Status Page

PROTOCOL 14-056

Closed to New Accrual

Closure Effective Date: 03/30/2016
No new subjects may be enrolled in the study as described above. Any questions regarding this closure should be directed to the study's Principal Investigator

Date Submitted: ***[12/22/14]***
Date Posted: ***[01/08/15]***

Alert Page

DF/HCC Protocol #: **14-056**

Protocol Clarifications (non-drug related e.g. eligibility criteria, study assessments)

Protocol Section 9, Study Calendars:

Monitoring phase:

- Patient Global Impressions- Fatigue (PGI-F) should be completed at baseline visit. This will be clarified in a future protocol amendment.
- PHQ-9 and FACT-B/ES should be completed at week 4 and week 8. This will be clarified in a future protocol amendment.
- (+/-) 7 day window applies to all weekly monitoring visits. This will be clarified in a future protocol amendment.

Intervention phase:

- Patient Global Impressions- Improvement (PGI-I) should be completed in place of PGI-F at **week 0 randomization** visit and **week 5 Rx visit.** This will be clarified in a future protocol amendment.
- (+/-) 7 day window applies to all visits. This will be clarified in a future protocol amendment.

Local Protocol #: **14-056**

TITLE: **Phase II Double-Blind Randomized Controlled Trial of Naltrexone for Treatment-Emergent Fatigue in Patients Receiving Radiation Therapy for Breast Cancer**

Coordinating Center: Dana-Farber Cancer Institute

***Principal Investigator (PI):**
Fremonta Meyer, MD
Psychosocial Oncology and Palliative Care
Dana-Farber Cancer Institute/Brigham and Women's Hospital
flmeyer@partners.org

Other Investigators:
Alphonse Taghian, MD PhD (MGH site PI)
Radiation Oncology
Massachusetts General Hospital
ataghian@partners.org

David Fisher, MD PhD (PI of Grant)
Dermatology
Massachusetts General Hospital
dfisher3@partners.org

Hadine Joffe, MD, MSc
Psychosocial Oncology and Palliative Care
Dana-Farber Cancer Institute
hjoffe@partners.org

Kelly Irwin, MD
Psychiatry (Psycho-oncology)
Massachusetts General Hospital
keirwin@partners.org

Ilana Braun, MD
Psychosocial Oncology and Palliative Care
Dana-Farber Cancer Institute
ilana_braun@dfci.harvard.edu

April Hirschberg, MD
Psychiatry (Psycho-oncology)
Massachusetts General Hospital
ahirschberg@partners.org

Julia Wong, MD
Radiation Oncology
Dana-Farber Cancer Institute
jwong@lroc.harvard.edu

Statistician:

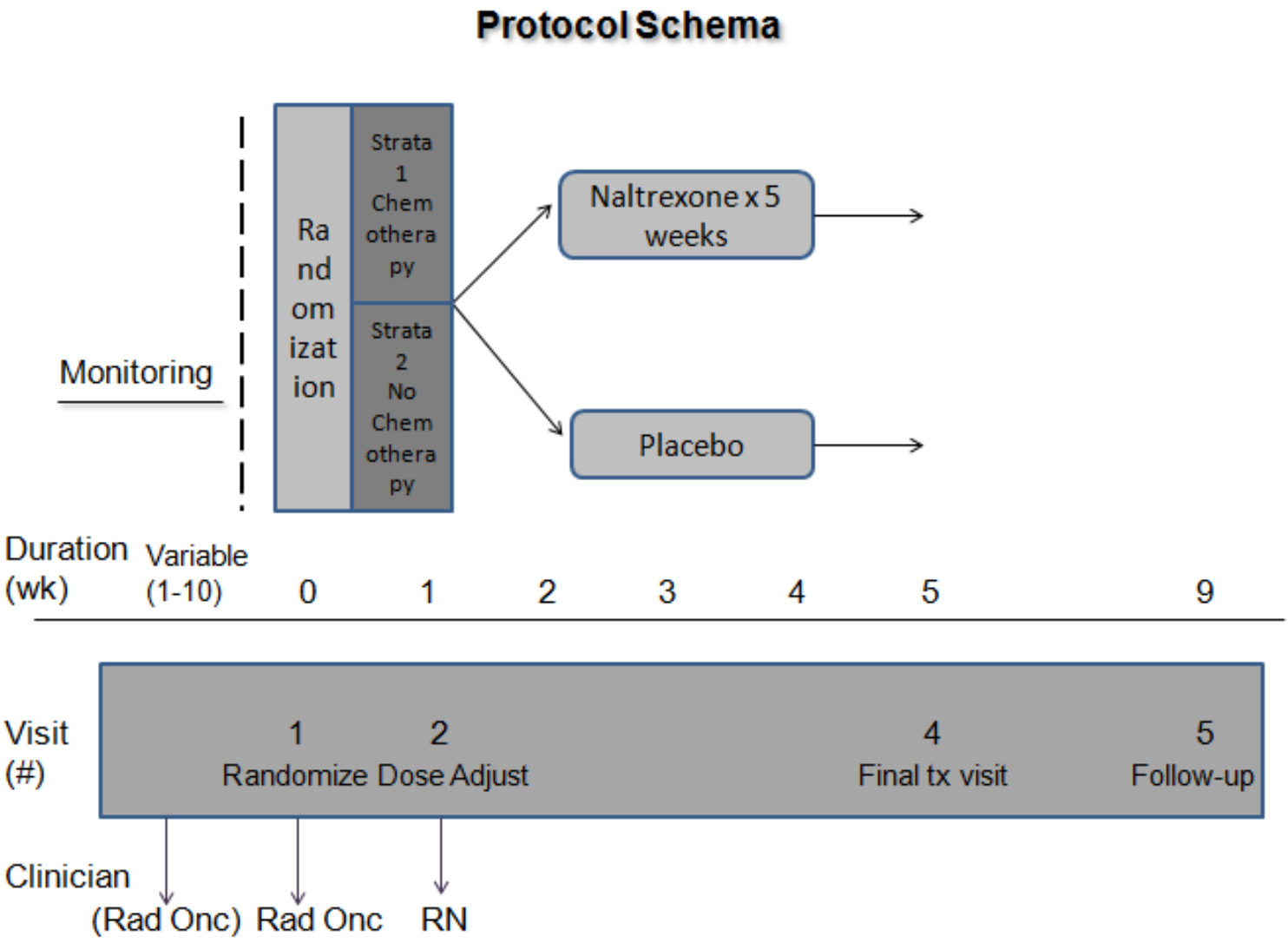
Andrzej Niemierko
Radiation Oncology
Massachusetts General Hospital
aniemierko@partners.org

NCI-Supplied Agent(s): Not applicable
Other Agent(s): Naltrexone or Placebo

IND #: IND exempt
IND Sponsor: Fremonta Meyer, MD / FDA

Protocol Version # / Version Date: Version 12 / May 3, 2018

SCHEMA


Protocol Schema
Monitoring
Randomization
Strata 1 Chemotherapy
Strata 2 No Chemotherapy
Naltrexone x 5 weeks
Placebo
Duration (wk)
Variable (1-10)
0
1
2
3
4
5
9
Visit (#)
1 Randomize
2 Dose Adjust
4 Final tx visit
5 Follow-up
Clinician
(Rad Onc)
Rad Onc
RN

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1. OBJECTIVES

The objective of this study is to determine whether the opioid antagonist naltrexone reduces radiation therapy-related fatigue more than placebo does in patients undergoing radiotherapy for breast cancer.

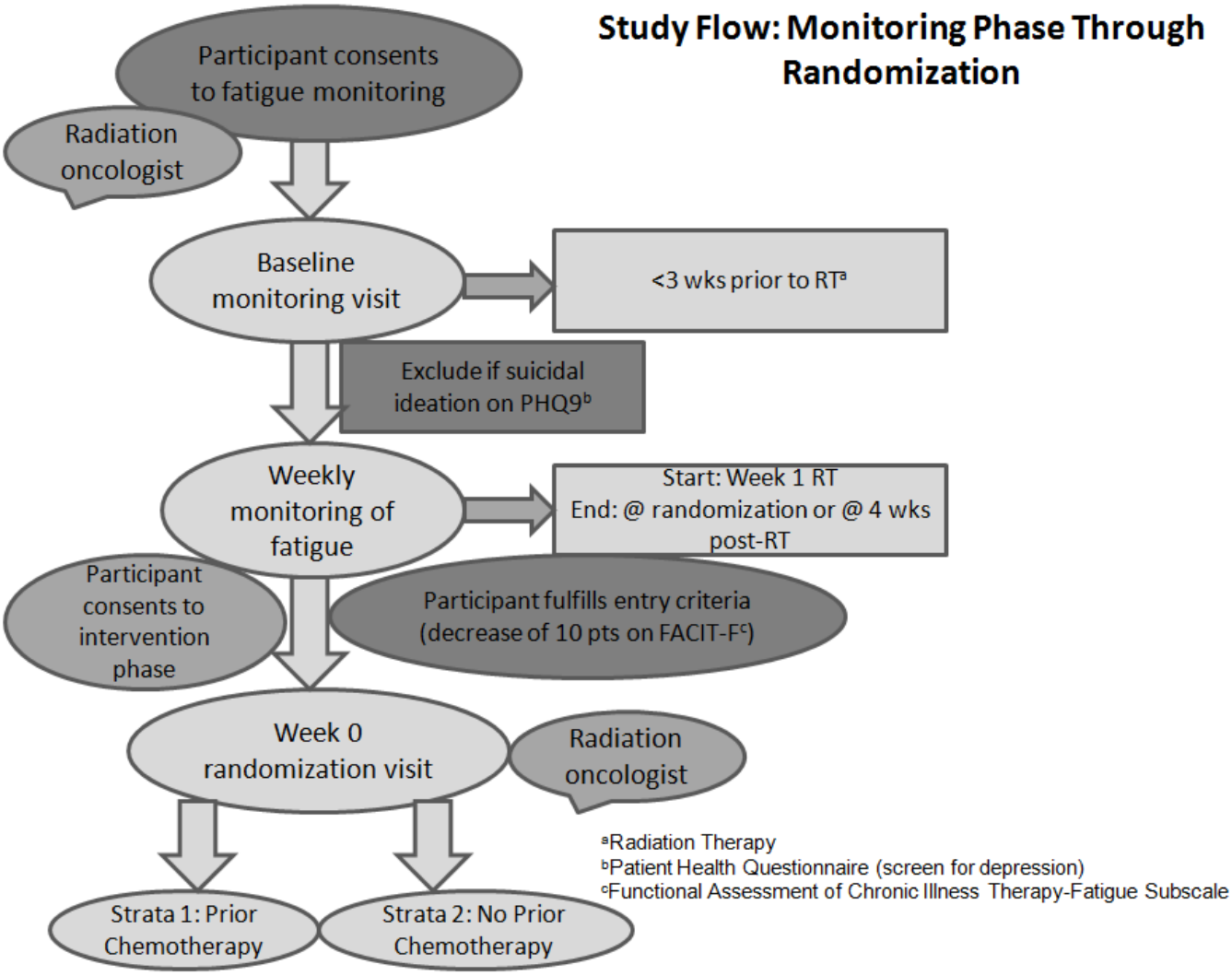
1.1 Study Design

A randomized, double-blind, parallel-arm 5-week clinical trial will be used to determine the effect of naltrexone on fatigue emerging during radiation therapy for non-metastatic breast cancer (see Protocol Schema). The trial has two phases (a monitoring phase and an intervention phase) requiring two separate consents.

Monitoring phase: Prior to initiating radiotherapy, participants will be approached and consented for the monitoring phase of the study, which involves longitudinal monitoring of fatigue in order to establish whether a patient develops fatigue after starting radiation. The level of pre-radiotherapy fatigue will be obtained during the final 3 weeks before, or within 3 days, that radiotherapy is started. Participants who provide baseline data and report suicidal ideation either spontaneously or on a self-report questionnaire will be excluded from subsequent weekly monitoring of fatigue. All other participants will undergo weekly monitoring of fatigue via a brief self-report questionnaire (Functional Assessment of Chronic Illness Therapy-Fatigue Subscale; FACIT-F) once radiation therapy begins. Those whose fatigue symptoms increase above the pre-specified threshold at any point during the monitoring period will be approached about enrollment into the intervention phase of the study. The monitoring period will continue up until one month after the conclusion of radiotherapy. Radiation oncologists will refer potentially eligible patients to the monitoring phase of the study. The clinical research coordinator will be trained to administer the screening consent and will follow participants during the monitoring phase of the study and notify the radiation oncologist if fatigue emerges/worsens after radiation therapy has begun, so that participation in the intervention phase of the study can be discussed with these patients.

Intervention phase: Radiation oncologists will consent patients who develop treatment-emergent fatigue developing during or within one month after completion of radiation therapy and who are interested in participating in the intervention phase of the study. After informed consent is obtained and final eligibility determination is complete, participants will have 5 study visits: one at study entry to initiate treatment (week 0), one to rule out any contraindication to the scheduled dose escalation (week 1), one at the conclusion of medication treatment for treatment outcome assessment and safety monitoring (week 5), and the last at four weeks after discontinuation of study drug vs. placebo (week 9). All intervention visits have a window of ± 7 days.

Study treatment: The treatment schedule includes a daily dose of double-blinded naltrexone vs. placebo for 5 weeks. Treatment will be initiated at 25 mg/day (or equivalent placebo) during the first week to improve tolerability. The dose will be escalated to 50 mg/day (or equivalent placebo) after one week barring significant early improvement in fatigue or adverse events precluding dose escalation, and participants will continue to take 50 mg/day (or 25 mg/day if dose is not escalated) for 4 weeks to complete a 5-week treatment period.



1.2 Primary Objectives

To determine the effect of naltrexone on treatment-emergent fatigue during radiation therapy for breast cancer. The primary comparison is between changes in fatigue scores in the naltrexone- versus the placebo-treated participants as measured by the FACIT-F subscale.

1.3 Secondary Objectives

1.3.1. To determine the effect of naltrexone on exploratory outcomes including: mood, anxiety, subjective cognitive function, sleep, pain, and quality of life, and the extent to which changes in fatigue correlate with changes in these symptom endpoints. These outcomes have been shown to be associated with cancer fatigue in prior studies involving breast cancer patients[1 2-4].

1.3.2. To determine the course, predictors, and correlates of fatigue during radiotherapy for breast cancer in a large controlled sample

2. BACKGROUND

2.1 Study Disease(s)

Fatigue is one of the most common side effects of both radiation therapy and chemotherapy. It is the greatest predictor of poor quality of life in cancer patients undergoing treatment, and very often results in an inability to perform activities of daily living easily accomplished prior to treatment (Hickok et al., 1996). More importantly, severe fatigue can result in breaks in treatment that adversely affect treatment efficacy and ultimately compromise survival.

Despite its importance as a side effect that impairs quality of life and reduces treatment adherence, treatment options for cancer-related fatigue are limited. Exercise programs and psychological interventions such as cognitive-behavioral therapy appear to have a positive effect on cancer-related fatigue[5], but are not accessible or feasible for all patients who might benefit. In terms of pharmacologic strategies, a recent meta-analytic review suggested that stimulants (e.g., methylphenidate) and hematopoietic agents (the latter only in the presence of anemia) may be effective[6]. However, the effect size of stimulants, albeit clinically significant, is small; hematopoietic agents such as erythropoietin are less widely used given associated increase in risk for thrombovascular events and mortality. Modafinil and armodafinil, both non-amphetamine based stimulant-like medications that improve fatigue related to obstructive sleep apnea and multiple sclerosis, have been the focus of more recent randomized trials. Specifically, a Phase III trial in patients with a wide variety of cancer types found that modafinil has significantly positive effects for severe, but not mild to moderate, cancer fatigue[7]. Trial durations for effective pharmacological interventions in cancer fatigue are variable, ranging from 2-12 weeks, many of which show benefit with 4 weeks.[6]

Although their use is widespread, stimulants and stimulant-like medications may exert nonspecific effects that are not tied to an underlying cancer-related mechanism of fatigue. Some work has suggested that cancer fatigue may be driven by the activation of pro-inflammatory cytokines, paving the way for study of cytokine inhibitors such as eternacept, which in a study of advanced cancer patients on chemotherapy appeared to reduce fatigue[8]. Other proposed mechanisms include disruptions in the hypothalamic-pituitary-adrenal axis, as shown by studies revealing altered cortisol responses in fatigued cancer survivors[9] and metastatic breast cancer patients[10]. However, at this point, there is limited direct clinical evidence to substantiate these theories. Thus, interventions to manage cancer-related fatigue continue to be empirical in nature, possibly accounting for their modest effect sizes.

The present study stems from a preclinical observation implicating upregulation of the endogenous opioid system as a potential underlying mechanism for fatigue in patients receiving radiotherapy. As in humans, irradiation (of the tail) has been shown to induce lethargy in rodent models and beta-endorphin levels increase in response to tail irradiation. Dr. Fisher's lab has observed that the opiate receptor antagonist naloxone reverses fatigue induced by irradiation. Preclinical data (further described in Section 2.3, Rationale) suggest that the elevations in beta-endorphin may be responsible for radiation-related fatigue, and that pharmacologic treatment with a mu-opioid receptor antagonist may ameliorate the fatigue symptoms. Thus, the primary aim of this study is to determine whether the widely used and FDA-approved opioid antagonist naltrexone might reduce radiation-emergent fatigue in humans.

Given results of pre-clinical studies, naltrexone is a viable treatment to investigate for

radiation-related fatigue in cancer patient populations who are not expected to require opioid therapy. Breast cancer patients receiving radiotherapy represent an important population to study because fatigue develops commonly during radiotherapy and concurrent therapy with opioids is rare. Notably, existing literature provides widely variable estimates (38-75%) of the prevalence of breast radiotherapy-emergent fatigue[11,12] as well as differing evidence as to the most important predictors of fatigue in this population. Longitudinal studies have found that fatigue levels gradually increase during a course of breast radiotherapy, particularly during the first four weeks of treatment.[13-15] Several studies have investigated clinical correlates of radiation-related fatigue in this population. Donovan found that patients (N=134) pre-treated with chemotherapy reported less fatigue during radiotherapy as compared to patients who did not receive chemotherapy, and that demographic and disease-related variables did not predict the extent of fatigue; however, psychological variables were not examined in this study.[16] Manir described anemia as the most important predictor of fatigue (N=72)[12] whereas other studies have found no relationship between hemoglobin levels and fatigue.[13] Recently, Taunk compared different radiotherapeutic regimens for early-stage breast cancer (overall N=80) and suggested that partial breast irradiation may reduce fatigue as compared to hypofractionated and standard whole breast irradiation.[17] However, in the largest cohort study to date (N=250), Reidunsdatter identified medical comorbidity as a more important determinant of increased fatigue during breast radiotherapy than radiotherapy type.[18] By contrast, Courtier reported that anxiety, elevated pre-treatment fatigue, and diagnoses other than invasive ductal carcinoma (e.g. DCIS or lobular subtypes) predicted radiation-emergent fatigue (N=100).[11] More study of the clinical correlates and course of fatigue during radiotherapy is warranted in the breast cancer population given the relatively small sample sizes, variable inclusion of relevant medical and psychosocial variables in models to predict fatigue, and conflicting findings to date. The monitoring phase of the present study offers an embedded opportunity to analyze the course, predictors, and correlates of radiotherapy-related fatigue in a controlled breast cancer population.

2.2 Drug Information

Mechanism of Action

Naltrexone hydrochloride is a competitive antagonist at mu and delta opioid receptors. As such, it blocks the binding of beta-endorphin to the mu opioid receptor. Although naltrexone has been shown to have variable effects on beta-endorphin levels[19-21], endorphin levels do not predict opioid activity in the presence of a mu opioid receptor antagonist like naltrexone.

Clinical Studies

In human studies, naltrexone has been effective in decreasing both use and cravings in patients with alcohol and opioid dependence[22,23] Naltrexone (in both oral and long-acting injectable IM formulations) is currently FDA approved for the treatment of alcohol and opioid dependence. Off-label studies have shown efficacy of naltrexone (in combination with bupropion) in causing significant weight loss in patients with uncomplicated obesity[24]. The agent has also been studied off-label for treatment of binge eating disorder and self-injurious behavior. The placebo-controlled studies that demonstrated the efficacy of naltrexone as an adjunctive treatment of alcoholism (in patients > 18 years of age) used a dose regimen of 50 mg po daily for up to 12 weeks; doses effective for obesity were somewhat lower (16-32mg). Clinically, the standard, widely-utilized, dose, attained in the vast majority of patients with alcohol and opioid

dependence, is 50mg daily. Furthermore, prior research suggests that women achieve higher serum levels of naltrexone than men, and that women are significantly less adherent to 100mg doses (due to decreased tolerability) than to placebo or 25-50mg doses [25].

The durations of most placebo-controlled trials of naltrexone for alcohol and opioid dependence have ranged from 12-52 weeks, although shorter positive trials (3-12 weeks) exist in the literature. Clinically, for treatment of alcohol and opioid dependence, an initial 4-month course of naltrexone is recommended, and the medication can be continued indefinitely in the setting of good response.[26] The present study differs in that the target population will receive naltrexone for radiotherapy-emergent fatigue, which has been shown in prior studies to improve spontaneously after the conclusion of radiation treatment, returning to pre-treatment levels in the majority of patients by three months after radiotherapy.[13,15] Therefore, a 5-week trial duration will be utilized in order to minimize the possibility of missing the appropriate time period in which to demonstrate treatment effect as opposed to spontaneous recovery. Further supporting the 5-week trial duration is the observation that patients often demonstrate therapeutic benefit from naltrexone within the first few days or weeks of treatment.[27]

Pharmacokinetics

Naltrexone has a volume of distribution of 1350 L, and is 21% protein bound. It is metabolized hepatically via dihydrodiol dehydrogenase and conjugation to its principal metabolite, 6-beta-naltrexol. It is 53-75% renally excreted, mostly as metabolites, less than 2% unchanged. The elimination half-life of 6-beta-naltrexone is 5-10 days.

Despite its hepatic metabolism, naltrexone does not interact with the cytochrome P450 enzyme system.

2.3 Rationale

Radiation Therapy

The majority of cancer patients receiving radiation therapy are treated with fractionated external beam radiation, in which a daily dose of radiation from an external source targets a tumor within the body. A significant portion of patients receiving external beam radiation experience fatigue three to four weeks into a typical five- to eight-week radiation course, regardless of the location of the tumor or the radiation field. This fatigue usually lasts for approximately three weeks after treatment and either resolves spontaneously, or can persist for weeks to months.

Interestingly, patients receiving radiation that targets only superficial structures (i.e. breast cancer patients) can become equally as fatigued as patients receiving radiation to deeper structures, and fatigue is more highly correlated with skin dose and field size than with depth of radiation[28,29]. In fact, the one commonality among radiation therapy regimens that cause fatigue is that there is a significant skin dose. This led us to hypothesize that factors produced in the skin in response to radiation may play a role in radiation-induced fatigue.

DNA damage resulting from radiation exposure causes upregulation of expression of p53 dependent genes in skin cells. One recently-identified p53-dependent gene upregulated in keratinocytes in response to radiation exposure encodes a long-lived endogenous opioid called β-

endorphin[30]. B-endorphin induction following radiation exposure was observed during studies elucidating the pathway through which ultraviolet radiation stimulates skin pigmentation (tanning). In the pigmentation response following ultraviolet radiation exposure, there is a p53-induced expression of pro-opiomelanocortin (POMC) in keratinocytes. POMC is cleaved into various biologically-functional peptides. One of these peptides, Melanocyte Stimulating Hormone (MSH), is important in the tanning response, acting in a paracrine fashion to stimulate melanocytes to produce pigment. Another peptide derived from POMC production and cleavage following multiple types of DNA damage is the endogenous opioid β-endorphin. Opioid drugs (such as morphine) often cause fatigue and lethargy when they are used to treat pain. Dr. Fisher's data in mice show that plasma β-endorphin levels are elevated significantly by 3 weeks into a 6-week regimen of daily tail radiation that models radiation therapy in cancer patients receiving radiation to superficial structures. In contrast to humans, mice do not exhibit fatigue in response to exogenous administration of opiate drugs[31]. However, quantitative behavioral studies indicated significant changes in phenotypes associated with morphine administration, including mechanical and thermal nociception, in tail-irradiated mice that did not occur in non-irradiated mock-treated counterparts. Furthermore, these changes were reversed upon administration of the opioid antagonist naloxone. In these tail-irradiated mice, β-endorphin plasma levels diminish over the 4 weeks following the end of the radiation regimen.

Chemotherapy

Patients receiving chemotherapy typically become debilitatingly fatigued, even more predictably than radiation therapy patients. As mentioned above, the increased production of β-endorphin following radiation exposure-induced DNA damage is a p53-dependent process. Many common chemotherapeutics are DNA damaging agents that induce p53, and therefore p53-dependent genes, to cause apoptosis of cancer cells[32]. As transcription of the gene encoding β-endorphin is responsive to p53, it is thus plausible that the fatigue caused in patients receiving chemotherapy is the result of increased β-endorphin production following chemotherapy-induced p53 up-regulation in target cells. A treatment that blocked the effects of β-endorphin might then also reduce any residual fatigue from chemotherapy.

2.4 Correlative Studies Background

At the blood draw obtained for eligibility determination immediately prior to randomization, whole blood samples will be banked for analysis of OPRM1 (mu opioid receptor) genetic variants, specifically the Asn40Asp missense variant which has a frequency of 0.10-0.15 in Caucasians, 0.21 in Ashkenazi Jews, 0.25-0.45 in East Asians, and 0.14 in Hispanics.[33] The Asn40Asp variant has been shown to bind beta-endorphin approximately three times more tightly than the most common allelic form of the receptor,[34] and it has predicted good clinical response to naltrexone in alcohol and opioid dependence.[33,35,36]

Banked specimens will also be available for future exploratory examination of pro-inflammatory biomarkers such as expression-regulating polymorphisms in pro-inflammatory cytokine genes, which in recent studies have correlated with increased fatigue severity, depressive symptoms and memory complaints.[37]

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria for Monitoring Phase

3.1.1 Age ≥ 18

3.1.2 Diagnosis of: invasive breast cancer (stage I-III), ductal carcinoma in situ, lobular carcinoma in situ, lobular carcinoma

3.1.3 Plan to receive radiation therapy, or within 3 days of starting radiation therapy

3.2 Exclusion Criteria for Monitoring Phase

3.2.1 Suicidal ideation, as determined via PHQ-9

3.2.2 Non-English speaking

3.3 Eligibility Criteria for Randomization Phase

3.3.1 Participants may have had prior breast surgery and/or chemotherapy.

3.3.2 Age ≥18 years.

Because no dosing or adverse event data are currently available on the use of naltrexone in cancer patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.3.3 Participants must have acceptable pre-treatment laboratory values as defined below:

– total bilirubin	within normal institutional limits
– AST(SGOT)/ALT(SGPT)	≤2.5 × institutional upper limit of normal
– creatinine	within normal institutional limits OR
– creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.
– TSH	<10 mIU/L

3.3.4 If child-bearing potential, willingness to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

3.3.5 Ability to understand and the willingness to sign a written informed consent document

3.3.6 Receiving radiation therapy of any type at DFCI, BWH, MGH, or affiliated network sites (including but not limited to partial breast irradiation, two-field, three-field, and four-field plans)

3.3.7 FACIT-F subscale score >=10 pre-radiation therapy and decrease in FACIT-F of 10 points or more as compared to prior FACIT

3.4 Exclusion Criteria

3.4.1 Participants with major depressive disorder and/or suicidal ideation as determined by PHQ-9.

3.4.2 Participants who are receiving any other investigational agents that might interact with study medication or influence the measurement of study outcomes.

3.4.3 Participants with known metastatic disease should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.4.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to naltrexone.

3.4.5 Participants who have used opioid-containing medications (including cough/cold medications containing codeine and/or antidiarrheals containing loperamide) in the past 2 weeks, or who are expected to require opioid-containing medications within the duration of the treatment period.

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

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

3.2.8 Participants using other contraindicated medications (thioridazine, yohimbine)

3.5 Inclusion of Women and Minorities

Women of all races and ethnic groups are eligible for this trial.

4. RECRUITMENT AND REGISTRATION PROCEDURES

4.1 Patient Recruitment

The study team will review radiation oncologist's schedules and Epic records for basic information to identify potential patients. With the radiation oncologist's permission, a trained individual will approach the patient to discuss this study. If a patient decides to participate in this study, written informed consent will be obtained.

4.2 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. There will be a two-part registration: the 1st part for the monitoring phase of the study and the 2nd part for the intervention phase. The relevant part of the registration must be completed prior to the initiation of fatigue monitoring (1st part) and therapy (2nd part). Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the QACT protocol-specific eligibility checklist. The CRC will be consenting participants to monitoring phase only. Intervention phase consent will be done by an MD who is listed as a co-investigator.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study may be canceled. Notify the QACT Registrar of registration cancellations as soon as possible.

4.3 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin treatment during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

- Obtain written informed consent from the participant prior to the performance of any protocol specific procedures or assessments.

- Complete the QACT protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. **To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist.**

Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for the treatment protocol. Registration to both treatment and ancillary protocols will not be completed if eligibility requirements are not met for all studies.

- Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295. For Phase I protocols, attach participant dose level assignment confirmation from the sponsor.

- The QACT Registrar will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant when applicable. The randomization will be a block randomization at each site (DFCI/BWH vs MGH).

- An email confirmation of the registration and/or randomization will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration and/or randomization.

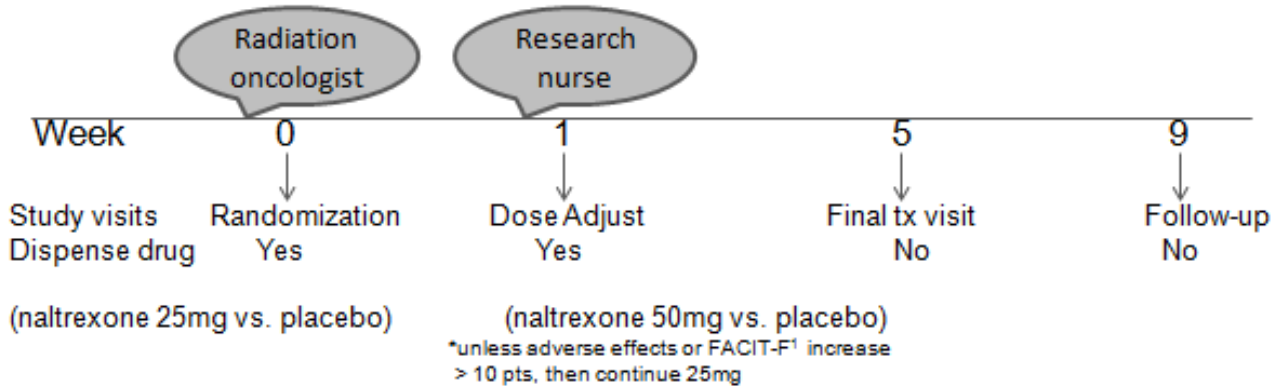
5. TREATMENT PLAN

5.1 Treatment Regimen

Patients consented to the intervention phase will be randomized to naltrexone (25mg for 1 week, followed by 50mg for 4 weeks) or matching placebo. All participants will be instructed to take the double-blinded medications in the morning with food. The medication should be swallowed whole. If the patient misses or vomits a dose, they can be re-dosed within an 8-hour time frame.

The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of the study.

Study Plan: Randomization Phase



[1]Functional Assessment of Chronic Illness Therapy-Fatigue Subscale

5.2 Pre-Treatment Criteria

No evidence of hepatic or renal impairment and serum HCG negative, as described in the eligibility criteria above

5.3 Agent Administration

All participants will be instructed to swallow the double-blinded medications in the morning with food.

Monitoring and Intervention Phases: Visit Breakdown – Refer to study calendar in section 9.

Monitoring Phase (duration: 1-10 weeks):

- Visit 1: Collection of baseline data.
    a. Patient demographic information and clinical characteristics will be collected by self-administered surveys.

b. Completion of self-reported fatigue, anxiety, depression, sleep and quality of life questionnaires.

- Visits 2-10 (in person or by phone): Monitoring procedures including completion of self-reported fatigue and other quality of life questionnaires

The occasional mis-timed (or missed) FACIT does not automatically constitute a protocol violation. However, in order to remain in compliance with the protocol, a minimum of 4 FACITs is needed for partial breast irradiation patients, 5 FACITs for hypofractionation patients, and 7 FACITs for standard (6 week) fractionation patients. The monitoring phase terminates either at entrance into the intervention phase of the study, or at 4 weeks after the conclusion of radiation therapy, whichever comes first.

Intervention Phase (duration 5 weeks):

- Visit 1a:
    a. consent for trial;
    b. review of concomitant medications;
    c. complete baseline fatigue questionnaire (unless completed within past week)—may be completed at Visit 1b;
    d. complete anxiety, depression, sleep and quality of life questionnaires (unless completed within past week)—may be completed at Visit 1b;
    e. urine HCG only in women with reproductive potential; blood draw to evaluate LFTs, Hct, BUN/Cr unless results are available within the previous month;
    f. specimens will be banked for future analysis of fatigue-related genetic polymorphisms and inflammatory biomarkers (participants can opt out of specimen banking)
- Visit 1b: laboratory study results reviewed to confirm eligibility; receive medication bottles and medication diary; receive patient education sheet on contraindicated medications and safety card (see Appendix A); Visit 2 (one week after starting study drug vs. placebo): fatigue/response and adverse event assessment for dose escalation, review of concomitant medications, fatigue assessment
- Visit 3 (five weeks after initiating study drug vs placebo): complete follow-up fatigue, anxiety, depression, sleep and quality of life questionnaires; review of concomitant medications; return medication bottles and diaries. Blood draw for LFTs.

5.4 General Concomitant Medication and Supportive Care Guidelines

For nausea, the suggested approach based on clinical guidance is for the patient to take naltrexone with a tablespoon of simethicone (e.g., Gas-X® and Mylicon®) or bismuth subsalicylate (e.g., Pepto-Bismol).

Drug Interactions with Naltrexone:

The following medications are contraindicated because their effect may be blocked:

- Cough/cold medications: if medication contains an opioid (e.g. codeine)
- Antidiarrheal medications: if medication contains an opioid (e.g. loperamide)

Opioid analgesics: Contraindicated because greater amount of opiate analgesia may be required than usual which may result in deeper and more prolonged respiratory depression than if the patient were not taking naltrexone
Thioridazine: May result in lethargy and somnolence
Yohimbine: May result in anxiety and increased pulse and blood pressure

Nonsteroidal anti-inflammatory drugs (NSAIDs): At doses above that used in this study, may result in liver enzyme elevations (i.e., AST and ALT) in combination with regular use of very high doses of naltrexone (200–250 mg/day).[38] This effect has only been observed above the recommended therapeutic dose range of naltrexone (i.e., >50–100 mg); therefore these medications are not considered to be contraindicated.

5.5 Duration of Therapy

Duration of therapy will be five weeks. In the absence of adverse event(s), treatment will continue for the entire five weeks unless one of the following criteria applies:

- Initiation of opioid-containing medications
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the study
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

5.6 Duration of Follow Up

Participants in the monitoring phase of the study will be followed for a maximum of 10 weeks, ending 4 weeks after cessation of radiotherapy or until they consent (if eligible) to participate in the intervention phase of the study. Those in the intervention phase will be followed until 4 weeks post-treatment. Participants removed from study for unacceptable adverse event(s) will be followed until the end of the study and beyond, until resolution or stabilization of the adverse event has occurred.

5.7 Criteria for Removal from Study

1. Initiation of opioid therapy, or newly expected need for opioid therapy while on study drug

2. Emergence of suicidal ideation
3. Moderate or severe hepatic impairment (AST and ALT > 3x ULN; Bilirubin > 1.5 ULN)
4. Moderate or severe renal impairment (Creatinine > 1.5x ULN)
5. Clinically significant respiratory or cardiac disease
6. Significant deviation from study protocol
7. Need to hold drug for more than 3 days, for any reason

Participants will be removed from the study when any of the criteria listed in Section 5.7 applies. The reason for study removal and the date the participant was removed must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

A QACT Treatment Ended/Off Study Form should be filled out when a participant completes study treatment and again when the participant comes off study. This form can be found on the QACT website or obtained from the QACT registration staff.

In the event of unusual or life-threatening complications, investigators must notify the Overall PI, Fremonta Meyer, MD, at 617-732-5700, pager ID 17231 or via email (flmeyer@partners.org) within 24 hours of discovery.

Psychiatric emergencies: Suicidal ideation is a rare (<=1%) adverse event associated with naltrexone use in individuals receiving IM naltrexone for alcohol and opioid dependence but it was not observed in those treated with naltrexone orally or in those receiving it for other indications (i.e., obesity, smoking cessation, binge eating disorder). Suicidal ideation will be assessed during the trial each time the PHQ-9 depression self-report questionnaire is completed. The CRC will be scoring the PHQ9 and if the score is greater than or equal to 10, the CRC will notify the participant's Radiation Oncologist as well as the study's psychiatrist so that they can discuss with the participant the options for clinical follow-up and further care. Suicidal ideation that is indicated on the PHQ-9 or spontaneously reported will constitute a serious adverse event. This evaluation will be conducted by one of the study clinicians with psychiatric expertise and/or by mental health staff in the MGH or BWH emergency rooms, if appropriate. These participants will be followed by study psychiatrists until a local mental health clinician is available for ongoing treatment. Study medication will be discontinued in any participant who develops suicidal ideation. The following established algorithm will be employed:

Specific Algorithms for Addressing Participant Reports of Suicidal Ideation

Algorithm based on response to *PHQ-9*:

ITEM 13.9: Over the last 2 weeks, how often have you been bothered by ….

…. Thoughts that you would be better off dead or of hurting yourself in some way?

If participant responds …. (shaded areas)

Not at all	Several days	More than half the days	Nearly every day
0	1	2	3

Algorithm based on participant volunteering possible suicidal ideation

Ask: ***Have you had thoughts of actually hurting yourself?***

If participant responds …. (shaded area)

NO	YES

<table>
<tr>
<td>Ask: Have you had thoughts of actually hurting yourself?
If participant responds …. (shaded area)
NO YES
Ask three screening questions about plan, probability and preventing factors:</td>
<td>Shaded response requires one of the following to be done <u>the same day</u>:
• Refer participant to study psychiatrist
• Send participant to an emergency room, or
• Send participant to another mental health professional</td>
</tr>
<tr>
<td><u>Plan:</u>
1. Have you thought about how you might actually hurt yourself?
NO YES [ask HOW?]</td>
<td></td>
</tr>
<tr>
<td><u>Probability:</u>
2. There's a big difference between having a thought and acting on a thought. How likely do you think it is that you will act on these thoughts about hurting yourself or ending your life sometime over the next month?
Not at all likely | Somewhat likely | Very likely</td>
<td></td>
</tr>
<tr>
<td><u>Preventing factors:</u>
3. Is there anything that would prevent or keep you from harming yourself?
NO YES [ask WHAT?]</td>
<td></td>
</tr>
<tr>
<td>Any shaded responses to the three screening questions requires one of the following to be done <u>the same day</u>:
• Refer participant to study psychiatrist
• Send participant to an emergency room, or
• Send participant to another mental health professional</td>
<td></td>
</tr>
</table>

5.8 DOSING DELAYS/DOSE MODIFICATIONS

Study drug will be increased to 50mg after 1 week of therapy unless fatigue has improved substantially on the lower dose or there are contraindications to this planned dose increase (including, but not limited to, adverse events grade II or higher that are thought to be related to study drug), as judged by the research nurse and study psychiatrist.

Some patients may tolerate the 25mg dose but develop toxicity after the dose is increased to 50mg. Hence, drug dose can be decreased from 50mg to 25mg in the setting of new-onset adverse events grade II or higher by CTCAE judged to be definitely or probably related to study drug.

Study drug (either at the 25mg or 50mg dose) can also be held for up to three days and then

restarted in setting of adverse events grade II or higher by CTCAE if these events are judged to be possible, unlikely or unrelated to study drug. If the drug must be held for more than three days, the participant will need to come off the study.

	Remain at 25 mg dose instead of increasing to 50 mg	**Dose reduction to 25 mg dose after increasing to 50 mg dose**	**Dose hold at either 25 mg or 50 mg dose for up to 3 days**
Conditions	• Substantially reduced fatigue on 25 mg dose • Adverse events grade II or higher determined by CTCAE guidelines • Other conditions deemed significant by the research nurse and study psychiatrist	• New onset adverse events grade II or higher by CTCAE guidelines definitely or probably related to study drug • Other conditions deemed significant by the research nurse and study psychiatrist	• Adverse events grade II or higher by CTCAE guidelines possibly, unlikely, or unrelated to study drug • Other conditions deemed significant by the research nurse and study psychiatrist

6. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 6.1) and the characteristics of an observed AE (Section 6.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

Adverse events will be monitored explicitly using a standardized adverse event form used in trials for psycho-active medications that will be reviewed by the study psychiatrists.

6.1 Expected Toxicities

Safety Profile

Gastrointestinal side effects of oral naltrexone (10-33%) include gastrointestinal symptoms such as nausea (>=10%), vomiting (>=3%), anorexia (<10%), constipation (<10%), and diarrhea (<10%). During controlled trials of oral naltrexone in alcohol dependence, approximately 5% of patients discontinued the drug because of nausea. CNS side effects of oral naltrexone include headache (>= 7%), dizziness (4—9%), nervousness (>= 4%), insomnia (>= 3%), anxiety (>= 2%), fatigue (>= 4%), drowsiness (<= 2%), increased energy (< 10%), irritability (< 10%), paranoia (< 1%), restlessness (< 1%), confusion (< 1%), disorientation (< 1%), hallucinations (< 1%), nightmares (< 1%), yawning (< 1%), and hot flashes (< 1%). Miscellaneous side effects include rash (<10%)., increased thirst (<10%), and chills (<10%). Serious side effects of naltrexone (<1%) include hepatotoxicity (only reported at doses of 300mg/day or higher) and eosinophilic pneumonia (only reported with depot administration of naltrexone).

In controlled clinical trials of the extended-release injectable suspension of naltrexone, suicidal ideation, suicide attempts, or completed suicides occurred in 1% of patients and in no patients treated with placebo. In some cases, the suicidal thoughts or behavior occurred after study discontinuation but were in the context of an episode of depression that began while the patient was taking naltrexone. Although the incidence of adverse psychiatric events is expected to be considerably lower in the present study population as compared to populations of patients with alcohol and opioid dependence, depression and suicidal ideation will be systematically monitored during the present study using standardized self-report instruments.

Naltrexone blocks the effects of opioid analgesics and should not be used in patients who are currently on opioid analgesia, who have received opioids within the past 7 days (14 days for longer-acting opioids such as methadone), or who are expected to require opioid analgesia within the next 7 days. If opioids are required, the patient should stop naltrexone and wait 3 days before initiating opioids. If necessary, reversal of opioid blockade before the 3-day time period is possible to achieve, but should be done only under medical supervision, as higher doses may be required to achieve effective analgesia creating a risk of respiratory depression. Such supervision should occur in medical settings with the provision for respiratory support. This would include a hospital emergency department or intensive care unit.

Potential study participants will be strongly cautioned about unpleasant side effects of opioid withdrawal that may occur if they are on opioids at the time study drug is initiated. In addition, medication lists in LMR will be reviewed by study staff to verify the participant's self-report of opioid use.

Participants may use standard doses of acetaminophen, NSAIDs, or aspirin for analgesia during the study. Subjects on daily NSAIDs of >800mg ibuprofen daily (or the equivalent) will have LFTs one week after initiation of study drug. All participants will be instructed to report any symptoms of abdominal pain lasting more than a few days, white bowel movements, dark urine, or yellowing of their eyes. In the setting of these symptoms, liver function tests will be checked immediately.

Finally, if participants require opioid analgesia emergently during the course of the study, they will be taken off study. Study staff will notify the PI and QACT so that the treatment assignment (naltrexone or placebo) can be unblinded prior to initiating opioid analgesia. If the participant was assigned to naltrexone, the opioid analgesia will need to occur in a supervised medical setting, as above.

6.1.1 Adverse Events List(s)

Adverse Event List(s) for naltrexone

Common (10-33%)	**Uncommon (1-10%)**	**Serious (<1%)**
Nausea	Vomiting Anorexia Diarrhea	Elevated liver function tests Suicidal ideation

	Constipation Rash Headache Dizziness Nervousness Insomnia Anxiety Irritability Increased thirst	

6.2 Adverse Event Characteristics

Reporting of adverse events:

All toxicities or adverse events occurring between the start of treatment and 30 days following the end of treatment will be recorded and graded as to severity and relationship to study drug. Any toxicity that is moderate or serious will be immediately reported by phone or email to the PI within 24 hours of discovery. All serious adverse reactions will be reported to the PI who will then notify the IRB.

A **serious adverse reaction** is defined as any of the following: life threatening; permanently disabling; requiring inpatient hospitalization or prolonging or hospitalization; death while on study treatment

A **moderate adverse reaction** is defined as the following: discomfort severe enough to cause interference with usual activities; persistent or requiring treatment

A **mild adverse reaction** is defined as the following: awareness of signs/symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs/symptoms are transient in nature

Preexisting medical conditions and symptoms related to known underlying diseases will not be recorded as adverse events unless they significantly worsen in severity during the course of the study.

Other than possible drug side effects, participants may also experience inconvenience and/or emotional distress, due to filling out instruments focusing on physical and emotional symptoms.

In case of subject distress, study psychiatrists can be contacted.

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event

varies in nature, intensity or frequency from the expected toxicity information which is provided.
- Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

6.3 Expedited Adverse Event Reporting

6.3.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

6.3.2 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC and DF/PCC will report SAEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

6.3.3 Protocol-Specific Expedited Adverse Event Reporting Exclusions

N/A

6.4 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

6.5 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

7. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

7.1 Naltrexone

7.1.1 Description

Naltrexone (a pure opioid antagonist) is a cyclopropyl derivative of oxymorphone similar in structure to naloxone and nalorphine (a morphine derivative). The chemical name is N-Cyclopropylmethylnoroxymorphone and the formula is $C_{20}H_{23}NO_4$. The molecular weight is 341.40092. The NIM PubChem Compound ID is 5360515. Pharmacokinetic information follows below:

Duration: Oral: 25-50 mg: 24 hours

Absorption: Oral: Almost complete

Distribution: V_d: ~1350 L; widely throughout the body but considerable interindividual variation exists

Metabolism: Extensively metabolized via noncytochrome-mediated dehydrogenase conversion to 6-beta-naltrexol (primary metabolite) and related minor metabolites; glucuronide conjugates are also formed from naltrexone and its metabolites

Oral: Extensive first-pass effect

Protein binding: 21%

Bioavailability: Oral: Variable range (5% to 40%)

Half-life elimination: Oral: 4 hours; 6-beta-naltrexol: 13 hours; I.M.: naltrexone and 6-beta-naltrexol: 5-10 days (dependent upon erosion of polymer)

Time to peak, serum: Oral: ~60 minutes; I.M.: Biphasic: ~2 hours (first peak), ~2-3 days (second peak)

Excretion: Primarily urine (as metabolites and small amounts of unchanged drug)

Despite its hepatic metabolism, naltrexone does not interact with the cytochrome P450 enzyme system.

7.1.2 Form

Naltrexone is available generically from various manufacturers as a scored 50mg tablet (white or yellow in color).

7.1.3 Storage and Stability

Naltrexone hydrochloride tablets will be stored in well-closed containers at 15-30 degrees Celsius.

7.1.4 Compatibility

Not applicable for this study

7.1.5 **Handling**

No special considerations apply to handling for this study

7.1.6 **Availability**

The agent is commercially available from various manufacturers and will be purchased by the DFCI and MGH Research Pharmacies. Naltrexone will be purchased and billed to the study via established mechanisms at each site. It will be provided free of charge to participants.

7.1.7 **Preparation**

The DFCI and MGH Research Pharmacies will each purchase and over-encapsulate study medication and matching placebo per standard operating procedures of each site and provide the study drug supply for patients anticipated to go on the trial at the respective sites.

7.1.8 **Administration**

Orally dosed, once per day, in the morning with food.

7.1.9 **Ordering**

The agent will be obtained via commercial sources.

7.1.10 **Accountability**

As the responsible party designated by the investigator, the DFCI and MGH Research Pharmacies will maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

7.1.11 **Destruction and Return**

At the end of the study, unused supplies of naltrexone will be destroyed according to institutional policies. Destruction will be documented according to the Drug Accountability Return Form.

8. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

At the blood draw obtained for eligibility determination immediately prior to randomization, whole blood samples will be banked for analysis of OPRM1 (mu opioid receptor) genetic variants, specifically the Asn40Asp missense variant which has a frequency of 0.10-0.15 in Caucasians, 0.21 in Ashkenazi Jews, 0.25-0.45 in East Asians, and 0.14 in Hispanics.[33] The Asn40Asp variant has been shown to bind beta-endorphin approximately three times more tightly than the most common allelic form of the receptor,[34] and it has predicted good clinical response to naltrexone in alcohol and opioid dependence.[33,35,36]

Banked specimens will also be available for future exploratory examination of pro-inflammatory biomarkers such as expression-regulating polymorphisms in pro-inflammatory cytokine genes, which in recent studies have correlated with increased fatigue severity, depressive symptoms and memory complaints.[37]

Participants may opt out of specimen banking if they wish to do so.

9. STUDY CALENDARS

*Note that study visits in both monitoring and intervention phase can be completed within 7 days of the scheduled date.

Study measures, type of procedure, and study visit schedule

Monitoring Phase (6-week radiation therapy schedule)

	Type	Baseline Visit	Weekly Monitoring Visits from Start of Radiation Therapy	**Meets Fatigue Eligibility Threshold**
Background Information				
Consent		X		
Demographics/Patient Characteristics Form	Self-report	X		
Clinical Variables[a]			X[a]	
Fatigue				
FACIT-Fatigue Subscale	Self-report	X[b]	X	X
PGI-F	Self-report	X[b]		
Sleep				
PSQI	Self-report	X[b]		
ISI	Self-report	X[b]		
ESS	Self-report	X[b]		
Berlin Questionnaire	Self-report	X[b]		
Other Target Symptoms				
GAD7	Self-report	X[b]		
PHQ9	Self-report	X[b]	X[c]	
FACT-B/FACT-ES	Self-report	X[b]	X[c]	
CPFQ	Self-report	X[b]		
PEG	Self-report	X[b]		
Safety monitoring				
Urine β-HCG				X
LFTs[d]				X
BUN/Creatinine[d]				X
Hematocrit[d]				X
TSH[d]				X
Subject Exit form (if applicable)				X[e]

a. Clinical Variables form completed once at end of radiation treatment for every patient in monitoring phase
b. baseline questionnaires to be completed within ≤ 21 days prior to, or within 3 days of starting radiation therapy, otherwise they need to be repeated.
c. During final week of RT, and 4 weeks after completion of RT
d. LFTs, BUN/Creatinine, Hematocrit will be accepted if drawn within 30 previous day; TSH within 6 months.

e. To be completed by study coordinator at time when patient is taken off-study for any reason. If patient continues on to Intervention Phase, this form will be completed when taken off intervention phase.

Study measures, type of procedure, and study visit schedule
Monitoring Phase (Partial Breast Irradiation (PBI))

	Type	Baseline Visit	Monitoring Visits	**Meets Fatigue Eligibility Threshold**
Background Information				
Consent		X		
Demographics/Patient Characteristics Form	Self-report	X		
Clinical Variables[a]			X[a]	
Fatigue				
FACIT-Fatigue Subscale	Self-report	X[b]	X[c]	X
PGI-F	Self-report	X[b]		
Sleep				
PSQI	Self-report	X[b]		
ISI	Self-report	X[b]		
ESS	Self-report	X[b]		
Berlin Questionnaire	Self-report	X[b]		
Other Target Symptoms				
GAD7	Self-report	X[b]		
PHQ9	Self-report	X[b]	X[d]	
FACT-B/FACT-ES	Self-report	X[b]	X[d]	
CPFQ	Self-report	X[b]		
PEG	Self-report	X[b]		
Safety monitoring				
Urine β-HCG				X
LFTs[e]				X
BUN/Creatinine [e]				X
Hematocrit [e]				X
TSH[e]				X
Subject Exit form (if applicable)				X[f]

a. Clinical Variables form completed once at end of radiation treatment for every patient in monitoring phase
b. baseline questionnaires to be completed within $\leq$ 21 days prior to, or within 3 days of starting radiation therapy, otherwise they need to be repeated.
c. Complete once at baseline, once within one week after start of radiation, then once 4 weeks after completion of RT
d. Complete once at baseline, once within one week after start of radiation, then once while obtaining the final monitoring FACIT 4 weeks after end of RT
e. LFTs, BUN/Creatinine, Hematocrit will be accepted if drawn within 30 previous day; TSH within 6 months.
f. To be completed by study coordinator at time when patient is taken off-study for any reason. If patient continues on to Intervention Phase, this form will be completed when taken off intervention phase.

Study measures, type of procedure, and study visit schedule

Monitoring Phase (Hypofractionation Radiation)

	Type	Baseline Visit	Monitoring Visits	**Meets Fatigue Eligibility Threshold**
Background Information				
Consent		X		
Demographics/Patient Characteristics Form	Self-report	X		
Clinical Variables[a]			X[a]	
Fatigue				
FACIT-Fatigue Subscale	Self-report	X[b]	X[c]	X
PGI-F	Self-report	X[b]		
Sleep				
PSQI	Self-report	X[b]		
ISI	Self-report	X[b]		
ESS	Self-report	X[b]		
Berlin Questionnaire	Self-report	X[b]		
Other Target Symptoms				
GAD7	Self-report	X[b]		
PHQ9	Self-report	X[b]	X[d]	
FACT-B/FACT-ES	Self-report	X[b]	X[d]	
CPFQ	Self-report	X[b]		
PEG	Self-report	X[b]		
Safety monitoring				
Urine β-HCG				X
LFTs[e]				X
BUN/Creatinine[e]				X
Hematocrit[e]				X
TSH[e]				X
Subject Exit form (if applicable)				X[f]

a. Clinical Variables form completed once at end of radiation treatment for every patient in monitoring phase
b. baseline questionnaires to be completed within $\leq$ 21 days prior to, or within 3 days of starting radiation therapy, otherwise they need to be repeated.
c. Complete once at baseline, weekly during RT, then once 4 weeks after completion of RT
d. Complete once at baseline, once during the final week of RT, then once while obtaining the final monitoring FACIT 4 weeks after end of treatment
e. LFTs, BUN/Creatinine, Hematocrit will be accepted if drawn within 30 previous day; TSH within 6 months.
f. To be completed by study coordinator at time when patient is taken off-study for any reason. If patient continues on to Intervention Phase, this form will be completed when taken off intervention phase.

Study measures, type of procedure, and study visit schedule

Intervention Phase

	Week 0 Randomization Visit	Week 1 Rx Visit (+/- 7 days)	Week 5 Rx Visit (+/- 7 days)	Week 9 Follow-up Visit (+/- 7 days)
Background Information				
Consent	X			
Fatigue				
FACIT-Fatigue Subscale	X	X	X	X
PGI-I	X		X	
Sleep				
PSQI	X		X	
ISI	X		X	
ESS	X		X	
Berlin Questionnaire			X	
Other Target Symptoms				
GAD7	X		X	
PHQ9	X		X	
FACT-B/FACT-ES	X		X	
CPFQ	X		X	
PEG	X		X	
Safety monitoring				
LFTs			X	
Concomitant medications	X	X	X	
Adverse Events assessment		X	X	
Health status/life events review				X
Dispense medication	X	X		
Review medication diary	X	X	X	
Study Summary				
Subject Exit form				X[a]
Study Visit duration (min)	40	15	40	15

a. To be completed by study coordinator at time when patient is taken off-study for any reason.

Effect measures listed in the Table of Procedures are described below. In addition to these effect measures, we will examine potential covariates that may play a role in the evolution of fatigue during breast radiotherapy. These include radiotherapy related characteristics such as breast volume; type of radiotherapy (e.g. fractionation schedule, number of fields, design of tangent fields [e.g. partial vs. full breast irradiation], boost dose [mini-tangents vs. electrons]. Exercise type/frequency and travel time to clinic will be assessed, as these parameters have correlated with radiotherapy-emergent fatigue in prior studies[39]. Finally, hematocrit will be measured at baseline.

The related symptom measure of obstructive sleep apnea will be evaluated via the Berlin Questionnaire and Epworth Sleepiness Scale:

Berlin Questionnaire (BQ): (Time: 2 minutes) The BQ will be done once at the beginning of the

study. It is an instrument used to identify patients at high risk for sleep apnea based on symptoms related to snoring and daytime sleepiness along with the presence of hypertension or obesity. It has been found to have high sensitivity and specificity in a primary care setting. [40]

Epworth Sleepiness Scale (ESS): (Time: 2 minutes) The ESS is a simple self-report scale of sleep propensity. The subject is asked to estimate the chances of dozing in each of 8 different situations on a scale of 0 to 3, with total scores ranging from 0 to 24. The ESS has been validated as a tool to differentiate normal subjects from those diagnosed with a sleep disorder. [41]

10. MEASUREMENT OF EFFECT

The effect of naltrexone (and placebo in the control group) will be defined as a difference (in raw FACIT score) between the pre-randomization FACIT and the follow-up FACIT.

FACIT-fatigue subscale: This 13-item self-report scale measuring fatigue and functional impairment as a result of fatigue has been validated in cancer patients.[42]. It shows strong internal consistency (coefficient alpha range = 0.93-0.95) and test-retest reliability of 0.82[43]. The scale is reverse-scored and the range is 0 (maximum fatigue) - 52 (minimum fatigue). According to ICD-10 criteria, a score <= 34 indicates significant cancer related fatigue. A methodologically robust review of validated cancer-specific fatigue scales recommends the FACIT-fatigue subscale as the preferred outcome measure for research.[44]

10.1 Other Response Parameters

Depression, anxiety, subjective cognitive function, sleep quality, insomnia, and quality of life outcome measures including pain will be assessed at study visits using the self-report measures listed below.

GAD7: *(4 minutes)* The Generalized Anxiety Disorder scale (GAD-7) is a 7-item self-report anxiety questionnaire which was initially validated in primary care populations; it has also been shown to be reliable and valid in the general population[45]. Of note, prior literature suggests that high baseline anxiety may be a risk factor for radiotherapy-emergent fatigue in breast cancer patients[11]

Cognitive and Physical Functioning Scale (CPFQ) (5 minutes): The CPFQ assesses both cognitive and physical functioning of individuals with mood and anxiety disorders. The CPFQ is a 7-item questionnaire that uses a 1-6 scale to measure impairment over the past month. The total score ranges from 6-42 points.

Insomnia Severity Index (ISI): (4 minutes) The ISI is a subjective self-report assessment of sleep quality, restedness upon arising, daytime fatigue, attention/concentration and disturbances in relationships and mood. It is reliable and valid and has 7 items that use a 5-point Likert-style scale. Scores can range from 0 to 28. Of the 7 questionnaire items, 3 assess the severity of insomnia and 1 question each assesses satisfaction with current sleep pattern, sleep interference,

"noticeability" of sleeping problem to others, and concern about sleeping problems.[46]

Pittsburgh Sleep Quality Index (PSQI); (6 minutes) The PSQI is a widely used 19-item self-rated measure of sleep quality occurring during the one-month prior to assessment.[47] The PSQI has good test-retest reliability in healthy controls, depressed subjects, and sleep-disordered subjects.[47] The total PSQI score distinguishes healthy controls from individuals with depression and problems initiating and maintaining sleep.[47]

Functional Assessment of Cancer Therapy-Breast (FACT-B): (8 minutes) The FACT-B is a 37-item self-report questionnaire intended to assess quality of life in breast cancer patients. The measure is composed of 5 subscales: physical well being (7 items), social/family well-being (7 items), emotional well-being (6 items), functional well-being (7 items), and breast cancer related items (10 items). Subjects are asked to indicate how they have felt in the past 7 days on a 5-point Likert scale ranging from 0=Not at all to 4=Very much with higher scores indicating better quality of life. The FACT-B demonstrates good internal consistency (Cronbach's α=0.88), good discriminative validity, and is sensitive to change.[48]

Functional Assessment of Cancer Therapy-Endocrine Subscale (FACT-ES): (4 minutes) Often used in combination with the FACT-B, the FACT-ES is intended to assess quality of life. Using the same 4 subscales of physical, social, emotional and functional well-being as the FACT-B, the FACT-ES contains an additional 19-item endocrine symptom subscale that assesses menopause symptoms. FACT-ES demonstrates good internal consistency, test-retest reliability, and sensitivity to change.[49]

Patient Global Impression-Fatigue (PGI-Fatigue): (1 minute) This is a scale designed to assess global severity of fatigue and change in the patient's fatigue over time. This scale will be taken by the patient to assess severity of present fatigue and improvement relative to baseline state. It consists of 2 global subscales, severity of fatigue and global improvement. The clinician will determine the onset and duration for the symptoms as well as the impact of the symptoms on behavior and function in order to determine fatigue severity. The subscales are rated on 7-point scales with the range 0=not assessed to 7=Extremely ill. They have been found to be valid and reliable measures of fatigue and are validated with the CPFQ measure described above.[50]

Patient Health Questionnaire (PHQ-9): (3 minutes) The PHQ-9 is the self-administered form of the Primary Care Evaluation of Mental Disorders (PRIME-MD), a widely used instrument designed to screen for psychiatric illnesses in primary-care settings. The PHQ-9 is a 9-item self-report questionnaire that assesses mood, depressive symptoms, and suicidal ideation. It is used widely as a diagnostic screening tool for major depressive disorder, and has been found to be as good as longer clinician-rated interviews in a variety of settings. If any subject indicates suicidal ideation on the PHQ-9, she will be evaluated according to the suicide protocol described above in order to determine appropriate treatment and safety measures.[51].

PEG: (1 minute). The PEG is an ultra-brief self-report scale measuring pain. It contains three items which assess average pain intensity (P), interference with enjoyable activities (E), and interference with general activity (G). It has been shown to have strong reliability, construct validity, and sensitivity to change in primary care and other ambulatory clinic patients.[52]

Demographics/Patient Characteristics Form: (3 minutes) This form will be completed by the patient to capture demographic, education, and prior health information.

Clinical Variables: Radiotherapy-related information to be completed by dosimetrist or physicist.

Subject Exit Form: This form will be completed by the study coordinator to capture summary of patient participation.

11. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

11.1 Data Reporting

11.1.1 Method

Data is collected in an independent database created by the study team.

11.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for collecting data variable within the study database.

11.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this study. The board is chaired by a medical oncologist from outside of DF/HCC and has external and internal representation. Information that raises any questions about participant safety or protocol performance will be addressed by the Overall PI, statistician and study team. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the trial.

The DSMB will meet twice a year to review accrual, toxicity, response and reporting information. Information to be provided to the DSMB may include: participant accrual; treatment regimen information; adverse events and serious adverse events reported by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

The study statistician, Andrzej Niemierko, will conduct the planned interim efficacy analysis. The PI will maintain oversight of administrative issues related to the analysis.

11.3 Multicenter Guidelines

N/A

11.4 Collaborative Agreements Language

N/A

12. STATISTICAL CONSIDERATIONS

Entry criteria of a drop of 10 points on FACIT-fatigue subscale was selected because a change of 10 points has been shown to constitute a clinically meaningful difference on this subscale[53]. The effect of naltrexone (and placebo in the control group) will be defined as a difference (in raw FACIT score) between the pre-randomization FACIT and the follow-up FACIT. FACIT-fatigue subscale scores are normally distributed in anemic and nonanemic cancer populations[42], with a standard deviation of 10 points. Setting power as 0.8, and significance as 0.05, assuming a two-sided type I error, 122 patients per arm are required to detect a "difference of a difference" of at least 3.6 points on FACIT-fatigue. The 3.6 point difference was selected because it is the approximate mean of prior effect sizes utilizing FACIT-fatigue in clinical trials of erythropoeitin or darbopoeitin vs. placebo. Assuming a 20% drop-out rate, approximately 150 patients per arm will be randomized.

An interim analysis will be conducted on one occasion, after collecting data for the first 75 patients in each arm. This analysis will be conducted in light of several possibilities: 1) the observed benefit of naltrexone is so promising that it would be unethical not to use it for all eligible patients, 2) the observed rate of side effects/toxicity is too high, 3) futility –it appears to be unlikely that there is a clinically significant difference between the naltrexone and placebo arms. The Haybittle–Peto boundary rule (with 0.001 significance threshold) will be employed to determine whether the trial should be stopped early. The final analysis will still use the 0.05 threshold of significance.
Futility testing will also be performed on the primary outcome at a low level (one-sided alpha 0.0025) on one occasion (after the first 75 patients are enrolled).

12.1 Study Design/Endpoints

The study is a randomized placebo-controlled trial. The primary outcome measure will be change score on the FACIT-fatigue subscale from randomization to the end of the study. Exploratory endpoints include changes in sleep continuity (sleep efficiency, total sleep time, sleep latency), quality-of-life measures, depression, anxiety, and subjective cognitive function.

Analysis of both the primary and exploratory endpoints will be by modified intention to treat.The mITT analysis (for both primary and exploratory endpoints) will be a per-protocol analysis; only patients who complete the entire trial according to the protocol will be counted towards the final results.

12.2 Sample Size/Accrual Rate

Sample size for the intervention phase of the study is 150 patients per arm randomized to treatment. Assuming a 4 year study duration, and 2 study sites, we will randomize 1-2

participants per study site every 2 weeks (~75 randomized participants / year). The sample size for the monitoring phase of the study is not fixed, but using a conservative estimate of 30% for radiation treatment-emergent fatigue, we will need to screen 3-6 participants per study site per 2 weeks (~225 screened participants / year).

12.3 Stratification Factors

Patients will be stratified according to whether or not they received chemotherapy.

12.4 Analysis of Secondary Endpoints

Secondary (exploratory) endpoints (changes in sleep continuity (sleep efficiency, total sleep time, sleep latency), quality-of-life measures, depression, anxiety, and subjective cognitive function) will be analyzed by modified intention to treat. Since no pre-existing data describes the magnitude of associations of our exploratory outcomes with naltrexone use in this population, we are unable to speculate on the statistical power required to detect an effect. Any relevant associations and their statistical significances will be calculated using descriptive statistics. In addition, radiation therapy status (currently receiving RT vs. recently completed RT) will be included as a covariate in the multivariate analysis.

12.5 Reporting and Exclusions

12.5.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment. Some patients may tolerate the 25mg dose but develop toxicity after the dose is increased to 50mg. Hence, drug dose can be decreased from 50mg to 25mg in the setting of moderate to severe adverse events by CTCAE judged to be definitely or probably related to study drug.

Study drug (either at the 25mg or 50mg dose) can also be held for up to three days and then restarted in setting of moderate or severe adverse events by CTCAE if these events are judged to be possible, unlikely or unrelated to study drug. If the drug must be held for more than three days, the participant will need to come off the study.

12.5.2 Evaluation of Response

All of the participants who meet the eligibility criteria, consent to randomization, and complete the entire treatment protocol will be included in the main analysis of effect.

For all dropouts, we will use an off-study form in order to obtain information about the reasons for not completing the study. We will use this information for post-hoc analyses to lessen the chance of bias due to missing data.

13. PUBLICATION PLAN

The results will be made public within 24 months of the end of data collection. A report is planned to be published in a peer-reviewed journal and that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes will be made public no later than three years after the end of data collection.

APPENDIX A INFORMATION ON POSSIBLE DRUG INTERACTIONS

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

The participant _____ is enrolled on a clinical trial using the experimental agent [naltrexone]. *This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the participant, but includes important information for others who care for this participant.*

Naltrexone blocks the effects of opioid containing medications, including pain medications such as Percocet, Vicodin, Oxycodone, Oxycontin, Dilaudid, Fentanyl, and Methadone; as well as Codeine and Loperamide. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**. These are the things that you and they need to know:

You will be asked to avoid taking any opioid containing medication which will not work because naltrexone blocks the effects of opioids, including pain relief. Furthermore, the use of narcotics will require that you drop out of the study. Naltrexone does not interfere with the effectiveness of non-narcotic pain relievers (e.g., acetaminophen [Tylenol], ibuprofen, and local or general anesthesia). If you need an opioid medication for a medical procedure (e.g., surgery) that can be scheduled in advance, your medication can be discontinued prior to your surgery. If you are scheduled for a surgical procedure, you must inform us so that we can let your treating physician, dentist, and/or anesthesiologist know that you may be taking naltrexone, an opiate blocker.

You will be asked to carry a medication card which will, in case of emergency, alert the medical personnel treating you that you may be taking naltrexone, an opioid blocker. This card, which should be kept on you at all times, will include appropriate drug information and precautions. A second card will be provided which must be given to a family member to keep at home for reference purposes.

INFORMATION ON POSSIBLE DRUG INTERACTIONS

You are enrolled on a clinical trial using the agent _____. This clinical trial is sponsored by the NCI. _____ blocks the effects of opioid containing medications. Because of this, it is very important to:

- Tell your doctors if you stop taking regular medicine or if you start taking a new medicine.
- Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, and pharmacist) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

- You must notify your doctors that you are on naltrexone if you require surgery, or if you develop pain requiring management with opioid containing medications

- Your study doctor's name is _____ and can be contacted at _____.

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Study Participant
Self-Administration
Study Drug Diary
Dana-Farber/Harvard Cancer Center

OTHER MEDICATIONS TAKEN

If you take a daily medication (prescribed or otherwise), please use one line per drug and indicate the start and stop dates under the "Date(s) Taken" section (i.e., 6/2/09 - 6/5/09).

Drug Name	Dose	Dates Taken	Reason Taken

Study Participant Initials _____ Date _____

FOR STUDY TEAM USE ONLY	
Staff Initials:	
Date Dispensed:	Date Returned:
# pills/caps/tabs dispensed:	# pills/caps/tabs returned:
# pills/caps/tabs that should have been taken:	
Discrepancy Notes:	

Participant Identifier: _____
Protocol # : 14-056
Your MD _____ Phone _____
Your RN _____ Phone _____

STUDY DRUG INSTRUCTIONS:

Study Drug: Naltrexone/Placebo
How Much: Your dose is
How Often: You will take each dose once a day
When: You should take your dose in the morning with food

SPECIAL INSTRUCTIONS:
If you miss or vomit a dose, you may retake the drug within 8 hours of missing or vomiting that dose.

Capsules must be swallowed whole

As a reminder, please bring any unused study drug, all empty containers, and this drug diary to your next clinic visit.

SYMPTOMS/SIDE EFFECTS

Please record any side effects experienced during this cycle. Include the date the particular symptom started and when it ended. Please evaluate the severity of the symptom according to the following scale:

DOSING LOG

Naltrexone RCT for Treatment-Emergent Fatigue in Patients Receiving Radiation Therapy for Breast Cancer

Cycle: ___

For each AM dose take:

Please indicate the date, time, amount taken and any comments.

	Date	Time and Amount Taken	Comments
Ex:	6/1/2009	8 am - 1	vomited pill
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

Naltrexone/Placebo

Cycle: ___

For each AM dose take:

Please indicate the date, time, amount taken and any comments.

	Date	Time and Amount Taken	Comments
Ex:	6/1/2009	8 am - 1	vomited pill
Day 8			
Day 9			
Day 10			
Day 11			
Day 12			
Day 13			
Day 14			
Day 15			
Day 16			
Day 17			

Mild: Awareness of sign or symptom; easily tolerated and did not affect ability to perform normal daily activities. Symptom did not require medication or therapeutic intervention.

Moderate: Significant discomfort which interfered with ability to perform normal daily activities. Symptom was easily resolved with at home medication or simple therapeutic intervention.

Severe: Marked discomfort with an inability to carry out normal daily activities. Symptom required new medication and/or therapeutic intervention in order to resolve.

Please Note: The severity should reflect the most severe level experienced during the time period.

Symptom	Start Date	End Date	Severity

Day 18			
Day 19			
Day 20			
Day 21			
Day 22			
Day 23			
Day 24			
Day 25			
Day 26			
Day 27			
Day 28			
Day 29			
Day 30			
Day 31			
Day 32			
Day 33			
Day 34			
Day 35			

Patient ID: _____ Date: _____

Visit: _____

The PEG

1. What number best describes your pain on average in the past week:

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

2. What number best describes how, during the past week, pain has interfered with your enjoyment of life?

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

3. What number best describes how, during the past week, pain has interfered with your general activity?

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

Patient signature/initials: _____

Date: _____

SAFTEE (1)

Below is a list of complaints people sometimes have. Please read each and circle the number corresponding to how much you have been bothered by that problem in the past week:

1 = not at all 2 = a little bit 3 = moderately 4 = quite a bit 5 = extremely

Head:

1. headaches	1	2	3	4	5
2. dizziness or faintness	1	2	3	4	5
3. loss of consciousness	1	2	3	4	5
4. seizures	1	2	3	4	5

Any other problems with your head (please specify):

5.	1	2	3	4	5
6.	1	2	3	4	5

Eyes:

7. eye irritation	1	2	3	4	5
8. swelling	1	2	3	4	5
9. blurred vision	1	2	3	4	5
10. double vision	1	2	3	4	5
11. poor vision	1	2	3	4	5
12. light bothering your eyes	1	2	3	4	5

Any other problems with your eyes (please specify):

13.	1	2	3	4	5
14.	1	2	3	4	5

Ears:

15. earache	1	2	3	4	5
16. discharge	1	2	3	4	5
17. trouble hearing	1	2	3	4	5
18. ringing or whistling or other noise in ears 1 2 3 4 5					

Any other problems with your ears (please specify):

19.	1	2	3	4	5
20.	1	2	3	4	5-

Mouth and Teeth:

21. sores in your mouth	1	2	3	4	5
22. dry mouth	1	2	3	4	5
23. too much saliva	1	2	3	4	5
24. swollen or sore tongue	1	2	3	4	5
25. bleeding gums	1	2	3	4	5
26. dental problems	1	2	3	4	5

Any other problems with your mouth or teeth (please specify):

27.	1	2	3	4	5
28.	1	2	3	4	5

Nose and Throat:

29. nasal congestion	1	2	3	4	5
30. nose bleeds	1	2	3	4	5
31. sore throat	1	2	3	4	5
32. laryngitis	1	2	3	4	5
33. difficulty swallowing	1	2	3	4	5

Any other problems with your nose or throat (please specify):

34.	1	2	3	4	5
35.	1	2	3	4	5

Chest:

36. chest pain	1	2	3	4	5
37. shortness of breath	1	2	3	4	5
38. wheezing	1	2	3	4	5
39. coughing	1	2	3	4	5
40. breast or nipple pain or discharge	1	2	3	4	5
41. breast tenderness	1	2	3	4	5

Any other trouble with your chest (please specify):

42.	1	2	3	4	5
43.	1	2	3	4	5

Heart:

44. rapid heart rate	1	2	3	4	5
45. irregular heart beat	1	2	3	4	5

Any other trouble with your heart (please specify):

46.	1	2	3	4	5
47.	1	2	3	4	5

Stomach and Abdomen:

48. stomach / abdominal discomfort	1	2	3	4	5
49. nausea	1	2	3	4	5
50. vomiting	1	2	3	4	5
51. heartburn	1	2	3	4	5

SAFTEE (2)

Below is a list of complaints people sometimes have. Please read each and circle the number corresponding to how much you have been bothered by that problem in the past week:

1 = not at all 2 = a little bit 3 = moderately 4 = quite a bit 5 = extremely

Any other trouble with stomach or abdomen (please specify):					
52.	1	2	3	4	5
53.	1	2	3	4	5
Bowel:					
54. diarrhea	1	2	3	4	5
55. constipation	1	2	3	4	5
56. gas	1	2	3	4	5
57. change in color of stools	1	2	3	4	5
58. hemorrhoids	1	2	3	4	5
59. painful bowel movements	1	2	3	4	5
Any other changes in your bowel movements (please specify):					
60.	1	2	3	4	5
61.	1	2	3	4	5
Appetite:					
62. appetite increase	1	2	3	4	5
63. appetite decrease	1	2	3	4	5
64. weight gain	1	2	3	4	5
65. weight loss	1	2	3	4	5
66. bad taste or change in taste	1	2	3	4	5
67. increased thirst	1	2	3	4	5
Any other change in appetite (please specify):					
68.	1	2	3	4	5
69.	1	2	3	4	5
Urination:					
70. painful urination	1	2	3	4	5
71. burning sensation with urination	1	2	3	4	5
72. difficulty in starting to urinate	1	2	3	4	5
73. decrease in force of urinary stream					
1 2 3 4 5					
74. more frequent urination	1	2	3	4	5
75. change in color of urine	1	2	3	4	5
Any other problems with urination (please specify):					
76.	1	2	3	4	5
77.	1	2	3	4	5

FEMALES:					
78. menstrual irregularity	1	2	3	4	5
79. cramps	1	2	3	4	5
80. heavy bleeding	1	2	3	4	5
81. spotting	1	2	3	4	5
82. tension	1	2	3	4	5
83. hot flashes	1	2	3	4	5
84. lengthening of menstrual period	1	2	3	4	5
85. shortening of menstrual period	1	2	3	4	5
Any other problems with menstrual period (please specify):					
86.	1	2	3	4	5
87.	1	2	3	4	5
Genital and Sexual Functioning:					
88. discomfort in genitals	1	2	3	4	5
89. swelling of or discharge from genitals	1	2	3	4	5
90. decrease in interest in sex	1	2	3	4	5
91. increase in interest in sex	1	2	3	4	5
92. delayed orgasm or inability to reach orgasm	1	2	3	4	5
93. **MALES:** difficulty achieving or maintaining an erection	1	2	3	4	5
Any other problems with genitals or sexual functioning (please specify):					
94.	1	2	3	4	5
95.	1	2	3	4	5

SAFTEE (3)

Below is a list of complaints people sometimes have. Please read each and circle the number corresponding to how much you have been bothered by that problem in the past week:

1 = not at all 2 = a little bit 3 = moderately 4 = quite a bit 5 = extremely

Muscles, Bones and Joints:					
96. aches, pains in muscles, bones or joints	1	2	3	4	5
97. swelling in legs or arms	1	2	3	4	5
98. tingling or numbness in hands or feet	1	2	3	4	5
Any other trouble with your muscles, bones, or joints (please specify):					
99.	1	2	3	4	5
100.	1	2	3	4	5
Walking and Moving:					
101. feeling unsteady on your feet	1	2	3	4	5
102. trouble with starting to move	1	2	3	4	5
103. controlling unwanted bodily movements	1	2	3	4	5
104. feeling restless or like you cannot stay still	1	2	3	4	5
105. shaking	1	2	3	4	5
106. feeling still or rigid	1	2	3	4	5
Any other difficulty with walking or moving (please specify):					
107.	1	2	3	4	5
108.	1	2	3	4	5
Scalp and Skin:					
109. rashes, itching, or irritation	1	2	3	4	5
110. bruising	1	2	3	4	5
111. increased irritation in sunlight	1	2	3	4	5
112. sweating a lot	1	2	3	4	5
Any other trouble with your scalp or skin (please specify):					
113.	1	2	3	4	5
114.	1	2	3	4	5

Other Areas:					
115. fever or chills	1	2	3	4	5
116. feeling tired or fatigued	1	2	3	4	5
117. too much energy	1	2	3	4	5
118. jumpiness or feeling jittery	1	2	3	4	5
119. feeling excited, overactive, or elated	1	2	3	4	5
120. problems falling asleep	1	2	3	4	5
121. problems staying asleep	1	2	3	4	5
122. waking up too early	1	2	3	4	5
123. sleeping too much	1	2	3	4	5
124. feeling drowsy during the day	1	2	3	4	5
125. trouble thinking, concentrating, or remembering	1	2	3	4	5
126. feeling down, depressed or blue	1	2	3	4	5
127. feeling anxious	1	2	3	4	5
128. irritability	1	2	3	4	5
Any other problems with your thinking, mood, energy, or other aspects of your health (please specify):					
129.	1	2	3	4	5
130.	1	2	3	4	5
131.	1	2	3	4	5
132.	1	2	3	4	5

Subject ID:_____
Visit #:____ Date: ____/____/____

PITTSBURG SLEEP QUALITY INDEX

INSTRUCTIONS:
The following questions related to your usual sleep habits during the past month only. Your answers should indicate the most accurate replay for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?

BED TIME _____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

NUMBER OF MINUTES _____

3. During the past month, what time have you usually gotten up in the morning?

GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different that the number of hours you spent in bed.)

HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you…

a) Cannot get to sleep within 30 minutes

Not during past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

b) Wake up in the middle of the night or early morning

Not during past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

c) Have to get up to use the bathroom

Not during past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

d) Cannot breathe comfortably

Not during past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

e) Cough or snore loudly

Not during past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

f) Feel too cold

Not during past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

g) Feel too hot

Not during past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

h) Had bad dreams

Not during past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

i) Have pain

Not during past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

j) Other reason(s), please describe _____

_____

Not during past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

6. During the past month, how would you rate your sleep quality overall?

Very good _____

Fairly good _____

Fairly bad _____

Very bad _____

7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

Not during past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____

Only a very slight problem _____

Somewhat of a problem _____

Very bad _____

Patient Initials/Signature: _____

Date: _____

Patient ID: _____
Date: _____
Visit#: _____

PHQ-9 — Nine Symptom Checklist

1. Over the last 2 weeks, how often have you been bothered by any of the following problems? Read each item carefully, and circle your response.

   a. Little interest or pleasure in doing things
   Not at all **Several days** **More than half the days** **Nearly every day**

   b. Feeling down, depressed, or hopeless
   Not at all **Several days** **More than half the days** **Nearly every day**

   c. Trouble falling asleep, staying asleep, or sleeping too much
   Not at all **Several days** **More than half the days** **Nearly every day**

   d. Feeling tired or having little energy
   Not at all **Several days** **More than half the days** **Nearly every day**

   e. Poor appetite or overeating
   Not at all **Several days** **More than half the days** **Nearly every day**

   f. Feeling bad about yourself, feeling that you are a failure, or feeling that you have let yourself or your family down
   Not at all **Several days** **More than half the days** **Nearly every day**

   g. Trouble concentrating on things such as reading the newspaper or watching television
   Not at all **Several days** **More than half the days** **Nearly every day**

   h. Moving or speaking so slowly that other people could have noticed. Or being so fidgety or restless that you have been moving around a lot more than usual
   Not at all **Several days** **More than half the days** **Nearly every day**

   i. Thinking that you would be better off dead or that you want to hurt yourself in some way
   Not at all **Several days** **More than half the days** **Nearly every day**

2. If you checked off any problem on this questionnaire so far, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

   Not Difficult at all **Somewhat Difficult** **Very Difficult** **Extremely Difficult**

Patient Initials/Signature: _____

Date: _____

Patient ID: _____
Date: _____
Visit #: _____

PATIENT GLOBAL IMPRESSIONS: SEVERITY OF FATIGUE

Symptoms of fatigue may include effects on:

*Your **physical wellbeing:***

Low or decreased energy, tiredness, decreased physical endurance or ability to sustain physical activity, general weakness, heaviness in the arms or legs, general heaviness, slowness or sluggishness, sleepiness, increased effort with physical tasks.

*Your **mood state:***

Decreased motivation or interest, decreased effort or initiative.

*Your **cognitive abilities:***

Decreased concentration, decreased attention, slowed thinking, reduced mental sharpness.

Within the past week, how troublesome (disturbing or distressing) have the identified symptoms of fatigue been for you?

CIRCLE THE NUMBER CORRESPONDING TO YOUR RATING

1	**Normal, no symptoms of fatigue**	***No symptoms of fatigue*** have been present in the past seven days
2	**Borderline symptoms**	There may have been ***subtle symptoms of fatigue*** but there was no meaningful impact on your behavior or function
3	**Mild fatigue**	There have been some ***clear symptoms of fatigue*** but they may have cause minimal, if any, emotional distress or difficulty for you in social or occupational situations
4	**Moderate fatigue**	There have been ***overt (definite) symptoms of fatigue*** causing noticeable, but modest, functional difficulties (impairment) or distress for you; These symptoms are interfering with (but not

		stopping) social, educational, or occupational function
5	**Marked fatigue**	There have been ***intrusive symptoms of fatigue*** that distinctly impair social or occupational activities or function and/or cause high levels of distress; The functional interference due to these symptoms is obvious to others
6	**Severe fatigue**	The ***symptoms of fatigue are very distressing*** to you and are disrupting behavior or function in multiple domains of function (social, occupation, school)
7	**Extreme fatigue**	***Symptoms of fatigue are drastically interfering*** in many life functions; You may be unable to work or attend school

Patient Initials/Signature: _____

Date: _____

Patient ID: _____
Date: _____
Visit #: _____

PATIENT GLOBAL IMPRESSIONS–IMPROVEMENT

Rate total improvement of fatigue within the past week whether or not it is due entirely to drug treatment

Compared to how you felt previously, how much have you changed over the past week?

CIRCLE THE NUMBER CORRESPONDING TO YOUR RATING

1	**Very much improved**	***Nearly all better***; good level of functioning; Minimal symptoms of fatigue if any at all; This level represents a very substantial change from the baseline assessment
2	**Much improved**	***Notably better*** with significant reduction of symptoms; Increase in the level of functioning but some symptoms of fatigue may remain
3	**Minimally improved**	***Slightly better***; There may be *only a modest change* in symptoms of fatigue or functional capacity
4	**No change**	***Symptoms of fatigue*** *remain essentially unchanged*
5	**Minimally worse**	***Slightly worse*** but may not be clinically meaningful; There may be only a modest worsening of symptoms or functioning
6	**Much worse**	***Notably worse*** with significant increase of symptoms of fatigue; Associated decrease in the level of functioning
7	**Very much worse**	***Severe exacerbation of symptoms*** and profound impact on behavior and/or functioning

Patient Initials/Signature: _____
Date: _____

Patient ID: _____

Date: _____

Visit #: _____

Table 1. Massachusetts General Hospital CPFQ

(a) How has your motivation/interest/enthusiasm been over the past month?					
1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent
(b) How has your wakefulness/alertness been over the past month?					
1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent
(c) How has your energy been over the past month?					
1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent
(d) How has your ability to focus/sustain attention been over the past month?					
1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent
(e) How has your ability to remember/recall information been over the past month?					
1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent
(f) How has your ability to find words been over the past month?					
1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent
(g) How has your sharpness/mental acuity been over the past month?					
1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

Please answer all questions by *circling* the *correct answer* or the answer which seems the most *appropriate* to you (consider 'normal' the time in your life prior to the past month when you were most satisfied with your cognitive and physical functioning).

ID:
Visit: Date: / /

Patient Initials/Signature: _____

Date: _____

Patient ID: _____
Date: _____
Visit#: _____

Insomnia Severity Index

For each question, please CIRCLE the number that best describes your answer.

Please rate the CURRENT (i.e. LAST 2 WEEKS) SEVERITY of your insomnia problem(s).

Insomnia Problem	None	Mild	Moderate	Severe	Very Severe
1. Difficulty falling asleep	0	1	2	3	4
2. Difficulty staying asleep	0	1	2	3	4
3. Problems waking up too early	0	1	2	3	4

4. How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?

Very Satisfied	Satisfied	Moderately Satisfied	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?

Not at all Noticeable	A Little	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

6. How WORRIED/DISTRESSED are you about your current sleep problem?

Not at all Worried	A Little	Somewhat	Much	Very Much Worried
0	1	2	3	4

7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) CURRENTLY?

Not at all Interfering	A Little	Somewhat	Much	Very Much Interfering
0	1	2	3	4

Patient Initials/Signature: _____

Date: _____

Subject ID: _____
Visit #:____ Date: ____/____/____

Generalized Anxiety Disorder – 7 questions

Instructions: for each question below, please circle the number of the statement that best matches how you feel

How often during the past 2 weeks have you felt bothered by:

1. **Feeling nervous, anxious, or on edge?**
   - 0 = not at all
   - 1 = several days
   - 2 = more than half the days
   - 3 = nearly everyday

2. **Not being able to stop or control worrying?**
   - 0 = not at all
   - 1 = several days
   - 2 = more than half the days
   - 3 = nearly everyday

3. **Worrying too much about different things?**
   - 0 = not at all
   - 1 = several days
   - 2 = more than half the days
   - 3 = nearly everyday

4. **Trouble relaxing?**
   - 0 = not at all
   - 1 = several days
   - 2 = more than half the days
   - 3 = nearly everyday

5. **Being so restless that it is hard to sit still?**
   - 0 = not at all
   - 1 = several days
   - 2 = more than half the days
   - 3 = nearly everyday

6. **Becoming easily annoyed or irritable?**
   - 0 = not at all
   - 1 = several days
   - 2 = more than half the days
   - 3 = nearly everyday

7. **Feeling afraid as if something awful might happen?**
   - 0 = not at all
   - 1 = several days
   - 2 = more than half the days
   - 3 = nearly everyday

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

(Please circle one option below)

- Not difficult at all
- Somewhat difficult
- Very difficult
- Extremely difficult

Patient Initials/Signature: _____

Date: _____

Spitzer RL, Kroenke K, Williams JB, Lowe B. A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7. [Journal Article] *Arch Intern Med*. 2006;166(10):1092-7.
Developed by Dr. Robert L. Spitzer, Dr. K. Kroenke, et al.

Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		Not At All	A Little Bit	Somewhat	Quite a Bit	Very Much
1	I feel fatigued	0	1	2	3	4
2	I feel weak all over	0	1	2	3	4
3	I feel listless ("washed out")	0	1	2	3	4
4	I feel tired	0	1	2	3	4
5	I have trouble starting things because I am tired	0	1	2	3	4
6	I have trouble finishing things because I am tired	0	1	2	3	4
7	I have energy	0	1	2	3	4
8	I am able to do my usual activities	0	1	2	3	4
9	I need to sleep during the day	0	1	2	3	4
10	I am too tired to eat	0	1	2	3	4
11	I need help doing my usual activities	0	1	2	3	4
12	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
13	I have to limit my social activity because I am tired	0	1	2	3	4

Scoring: Items are scored as follows: 4=Not At All; 3=A Little Bit; 2=Somewhat; 1=Quite A Bit; 0=Very Much, EXCEPT items #7 and #8 which are reversed scored. Score range 0-52. A score of less than 30 indicates severe fatigue. The higher the score, the better the quality of life.

Item Number	Reverse Item?		Item Response	Item Score
1	4	-		=
2	4	-		=
3	4	-		=
4	4	-		=
5	4	-		=
6	4	-		=
7	0	+		=
8	0	+		=
9	4	-		=
10	4	-		=
11	4	-		=
12	4	-		=
13	4	-		=

Sum individual item scores: _____
Multiply by 13: _____
Divide by number of items answered: _____

For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines on-line at www.facit.org.

Source: Webster, K., Cella, D., & Yost, K. (2003). The functional assessment of chronic illness therapy (FACIT) measurement system: properties, applications and interpretation. *Health and Quality of Life Outcomes, 1*(79), 1-7.

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CLINICAL NURSING WEBSITE: www.ConsultGeriRN.org

Patient ID: _____
Date: _____
Visit#: _____

FACT-B (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Patient ID: _____
Date: _____
Visit#: _____

FACT-B (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Patient ID: _____
Date: _____
Visit#: _____

FACT-B (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
B1	I have been short of breath	0	1	2	3	4
B2	I am self-conscious about the way I dress	0	1	2	3	4
B3	One or both of my arms are swollen or tender	0	1	2	3	4
B4	I feel sexually attractive	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
B6	I worry that other members of my family might someday get the same illness I have	0	1	2	3	4
B7	I worry about the effect of stress on my illness	0	1	2	3	4
B8	I am bothered by a change in weight	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4

Patient Initials/Signature: _____

Date: _____

Patient ID: _____
Date: _____
Visit#: _____

FACT-ES (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some -what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some -what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Patient ID: _____
Date: _____
Visit#: _____

FACT-ES (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Patient ID: _____
Date: _____
Visit#: _____

FACT-ES (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
ES1	I have hot flashes	0	1	2	3	4
ES2	I have cold sweats	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
ES4	I have vaginal discharge	0	1	2	3	4
ES5	I have vaginal itching/irritation	0	1	2	3	4
ES6	I have vaginal bleeding or spotting	0	1	2	3	4
ES7	I have vaginal dryness	0	1	2	3	4
ES8	I have pain or discomfort with intercourse	0	1	2	3	4
ES9	I have lost interest in sex	0	1	2	3	4
ES10	I have gained weight	0	1	2	3	4
An9	I feel lightheaded (dizzy)	0	1	2	3	4
O2	I have been vomiting	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
An10	I get headaches	0	1	2	3	4
Tax1	I feel bloated	0	1	2	3	4
ES11	I have breast sensitivity/tenderness	0	1	2	3	4
ES12	I have mood swings	0	1	2	3	4
ES13	I am irritable	0	1	2	3	4
BRM 1	I have pain in my joints	0	1	2	3	4

Patient Initials/Signature: _____

Date: _____

Patient ID: _____
Date: _____
Visit#: _____

Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the situations described below, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the most appropriate number for each situation:-

0 = Would never doze
1 = Slight chance of dozing
2 = Moderate chance of dozing
3 = High chance of dozing

Situation	Chance of dozing
Sitting and reading.....	
Watching TV.....	
Sitting, inactive in a public place (e.g. a theatre or a meeting).....	
As a passenger in a car for an hour without a break.....	
Lying down to rest in the afternoon when circumstances permit.....	
Sitting and talking to someone.....	
Sitting quietly after a lunch without alcohol.....	
In a car, while stopped for a few minutes in the traffic.....	

Patient Initials/Signature: _____

Date: _____

Patient ID: _____
Date: _____
Visit#: _____

BERLIN QUESTIONNAIRE

Height (m) _____ Weight (kg) _____ Age_____ Male / Female

Please choose the correct response to each question.

CATEGORY 1

1. **Do you snore?**
   - ☐ a. Yes
   - ☐ b. No
   - ☐ c. Don't know

If you snore:

2. **Your snoring is:**
   - ☐ a. Slightly louder than breathing
   - ☐ b. As loud as talking
   - ☐ c. Louder than talking
   - ☐ d. Very loud – can be heard in adjacent rooms

3. **How often do you snore?**
   - ☐ a. Nearly every day
   - ☐ b. 3-4 times a week
   - ☐ c. 1-2 times a week
   - ☐ d. 1-2 times a month
   - ☐ e. Never or nearly never

4. **Has your snoring ever bothered other people?**
   - ☐ a. Yes
   - ☐ b. No
   - ☐ c. Don't Know

5. **Has anyone noticed that you quit breathing during your sleep?**
   - ☐ a. Nearly every day
   - ☐ b. 3-4 times a week
   - ☐ c. 1-2 times a week
   - ☐ d. 1-2 times a month
   - ☐ e. Never or nearly never

CATEGORY 2

6. **How often do you feel tired or fatigued after your sleep?**
   - ☐ a. Nearly every day
   - ☐ b. 3-4 times a week
   - ☐ c. 1-2 times a week
   - ☐ d. 1-2 times a month
   - ☐ e. Never or nearly never

7. **During your waking time, do you feel tired, fatigued or not up to par?**
   - ☐ a. Nearly every day
   - ☐ b. 3-4 times a week
   - ☐ c. 1-2 times a week
   - ☐ d. 1-2 times a month
   - ☐ e. Never or nearly never

8. **Have you ever nodded off or fallen asleep while driving a vehicle?**
   - ☐ a. Yes
   - ☐ b. No

If yes:

9. **How often does this occur?**
   - ☐ a. Nearly every day
   - ☐ b. 3-4 times a week
   - ☐ c. 1-2 times a week
   - ☐ d. 1-2 times a month
   - ☐ e. Never or nearly never

CATEGORY 3

10. **Do you have high blood pressure?**
   - ☐ Yes
   - ☐ No
   - ☐ Don't know

Patient Initials/Signature: _____ Date: _____

BERLIN QUESTIONNAIRE

Height (m) _____ Weight (kg)_____ Age_____ Male / Female

Please choose the correct response to each question.

CATEGORY 1

1. **Do you snore?**
   - ☐ a. Yes
   - ☐ b. No
   - ☐ c. Don't know

If you snore:

2. **Your snoring is:**
   - ☐ a. Slightly louder than breathing
   - ☐ b. As loud as talking
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CATEGORY 3

10. **Do you have high blood pressure?**
    - ☐ Yes
    - ☐ No
    - ☐ Don't know

Are you Planning to Start Radiation Treatment for Breast Cancer? Worried about Fatigue?

The Dana-Farber Cancer Institute and Brigham and Women's Hospital are seeking ***anyone 18 and over beginning radiation treatment for breast cancer*** to participate in an observational research study to monitor the development of fatigue during radiation.

Participation includes completion of weekly questionnaires from the start of radiation treatment to 4 weeks after treatment.

If you develop significant fatigue you ***may*** be eligible for supplemental treatment with an investigational drug.

If you are interested please contact study team at
DFCIRadiationFatigueStudy@partners.org

DANA-FARBER CANCER INSTITUTE

BRIGHAM AND WOMEN'S HOSPITAL

Are you Planning to Start Radiation Treatment for Breast Cancer? Worried about Fatigue?

The Massachusetts General Hospital Cancer Center is seeking ***anyone 18 and over beginning radiation treatment for breast cancer*** to participate in an observational research study to monitor the development of fatigue during radiation.

Participation includes completion of weekly questionnaires from the start of radiation treatment to 4 weeks after treatment.

If you develop significant fatigue you ***may*** be eligible for supplemental treatment with an investigational drug.

If you are interested please contact:

Lily at 617-726-1923 or email ldavis22@partners.org

Julia at 617-726-3196 or email jdalleva@partners.org

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

Subject ID:_____
Visit #:____ Date: ____/____/____

Clinical Variables

Radiotherapy-related variables (to be completed by dosimetrist or physicist):

Treated breast volume (cc): _____
Skin volume (cc) (optional - requires contouring): _____
Fractionation schedule
Fraction dose (Gy/cGy): _____
Number of fractions: _____
Number of fields (excluding subfields): _____
Circle if applicable: supraclavicular axillary
Boost modality (circle one): electrons mini-tangents
Boost fraction dose (Gy/cGy): _____
Number of boost fractions: _____
Boost target volume (cc): _____
V20, V5 ipsilateral lung (%): _____
V5 heart (%):_____

Mean heart dose (cGy): (optional) _____
Volume of tissue receiving 6000 cGy (cc): (optional) _____
Volume of tissue receiving 5000 cGy (cc): (optional) _____
Volume of tissue receiving 4000 cGy (cc): (optional) _____
Volume of tissue receiving 2000 cGy (cc): (optional) _____
Volume of tissue receiving 1000 cGy (cc): (optional) _____

Did subject miss >= 5 scheduled fractions? : yes no
If yes,
Reasons: severe skin reaction (yes/No)
Other causes: _____

Did subject miss >= 5 scheduled fractions? : ☐yes ☐no

Dermatologic variables

Fitzpatrick Scale (phototyping): (to be rated by CRC):

☐ type I: white skin, freckles, always burns, never tans
☐ type II: white skin, usually burns, tans minimally
☐ type III: cream-white skin, tans uniformly, occasionally burns
☐ type IV Mediterranean type skin color, rarely burns, always tans well
☐ type V: brown skin, very rarely burns, tans very easily
☐ type VI: very dark brown to black skin, never burns, tans very easily

Subject ID: _____
Visit #:____ Date: ____/____/____

Demographic Information

Age: _____ Date of Birth: ____/____/____

With what racial groups do you most closely identify?

- ☐ White/Caucasian
- ☐ Black or African-American
- ☐ Asian
- ☐ Native Hawaiian or other Pacific Islander
- ☐ Other (please specify)_____
- ☐ American Indian or Alaska Native
- ☐ Decline to answer

With what ethnic groups do you most closely identify?

- ☐ Hispanic/Latina
- ☐ Non-Hispanic/ Non-Latina
- ☐ Decline to answer

What is your marital status?

- ☐ Single (Never married)
- ☐ Divorced/ Separated
- ☐ Married
- ☐ Widowed
- ☐ Living in a marriage-like relationship

What is the highest level of schooling you have completed?

- ☐ Didn't go to high school
- ☐ Some high school
- ☐ High school diploma or GED
- ☐ Some college or technical school
- ☐ Graduated college (4 year college degree)
- ☐ Complete Graduate School

Employment Status (check all that apply)

- ☐ Full-time
- ☐ Student
- ☐ Part-time
- ☐ Retired
- ☐ Homemaker
- ☐ Disabled
- ☐ Unemployed
- ☐ Other, please specify_____

How many live births have you had? _____

How many children do you have living at home? _____

Cigarette smoking:

☐ Never

☐ Former, quit date ☐☐/☐☐☐☐ (month,year)

☐ Current (# Cigarettes/ day _____)

Current alcohol consumption:

☐ No

☐ Yes (Drinks/week _____)

What is your travel time to the radiation clinic (in minutes)?

_____

How much do you exercise, in a manner that raises your heart rate (average number of minutes per week)? _____

How much exposure to the sun have you gotten over the last month (average number of minutes per day)?

_____

Do you wear sunscreen and/or protective clothing when exposed to sun?

_____

What is your natural hair color? _____

Menopause

When was your last menstrual period?

Month_____ Year_____

Have you had a menstrual period in the last 5 months?

☐ No

☐ Yes

Did your menses stop or become irregular during chemotherapy?

☐ No

☐ Yes

☐ Not applicable

How old were you when you first started having hot flashes?

☐ Never had hot flashes

_____ years old

At what point did you begin having hot flashes? (Check all that apply.)

☐ Never had hot flashes
☐ When menstrual periods became irregular
☐ Had a hysterectomy
☐ When both ovaries were removed
☐ During or after chemotherapy
☐ After anti-estrogen therapy (Tamoxifen, Evista, Femara, Arimidex, Aromasin) was started
☐ Don't know
☐ Other (specify)_____

Fatigue

Have you ever had fatigue BEFORE breast cancer that interfered with your daily activities?

☐ No
☐ Yes

If yes ->

Please answer the following questions related to the period of MOST SEVERE fatigue you experienced in the past.

How old were you when you had this fatigue? ____

How long did it last? (in months) ____

If yes, what was the cause of the fatigue (check any/all that apply)?:

☐ Insomnia or sleep apnea
☐ Thyroid problems
☐ Menopause
☐ Stress or anxiety
☐ Depression
☐ Infection
☐ Asthma or allergies
☐ Anemia
☐ Don't know
☐ Other (specify)_____

Other medical problems

Have you ever experienced any of the following conditions:

- ☐ Insomnia
- ☐ Sleep apnea
- ☐ Thyroid problems
- ☐ Diabetes
- ☐ High blood pressure
- ☐ Depression
- ☐ Anxiety
- ☐ Anemia
- ☐ Asthma or allergies
- ☐ Other medical condition (specify)_____

Depression

Has a medical professional or mental health provider ever told you that you had depression?

- ☐ No
- ☐ Yes

How old were you when you first saw a doctor or other clinician about depression?
_____ years old

How old were you when you last saw a doctor or other clinician about depression?
_____ years old

Was your depression diagnosed BEFORE your breast cancer?

- ☐ No
- ☐ Yes

Have you ever been treated for depression?

- ☐ No
- ☐ Yes

If yes, what were you treated with?

- ☐ Antidepressant
- ☐ Therapy
- ☐ Other (specify)_____

Patient Initials/Signature: _____

Date: _____

Naltrexone RCT for Treatment-Emergent Fatigue in Women Receiving Radiation Therapy for Breast Cancer
Protocol 14-056

PI: Fremonta Meyer MD

Subject Exit Form

Subject ID: _____ **Date: ____ / ____ / ___**

Date of study termination (or last correspondence, if lost to follow-up): ____/_____/ __

Last Visit Completed: ____

Did subject receive study drug? ☐ Yes ☐ No
If yes, date when drug was initiated: ____/_____ / _____
date when drug was discontinued: _____/_____ / _____

Was the subject eligible for the intervention phase? ☐**yes** ☐**no**

Reason for ineligibility:
☐**FACIT-F drop of less than 10 points during radiotherapy**
☐**FACIT –F <=10 prior to radiotherapy**
☐**Major depression and/or suicidal ideation on PHQ9 (please circle which)**
☐**Recent use of opioids or expected requirement for opioids**
☐**Abnormal lab values (please specify which:)**

_____

☐**Other: (please specify)**

_____

_____

If ineligible for the intervention, did the subject complete the entire monitoring phase?
☐**yes** ☐**no**

_____

Reason for exiting either phase of study:

___ Requirement for opioids
___ Lost to follow up
___ Loss of interest
___ Too much time involved for participation
___Other (please specify): Adverse event
___ Geographic relocation
___ Development of medical safety issues
___ Noncompliance with visits

_____

Comment on reason for exiting study (optional):_____

_____

_____

PI: Fremonta Meyer MD
Who initiated termination: ___ Clinician ___ Subject

Form completed by: _____Date: ____/___/__ _

RA/PI Signature: _____ Date: ____/____/____

Patient ID: _____
Date: _____
Visit#: _____

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
1	I feel fatigued	**0**	**1**	**2**	**3**	**4**
2	I feel weak all over	**0**	**1**	**2**	**3**	**4**
3	I feel listless ("washed out")	**0**	**1**	**2**	**3**	**4**
4	I feel tired	**0**	**1**	**2**	**3**	**4**
5	I have trouble starting things because I am tired	**0**	**1**	**2**	**3**	**4**
6	I have trouble finishing things because I am tired	**0**	**1**	**2**	**3**	**4**
7	I have energy	**0**	**1**	**2**	**3**	**4**
8	I am able to do my usual activities	**0**	**1**	**2**	**3**	**4**
9	I need to sleep during the day	**0**	**1**	**2**	**3**	**4**
10	I am too tired to eat	**0**	**1**	**2**	**3**	**4**
11	I need help doing my usual activities	**0**	**1**	**2**	**3**	**4**
12	I am frustrated by being too tired to do the things I want to do	**0**	**1**	**2**	**3**	**4**
13	I have to limit my social activity because I am tired	**0**	**1**	**2**	**3**	**4**

Patient Initials/Signature: _____

Date: _____