

A Randomized Double-Blind Placebo-Controlled Study of Oral Coenzyme Q10 to Relieve Self-Reported Cancer Treatment Related Fatigue in Breast Cancer Patients

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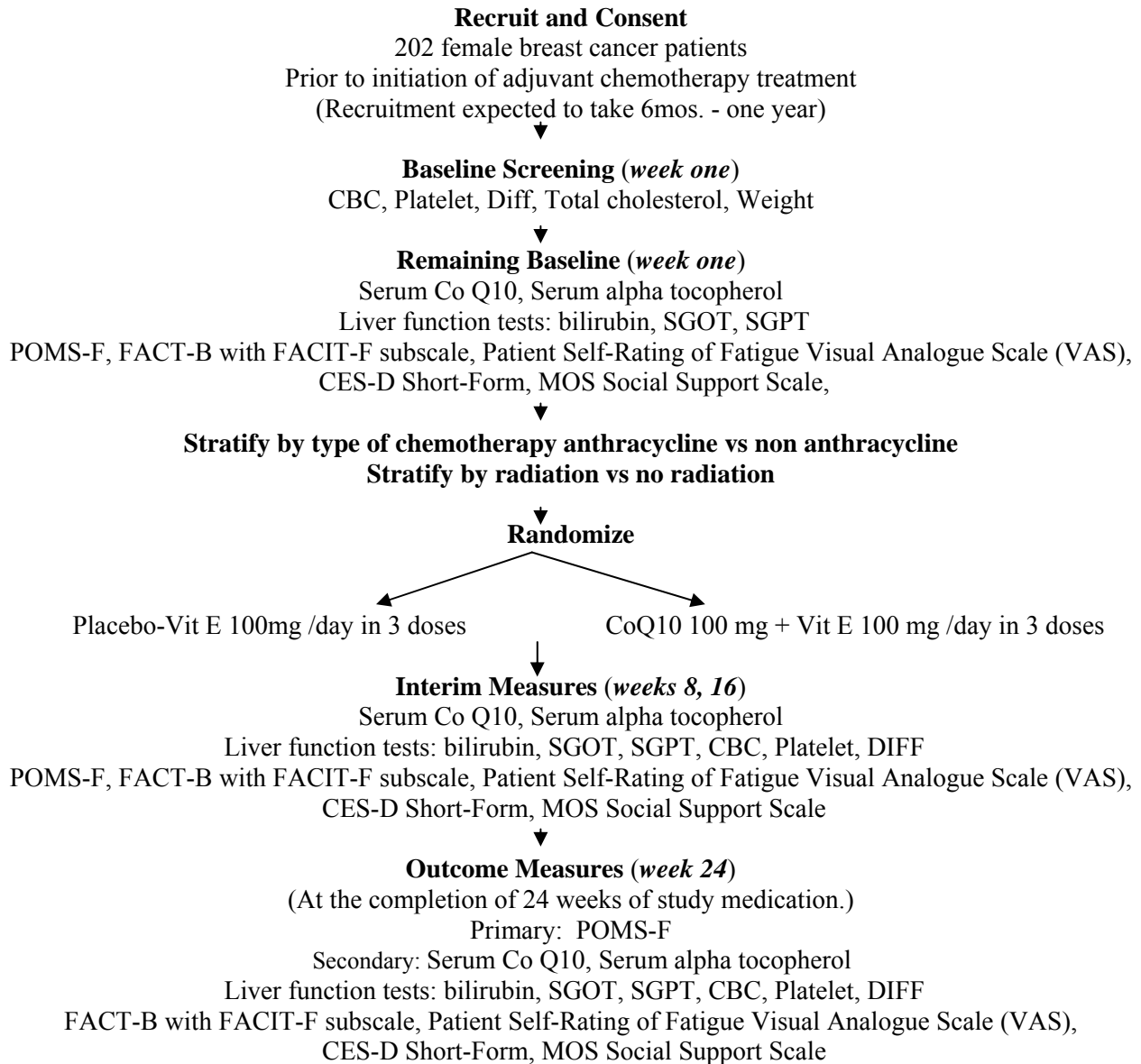
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Schema



- Eligibility:** Signed Consent
Hb \geq 11g/dl ; supportive measures (erythropoietin, transfusion, iron therapy) should be utilized to assist with maintaining Hgb levels
Total cholesterol \geq 160mg/dL.
Female with primary cancer diagnosis (breast)
Planned adjuvant chemotherapy
KPS \geq 60
Bilirubin \leq 1.5 x ULN
SGOT \leq 2.5 x ULN
SGPT \leq 2.5 x ULN

Ineligibility: Recent involuntary weight loss (> 5% of body weight in the past 3 months)

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Statin therapy - current or planned during study. Below is a list of some commonly used statin drugs. (Note: This is a helpful guide, not a complete list.)

Atorvastatin (Lipitor)
Cerivastatin
Fluvastatin (Lescol)
Lovastatin (Mevacor, Altacor, Advicor)
Mevastatin
Pravastatin (Pravachol)
Rosuvastatin
Simvastatin (Zocor)

Current or planned use of the following medications for fatigue (See Section 4.4):

Corticosteroids (intermittent use as part of chemotherapy regimen is allowed)

Amphetamines or other stimulants including methylphenidate (Ritalin) or modafinil (Provigil)

Patients diagnosed with uncontrolled hypertension

Breast cancer patients who are male

Pregnant women are excluded from participation in this study. A Serum pregnancy test is required within 1 week of registration if the patient is a woman of childbearing potential.

Anticoagulant therapy – current or planned during study (except for maintenance of catheter patency)

Patients with uncontrolled thyroid dysfunction

Study Duration (Length of time open for accrual): 18 months

Sample Size: 101 per arm for a total of 202 participants

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1.0 Background and Rationale

Coenzyme Q10

Coenzyme Q10 (2, 3, dimethoxy-5 methyl-6-decaprenyl benzoquinone), also known as ubiquinone, is a fat-soluble quinone with properties similar to vitamins (Greenberg and Frishman 1988). Coenzyme Q10 (Co Q10) is an antioxidant and a redox coenzyme of the respiratory chain (Langsjoen et al. 1988, Overvad et al. 1999, Alt. Med Rev 1998, Forsmarch et al. 1997). Co Q10 occurs naturally in organs of several animal species (Crane et al. 1957), and in relatively high levels in the heart, liver, kidney and pancreas of humans (Greenberg and Frishman 1988). Biochemically, Co Q10 works in several ways. The coenzyme 1) has a direct regulatory role on succinyl and NADH dehydrogenases, 2) acts as a catalyst and plays an integral role in regulating the cytochrome b-c1 complex, and 3) may have direct membrane stabilizing properties separate from its role in oxidative phosphorylation (Greenberg and Frishman 1988, Crane and Navas 1997). Thus, Co Q10 works within human cells to create energy for cell growth and maintenance (Crane et al. 1993, Overvad et al. 1999, Pepping 1999).

Animal research (Zamora et al. 1991) demonstrated that Co Q10 in combination with selenium and beta-carotene, reduced alanine release in RBCs suggesting that Co Q10 (and beta carotene) may act as antioxidants in red blood cells. Zamora and others (1991) also demonstrated that Co-enzyme Q10 effectively diminished alanine release in rat red blood cells indicating protection of the cell membrane. This is important because Davies (1988) reported that proteolytic systems might play a secondary antioxidant defense role in the prevention of damage to amino acids. Therefore, as red blood cells are protected against oxidative stress, levels of alanine in the red blood cell are not elevated, thus making alanine in RBCs a potential biomarker of the effectiveness of CoQ 10 in preventing oxidative stress on red blood cells. Considering the potential antioxidant effects and potential clinical benefits of CoQ10, the supplement has been of interest to researchers.

Most research on the therapeutic effects of Co Q10 has focused on cardiac diseases including angina, hypertension, arrhythmia, and congestive heart failure (Folkers et al. 1978, Takeo et al. 1986, Baggio et al. 1993, Morisco et al. 1993, Pepping 1999, Overvad et al. 1999). Baggio et al. (1993) studied 2,500 patients with NYHA class II and III sign and symptoms of congestive heart failure who were given a daily dose of Co Q10 ranging from 50-150mg. Preliminary data analysis demonstrated improvement in cyanosis (81%), edema (76.9%), pulmonary rates (78.4%), liver enlargement (49.3%), dyspnea (54.2%), jugular reflux (81.5%), palpitations (75.6%), sweating (82.4%), insomnia (60%), vertigo (73%), and nocturia (50.7%). Fifty four percent of the preliminary sample analysis showed improvement of at least three symptoms. A randomized study of New York Heart Association (NYHA) class III and IV congestive heart patients demonstrated fewer hospitalizations and less pulmonary edema among the treatment group of patients (Morisco et al. 1993).

Therapeutically, ubiquinone has been shown to improve cardiac function. Although it does not appear to have a significant hemodynamic effect in angina, Co Q10 improves myocardial contractility in heart failure (Folkers et al. 1978, Takeo et al. 1986). Overvad's review of Co Q10 reported that of nine studies assessing ubiquinone for heart failure, eight demonstrated positive results. Improvements were observed in ejection fraction, cardiac output, physical capacity, NYHA class, stroke volume and quality of life (Overvad et al. 1999). Among the studies cited in this review, Morisco and colleagues (1994) saw improvement in ejection fraction and cardiac output during exercise in six patients with NYHA II-IV disease when treated with 150 mg of Co Q10 per day for two months. Another cross over study of 14 class IV patients demonstrated improved ejection fraction, stroke volume, cardiac output, and lowered end diastolic volume index (Judy et al. 1986). Langsjoen et al. (1988) studied 88 patients with cardiac myopathy and found that between 75-85% showed improvement in cardiac output ejection fraction and physical function tests. Of particular interest was the finding that clinical responses to Co Q10 were found to be greatest in those with ejection fractions of 10-30% with relative changes of 115-120%. Time to improvement ranged from one month to three months.

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Research suggests that the coenzyme acts as a free radical scavenger by stabilizing cell membranes and preventing depletion of metabolites necessary for the re-synthesis of ATP (Greenberg and Frishman 1988). Further, Co Q10 prevents cellular damage during myocardial ischemia (Greenberg and Frishman 1988). A deficiency of Co Q10 has been associated with heart disease (Folkers et al. 1970), and patients with the lowest tissue levels of endogenous Co Q10 show the most benefit (Greenberg and Frishman 1988) from Co Q10 supplementation. Studies addressing the effects of Co Q10 on fatigue have been limited to cardiac fatigue, and rely on outcome measures such as exercise tolerance and stress tests (Langsjoen et al. 1988, Khatta et al. 2000) as well as clinical signs such as cyanosis, edema, and dyspnea (Baggio et al 1993).

Deficiencies of Co Q10 have also been documented in cancer patients (Folkers et al 1997, Folkers 1996, Lockwood et al. 1995, Ren and Lien 1997, Folkers 1974). Nutritional conditions such as protein deficiency, starvation, hypervitaminosis A, and some inhibitors of cholesterologenesis are reported to decrease the hepatic level and biosynthetic ability of Co Q10 in rats (Ramasarma 1972). Despite these observations, very little research has been conducted that examines the therapeutic role of Co Q10 in cancer treatment. Of the existing studies, the majority examine the effects of ubiquinone on tumor suppression (Lockwood, et al. 1994a, Lockwood et al. 1994b, Palazzoni et al. 1997). Lockwood reported tumor shrinkage with administration of oral Co Q10 to breast cancer patients. Studies of Co Q10 levels in cancerous tissue have shown that higher levels are present in thyroid, epithelial, and colorectal neoplasms (Mancini et al. 1991, Rusciani et al. 1986, Romagnoli et al. 1994). In contrast, Portakal and colleagues (2000) found lower levels of CoQ10 in neoplastic breast cancer as well as higher antioxidant enzyme activity, suggesting that malignant cells overexpress antioxidant enzymes and consume Co Q10.

Another body of literature addresses the role of Co Q10 in the prevention of adriamycin-induced cardiac toxicity (Berrazoli et al. 1975a, Berrazoli et al. 1975b; Combs et al. 1977; Folkers et al. 1978, Furukawa et al 1980, Takahashi et al 1980, Yamanaka et al 1980, Judy et al. 1984, Folkers and Walaniuki 1985, Iarussi et al. 1994). Several animal studies demonstrate protection against adriamycin-induced cardiac damage in rat hearts (Takahashi et al. 1980, Folkers et al. 1978). Eighty to eighty-six percent of mice pretreated with Co Q10 for four days prior to Adriamycin therapy survived compared to 36-42% survival among mice not treated.(Combs et al.1977). In another animal study, rats receiving Adriamycin developed up to a 50% increase in the QRS complex duration (Folkers et al. 1978). Co Q10 administered for seven days restored normal QRS complex duration on electrocardiograph. These findings corroborate earlier animal research (Greenberg and Frishman 1988, Serizawa et al, 1988). Serum Co Q10 levels in six children and adolescents receiving adriamycin and six who did not receive adriamycin therapy were compared pre and post treatment in order to test the hypothesis that doxorubicin therapy would cause a dose related decrease in serum Co Q10 levels in these patients (Eaton et al. 2000). Surprisingly, the plasma concentrations of Co Q10 increased significantly post-treatment. The researchers concluded that the increase in Co Q10 was the result of release of the enzyme from apoptotic or necrotic cardiac tissue.

Normal blood levels of Co Q10 range between 0.30 to 3.84 mcg/ml plasma (Jolliet et al. 1998, Overvad et al. 1999, Pepping 1999). Males have higher levels than females, and older adults have lower levels of Co Q10 than younger adults (Ernster and Forsmarch-Andree 1993). Supplementation studies have used ranges of 90-390 mg/ day (PDQ 2001) and some research suggests that a dose of 150 to 300 mg of Co Q10 may be needed to demonstrate effect (Serizawa et al. 1988, Lockwood et al. 1994, Langsjoen et al 1990). Side effects of Co Q10 may include insomnia, elevated liver enzymes, rash, nausea, epigastric pain, dizziness, photophobia, irritability, headache, and heartburn (Baggio et al. 1993, Feigin et al. 1996); however, regardless of the dosage used few untoward effects have been observed (Langsjoen et al. 1990).

Okamata found Co Q10 levels to be lower in cancer patients receiving total parenteral nutrition (TPN) than among non-cancer patients following 4 weeks of TPN (Okamoto et al. 1986); however, it is not yet clear whether cancer itself directly influences Co Q10 metabolism. Co Q10 has also been shown to protect mitochondrial inner membrane lipids and proteins and mitochondrial DNA against oxidative

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damage (Takayanagi et al. 1980). These research findings suggest that Co Q10 may potentially relieve cancer-related fatigue via its effect on preservation of energy generating cellular processes.

Cancer Related Fatigue

Cancer-related fatigue is the most common, and possibly the least addressed, side effect in cancer patients (Vinciguerra et al. 2001, Wang et al. 2001, Miaskowski and Portenoy 1998, Vogelzang et al 1997, Glaspy et al. 1997). Although interest in cancer related fatigue has increased recently (Cella et al. 1998, Rodriguez et al. 2001), causes for fatigue are not well understood. Most researchers acknowledge the multidimensional nature of cancer fatigue citing factors directly related to the disease process, psychological and emotional demands of the disease (Okuyama et al. 2001, Rodriguez et al. 2001, Gillis et al. 2001), and treatment related factors (Gillis et al. 2001, Miaskowski and Portenoy 1998). Treatment related factors include dehydration, infection, malnutrition, altered muscle metabolism cytokine production and anemia. Anemia, a frequent side effect of cancer treatment, may be a major contributor to fatigue (Cella et al. 1998, Arbuckle et al. 2001).

Studies indicate that breast cancer patients may experience fatigue similar to other cancer patients (Blesch et al 1991), particularly fatigue associated with chemotherapy induced anemia (Groupman and Itri 1999). The occurrence of more severe anemia, i.e., grades 3 (6.5-7.9 gHg/dL) and 4 (<6.5g Hg/dL), in breast cancer patients undergoing chemotherapy may range from less than 1 % to as high as 80%, depending on the agents and doses used (Groupman and Itri 1999). Further, Broeckel and colleagues (1998) found among a sample of 61 breast cancer patients, that fatigue may continue following termination of chemotherapy. This finding was later supported in a review of literature on long-term fatigue breast cancer patients (Jacobsen and Stein 1999). The authors concluded that long-term fatigue in breast cancer patients was limited to those patients undergoing bone marrow transplant or adjuvant chemotherapy. A study of 77 patients with breast (44) and lung (33) cancer revealed no significant difference in mean fatigue scores (as measured by a visual analogue scale) between the two groups of patients. A multi-center study assessing fatigue using the FACIT-F in 576 cancer patients (38% breast cancer patients) reported a median score of 18 (Stone et al. 2000). Interestingly, 52% of respondents had not discussed fatigue or reported it to their physician. Furthermore, when asked to name which symptom—pain, nausea and vomiting, or fatigue—most affected daily life, 52% of participants cited fatigue. Not surprisingly, aversive chemotherapy related side effects are associated with increased severity of fatigue (Sadler and Jacobsen 2001; Jacobsen et al 1999). Jacobsen and colleagues (1999) employed the Profile of Mood States Fatigue Subscale (POMS-F) to assess fatigue in cancer patients at points between chemotherapy cycles. Using simple effects analysis the authors discovered that the amount of time each day that patients experienced fatigue increased significantly between the assessments taken between second and third cycle and assessment obtained between the third and fourth cycles of chemotherapy. In the same study, measures were taken in the clinic prior to the each round of chemotherapy, using the Memorial Symptom Assessment Scale (MSAS). Comparisons of the POMS-F and MSAS, suggests that patients undergoing chemotherapy may experience what has been described as the “roller coaster” pattern of fatigue. The mean fatigue found with the POMS-F was 9.9 (Jacobsen et al. 1999). Increasing severity of fatigue with repeated rounds of chemotherapy seems to be associated with concomitant aversive treatment side effects (Sadler and Jacobsen 2001).

Cancer-related anemia may be treated with blood transfusion and, more recently, erythropoietin (Miaskowski and Portenoy 1998, Dimitri et al. 1998, Vogelzang et al. 1997, Glimelius 1998, Abels et al. 1991). Although relatively safe for use in cancer patients (Miaskowski and Portenoy 1998, Abels et al. 1991), erythropoietin is effective in only 50-60% of anemia patients. Furthermore, fatigue may commonly occur in the absence of anemia. Finally, erythropoietin is expensive and may not be a cost-effective option for cancer patients who experience mild to moderate fatigue (Miaskowski and Portenoy 1998). A safe, inexpensive alternative treatment for cancer related fatigue is needed. Many cancer patients use complementary and alternative medicines (CAM), believe them to be efficacious, and safer than biomedicine with fewer side effects. CoQ10 is one commonly used; however, its touted benefit has not been scientifically validated. Therefore, we

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propose a randomized, double-blind placebo controlled study to examine the effect of Co-Q 10 on fatigue levels in breast cancer patients receiving adjuvant chemotherapy.

2.0 Goals and Objectives

The overall goal of this study is to determine the efficacy of administering oral Co Q10 combined with Vitamin E to relieve self-reported cancer treatment-related fatigue in female breast cancer patients receiving chemotherapy. Specifically, the primary study aim is to:

- 2.1 Assess the effect of Co Q10 on cancer treatment-related fatigue

Secondary study aims are to:

- 2.2 Assess the effect of Co Q10 on overall Quality of Life
- 2.3 Assess the effect of Co Q10 on depression

Primary outcome measures: self reported fatigue as measured by the POMS-F.

Secondary Outcome Measures: Hemoglobin, Serum Co Q10, Serum alpha tocopherol, FACT-B with FACIT-F subscale, Patient Self-Rating of Fatigue, CES-D Short-Form, MOS Social Support.

3.0 Participant Selection Criteria

Eligibility: Signed Consent

Hg \geq 11g/dl ; supportive measures (erythropoietin, transfusion, iron therapy) should be utilized to assist with maintaining Hgb levels

Total cholesterol \geq 160mg/dL.

Female with primary cancer diagnosis (breast)

Planned adjuvant chemotherapy

KPS \geq 60

Bilirubin \leq 1.5 x ULN

SGOT \leq 2.5 x ULN

SGPT \leq 2.5 x ULN

Ineligibility: Recent involuntary weight loss (> 5% of body weight in the past 3 months)

Statin therapy - current or planned during study. Below is a list of some commonly used statin drugs. (Note: This is a helpful guide, not a complete list.)

Atorvastatin (Lipitor)

Cerivastatin

Fluvastatin (Lescol)

Lovastatin (Mevacor, Altacor, Advicor)

Mevastatin

Pravastatin (Pravachol)

Rosuvastatin

Simvastatin (Zocor)

Current or planned use of the following medications for fatigue (See Section 4.4):

Corticosteroids (intermittent use as part of chemotherapy regimen is allowed)

Amphetamines or other stimulants including methylphenidate (Ritalin) or modafinil (Provigil)

Patients diagnosed with uncontrolled hypertension

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Breast cancer patients who are male

Pregnant women are excluded from participation in this study. A Serum pregnancy test is required within 1 week of registration if the patient is a woman of childbearing potential.

Anticoagulant therapy – current or planned during study (except for maintenance of catheter patency)

Patients with uncontrolled thyroid dysfunction

Inclusion of Women and Minorities

Patients who meet the eligibility criteria will be included in this study without regard to race, or ethnicity. Race and ethnicity are not expected to influence response to toxicity from the treatment. The proposed study population is illustrated in the table below.

Race/Ethnicity

Gender	White, not of Hispanic Origin	Black, not of Hispanic Origin	Hispanic	Asian or Pacific Islander	Unknown	Total
Male	0	0	0	0	0	0
Female	166	20	10	6	0	202
Total	166	20	10	6	0	202

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).

Patients will be recruited by physicians and research nurses in an outpatient oncology department. Patient information may be reviewed by research nurses to determine possible study eligibility prior to the patient’s clinic visit.

4.0 Treatment Plan

4.1 Study design

<i>Measurements</i>	<i>Eligibility Criteria</i>
Baseline: Total Cholesterol	≥ 160 mg/dl
Serum Co Q10	N/A
Serum alpha tocopherol	NA
CBC with platelets and DIFF	Hgb ≥ 11g/dl
Weight	<u>< 5% body weight loss</u>
KPS	≥ 60
Liver function tests	
-SGOT	< 2.5 x ULN
-SGPT	< 2.5 x ULN
-Bilirubin (Total)	< 1.5 x ULN

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Subjects: Two hundred and two newly diagnosed female breast cancer patients who will receive adjuvant chemotherapy during their treatment for cancer will be recruited to participate in this double-blind randomized placebo controlled study. Participants will be randomized to receive daily oral supplements of either 300 mg Co Q10 per day or placebo, each combined with 300 IU Vitamin E (Overvad et al. 1999, Pepping 1999) divided into three doses daily (i.e. 1 capsule three times a day) of 100 mg CoQ10/placebo with 100 IU vitamin E for six months (24 weeks).

Potential participants will be recruited and consented by staff at the CCCWFU breast clinic and Research Base site clinics prior to the initiation of adjuvant chemotherapy. Baseline screening measures (hemoglobin, liver function, total cholesterol, microscopic UA, and weight) will be obtained. Weight will be obtained with the participants wearing light clothing and no shoes on the same scale to be calibrated prior to each weight. Those meeting the eligibility criteria will have the remaining baseline measures taken (i.e., **Serum Co Q10, serum alpha tocopherol**, FACT-B with the FACIT-F additional concerns subscale, POMS-F, Patient Self-Rating of Fatigue, CES-D Short Form, and MOS Social Support). Serum Co Q10 and alpha tocopherol levels will provide markers of adherence as well as indication of degree of metabolism of the supplement. Participants will be stratified by type of chemotherapy (anthracycline vs. no anthracycline) and radiation as a part of their treatment (yes or no), then randomized to either the intervention or control arm. Once randomized, participants will be given bottled supplements and instructions (both verbal and written) to begin taking the supplement on the day of their first chemotherapy treatment. Participants will be instructed to take the tablets orally three times a day with food, for six months (24 weeks). Participants will be instructed to avoid taking any additional supplements containing Co Q10 or vitamin E for the course of the study. Adherence to supplementation instructions will be measured by the serum Co Q 10 and serum alpha tocopherol levels and reported as a part of the study findings.

All measures will be collected at baseline, interim measures will be obtained at 8 and 16 weeks and the final measures will be made at the completion of 24 weeks. Interim measures at the 8 and 16 week time points were selected in order to coincide with participant treatment or follow up visits and to account for the “roller coaster” pattern of fatigue over the course of chemotherapy documented by others (Jacobsen et al. 1999). Further, participants in this study will undergo a variety of chemotherapy regimens, both in agents used and in the number of cycles received. Therefore, measurements at the second and fourth month of chemotherapy will assess the effect of Co Q10 on fatigue with repeated rounds of chemotherapy and possible increases in treatment side effects associated with increased fatigue (Sadler and Jacobsen 2001).

Any changes noted in overall quality of life, fatigue, or depression, can be analyzed in the context of treatment arm, chemotherapy round, radiation therapy and other documented symptoms that the participant may be reporting. Participants will be asked to maintain a diary noting the time and day of each supplement taken. Participants will be asked to bring all the supplement bottles with them to the interim and final visits in order to complete a pill count. At each visit participants will be asked to report any supplements taken other than study drugs and reminded at each visit to avoid any extra supplementation. In order to document the occurrence of side effects of Co Q10, participants will be asked to report the frequency and severity of side effects of Co Q10 at each visit.

Administration and dosage: Co Q10 is lipophilic; therefore a lipid carrier (Vitamin E) will be combined with each supplement. Based on the literature demonstrating greater effect with higher dosages, minimal side effects and lower Co Q10 levels in women, the dosage of Co Q10 will be 300 mg per day combined with Vitamin E, 300 IU daily, to be taken orally in three doses each containing 100 CoQ10/placebo and 100 IU vitamin E. Participants will be instructed to take pills at mealtimes (or with food).

The instruments in this study will provide the primary outcome measure, fatigue, as well as overall quality of life, and social support. Fatigue may be mediated by the level of instrumental social support available to an individual i.e., assistance with child care, house and yard work, grocery shopping, etc. as well as

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psychological and emotional support. Therefore it is important to examine social support as confounding variable in the study. Similarly, the association of depression with increased fatigue is well documented and thus will be assessed. Both social support and depression affect the overall quality of life and will provide useful information about the total quality of life of participants in combination with the FACT-B. The Profile of Moods State Fatigue subscale (POMS-F) has been used more extensively in studies of fatigue among cancer patients (Sadler and Jacobsen 2001, Jacobsen et al. 1999) than the FACIT-F. The FACIT-F was designed to be used with the FACT, and we believe it is an appropriate measure to use, since we are using the FACT-B in this study. This study will incorporate both surveys to measure fatigue in order to compare the two surveys and provide baseline data for future studies of fatigue. Finally, participants will be asked to rate their fatigue on a visual analogue scale in order to assess the current feeling of fatigue.

FACT-B- Health related quality of life will be assessed by the Functional Assessment of Cancer Therapy – Breast (FACT-B). This instrument is a multidimensional quality of life instrument developed for use with cancer patients (Cella et al, 1993) and consists of four subscales (which make up the FACT-G) and one subscale specific to breast cancer. The subscales assess the participant’s physical well-being, social/family well-being, emotional well-being, and functional well-being, and concerns related to breast cancer. The Fact-B is scored by calculating the five subscales as well as an overall total score. These measures have established reliability and validity, and extensive information on their psychometric properties is available (Cella, 1997).

FACIT-F Fatigue Scale- Fatigue will be assessed using the 13-item fatigue module developed for use with the FACT. (Yellen et al., 1997). A single summary scale is calculated for this subscale.

Patient Self-Rating of Fatigue. The participant will be asked to complete a single question asking them to rate their overall level of fatigue from ‘0’ (absolutely no fatigue) to ‘10’ (the worst possible fatigue imaginable). This item will be correlated with the FACIT-F as another indicator of the participant’s level of energy/vigor and fatigue.

Profile of Mood States Fatigue Subscale (POMS-F) is a seven item subscale of the POMS, a 65-item, self-report scale measuring six affective states: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. Items are rated for the past week on a 5-point scale ranging from 0 ("not at all") to 4 ("extremely"). The POMS Fatigue subscale score is calculated by summing sub-scale items. The POMS has well-documented reliability and validity with medical populations (McNair et al. 1992; McNair and Lorr 1964) and the POMS-F subscale has been used to measure fatigue in cancer patients.

Centers for Epidemiologic Studies-Depression (CES-D) Short-Form. Depressive symptomatology will be measured using the Centers for Epidemiologic Studies-Depression Short Form (Radloff, 1980). Depression has been found to be a major predictor of adherence to treatment regimens, to effect feelings of fatigue, and to condition survival. This instrument contains 8 items regarding the participant’s affective status. This measure has excellent psychometric properties and has been used in a variety of patient and research populations.

MOS Social Support Questionnaire. The social support questionnaire developed in conjunction with the Medical Outcomes Study, completed by the RAND Corporation, will be used to assess the amount of instrumental and emotional support available to the participants (Sherbourne and Stewart, 1991). Social support has been found to be an important predictor of adherence to treatment regimens, one's emotional health, and overall health-related quality of life. This 20-item measure produces a total score, as well as 4 subscale scores: tangible support, affectionate support, positive social interactions, emotional-informational support. Extensive information is available regarding its psychometric properties.

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4.2 Treatment Schedule

Supplements will be taken for 24 weeks beginning on the day of the first chemotherapy treatment. Patients must start taking supplements no later than 4 days after chemotherapy treatment. Interim measures will be obtained at 8 and 16 weeks. At the completion of 24 weeks, the supplements will be discontinued and outcome measures obtained.

Assessments of fatigue will be conducted at the specified intervals just prior to initiation of the subsequent chemotherapy cycle. The type and frequency of chemotherapy is expected to vary among participants. Therefore, this information will be recorded at each assessment to note the date of last chemotherapy treatment in relation to assessment of fatigue. Every effort will be made to assess fatigue in each participant just prior to the next chemotherapy cycle.

4.3 Treatment Duration

The study will be conducted for 24 weeks among a randomized group of 202 breast cancer patients. The study will be double-blind so that neither the participants nor researcher will know who receives placebo/vitamin E and who receives the coenzyme Q10/vitamin E supplement.

4.4 Ancillary Medications

We recognize that participants may develop symptoms requiring the use of corticosteroids or amphetamines as indicated for fatigue management. Doses and length of administration will be recorded. In addition, patients who receive intermittent corticosteroids as part of a pre-chemotherapy antiemetic regimen are eligible for this study. The use of such medically necessary medications does not necessitate withdrawal from the study and all treatment medications and dosages will be recorded.

5.0 Pharmaceutical Information:

Co Q10, a key component of the electron transport chain plays an important part in the production of ATP energy. Co Q10 will be supplied in 100 mg capsules with dark red gel which will include 100 IU of vitamin E. Placebo capsules that contain only vitamin E will also be filled with dark red gel. Biologics will purchase, store and distribute the supplement and placebo. Biologics is assisting in the procurement of both CoQ10 capsules and placebo. Softgel Technologies will manufacture CoQ10/Vitamin 100mg/100 IU and Vitamin E 100 IU in matched soft gels.

* Please notify Andrea Rice at (336) 716-2573 or by e-mail at arice@wfubmc.edu to order lab specimen kits prior to enrolling patients.

Analytical Method for Alphatocopherol

The analytical procedure to be employed to measure alpha tocopherol is a modification of the HPLC methodology by Hess et al. (1991). All steps are performed in subdued amber lighting. Two hundred microliters of the unknown plasma sample (or standard in ethanol) are mixed with 50 microliters of the internal standard (tocol) and 1 milliliter of BHT ethanol and vortexed for 30 seconds. Two milliliters of hexane are added, and then the solution is vortexed and centrifuged (at 1500xg for 10 minutes). The upper hexane layer is removed and transferred into a borosilicate glass culture tube. The ethanol layer is extracted again with 2 more milliliters of hexane. The combined hexane layers are evaporated to dryness under a stream of nitrogen. The dry residue is reconstituted with 200 microliters of BHT ethanol. Thirty five microliters are injected onto the HPLC system. The HPLC instrumentation includes a C₁₈ (4.6 x 250 mm) analytical column. The mobile phase (1) consists of acetonitrile/tetrahydrofuran/methanol/1% ammonium acetate (660:220:68:28 by volume) and is pumped isocratically at a flow rate of 1.5 ml/min. The column eluent is monitored at 292 nm.

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Analytical Method for CoQ10

Due to the labile nature of reduced CoQ10 and its inability to be detected with an UV detector, it is necessary to oxidize the sample to quantitate the total amount of CoQ10. The analytical procedure to be used to measure CoQ10 is a modification of the method by Kaikkonen et al (1999). Two hundred microlitres of the unknown plasma sample (or standard in ethanol) is mixed with 1 milliliter of buffer and 1 milliliter of ethanol and 200 microliter of CuCl_2 and allowed to oxidize at room temperature. At the end of this incubation, 50 microliter of the internal standard (tocol) is added. The mixture is then rapidly extracted with 4 milliliters of hexane, vortexed and then centrifuged (at 1500xg for 10 minutes). The upper hexane layer is removed and transferred into a borosilicate glass culture tube. The ethanol/buffer layer is extracted again with 4 more milliliters of hexane. The combined hexane layers are evaporated to dryness under a stream of nitrogen. The dry residue is reconstituted with 200 microlitres of BHT ethanol. Thirty five microliters are injected onto the HPLC system. The HPLC instrumentation includes a C_{18} (4.6 x 250 mm) analytical column. The mobile phase (1) consists of acetonitrile/tetrahydrofuran/methanol/1% ammonium acetate (660:220:68:28 by volume) and is pumped isocratically at a flow rate of 1.5 ml/min. The column eluent is monitored at 292 and 275 nm.

CoQ₁₀ Concentrations Measured in Humans:

Plasma: Males: 0.78 micrograms/ml plasma (0.15 = 1 SD)
 Females: 0.73 micrograms/ml plasma (0.17 = 1 SD)

Alpha tocopherol 2.68-9.17 (1.78=1 SD)

5.1 Treatment Toxicity

Co Q10, regardless of the dosage used, causes few untoward effects (Langsjoen et al. 1990). Thus we do not expect any adverse effects from this study. Side effects of taking Co Q10 may include insomnia, elevated liver enzymes, rash, nausea, epigastric pain, dizziness, photophobia, irritability, headache, anorexia, and heartburn (Baggio et al. 1993, Feigin et al. 1996, Alternative Therapies 1999, Alternative Medicine Review 1998), and participants will be informed of these side effects and instructed to report any occurrences to the physicians and study nurses. Any reported side effects will be carefully documented as required by the Wake Forest University School of Medicine Institutional Review Board (IRB). Co Q10 use in cancer related fatigue is a new area of exploration, any reported side effects will be examined in relation to cancer treatment, stage, age of participants and other demographic variables. In addition, all participants will receive CBC, platelet, DIFF, and liver function tests (Shults 1998).

In the event of severe toxicity that is possibly, probably, or definitely attributed to protocol treatment, the study drug should be held for one week and then restarted at full dose. If toxicity recurs, the participant will be removed from the study. In the event of life threatening toxicity that is possibly, probably, or definitely attributed to protocol treatment, the participant will be removed from the study.

The NCI Common Toxicity Criteria Version 3.0 will be used to assess treatment toxicity.

5.2 Reporting Toxicity

Any grade 4 toxicity should be reported immediately to the study Chair (Dr. Glenn Lesser,) 336-716-9527, and treatment will be held and potentially discontinued.

In addition, all adverse events should be reported to the CCCWFU data management center to Rhonda Kimball, WFUHS, Comprehensive Cancer Center of Wake Forest University CCOP Research Base, Medical Center Boulevard, Winston-Salem, NC 27157. The data management center will report to the CCCWFU IRB and Principal Investigator.

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Adverse Event Reporting

Toxicity Criteria: Toxicity will be determined using the NCI Common Toxicity Criteria (CTC), version 3.0 for Toxicity and Adverse Event Reporting (CTEP home page: <http://ctep.info.nih.gov>).

Reporting Toxicity: See Guidelines: Expedited Adverse Event Reporting Requirements for NCI Investigational Agents (January 2001), Section 1: Adverse Event Terminology and Definitions and Attachments B: Adverse Event Reporting for Commercial Agents (CTEP home page: <http://ctep.info.nih.gov>).

Please Note:

Notify the study chairman immediately by telephone of an unexpected, life-threatening (grade 4) or unexpected, fatal (grade 5) adverse event with an attribution of possible, probable, or definite. These events must be reported within ten working days to the FDA, DCP/NCI, and CCCWFU Research Base Protocol Office (fax: 336-713-6565).

6.0 Response Evaluation Criteria: Tumor treatment response evaluation is not applicable to this protocol. The primary endpoint for this study is fatigue as measured by the POMS-F. We can detect an approximate 30% relative difference (e.g., 9.90 vs. 6.93) in fatigue as quantitated by the POMS-F with 80% power at the 5% two-sided level of significance

7.0 Study Parameters

NOTE: Baseline lab work must be drawn within two weeks prior to registration

Assessment	Screening Baseline	Remaining Baseline	Week 8	Week 16	Week 24
CBC, platelet, DIFF (e)	X		X	X	X
Total Cholesterol	X				
Serum Co Q10 (b) (c)		X	X	X	X
Serum alpha tocopherol (b) (c)		X	X	X	X
Liver Function (f): (Bilirubin, SGOT, SGPT), Creatinine (d)	X		X	X	X
Pregnancy Test (a) (serum)	X				
KPS > 60	X		X	X	X
Weight	X		X	X	X
CES-D Short Form		X	X	X	X
Patient Self-Rating Fatigue Scale (VAS)		X	X	X	X
POMS-F		X	X	X	X
FACIT – F		X	X	X	X
FACT – B		X	X	X	X
MOS Social Support		X	X	X	X
Pill Count			X	X	X

(a) A serum pregnancy test is required within one week prior to registration if the patient is a woman of childbearing potential.

(b) Baseline and 24 week CoQ10 and alpha tocopherol levels must be drawn at specified times. (24 week labs are drawn after the completion of 24 weeks of study medication.). 8 week and 16 week levels may be drawn within 1 week pre- or post- specified time due to chemotherapy schedule (every 3 or every 4 weeks).

(c) Serum CoQ10 and alpha tocopherol levels do not have to be drawn prior to registration but must be drawn prior to first chemotherapy treatment.

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- (d) Due to delay in lab results, patient may be registered within 24 hours of first chemotherapy treatment if labs were drawn prior to treatment.
- (e) It is recommended that standard care during chemotherapy include regular assessment of CBC with platelet and differential.
- (f) It is recommended that standard care during chemotherapy include assessment of liver function prior to each cycle of chemotherapy.

8.0 Registration/ Data Management Procedures:

All patients entered on protocol **must** be registered with the CCCWFU Research Base Protocol Registrar. The protocol must be submitted to and approved by the participating institution's Investigational Review Board (IRB) prior to participant registration. A Form 310 and copy of the participating institution's IRB approved consent(s) must be submitted to the registrar at time of or prior to initial patient registration.

8.1 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. Entry fields highlighted in pink are not required, but the information should be entered if available. At the bottom of the registration page under comments, please enter your name and comment number. If further information is needed by Biologics or Data Management, they will contact you. Once the patient information has been entered and submitted, a confirmation page will appear. Print this confirmation sheet for your records. The CCCWFU Protocol Registration/Eligibility form (Appendix II), the initial flow sheet and signed consent and HIPAA forms should be faxed to 336-713-6476 or mailed to Data Management:

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

The Eligibility Checklist/Registration, initial flow sheet, 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 registrar at 336-713-6767 between 8:30am and 4:00pm EST, Monday through Friday.

A form 310 and an IRB approved consent form must be received by the Research Base Data Management Center at the time of patient registration, or prior to patient registration.

***All drugs required for the patient to complete the study will be delivered in one shipment. Patients must start study drug within 4 days of chemotherapy treatment.*

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8.2 Data Management Procedures

The CCCWFU Research Base data collection system utilizes protocol specific forms. Data forms will be submitted according to the schedule below. Submit by mail to: CCCWFU Research Base Data Management Center, Comprehensive Cancer Center, Medical Center Blvd., Winston-Salem, NC 27157-1020 (or fax to 336-713-6476), Attention: Rhonda Kimball

<u>Form</u>	<u>Submission Schedule</u>
Eligibility Checklist/Registration Form, Screening baseline labs Flow Sheet Consent Form HIPAA authorization	Before registration
Remaining Baseline Surveys CESD, VAS, POM-S, FACIT-F, FACT-B, MOS Support CoQ10 and alpha tocopherol	Within one week of registration
Flow Sheets, Medication Diary, Pill Count	At end of protocol; send as single batch. Within one week after visits: week 8, 16 & 24

9.0 Statistical Considerations:

9.1 Objectives

This trial is designed to assess the effect of Co Q10 on treatment related fatigue among patients receiving adjuvant chemotherapy for breast cancer. Patients who meet the eligibility criteria will be randomized to receive either Co Q10 or a placebo with equal probability. The primary end point used to quantitate treatment efficacy for this randomized controlled trial is fatigue assessed twenty-four weeks following randomization. Secondly, the effects of treatment on overall health-related quality of life and depression will be assessed. All of these outcomes will be measured at baseline and at 8, 16, and 24 weeks following randomization. The primary evaluation will be done with the measurements collected at the 24-week visit. Fatigue will be quantified using the 7-item Profile of Mood States Fatigue Scale (POMS-F). Quality of life will be quantified using the general Functional Assessment of Cancer Therapy survey (FACT-G) with the breast specific subscale added (FACT-B). Depression will be measured using the CES-D instrument. Analyses will be carried out based on an 'intent to treat' approach. That is, all randomized participants (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.

9.2 Design

A prospective, randomized, double-blind two-stage design will be used to assess the effect of Co Q10 therapy on the outcomes described above. The primary effect of Co Q10 will be estimated by comparing the mean level of fatigue for those participants receiving Co Q10 to that of participants receiving placebo. The estimated mean (\pm standard deviation) fatigue level in breast cancer patients, based on the POMS-F, is 9.9 ± 7.0 (Jacobsen et al. 1991). Assuming the mean and variability of fatigue in our patients are similar to these reported values and assuming a 10% loss to follow-up at 24 weeks, the number of participants needed in each group in a single stage design to detect specified differences in fatigue is shown in Table 1 below. We see that with 99 participants in each group of a single stage design, we could detect an approximate 30% relative difference (e.g., 9.90 vs 6.93) in fatigue as quantitated by the POMS-F with 90% power at the 5% two-sided level of significance.

Table 1. Sample size per group required for detecting specified group differences in POMS-F *

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Approximate Relative Effect **	Absolute Difference	80% Power		90% Power	
		1-sided	2-sided	1-sided	2-sided
20%	1.98	173	220	239	293
25%	2.475	111	141	153	189
30%	2.97	78	99	107	131

* mean ± sd = 9.9 ± 7.0 (ref: S1)

** Assuming a mean of approximately 9.9 in the placebo group

Interim Monitoring

For ethical and efficiency considerations, we will incorporate a single interim analysis into the design. This will allow us to stop early if one treatment demonstrates a striking benefit or if there appears to be little chance of ever showing a treatment benefit. We will incorporate a stopping boundary that is intermediate to those proposed by Pocock (1977) and O'Brien and Fleming (1979). In addition, we will allow early stopping for acceptance, unlike the initially proposed boundaries of Pocock or O'Brien and Fleming. The acceptance and rejection boundaries, as determined using the S-Plus software module SeqTrial (2000), are summarized in Table 2.

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Table 2. Interim and final stopping rules for monitoring differences in fatigue

Stage	Total Number of Patients #	Decision Rule
1	101	If $ Z ^* > 2.4725$, stop the trial and reject H_0 If $ Z < 0.3696$, stop the trial and accept H_0 Otherwise continue
2	202	If $ Z > 2.0083$, stop the trial and reject H_0 Otherwise If $ Z < 2.0083$, stop the trial and accept H_0

* Statistic for testing differences in quality of life between treatment groups

Assuming a 10% loss to follow-up

A maximum of 202 patients will be randomized, approximately 101 to each arm. The interim analysis will occur after 101 patients have been accrued. If the absolute value of the test statistic comparing the two treatment arms is greater than 2.472 (i.e., two-sided p-value < .0134) during the interim analysis, the study will be stopped and the null hypothesis rejected. If the test statistics is between ± 0.3696 (i.e., two-sided p-value > .7116) then the study will be stopped and the null hypothesis accepted. Otherwise the trial will continue until 202 patients have been accrued, at which point the null hypothesis will be rejected if the absolute value of the test statistic is greater than 2.008 (p-value < .0446).

The two-stage design has a larger maximum sample size (202 vs 198) but a smaller expected sample size compared to that of a single stage design (Table 3). The expected sample size depends on the true difference in fatigue between treatment groups as illustrated in Table 3 below. We see that under the null hypothesis, the probability of stopping at the first stage is 30%, and the expected sample size is approximately 155. Under the alternative hypothesis, the probability of stopping early is 37% and the expected sample size is approximately 149.

Table 3. Probability of stopping and expected sample size for two-stage design

True Difference in Fatigue	Probability of Acceptance/Rejection		Expected Sample Size
	Stage 1	Stage 2	
0.0	.288/.014	.662/.036	154.5
2.97	.041/.326	.160/.473	148.6

9.3 Randomization

Participants will be stratified by planned radiation therapy (Yes vs No) and type of chemotherapy (anthracycline vs nonanthracycline) and randomized to receive Co Q10 or placebo 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 infer future assignments from past assignments. Because block sizes are determined randomly, no one will know what the next treatment assignment will be; therefore, selection bias (the differential selection of patients to Co Q10 versus placebo) should not be an issue. Additionally, this is a double-blinded study, making the possibility of selection bias even less of a concern. Treatment sequences will be generated using a randomization program, and participants will be assigned to a blinded arm upon registration.

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9.4 Statistical 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 side effects or other unusual results will be reported to the CCCWFU Clinical Research Oversight Committee and the Research Base DSMB for further action.

Chi-squared tests (for categorical variables) and t-tests (for continuous variables) will be used for assessing the baseline comparability of the two groups. Analysis of covariance will be used to assess group differences in fatigue (and other continuous measures) after adjusting for pretreatment values and participant characteristics such as performance status, age, radiation treatment, and type of chemotherapy. Adjustments will be made 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., CESD classified as depression or not) between groups after adjustment for covariates. Methods proposed by Hosmer and Lemeshow will be used to assess the goodness of fit of these models.

Outcomes will be measured at baseline and at 8, 16, and 24 weeks thereafter. In addition to the 24-week post randomization analyses mentioned above, all of the outcome data will be analyzed using growth curve models or repeated measures analysis of (co) 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). It is unlikely that there will be much missing data; however, some data will be missing due to missed visits and patients dropping out of the study. We propose to analyze the data using SAS Proc Mixed, a program for the general analysis of covariance for data with repeated measures. This program provides maximum likelihood estimates for repeated measures problems, allowing for unbalanced designs, missing data at some times, structured or unstructured covariance matrices, and growth curve parameterizations of time effects. Various covariance structures will be assessed, but it is likely that an autoregressive model will prove most useful. Logistic regression, using generalized estimating equations to account for within subject correlation (SAS Proc Genmod), will be used to analyze repeated dichotomous outcomes (e.g., depression). Both fixed (e.g., age, race, performance status) and time-varying covariates (e.g., social support) will be used in the repeated measures models. Correlational analyses will be done to assess the relationships of continuous variables. Simple associations between variables will be examined using bivariate plots and spline fitting algorithms. Spearman and Pearson correlations will be calculated to quantitate the strength of the monotonic and linear relationships between continuous measures.

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