Comprehensive Cancer Center of Wake Forest University
CCOP Research Base CCCWFU # 97106: NCI # WFU 05-04-01

**Title: A Randomized Study to Determine whether ArginMax Improves the Sexual Function and Quality of Life in Female Cancer Survivors**


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Comprehensive Cancer Center of Wake Forest University
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**WFU IRB #:**
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Amend # 6 – 03-11-08
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Comprehensive Cancer Center of Wake Forest University
CCOP Research Base CCCWFU # 97106: NCI # WFU 05-04-01

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**A Randomized Study to Determine whether ArginMax Improves the Sexual Function and Quality of Life in Female Cancer Survivors**

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**SCHEMA**

| | | | |
|---|---|---|---|
| **Stratification:** | **Pelvic** | **vs** | **Non Pelvic Malignancies** |
| | **Performance status** | | **0,1 vs 2** |
| | **Ovary functional** | | **yes vs no** |

**Baseline ECOG: 0-2**

**Randomization**

**Arm 1**
**ArginMax 3 caplets twice daily x12 wks**

**Arm 2**
**Placebo 3 caplets twice daily x 12 wks**

**Required Sample Size:** 144 women have been accrued to this study. An additional 39 minority patients will be accrued. (See section 15.1 last paragraph)

**Study Duration:** 2 years

**Eligibility:**
1. Any female cancer survivor who identifies herself as concerned with her sexual quality of life and answering yes to all three of the screening questions.
   - Are you dissatisfied with your sexual quality of life?
   - Do you have problems with sexual arousal or fulfillment?
   - Are you interested in improving your sex life?
2. At least 6 months following completion of all cancer therapy. Hormonal therapy and treatment with Herceptin are allowed.
3. No evidence of active cancer based on physical exam and/or radiographic images obtained within 3 months of study.
4. Must be minority (non-white) female.

# 1. BACKGROUND

## 1.1 STUDY DISEASE

Sexual dysfunctions are characterized by disturbances in sexual desire and in the psychophysiological changes associated with the sexual response cycle in men and women. (DSM IV) Data from the National Health and Social Life Survey (NHLSLS) in 1992 sampled 1749 women and confirmed that poor to fair health and emotional problems or stress were two predictors for low desire, arousal disorder and sexual pain.(2) Treatment for all types of cancers can have psychosexual consequences. (3) Anderson estimates that sexual functioning morbidity occurs for up to 90% of cancer patients who have the disease at the most prevalent sites. (4) A qualitative study found that altered psychosexual status is affected by loss of sexual sensations, loss of menstruation (associated with old age) and loss of womanhood. (5) Wilmoth states that the core variable, altered sexual self, did not appear to be unique to women with breast cancer. It appears to mirror the experience of healthy women as they acknowledge their perimenopausal status. However, cancer has sudden and pronounced effects compared to natural aging which is more gradual. Effects can be multifactorial and either physical or psychological. Women may have reduced sexual desire, dyspareunia, increased vaginal dryness and reduced sexual attractiveness. Fatigue and decreased emotional well-being can also lead to reduced sexual functioning. Surgical intervention may contribute to scarring, loss of self-concept because of organ removal, and pain. A recent report of 206 patients with breast cancer surveyed women before and after cancer therapy for their sexual satisfaction. (6) Women with advanced cancer and early cancer both reported decreased satisfaction following treatment (73% vs 56% and 73% vs 50%). Treatment for cervical cancer can result in anatomic and physiological changes (e.g., changes in vaginal lubrication, vaginal stenosis) that potentially may affect sexual functioning.

Although research on sexual dysfunction after treatment for cervical cancer has been conducted for over 30 years, little more is known today than in the 1970s about the causes of sexual problems after cervical cancer, the relation between type of treatment for cervical cancer and prevalence of different types of sexual problems, or the kinds of behavioral or medical interventions that may remediate them effectively. Such sexual problems as loss of interest in sex or pain with sexual activity are common in women who survive cervical cancer.(7,8) Bergmark et al. found that a similar percentage of cervical cancer survivors (5 years from diagnosis) and controls reported low sexual desire, but that this reduced desire was more distressing to survivors. Survivors reported less vaginal lubrication and genital swelling when sexually aroused compared with controls and were more distressed by these problems. They also reported more dyspareunia, vaginal bleeding during intercourse, and vaginal changes (reduction in length or elasticity of the vagina) compared with healthy controls but were similar in frequency of intercourse and the prevalence of problems with orgasm.

Radiation may cause physical problems depending on the area of the body treated including diarrhea, ovarian dysfunction, vaginal shortening/stenosis, shortness of breath, and skin changes. Persistent sexual dysfunction and adverse vaginal changes were reported throughout the 2 years after RT, with small changes over time: approximately 85% had low or no sexual interest, 35% had moderate to severe lack of lubrication, 55% had mild to severe dyspareunia, and 30% were dissatisfied with their sexual life. (9) Chemotherapy can cause peripheral neuropathy, fatigue, weight changes, alopecia and other systemic symptoms that may affect emotional well being. A recent review of studies evaluating sexual functioning in survivors of breast cancer has been published and concludes that women

receiving chemotherapy are at higher risk for sexual dysfunction. Prevalence rates for sexual dysfunction vary from 15% for physiological arousal difficulties to 64% for reduced sexual desire. (10) Differences in sexual functioning between women receiving mastectomy or lumpectomy were subtle.

There is a general lack of knowledge about the types and frequency of sexual problems that occur in women cancer survivors. Anderson indicated that among women who had no sexual dysfunction prior to undergoing cancer treatment, approximately 50% were diagnosed with at least one dysfunction during the post treatment year. (11) The proposed study will offer an intervention to patients who have identified themselves as having sexual arousal dysorder.(12) Assessment of all patients with validated tools will provide information needed to assess the affect that ArginMax may have on these patients. It will also help identify particular areas that may lead to future research interventions (timing of interventions as well as particular symptoms leading to sexual dysfunction.)

Various instruments to diagnose and measure female sexual function have been developed. Validation insures that reliability, validity, responsiveness, and ability to measure minimal meaningful differences are demonstrated. The Female Sexual Function Index (FSFI) is a brief, 19-item self-report measure of female sexual function that provides scores on five domains of sexual function as well as a total score. It takes approximately 15 minutes to administer. It was developed on a female sample of normal controls (ages ranged from 21-68) and age-matched subjects with female sexual dysfunction (FSD). It has been shown to discriminate reliably between female sexual dysfunction and control patients on each of the five domains of sexual function.(13)In addition each patient will be assessed with the FACT-G. This is a brief, validated instrument that is used to assess the emotional, social, functional and physical well being of the cancer patient.(14) Because there are now normative values for the overall score in cancer patients and in the general US population it would make our findings comparable to these populations.

## 1.2 STUDY AGENT(S)

Arginine is believed to be required to carry out the synthesis of nitric oxide that relaxes blood vessels and allows more blood to flow through the arteries and may be responsible for orgasmic sensations. (15) It has been hypothesized that taking extra Arginine will increase nitric oxide levels and increase blood flow to the penis.

(16) A double-blind placebo controlled trial of 50 men with erectile dysfunction tested Arginine and 33% of participants showed improvement compared to 10% in the placebo arm. (17) Female sexual arousal disorder, defined as an inability to achieve or maintain sufficient sexual excitement, including clitoral erection and genital engorgement, is physiologically analogous to male erectile dysfunction in that a deficiency in genital blood circulation compromises the hemodynamics of erection/engorgement. (18) A study using L-arginine with yohimbine tested the subjective and physiological sexual arousal in postmenopausal women with female sexual arousal disorder. Physiological responses were increased compared to a placebo group. (19) A double-blind placebo-controlled study of ArginMax was open to women over the age of 21 years with an interest in improving their sexual function. (20) After 4 weeks 73.5% of the ArginMax group improved in satisfaction with their overall sex life, compared with 37.2% of the placebo group ($p<0.01$). Notable improvements were also observed in sexual desire, reduction of vaginal dryness, frequency of sexual intercourse, and orgasmic and clitoral sensation. No significant side effects were noted.

1.3 **RATIONALE**

As more patients survive cancer diagnosis and treatment, quality of life issues are gaining importance. It is apparent that all cancers and their treatments may have psychosexual effects. Ekwall et al showed that for women with gynecological cancer, the maintenance of a positive self-image and feelings of sexuality was one of the three issues of central importance in contributing to the quality of their daily living. (1) Little research is available to support intervention that may be effective in improving these problems. This study will identify women who have completed cancer therapy and are disease free and who identify themselves as having sexual arousal disorder.

## 2. OBJECTIVES

Hypothesis: ArginMax will improve sexual function for women who are at least 6 months from active treatment of cancer and are without evidence of cancer.

2.1 **Primary Protocol Objective**

The primary goal is to determine whether ArginMax improves the quality of life and sexual function for women cancer survivors by using the FACT-G and FSFI instruments.

2.2 **Secondary Protocol Objectives**

1) To assess differences in quality of life between the two groups.
2) To determine differences in toxicity between the two groups.
3) To describe the sexual function symptom clusters (if any) in women cancer survivors.
4) To assess the effect of race on sexual function and quality of life.

## 3. PATIENT SELECTION

3.1 **Eligibility Criteria**

3.1.1 Any female cancer survivor who identifies herself as concerned with her sexual quality of life and answering yes to all three of the screening questions.

- Are you dissatisfied with your sexual quality of life?
- Do you have problems with sexual arousal or fulfillment?
- Are you interested in improving your sex life?

3.1.2 Must express interest in sexual activity.

3.1.3 At least 6 months following completion of all cancer therapy. Hormonal therapy and treatment with Herceptin are allowed.

3.1.4 No evidence of active cancer based on physical exam and/or radiographic images obtained within 3 months of study.

3.1.5 Absence of any mental, medical or physical disorder known to affect sexual function.

3.1.6 No participation in another study with an investigational study drug or device during the 30 days prior to start of study drug.

3.1.7 Lab values must meet the following criteria at study entry: WBC ≥ 2000, Hgb ≥ 10gm/dl, creatinine ≤ 1.5 x ULN, plt ≥ 100,000, T Bili ≤ 1.5

3.1.8 ECOG performance status must be 0-2.

3.1.9 Must be able to take oral medication

3.1.10 Must be 18 years old or older

3.1.11 Must be minority (non-white) female.

### 3.2 **Exclusion Criteria**

3.2.1 History of allergic reactions attributed to compounds of similar chemical or biologic composition to ArginMax.

3.2.2 Currently taking any blood thinner such as aspirin (one 81mg aspirin, or one baby aspirin per day allowed), Persantine, Heparin, Lovenox, or Coumadin (low dose Coumadin for catheter patency is allowed).

3.2.3 Patients currently taking Ginkgo Biloba are not allowed on this study.

3.2.4 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac, arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements and/or ability for sexual function.

3.2.5 Pregnant women are excluded from this study because ArginMax may be an agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ArginMax, breastfeeding should be discontinued if the mother is treated with ArginMax.

3.2.6 Because patients with immune deficiency are at increased risk of lethal infections when treated with marrow-suppressive therapy, HIV-positive patients receiving combination anti-retroviral therapy are excluded from the study because of possible pharmacokinetic interactions with ArginMax. Appropriate studies will be undertaken in patients receiving combination anti-retroviral therapy when indicated.

3.2.7 Any planned surgery during study participation.

## 4. SUPPLEMENT THERAPY

### 4.1 **Supplement Information**

ArginMax is a nutritional supplement consisting of extracts of L-arginine, ginseng, ginkgo, and damiana, multivitamins, and minerals. See Table 1, page 6.

Postulated improvements resulting from this study drug for patients would be an improvement in sexual arousal by increasing pelvic vascular blood flow and pelvic vasocongestion, vaginal engorgement, swelling of the external genitalia, and clitoral erection. Components of sexual

dysfunction that would not be expected to benefit would be those resulting from problems classified as sexual pain disorders such as vaginismus or dyspareunia. Because of these effects patients will be stratified as to whether they have been diagnosed with pelvic malignancies or non-pelvic malignancies.

ArginMax contains 50mg of Ginkgo Biloba which is a mild blood thinner. Therefore, ArginMax should not be combined with any strong blood thinners like warfarin. It is recommended that ArginMax be discontinued four weeks prior to any surgery. Although the dose in ArginMax is lower than that known to cause problems, we err on the side of caution.

There has been a single study in vitro that showed Herpes needed L-Arginine to grow. Studies in people have never shown that dietary Arginine influences or causes breakouts. A complete literature search has revealed no unusual breakouts. Many people take Lysine to control their herpes. If so, it is recommended taking ArginMax at a different time of day than Lysine since they compete for absorption.

The initial analysis will be performed and checked by Daily Wellness. A single lot # will be used in this study. The specific specs and analyses for this single lot # at the time of manufacturing will be provided for the researcher's review.

The company uses only high quality GMP or ISO 9000 suppliers. A Certificate of Analysis (C of A) is sent by the supplier with every lot that shows lab testing for active ingredients and lack of contaminants. These are double checked with outside testing only when approving a new supplier, and then only randomly thereon. There has never been a discrepancy between the company's data and the suppliers' data.

If a special outside testing for the product used in this trial is done, they would only test for "marker" compounds, e.g. L-arginine, ginsenosides in ginseng, Vitamin E (oil soluble), and one or two of the B-vitamins (less stable, water soluble). The manufacturer claims it is too expensive to test every single ingredient, and there are plenty of data on which vitamins are least stable. They get a Certificate of Content (C of C) from the manufacturer certifying that they triple checked the amounts added of all other ingredients.

All of the company's label claims have been approved by the FDA (in spite of their disclaimer) and can be proven by their issuance of Certificates of Free Sale (CFS) for all of the company's products.

A third party analysis by American Analytical Chemistry Labs Corporation indicated the following Supplement facts on the following table.

Table 1. **Supplement Facts for Women**

| **AMOUNT PER SERVING** | |
|---|---|
| Vitamin A (as retinyl palmitate) | 5070 IU |
| Vitamin C (as ascorbic acid) | 61.16 mg |
| Vitamin E (as natural d-alpha-tocopheryl succinate) | 31.17 IU |
| Thiamin (as thiamin mononitrate) | 1.85 mg |
| Riboflavin | 1.84 mg |
| Niacin (as niacinamide) | 20.19 mg |
| Vitamin B-6 (as pyrdoxine hydrochloride) | 2.10 mg |
| Folate (as folic acid) | 413 mcg |
| Vitamin B-12 (as cyanocobalamin) | 6.66 mcg |
| Biotin | 328 mcg |
| Pantothenic acid (as calcium pantothenate) | 12.79 mcg |
| Calcium (as calcium carbonate) | 492 mg |
| Iron (as ferrous gluconate) | 9.58 mg |
| Zinc (as zinc gluconate) | 10.08 mg |
| L-Arginine | 2436 mg |
| Korean Ginseng (Panax Ginseng)- root extract | 45.64 ng |
| Ginkgo Biloba- leaf extract | 13.02 mg |
| Damiana (Turnera Aphrodisiaca) leaf | Too little to be detected |
| * Percent Daily Value (%DV) are based on a 2000 calorie diet.<br># Daily Value not established. | |

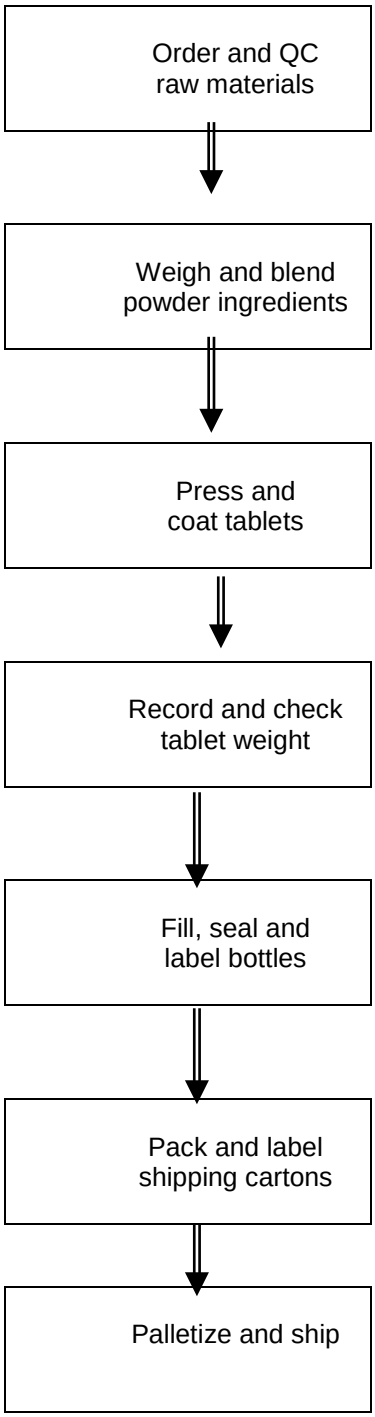
An early report suggested that damiana which is contained in ArginMax had progesterone binding properties. (21) PR binding herbs were found to be neutral or have antagonistic properties in vitro. A more recent report using a human endometrial adenocarcinoma cell line, Ishikawa, which contains an alkaline phosphatase (AP) enzyme sensitive to estrogen stimulation, was used in a bioassay to determine whether Panax ginseng or ArginMax contained estrogenic components. Results demonstrated that neither ArginMax nor Panax ginseng stimulated AP at any of the concentrations tested. And the conclusions were that no estrogenic activity was evident in the sample of Panax ginseng extract tested or in a sample of ArginMax containing this extract in combination with other ingredients. For this reason there seems to be no reason to exclude patients with estrogen or progesterone receptor positive tumors from this study. (22)

4.1.1 **Availability**
**Commercially Available/Sponsor Supplied Agents**

ArginMax is manufactured by Daily Wellness and will be provided to patients at no cost. Daily Wellness will provide ArginMax and placebo. See manufacturing process in table on next page.

DAILY WELLNESS COMPANY®

**ArginMax Tablet Manufacturing Process:** **QC Steps**




1- Verify ingredient name, part # and control #
2- Check appearance and aroma per specifications*
3- Random analytical sampling, as needed*

4- Weigh each material per formula sheet
5- Label with name, lot number and amount
6- Verify and sign off on weights
7- Blend 15 minutes and inspect for homogeneity

7- Calibrate machinery to proper weight per formula
8- Weigh 10 tablets to compare with target ± 1%
9- Adjust if needed and recalibrate
10- Fill out mixing control sheet

11- Record weight every 30 minutes during run
12- Visually inspect at least 10% of run for defects
13- Recalibrate if needed

14- Inspect packaging materials
15- Check ink jet for lot code and expiration date
16- Check heat seals/ neck seals
17- Check samples throughout run
18- Document on QC check sheet

19- Inspect product as it is cased
20- Code with lot # and expiration date
21- Record quantity packed
22- Retain samples for later QA checks

23- Inspect pallet load
24- Verify quantity packed
25- Check shipping address

* Each ingredient comes with a specification sheet and a certificate of analysis. Conformance to these specs and analyses is checked for new suppliers, and then randomly thereafter to ensure ongoing compliance. Only high quality suppliers are selected for purchases. Quality based on their GMP specs and other standards.

### 4.1.2 **Agent Ordering and Distribution**

ArginMax and matching placebo will be provided free of charge by The Daily Wellness Company. The study drug will be shipped to Biologics in bottles containing a 4-week supply each and will be stored at room temperature.

CCCWFU plans to accrue 42 additional patients with each patient participating for a total of 12 weeks. Each patient will take 3 caplets of ArginMax or placebo twice daily for 12 weeks. Each bottle will contain a patient-specific label. In addition to this, and to ensure easy identification, Biologics will label each lid with a color-coded sticker entitled: *Bottle 1*, *Bottle 2* and *Bottle 3*. Each bottle will contain 168 caplets.

Upon registration Biologics will automatically be notified and will call the site for further information. Biologics will provide shipment to the participating site for each patient enrolled.

4.1.3 **Storage & Stability**

**Storage Instructions:** Store at room temperature 25$^{o}$ C and avoid exposure to excessive heat.

4.1.4 **Preparation – N/A**

4.1.5 **Toxicities**

The ingredients in ArginMax have a long history of use in humans and are not known to interact in an adverse way at the recommended dose with any foods. Adverse events have been occasional mild GI distress, headaches and infrequently heavier menstrual cycles. This toxicity information is provided by the Daily Wellness Company.

4.1.6 **Administration – N/A**

4.2 **Treatment Plan**

Oral ArginMax or placebo will be provided to patients at no cost. All patients will take 3 caplets in the morning and 3 caplets in the evening daily by mouth. Pill diaries will be provided. Sexual Function, Quality of Life, Toxicity assessment, and concurrent medications will be assessed prior to study entry, and at 4, 8 and 12 weeks.

4.3 **Dose Modification**

4.3.1 Toxicity Management- Patients who are unable to take oral medication for any reason should be excluded from this trial. Any patient with a grade 3 or higher sequelae or drug related adverse event after taking the medication will be withdrawn from the trial.

4.3.2 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).

4.3.3 Dose Modification – If unable to tolerate three BID, dose may be reduced as follows: Two BID, if not tolerated, one BID, if not tolerated discontinue, take patient off treatment only. Clearly indicate on the flow sheet that the patient is no longer taking the treatment drug. Also, continue to follow patient on study. Continue to submit all patient completed data management forms. Contact DMC at (336) 713-3172 for any questions.

4.4 **Treatment Schedule –** N/A

4.5 **Pre-Medication –** N/A

4.6 **Treatment Duration**
Patient will continue study for 12 weeks.

4.7 **Concomitant Treatment**
Patients should receive full concomitant care as needed.

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

Baseline evaluations and labs are to be conducted within 3 months prior to registration.

| | Pre-Study | Wk 1 | Wk 2 | Wk 3 | Wk 4 | Wk 5 | Wk 6 | Wk 7 | Wk 8 | Wk 9 | Wk 10 | Wk 11 | Wk** 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Study Agent* | | X | X | X | X | X | X | X | X | X | X | X | X |
| Telephone Contact Form | | | | | X | | | | X | | | | X |
| Demographics | X | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | |
| Concurrent meds (D) | X | | | | X | | | | X | | | | X |
| Physical exam | X | | | | | | | | | | | | |
| Pulse | X | | | | | | | | | | | | |
| Blood Pressure | X | | | | | | | | | | | | |
| Height/Weight | X | | | | | | | | | | | | |
| Performance status | X | | | | | | | | | | | | X |
| Hgb, WBC, platelets (A) | X | | | | | | | | | | | | |
| Creatinine, T. Bili (A,B) | X | | | | | | | | | | | | |
| B-HCG (C) | X | | | | | | | | | | | | |
| TAS (Toxicity Assessment Sheet) (D) | X | | | | X | | | | X | | | | X |
| FACT – G (E) | X | | | | X | | | | X | | | | X |
| FSFI (E) | X | | | | X | | | | X | | | | X |
| Screening Questionnaire | X | | | | | | | | | | | | |
| Medication Diary | | | | | X | | | | X | | | | X |
| Radiographic Images (F) | X | | | | | | | | | | | | |

** 12 Week assessment should be completed after patient has finished 12 weeks of study medication.
A: Baseline labs should be completed within 3 months prior to registration.
B. Chemistry panel to include creatinine and total bilirubin.
C: Negative serum pregnancy test within 10 days of registration in women of childbearing potential.
D: Toxicity Assessment Sheet (TAS) and concurrent medication sheet needs to be filled out at weeks 4, 8 & 12 if problem noted on telephone contact form.
E: FACT-G & FSFI may be mailed to patient to fill out for weeks 4, 8 & 12
F: Not required unless using to verify no evidence of disease.

## 12. REGISTRATION PROCEDURES

### 12.1 Online 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 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, 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:

Research Base Data Management Center
Radiation Oncology
1st Floor Cancer Center WFUBMC
Medical Center Boulevard
Winston-Salem, NC 27157

The Eligibility Checklist/Registration, protocol-specific consent, HIPAA and confirmation 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 at (336) 713-6507 between 8:30am and 4:00pm EST, Monday through Friday.

A form 310 or IRB protocol approval letter and an IRB approved consent form must be received by the Research Base Protocol Information Office – Attn: Site Coordinator at least 24 hours prior to patient registration. Fax number (336) 716-6275.

## 13. DATA SUBMISSION PROCEDURES

The Registration Form/Eligibility checklist should be completed online prior to placing the patient on study. 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 or fax to (336) 713-6476:

| Form | Submission Schedule |
|---|---|
| Registration Form/Eligibility Checklist | Upon Registration |
| Consent Forms; Screening Questionnaire | Upon Registration |
| Initial Labs & Scans | Upon Registration |
| FACT-G | Upon Registration, within 2 weeks following, 4 week, 8 week, 12 week |
| FSFI | Upon Registration, within 2 weeks following 4 week, 8 week, 12 week |
| Flow Sheet, Toxicity Assessment Sheet (TAS), Concurrent Medication Sheet | Upon Registration, within 2 weeks following 4 week, 8 week, 12 week |
| Medication Diary | Within 2 weeks following 4 week, 8 week, 12 week |
| Telephone Contact Form | Within 2 weeks following 4 week, 8 week |

## 14. ADVERSE EVENT REPORTING

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

## 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 too 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 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 (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 which precipitates 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. Research Base Data Management Center, Radiation Oncology, Wake Forest University Baptist Medical Center, Medical Center Blvd., Winston Salem, NC 27157. The material must be labeled: “Attention: Adverse Event Reporting”. Fax number (336) 713-6476

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.

## 14.4 Cancer Prevention Agents – Commercially Available

Cancer Prevention Study 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. Adverse Event Reporting for all commercially available drugs should be reported via the FDA Form 3500A (MedWatch).

**Table A: Adverse Events occurring within 30 days of study completion must be reported via MedWatch**

| | 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

## 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.

### 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. STATISTICAL CONSIDERATIONS

### 15.1 Study Design

The primary objective of this randomized trial is to assess the effect of ArginMax on sexual function in women cancer survivors. Patients who meet the eligibility criteria will be randomized to receive either ArginMax or a placebo with equal probability. The primary end point used to quantitate treatment efficacy for this trial is sexual function assessed twelve weeks following randomization. Sexual function will be quantified using the Female Sexual Function Index (FSFI). Secondary objectives are to assess the effect of ArginMax on the sexual function subscales, general quality of life and to describe the toxicities associated with its use. Quality of life will be quantified using the FACT-G instrument. Toxicities will be documented using NCI Common Toxicity Criteria for Adverse Events, version 3.0. Analysis of all outcome measures will be carried out based on an 'intent to treat' approach. That is, all randomized patients (assuming they met the eligibility criteria) will be used in all analyses, whether or not they were actually treated or whether or not they were treated appropriately.

A double-blind randomized, parallel group design will be used to assess the efficacy of ArginMax. For design purposes we will base our sample size on data provided by Rosen et al on the sexual function of normal women and women diagnosed with sexual dysfunction. (23) In their study, the means ± standard deviations for FSFI in these two groups of women were 30.5 ± 5.29 and 19.2 ± 6.63, respectively. We assume that sexual function in cancer survivors will be intermediate between these two levels and anticipate a mean ± standard deviation of approximately 25 ± 6. Table 4 below shows the sample sizes needed in each group to detect relative differences between groups in FSFI of 10% to 25% with 80% to 90% power at the 5% 1 or 2-sided level of significance, assuming a 20% loss to follow-up at twelve weeks. These sample size estimates assume that a single-stage design will be utilized and that a two-sample t-test will be used to compare post-treatment means between treatment groups. The final analysis will adjust for baseline levels of sexual function and other baseline covariates, which will increase the precision of the estimate of treatment effect and increase the power of the group comparison.

Table 4. Sample size needed in each group to ensure sufficient power for detecting clinically meaningful differences

| *Approximate Relative Difference* | *Absolute Difference* | *80% Power* | | *90% Power* | |
|---|---|---|---|---|---|
| | | 1-sided | 2-sided | 1-sided | 2-sided |
| 10% | 2.50 | 90 | 115 | 125 | 154 |
| 15% | 3.75 | 41 | 53 | 56 | 69 |
| 20% | 5.00 | 24 | 30 | 33 | 40 |
| 25% | 6.25 | 16 | 20 | 21 | 26 |

We see that 69 women would be needed in each group in a single stage design to provide 90% power for detecting a 15% treatment effect (a 3.75 unit absolute difference) at the 5% two-sided level of significance.

Interim Monitoring

For ethical and efficiency considerations, we will incorporate a single interim analysis into the design that allows stopping both for rejection and 'acceptance' of the null hypothesis. The acceptance and rejection boundaries, determined by the S-Plus software module SeqTrial (using null and alternative boundary shape parameters of .75), are summarized in Table 5.

Table 5. Interim and final stopping rules for monitoring differences in sexual function

| Stage | Total Number of Patients # | Decision Rule |
|---|---|---|
| 1 | 72 | If $\|Z\|^* > 2.4056$, stop the trial and reject $H_0$<br>If $\|Z\| < 0.4563$, stop the trial and accept $H_0$<br>Otherwise continue |
| 2 | 144 | If $\|Z\| > 2.0229$, stop the trial and reject $H_0$<br>Otherwise<br>If $\|Z\| < 2.0229$, stop the trial and accept $H_0$ |

* Asymptotically normal test statistic for assessing differences in sexual function between treatment groups
# Assuming a 20% loss to follow-up

A maximum of 144 patients will be randomized, approximately 72 to each arm. The interim analysis will occur after 72 patients have been accrued. If the absolute value of the test statistic comparing the two treatment arms is greater than 2.4056 (i.e., two-sided p-value < .0162) during the interim analysis, the study will be stopped and the null hypothesis rejected. If the test statistics is between $\pm$ 0.4563 (i.e., two-sided p-value > .6482) then the study will be stopped and the null hypothesis accepted. Otherwise the trial will continue until 144 patients have been accrued, at which point the null hypothesis will be rejected if the absolute value of the test statistic is greater than 2.0229 (fixed sample p-value < .043).

The two-stage design has a larger maximum sample size (144 vs 138) but a smaller expected sample size compared to that of a single stage design (Table 6). The expected sample size depends on the true difference in sexual function between treatment groups as illustrated in Table 6 below. We see that under the null hypothesis, the probability of stopping at the first stage is 37%, and the expected sample size is approximately 93.1. Under the alternative hypothesis, the probability of stopping early is 51% and the expected sample size is approximately 85.1.

Table 6. Probability of stopping and expected sample size for two-stage design

| True Difference in Sexual Function | Probability of Acceptance/Rejection | | Expected Sample Size |
|---|---|---|---|
| | Stage1 | Stage 2 | |
| 0.0 | .3518/.0162 | .5982/.0338 | 93.1 |
| 3.75 | .0261/.4817 | .0739/.4183 | 85.1 |

Power for Secondary Outcome Measures

Overall quality of life as quantified by the FACT-G and each sexual function subscale will be analyzed separately. The mean ± standard deviation for FACT-G in a series of 466 mixed cancer patients was 82 ± 16 (24). Means and standard deviations for the subscales were estimated from data provided in the paper by Rosen et al (23), by pooling the estimates across the FSAD and control patients. These estimates are shown in Table 7 below. Assuming a similar variability for these measures in our study and assuming that a second stage is required, Table 7 shows the differences we will be able to detect between treatment groups with 80% and 90% power (again assuming a 20% loss to follow-up so that our total sample size will be approximately 116 patients). We anticipate that we will be able to detect a difference of 8.4 in FACT-G (an approximate 10.2% relative difference) with 80% power and a difference of 9.7 with 90% power. This corresponds approximately to the difference in FACT-G seen between cancer patients who were ECOG performance status 0 and those who were performance status 1 (FACIT Manual). We will be able to detect approximate 20% relative differences between groups in each of the sexual function subscales with 90% power.

Table 7. Differences detectable in secondary outcome measures with 80% and 90% power at the 5% two-sided level of significance.

| | | *Difference Detectable* | | | |
|---|---|---|---|---|---|
| | | 80% Power | | 90% Power | |
| Outcome | Mean (SD) | Absolute | Relative (%) | Absolute | Relative (%) |
| Fact-G | 82.0 (16.0) | 8.40 | 10.2 | 9.71 | 11.8 |
| Subscale* | | | | | |
| Desire | 5.8 (2.0) | 1.05 | 18.1 | 1.22 | 20.9 |
| Arousal | 13.3 (4.2) | 2.22 | 16.7 | 2.57 | 19.3 |
| Lubrication | 14.8 (4.5) | 2.34 | 15.8 | 2.71 | 18.3 |
| Orgasm | 9.9 (3.6) | 1.91 | 19.3 | 2.21 | 22.3 |
| Satisfaction | 10.5 (3.3) | 1.74 | 16.6 | 2.01 | 19.1 |
| Pain | 12.0 (3.8) | 2.01 | 16.7 | 2.32 | 19.3 |

* Note that the subscale means do not add to the total score used above because weights were applied to the subscale means when calculating the overall score.

Another secondary outcome measure is the occurrence of adverse events. Assuming that this outcome will be dichotomized, we will have at least 80% power for detecting a 26% or greater difference between treatment groups in the occurrence of an adverse event.

Another objective, added to this study once the original accrual goal was reached, is to assess the effect of race on sexual function and quality of life. Race will be coded as Hispanic and non-Hispanic white versus others and this indicator variable will be entered in the longitudinal repeated measures models (or mixed effects models) along with the treatment indicator and other covariates of interest. Note that we will also assess the

treatment by race interaction (i.e., does the effect of treatment differ by race), but the sample size will be determined based on the main effect of race and not the interaction. At the completion of accrual, we had accrued 142 white and 3 black participants. We will increase the number of white participants to 144 in order to have 90% power for testing the main hypothesis in this subgroup of women. In addition, in order to have 90% power for detecting a 3.75 unit difference between race groups in sexual function at the 5% two-sided level of significance, given that we will have 144 whites, we would need a total of 34 non-white patients, or 31 more than we have currently accrued. Assuming a 20% drop-out rate, we will need to recruit an additional 3 white patients and 39 non-white patients.

15.2 Feasibility

The Comprehensive Cancer Center of Wake Forest University Community Clinical Oncology Program Research Base is comprised of 18 CCOPs and 6 non-CCOPs representing over 100 cancer centers (mostly community cancer centers, but also Wake Forest, East Carolina, and Louisiana State Universities). Currently, the CCCWFU CCOP Research base has 5 open cancer control studies, none of which compete with the proposed trial. Accrual to these studies is 4-8 patients per month. Assuming this study will accrue 6 patients per month, accrual should be complete within about 24 months.

15.3 Randomization

Women will be stratified by performance status (ECOG 0-1 vs 2), type of malignancy (pelvic vs non-pelvic), and ovarian functional status (yes vs no) and randomized within strata to receive ArginMax or placebo with equal probability, using random permuted block 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 patient will not unblind the entire arm.

15.4 Inclusion of Women and Minorities

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

| **Gender** | **Race/Ethnicity** | | | | | | |
|---|---|---|---|---|---|---|---|
| | White | Black | Hispanic | Asian | Hawaiian or Pacific Islander | American Indian | Total |
| Female | 136 | 26 | 17 | 5 | 1 | 1 | 186 |
| Total | 136 | 26 | 17 | 5 | 1 | 1 | 186 |

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*

15.5 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 or consult.

15.6 Analysis Plan

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 WFUSM, and quality control information (retention, missing data, 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) and approximate confidence intervals for the continuous measures (e.g., sexual function, quality of life). Two-sample t-tests will be used to assess the unadjusted effect of ArginMax on sexual function and quality of life after 12 weeks of treatment. Chi-squared tests will be used to assess unadjusted treatment differences in the binomial responses such as proportion of patients experiencing toxicities or adverse events.

The primary analysis will be an analysis of covariance which will be used to assess treatment differences in the week 12 sexual function 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. Results of the interim analysis will be compared to the stopping rules detailed above and will be presented to the Cancer Center DSMB. Analysis of covariance will also be used to analyze the secondary outcome measures.

The primary and secondary outcome variables will be measured at baseline, 4, 8, and 12 weeks as described above. In addition to the twelve-week analyses mentioned above, all of the outcome data will be analyzed using growth curve models or repeated measures analysis of (co)variance. Indeed this approach is more powerful if the treatment effect is realized by four weeks and is maintained over the course of the trial. 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. We propose to analyze the data using SAS Proc Mixed, a program that provides several computational methods for obtaining maximum likelihood estimates for repeated measures problems, allows for unbalanced designs, missing data at some times, structured or unstructured covariance matrices, and growth curve parameterizations of time effects.

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