which may include the clinic physician, resident, research nurse or research assistant, will review cancer registry and medical chart information to identify patients eligible for this protocol. Patients identified using these methods will be asked to join the study during their next clinic visit / consult. Patients not scheduled for a clinic visit within the next 6 weeks may be sent a letter from their physician informing them about the study, and indicating that a research nurse/assistant will be calling them within the next 2 weeks to tell them more about the study and to see if they are eligible to participate.

Patients screened during a clinic visit who are eligible and willing to participate in the study, will be asked to complete the informed consent form at that visit, if possible. Patients signing the informed consent form will be asked to complete a hot flash diary for the next 7 days to document their baseline level of hot flashes. This week long period will also enable study personnel to determine if the patient is having 28 or more hot flashes per week, and is able to comply with completing the diary correctly during the entire 7 day period. Patients experiencing difficulty in completing the diary correctly and/or completely will be counseled as to how to complete the diary correctly, and will be asked to complete a second 7 day hot flush diary to see if their recording of vasomotor symptoms improves. At the end of the 7 day period, if the patient still has not completed the diary correctly and/or completely, the patient will not progress to the pill and powder taking phase of the study and will be dropped. Patients who are having less than 28 hot flashes per week, will not proceed to the pill and powder taking phase, as they will be ineligible for the protocol.

Comprehensive Cancer Center of Wake Forest University
CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

15.7 Analysis

Descriptive reports will consist of summary statistics (means, standard deviations, proportions, etc.) for patient characteristics and outcome measures by treatment arm, actual versus projected accrual, participation by the various CCOPs and WFU, and quality control information (missing data, range, field, consistency, and validity checks, etc.). Tables, graphs, and charts will be used to illustrate the data when appropriate. Any untoward adverse events or other unusual results will be reported to the IRB and the CCCWFU Clinical Research Oversight Committee for further action.

Each of the outcomes described above will be analyzed and reported separately. Exact confidence intervals will be provided for the estimated proportions (e.g., toxicities, adverse events, proportion exhibiting a 50% improvement in hot flashes) and approximate confidence intervals for the continuous measures (e.g., percentage reduction in hot flash scores, raw hot flash scores, quality of life). Linear regression (i.e., a two-sample t-test) will be used to assess the unadjusted effects of each treatment on the percentage reduction in the hot flash score during the 12th week and in post-treatment quality of life. Chi-squared tests will be used to assess unadjusted treatment differences in the binomial outcomes such as proportion of patients responding to treatment (as defined above) and successful adherence.

Analysis of covariance will be used to assess treatment differences in the week 12 hot flash score percentage change and quality of life after adjusting for pretreatment values and pretreatment patient characteristics. Adjustments will be made to ensure the analyses match the design, to correct for chance imbalances in important prognostic factors and to improve the precision of the group comparisons by accounting for that part of the variance due to the variability in the patient characteristics. Regression diagnostics, residual plots, and exploratory analyses will be done to find appropriate transformations for the variables in these analyses. Order of priority in choosing a transformation will be to satisfy the 1) linearity assumption, 2) homogeneity of variances assumption, and 3) normality assumption. Logistic regression will be used to assess differences in dichotomous outcomes (e.g., specific toxicities should sample sizes be large enough) between groups after adjustment for covariates.

Vasomotor symptom diaries are completed daily and mean scores will be calculated weekly based on these daily values. These repeated measures will be analyzed using a mixed model analysis of variance. The major hypotheses will be tested by the significance of the group by time interactions and the individual group comparisons (when no interaction is present and when baseline values are treated as covariates). There are likely to be missing end point measurements due to missed visits or patients dropping out of the study, and we propose to analyze the data using SAS Proc Mixed. This program provides computational algorithms for obtaining maximum likelihood estimates, allows for unbalanced designs, missing data at some times, structured or unstructured covariance matrices, and growth curve parameterizations of time effects. A maximum likelihood approach is appropriate if data are missing at random. If, however, the data are not missing at random, data analysis is more difficult and inferences must be made cautiously. It is possible that some of the missing data in this study will be related to the unobserved outcome measures. For example, those men with increased vasomotor symptoms might be more likely to drop out of the study. Sensitivity analyses will be done to examine the effects that assumptions about missing data have on the results, and model-based strategies and post-hoc stratification analyses will be explored.

Comprehensive Cancer Center of Wake Forest University
CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

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Comprehensive Cancer Center of Wake Forest University
CCOP Research Base CCCWFU # 97405: NCI # WFU-CCC 06-02-06

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