



**Protocol Resources**

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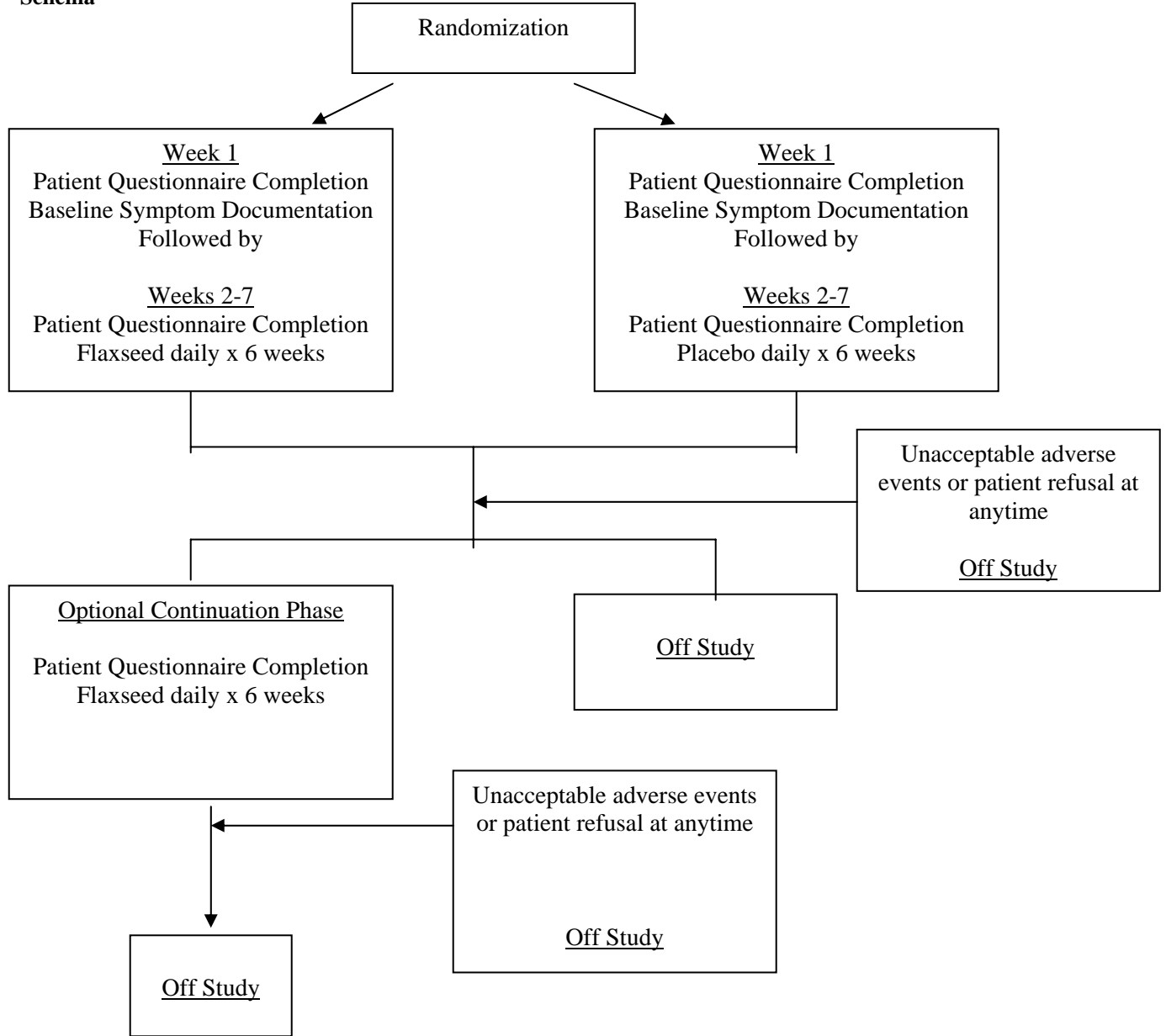
- No waivers of eligibility per NCI

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**Schema**



- Cycle 1 (double blind phase) = 21 days (weeks 1-3)
- Cycle 2 (double blind phase) = 14 days (weeks 4-5)
- Cycle 3 (double blind phase) = 14 days (weeks 6-7)
- Cycle 4 (continuation phase) = 14 days (weeks 1-2)
- Cycle 5 (continuation phase) = 14 days (weeks 3-4)
- Cycle 6 (continuation phase) = 14 days (weeks 5-6)

Note that 'cycle' information is an NCCTG data management tool to facilitate consistent remote date entry.

Generic name: Flaxseed	Generic name: Placebo
Brand name(s): Flaxseed	Brand name(s): Placebo
NCCTG Abbreviation: FLAX	NCCTG Abbreviation: PLACEB
Availability: NCCTG Research Base Pharmacy	Availability: NCCTG Research Base Pharmacy

## 1.0 Background

### 1.1 The Hot Flash Problem

Hot flashes are experienced by up to 75% of women in the general population as they travel through the menopause transition (Gracia & Freeman, 2004; Couzi, Helzlsouer & Fetting, 1995). For most women, hot flashes persist for up to 2 years and then subside. However, for women receiving treatment for breast cancer, the need to take endocrine therapy, such as tamoxifen or an aromatase inhibitor is associated with the side effect of hot flashes. As these medications are taken for at least five years, this subset of women may experience a prolonged symptomatic menopause.

For women who are breast cancer survivors, menopause can also occur earlier in life, before the average of age of menopause (50) due to follicular ovarian function cessation initiated prematurely by chemotherapy. The result of premature menopause can be the experience of distressing hot flashes. It has been reported that menopausal symptoms may be more severe in breast cancer survivors compared with women experiencing natural menopause (Carpenter, Johnson, Wagner, et al., 2002). In this study, the women with breast cancer had three times the severity and bother associated with their hot flashes compared to women without a history of breast cancer. It should be noted that half of the women with breast cancer were on tamoxifen and 27% of the women without breast cancer were on HRT. Therefore, the difference in hot flash severity, frequency and bother could be attributable to concomitant medications as well as lack of effective treatments and not an inherent physiologic phenomenon.

Previous hot flash trials including 50% or more breast cancer survivors indicate that, despite eligibility criteria of 4 hot flashes per day, women experienced a mean of 8 or 9 hot flashes per day. The mean severity of these hot flashes was rated as moderate according to the women participating in these trials. (Barton et al, 2007; Loprinzi et al, 2007).

Even though menopause and the symptoms accompanying it are expected events in a woman's life, this event can be accompanied by psychological and physiological trauma. This is particularly true when menopause is acutely and prematurely initiated, or when the primary effective treatment option for control of menopausal symptoms (i.e. estrogen) is contraindicated (Consensus Statement, 1998).

In a recent dose finding trial evaluating citalopram for hot flashes, the use of an activity interference scale, the Hot Flash Related Daily Interference Scale (Carpenter, 2001), revealed the mean interference from hot flashes at baseline with regard to sleep was 3 on a 0 to 10 scale and 2 with regard to work (Barton, ASCO, 2008).

Hot flashes are not just a physiologic phenomenon but are accompanied by both emotional and behavioral responses. When asked to record what factors led to a designation of mild, moderate, severe or very severe hot flashes, women listed several negative emotions that accompanied their hot flashes. These emotions included panic, irritation, being embarrassed or annoyed and distressed (Finck, Barton, Loprinzi, et al., 1998). The more severe the hot flash, the more negative the emotion. Behaviors were

also undertaken as a result of the hot flash experience. Again, the more drastic behaviors were associated with more severe hot flashes; major sleep disturbance, bed linen changes, and cold showers (Finck, Barton, Loprinzi, et al., 1998).

In addition, hot flashes can be a source of bother, distress and negatively impact quality of life. In one study, hot flashes were associated with more interference in terms of work, social life, leisure, sleep, concentration, relationships, sex and mood than was found for those postmenopausal women who were not having hot flashes; (Carpenter, Johnson, Wagner, et al., 2002). This sample included women who were breast cancer survivors as well as those who were not. Decreased physical and emotional quality-of-life has been correlated with a higher prevalence and severity of menopausal symptoms, particularly hot flashes. Therefore, though hot flashes are not a life threatening symptom, they can negatively impact a woman's life.

## 1.2 Hormonal Treatment Options: Pros and Cons

Estrogens and progestational agents are the most effective agents known to date for reducing hot flashes, with reductions of about 80% (Couzi, Helzlsouer & Fetting, 1995; Notelovitz, Lenihan, McDermott, et al., 2000). Nonetheless, there is concern about giving estrogen to women who have had breast cancer, and the current sentiment of many is that estrogen therapy should not be prescribed for breast cancer survivors until there is evidence from prospective, randomized trials that prove it safe. Based on recent articles from the Women's Health Initiative, once perceived benefits of estrogen based therapy (such as improved cardiac status and cognition), are now being questioned (Craig, Maki & Murphy, 2005; Rossouw & Women's Health Initiative Investigators, 2002). Furthermore, risks in the general population related to vascular events and breast cancer risk are being quantified, and the risk benefit ratio of estrogen based therapy leaves many women deciding against this option.

With some similarities to estrogen, there is theoretical concern that progestational agents may stimulate tumor growth. Therefore, progestins are not readily utilized in many women with a history of breast cancer. In addition, with the information from the WHI citing the increased risk of cancer with an estrogen/progesterone combination as opposed to estrogen alone makes progestational agents less attractive (Rossouw & Women's Health Initiative Investigators, 2002). Finally, progestational agents are associated with weight gain and negative mood in the literature and are not popularly thought of to positively impact the menopausal experience despite a lack of such evidence in trials utilizing progesterones for hot flashes (Goodwin, Green, Moinpour, Bearden et al, 2008; Loprinzi, Levitt, Barton, et al, 2006; Loprinzi, Michalak, Quella et al, 1994).

## 1.3 Newer Treatment Options

Clearly, alternatives to the problem of menopausal symptoms, hot flashes in particular, are needed. Through the North Central Cancer Treatment Group (NCCTG) and the Mayo Clinic Cancer Center mechanisms, we have been studying such alternatives over the past decade. Until the year 2000, the best of these alternatives, clonidine, reduced hot flashes by about 40% (Goldberg, Loprinzi, O'Fallon, et al., 1994; Pandya, Morrow, Roscoe, et al., 2005), which is better than the 20-25% reduction that is consistently seen with a placebo (Sloan, Loprinzi, Novotny, et al., 2001; Loprinzi, Kugler, Sloan, et al., 2000), but is accompanied by unwanted toxicities such as sedation, dry mouth, and

itching (if a patch is used).

Since the year 2000, two novel alternative classes of medications have become known to effectively ameliorate hot flashes. The first is gabapentin, a gamma-aminobutyric acid (GABA) analogue that has been used in a variety of disorders; neurologic (anticonvulsant), psychiatric disorders, and chronic pain management. It is also effective in controlling hot flashes. The exact mechanism is unclear, but it may reduce noradrenergic hyperactivity (Guttuso, 2000). Gabapentin was first reported to be a promising new therapy for relief of hot flashes in a case series report. This was followed by two pilot trials and two placebo controlled trials, all reporting positive results (Guttuso, Kurlan, McDermott, et al., 2003; Pandya, Morrow, Roscoe, et al., 2005; Loprinzi, Sloan, Perez, et al., 2002; Pandya, Thummala, Griggs et al, 2004).

The first placebo-controlled trial in 59 postmenopausal women found that 900 mg/ day of gabapentin decreased hot flash frequency by 45% and overall hot flash score by 54% (Guttuso, Kurlan, McDermott, et al., 2003). This was significantly better than placebo, which had decreases of 29% and 31% respectively. Side effects of gabapentin included somnolence, dizziness, and edema. These side-effects are not very well accepted for many women.

Another study was in 371 evaluable women with breast cancer, reporting that placebo reduced hot flashes by 18%, 100mg three times per day of gabapentin reduced hot flashes by 28% and 300 mg three times per day of gabapentin reduced hot flashes by 41% after 4 weeks and 15%, 30% and 44% after 8 weeks, respectively (Pandya, Morrow, Roscoe, et al., 2005). More recently, a trial evaluating up to 2400 mg of gabapentin (800 mg three times a day) was completed comparing gabapentin to estrogen and placebo. Investigators found that this higher dose of gabapentin relieved hot flashes equal to estrogen, but patients reported more headaches, dizziness and disorientation in the gabapentin arm (Reddy, Warner, Guttuso, et al., 2006).

A second novel group of useful agents for alleviating hot flashes, the newer antidepressants, has also been elucidated. Most of these agents, with the exception of sertraline, have been studied in placebo-controlled trials and have been found to provide a 50% or better reduction in hot flash frequency or score (Barton & Loprinzi, 2004). The medications studied in phase III randomized placebo-controlled trials include venlafaxine (Loprinzi, Kugler, Sloan, et al., 2000), fluoxetine (Loprinzi, Barton, Sloan, et al., 2002), sertraline (Gordon, Kerwin, Boesen, et al., 2006; Kimmick, Lovato, McQuellon, et al., 2006), citalopram (Barton, LaVasseur et al, 2008), and paroxetine (Stearns, Beebe, Iyengar, et al., 2003; Stearns, Slack, Greep, et al., 2005). Sertraline appears to be less effective in managing hot flashes, with a reduction of about 25-30% (Gordon, Kerwin, Boesen, et al., 2006). Side effects of these antidepressant agents can include nausea, dry mouth, appetite increase or loss, and constipation.

There are several limitations regarding the use of antidepressants for hot flashes. The first is that many women do not like the idea of being on an antidepressant. The second is that there is a fear of sexual side effects with serotonin reuptake inhibitors which makes their long term use unpopular in a population (breast cancer survivors) who already are experiencing negative changes in their sexual health as a result of their cancer diagnosis (Physician's Desk Reference, 2006). Therefore, other options are needed.

#### 1.4 Complementary Therapies For Hot Flashes

Complementary therapies are popular remedies used by women to decrease menopausal symptoms, including hot flashes. A minority of these therapies have been studied in rigorous, randomized, controlled trials. Of the agents studied to date, despite preliminary data, few have been found to be clinically important in reducing hot flashes. Studied agents include vitamin E (Barton, Loprinzi, Quella, et al., 1998), soy isoflavones (Loprinzi, Quella, Barton, et al., 1999), black cohosh (Pockaj, Gallagher, Loprinzi, et al., 2006) and acupuncture (Vincent, Barton, Mandrekar, et al., 2007). Several non-pharmacologic interventions have been explored in pilot trials and are currently in phase II or phase III clinical trials including paced breathing (Wijma, Melin, Nedstrand, et al., 1997; Freedman, 2005) and hypnosis (Elkins, Marcus, Palamara, et al., 2004; Elkins, Marcus, Stearns, et al., 2006). None of these have been definitively proven helpful at this time.

#### 1.5 Rationale For This Hot Flash Study

Due to the fact that the known effective non hormonal agents decrease hot flashes as much as 30% less than hormonal agents, that these non hormonal agents may not be helpful for as many as 1/3 of the patients who try them and that women may not want to risk the unwanted effects of antidepressants and anticonvulsants; more effective and acceptable options with tolerable toxicities or side-effects for hot flashes are still needed. One dietary treatment, flaxseed, has shown promise in at least 1 pilot trial and deserves more definitive study as a potentially effective option to relieve hot flashes.

#### 1.6 What Is Flaxseed?

Flaxseed is an annual plant that is cultivated in temperate and tropical areas. The seeds, as well as the oil from the seed, are the main components of the plant that are considered to have physiologic properties (Basch, Bent, Collins, et al., 2007).

Flaxseed is the richest source of lignans, which is one of three major classes of phytoestrogen. The lignans associated with flaxseed are primarily secoisolariciresinol (SDG), the essential fatty acid alpha-linolenic acid, (which is a biologic precursor to omega 3 fatty acids), as well as fiber. Lignans are thought to have estrogen agonist and antagonist effects as well as antioxidant properties. Lignans are converted by colonic bacteria to enterodiol and enterolactone which are metabolites believed to have important physiologic properties such as decreased cell proliferation and inhibition of aromatase, 5 alpha reductase and 17 beta hydroxysteroid activity. Numerous in vitro studies done since the early 1990s report properties of aromatase inhibition with enterolactone having moderate inhibitory properties and enterodiol being weaker with respect to aromatase inhibitory activity. (Wang, 1994; Aldercreutz 1992,1993). These properties have been speculated to potentially reduce the risk of hormone sensitive cancers such as breast and prostate cancer. Flaxseed has been shown in studies to reduce serum levels of 17-beta-estradiol and estrone sulfate and alter the urinary ratio of urinary estrogen metabolites (2 hydroxyestrogen and 16 alpha-hydroxyestrogen) (Basch, Bent, Collins, et al., 2007; Natural Medicines Comprehensive Database, 2004). Flaxseed has also been shown in breast cancer cell lines, ZR-75-1, and in rats, to inhibit cell proliferation and tumor growth respectively (Hirano, 1990; Thompson, 1996). According to a 2007 report from the Breast Cancer and the Environment Research Center (BCERC), there is currently no

evidence to suggest that breast cancer risk is increased with exposure to plant lignans. In fact, as described above, studies to date (two prospective cohort and two case control studies) find an inverse relationship between enterolactone and breast cancer, suggesting a chemopreventive role. (Barlow and Johnson, BCERC, 2007). The BCERC is a network funded by the National Institute of Environmental Health Sciences and the National Cancer Institute.

### 1.7 Potential Properties of Flaxseed:

Flaxseed and its lignans may have potent anti-estrogenic effects on estrogen receptor-positive breast cancer and may have benefits in breast cancer prevention efforts (Bergman-Jungstrom, Thompson & Dabrosin, 2007; Touillaud, Thiebaut, Fournier, et al., 2007). One recent study done in France, looked at four types of lignans, including that found in flaxseed (Secoisolariciresinol) in a prospective cohort study to see if intake predicted breast cancer incidence (Touillaud, Thiebaut, Fournier, et al., 2007). The authors report lowered risk of breast cancer among over 58,000 postmenopausal women who had the third highest quartile of lignan intake, including secoisolariciresinol.

Several studies support the role of flaxseed in increasing urinary excretion of estrogen metabolites as well as lignans (Brooks, Ward, Lewis, et al., 2004; Haggans, Hutchins, Olson, et al., 1999; Haggans, Travelli, Thomas, et al., 2000). It is hypothesized that increased urinary estrogen metabolism and excretion results in less estrogen being available to target organ tissues, therefore decreasing proliferation of breast tissue leading to the development of cancer.

One study evaluating the effect of flaxseed on biological markers in postmenopausal women demonstrated a reduction in tumor growth and increase in urinary lignan excretion (Thompson, Chen, Li, et al., 2005). Specifically, Ki -67 labeling index and c-erb B2 expression, and an increase in apoptosis was also observed. In both premenopausal and postmenopausal women, flaxseed consumption was found to increase urinary estrogen metabolite excretion resulting in a decrease in estrogen availability to cells (Haggans, Hutchins, Olson, et al., 1999; Haggans, Travelli, Thomas, et al., 2000). Chen et al (Chen, Hui, Ip, et al., 2004) reported that both flaxseed and tamoxifen increased tumor inhibitory effect in estrogen dependent breast cancer.

### 1.8 Preliminary Data related to hot flashes

A small, randomized clinical trial with 25 women evaluating diet and flaxseed versus diet and estrogen +/- progesterone therapy for lipid effects also looked at the impact of the two arms on menopause symptoms as measured by the Kupperman Index. The investigators used 40 grams per day of flaxseed (21 mg of lignans) versus 0.625 mg of conjugated estrogen and concluded that both arms were equally efficacious in reducing mild menopausal symptoms (Lemay, Dodin, Kadri, et al., 2002).

A larger placebo-controlled trial with 179 women evaluating 40 grams of flaxseed (21 mg of lignans) over one year on numerous endpoints, did not find that the flaxseed reduced hot flashes per the MENQOL any more than did the wheat germ placebo (Dodin, Lemay, Jacques et al., 2005). Yet another study using flaxseed muffins delivering 50 mg/day of lignans versus soy muffins versus a placebo muffin found a significant decrease in the severity of hot flashes for those on flaxseed but no significant differences

in frequency (Lewis, Nickell, Thompson et al., 2006).

It should be noted that the clinical trials done with flaxseed to date have used 40 grams of flaxseed. The manuscripts note 21 mg of lignans. There could be an important discrepancy occurring in these reports. Standardized flaxseed contains 1% lignans. Therefore, if 40 grams of flaxseed was indeed used, then the mg of lignans in these studies should have been around 400 mg, not 21 (personal communication, Loren Ward, Glanbia Nutritionals, 1/6/09). It is not clear why this discrepancy exists.

Based on the mixed pilot data, we conducted a pilot trial with 40 grams of flaxseed (1 % secoisolariciresinol diglucoiside (SDG)) to evaluate its impact on hot flash reduction. This dose and product represents 400 mg of lignans. This was a phase II, open label trial with one week of baseline and 6 weeks of treatment with flaxseed. Thirty women who were both pre- and postmenopausal were recruited. The women could have a personal history of breast cancer or no breast cancer and wanted to avoid hormone therapy for hot flashes (Pruthi, Thompson, Novotny, et al., 2007). The participants on the study were not permitted to use estrogen. Women were permitted use of tamoxifen, raloxifene or aromatase inhibitors if they had been on a constant dose of the medication for more than 4 weeks and did not plan to stop the therapy during the study period. Crushed flaxseed was administered at 20 grams twice daily to be sprinkled on cereal, yogurt or mixed in a beverage. Participants were asked to complete a daily hot flash diary and provide weekly toxicity reports and health related quality of life information. The first week of the trial was a baseline week and no supplement was ingested. Participants were then asked to start the flaxseed. The pilot data demonstrated a mean decrease in hot flash scores of 57% and mean reduction in daily hot flash frequency of 50%, from 7.3 hot flashes to 3.6. Participants reported mild to moderate abdominal distension (50%) and mild diarrhea and flatulence. Six withdrew from the study due to toxicities. This is the first pilot study to evaluate dietary flaxseed therapy with respect to hot flash activity as a primary endpoint. The reduction in hot flash score and frequency was greater than what would be expected with placebo, thus warranting a larger, placebo controlled trial using hot flash reduction as the primary endpoint (Pruthi, Thompson, Novotny, et al., 2007).

Toxicities of flaxseed: In general, flaxseed is a food substance that is well tolerated and few side effects have been identified. Flaxseed is commonly used for constipation and as such, can be associated with side effects similar to other fiber products; diarrhea, abdominal distention and discomfort, nausea and vomiting (Basch, 2007, JSIO). Dermatologic problems such as rash or palmar pruritis have also been noted in case reports (Basch, 2007). There is one study using flaxseed oil (which is a slightly different agent) in rheumatoid arthritis that increased bleeding times but no other clinical or laboratory parameter (Nordstrom DC, Honkanen VE, Nasu Y et al. 1995). It is hypothesized that flaxseed can interact with anti-coagulants or anti-platelets to increase the risk of bleeding but no definitive proof of this has been published. Theoretically, flaxseed can also lower blood pressure and blood glucose. Therefore, to err on the conservative side, we are excluding participants with conditions that could theoretically be impacted by flaxseed such as diabetes, hypotension and use of anticoagulants.

Study Summary

The study proposed is a phase III randomized placebo-controlled trial to test a high lignan concentration of flaxseed in a placebo controlled trial. Participants with hot flashes will be randomized to 7.5 grams of flaxseed (5% lignans or 410 mg) in the form of a bar, similar to a granola bar. Specific nutritional specifications are in Appendix XI. This bar has been formulated for use in previous studies and is good tasting, well tolerated and very well adhered to by previous study participants (telephone communication, Loren Ward, Glanbia Nutritionals, 1/06/09). The bar was also taste tested by several NCCTG staff, including the PI of this trial. An identical appearing bar without flaxseed or lignan content will serve as the placebo. One bar should be eaten daily and can be eaten throughout the day or at one time as desired. This product has a higher lignan content than was used in our pilot trial, so we can use less and have a lower fiber content, theoretically making this product more tolerable in terms of gastrointestinal toxicity. The study will contain the usual first week without study agent to ascertain baseline data and then will consist of 6 weeks of treatment to the randomized arm. The primary outcome measure will be the hot flash score at week 7. Secondary outcomes include toxicities, mood, general menopausal symptoms, and hot flash related daily interference on activities.

## **2.0 Goals**

### **2.1 Primary**

2.11 To evaluate the efficacy of flaxseed on hot flash scores in women with a history of breast cancer, or in women who do not wish to take estrogen therapy for fear of increased risk of breast cancer, as measured by a daily prospective hot flash diary.

### **2.2 Secondary**

2.21 To evaluate the side effect profile of flaxseed in this population.

2.22 To evaluate the effects of flaxseed on mood (per the Profile of Mood States), daily interference from hot flashes (per the Hot Flash Related Daily Interference Scale) and broader menopausal symptoms (per the Menopause Specific Quality of Life ) and perception of benefit (per the Global Impression of Change).

## **3.0 Patient Eligibility**

### **3.1 Inclusion Criteria**

3.11  $\geq 18$  years of age.

3.12 Women with a history of breast cancer or other cancer (currently without malignant disease) or women who have no history of breast cancer but who wish to avoid estrogen due to a perceived increased risk of breast cancer.

3.13 Bothersome hot flashes (defined by their occurrence  $\geq 28$  times per week and of sufficient severity to make the patient desire therapeutic intervention).

- 3.14 Women who are postmenopausal as defined by (1) absence of a period in the past 12 months; or (2) bilateral oophorectomy. Note: Women with at least one ovary but without a uterus should be deemed postmenopausal by either (1) age over 55 or (2) a combination of estrogen within a postmenopausal range (per local lab) and FSH over 40 mIU/mL.
- 3.15 Presence of hot flashes for  $\geq 1$  month prior to randomization.
- 3.16 Life expectancy  $\geq 6$  months.
- 3.17 ECOG Performance Status (PS) 0 or 1 *This form is now on the NCCTG website <https://ncctg.mayo.edu/ncctg/forms/NonProtocolSpecificForms>.*
- 3.18 Ability to complete questionnaire(s) by themselves or with assistance.
- 3.19a Provide informed written consent.
- 3.2 Exclusion Criteria
- 3.21 Any of the following current ( $\leq 4$  weeks) or planned therapies (EXCEPTION: tamoxifen, raloxifene, or aromatase inhibitors are allowed, but the patient must have been on a constant dose for  $\geq 4$  weeks and must not be expected to stop the medication during the study period):
- Androgens
  - Estrogens
  - Progestational agents
- 3.22 History of allergic or other adverse reaction to flaxseed.
- 3.23 Current ( $< 7$  days prior to registration) or planned use of other agents for treating hot flashes (i.e.: gabapentin, clonidine, antidepressants) except stable dose of vitamin E (as a general vitamin supplement), if no more than 800 IU/day, is allowed as long as it was started  $> 30$  days prior to study initiation and is to be continued through the study period. Women who have been using antidepressants for mood and have been on a stable dose for over a month and meet the eligibility criteria for hot flash frequency and duration are eligible.
- 3.24 Women of childbearing potential, premenopausal women.
- 3.25 Other herbal supplements for any reason, including soy and soy supplements such as powders, pills and milk
- 3.26 Diagnosis of irritable bowel syndrome, colitis, Crohns disease or any GI condition where the patient should not consume and/or has an intolerance/allergies to seeds or nuts.
- 3.27 Anticoagulant or anti-platelet (1 mg. Coumadin for central line patency is allowed) therapy. Note: 81mg and below aspirin is allowed

- 3.28 Anti-hypertensives, as flaxseed may potentiate this therapy.
- 3.29 Diabetes requiring oral or injectable anti-hyperglycemics.
- 3.29a Treatment with anti-cancer therapies of any kind except trastuzumab and endocrine therapies are allowed (tamoxifen, aromatase inhibitors, raloxifene as defined in 3.21).

#### 4.0 Test Schedule

Tests and Procedures	≤ 100 days prior to registration	Week 1 (Baseline Week)	Daily during study (Weeks 2-7)	Weekly (Weeks 2-7)	Completion of Week 7	Optional Continuation Phase x 6 weeks
History and exam, PS	X					
FSH/estradiol (if necessary to determine menopause status)	X					
Hot Flash Daily Diary (Appendix IV)		X	X			X <sup>3</sup>
Side Effect Experience Questionnaire (Appendix V)		X		X		X <sup>3</sup>
MENQOL (Appendix VIII)		X		X		
POMS (Appendix VI) HFRDIS (Appendix VII) Subject Global Impression of Change (Appendix IX)		X <sup>1</sup>			X	X <sup>3</sup>
Adverse Event Assessment		X		X	X	X
Nurse/CRA phone call				X <sup>2</sup>	X	X <sup>2</sup>

1. The Global Impression of Change is only done at the end of the 7<sup>th</sup> week in the double blind phase.
2. Every other week during the double blind phase - weeks 2, 3, 5, 7 (week 2 phone call to assess compliance only, AE assessment does not need to be done for week 2). For the continuation phase, the patient should be called weeks 2, 4, and 6. The CRA/Nurse Phone Call Script (Appendix X) may be used to assist in data collection. The final phone calls (week 7 for double blind phase and week 6 for optional continuation phase) are to be made at the completion of the week.
3. During the continuation phase, participants are asked to complete the daily hot flash diary, weekly side effect experience questionnaire and, at the end, the HFRDIS. The Subject Global Impression of Change and POMS will not be done during the continuation phase.

## 5.0 Stratification Factors:

Stratification of the variables will be achieved through established NCCTG procedures of dynamic allocation that balance the marginal distributions (Pocock, 1975). The 16 level combinations involved in these four stratification factors are within the maximum recommended of one half of the group sample size for the study (Therneau, 1993).

- 5.1 Age: 18-49 vs. 50.
- 5.2 Tamoxifen/Selective Estrogen Receptor Modulator (SERM)/Aromatase inhibitor (AI): Yes vs. no.
- 5.3 Duration of hot flashes: 9 months vs. > 9 months.
- 5.4 Daily frequency of hot flashes: 4 to 9 vs. 10.

## 6.0 Registration/Randomization Procedures

### 6.1 Double Blind Phase

#### 6.11 Randomization procedures

- 6.111 To randomize a patient, access the NCCTG web page at <https://ncctg.mayo.edu/training> and enter the remote registration/randomization application. The remote registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the NCCTG Registration Office at (507) 284-4130 between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for remote registration are available on the NCCTG web page and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a NCCTG subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study product. Patient registration via the remote system can be confirmed in any of the following ways:

- Contact the NCCTG Registration Office (507) 284-4130. If the patient was fully registered, the Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to “Instructions for Remote Registration” in section “Finding/Displaying Information about A Registered Subject.”

- 6.112 IRB approval(s) is required for each treating site. A signed Cancer Trials Support Unit (CTSU) IRB Certification Form is to be on file at the CTSU Regulatory Office (fax 215-569-0206). This form can be found at the following Web site: [www.ctsu.org/rss2\\_page.asp](http://www.ctsu.org/rss2_page.asp). Guidelines can be

found under Quick Fact Sheets.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the CTSU Regulatory Office (fax 215-569-0206). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the CTSU is no longer necessary.

- 6.113 Prior to accepting the registration/randomization, the remote registration/randomization application will verify the following:
- IRB approval at the registering institution
  - Patient eligibility
  - Existence of a signed consent form
  - Existence of a signed authorization for use and disclosure of protected health information (*U.S.A. institutions only*)
- 6.114 Treatment on this protocol must commence at the accruing membership under the supervision of an NCCTG member physician or allied health staff.
- 6.115 Study Week 2 Treatment (date of first bar) cannot begin prior to randomization and must begin 28 days after randomization.
- 6.116 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.
- 6.117 All required baseline symptoms (see Section 10.3) must be documented and graded.
- 6.118 Patient questionnaire booklet availability checked; copies are not acceptable for this submission.
- 6.12 Randomization Procedures:
- 6.121 The factors defined in Section 5.0, together with the registering membership, will be used as stratification factors.
- 6.122 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups (Pocock, 1975).
- Flaxseed in the form of a bar
  - Identical placebo in the form of a bar
- 6.13 Procedures for Double-Blinding the Treatment Assignment

- 6.131 After the treatment assignment has been ascertained by the remote registration/randomization application, the patient's study product code number will be displayed on the confirmation of registration screen.
- 6.132 In the unlikely event that more is needed, the data manager/nurse/pharmacist at the patient's institution must contact the Registration Office for a code number if additional study product is needed for the patient.
- 6.133 The number of the treatment package assigned to the patient will be recorded on the dosing form.

## 6.2 Optional Continuation Phase

- 6.21 The double-blind phase of the study must be completed prior to the treatment code being broken; that is, after the treating site has received the completed patient questionnaire booklet.
- 6.22 If the patient and physician want to continue with the flaxseed, or if on placebo, begin the flaxseed, fax (507/284-0885) a completed continuation phase eligibility checklist to the Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.
- 6.23 Treatment cannot begin prior to registration and must begin  $\leq 28$  days after registration to the continuation phase.

## 7.0 Protocol Treatment

### 7.1 Treatment Schedule – Double Blind Phase

Product	Dose Level	Route	Day	Duration of Treatment <sup>1</sup>
FLAX*	1 Nutrigrad™ flaxseed bar containing 7.5 grams flaxseed, 410 mg lignans,	Oral	Daily, can munch on the bar throughout the day or eat at one or two sittings	Weeks 2-7
PLACEBO	Identical looking bar with same calorie and total fat content but without flaxseed, lignans	Oral	Daily, can munch on the bar throughout the day or eat at one or two sittings	Weeks 2-7

\* Note: Total dose of flaxseed is 7.5 grams/day delivering 410 mg of lignans.

1. During week 1 patients will complete baseline symptom documentation questionnaires; they will not take the study product.

- 7.11 At study entry, the patient will be given a booklet of forms to be filled out, and

the procedure for completing each page of the set will be carefully explained. Forms in the booklet will include the Hot Flash Diary (Appendix IV), Side Effect Experience Questionnaire (Appendix V), Profile of Mood States (POMS) (Appendix VI), Hot Flash Related Daily Interference Scale (HFRDIS) (Appendix VII), Menopause Specific Quality of Life (MENQOL) (Appendix VIII), and Global Impression of Change (Appendix IX).

- 7.12 The Hot Flash Diary labeled “first study week (baseline)” should be filled out daily during the first 7 days (week 1) following study entry to document the patient’s baseline hot flashes.
- 7.13 The Hot Flash Diary labeled “second study week” should be filled out daily during the second 7 days (week 2) after study entry and likewise for study weeks 3, 4, 5, 6, and 7.
- 7.14 The Side Effect Experience Diary and MENQOL should be completed weekly at the end of each week for weeks 1–7.
- 7.15 The POMS and HFRDIS should be completed only twice, at the end of the baseline week and at the completion of the 7<sup>th</sup> week.
- 7.16 The Global Impression of Change should be completed at the end of the 7<sup>th</sup> week.
- 7.17 Each patient will be contacted by the study nurse or other research personnel by telephone weeks 2, 3, 5, and 7 to assess product tolerability, document compliance, encourage completion of the booklet, and address problems. Week 7 phone call should be made at the completion of week 7.
- 7.18 Patient questionnaire booklets should be returned to the investigator at the end of the 7 study weeks. The patient should be supplied with addressed/stamped envelopes for returning the forms.
- 7.19 In the event of an emergency, call the Registration Office at (507) 284-4130 to break the code on Monday through Friday, 8:00 a.m. to 4:30 p.m. central time. If the code must be broken after hours, assume the patient was assigned to active treatment and treat accordingly. Place a call to the Registration Office and leave a message informing them of the need to un-blind a patient. Provide contact information so that the Registration Office personnel can return the call the next business day.

## 7.2 Treatment Schedule – Optional Continuation Phase

Product	Dose Level	Route	Day	Duration of Treatment
FLAX	1 Nutrigrad™ flaxseed bar with 7.5 grams flaxseed, 410 mg lignans	Oral	One bar daily, can munch on bar throughout the day or eat at one or two sittings	Weeks 1-6

- 7.21 After the double blind phase patient questionnaire booklet has been completed and returned to the investigator, the patient will be told whether she was on flaxseed or placebo. If the patient wishes to continue or start the flaxseed, and healthcare provider approves that this is an appropriate option, she may be registered on the Optional Continuation Phase of the study. You will need to contact the registration office as instructed in 7.19 for information to un-blind the patient.
- 7.22 At study entry, the patient will be given a booklet of forms to be filled out, and the procedure for completing each page of the set will be carefully explained. Forms in the booklet will include the Hot Flash Diary (Appendix IV), Side Effect Experience Questionnaire (Appendix V), and Hot Flash Related Daily Interference Scale (HFRDIS) (Appendix VII). These forms will not need to be completed prior to starting the continuation phase, as they will have been completed at week 7, the end of the double blind phase.
- 7.23 The Hot Flash Diary labeled “continuation phase” should be filled out daily during the first 7 days (week 1) following study entry and likewise for continuation phase weeks 2 through 6.
- 7.24 The Side Effect Experience Questionnaire should be completed weekly at the end of each week for weeks 1–6.
- 7.25 The HFRDIS should be completed only once, at the end of the last week, week 6.
- 7.26 Each patient will be contacted by the study nurse or other research personnel by telephone weeks 2, 4, and 6 to assess product tolerability, document compliance, encourage completion of the booklet, and address problems. Week 6 phone call should be made at the end of week 6.
- 7.27 Patient questionnaire booklets should be returned to the investigator at the end of the 6 week continuation phase. The patient should be supplied with addressed/stamped envelopes for returning the forms.

## 8.0 Dosage Modification Based on Adverse Events

- 8.1 If the patient develops any symptoms attributed to the flaxseed which are considered by the patient and/or physician to be of unacceptable severity, then the study product should be decreased by one-half bar per day or stopped. Reasons for modifications or early stopping should be documented clearly on the end of active treatment form and specific AE's graded.

## 9.0 Ancillary Treatment

- 9.1 All ancillary treatments as appropriate for symptom control and cancer therapy may be administered as clinically indicated with the exception of treatment for hot flashes (e.g. Bellergeral, megestrol acetate, antidepressants, estrogen treatment or clonidine) as described in Sections 3.21 and 3.23. If they do begin these they must come off study. Participants should also not begin any new dietary supplements during the course of this study.

## 10.0 Adverse Event (AE) Reporting and Monitoring

- 10.1 This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) active version (v4.0) for adverse event monitoring and reporting. The CTCAE active version can be accessed from the CTEP home page (<http://ctep.cancer.gov>). All appropriate treatment areas should have access to a copy of the CTCAE active version.
- 10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE. Next, determine whether the event is expected or unexpected (see Section 10.12) and if the adverse event is related to the medical treatment or procedure (see Section 10.13). With this information, determine whether an adverse event should be reported as an expedited report (see Section 10.2). Important: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.3 and 18.0).
- Expedited adverse event reporting requires submission of an Adverse Event Expedited Reporting System (AdEERS) report(s). Other expedited reporting requirements and systems may also apply. Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.2 and 10.3. All expedited AE reports must also be sent to the local Institutional Review Board (IRB) according to local IRB's policies and procedures.
- 10.12 Expected vs. Unexpected
- The determination of whether an AE is expected is based on the agent-specific information provided in Section 15.0 of this protocol.
  - Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of this protocol.
- 10.13 Assessment of Attribution

*When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:*

Definite - The adverse event *is clearly related* to the agent(s).

Probable - The adverse event *is likely related* to the agent(s).

Possible - The adverse event *may be related* to the agent(s).

Unlikely - The adverse event *is doubtfully related* to the agent(s).

Unrelated - The adverse event *is clearly NOT related* to the agent(s).

## 10.2 Expedited Adverse Event Reporting Requirements

### 10.21 Standard Expedited Reporting for Commercial Agents

	Grade 4 or 5 Unexpected with Attribution of Possible, Probable, or Definite	Increased Incidence of an Expected AE <sup>1</sup>
Submit a full expedited commercial report via AdEERS within 7 working days <sup>2</sup>	X	X

1. Any increased incidence of a known AE (as reported in the package insert or the literature), including adverse events resulting from a drug overdose.
2. In the rare event when Internet connectivity is disrupted, a report may be prepared using the Adverse Event Expedited Report – Single Agent or Multiple Agents paper template (accessible from the CTEP Home Page at <http://ctep.cancer.gov>). Contact the NCCTG SAE Coordinator (as identified on the NCCTG Protocol Resources page) for back-up submission instructions.

### 10.22 Other Required Expedited Reporting

<b>EVENT TYPE</b>	<b>REPORTING PROCEDURE</b>
Secondary AML/MDS	Reporting for this event required during and after completion of study treatment.  Submit the NCI/CTEP Secondary AML/MDS Report form within 15 days via fax or mail to the NCCTG SAE Coordinator, NCCTG Operations Office, 200 First Street SW, Rochester, MN 55905, Fax (507)284-9628. The Operations Office will submit to NCI.
Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report	If an AdEERS report has been submitted, this form does not need to be submitted.  Submit the Non-AER form electronically via the NCCTG Remote Data Entry System within 5 working days of the date the CRA is aware of the event(s) necessitating the form.

- 10.3 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per Common Terminology Criteria for Adverse Events (CTCAE) active version grading unless otherwise stated:

System Organ Class (SOC)	Adverse Event	Baseline (at on-study)	Each evaluation
Gastrointestinal Disorders	Nausea	X	X
	Vomiting	X	X
	Abdominal distension	X	X
	Flatulence	X	X
	Diarrhea	# stools per day	X
Skin and Subcutaneous Tissue Disorders	Rash maculopapular	X	X
	Pruritus	X	X
Vascular Disorders	Hematoma	X	X
	Vascular Disorders –Other, specify	X	X

- 10.31 Submit to the NCCTG Research Base via the Nadir/AE Log the following AEs experienced by a patient and not specified in Section 10.3:

10.311 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.312 Grade 3 and 4 AEs regardless of attribution to the study treatment

10.313 Grade 5 AEs (Deaths)

10.3131 Any death within 30 days of the patient's last study treatment or procedure.

10.3132 Any death more than 30 days from the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

- 10.32 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

## 11.0 Treatment Evaluation

All required patient completed questionnaires should not take longer than 20 minutes to complete at any given data point.

- 11.1 Goal 2.1: The hot flash score will be determined by the hot flash daily diary.

Participants are asked to complete this diary in real time, tracking the severity and frequency of their hot flashes for every 24 hour period for each of the 7 days in a week throughout all study weeks. The primary endpoints for analysis will be the change in the weekly average hot flash score from baseline to week 7 (the 6th week of treatment).

The hot flash diary is a prospective, self report diary that was developed by the Mayo Oncology Symptom Management Research team (Sloan, Loprinzi, Novotny, et al., 2001).

Women complete this diary in real time, so that as they experience each hot flash, they are asked to record it along with its severity. Participants are asked to record the number and severity of each hot flash in each 24 hour period over each 7 day week throughout the study including a baseline week in which no study product is taken. The weekly average of hot flash score is the primary outcome measure that will be derived from this diary. The hot flash score is a measure of frequency and severity. The hot flash severities are graded from 1 to 4, ranging from mild, to moderate, to severe to very severe. The daily hot flash score is computed by multiplying the mean grade of severity by the frequency during every 24 hour period.

This diary has been used in over 19 prospective, clinical trials involving over 1500 people (men and women) with hot flashes and has shown good reliability and validity (Sloan, Loprinzi, Novotny, et al., 2001; Loprinzi, Kugler, Sloan, et al., 2000). The efficacy of various agents has been replicated using this instrument in controlled clinical trials in numerous settings and groups.

- 11.2 Goal 2.2: A descriptive report of the toxicities experienced by participants will be measured with the Side Effect Experience Questionnaire. Participants will complete this questionnaire weekly. In addition, any adverse events reported by study personnel or practitioners and graded by common toxicity criteria will also be used for this endpoint.
- 11.3 Goal 2.3: The secondary outcome measures will include the Profile of Mood States, total mood disturbance and each subscale, Hot Flash Related Daily Interference Scale, the MENQOL and the Global Impression of Benefit. All endpoints for the secondary analysis will be change from baseline to week 7 (treatment week 6), except for Global Impression of Benefit which is only evaluated at the end of the study before the patient is unblinded.

Profile of Mood States is being used to look at total mood disturbance as well as the subscales of tension-anxiety, fatigue-inertia, and vigor-activity as these are expected emotions accompanying the hot flash experience that could be improved by the study treatment. The Profile of Mood States is a well known, well validated, reliable measure of psychological distress which includes 6 subscales of fatigue-inertia, vigor-activity, tension-anxiety, depression-dejection, anger-hostility, and confusion-bewilderment. The entire scale can be scored to provide a measure of total mood disturbance (Curran, Andrykowski & Studts, 1995). This is not a measure to diagnose psychological illnesses such as depression. The measure contains adjectives related to mood which are scored from 0 (not at all) to 4 (extremely). The POMS – SF has good validity as the total mood disturbance score correlates highly with the original POMS in samples (.93) (Curran, Andrykowski & Studts, 1995). The POMS-SF has been used in community populations as well as in populations of cancer patients. Internal consistency ranges from .80 to .91 for the subscales. Mood has been positively impacted in other hot flash trials, and is an important comorbidity in menopause. Therefore, we wish to look at the impact of

flaxseed on mood in this trial, as we have in other hot flash trials.

Hot Flash Related Daily Interference Scale - This tool is being used to evaluate the specific impact of the study treatment on the effect hot flashes have on various life activities such as work, social, leisure and relationships. This tool was developed and validated by Janet Carpenter, PhD, RN, on women who were breast cancer survivors as well as in a community sample of postmenopausal women (Carpenter, 2001). The scale is psychometrically sound for the purposes of this study, as demonstrated in other applications (Carpenter, 2001). Inter-item correlations ranged from .59 to .95 with a Cronbach's alpha of 0.96. The scale demonstrated convergent validity with hot flash severity and bother, discriminated between women with hot flashes and those without, was sensitive to change and demonstrated construct validity with the Positive and Negative Affect Scale as well the Profile of Mood States-Short Form.

The Menopause Specific Quality of Life (MENQOL-Intervention Questionnaire) – We are interested in each of the 4 domain scores (vasomotor items 1-3, psychological items 4-10, physical items 11-26 and sexual items 27-29), as well as the summary score for secondary endpoints. The domain scores are the sum of the items divided by the number of items to obtain a mean score. The summary score is the mean of all 4 domain scores. Since flaxseed is hypothesized to have SERM-like properties, we feel it is important to include this general menopause scale to look at broader effects. This original quality of life questionnaire was developed with women who were 2 to 7 years post menopausal and who were not on hormone replacement therapy. This slightly revised version was developed to include 3 potential negative side effects of treatments (Lewis, Hilditch & Wong, 2005), breast pain, vaginal bleeding and leg pain or cramps. These items are not part of a subscale. It is a 32 item measure with responses on a 7 point likert scale with word anchors of “not at all bothered” to “extremely bothered”. Construct validity was ascertained with several measures of hot flashes, general well being, vaginal symptoms and libido measures, psychosomatic and psychological measures as well as the Life Satisfaction Index. The MENQOL-intervention questionnaire is a condition-specific instrument used to measure the impact of menopause symptoms on quality of life and to evaluate interventions aimed at treating these symptoms. Test-retest reliability was sufficient with intraclass correlation coefficients ranging from .73 for the vasomotor subscale to .83 for the sexual subscale over a 14 day interval. Domain internal consistency was good with Cronbach's alphas of .72 (sexual), .86 (psychosocial), .88 (physical) and .77 (vasomotor) (Hilditch, Lewis, Peter, et al., 1996).

Side Effect Experience Questionnaire - is a self report weekly diary of expected side effects/potential benefits of flaxseed. It will measure the severity of the side effects experienced as well as allow space to write in side effects not covered. This questionnaire is set of individual items specific to flaxseed and each item will be evaluated as change from baseline separately. This questionnaire is not a validated questionnaire measuring a single concept but is simply a way to measure patient reported side effects. The questionnaire has validity in that the individual questions are modeled after other numeric analog scales which are the methodologic foundation for numerous validated instruments measuring various subjective symptoms such as fatigue (Brief Fatigue Inventory, Mendoza et al, 1999) and pain (Brief Pain Inventory, Daut, Cleeland, Flanery, 1983)

Global Impression of Change: The Subject Global Impression of Change is a 7 point

item in which the patient rates the change in the overall status since beginning the study product (ranging from very much better, moderately better, a little better, about the same, a little worse, moderately worse, to very much worse). It has been used extensively for determination of minimally clinically significant differences in numerous oncology clinical trials (Osoba, 2002; Sloan, Symonds, Vargas-Chanes, Fridley, 2003). We are using this instrument to measure the patient's perception of benefit from the study product.

## 12.0 Descriptive Factors

- 12.1 Breast cancer history: Yes vs. no.
- 12.2 Time since menopause: 1 year vs. >1 year but 2 years vs. >2 years but 3 years vs. > 3 years.
- 12.3 Anti-estrogen therapy: Aromatase inhibitor vs tamoxifen vs. other (specify).
- 12.4 On antidepressive therapy: yes vs. no. If yes, specify if SSRI vs. other.

## 13.0 Treatment/Follow-up Decision at Evaluation of Patient

- 13.1 A patient is deemed *ineligible* if at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered.
  - If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted.
  - If the patient never received treatment, on-study material must be submitted.
- 13.2 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted.
- 13.3 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted.

## 14.0 Body Fluid Biospecimens: None

## 15.0 Product Information

The flaxseed bar has 190 calories, 7.5 grams of flaxseed providing 410 mg of lignans. The protein content will be 6 grams and the fiber content will be 20%. The detailed typical specification is included in appendix XI. The product will have been quality tested and contents verified by an independent company, arranged by Glanbia Nutritionals.

IND exempt

### 15.1 Flaxseed

15.11 Preparation and storage: Nutrigrad™ flaxseed bars should be kept in a cool, dry place.

15.12 Known potential adverse events:

More Common: Abdominal distension, gas, diarrhea, nausea

Less Common: Vomiting, bleeding, rash, palmar pruritus

15.13 Study product procurement:

The NCCTG research base pharmacist will obtain the flaxseed bars and placebo bars from Glanbia Nutritionals, owner of Pizzey's Milling Nutritional Company.

Each institution will order starter supplies of blinded study product from the NCCTG research base pharmacist. Submit the NCCTG Clinical Drug Order/Return Form request to:

Medical Oncology Pharmacist  
Mayo Clinic  
Gonda 10-178  
Rochester, MN 55905  
FAX (507) 284-3464

Registration Office personnel will monitor the supply of coded study product at each participating institution and will arrange for the Research Base pharmacy to send further supplies to the participating institutions as needed.

**For the optional continuation phase:** Each institution will order flaxseed bars for use from the NCCTG research base pharmacist as needed. Submit the NCCTG Clinical Drug Order/Return Form request to:

Medical Oncology Pharmacist  
Mayo Clinic  
Gonda 10-178  
Rochester, MN 55905  
FAX (507) 284-3464

Each site will be responsible for monitoring the supply of bars used in the continuation phase and must use the NCCTG Clinical Drug Order/Return Form to order additional bars.

*Outdated or remaining bars are to be destroyed on-site as per procedures at each institution.*

#### 15.14 Nursing guidelines:

- 15.141 Instruct patients to drink plenty of water throughout the day, at least five 8-ounce glasses.
- 15.141 Instruct patients to avoid other herbal/dietary supplements.
- 15.142 Advise patients to call if side effects develop.

#### 15.2 Placebo

A matching placebo bar will be provided. It will be identical in appearance to the flaxseed bar. The specifications for this matching placebo bar are in appendix XI. It has 2 grams of protein, 20% dietary fiber and 200 calories. It will not contain the dietary lignans found in flaxseed.

### 16.0 Statistical Considerations and Methodology

- 16.1 **Study design:** This study consists of two sequential trials: (a) a randomized two-arm placebo controlled phase III trial to assess the efficacy and toxicity of flaxseed vs placebo for hot flashes over a six-week treatment period; and (b) an optional continuation phase of 6 weeks to obtain longer term information about the effects of flaxseed for the management of hot flashes and to allow the placebo arm to try the flaxseed.
- 16.2 **Randomization:** Following stratification, the treatment assignment will be calculated using a dynamic allocation procedure that balances the marginal distributions of the stratification factors among the two arms. The factors defined in Section 5.0, together with institution, will be used as stratification factors. Patients will be allocated equally among the two treatment arms.
- 16.3 **Primary endpoint:** The intra-patient difference in hot flash activity between baseline (study week 1) and treatment termination (study week 7) is the primary endpoint. The hot flash activity will be measured by the weekly average hot flash score (Sloan, Loprinzi, Novotny et al 2001) which is a composite entity of both frequency and severity of hot flashes. The daily hot flash score is computed by the grade of severity multiplying the frequency of the same grade hot flashes according to the hot flash diary over a 24 hour period. Taking the average of daily hot flash scores over a week produces the weekly average hot flash score. The weekly frequency and maximum grade of hot flashes are considered as complementary aspects of the primary endpoint.
- 16.31 **Goal 2.11:** The primary method of analysis will be the independent sample *t*-test to examine the change of weekly average hot flash score from baseline to treatment termination between flaxseed and placebo arms. The 95% confidence interval will be constructed for mean reductions in weekly average hot flash score. In addition, as confirmatory analyses, the weekly average hot flash scores, weekly frequency of hot flashes, and weekly maximum grade severity of hot flashes will be explored in repeated-measures ANOVA or Generalized Linear Mixed Models (GLMM) analysis to account for the longitudinal trend and other risk factors.
- 16.4 **Secondary endpoints:** There are a number of secondary endpoints that may be affected

by flaxseed treatments. Each may be used first as a separate endpoint and subsequently as a covariate controlled for in the analysis of the primary endpoint (Sloan & Dueck, 2004).

- 16.41 Goal 2.12: The change from baseline in the severity of symptoms as measured by single items in the Side Effect Experience Questionnaire will be analyzed by an independent sample t-test for continuous data. The frequency and maximum grade of adverse events reported via the CTCAE active version throughout the 7 weeks between flaxseed versus placebo arms will be compared using chi square test.
- 16.42 Goal 2.13: The change of mood as measured by the POMS from baseline to treatment termination between flaxseed versus placebo arms will be compared using an independent t-test for continuous data. Each subscale as well as total score will be analyzed separately.
- 16.43 Goal 2.13: The change of daily interference as measured by the HFRDIS from baseline to treatment termination between flaxseed versus placebo arms will also be evaluated with an independent t-test for continuous data. Each question as well as the total score will be analyzed separately.
- 16.44 Goal 2.13: The change of menopause specific quality of life as measured by the MENQOL from baseline to treatment termination between flaxseed versus placebo arms using chi square tests as this instrument yields ordinal data. Each of the four domains as well as a summary score will be analyzed separately. In addition, the final three items (30 – 32) will be compared as single items.
- 16.45 Goal 2.13: At end of study, we will look at perceptions of benefit per the Global Impression of Change between the flaxseed and placebo arm by a chi-square test.
- 16.5 Further analyses: Examination of the impact of covariates on the basic efficacy results for the primary endpoint of hot-flash activity will be carried out in two stages.
  - 16.51 Univariate correlation analysis involving Spearman's correlation coefficients will be carried out to examine the relationship between the reduction in hot-flash activity and the secondary endpoints of mood changes and changes in QoL. Further socio-demographic variables may be added to this process if they appear to be related to reduction in hot-flash activity as evidenced by Spearman correlations of at least 0.5. This level was chosen so that spurious and weak correlations are excluded from the analysis. The degree of correlation among 24 QoL and mood change will also be examined to avoid the potential problem of collinearity. Second, repeated-measures ANOVA/GLMM procedures incorporating the covariates of mood and QoL will be used to perform a conditional analysis of treatment effect in the presence of the important covariates.
  - 16.52 The data from continuation phase of six weeks will be analyzed in a descriptive manner only as it is open label. The mean reduction in hot flash frequency, severity and score will be calculated for the group over the 6 weeks of the continuation phase. Frequency and severity of any reported side effects

will also be described. For the HFRDIS analysis, change from week 7 of the double blind to the end of the continuation phase (week 6) will be analyzed. Participants who were initially on placebo will be analyzed separately from those who had already been on flaxseed. We will look at continuation of response for those already on flaxseed and will look at reduction in hot flashes for those who had been on placebo.

- 16.6 Power and sample size: Previous hot flash clinical trial data indicate that the mean reduction in hot flash score from baseline to the end of 4 weeks treatment is 3.6 with a standard deviation of 7.08 for patients in the placebo arms (Sloan, Loprinzi, Novotny et al 2001). We assume this observation will apply to the proposed clinical trial investigating flaxseed effect with a treatment period of 6 weeks as well. Since approximately 3.5 unit reduction in hot flash score will be expected for the placebo, an additional 3.5 unit reduction will be generally considered clinically important for the flaxseed treatment. That is, we expect flaxseed to reduce hot flash score at least 7.0 unit from baseline comparing with a reduction of approximately 3.5 unit of the placebo effect. A half standard deviation is considered a moderate effect size by Cohen (1998) and has been described as clinically meaningful (Sloan et al. 2006).
- 16.61 A two-sided independent sample *t*-test of the primary endpoint with 64 patients per treatment arm will have 80% power at 5% Type I error rate to detect a difference of 3.5 unit hot flash score reduction from baseline between flaxseed (7.0 unit) and placebo arms (3.5 unit). This sample size will be inflated by 20% to account for missing data (e.g., patient ineligibility, cancellation, or other reasons). The total number of patients accrued hence will be 154 patients, 77 per arm.
- 16.62 Accrual considerations: We will accrue 77 patients per arm for a total of 154 patients. Given our previous experience with hot flash studies we estimate an accrual rate of 15 patients per month so that we expect to complete accrual within about 12 months.
- 16.7 Subset analyses and stopping rules: This study will be monitored in accordance with the NCCTG Data Monitoring Committee, an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DMC every six months as per NCI guidelines. The final analysis of the randomized study will be initiated once the final patient entered has completed the six-week course of treatment. At this time, the results will be made available to the research team to facilitate the final analysis.

This study will be monitored by the Clinical Data Update System (CDUS) version 2.0. An abbreviated report containing cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

#### 16.71 Adverse Event Stopping Rule

The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during

the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (flaxseed) (i.e., an adverse event with attribute specified as “possible”, “probable”, or “definite”) that satisfy the following:

- if 5 or more patients in the first 20 treated patients in the flaxseed versus placebo arm (or 25% of all patients after 20 are accrued) experience a grade 4 or higher non-hematologic adverse event, and the toxicity rate is higher in the flaxseed arm than the placebo arm..

We note that we will review grade 4 and 5 adverse events deemed “unrelated” or “unlikely to be related”, to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.72 Subset analyses for minorities: This study will be available to all eligible patients, regardless of race or ethnic origin. There is no information currently available regarding flaxseed effects in subsets defined by race or ethnicity, and there is no reason to expect such differences to exist. Nonetheless, the planned analyses will, as always, look for differences in treatment effect based on racial groupings.

16.8 Missing data: We will perform statistical analysis of primary and secondary endpoints following the intent-to-treat principle. From our past experience, patients may withdraw early from the study during the 6 weeks treatment period. Many of these drop-outs may be non-random, for example, patients who may not be getting the relief they desire or have side effects they do not wish to tolerate. We will investigate the pattern of missing by applying graphical and statistical methods. Sensitivity analysis will be conducted if severe missing (>20%) will be observed: a) statistical analysis with complete data only (baseline and at the end of 6 weeks treatment); b) statistical analysis with last value carried forward imputation; c) longitudinal data analysis with all the data available at each time point.

We will also consider a number of other imputations for missing data if deems necessary, such as nearest neighbor, mean value, and zero value carried forward approaches (Fairclough & Peterson, 1998).

16.9a Special considerations for minority recruitment:

Recognizing that minorities are underrepresented in clinical trials as a whole, the NCCTG is committed to do what it can to improve minority recruitment. As a result, we have purposed to include a minority recruitment component for symptom trials that are likely to be fast accruing and close early, without giving minority based CCOP’s sufficient time to enact recruitment efforts. Our hot flash trials, particularly evaluating complementary therapies, have been exceedingly fast accruing trials. We would, therefore, like to keep this trial open BEYOND the primary accrual goals, to accrue minority participants.

Enrollment figures currently project about a 15% minority participation rate, or 24 participants. The targeted enrollment will seek an additional 56 minority participants in order to have sufficient numbers in each group for a subset analysis. Concurrent with the initial trial, we will accrue from specific ethnic subpopulations in South Dakota, Arizona, Louisiana and Georgia as well as other NCCTG member sites. Therefore, we will keep the study open until we have a total of 80 minority participants.

The completion of the trial will not be dependent on the minority accrual, but will proceed and close when targeted accrual numbers have been reached. Data cleaning and analysis on the originally planned 154 participants will begin. However, the protocol will remain open beyond this time to complete the additional minority accrual of 56 patients with a target total of 80 minority participants. Therefore, the total accrual will be 210 patients.

Planned subset analysis for minorities will be the same as that for the primary and secondary endpoints described in section 16.0. Forty patients per treatment arm will provide 80% power for the primary analysis detecting an effect size of 0.634 at the 5% significance level with the same two-sided two sample *t*-test for the primary analysis. The effect size detectable is slightly larger than the generally accepted clinically meaningful effect size of 50% times the standard deviation, and so we will be able to assess whether the impact of flaxseed on hot flashes is starkly different in the subpopulation of minorities.

There is no information currently available regarding differential agent effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analyses will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for such subset analyses.

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	30	0	0	30
Not Hispanic or Latino	180	0	0	180
<b>Ethnic Category: Total of all subjects*</b>	210	0	0	210
Racial Category				
American Indian or Alaskan Native	10	0	0	10
Asian	7	0	0	7
Black or African American	31	0	0	31
Native Hawaiian or other Pacific Islander	2	0	0	2
White	160	0	0	160
<b>Racial Category: Total of all subjects*</b>	210	0	0	210

*\*These totals must agree. Enter actual estimates (not percentages)*

<b>Ethnic Categories:</b>	<p><b>Hispanic or Latino</b> – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” can also be used in addition to “Hispanic or Latino.”</p> <p><b>Not Hispanic or Latino</b></p>
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**17.0 Pathology Considerations:** None

## 18.0 Records and Data Collection Procedures

### 18.1 Submission Timetable

Forms	Active-Monitoring Phase (Compliance with Test Schedule)			At each occurrence	
	Initial Material	Follow-up Material			
	2 weeks after registration	At each evaluation	At end of treatment	Grade 4 or 5 Non-AER Reportable Events/ Hospitalization	ADR/ AER
On-Study Form	X				
Baseline Adverse Events Form	X				
Concurrent Treatment Form	X	X <sup>4</sup>	X		
Evaluation/ Treatment Form		X <sup>4</sup>	X		
End of Active Treatment/Cancel Notification Form	X <sup>3</sup>		X <sup>5</sup>		
Adverse Event Form		X <sup>4</sup>	X		
Patient Questionnaire Booklet <sup>1</sup>			X		
Patient Questionnaire Booklet Compliance			X <sup>2</sup>		
ADR/AER (see Section 10.0)					X
Grade 4 or 5 Non-AER Reportable Events/ Hospitalization Form				X	

1. Patient questionnaire booklets **must** be used; copies are not acceptable for this submission.
2. This form must be completed **only** if the booklet(s) contains absolutely **NO** patient provided assessment information.
3. Submit this form only if withdrawal/refusal prior to beginning protocol therapy occurs.
4. Complete at each phone call during the double blind phase and the optional continuation phase with the exception of the week two phone call during the double blind phase (see Section 4.0).
5. Submit after week 7 of the double blind phase if patient does not go on to the optional continuation Phase.

## 19.0 Budget

- 19.1 Costs charged to patient: routine clinical care
- 19.2 Tests to be research funded: none.
- 19.3 Other budget concerns: The flaxseed/placebo bars will be provided for patients free of charge by Glanbia Nutritionals.

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## Appendix I

# NCI Informed Consent Template for Cancer Treatment Trials (English Language)

**\*NOTES FOR LOCAL INVESTIGATORS: [NOTE: Retain this section and asterisk item below for NCCTG model consents]**

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This template for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is <http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/>
- A blank line, \_\_\_\_\_, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer...What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at <https://cissecure.nci.nih.gov/ncipubs/> or call 1-800-4-CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*\*These notes for {authors and} investigators are instructional and should not be included in the informed consent form given to the prospective research participant.*

## **N08C7, A Phase III, Randomized, Placebo-controlled, Double-Blind Trial of Flaxseed for the Treatment of Hot Flashes**

*This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.*

**This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.**

You are being asked to take part in this research study because you have you have hot flashes and do not want to take estrogen.

### **Why is this research study being done?**

The purpose of this research study is to compare the effects, good and/or bad, of flaxseed with placebo on hot flashes. The study will also look at side effects, changes in mood, interference with activity, effect on other menopausal symptoms, and your impression of benefit from taking the study product. In this study, you will get either flaxseed or a placebo (an inactive product).

### **How many people will take part in the research study?**

About 210 women will take part in this study.

### **What will happen if I take part in this research study?**

Before you begin the study you will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your healthcare provider.

- Medical history (questions about your health and any medications you are taking)
- General physical examination
- A blood test may be done to make sure that you are postmenopausal if needed

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance as in the flip of a coin. A computer program will place you in one of the study groups. Neither you nor your healthcare provider can choose the group you will be in. You will have an equal chance of being placed in any group.

If you are in group 1, you will complete a daily diary and additional questionnaires at the end of each week for seven weeks. On the first day of week 2, you will begin taking flaxseed by eating one study bar, each day. You will continue to take flaxseed, eat one study bar daily, for 6 weeks. Your daily diary and weekly questionnaires should not take longer than 20 minutes per week to complete. You will get a pre-addressed envelope to return your questionnaires to your healthcare provider.

If you are in group 2, you will complete a daily diary and additional questionnaires at the end of each week for seven weeks. On the first day of week 2, you will begin taking a placebo (inactive product), one study bar, like a protein bar, each day. Your daily diary and weekly questionnaires should not take longer than 20 minutes per week to complete. The daily hot flash diary will ask you about the number and intensity or severity of your hot flashes over each 24 hour period. The other questionnaires ask about possible side effects, mood, how hot flashes interfere with daily activities and other related menopause symptoms such as joint aches and pains, tension, sleep and night sweats. You will get a pre-addressed envelope to return your questionnaires to your healthcare provider.

The tables below describe the flow of the study for each group.

**Group 1**

Week(s)	Number of doses of flaxseed	Questionnaires
1	No flaxseed this week	Daily Diary, complete questionnaires at end of the week
2-7	Flaxseed in study bar once per day	Daily Diary, complete questionnaires at the end of each week

**Group 2**

Week(s)	Number of doses of placebo	Questionnaires
1	No placebo this week	Daily Diary, complete questionnaires at the end of each week
2-7	Placebo bar once per day	Daily Diary, complete questionnaires at end of the week

Someone from the study team will call you during weeks 2, 3, 5, and 7 to see how you are doing and to answer questions.

The following medications should not be used during this study: new antidepressants, dietary/herbal supplements, high blood pressure medication or hormones. You should not start taking any other medications for hot flashes during this study. During weeks 2-7 you should drink at least five 8-ounce glasses of water daily.

At the end of the study, after you have returned the questionnaire booklet to your healthcare provider, you will be told whether you were taking flaxseed or the placebo. At this time, at the end of the randomized phase of the study, participants will have a chance to enroll in a continuation study and will receive flaxseed bars for an additional 6 weeks. There is no placebo in the continuation study.

If you decide that you want to continue the flaxseed or start the flaxseed if you were taking the placebo, you may enter this continuation phase of the study with the approval of your healthcare provider. During the Optional Continuation Phase, you will take flaxseed by eating one study bar each day for 6 weeks. Also, you will complete a daily diary and additional questionnaires at the end of each week for six weeks. Your daily diary and weekly questionnaires should not take longer than 20 minutes per week to

complete. The same type of questionnaires as described in the first phase of the study will be used. These questionnaires and diary ask about the number and intensity of hot flashes, possible side effects, mood and the impact of hot flashes on daily activities. You will get a pre-addressed envelope to return your questionnaires to your healthcare provider.

Week(s)	Number of doses of flaxseed	Questionnaires
1-6	One bar	Daily Diary, complete questionnaires at end of the week

Someone from the study team will call you at during weeks 2, 4, and 6 to see how you are doing and to answer questions.

### **Can I stop being in the research study?**

Yes. You can decide to stop at any time. Tell the healthcare provider if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the healthcare provider if you are thinking about stopping so any risks from the flaxseed can be evaluated by your healthcare provider. Another reason to tell your healthcare provider that you are thinking about stopping is to discuss what followup care and testing could be most helpful for you.

The healthcare provider may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

### **What side effects or risks can I expect from being in the research study?**

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Most side effects go away soon after you stop taking the flaxseed. In rare cases, side effects can occur that may be serious, long lasting, or may never go away.

You should talk to your healthcare provider about any side effects that you have while taking part in the study.

Risks and side effects related to the flaxseed include those which are:

#### **Likely**

- Feeling of fullness and tightness in the belly (abdominal distension/bloating)
- Too much gas passed from the rectum (flatulence)
- Loose stools (diarrhea)
- Feeling sick to your stomach (nausea)

**Less Likely**

- Throwing up (vomiting)
- Bleeding
- Rash
- Itching sensation (pruritus)

As with any medication or food product, allergic reactions are a possibility

For more information about risks and side effects, ask your healthcare provider.

**Are there benefits to taking part in the research study?**

Taking part in this study may or may not make your health better. While doctors hope flaxseed will be more useful against hot flashes compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about flaxseed as a treatment for hot flashes. This information could help future hot flash patients.

**What other choices do I have if I do not take part in this research study?**

You do not have to be in this study to receive treatment for your hot flashes.

Your other choices may include:

- Getting treatment or care for your hot flashes without being in a study
- Taking part in another study
- Getting no treatment

Talk to your healthcare provider about your choices before you decide if you will take part in this study.

**Will my medical information be kept private?**

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- NCCTG researchers
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

*[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]*

**What are the costs of taking part in this research study?**

The study product/placebo will be provided free of charge while you are taking part in this study. You

and/or your health plan may also have to pay for other drugs, products or treatment that are given to help control side effects as well as the cost of tests or exams to evaluate possible side effects.

You will not be paid for taking part in this study.

*For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.*

*Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.*

**What happens if I am injured because I took part in this research study?**

It is important that you tell your healthcare provider, \_\_\_\_\_ [investigator's name(s)], if you feel that you have been injured because of taking part in this study. You can tell the healthcare provider in person or call him/her at \_\_\_\_\_ [telephone number].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

**What are my rights if I take part in this research study?**

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

**Who can answer my questions about the research study?**

You can talk to your healthcare provider about any questions or concerns you have about this study. Contact your healthcare provider \_\_\_\_\_ [name(s)] at \_\_\_\_\_ [telephone number].

For questions about your rights while taking part in this study, call the \_\_\_\_\_ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at \_\_\_\_\_ (telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

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## Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

**1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615**

You may also visit the NCI Web site at <http://cancer.gov/>

- For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>
- For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>
- For NCI's general information about cancer in Spanish, go to <http://www.cancer.gov/espanol>

**You will get a copy of this form. If you want more information about this study, ask your healthcare provider.**

## Signature

I have been given a copy of all \_\_\_\_\_ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

**Printed Participant Name:** \_\_\_\_\_

**Participant Signature:** \_\_\_\_\_

**Date:** \_\_\_\_\_

**Printed name of person obtaining informed consent:**

\_\_\_\_\_

**Signature of person obtaining informed consent:**

\_\_\_\_\_

**Date** \_\_\_\_\_

*This model informed consent form has been reviewed by the DCP/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. Sections “What are the risks of the research study” or “What other choices do I have if I don’t take part in this research study?” should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the North Central Cancer Treatment Group Operations Office for approval before a patient may be registered to this study.*

*Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This information should be specific for each institution.*

**Appendix II**  
**PATIENT INFORMATION SHEET**  
**Double Blind Phase**

**Hot Flash Study Booklet Information**

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**You have been given a booklet to complete for this study. The booklet contains some questions about your ‘quality of life’. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.**

1. The booklet is divided up into 7 weeks.
2. The booklet contains sets of questions per week:
  - a. *Hot Flash Diary*
  - b. *Side Effect Experience Questionnaire*
  - c. *Profile of Mood States*
  - d. *Hot Flash Related Daily Interference Scale*
  - e. *Menopause Specific Quality of Life*
  - f. *Subject Global Impression of Change (week 7 double blind phase only)*
3. Directions on how to complete each set of questions are written on the top of each set.
4. The Hot Flash Diary:
  - a. The Hot Flash Diary is very important for this study and should be completed daily.
  - b. On page 2 of this booklet, you will find examples of the different hot flash intensities: mild, moderate, severe, and very severe hot flash. This is to help you to decide the intensity of your hot flash, but it is not an absolute rule. Your hot flashes may differ in some ways or may fall just between two descriptions. Try to get as close as you can, but do not worry if your hot flashes do not match exactly what is given.
  - c. It has been helpful for some patients to carry a small notebook and pen with them to record their hot flashes during the day, then to sit down every evening, and transfer their numbers to the diary. Keeping track on a small notebook or paper during the day is the best way to more precisely keep track of the number of hot flashes you are having.
  - d. Write any comments on the bottom of the diary if you wish.
5. A study coordinator or nurse will call you weeks 2, 3, 5 and 7 to answer any questions you might have. You will be given the study coordinator’s or nurse’s name and telephone number. You can call anytime with any concerns or questions.
6. It is very important that you return the booklet to us, whether you finish the study or not.
7. ***At the end of week 7:*** Return the booklet that you completed in the envelope provided.

**We would like to thank you for taking the time to help us.**

**Appendix II**

**PATIENT INFORMATION SHEET**  
**Optional Continuation Phase**

**Hot Flash Study Booklet Information**

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**You have been given a booklet to complete for this study. The booklet contains some questions about your ‘quality of life’. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.**

1. The booklet is divided up into 6 weeks.
2. The booklet contains sets of questions per week:
  - a. *Hot Flash Diary*
  - b. *Side Effect Experience Questionnaire*
  - c. *Hot Flash Related Daily Interference Scale*
3. Directions on how to complete each set of questions are written on the top of each set.
4. The Hot Flash Diary:
  - a. The Hot Flash Diary is very important for this study and should be completed daily.
  - b. On page 2 of this booklet, you will find examples of the different hot flash intensities: mild, moderate, severe, and very severe hot flash. This is to help you to decide the intensity of your hot flash, but it is not an absolute rule. Your hot flashes may differ in some ways or may fall just between two descriptions. Try to get as close as you can, but do not worry if your hot flashes do not match exactly what is given.
  - c. It has been helpful for some patients to carry a small notebook and pen with them to record their hot flashes during the day, then to sit down every evening, and transfer their numbers to the diary. Keeping track on a small notebook or paper during the day is the best way to more precisely keep track of the number of hot flashes you are having.
  - d. Write any comments on the bottom of the diary if you wish.
5. A study coordinator or nurse will call you weeks 2, 4, and 6 to answer any questions you might have. You will be given the study coordinator’s or nurse’s name and telephone number. You can call anytime with any concerns or questions.
6. It is very important that you return the booklet to us, whether you finish the study or not.
7. ***At the end of week 6:*** Return the booklet that you completed in the envelope provided.

**We would like to thank you for taking the time to help us.**

## Appendix III

### PATIENT INFORMATION SHEET Hot Flash Definitions for the Female Patient

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Please refer to these examples of hot flashes that have been given by cancer survivors in previous studies when describing their hot flash severity. One or more of these descriptions may help to categorize your hot flash as mild, moderate, severe, or very severe.

#### **Mild**

Duration: Lasting less than 5 minutes

Physical symptoms: Warmth, felt uncomfortable, red face

Emotional symptoms: Not expected

Action needed: Usually no action taken

#### **Moderate**

Duration: Lasting up to 15 minutes

Physical symptoms: Head, neck, ears, or whole body felt warm; tense, tight muscles; clammy (wet) skin; a change in heart rate or rhythm (heart speeds up or changes beat); some sweating; dry mouth

Emotional symptoms: Felt irritated, felt agitated (restless), felt as though energy was drained out, felt embarrassed when having a hot flash in front of others, felt tired, felt annoyed

Action needed: Needed to use a fan, awakened sometimes at night, needed to uncover, took off layers of clothing, drank water, opened the windows even when cold outside, wore lighter clothing

#### **Severe**

Duration: Lasting up to 20 minutes

Physical symptoms: Warmth, sometimes described as a raging furnace or burning up; a change in heart rate or rhythm (heart speeds up or changes beat); felt faint; headache; severe sweating; weakness, a prickling, stinging sensation over skin; chest heaviness

Emotional symptoms: Embarrassment, anxiety, feelings of having a panic attack

Action needed: Needed to stop what was being done at that time, usually awakened at night and removed covers, needed to remove clothes, opened windows, kept the house a cool temperature, frequently used fans

#### **Very Severe**

Duration: Lasting up to 45 minutes

Physical symptoms: Boiling heat, rolling sweat, difficulty breathing, felt faint, felt dizzy, feet and/or legs cramping, a change in the heart rate or rhythm (heart speeds up or changes beat), felt slightly sick to stomach

Emotional symptoms: Felt distressed, had the urge to escape, had difficulty functioning

Action needed: Awakened frequently at night, needed to change sheets and pajamas, needed to take a cold shower, needed to hold ice on skin.

**Appendix IV  
Hot Flash Diary**

First Study Week (Baseline) Double Blind Phase  
Do Not Take Any Study Product This Week

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**Directions:**

The hot flash diary is divided into 7 sections, one for each day of your week.  
Enter the date your week started.  
Enter the day of the week in the top row of each section.  
In the # (number) column for each day of your week, write in the number of mild, moderate, severe and very severe hot flashes experienced in the box next to the hot flash type for that day.  
See page 2 of this booklet for the definitions of each type of Hot Flashes.

**Example:**

Day: <b>Tuesday</b>	
<b>#</b>	<b>Type</b>
<b>0</b>	mild
<b>2</b>	moderate
<b>3</b>	severe
<b>0</b>	very severe

Date week started: \_\_\_ / \_\_\_ / \_\_\_\_\_  
                                  m m   d d   y y y y

Day:		Day:		Day:		Day:		Day:		Day:		Day:	
<b>#</b>	<b>Type</b>	<b>#</b>	<b>Type</b>	<b>#</b>	<b>Type</b>	<b>#</b>	<b>Type</b>	<b>#</b>	<b>Type</b>	<b>#</b>	<b>Type</b>	<b>#</b>	<b>Type</b>
	mild		mild		mild		mild		mild		mild		mild
	moderate		moderate		moderate		moderate		moderate		moderate		moderate
	severe		severe		severe		severe		severe		severe		severe
	very severe		very severe		very severe		very severe		very severe		very severe		very severe

**\*A day should be considered to be a 24-hour period (i.e. 7 a.m. to 7 a.m. or midnight to midnight).**

**Appendix IV  
Hot Flash Diary**

Weeks 2-7 (Double Blind Phase)/1-6 (Optional Continuation Phase)  
Start Study Product (week 2 double-blind only)

**Directions:**

The hot flash diary is divided into 7 sections, one for each day of your week.

Enter the date your week started.

Enter the day of the week in the top row of each section.

In the # (number) column for each day of your week, write in the number of mild, moderate, severe and very severe hot flashes experienced in the box next to the hot flash type for that day.

See page 2 of this booklet for the definitions of each type of Hot Flashes.

**Example:**

Day: <b>Tuesday</b>	
<b>#</b>	<b>Type</b>
<b>0</b>	mild
<b>2</b>	moderate
<b>3</b>	severe
<b>0</b>	very severe

Date week started: \_\_\_ / \_\_\_ / \_\_\_  
m m d d y y y y

Day:		Day:		Day:		Day:		Day:		Day:		Day:	
<b>#</b>	<b>Type</b>	<b>#</b>	<b>Type</b>	<b>#</b>	<b>Type</b>	<b>#</b>	<b>Type</b>	<b>#</b>	<b>Type</b>	<b>#</b>	<b>Type</b>	<b>#</b>	<b>Type</b>
	mild		mild		mild		mild		mild		mild		mild
	moderate		moderate		moderate		moderate		moderate		moderate		moderate
	severe		severe		severe		severe		severe		severe		severe
	very severe		very severe		very severe		very severe		very severe		very severe		very severe

**\*A day should be considered to be a 24-hour period (i.e. 7 a.m. to 7 a.m. or midnight to midnight).**

**Appendix IV**  
**Hot Flash Diary**

Please circle the number to the right of each phase to describe how often DURING THE PAST WEEK were you able to eat your study bar as directed?

1. 100% of the time – ate one bar every day
2. 75 to 99% - missed half a bar some days, but ate at least half a bar every day
3. 50 to 75%- missed one bar occasionally or did not eat entire bar on several days
4. 25 to 50%- did not eat half of a bar every day or missed an entire bar on more than two days of the week
5. 0 to 25% - Was not able to eat even half a bar on most days

## Appendix V

## Side Effect Experience Questionnaire – Flaxseed study

Please let us know what symptoms you have experienced over the past week. Please circle one number for each item.

1. Over the past week, have you experienced vomiting?

Not at all

0 1 2 3 4 5 6 7 8 9 10 As bad as it can be

2. Over the past week, have you experienced nausea?

Not at all

0 1 2 3 4 5 6 7 8 9 10 As bad as it can be

3. Over the past week, have you experienced diarrhea?

Not at all

0 1 2 3 4 5 6 7 8 9 10 As bad as it can be

4. Over the past week, did you experience bloating?

Not at all

0 1 2 3 4 5 6 7 8 9 10 As bad as it can be

5. Over the past week, did you experience abnormal sweating?

Not at all

0 1 2 3 4 5 6 7 8 9 10 As bad as it can be

6. Over the past week, did you experience constipation?

Not at all

0 1 2 3 4 5 6 7 8 9 10 As bad as it can be

7. Over the past week, did you experience any rash?

Not at all

0 1 2 3 4 5 6 7 8 9 10 As bad as it can be

8. Over the past week, did you experience trouble sleeping?

Not at all

0 1 2 3 4 5 6 7 8 9 10 As bad as it can be

9. Over the past week, did you experience any problems with gas? (Flatulence)

Not at all

0 1 2 3 4 5 6 7 8 9 10 As bad as it can be



## Appendix VI Profile of Mood States (POMS)

NAME \_\_\_\_\_ DATE \_\_\_\_\_

SEX: Male (♂) Female (♀) Identification No. \_\_\_\_\_

Below is a list of words that describe feelings people have. Please read each one carefully. Then fill in ONE circle under the answer to the right which best describes HOW YOU HAVE BEEN FEELING DURING THE PAST WEEK INCLUDING TODAY.

**The numbers refer to these phrases.**

- ① = Not at all
- ② = A little
- ③ = Moderately
- ④ = Quite a bit
- ⑤ = Extremely

	Not at all A little Moderately Quite a bit Extremely		Not at all A little Moderately Quite a bit Extremely		Not at all A little Moderately Quite a bit Extremely
1. Tense .....	① ② ③ ④	12. Uneasy .....	① ② ③ ④	23. Weary .....	① ② ③ ④
2. Angry .....	① ② ③ ④	13. Fatigued .....	① ② ③ ④	24. Bewildered .....	① ② ③ ④
3. Worn out .....	① ② ③ ④	14. Annoyed .....	① ② ③ ④	25. Furious .....	① ② ③ ④
4. Lively .....	① ② ③ ④	15. Discouraged ...	① ② ③ ④	26. Efficient .....	① ② ③ ④
5. Confused .....	① ② ③ ④	16. Nervous .....	① ② ③ ④	27. Full of pep .....	① ② ③ ④
6. Shaky .....	① ② ③ ④	17. Lonely .....	① ② ③ ④	28. Bad-tempered .	① ② ③ ④
7. Sad .....	① ② ③ ④	18. Muddled .....	① ② ③ ④	29. Forgetful .....	① ② ③ ④
8. Active .....	① ② ③ ④	19. Exhausted .....	① ② ③ ④	30. Vigorous .....	① ② ③ ④
9. Grouchy .....	① ② ③ ④	20. Anxious .....	① ② ③ ④		
10. Energetic .....	① ② ③ ④	21. Gloomy .....	① ② ③ ④		
11. Unworthy .....	① ② ③ ④	22. Sluggish .....	① ② ③ ④		

**MAKE SURE  
YOU HAVE ANSWERED  
EVERY ITEM.**

POMS-B, by Douglas M. McNair, Ph.D., Joan Lorr Ph.D., Leo F. Droppleman, Ph.D.  
 Copyright © 2003, 1989, Douglas M. McNair, Ph.D., Joan Lorr, Ph.D., Leo F. Droppleman, Ph.D., under exclusive license to Multi-Health Systems Inc. All rights reserved. In the USA, P.O. Box 950, North Tonawanda, NY 14120-0950, 1-800-456-3003. In Canada, 3770 Victoria Park Ave., Toronto, ON M2H 3M6, 1-800-268-6011. Internationally, +1-416-492-2627. Fax, +1-416-492-3343.

SHORT FORM

## Appendix VII

Hot Flash Related Daily Interference Scale (HFRDIS)

Please circle one number to the right of each phrase to describe how much **DURING THE PAST TWO WEEKS**, hot flashes have **INTERFERED** with each aspect of your life.

	<b>Do not interfere</b>										<b>Completely interfere</b>
<b>1. Work</b> (work outside the home and housework)	0	1	2	3	4	5	6	7	8	9	10
<b>2. Social activities</b> (time spent with family, friends, etc)	0	1	2	3	4	5	6	7	8	9	10
<b>3. Leisure activities</b> (time spent relaxing, doing hobbies, etc.)	0	1	2	3	4	5	6	7	8	9	10
<b>4. Sleep</b>	0	1	2	3	4	5	6	7	8	9	10
<b>5. Mood</b>	0	1	2	3	4	5	6	7	8	9	10
<b>6. Concentration</b>	0	1	2	3	4	5	6	7	8	9	10
<b>7. Relations with others</b>	0	1	2	3	4	5	6	7	8	9	10
<b>8. Sexuality</b>	0	1	2	3	4	5	6	7	8	9	10
<b>9. Enjoyment of life</b>	0	1	2	3	4	5	6	7	8	9	10
<b>10. Overall quality of life</b>	0	1	2	3	4	5	6	7	8	9	10

Menopause Specific Quality of Life  
(MENQOL)

Please read each symptom listed below and mark the appropriate box by putting an X or a check mark in the box. Mark the box "no" if you are not bothered by the symptom and move on to the next symptom listed. If you are bothered by a symptom, please mark the box "yes" and then mark how bothered you are by marking a box numbered 0 to 6.

		Not at all $\xrightarrow{\hspace{1.5cm}}$ Extremely						
		bothered <span style="float:right">bothered</span>						
		0	1	2	3	4	5	6
1. HOT FLUSHES OR FLUSHES	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. NIGHT SWEATS	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. SWEATING	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. DISSATISFACTION WITH MY PERSONAL LIFE	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. FEELING ANXIOUS OR NERVOUS	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. POOR MEMORY	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. ACCOMPLISHING LESS THAN I USED TO	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. FEELING DEPRESSED, DOWN OR BLUE	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. BEING IMPATIENT WITH OTHER PEOPLE	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. FEELINGS OF WANTING TO BE ALONE	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. FLATULENCE (WIND) OR GAS PAINS	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. ACHING IN MUSCLES AND JOINTS	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. FEELING TIRED OR WORN OUT	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. DIFFICULTY SLEEPING	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15. ACHES IN BACK OF NECK OR HEAD	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. DECREASE IN PHYSICAL STRENGTH	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

		Not at all <span style="display: inline-block; width: 100px; border-bottom: 1px solid black;"></span> → Extremely bothered <span style="float: right;">bothered</span>							
		0	1	2	3	4	5	6	
17. DECREASE IN STAMINA	<input type="checkbox"/>	<input type="checkbox"/> → <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	No	Yes	0	1	2	3	4	5	6
18. LACK OF ENERGY	<input type="checkbox"/>	<input type="checkbox"/> → <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	No	Yes	0	1	2	3	4	5	6
19. DRY SKIN	<input type="checkbox"/>	<input type="checkbox"/> → <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	No	Yes	0	1	2	3	4	5	6
20. WEIGHT GAIN	<input type="checkbox"/>	<input type="checkbox"/> → <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	No	Yes	0	1	2	3	4	5	6
21. INCREASED FACIAL HAIR	<input type="checkbox"/>	<input type="checkbox"/> → <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	No	Yes	0	1	2	3	4	5	6
22. CHANGES IN APPEARANCE, TEXTURE OR TONE OF MY SKIN	<input type="checkbox"/>	<input type="checkbox"/> → <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	No	Yes	0	1	2	3	4	5	6
23. FEELING BLOATED	<input type="checkbox"/>	<input type="checkbox"/> → <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	No	Yes	0	1	2	3	4	5	6
24. LOW BACKACHE	<input type="checkbox"/>	<input type="checkbox"/> → <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	No	Yes	0	1	2	3	4	5	6
25. FREQUENT URINATION	<input type="checkbox"/>	<input type="checkbox"/> → <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	No	Yes	0	1	2	3	4	5	6
26. INVOLUNTARY URINATION WHEN LAUGHING OR COUGHING	<input type="checkbox"/>	<input type="checkbox"/> → <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	No	Yes	0	1	2	3	4	5	6
27. DECREASE IN MY SEXUAL DESIRE	<input type="checkbox"/>	<input type="checkbox"/> → <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	No	Yes	0	1	2	3	4	5	6
28. VAGINAL DRYNESS	<input type="checkbox"/>	<input type="checkbox"/> → <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	No	Yes	0	1	2	3	4	5	6
29. AVOIDING INTIMACY	<input type="checkbox"/>	<input type="checkbox"/> → <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	No	Yes	0	1	2	3	4	5	6
30. BREAST PAIN OR TENDERNESS	<input type="checkbox"/>	<input type="checkbox"/> → <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	No	Yes	0	1	2	3	4	5	6
31. VAGINAL BLEEDING OR SPOTTING	<input type="checkbox"/>	<input type="checkbox"/> → <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	No	Yes	0	1	2	3	4	5	6
32. LEG PAINS OR CRAMPS	<input type="checkbox"/>	<input type="checkbox"/> → <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	No	Yes	0	1	2	3	4	5	6

**Appendix IX**  
**SUBJECT GLOBAL IMPRESSION OF CHANGE**

1. Since beginning the study product, my hot flashes are :

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

2. Since beginning the study product, my menopausal symptoms in general are:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

3. Since beginning the study product, my overall quality of life is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

To be completed ONLY at the end (after completion of week 7) of the study:

4. During this study, I think that I was on:

\_\_\_\_\_ the flaxseed  
\_\_\_\_\_ the placebo

5. Were you satisfied with the effect this treatment had on your hot flashes?

\_\_\_\_\_ Yes

\_\_\_\_\_ No

6. The treatment I had for my hot flashes during this study was:

A. Not helpful

B. Not worth the side effects

C. Helpful to Very helpful but with some side effects to be considered

D. Helpful to Very helpful with few to no side effects

## Appendix X Nurse/CRA Phone Contact Guide

Patient Phone No. \_\_\_\_\_

Best Dates/Times to call \_\_\_\_\_

### **FOLLOW UP:**

1. Please make an appointment to call the patient at home during week 2, which is the first week they will be taking the bars. This phone call contact will NOT require AE documentation or separate forms completion. The purpose of this contact is to assess the patient's acceptance of the bar. Please try to ascertain the extent to which the patient finds the bar edible and their ability to adhere to the protocol assignment of eating one bar per day. Problem solve any issues that are assessed.

2. Follow up phone call schedule: Call patient at home weeks 2, 3, 5, and 7 during the double blind phase and weeks 2, 4, and 6 during continuation phase to assess product tolerability, document compliance, encourage completion of the booklet, and address problems. Note: The final calls (week 7 for the Double Blind Phase and week 6 for the Optional Continuation Phase) to be made at the completion of the week.

- It is important to reinforce “real time” capture of hot flashes and daily completion of diary as well as weekly side effects on side effect experience diary

3. Items to document:

- Date of phone call
- Study week
- Side effects:
  - Nausea - Severity and attribution, if appl.
  - Vomiting - Severity and attribution, if appl
  - Abdominal distension - Severity and attribution, if appl
  - Flatulence - Severity and attribution, if appl
  - Diarrhea - Severity and attribution, if appl
  - Rash maculopapular - Severity and attribution, if appl
  - Pruritus - Severity and attribution, if appl
  - Hematoma- Severity and attribution, if appl
  - Vascular Disorders – Other, specify- Severity and attribution, if appl
  - Any others - Severity and attribution, if appl.
- # Hot flashes/24 hours
- Average hot flash severity – Mild, Moderate, Severe or Very Severe
- Any changes in medications or other treatments (ie behavioral, diet, etc)
- Questions/Comments

4. Reinforce compliance with study product.

5. Reinforce completion of questionnaires and request return of them at end of week 7 (double blind phase) and week 6 (continuation phase) if applicable.

Note – If patient decides to stop study before week 7 of the Double Blind Phase or week 6 of the Optional Continuation Phase, ask them to fill out the questionnaires up to that point at the end of the booklet and return in the envelope provided.

**At end of study, remind the patient she will be unblinded and given the opportunity to participate in the Optional Continuation Phase.**

Appendix XI  
Nutritional Specifications of Flaxseed Product

Lignan Study Bar 1:  
NutriGrād Flaxseed

<b>Nutrition Facts</b>	
Serving Size : 1 bar (53g)	
Servings Per Container : 1	
Amount Per Serving	
<b>Calories 190</b>	<b>Calories from Fat 35</b>
% Daily Value*	
<b>Total Fat 4g</b>	<b>6%</b>
Saturated Fat 0.5g	3%
Trans Fat 0g	
Polyunsaturated Fat 1.5g	
<b>Cholesterol 0mg</b>	<b>0%</b>
<b>Sodium 125mg</b>	<b>5%</b>
<b>Total Carbohydrate 40g</b>	<b>13%</b>
Dietary Fiber 5g	20%
Sugars 10g	
<b>Protein 6g</b>	
Vitamin A 0%	• Vitamin C 0%
Calcium 0%	• Iron 10%
*Percent Daily Values are based on a 2,000-calorie diet. Your daily values may be higher or lower depending on your calorie needs.	
	Calories: 2,000    2,500
Total Fat	Less than 65g    85g
Saturated Fat	Less than 25g    25g
Cholesterol	Less than 300mg    300 mg
Sodium	Less than 2,400mg    2,400mg
Total Carbohydrate	300g    375g
Dietary Fiber	25g    30g
Calories per gram:	
Fat 9 • Carbohydrate 4 • Protein 4	

Each Bar Contains:  
7.5 g NutriGrād Flaxseed  
0.41 g Lignans

**Ingredients:**

Corn syrup, toasted oats, crisp rice (rice, sugar, salt, high fructose corn syrup, malt flavoring, reduced iron, niacinamide, thiamin hydrochloride, calcium pantothenate, pyridoxine hydrochloride, folic acid, BHT), flaxseed, maltodextrin, natural and artificial flavors, glycerine, vegetable oil, sugar, honey and sucralose.

Lignan Study Bar 2:  
No Flaxseed

<b>Nutrition Facts</b>	
Serving Size : 1 bar (53g)	
Servings Per Container : 1	
Amount Per Serving	
<b>Calories 200</b>	<b>Calories from Fat 35</b>
% Daily Value*	
<b>Total Fat 4g</b>	<b>6%</b>
Saturated Fat 0.5g	3%
Trans Fat 0g	
Polyunsaturated Fat 1.5g	
<b>Cholesterol 0mg</b>	<b>0%</b>
<b>Sodium 150mg</b>	<b>6%</b>
<b>Total Carbohydrate 37g</b>	<b>12%</b>
Dietary Fiber 5g	20%
Sugars 10g	
<b>Protein 2g</b>	
Vitamin A 0%	• Vitamin C 0%
Calcium 0%	• Iron 10%
*Percent Daily Values are based on a 2,000-calorie diet. Your daily values may be higher or lower depending on your calorie needs.	
	Calories: 2,000    2,500
Total Fat	Less than 65g    85g
Saturated Fat	Less than 20g    25g
Cholesterol	Less than 300mg    300 mg
Sodium	Less than 2,400mg    2,400mg
Total Carbohydrate	300g    375g
Dietary Fiber	25g    30g
Calories per gram:	
Fat 9 • Carbohydrate 4 • Protein 4	

Each Bar Contains:  
0 g Flaxseed  
0 g Lignans

**Ingredients:**

Corn syrup, toasted oats, crisp rice (rice, sugar, salt, high fructose corn syrup, malt flavoring, reduced iron, niacinamide, thiamin hydrochloride, calcium pantothenate, pyridoxine hydrochloride, folic acid, BHT), resistant maltodextrin, vegetable oil, maltodextrin, glycerine, sugar, honey, natural and artificial flavors, caramel color and sucralose.