Title page

EFFECTS OF FISH OIL AND PHYSICAL ACTIVITY ON FATIGUE IN PATIENTS WITH ADVANCED CANCER

Study Interventions:	Icosapent ethyl, matching placebo, and standardized Physical Activity
[Study purpose:]	Phase II preliminary efficacy trial
Clinical study phase:	II
Principal Investigator:	**Sriram Yennu, MD, MS** **Associate Professor** **University of Texas M.D. Anderson Cancer Center** **Department of Palliative, Rehabilitation, and Integrative Medicine – Unit 1414** **1515 Holcombe Blvd, Houston, TX 77030** **713-792-3938**
Co-Principal Investigator:	**Eduardo Bruera, MD** **Professor and Chair** **University of Texas M.D. Anderson Cancer Center** **Department of Palliative, Rehabilitation, and Integrative Medicine – Unit 1414** **1515 Holcombe Blvd, Houston, TX 77030** **713-792-6084**
Co-Investigators:	**Cathy Eng MD, Professor ; David Fogelman MD, Assistant Professor; Department of GI Medical Oncology; University of Texas M.D. Anderson Cancer Center** **Karen Basen-Engquist PhD, Professor, Department of Behavioral Science, University of Texas M.D. Anderson Cancer Center** **Kenneth Hess PhD, Professor; Diane Liu, Principal Statistical Analyst, Department of Biostatistics, University of Texas M.D. Anderson Cancer Center** **James Reuben PhD, Professor, Department of Hematopathology – Research, University of Texas M.D. Anderson Cancer Center** **Rony Dev MD, Associate Professor, Department of Palliative, Rehabilitation and Integrative Medicine**

Data Manager:

Janet L. Williams, MPH
Supervisor, Data Analysis
University of Texas M.D. Anderson Cancer Center
Department of Palliative, Rehabilitation and Integrative Medicine – Unit 1414
1515 Holcombe Blvd, Houston, TX 77030
713-792-9153

Statistician:

Kenneth Hess, PhD
Professor
University of Texas M.D. Anderson Cancer Center
Department of Biostatistics – Unit 1411
1515 Holcombe Blvd, Houston, TX 77030
713-794-4157

The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Synopsis

Title
Effects of fish oil and physical activity on fatigue in Patients with Advanced Cancer
Clinical study phase : II

Study objective(s)

Primary Objective: 1. To determine the effect of the combination of Icosapent ethyl 2 gm orally daily plus physical activity for the reduction of cancer related fatigue [FACIT-F subscale] at the end of 8 weeks in patients with advanced cancer by comparing the difference between the FACIT-F subscale score at baseline and at 57±5 days, between patients who will receive either Icosapent ethyl plus physical activity and placebo plus physical activity.

Secondary Objectives:

1. To determine the feasibility, adherence, and satisfaction of using the combined intervention for the reduction of cancer related fatigue in patients with advanced cancer.

2. To explore the effects of the combination of Icosapent ethyl 2 gm orally daily plus physical activity on quality of life-related variables, mood (HADS – Hospital Anxiety and Depression Inventory), quality of life domains (FACT-G), Cancer related Symptoms (Edmonton Symptom Assessment Scale – ESAS) in these patients.

3. To explore the effects of combined intervention on serum C - reactive protein and intracellular cytokine levels [IL-6, TNF-α, IL-10, IL-1RA] before and after treatment.

4. To explore its side effects and tolerability of the combined study interventions in these patients.

5. To explore the effect of multimodal therapy on body composition.

6. To explore the effect of the proposed treatment in this study on the overall survival time in patients.

We hypothesize that:

- The combination of Icosapent ethyl plus physical activity is capable of significantly reducing the severity of CRF between baseline and end of week 8 [FACIT-F subscale].
- Physical activity is capable of reducing the severity of CRF between baseline and end of week 8.

Background

Cancer-related fatigue (CRF) is the most frequently reported symptom associated with cancer and its treatment. CRF is more severe and debilitating in patients with advanced cancer than in those with early cancer or in cancer survivors. Its frequency ranges from 60% to 90% in patients who are receiving palliative care. As a result of improved therapy, patients with advanced cancer are living longer, and due to advances in treatment for pain and nausea, clinicians are more frequently recognizing CRF as an important symptom that negatively affects quality of life (QOL), interferes with daily activity, has

potentially devastating social and economic consequences, and affects the ability to receive palliative cancer therapy. However, only few studies have been conducted to determine whether established therapies for CRF such as physical activity are effective in palliative care patients. In addition, prior pharmacological studies for CRF in palliative care have shown mixed results. Given the high frequency of adverse effects of CRF and the limited treatment options in advanced cancer patients, further research on new treatment strategies is greatly needed. The rationale for the proposed study is that, CRF is a frequent and serious consequence of cancer and cancer related treatment. As palliative care moves to early integration, palliative care is increasingly been provided in an outpatient setting, a vast majority of advanced cancer patients are receiving some form of active therapy such as targeted therapy. CRF is common, limits the use of targeted therapy in advanced cancer patients and significantly impacts QOL. Several strategies have been proposed for management of CRF, none of these strategies result in clinically relevant improvement (defined as at least 10 point improvement in the Functional Assessment of Cancer Illness Therapy-Fatigue (FACIT-F) scores or equivalent in other validated scales) of CRF despite showing modest benefit as compared to placebo. The most plausible reason is that these interventions have been unable to target the multifactorial target mechanisms that cause CRF. Our group has shown that dexamethasone results in improvement of fatigue; however, these agents may be useful only for a short duration due to the side-effect profile. On the basis of previously described mechanisms and the results of pilot studies, Ecosapentaenoic Acid (EPA) or fish oil has beneficial effect on fatigue in patients with cancer. Previous fish oil studies however had several limitations including the dose (low dose <2gm), short duration of treatment (~3 weeks), number of capsules (>10), and no validated measure for fatigue such as FACIT-F. The duration of efficacy, and possible mechanisms EPA in reduction of CRF, has not been characterized. In addition, not all assessment tools used in previous studies were validated, and there was no attempt to understand the pathophysiologic characteristics of EPA using laboratory correlates in fatigued cancer patients. The effects of EPA on CRF and cytokine levels must be defined through randomized controlled studies using validated tools and laboratory correlates. In cancer patients receiving treatment and in cancer survivors, physical activity (PA) or exercise has been shown to improve CRF. Randomized clinical trials among cancer patients who participated in an physical activity program showed significant increases in cardiovascular capacity; improved overall health-related QOL; less fatigue; fewer sleeping problems; and increased self-reported physical functioning, general well-being, self-esteem, and energy. A recent Cochrane meta-analysis of 28 clinical trials that included more than 2,000 cancer patients confirmed these findings. However, the evidence suggests that physical activity has a very modest benefit (effect size 0.23) in improving CRF. This lack of robust response (defined as >/=10 points on the FACIT-F subscale) to these treatments may be due to a lack of effect on the multidimensional and multifactorial nature of CRF. Hence there is a need to test combined therapies for CRF such as fish oil plus physical activity, since these treatments individually target the multidimensional causative factors contributing to CRF in advanced cancer.

Indication Cancer Related Fatigue

Diagnosis and main criteria for inclusion

Inclusion:

1) Diagnosis of advanced cancer
2) Patients should describe fatigue as being present for a minimum of 2 weeks

3) Patients should rate the severity of fatigue as 4/10 in a 0-10 ESAS scale, where 0=no fatigue, 10= worse fatigue possible
4) If patients are on opioids for the treatment of cancer pain, they must have had no major dose change (>25%) for at least 48 hours prior to study entry. Change in opioid dose after study entry is allowed
5) Presence of relatively intact cognition defined by normal memorial delirium assessment scale (<7/30); sign written informed consent
6) Patients must be 18 years or older
7) Patient willing to keep a daily diary, engage in telephone follow up with a nurse
8) Patient must have telephone access to be contacted by the research nurse
9) Hemoglobin of >/=10 g/dl within 2 weeks of enrollment. If the patient has not had blood drawn for a hemoglobin level in the past two weeks, one will be done to determine the eligibility
10) Patients should have a Zubrod </= 1

Exclusion:

1) Major contraindication to fish oil i.e. hypersensitivity to fish/oil or physical activity
2) Currently on fish oil or has been on fish oil within the last 10 days
3) Inability to complete the baseline assessment forms or to understand the recommendations for participation in the study
4) Pregnant or lactating women. Childbearing age women are not on birth control
5) Reports a fall in the past 30 days
6) Patient reported regular participation in moderate- or vigorous-intensity physical activity for at >/=30 minutes at least 5 times a week and strength training for >/=2 days/week
7) Active or clinically significant cardiac disease (e.g., New York Heart Association functional class II or more)
8) Signs of third spacing as determined by the treating physician (e.g., pedal edema, pleural effusion, ascites)

Study design

We will randomize 96 eligible patients in the Biostatistics Clinical Trial Conduct website to receive either Icosapent ethyl 2 gm orally daily plus physical activity, or placebo plus physical activity, or placebo plus control physical activity (1:1:1) for 8 weeks

Type of control

In this randomized controlled study, patients will be randomized to either combination of Icosapent ethyl 2 gm orally daily plus physical activity; or placebo plus physical activity or placebo plus control physical activity for 8 weeks. The placebo will appear identical to the drug, but will contain methylcellulose as the inert ingredient. Assessment will be performed at baseline to Day 57±5 ±5 as per Table 4. In the proposed study we plan to use fish oil preparation, Icosapent ethyl [an ethyl ester of EPA] 0.5 gram capsules [Amarin Pharma Inc, Bedminster, NJ, 2012]. The objective of 8 weeks of treatment is to evaluate the efficacy of the combined intervention for cancer related fatigue.

The rationale for placebo and control arm for physical activity is to control for placebo effect, attention to participants' expectation and the subjective elements of diagnosis or assessment. See Table 4 for the study assessments. All patients at the primary end point (8 weeks) will have an option to receive Icosapent ethyl 2 gm orally daily plus physical activity for 4 more weeks in an open label basis.

Number of subjects
96 patients

Plan for statistical analysis

The primary objective is to study is to determine the difference between the FACIT-F subscale score at baseline and at Day 57±5 ± 5 days, between patients who will receive either fish oil and exercise and placebo and exercise.

In a recent cancer related intervention study by our team using oral dexamethasone (DM) compared to placebo was associated with improvement in FACIT-F subscale scores (mean, SD) of 9.6 (11) vs. 3.1 (9.7) (p=0.005) at day 15. However, we are investigating a different intervention (combination of fish oil and physical activity) and therefore we propose to detect a FACIT-F subscale change of 9.5 (standard deviation of 10) in Icosapent ethyl 2 gm orally daily plus physical activity group against 3 (standard deviation of 10) in placebo plus physical activity group, with 30 patients in each group, we have an 80% power to detect this difference (effect size 0.65) using a two-sided t-test with a significance level of 0.10. We will also collect information regarding the change in FACIT-F subscale score in 30 patients with placebo plus control physical activity, although not being compared with patients on fish oil and exercise. With a total of 30 patients in this group, we will have an 80% power to detect an effect size of 0.465 in the change in FACIT-F subscale score using a single group t-test with a 0.100 two-sided significance level. We will enter a total of 96 patients to allow for possible 5% dropout rate. For the primary endpoint, we will compare the difference between the FACIT-F subscale score at baseline and at 57±5 days, between patients who will receive Icosapent ethyl plus physical activity and placebo plus physical activity using t-test. Wilcoxon rank sum test may be considered if the distribution of the data is not normal. We will also compare the change of FACIT-F subscale scores among all three groups using ANOVA or Kruskal-Wallis test, whichever appropriate. At the end of the study, overall survival time in each group will be estimated using Kaplan-Meier method and may be compared among three treatment groups using log-rank test.

Adherence will be calculated as the % of total prescribed strength training sessions, the % of total prescribed walking regimen minutes completed (physical activity), and the percentage of total prescribed pills taken (study medication). The adherence rate, as defined, is a continuous variable. At the end of the study, we will estimate the average adherence of prescribed strength, of total prescribed walking regimen minutes and of total prescribed pills taken separately using mean, standard deviation, median, and range. The adherence rate can also be compared among all three groups using Kruskal-Wallis test. We will estimate 95% confidence intervals for the proportion of patients completing the intervention, the adherence rate, and the proportion of patients with a satisfaction over time. With 30 patients in each arm, a 95% confidence interval for a proportion of 73% (22/30), for example, can be estimated as (54%, 88%).

Data of variables of interest will be summarized using standard descriptive statistics, such as mean, standard deviation, median, and range for continuous variables, frequency and proportion for categorical variables. Correlation will be assessed among continuous variables using Pearson or Spearman correlation coefficient, whichever is appropriate. Association between categorical variables will be examined by Chi-Squared test or Fisher's exact test when appropriate. Boxplot and histogram will be applied to demonstrate distribution of variables of interest.

Since FACIT-F scores will be obtained at 0, 15, 29, 43 and 57±5 days, and other QOL variables and cytokine markers will also be obtained repeatedly over time, we will also evaluate the effect of treatment on the changes of these measured over time using repeated measure analysis in which intra-patient correlation of the measures are accounted for. However due to the small scale and exploratory nature of the study, we will report p-value as is without adjusting for multiplicity.

To address issues related to missing data, we may perform multiple imputation analyses. If the data does not appear to be normally distributed, transformation may be employed to the data, or appropriate nonparametric methods will be used for data analysis. Toxicity data will be summarized by treatment, grade and relationship using frequencies and cross-tabulation.

List of abbreviations

ADL	Activities of Daily Living
AE	Adverse Events
ALT	Alanine aminotransferase
Ang	Angiopoietin
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BID	bis in die, twice daily
BUN	Blood Urea Nitrogen
c-KIT	Stem Cell Factor Receptor Tyrosine Kinase
CAM	Complementary and Alternative Medicine
CR	Complete Response
C-RAF	C isoform of Rapidly Accelerated Fibrosarcoma protein
CRF	Cancer-related Fatigue
CRP	C-Reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
DCE	Dynamic Contrast Enhanced
DM	Dexamethasone
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EORTC-QLQ-30	European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire
EPA	Ecosapentaenoic Acid
ERK	Extracellular Signal-regulated Kinases
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FACT-G	Functional Assessment of Cancer Therapy -- General
FDA	Food and Drug Administration
FGFR	Fibroblast Growth Factor Receptor
FLT3	FMS-like Tyrosine Kinase 3
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HCC	Hepatocellular Carcinoma
HFSR	Hand-foot-skin reaction

IB	Investigator's Brochure
IC50	Half Maximal Inhibitory Concentration
HADS	Hospital Anxiety and Depression Inventory
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IR	Immediate Release
IRB	Institutional Review Board
MAPK	Mitogen Activated Protein Kinase
mCRC	Metastatic colorectal cancer
MEK	MAP Kinase / ERK Kinase 1
MFSI-SF	Multidimensional Fatigue Symptom Inventory-Short Form
NM	Nano molar
NYHA	New York Heart Association
PA	Physical Activity
PD	Progressive Disease
PFS	Progression free survival
PO	per oris, oral
PR	Partial Response
PROMIS	Patient Reported Outcomes Measurement Information System
PS	Performance Status
PSQI	Pittsburgh Sleep Quality Index
PTT	Partial thromboplastin time
QD	quaque die, once daily
QOL	Quality of Life
RAF	Rapidly Accelerated Fibrosarcoma
RAS	Rat sarcoma
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria for Solid Tumors
RET	Rearranged during transfection
RTK	Receptor Tyrosine Kinase
SAE	Serious Adverse Event
SD	Stable Disease
SUSARs	Suspected Unexpected Serious Adverse Reactions
TIE2	Tyrosine kinase with Immunoglobulin and Epidermal Growth Factor (EGF) homology domain 2
TTP	Time to Progression
UTMDACC	University of Texas M.D. Anderson Cancer Center
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor

1. Introduction

1.1 Background

Cancer related fatigue (CRF) is a frequent and serious consequence of cancer and cancer related treatment (Yennurajalingam et al. 2010; 2012). As a result of improved therapy, patients with advanced cancer are living longer, and due to advances in treatment for pain and nausea, clinicians are more frequently recognizing CRF as an important symptom that negatively affects quality of life (QOL), interferes with daily activity, has potentially devastating social and economic consequences, and affects the ability to receive palliative cancer therapy.[6] CRF is common, limits the use of targeted therapy in advanced cancer patients and significantly impacts QOL An explorative study indicate that compared with cancer survivors, patients with advanced cancer had higher levels of physical fatigue. [12] Several strategies have been proposed for management of CRF including physical activity, erythropoietin stimulating agents and psychostimulants.[1] However, none of these strategies result in clinically relevant improvement (defined as at least 10 point improvement in the Functional Assessment of Cancer Illness Therapy-Fatigue (FACIT-F) scores or equivalent in other validated scales) of CRF despite showing modest benefit as compared to placebo (Reddy S et al. 2007). The most plausible reason is that these interventions have been unable to target the multifactorial target mechanisms that cause CRF.

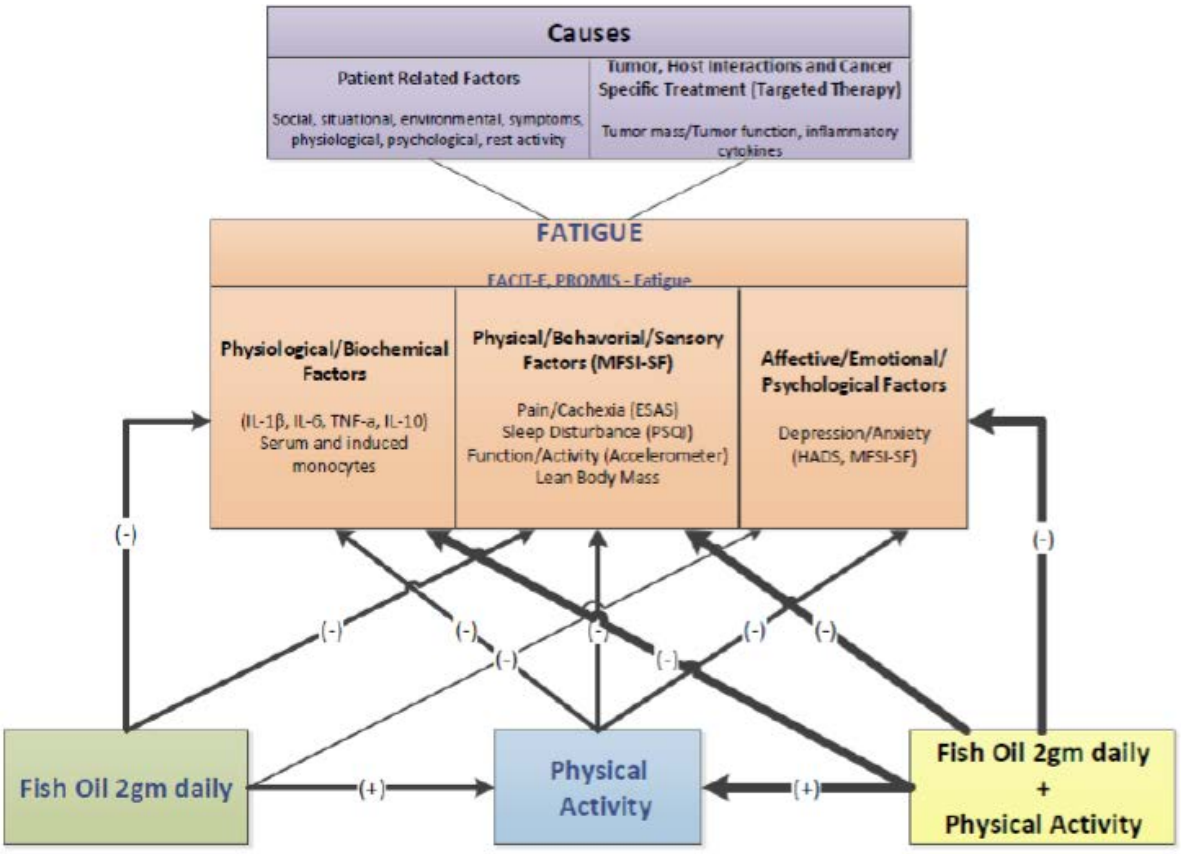

Figure 1. Conceptual Model (adaptation of the integrated Fatigue Model) shows various causative factors of multidimensional fatigue and potential targets of the study interventions, darker lines indicate stronger relationship.

In cancer patients receiving treatment and in cancer survivors, PA or exercise has been shown to improve CRF (Cramp F et al. 2012). Randomized clinical trials among cancer patients who participated in an PA program showed significant increases in cardiovascular capacity; improved overall health-related QOL; less fatigue; fewer sleeping problems; and increased self-reported physical functioning, general well-being, self-esteem, and energy [17, 18]. Published data from studies by Bourke et al.(n=18) [19], Valence et al. (n=178) [20], and Shariah et al.(n=36)21 support beneficial effects of PA in patients colorectal cancer. A recent Cochrane meta-analysis (Cramp F et al. 2012) of 28 clinical trials that included more than 2,000 cancer patients confirmed these findings. However, the evidence suggests that PA has a very modest benefit (effect size 0.23) in improving CRF [22]. This lack of robust response (defined as ≥10 points on the FACIT-F subscale) 13 to these treatments may be due to a lack of effect on the multifactorial nature of CRF [23]. Hence there is a need to test combined therapies for CRF such as fish oil with physical activity, since these treatments individually target the multidimensional causative factors contributing to CRF in advanced cancer.

Conceptual Model: We adapted the Integrated Fatigue Model (Fig. 1) for this study to explain the complex multifactorial etiology of CRF and its treatments.[24, 25] Physical, behavioral, affective, and physiological/biochemical factors are the manifestation of multidimensional CRF in advanced cancer. PA or Exercise uniquely affects health-related fitness outcomes, anxiety, depression, inflammation and cognition that have been shown to mediate CRF.[3, 26] Fish Oil has direct central nervous system effects, pain, mood, cachexia inflammation, which can affect CRF.[8, 27] Exercise modulates the effect of the inflammatory cytokines that are significantly associated with moderate to severe CRF.3, 28, 29 Therapies combining exercise with fish oil have the potential to improve CRF directly, but they may also improve CRF through their joint effects.

1.2 Rationale of the study

Our group has shown that anti-inflammatory agents such as dexamethasone results in clinically significant improvement of fatigue; however, these agents are useful only for a short duration due to the side-effect profile (Yennurajalingam et al. 2013). On the basis of previously described mechanisms and the results of pilot studies, Ecosapentaenoic Acid (EPA) or fish oil has a beneficial effect on fatigue, primarily in the general population and in patients with cancer. [15, 16] Previous fish oil studies had several limitations including the dose (low dose <2gm), short duration of treatment (2-3 weeks), number of capsules (>10), and no validated measure for fatigue such as FACIT-F. The duration of efficacy, and possible mechanisms Icosapent ethyl [an ethyl ester of EPA] in reduction of CRF, has not been characterized. In addition, not all assessment tools used in previous studies were validated, and there was no attempt to understand the pathophysiologic characteristics of Icosapent ethyl using laboratory correlates in fatigued cancer patients. The effects of Icosapent ethyl on CRF and cytokine levels must be defined through randomized controlled studies using validated tools and laboratory correlates.

Significance: CRF is more severe and debilitating in patients with advanced cancer than in patients with early cancer or in cancer survivors.[1, 3, 30] However, because of the limited number of clinical trials

studying CRF in advanced cancer as a primary outcome, few standard treatment options currently exist.[3, 8, 31, 32] Recently, the National Institutes of Health state-of-the-science Conference issued a statement that calls for the development of new treatments for CRF.[3, 23, 33] They stated that "Studies are needed to investigate the effectiveness of combinations of both pharmacologic and non-pharmacologic treatments." The results of the proposed project would help us prescribe a safe and effective intervention, treatments that have shown preliminary evidence of efficacy in improving CRF in advanced cancer patients.[3] The proposed research is significant because it will be the first to test the effects of the combination of Icosapent ethyl 2 gm orally daily plus PA in advanced cancer patients, a group that is living longer as more treatments are available yet experience the most severe levels of CRF among cancer patients because of the lack of effective treatment options.[1, 6] As preliminary studies[22, 34-36] indicate, we anticipate that this combination therapy, if effective, will provide more robust and clinically effective improvement of CRF,[13] which would facilitate patients continuing cancer therapy since it would be tolerated and effective in controlling disease. This study will provide important evidence to show the joint effects of fish oil and PA in improving CRF. Other important benefits of this study are that it will provide important data on the role of combination intervention in other QOL measures such as anxiety, depression, and the role of combined interventions on objective measures of physical activity, strength, and pro-inflammatory cytokines.

1.4. Preliminary Studies

Pharmacologic Treatment of Fatigue: Our team's studies in patients with advanced cancer allowed us to establish the high frequency, severity and multifactorial nature of fatigue.[4, 34-37, 40, 44-48] We conducted studies of various assessment methods for fatigue and were able characterize fatigue in this patient population.[4, 49-52] In a preliminary study of 31 advanced cancer patients, we found that methylprednisolone 32mg/day significantly improved CRF ($p<0.01$) compared with placebo with no significant differences in side-effects between groups.[35] As shown in Table 1, this study was unable to detect sustained responses to Day 33 perhaps due to low doses, type of the steroid, and lack of validated tools. In a recently published36 RCT study of 84 patients with advanced cancer, oral Dexamethasone (DM) at 8 mg/day for 14 days was found to be effective in alleviating CRF compared with placebo. The mean improvement in the FACIT-F subscale at Day 15 was significantly higher in the DM group than in the placebo (9 [10.3] vs. 3.1 [9.59], P=0.008).[36]

Prior EPA (fish oil) study by our team in advanced cancer patients:

Our team conducted a study in 60 advanced cancer patients with decreased weight and appetite who were randomly assigned to fish oil capsules or placebo (daily dose of 18 gelatin capsules containing either 1,000 mg of fish oil (Marine Lipid Concentrate Capsule [Banner Pharmacaps, Halifax, Canada] containing 180 mg of EPA, 120 mg of docosahexaenoic acid [DHA], and 1 mg of vitamin E) or 1,000 mg of a placebo (olive oil) [16]. Appetite, tiredness, nausea, well-being, caloric intake, nutritional status, and function were prospectively assessed at days 1 and 14. Fish oil did not significantly influence appetite, tiredness, nausea, well-being, caloric intake, nutritional status, or function after 2 weeks compared with placebo in patients with advanced cancer and loss of both weight and appetite. The tiredness or fatigue improved significantly ($p= 0.04$) in patients who received higher dosage (Table 1). However the dose (1.8gm of EPA, short duration of treatment (2 weeks), number of capsules, and no validated measure for fatigue were the limitations of this study.

Table 1. Differences between Placebo and Fish Oil group at Baseline and Day 14

Variable*	Placebo† (n = 30)	P‡	Fish Oil† (n = 30)	Correlation‡ with Dose r	P
Appetite VAS, 0–100 mm	−9.0 ± 27	NS	−9.8 ± 20	0.15	NS
Tiredness VAS, 0–100 mm	4.2 ± 33	.19	−5.5 ± 22	0.38	.04
Nausea VAS, 0–100 mm	0.5 ± 37	NS	−5.2 ± 22	−0.28	.13
Overall well-being VAS, 0–100 mm	−9.8 ± 32	NS	−4.6 ± 20	0.08	NS
Weight, kg	−0.89 ± 3.8	NS	0.03 ± 2.8	0.008	NS
Caloric intake, kcal	−57 ± 1299	NS	51 ± 1177	−0.06	NS
KPS, score, 0–100	−6.9 ± 10	NS	0.0 ± 8	−0.19	NS
EFAT, score, 0–30	0.2 ± 2	NS	0.3 ± 3	0.04	NS

*Data are shown as the mean ± SD and report the difference between day 14 and baseline (negative numbers denote improvement in VAS).
†Differences in the fish oil and placebo group, respectively.
‡Pearson's correlation between the number of capsules taken and the variable (fish oil group only).

Prior PA Studies by our team:

Prior studies led by Dr. Basen-Engquist tested interventions in patients with highly symptomatic prostate cancer (TPRB-98-103-01-PBP)[53], mCRC, and in breast cancer (CA89519).[54] The breast cancer study showed improved 6-minute walk performance and QOL.[54] In an R01-funded study of PA in endometrial cancer survivors,[55] the intervention was completed with a high percentage and was well received among the participants. The same methods will be used in the proposed study. In the next few months, a 154 person trial comparing a home-based PA intervention to a relaxation intervention for improving physical functioning and managing symptoms in advanced colorectal cancer patients (R21 CA137333) will be completed. To date only 5 patients in the PA arm have experienced adverse events (AE; 9 AE total, 1 definitely attributable to physical activity, 8 possibly attributable. All AE were grade 1 (5) or grade 2 (4). None of the AEs were due to falls.

An ongoing study in highly symptomatic prostate cancer patients, NCT01410942, conducted by the same team as that in the proposed study (PI: Yennu; Dr. Basen-Engquist (Co-I), uses the same standardized exercise regimen in combination with study drug. Table 2 shows the adherence rates and safety data of the first 12 patients enrolled (blinded). The enrolled patients in this ongoing study had no difficulty in completing all the assessments. Based on the preliminary data presented, we conclude that this proposed PA would be feasible and safe.

Table 2. Preliminary adherence rates and safety data of first 12 patients (blinded)

Preliminary data of adherence and safety of exercise and attention control exercise patients on an ongoing multimodal fatigue study (NCT01410942)							
Pt. no	% calls completed	Goals met week 2	Goals met week 3	Goals met week 4	Goals met week 5	Goals met week 6	Exercise side effects
1	100%	yes	yes	yes	yes	yes	none
2	100%	yes	yes	no/ foot pain	yes	yes	none
3	100%	no/back pain	no/back pain	no/epidural back	no	yes	none from exercise
4	100%	yes	yes	no/fatigue	yes	yes	none
5	100%	yes	no/no time	no/no reason	yes	yes	none
6	100%	no/soreness	no/no time	no/fatigue	no	no/fatigue	soreness
7	40%	no	no answer	no answer	no answer	yes	none
8	100%	no	no/no time	yes	no	no/shoulder pain	yes/shoulder pain
9	80%	no/fatigue	no	no/no time	no answer	no	none
10	60%	yes	no/fatigue	no/no time	w/d	w/d	none
11	withdrew						
12	80%	no/fatigue	yes	no/fatigue	no answer	yes	fatigue

Prior Inflammatory cytokine and CRF studies by our team:
Prior studies [56-59] by our group showed wide variability in serum cytokine levels in patients with advanced cancer and hence the need to assess cytokines levels in LPS activated monocytes. PA results in modulation of TNF-α, IL-1β, and IL-6,[60] interleukin-1 receptor antagonist (IL-1RA), TNF-receptors (TNF-R), and IL-10 levels.[61] Since most of these factors are produced by activated monocytes/macrophages, we propose to assess the synthesis of these factors by resting (unstimulated) as well as LPS-activated peripheral blood monocytes isolated from patients before and after study treatment.

Figure 2 shows the synthesis of TNF-α by LPS-activated monocytes isolated from patients at baseline (D0) and at weeks 1- 5 after treatment with dexamethasone (DM). In patients treated with 8 mg DM daily (dark histograms), the percentage of LPS-activated monocytes that synthesized TNF-α decreased, whereas in patients receiving placebo (light histograms) for the first 2 weeks there was no change in the percentage of LPS-activated monocytes that synthesized TNF-α from D0 until week 2. Thereafter, when placebo patients (light histograms) switched to open-label DM, there was a decrease in the percentage of LPS-activated monocytes that synthesized TNF-α. Hence analyses of the levels of cytokines from induced monocytes would help to determine their association with change CRF and treatment, as shown in our previous studies.[34, 57, 62]

Change in TNF-α production by LPS-activated monocytes from dexamethasone-treated patients and placebo-treated patients in double-blind phase (Days 8 and 15) and in dexamethasone-only open-label phase (Days 29 and 35).

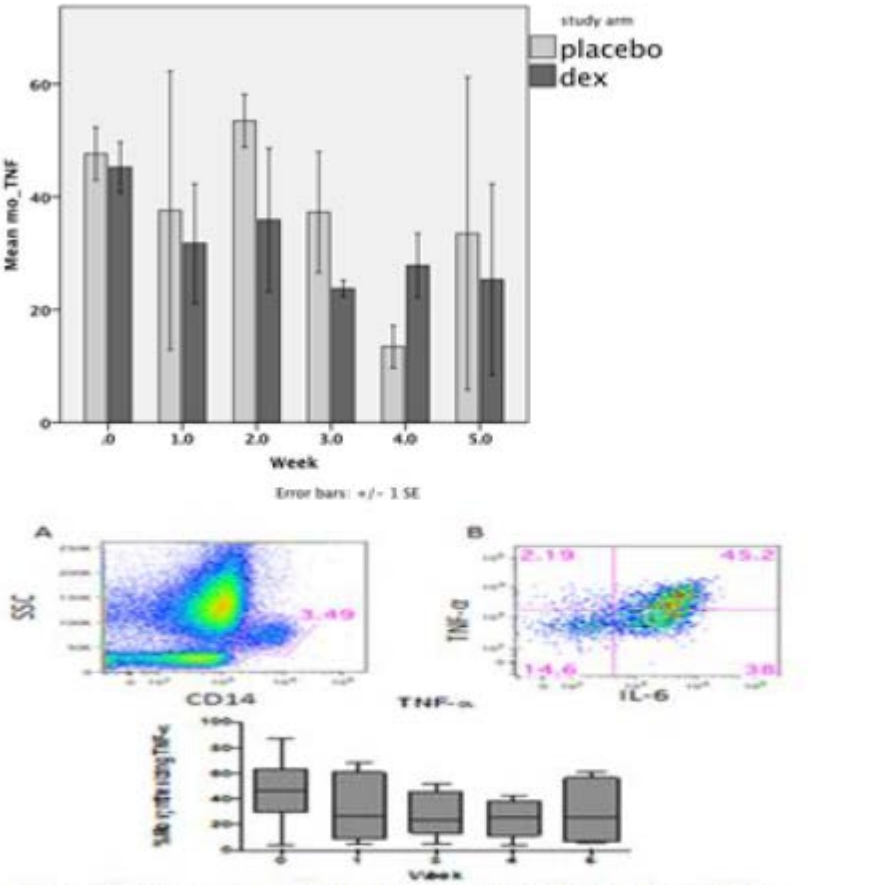

Figure 2. Monocyte Phenotype and LPS-induced cytokine synthesis. (A) Monocytes are enumerated in whole blood as $CD14^{+}SSC^{mid}$ cells. (B) After a 4 hour incubation with LPS, the percentage of cell synthesizing cytokines can be enumerated. C) TNF-α synthesis by monocytes decreases in patients treated with 8mg dexamethasone daily.

2. Study objectives

Primary Objective: 1. To determine the effects of the combination of Icosapent ethyl 2 gm orally daily plus PA for the reduction of cancer related fatigue [FACIT-F subscale] at the end of 8 weeks in patients with advanced cancer by comparing the difference between the FACIT-F subscale score at baseline and at 57*±5* days, between patients who will receive either Icosapent ethyl plus PA or placebo plus physical activity.

Secondary Objectives:

1. To determine the feasibility, adherence, and satisfaction of using the combined intervention for the reduction of cancer related fatigue in patients with advanced cancer.

2. To explore the effects of the combination of Icosapent ethyl 2 gm orally daily plus PA on quality of life-related variables, mood (HADS – Hospital Anxiety and Depression Inventory), quality of life domains (FACT-G), Cancer related Symptoms (Edmonton Symptom Assessment Scale – ESAS) in these patients.

3. To explore the effects of combined intervention on serum C - reactive protein and intracellular cytokine levels [IL-6, TNF-α, IL-10, IL-1RA] before and after treatment.

4. To explore its side effects and tolerability of the combined study interventions in these patients.

5. To explore the effect of multimodal therapy on body composition.

6. To explore the effect of the proposed treatment in this study on the overall survival time in patients

We hypothesize that:

- The combination of Icosapent ethyl plus PA is capable of significantly reducing the severity of CRF between baseline and end of week 8 [FACIT-F subscale].
- Physical activity is capable of reducing the severity of CRF between baseline and end of week 8.

3. Investigator[s] and other study participants

Principal Investigator: Sriram Yennu MD, MS, UT MD Anderson Cancer Center (UTMDACC)

Co- Principal Investigator: Eduardo Bruera MD, UT MDACC;

Co- Investigators: Cathy Eng MD; David Fogelman MD; Karen Basen-Engquist PhD;

Rony Dev MD, James M Reuben PhD, Kenneth Hess, and Diane Liu MS, UT MDACC.

4. Study Design

4.1 Study population

Patients with advanced cancer will be recruited from UTMDACC. At UTMDACC, patients will be recruited from medical oncologists working in outpatient clinics, and in our own outpatient supportive care center. Patients will be screened for eligibility criteria. Patients who are eligible and who provide written informed consent to participate in this research study will be admitted to the double-blind phase of the study described below. Consent forms and assessments will be available and administered by the study-assigned research nurse. Feasibility: Is based on the prior successful accrual in similar symptom control trials by our group in these sites and great interest in Complementary and Alternative Medicine (CAM) in this population (48%).

5. Eligibility

5.1.1 Inclusion criteria

Inclusion Criteria:

a) Diagnosis of advanced cancer

b) Patients should describe fatigue as being present for a minimum of 2 weeks;

c) Patients should rate the severity of fatigue as 4/10 in a 0-10 ESAS scale, where 0=no fatigue, 10= worse fatigue possible;

d) If patients are on opioids for the treatment of cancer pain, they must have had no major dose change (>25%) for at least 48 hours prior to study entry. Change in opioid dose after study entry is allowed;

e) Presence of relatively intact cognition defined by normal memorial delirium assessment scale (<7/30); sign written informed consent;

f) Patients must be 18 years or older. The questionnaires used in this study have been validated only in the adult population;

g) Patient willing to keep a daily diary, engage in telephone follow up with a nurse;

h) Patient must have telephone access to be contacted by the research nurse;

i) Hemoglobin of >/=10 g/dl within 2 weeks of enrollment. If the patient has not had blood drawn for a hemoglobin level in the past two weeks, one will be done to determine the eligibility.

j) Patients should have a Zubrod </= 1.

k) Life expectancy of >/= 4 months.

l) Subjects must be able to understand and be willing to sign the written informed consent form. A signed informed consent form must be appropriately obtained prior to the conduct of any trial-specific procedure.

m) Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements:

- Total bilirubin ≤ 1.5 x the upper limits of normal (ULN)
- Alanine aminotransferase (ALT) and aspartate amino-transferease (AST) ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
- Alkaline phosphastase limit ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
- Serum creatinine ≤ 1.5 x the ULN
- International normalized ratio (INR)/ Partial thromboplastin time (PTT) ≤ 1.5 x ULN. (Subjects who are prophylactically treated with an agent such as warfarin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in coagulation parameters

exists. Close monitoring of at least weekly evaluations will be performed until INR/PTT is stable based on a measurement that is pre-dose as defined by the local standard of care. (See Section 3.3)

- Platelet count > 100000 /mm3, hemoglobin (Hb) >/= 10 g/dL, absolute neutrophil count (ANC) 1500/mm3. Blood transfusion to meet the inclusion criteria will not be allowed.

n) Women of childbearing potential must have a negative serum pregnancy test performed within 7 days prior to the start of study drug. Post-menopausal women (defined as no menses for at least 1 year) and surgically sterilized women are not required to undergo a pregnancy test. The definition of adequate contraception will be based on the judgment of the investigator.

o) Subjects (men and women) of childbearing potential must agree to use adequate contraception beginning at the signing of the ICF until at least2 months after the last dose of study drug. The definition of adequate contraception will be based on the judgment of the principal investigator or a designated associate.

p) Subject must be able to swallow and retain oral medication.

q) Patients on pain medications (non-opioids), including NSAIDS and acetaminophen, may be enrolled as long as they have been using it chronically, at least more than 2 weeks.

5.1.2 Exclusion criteria

Exclusion Criteria:

a) Major contraindication to fish oil i.e. hypersensitivity to fish/ fish oil or physical activity;

b) Currently on fish oil or has been on fish oil within the last 10 days;

c) Inability to complete the baseline assessment forms or to understand the recommendations for participation in the study.

d) Pregnant or lactating women. Childbearing age women are not on birth control.

e) Reports a falls in the past 30 days;

f) Patient reported regular participation in moderate- or vigorous-intensity PA for at ≥30 minutes at least 5 times a week and strength training for ≥2 days/week;

g) Signs of third spacing as determined by the treating physician (e.g., pedal edema, pleural effusion, ascites)

h) Previous assignment to treatment during this study. Subjects permanently withdrawn from study participation will not be allowed to re-enter study.

i) Uncontrolled hypertension (systolic pressure >140 mm Hg or diastolic pressure > 90 mm Hg [NCI-CTCAE v4.0] on repeated measurement) despite optimal medical management.

j) Active or clinically significant cardiac disease including:

- Congestive heart failure – New York Heart Association (NYHA) > Class II.
- Active coronary artery disease.
- Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin.
- Unstable angina (anginal symptoms at rest), new-onset angina within 3 months before randomization, or myocardial infarction within 6 months before randomization.

k) Evidence or history of bleeding diathesis or coagulopathy.

l) Any hemorrhage or bleeding event ≥ NCI CTCAE Grade 3 within 4 weeks prior to start of study medication.

m) Subjects with thrombotic, embolic, venous, or arterial events, such as cerebrovascular accident (including transient ischemic attacks) deep vein thrombosis or pulmonary embolism within 6 months of start of study treatment within 6 months of informed consent.

n) Patients with any previously untreated or concurrent cancer that is distinct in primary site or histology except cervical cancer in-situ, treated ductal carcinoma in situ of the breast, curatively treated nonmelanoma skin carcinoma, noninvasive aerodigestive neoplasms, or superficial bladder tumor. Subjects surviving a cancer that was curatively treated and without evidence of disease for more than 3 years before registration are allowed. All cancer treatments must be completed at least 3 years prior to registration.

o) Patients with phaeochromocytoma.

p) Known history of human immunodeficiency virus (HIV) infection or current chronic or active hepatitis B or C infection requiring treatment with antiviral therapy.

q) Ongoing infection > Grade 2 NCI-CTCAE v4.0.

r) Symptomatic metastatic brain or meningeal tumors.

s) Presence of a non-healing wound, non-healing ulcer, or bone fracture.

t) Major surgical procedure or significant traumatic injury within 28 days before start of study medication

u) Renal failure requiring hemo-or peritoneal dialysis.

v) Dehydration Grade >1 NCI-CTCAE v4.0.

w) Patients with seizure disorder requiring medication.

x) History of Persistent proteinuria CTCAE v4.0 NCI

y) Interstitial lung disease with ongoing signs and symptoms at the time of informed consent.
z) Pleural effusion or ascites that causes respiratory compromise (≥ NCI-CTCAE version 4.0 Grade 2 dyspnea).

aa) History of organ allograft (including corneal transplant).
bb) Known or suspected allergy or hypersensitivity to any of the study drugs, study drug classes, or excipients of the formulations given during the course of this trial.
cc) Any malabsorption condition.
dd) Women who are pregnant or breast-feeding.
ee) Any condition which, in the investigator's opinion, makes the subject unsuitable for trial participation.
ff) Substance abuse, medical, psychological or social conditions that may interfere with the subject's participation in the study or evaluation of the study results.

5.1.3 Excluded therapies and medications, previous and concomitant

- Concurrent use of another investigational drug or device therapy (i.e., outside of study treatment) during, or within 4 weeks of trial entry (signing of the informed consent form).

- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days before start of study medication.

- Therapeutic anticoagulation with Vitamin-K antagonists (e.g., warfarin) or with heparins and heparinoids.
-
    - However, prophylactic anticoagulation as described below is allowed:
        - Low dose warfarin (1 mg orally, once daily) with PT-INR ≤ 1.5 x ULN is permittedWe will monitor the PT/INR weekly for patients on warfarin and liver function test every 2 weeks (Total bilirubin, and AST (SGOT) and ALT (SGPT) if hepatic metastases are present or if patients are on potentially hepatoxic agents such as acetaminophen or statins.
        - Low dose aspirin ≤ 100 mg daily).
        - Prophylactic doses of heparin.
- Use of any herbal remedy (e.g. St. John's wort [Hypericum perforatum])

- Use of Dexamethasone for cancer related fatigue

5.2 Withdrawal of subjects from study

5.2.1 Withdrawal

Subjects **must be withdrawn from the trial** (treatment and procedures) for the following reasons:

- Subject withdraws consent from study treatment and study procedures. A subject must be removed from the trial at his/her own request or at the request of his/her legally acceptable representative. At any time during the trial and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Pregnancy. Pregnancy will be reported as an SAE. (Note: subjects who have been withdrawn from treatment with study drug because of pregnancy should not undergo CT scans [with contrast]/MRI or bone scans while pregnant.)
- If, in the investigator's opinion, continuation of the trial would be harmful to the subject's well-being.
- Subject is lost to follow-up.
- Death.

Subjects **may be** withdrawn from the study for the following reasons:

- The subject is non-compliant with study drug, trial procedures, or both; including the use of anti-cancer therapy not prescribed by the study protocol.
- Severe allergic reaction to fish oil.
- The development of a second cancer.
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.
- Deterioration of ECOG performance status to 4.
- Use of illicit drugs or other substances that may, in the opinion of the investigator, have a reasonable chance of contributing to toxicity or otherwise skewing trial result.

Any subject removed from the trial will remain under medical supervision until discharge or transfer is medically acceptable.

In all cases, the reason for withdrawal must be recorded in the CRF and in the subject's medical records. Details for the premature termination of the study as a whole (or components thereof [e.g. centers, treatment arms, dose steps]) are provided in Section 10 (Premature termination of the study).

5.2.2 Screen Failures/Dropouts

A subject who discontinues study participation prematurely for any reason is defined as a “dropout” if the subject has already been randomized; assigned to treatment/run-in/wash-out; administered at least one dose of study drug.

A subject who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before the time point used for the definition of “dropout” (see above) is regarded a “screening failure”.

5.2.3 Replacement

No withdrawn subjects will be replaced.

6. Treatment[s]

We will randomize 96 eligible patients in the Biostatistics Clinical Trial Conduct website to receive either Icosapent ethyl (Vascepa) 2 gm orally daily plus physical activity, or placebo plus physical activity, or placebo plus control PA(1:1:1) for 8 weeks (see treatment schema below).

6.1 Treatments to be administered

In this study, patients will be randomized to either combination of Icosapent ethyl 2 gm orally daily plus physical activity; or placebo plus PA or placebo plus control PA for 8 weeks (See Fig. 3 below for the treatment schema). The placebo will be identical to the drug, but will contain methylcellulose as the inert ingredient. Assessment will be performed at baseline to Day 57±5 as per Table 4.

Icosapent *ethyl* (Vascepa)

In the proposed study we plan to use fish oil preparation, Icosapent *ethyl* [an ethyl ester of EPA] 0.5 gram capsules [Amarin Pharma Inc, Bedminster, NJ, 2012]. The placebo will be identical to the drug, but will contain methylcellulose as the inert ingredient. Assessment will be performed at baseline to Day 57±5. The objective of 8 weeks of treatment is to evaluate the efficacy of the combined intervention for cancer related fatigue.

The rationale for placebo and control arm for PA is to control for placebo effect, attention to participant's expectation and the subjective elements of diagnosis or assessment. See Table 4 for the study assessments. All patients at the primary end point (8 weeks) will have an option to receive Icosapent ethyl 2 gm orally daily plus PA for 4 more weeks in an open label basis.

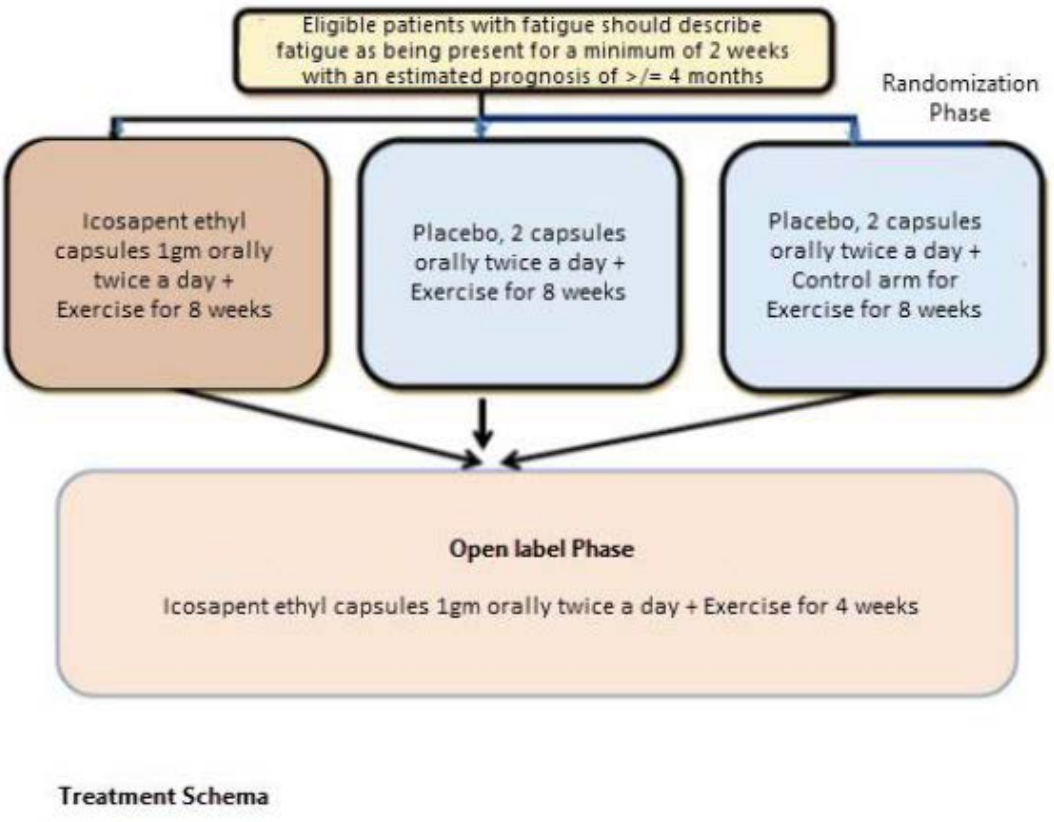

Figure 3

Exercise Prescription.

For this study, we plan to use an exercise intervention based on the American College of Sports Medicine (ACSM) exercise recommendations for cancer survivors. 64 The exercise intervention will include resistance training 3 days/week and moderate intensity walking for upto150 minutes per week.

Participants will have weekly supervised (in person or by telephone) sessions with an ACSM-certified cancer exercise specialist. At the supervised, in person session the patient will perform the resistance exercise and moderate intensity walking up to 30 minutes, depending on the patient's tolerance.

The goal of the resistance exercises is to enhance the individual's ability to go from a seated to standing position independently. The resistance exercise program has been designed to strengthen the major muscles of the lower body, including the quadriceps, hamstrings, gluteus maximus, and hip flexor group.

These exercises will include (but will not be limited to) squats, lunges, leg extensions, leg curls, and hip extensions. We focus on the lower body to simplify the exercise plan, given the short timeframe of the intervention, and because lower body strength is critical to patient mobility and functioning. We will use resistance tubes as our mode of resistance. These tubes are color-coded to indicate their specific

resistance level: light, moderate, or hard. The resistance exercise sessions are to be completed 3 days a week, allowing at least 48 hours between each session. This allows the muscles adequate time for rest and prevents overtraining. The participant will begin with 1 set of 10 to 12 repetitions at lightest resistance progressing to 2 sets of 12 repetitions as exercise tolerance increases. Resistance will then be increased as the participant's endurance and strength progresses. The graded resistance program will be designed so that the individual begins with a lighter resistance and progresses to heavier resistance once a level has been mastered. Since the level of aerobic fitness will vary among participants, the frequency and duration of the walking program will be established based on exercise physiologist's assessment of the participant's baseline aerobic fitness level (six-minute walk test). For example, the recommendation may be to walk 10 minutes 1-3 times a day or up to a 30-minute walk once a day at a moderate intensity level. Participants will work toward the goal of 150 minutes of moderate intensity walking per week.

To encourage and monitor adherence to the walking program, we will provide participants with a pedometer and an exercise log to record their resistance exercise sessions, time spent in moderate intensity walking, and the number of steps they take each day. Participants will be asked to walk a minimum of 5 days a week at the duration established by the exercise physiologist. In the first week of the intervention, the exercise physiologist will meet with each participant to evaluate his or her current strength and aerobic fitness level and to teach the assigned exercises. Each week the exercise physiologist will assess their progress and help them identify and overcome any barriers to completing the exercise program, and to evaluate for adverse events or health problems. The frequency, intensity, and duration of the assigned exercises will also be evaluated and adjusted as necessary.

The participants will be randomized to either the intervention described above or a control exercise program consisting of stretching exercises only. Participants in the control exercise intervention will meet with the exercise physiologist in the first week of the intervention in order to learn the stretches and receive written instructions on how they should be done. Participants will have weekly supervised sessions with an ACSM-certified cancer exercise specialist. With use of an outcome measures outlined in Table 1, we will analyze differences between participants receiving the exercise intervention and the control physical activity.

To ensure adherence to the exercise protocol, video recordings will be made. Dr. Basen-Engquist will randomly review sessions to evaluate the exercise physiologist's adherence to the protocol.

6.2 Blinding

In compliance with applicable regulations, in the event of a SUSARs, the patient's treatment code will usually be unblinded before reporting to the health authorities, ethic committees and investigators (see Section 7.3.3.3) if the SUSAR was related to the blinded treatment.

Emergency unblinding by the investigator

Unblinding may occur for emergency purposes only. Investigators should note that the occurrence of a serious adverse event or progressive disease should not routinely precipitate the immediate unblinding of the label. If unblinding is necessary for the treatment of a subject for a serious adverse event, every

attempt should be made to contact the Principal Investigator prior to unblinding. If this is not feasible, then Principal Investigator must be contacted within 24 hours of unblinding.

6.4. Drug logistics and accountability

All study drugs (Icosapent ethyl/Placebo) will be stored at the investigational site in accordance with Good Clinical Practice (GCP) and Good Manufacturing Practices (GMP) requirements and the instructions given by the clinical supplies department of the Institution and will be inaccessible to unauthorized personnel.

6.5. Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocolDevelopment for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.)

6.6. Destruction and Return

At the end of the study, unused study medication (Icosapent ethyl/Placebo) should be destroyed according to institutional policies.

Treatment compliance

An adequate record of receipt, distribution, and return of all study drugs (Icosapent Ethyl/Placebo) must be kept in the form of a Drug Accountability Form.

Subject compliance with the treatment and protocol includes willingness to comply with all aspects of the protocol, and to have blood collected for all safety evaluations. At the discretion of the principal investigator, a subject may be discontinued from the trial for non-compliance with follow-up visits or study drug.

6.7. Prior and concomitant therapy

All medication that is considered necessary for the subject's welfare, and which is not expected to interfere with the evaluation of the study treatment, may be given at the discretion of the investigator.

All medications (including contrast media) taken within 2 weeks prior to the start of the study and during the study must be recorded in the subject's source documentation and in the CRF (including start/stop dates, dose frequency, route of administration, and indication). Specific caution should be taken when considering or administering a concomitant medication that is metabolized by the cytochrome enzymes CYP2C8, CYP2B6 and CYP2C9. Such concomitant medication should be avoided, if possible.

Permitted concomitant therapy includes:

- Standard therapies for concurrent medical conditions.
- Supportive care for any underlying illness.
- Palliative radiation therapy is allowed if the target lesion(s) are not included within the radiation field and no more than 10% of the bone marrow is irradiated.
- Granulocyte colony-stimulating factor (G-CSF) and other hematopoietic growth factors may be used in the management of acute toxicity, such as febrile neutropenia, when clinically indicated or at the investigator's discretion. However, they may not be substituted for a required dose reduction. Subjects are permitted to take chronic erythropoietin.
- Treatment with nonconventional therapies (such as acupuncture), and vitamin/mineral supplements are permitted provided that they do not interfere with the study endpoints, in the opinion of the investigator.
- Bisphosphonates
- Subjects who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that their medication dose and INR/PTT are stable. Close monitoring (day5 of cycle 1 and day 1 of each cycle) is mandatory. If either of these values are above the therapeutic range, the doses should be modified and the assessments should be repeated weekly until they are stable.

The following are not permitted:

- Other investigational treatment during or within 30 days before starting study treatment
- Systemic antitumor therapy, including cytotoxic therapy, signal transduction inhibitors, immunotherapy, and hormonal therapy
- Bone marrow transplant or stem cell rescue
- Use of any herbal remedy (e.g. St. John's wort [Hypericum perforatum])
- Please note: Patients should be seen frequently / early during treatment as per Prescribing Information
- Monitor blood pressure weekly for the first 6 weeks of treatment and every cycle or more frequently as clinically indicated.

7.0. Outcome Measures/Planned Assessments

7.1. Timing of assessments

	Table 4. Study assessments for Icosapent ethyl/Placebo.									
ASSESSMENTS	**Baseline**	**Day 8* (± 3)**	**Day 15* (± 3)**	**Day 21* (± 3)**	**Day 29 (± 3)**	**Day 36* (± 5)**	**Day 43* (± 5)**	**Day 50* (± 5)**	**Day 57 (± 5)**	**1 month post open label phase‡ (± 5)**
History/ Physical exam	**X**				**X**				**X**	
Zubrod score	**X**									**X**
Medication review	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
FACIT-F subscale, FACT-G, MFSI-SF, PROMIS-Fatigue, HADS, PSQI	**X**		**X**		**X**		**X**		**X**	**X**
ESAS	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Physical Performance Tests (30 second chair stand test six-minute walk test, accelerometer, Godin leisure-time PA questionnaire)	**X**				**X**				**X**	**X**
Body composition Body Mass Index (Bio Impedence), Resting energy expenditure using indirect calorimetry§	**X**				**X**				**X**	**X**
Cytokines (CRP, Serum IL-1b, TNF-α, IL-6; Intracellular cytokines IL-6 R; TNF R, IL-1R, IL-10)	**X**				**X**				**X**	
Electrolytes liver function tests, PT/INR, CBC****	**X**		**X**		**X**		**X**		**X**	**X**
Toxicity evaluation		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Global Symptom Evaluation									**X**	

‡ patients in control arm and the intervention arm will have an option of treatment in drug or placebo +exercise arms
***Assessment by phone or in person**
****PT/INR at baseline only unless patient is being treated with prophylactic anticoagulants. CBC at baseline only unless more frequently testing is clinically indicated.**
-Assessments are performed by the Palliative Care team and complements the standard of care provided by the GI medical oncologists

7.2. Assessments

7.2.1 Physical Activity/ Function:

We will use the **30 second chair stand test**, six-minute walk test and an accelerometer. A self-report exercise questionnaire, the Godin leisure-time PA questionnaire, will be used to complement the objective measures. IM Systems-three dimensional accelerometers ("Biotrainer-Pro") will be used to objectively measure physical activity. These accelerometers complement the self-report for estimating PA and can record PA in 15-second increments for 5 days. Patients will wear the accelerometer for 5 days during the week before each assessment. When participants return the accelerometers the data will be uploaded into the project database, and the amount of time spent in moderate to vigorous activity will be calculated.

30 second chair stand test: The 30 second sit-to-stand task assesses lower body strength.[65] A standard chair without arms with an approximate height of 17 inches will be used. After a demonstration, a practice trial of one repetition will be done to check for proper form. On the start signal, the participant rises to a full stand and then returns to a fully seated position. The patient completes as many full stands as possible within a 30 second period.

In the **six-minute walk test**, participants are asked to walk as fast and as far as they can for six minutes, and the distance walked is measured. The test will be conducted in an area with a 250 foot hallway and minimal traffic. The six-minute walk test has high test-retest and inter-tester reliability, and its validity is supported by correlations with self-report measures of fatigue and functional status. [66] The patient will be strongly encouraged to give a maximum effort.

7.2.2 Patient-reported outcomes

Functional Assessment of Cancer Illness Therapy (FACIT-F): is a well-validated QOL instrument.67 This FACIT-F fatigue subscale was chosen as the primary outcome measure since it has been widely used in CRF treatment trials by our team and by others.[34, 37, 40, 45, 68] The 13-item fatigue subscale is a patient-rated assessment of intensity of fatigue and its related symptoms on a scale of 0 to 4. This scale has been shown to have strong internal consistency (α = 0.93–0.95), sensitivity of 0.92, and specificity of 0.6923.

Pittsburg Sleep Quality Index (PSQI): This instrument provides a brief, clinically useful assessment of a variety of sleep disturbances that might affect sleep quality. [69]

Patient-Reported Outcomes Measurement Information System (PROMIS): measures key symptoms and health concepts applicable to advanced cancer, enabling efficient and interpretable clinical trial research and clinical practice application of patient-reported outcomes (PROs).[70, 71] The PROMIS fatigue measure used in the study was found to be highly correlated with the legacy measures.[23]

Multidimensional Fatigue Symptom Inventory (MFSI-SF) consists of 30 items designed to assess the multidimensional nature of fatigue.[72] Ratings are summed to obtain scores for 5 subscales (general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor).

Hospital Anxiety Depression Scale (HADS): This 14-item questionnaire has been validated in a number of clinical situations and has been widely used in medically ill patients.[73]

The Edmonton Symptom Assessment Scale (ESAS) measures 10 common symptoms in the past 24 hours (pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, sleep, and feeling of well-being) during the previous 24 hours; This questionnaire has been found to valid and reliable in cancer populations.[74]
Please see Table 4 for the timing of the assessments

7.2.3. Cytokine assessments: Peripheral blood will be collected at baseline, Day 29 and Day 57*±5* (Table 4). On completion of the study, the change in levels of synthesis of cytokines in LPS-induced monocytes will be correlated with the proportion of patients with decreased fatigue and with those who have no decrease in fatigue. Methods: Briefly, 1 mL of peripheral blood will be incubated with 10 µg/mL LPS for 5 h and with brefeldin A for the last 3 h of incubation to block the intracellular transport of the de novo cytokine synthesis from the Golgi. Thereafter, LPS-activated monocytes will be stained for surface expression of CD14 and CD33 and for the presence of cytoplasmic cytokines, as previously described,[56] by using a panel of cytokine-specific monoclonal antibodies conjugated with phycoerythrin to detect one of the cytokines. The cytokine assessments will be performed in Dr. James Reuben's laboratory.

7.2.4. Body Composition: Cancer induced lean body mass loss/ fat loss occurs in a higher frequency in advanced cancer patients resulting in severe CRF, functional impairment and their inability to tolerate therapy. Resting energy expenditure, at baseline and Day 57*±5*. However all patients will be assessed for body mass index, phase angle evaluation using Bio electric impedance [Tanita bioelectrical impedance analysis body composition scale].[75-78]

7.2.5. Medical history

Medical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected:

- Not pertaining to the study indication.
- Start before signing of the informed consent.
- Considered relevant to the study.

7.2.6. Blood Collection

Patients who completed questionnaires over the telephone but are unable to return to UTMDACC will have their blood collected by their local physician and the results sent to the UTMDACC study team.

7.2.7. Patient Remuneration

After completion of the study assessments, patients will receive parking reimbursement for up to $12.00 at baseline, Day 29 (± 3 days), and Day 57 (**±** 3 days) for a total of up to $36.00.

7.3. Safety

All subjects who receive at least one dose of study treatment will be valid for the safety analysis.
All observations pertinent to the safety of the study treatment will be recorded and included in the final report.

Safety variables include the following: AEs, laboratory changes (complete blood counts, electrolytes, chemistry, and coagulation), changes in vital signs (blood pressure, heart rate, respiratory rate, and temperature) and ECG and, in some instances, changes in chest x-ray images, as produced at the investigator's discretion (e.g., for evaluation for pneumonia).

All AEs whether considered drug-related or not, will be reported in with a diagnosis, start/stop dates, action taken, whether treatment was discontinued, any corrective measures taken, outcome, and other possible causes. For all events, the relationship to treatment and the intensity of the event will be determined by the investigator.

This trial will use the NCI-CTCAE v4.0 criteria for assessment of toxicity and SAE reporting with regard to toxicity grade.

7.3.1. Adverse events

Definitions

Definition of adverse event (AE)

> In a clinical study, an AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the subject should not be recorded as AE (however, the condition for which the surgery is required may be an AE if worsens compared to baseline).

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g. seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at *unchanged intensity*, are recorded as medical history (e.g. allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events.

Definition of serious adverse event (SAE)
An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death.

b. Is life-threatening.

> The term 'life-threatening' in the definition refers to an event in which the patient was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization.

> A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:
>
> - The admission results in a hospital stay of less than 12 hours.
>
> - The admission is pre-planned. (i.e. elective or scheduled surgery arranged prior to the start of the study)
>
> - The admission is not associated with an AE. (e.g. social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity.
Disability means a substantial disruption of a person's ability to conduct normal life's functions.

e. Is a congenital anomaly / birth defect.

f. Is another medically important serious event as judged by the investigator.

7.3.2. Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

7.3.2.1. Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 7.3.1

7.3.2.2. Intensity

The intensity of the AE is classified according to the CTCAEv4.0. Grade refers to the severity (intensity) of the AE:

CTCAEv4 Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention is not indicated.

CTCAEv4 Grade 2: moderate; minimal, local, or noninvasive intervention is indicated; limiting to age-appropriate instrumental activities of daily living (ADL; instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).

CTCAEv4 Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization is indicated; disabling; limiting to self-care ADL (self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

CTCAEv4 Grade 4: life-threatening consequences; urgent intervention is indicated.

CTCAEv4 Grade 5: death due to an AE.

7.3.2.3. Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information.
The causality assessment should be done separately for each study treatment.

The assessment is based on the question whether there was a “reasonable causal relationship” to the study treatment in question.

Possible answers are “yes” or “no”.
An assessment of “no” would include:

1. The existence of a clear alternative explanation, e.g. mechanical bleeding at surgical site.

Or

2. Non-plausibility, e.g. the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of “yes” indicates that there is a reasonable suspicion that the AE is associated with the use of the study treatment.

Factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.

- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge):

- Subject's response after de-challenge or subjects response after re-challenge should be considered in the view of the usual clinical course of the event in question.

- Underlying, concomitant, intercurrent diseases: Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

- Concomitant medication or treatment: The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.

- The pharmacology and pharmacokinetics of the study treatment: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject's pharmacodynamics should be considered.

[Causal relationship to protocol-required procedure(s)]

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a "reasonable causal relationship" to protocol-required procedure(s).

Possible answers are "yes" or "no".

7.3.3. Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

The study treatment action should be recorded separately for each study treatment.

- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Dose increased
- Not applicable
- Unknown

7.3.3.1.1. Other specific treatment(s) of adverse events

- None
- Remedial drug therapy

7.3.3.1.2. Outcome

The outcome of the AE is to be documented as follows:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

7.3.3.2. Assessments and documentation of adverse events

7.3.3.3. Reporting of serious adverse events

The definition of serious adverse events (SAEs) is given in Section 7.3.1.

Each serious adverse event must be followed up until resolution or stabilization, by submission of updated reports to the designated person. An isolated laboratory abnormality that is assigned grade 4, according to CTC definition, is not reportable as an SAE; unless the investigator assesses that the event meets standard ICH criteria for an SAE. CTC grade 4 baseline laboratory abnormalities that are part of the disease profile should not be reported as an SAE, specifically when they are allowed or not excluded by the protocol inclusion/exclusion criteria.

Throughout the course of the STUDY, the Principal Investigator and study personnel agree to comply with the obligations of adverse event reporting as set forth below, 'Safety Reporting Requirements' and with FDA regulations.

SPONSOR/ INSTITUTION is responsible for all the pharmacovigilance obligations and safety reporting pursuant to the applicable law and regulations in the country where the STUDY is performed.

Additionally, the SPONSOR/INSTITUTION shall immediately, within 24 hours at the latest, report to IRB/DSMB by fax or and/or email. **Safety Reporting Requirements**

The PRINCIPAL INVESTIGATOR must accept full responsibility for the trial and the safety of the subjects participating in the trial. The PRINCIPAL INVESTIGATOR is responsible for the ongoing safety evaluation of the study and shall provide to IRB/DSMB all Serious Adverse Events (SAEs) within 24 hours of the PRINCIPAL INVESTIGATOR'S awareness.

Definitions:

The following definitions, which are consistent with FDA and ICH regulations/guidance, will be used:

Adverse Event (AE):

An adverse event is any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

Serious Adverse Event (SAE):

A serious adverse event includes any event that:

Results in death.

Is life-threatening.

NOTE: The term 'life-threatening' refers to an event during which the subject was at immediate risk of death from the adverse event. It does not refer to an event which hypothetically might have caused death if it had been more severe.

Requires inpatient hospitalization or prolongation of existing hospitalization.

NOTE: In general, hospitalization means that the subject has been detained at the hospital or emergency ward for observation or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment planned prior to study enrollment is neither an SAE nor an AE.

Results in persistent or significant disability or incapacity.

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly or birth defect.

Is an important medical event.

An event may be considered an important medical event when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an

emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Adverse Drug Reaction (ADR):

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means in view of the investigator and/or company that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility and that the adverse event is associated with the use of the drug.

Serious Adverse Drug Reaction (SADR):

A Serious Adverse Drug Reaction is an event that meets any of the criteria for seriousness as previously defined and has a possible causal relationship to the study drug.

Requirements for Reporting of Serious Adverse Events:

All SAEs must be reported to IRB/DSMB within 24 hours of the Principal Investigator's awareness and must include the following minimum information:

1. The name and contact information of the reporter

2. The name of the study drug(s)

3. A description of the reported SAE

4. A patient identified by one or more of the following:

a. Patient initials

b. Patient number

c. Knowledge that a patient who experienced the adverse event exists

d. Age

e. Sex

5. An investigator assessment of study drug causality. For studies with combination therapy, a separate causality assessment should be provided for each study drug.

Additional data which would aid the review and causality assessment of the case include but are not limited to:

The date of onset

The severity

The time from administration of study drug(s) to start of the event

The duration and outcome of the event

Any possible etiology for the event

The final diagnosis or syndrome, if known

Action(s) taken, if any

For blinded studies, the Principal Investigator will provide the treatment assignment upon request for patients who experience SAEs. The Principal Investigator will provide the final treatment assignment immediately after the end of the study.

Expedited Reporting of Other Safety Information:

The Investigator/ Sponsor shall report to IRB/DSMB within 24 hours of the investigator's awareness of other events such as:

An adverse event related to study specific procedures

Any new and important event related to treatment with the study drug(s).

Any pregnancy during which a female patient was exposed to the study drug(s)

Any pregnancy in the partner of a male patient, where the male patient was exposed to study drug at the time of conception or conception occurred within two weeks of the last dose of study drug(s).

Any other relevant safety information including but not limited to reports on drug interaction, overdose, drug abuse or misuse, drug dependency, withdrawal syndrome, medication error, occupational exposure and lack of drug effect (LODE) occurring at any time during the treatment phase;

Any communication concerning safety related information to regulatory authorities or ethics committees including but not limited to:

- Development Safety Update Reports (DSUR) / relevant parts of IND reports for the STUDY;

- Any other safety related reports, issues and queries that are either raised by or

communicated to regulatory authorities or ethics committees;

The Investigator/Sponsor may report SAEs using:

A MedWatch form available at http://www.fda.gov/medwatch/

7.3.3.4. Expected adverse events due to Icosapent ethyl

Below is the overview of the known side-effects reported by the use of study drug.

- **Musculoskeletal:** Arthralgia (2.3%)

7.3.4. Pregnancies

The investigator must report to IRB/DSMB any pregnancy occurring in a study subject, or in his partner, during the subject's participation in this study. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE.

For a study subject, the outcome of the pregnancy should be followed up carefully, and any abnormal outcome of the mother or the child should be reported.

For the pregnancy of a study subject's partner, all efforts should be made to obtain similar information on course and outcome, subject to the partner's consent.

For all reports, the forms provided are to be used.

Progressive disease

If progressive disease leads to signs and symptoms that meet the criteria for an SAE (i.e., hospitalization, disability, death, or important medical event), the signs and symptoms should be reported as an SAE and not the underlying progressive disease.

Death

If any subject dies during the trial or within 30 days of the end-of-treatment visit, the investigator will inform IRB/DSMB and record the cause of death in detail (using the SAE Form) within 24 hours.

8. Statistical methods and determination of sample size

The primary objective is to study is to determine the difference between the FACIT-F subscale score at baseline and at Day 57± 5 days, between patients who will receive either fish oil and PA and placebo and PA.

Interim Analysis Plan

We plan to implement the Bayesian toxicity monitoring rule for severe toxicity (defined as any Grade 3 or 4 toxicity that is attributable to the FISH OIL treatment regimen as per NCI CTCAE V4 criteria) separately for each arm. We will stop the treatment arm if there is an 85% posterior probability to observe a larger than 30% severe toxicity rate in that arm, i.e., $Pr(Ptox > 0.3 \mid data) > 0.85$, given that the prior of severe toxicity rate follows a beta distribution, beta(0.3, 0.7)79,80. The cohort of monitoring will be every 5 patients starting from the first 10 patients. Given this rule, the accrual for a specific arm will be stopped if [# severe toxicities/Total # of patients treated]>=5/10, 7/15, 9/20, 11/25, 12/30, 13/32. Given these boundaries, we will have a 5%, 27% and 67% chance to stop an arm early if the true severe toxicity rate is 20%, 30% and 40% for that arm, respectively.

Sample size calculation:

In a recent cancer related intervention study by our team using oral dexamethasone (DM) [Yennurajalingam, S., S. Frisbee-Hume, et al. (2013)] compared to placebo was associated with improvement in FACIT-F subscale scores (mean, SD) of 9.6 (11) vs. 3.1 (9.7) (p=0.005) at day 15.

However, we are investigating a different intervention (combination of fish oil and physical activity) and therefore we propose to detect a FACIT-F subscale change of 9.5 (standard deviation of 10) in Icosapent ethyl 2 gm orally daily plus PA group against 3 (standard deviation of 10) in placebo plus PA group, with 30 patients in each group, we have an 80% power to detect this difference (effect size 0.65) using a two-sided t-test with a significance level of 0.10. We will also collect information regarding the change in FACIT-F subscale score in 30 patients with placebo plus control physical activity, although not being compared with patients on fish oil and exercise. With a total of 30 patients in this group, we will have an 80% power to detect an effect size of 0.465 in the change in FACIT-F subscale score using a single group t-test with a 0.10 two-sided significance level. We will enter a total of 96 patients to allow for possible 5% dropout rate.

For the primary endpoint, we will compare the difference between the FACIT-F subscale score at baseline and at 57±5 days, between patients who will receive Icosapent ethyl plus PA and placebo plus PA using t-test. Wilcoxon rank sum test may be considered if the distribution of the data is not normal. We will also compare the change of FACIT-F subscale scores among all three groups using ANOVA or Kruskal-Wallis test, whichever appropriate. At the end of the study, overall survival time in each group will be estimated using Kaplan-Meier method and may be compared among three treatment groups using log-rank test.

This study is considered feasible if patient is adherent to the study. Adherence will be calculated as the mean of the percentage of total prescribed strength training sessions, the percentage of total prescribed walking regimen minutes completed (PA), and the mean (across all patients) percentage of total prescribed pills taken (study medication). The adherence rate, as defined, is a continuous variable. At the end of the study, we will estimate the average adherence of prescribed strength, of total prescribed walking regimen minutes and of total prescribed pills taken separately using mean, standard deviation, median, and range. This study intervention of combination of Icosapent Ethyl and Physical activity will be considered feasible as evidenced by adherence rate is >/=75% to daily combined therapy during the 8-week intervention. The adherence rate can also be compared among all three groups using Kruskal-Wallis test. We will estimate 95% confidence intervals for the proportion of patients completing the intervention, the adherence rate, and the proportion of patients with a satisfaction over time. With 30 patients in each arm, a 95% confidence interval for a proportion of 73% (22/30), for example, can be estimated as (54%, 88%).

Data of variables of interest will be summarized using standard descriptive statistics, such as mean, standard deviation, median, and range for continuous variables, frequency and proportion for categorical variables. Correlation will be assessed among continuous variables using Pearson or Spearman correlation coefficient, whichever is appropriate. Association between categorical variables will be examined by Chi-Squared test or Fisher's exact test when appropriate. Boxplot and histogram will be applied to demonstrate distribution of variables of interest.

Since FACIT-F scores will be obtained at 0, 15, 29, 43 and 57±5 days, and other QOL variables and cytokine markers will also be obtained repeatedly over time, we will also evaluate the effect of treatment on the changes of these measured over time using repeated measure analysis in which intra-

patient correlation of the measures are accounted for. However due to the small scale and exploratory nature of the study, we will report p-value as is without adjusting for multiplicity.

To address issues related to missing data, we may perform multiple imputation analyses. If the data does not appear to be normally distributed, transformation may be employed to the data, or appropriate nonparametric methods will be used for data analysis.

Toxicity data will be summarized by treatment, grade and relationship using frequencies and cross-tabulation.

9. Data handling and quality assurance

The Data safety monitoring board at MD ACC will review and handle the data safety and quality assurance.

9.1 Audit and inspection

Inspections by regulatory health authority representatives i.e. FDA and IEC(s)/IRB(s) are possible.

9.2 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

10. Premature termination of the study

- If risk-benefit ratio becomes unacceptable owing to, for example,

  o Safety findings from this study (e.g. SAEs)

  o Results of any interim analysis

  o Results of parallel clinical studies

  o Results of parallel animal studies (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).

- If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The investigator has the right to close his/her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties.
- All affected institutions (e.g. IEC(s)/IRB(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law.

- In case of a partial study closure, ongoing subjects, including those in post study follow-up, must be taken care of in an ethical manner.

Details for individual subject's withdrawal can be found in Section 5.2.1.

11. Ethical and legal aspects

11.1 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the investigator abide by Good Clinical Practice (GCP) guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s)/IRBs will be obtained for all participating centers before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the EC/IRB approval must be obtained.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IEC/IRB approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution. Any deviations from the protocol must be explained and documented by the investigator.

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and properly documented.

11.2 Subject information and consent

See attached UT MD Anderson Cancer Center consent document.

11.3. Publication policy

The Principal Investigator should ensure that the information regarding the study be publicly available on the internet at www.clinicaltrials.gov.

11.4. Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

12. Reference list

1. Berger AM, Abernethy AP, Atkinson A, et al. Cancer-Related Fatigue. Journal of the National Comprehensive Cancer Network. 2010;8: 904-931.

2. de Raaf PJ, de Klerk C, Timman R, Hinz A, van der Rijt CCD. Differences in Fatigue Experiences Among Patients With Advanced Cancer, Cancer Survivors, and the General Population. Journal of Pain and Symptom Management. 2012;44: 823-830.

3. Butt Z, Rosenbloom SK, Abernethy AP, et al. Fatigue is the Most Important Symptom for Advanced Cancer Patients Who Have Had Chemotherapy. Journal of the National Comprehensive Cancer Network. 2008;6: 448-455.

4. Yennu S, Urbauer D, Bruera E. Factors associated with the severity and improvement of fatigue in patients with advanced cancer presenting to an outpatient palliative care clinic. BMC Palliative Care. 2012;11: 16.

5. Yennurajalingam S, Bruera E. Palliative Management of Fatigue at the Close of Life. JAMA. 2007;297: 295 - 304.

6. Pollack LA RJ, Crammer C, Stefanek M. Introduction: charting the landscape of cancer survivors' health-related outcomes and care. Cancer. 2009;115.

7. Peuckmann V, Elsner F, Krumm N, Trottenberg P, Radbruch L. Pharmacological treatments for fatigue associated with palliative care. Cochrane Database Syst Rev. 2010: CD006788.

8. Yennurajalingam S, Bruera E. Palliative Management of Fatigue at the Close of Life. JAMA: The Journal of the American Medical Association. 2007;297: 295-304.

9. Minton O, Stone P, Richardson A, Sharpe M, Hotopf M. Drug therapy for the management of cancer related fatigue. Cochrane Database Syst Rev. 2008: CD006704.

10. Bruera E, Yennurajalingam S. Palliative Care in Advanced Cancer Patients: How and When? The Oncologist. 2012;17: 267-273.

11. Hui D, Karuturi MS, Tanco KC, et al. Targeted Agent Use in Cancer Patients at the End of Life. Journal of Pain and Symptom Management. 2013;46: 1-8.

12. de Raaf, PJ, Sleijfer, S, Lamers, CHJ., Jager, A, Gratama, JW. and van der Rijt, CCD., Inflammation and fatigue dimensions in advanced cancer patients and cancer survivors. Cancer.2012; 118: 6005–6011.

13. Reddy S BE, Pace E, Zhang K, Reyes-Gibby CC. Clinically important improvement in the intensity of fatigue in patients with advanced cancer. J Palliat Med. 2007;10: 1068-1075.

14. Yennurajalingam S, Frisbee-Hume S, Palmer JL, et al. Reduction of Cancer-Related Fatigue With Dexamethasone: A Double-Blind, Randomized, Placebo-Controlled Trial in Patients With Advanced Cancer. Journal of Clinical Oncology. 2013;31: 3076-3082.

15. Fearon KC BM, Moses AG, Ahmedzai SH, Taylor GS, Tisdale MJ, Murray GD. Double-blind, placebo-controlled, randomized study of eicosapentaenoic acid diester in patients with cancer cachexia. J Clin Oncol. 2006;24: 3401-3407.

16. Bruera E SF, Palmer JL, Willey J, Calder K, Amyotte G, Baracos V. Effect of fish oil on appetite and other symptoms in patients with advanced cancer and anorexia/cachexia: a double-blind, placebo-controlled study. J Clin Oncol. . 2003;21: 3401-3407.

17. Albrecht T, Taylor A. Physical Activity in Patients With Advanced-Stage Cancer: A Systematic Review of the Literature. Clinical Journal of Oncology Nursing. 2012;16: 293-300.

18. Yeo TP, Burrell SA, Sauter PK, et al. A Progressive Postresection Walking Program Significantly Improves Fatigue and Health-Related Quality of Life in Pancreas and Periampullary Cancer Patients. Journal of the American College of Surgeons. 2012;214: 463-475.

19. Bourke L, Thompson G, Gibson DJ, et al. Pragmatic Lifestyle Intervention in Patients Recovering From Colon Cancer: A Randomized Controlled Pilot Study. Archives of Physical Medicine and Rehabilitation. 2011;92: 749-755.

20. Vallance JK, Boyle T, Courneya KS, Lynch BM. Associations of objectively assessed physical activity and sedentary time with health-related quality of life among colon cancer survivors. Cancer. 2014;120: 2919-2926.

21. Shariati A HS, Fayyazi S, Tabesh H, Kalboland MM. The effect of exercise on the severity of the fatigue in colorectal cancer patients who received chemotherapy in Ahwaz. Iran J Nurs Midwifery Res. . 2010;15: 145-149.

22. Cramp F B-DJ. Exercise for the management of cancer-related fatigue in adults. Cochrane Database Syst Rev. 2012.

23. Barsevick AM, Irwin MR, Hinds P, et al. Recommendations for High-Priority Research on Cancer-Related Fatigue in Children and Adults. Journal of the National Cancer Institute. 2013.

24. Piper BF LA, Dodd MJ. Fatigue mechanisms in cancer patients: developing nursing theory. Oncol Nurs Forum. 1987;14: 17-23.

25. Mock V, St. Ours C, Hall S, et al. Using a conceptual model in nursing research – mitigating fatigue in cancer patients. Journal of Advanced Nursing. 2007;58: 503-512.

26. McNeely ML CK. Exercise programs for cancer-related fatigue: evidence and clinical guidelines. J Natl Compr Canc Netw. 2010;8: 945-953.

27. Murphy RA, Yeung E, Mazurak VC, Mourtzakis M. Influence of eicosapentaenoic acid supplementation on lean body mass in cancer cachexia. Br J Cancer. 2011;105: 1469-1473.

28. Mathur N, Pedersen BK. Exercise as a Mean to Control Low-Grade Systemic Inflammation. Mediators of Inflammation. 2008;2008.

29. Petersen AMW, Pedersen BK. The anti-inflammatory effect of exercise. Journal of Applied Physiology. 2005;98: 1154-1162.

30. Lundh Hagelin C, Wengström Y, Åhsberg E, Fürst C. Fatigue dimensions in patients with advanced cancer in relation to time of survival and quality of life. Palliative Medicine. 2009;23: 171-178.

31. Minton O, Richardson A, Sharpe M, Hotopf M, Stone PC. Psychostimulants for the management of cancer-related fatigue: a systematic review and meta-analysis. J Pain Symptom Manage. 2011;41: 761-767.

32. Minton O, Richardson A, Sharpe M, Hotopf M, Stone P. Drug therapy for the management of cancer-related fatigue. Cochrane Database Syst Rev. 2010: CD006704.

33. Panel NIoHS-o-t-S. National Institutes of Health State-of-the-Science Conference Statement: Symptom Management in Cancer: Pain, Depression, and Fatigue, July 15–17, 2002. Journal of the National Cancer Institute. 2003;95: 1110-1117.

34. Yennurajalingam S F-HS, Delgado-Guay MO, Bull J, Bruera E. Dexamethasone (DM) for cancer-related fatigue: A double-blinded, randomized, placebo-controlled trial. J Clin Oncol. 2012;Suppl.

35. Bruera E RE, Cedaro L, Carraro S, Chacon R. Action of oral methylprednisolone in terminal cancer patients. . Cancer Treat Rep. 1985;69.

36. Yennurajalingam S, Frisbee-Hume S, Palmer JL, et al. Reduction of Cancer-Related Fatigue With Dexamethasone: A Double-Blind, Randomized, Placebo-Controlled Trial in Patients With Advanced Cancer. Journal of Clinical Oncology. 2013.

37. Bruera E, Valero V, Driver L, et al. Patient-Controlled Methylphenidate for Cancer Fatigue: A Double-Blind, Randomized, Placebo-Controlled Trial. Journal of Clinical Oncology. 2006;24: 2073-2078.

38. Bruera E, Yennurajalingam S, Palmer JL, et al. Methylphenidate and/or a Nursing Telephone Intervention for Fatigue in Patients With Advanced Cancer: A Randomized, Placebo-Controlled, Phase II Trial. Journal of Clinical Oncology. 2013;31: 2421-2427.

39. Bruera E, Strasser F, Shen L, et al. The effect of donepezil on sedation and other symptoms in patients receiving opioids for cancer pain: a pilot study. Journal of Pain and Symptom Management. 2003;26: 1049-1054.

40. Bruera E, El Osta B, Valero V, et al. Donepezil for Cancer Fatigue: A Double-Blind, Randomized, Placebo-Controlled Trial. Journal of Clinical Oncology. 2007;25: 3475-3481.

41. Jean-Pierre P, Morrow GR, Roscoe JA, et al. A phase 3 randomized, placebo-controlled, double-blind, clinical trial of the effect of modafinil on cancer-related fatigue among 631 patients receiving chemotherapy. Cancer. 2010;116: 3513-3520.

42. Minton O, Stone P. A systematic review of the scales used for the measurement of cancer-related fatigue (CRF). Ann Oncol. 2009;20: 17-25.

43. Brenu E, van Driel M, Staines D, et al. Longitudinal investigation of natural killer cells and cytokines in chronic fatigue syndrome/myalgic encephalomyelitis. Journal of Translational Medicine. 2012;10: 88.

44. Bruera E ES, Hagen N, Spachynski K, Belzile M, Hanson J, Summers N, Brown B, Dulude H, Gallant G. Effectiveness of megestrol acetate in patients with advanced cancer: a randomized, double-blind, crossover study. Cancer Prev Control. 1998;2: 74-78.

45. Bruera E, Driver L, Barnes EA, et al. Patient-Controlled Methylphenidate for the Management of Fatigue in Patients With Advanced Cancer: A Preliminary Report. Journal of Clinical Oncology. 2003;21: 4439-4443.

46. Bruera E, Neumann CM, Pituskin E, Calder K, Ball G, Hanson J. Thalidomide in patients with cachexia due to terminal cancer: Preliminary report. Annals of Oncology. 1999;10: 857-859.

47. Yennurajalingam S, Palmer J, Zhang T, Poulter V, Bruera E. Association between fatigue and other cancer-related symptoms in patients with advanced cancer. Supportive Care in Cancer. 2008;16: 1125-1130.

48. Yennurajalingam S, Palmer JL, Chacko R, Bruera E. Factors Associated with Response to Methylphenidate in Advanced Cancer Patients. Oncologist. 2011;16: 246-253.

49. Yennurajalingam S, Palmer J, Zhang T, Poulter V, Bruera E. Association between fatigue and other cancer-related symptoms in patients with advanced cancer. Support Care Cancer. 2008;16: 1125 - 1130.

50. Yennurajalingam S, Urbauer DL, Casper KLB, et al. Impact of a Palliative Care Consultation Team on Cancer-Related Symptoms in Advanced Cancer Patients Referred to an Outpatient Supportive Care Clinic. Journal of Pain and Symptom Management. 2011;41: 49-56.

51. Bruera E KN, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. Journal of palliative care. 1991; 7: 6.

52. Bruera, Michaud, Vigano, Neumann, Watanabe, Hanson. Multidisciplinary symptom control clinic in a cancer center: a retrospective study. Supportive Care in Cancer. 2001;9: 162-168.

53. Taylor CLC, deMoor C, Smith MA, et al. Active for Life After Cancer: a randomized trial examining a lifestyle physical activity program for prostate cancer patients. Psycho-Oncology. 2006;15: 847-862.

54. Basen-Engquist K, Taylor CLC, Rosenblum C, et al. Randomized pilot test of a lifestyle physical activity intervention for breast cancer survivors. Patient Education and Counseling. 2006;64: 225-234.

55. Basen-Engquist K, Scruggs S, Jhingran A, et al. Physical activity and obesity in endometrial cancer survivors: associations with pain, fatigue, and physical functioning. American Journal of Obstetrics and Gynecology. 2009;200: 288.e281-288.e288.

56. Reuben JM, Lee B-N, Johnson H, Fritsche H, Kantarjian HM, Talpaz M. Restoration of Th1 Cytokine Synthesis by T Cells of Patients with Chronic Myelogenous Leukemia in Cytogenetic and Hematologic Remission with Interferon-α. Clinical Cancer Research. 2000;6: 1671-1677.

57. Foster SB, Lu M, Glaze DG, et al. Associations of cytokines, sleep patterns, and neurocognitive function in youth with HIV infection. Clinical Immunology. 2012;144: 13-23.

58. Yennurajalingam S WJ, Palmer JL, Allo J, Del Fabbro E, Cohen EN, Tin S, Reuben JM, Bruera E. The role of thalidomide and placebo for the treatment of cancer-related anorexia-cachexia symptoms: results of a double-blind placebo-controlled randomized study. J Palliat Med. 2012;15: 1059-1064.

59. Wang XS, Shi Q, Williams LA, et al. Serum interleukin-6 predicts the development of multiple symptoms at nadir of allogeneic hematopoietic stem cell transplantation. Cancer. 2008;113: 2102-2109.

60. Ostrowski K, Rohde T, Zacho M, Asp S, Pedersen BK. Evidence that interleukin-6 is produced in human skeletal muscle during prolonged running. The Journal of Physiology. 1998;508: 949-953.

61. Ostrowski K, Rohde T, Asp S, Schjerling P, Pedersen BK. Pro- and anti-inflammatory cytokine balance in strenuous exercise in humans. The Journal of Physiology. 1999;515: 287-291.

62. Naing A RJ, Camacho LH, Gao H, Lee BN, Cohen EN, Verschraegen C, Stephen S, Aaron J, Hong D, Wheler J, Kurzrock R. Phase I Dose Escalation Study of Sodium Stibogluconate (SSG), a Protein Tyrosine Phosphatase Inhibitor, Combined with Interferon Alpha for Patients with Solid Tumors. J Cancer. 2011;2: 81-89.

63. Yennurajalingam S, Palmer JL, Chacko R, Bruera E. Factors Associated with Response to Methylphenidate in Advanced Cancer Patients. The Oncologist. 2011;16: 246-253.

64. Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Medicine & Science in Sports & Exercise. 2010;42: 1409-1426.

65. Rikli RE, Jones CJ. Development and validation of a functional fitness test for community-residing older adults. Journal of Aging and Physical Activity. 1999;7: 129-161.

66. Simmonds MJ. Physical function in patients with cancer: Psychometric characteristics and clinical usefulness of a physical performance test battery. Journal of Pain and Symptom Management. 2002;24: 404-414.

67. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. Journal of Clinical Oncology. 1993;11: 570-579.

68. Minton O, Richardson A, Sharpe M, Hotopf M, Stone P. A Systematic Review and Meta-Analysis of the Pharmacological Treatment of Cancer-Related Fatigue. Journal of the National Cancer Institute. 2008;100: 1155-1166.

69. Buysse DJ, Reynolds Iii CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. Psychiatry Research. 1989;28: 193-213.

70. Yost KJ, Eton DT, Garcia SF, Cella D. Minimally important differences were estimated for six Patient-Reported Outcomes Measurement Information System-Cancer scales in advanced-stage cancer patients. Journal of Clinical Epidemiology. 2011;64: 507-516.

71. Rothrock NE, Hays RD, Spritzer K, Yount SE, Riley W, Cella D. Relative to the general US population, chronic diseases are associated with poorer health-related quality of life as measured by the Patient-Reported Outcomes Measurement Information System (PROMIS). Journal of Clinical Epidemiology. 2010;63: 1195-1204.

72. Stein KD, Jacobsen PB, Blanchard CM, Thors C. Further validation of the multidimensional fatigue symptom inventory-short form. Journal of Pain and Symptom Management. 2004;27: 14-23.

73. Johnston M, Pollard B, Hennessey P. Construct validation of the hospital anxiety and depression scale with clinical populations. Journal of Psychosomatic Research. 2000;48: 579-584.

74. Bruera E. KN, Miller MJ, Selmser P, Macmillan K:The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. J Palliat Care. 1991;7: 6 - 9.

75. Dalal S, Hui D, Bidaut L, et al. Relationships Among Body Mass Index, Longitudinal Body Composition Alterations, and Survival in Patients With Locally Advanced Pancreatic Cancer Receiving Chemoradiation: A Pilot Study. Journal of Pain and Symptom Management. 2012;44: 181-191.

76. Yennurajalingam S WJ, Palmer JL, Allo J, Del Fabbro E, Cohen EN, Tin S, Reuben JM, Bruera E. The role of thalidomide and placebo for the treatment of cancer-related anorexia-cachexia symptoms: results of a double-blind placebo-controlled randomized study. J Palliat Med. . 2012;15: 1059-1064.

77. Hui D, Bansal S, Morgado M, Dev R, Chisholm G, Bruera E. Phase angle for prognostication of survival in patients with advanced cancer: Preliminary findings. Cancer. 2014;120: 2207-2214.

78. Del Fabbro E, Parsons H, Warneke CL, et al. The Relationship Between Body Composition and Response to Neoadjuvant Chemotherapy in Women with Operable Breast Cancer. The Oncologist. 2012;17: 1240-1245.

79. Peter Thall, Richard Simon, and Eli Estey. Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. Statistics in Medicine 14:357-379, 1995.

80. Peter Thall, and Hsi-Guang Sung. Some extensions and applications of Bayesian strategy for monitoring multiple outcomes in clinical trials. Statisticsin Medicine, 17:1563-1580, 1998.

13. Amendments N/A

14. Appendices: See attachment

14.3. Examples of a low fat meal

Two slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jelly and 8 ounces of skim milk. (Approximately 319 calories and 8.2 grams of fat)

One cup of cereal (i.e. Special K), 8 ounces of skimmed milk, one piece of toast with jam (no butter or marmalade), apple juice, and one cup of coffee or tea (2 g fat, 17 g protein, 93 g of carbohydrate, 520 calories).