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UNIVERSITY OF ROCHESTER CANCER CENTER

A Phase II Study of the Effects of Physical Activity and Low-Dose Ibuprofen on Cognitive Function in Cancer Patients Undergoing Chemotherapy

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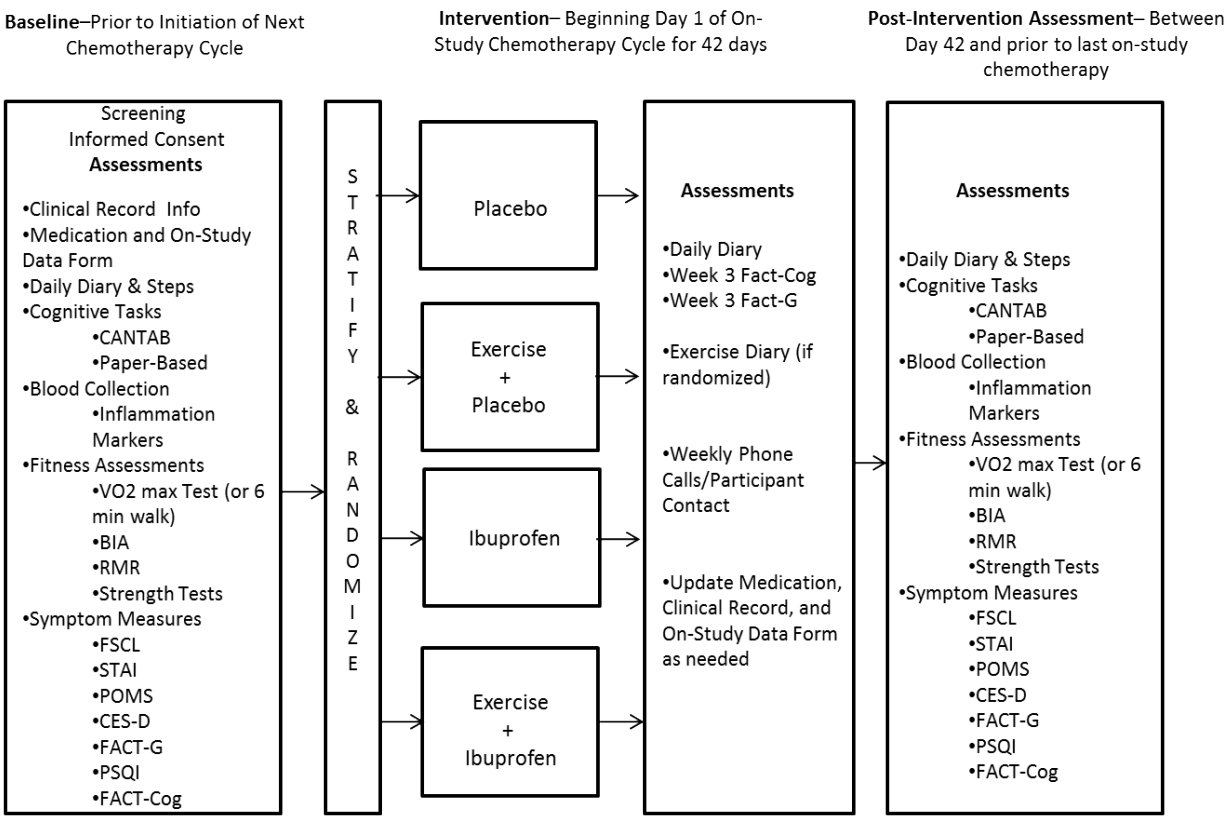
Study Schema



1.0 Background

1.1 Cognitive Impairment in Cancer Patients as a Public Health Problem

Due to the decreasing mortality rate of cancer, there are more than 10 million cancer survivors in the United States.[1, 2] Because many of these survivors do not succumb to cancer, other health problems, including cognitive difficulties due to treatment, are a major concern.

Up to 75% of cancer patients will experience some form of cognitive impairment (e.g. problems with memory, attention, and executive functioning) during the treatment of their cancer and, for many, this impairment will persist for many months or years following treatment.[3-7] Cognitive problems in those who receive chemotherapy are more severe than in those who receive locoregional therapy (e.g. radiation, surgery).[5] These cognitive problems can negatively impact activities of daily living such as 1) performance at work, 2) caring for family members and 3) accessing necessary medical and other health services. Until the past decade, this condition was largely under-studied, and no effective

treatment exists.

1.2 The Etiology of Chemotherapy-Related Cognitive Impairment: A Possible Link Between Cognitive Impairment and Inflammation

The etiology of cognitive impairment in cancer patients receiving chemotherapy is unknown, but some clues have been identified. Findings from a small number of neuroimaging studies have shown that chemotherapy affects specific brain regions. Location-specific brain dysfunction is supported by Magnetic Resonance Imaging (MRI) studies that have identified abnormalities in brain metabolism and blood flow in areas involved in cognition including the prefrontal lobe, hippocampus, parahippocampal gyrus, cingulate gyrus, and precuneus regions.[8, 9] Whether chemotherapeutic agents can enter the brain at high enough levels to cause direct neurotoxicity leading to these abnormalities—or whether these effects on metabolism are indirect—is unknown.

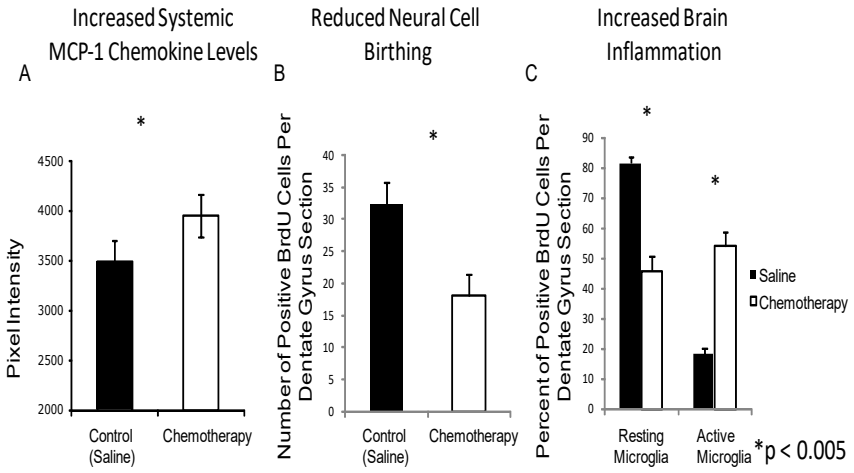
Recent literature suggests that elevated levels of pro-inflammatory cytokines may be causally related to cognitive problems in cancer patients.[10] Over three decades ago, the brain was considered an immune-privileged organ due to tight regulation by the blood brain barrier and lack of brain-resident lymph nodes. Now, we appreciate an immunological capacity within the brain. For instance, although at low levels, cytokine-producing T lymphocytes can be identified within the brain,[11] and neurons, astrocytes, and microglia have all been found capable of pro-inflammatory cytokine production.[12] We also know that interaction occurs between the peripheral blood and the CNS; increased levels of pro-inflammatory molecules in the peripheral blood can induce CNS glial changes, subsequent cytokine production, and cognitive problems (e.g. memory).[13-16] Many of the pioneering studies linking inflammation to cognitive problems were conducted in the context of neurodegenerative diseases; [17] inflammatory processes are now implicated in a number of these disorders including Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and human immunodeficiency type 1 dementia. For example, a recent small-scale prospective clinical study revealed that high peripheral blood mononuclear cell (PBMC) production of IL-1β and TNF-α correlates with a higher risk of the subsequent development of AD.[18] Additionally, traumatic brain injury (TBI) early in life—with the consequent elevation of inflammatory mediators—and the later development of AD are positively correlated in some studies,[19] suggesting that a heightened inflammatory status may contribute to cognitive difficulties.

Recent studies have shown that elevated levels of inflammatory cytokines are a consequence of immunotherapy, immunotherapy in combination with chemotherapy, and chemotherapy alone, and it is therefore plausible that these elevated levels of cytokines play a role in cognitive difficulties in cancer patients. For example, studies in cancer patients who have received high doses of IL-2 and IFN-alpha,[20] or interferon-alpha and chemotherapy[21] for treatment of cancer have been conducted; both of these studies revealed associations of

treatment with cognitive problems in this population. Interleukin-2 immunotherapy leads to impairments in spatial working memory and IFN-alpha immunotherapy leads to impairments in reaction time,[20] while IFN-alpha plus chemotherapy leads to problems in spatial working memory.[21] Chemotherapy has also been associated with increased levels of pro-inflammatory cytokines, IL-1β [22], and alterations in IL-6, IL-8, and TNF-α levels.[23]

My data from mice show that cyclophosphamide chemotherapy increased blood levels of the inflammatory molecule MCP-1 (Fig. 1A), increased microglial activation (indicating brain inflammation, Fig. 1C) and reduced neural precursor proliferation (implicating impaired memory processes, Fig. 1B, [24]). Collectively, these data from human and animal studies suggest that chemotherapy elicits an inflammatory response that might produce neural cell damage and impaired cognitive functioning. These studies support our hypothesis that inflammation may contribute to chemotherapy-related cognitive difficulties in cancer patients.

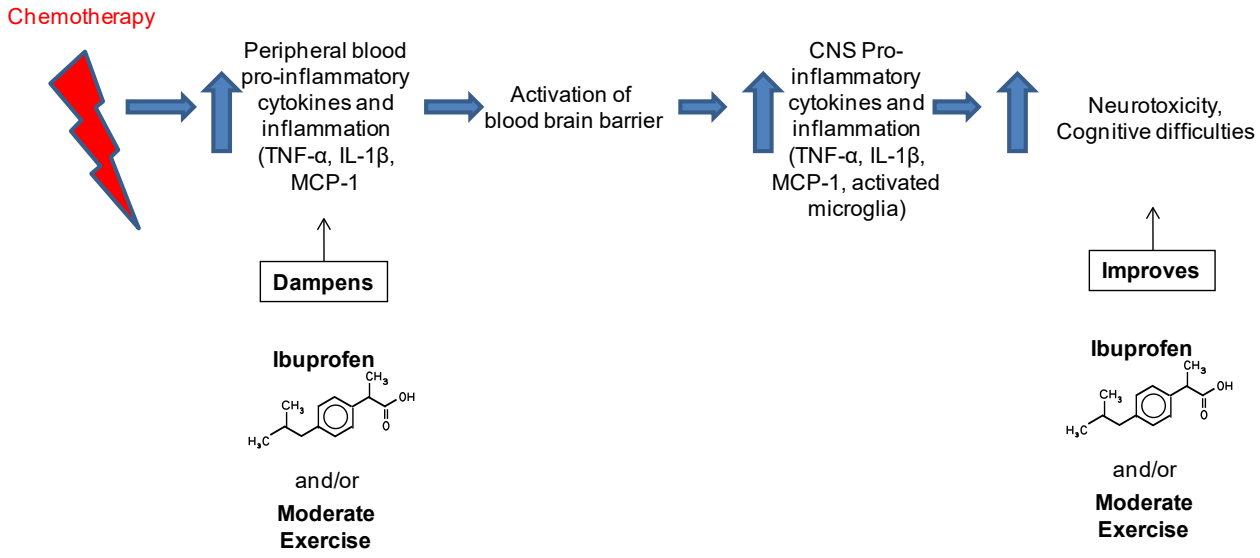
Figure 1



Possible mechanisms for explaining how heightened levels of pro-inflammatory cytokines due to cancer and cancer treatment may contribute directly to problems in cognitive functioning include 1) activation of the blood brain barrier to induce glial changes and subsequent cytokine production in the CNS, 2) creation of leakiness in the blood brain barrier causing increased concentrations of toxic substances to enter the brain, and 3) interaction with the vagus nerve triggering central nervous system induced inflammatory signals.

We propose a model whereby the combined insult of cancer and cancer chemotherapy leads to heightened levels of pro-inflammatory molecules that activate the blood brain barrier, allowing for brain inflammation and associated problems in cognition. Moreover, interventions (e.g. exercise, anti-inflammatory medication) aimed at dampening chronic inflammation will alleviate cognitive problems experienced by those receiving chemotherapy (Figure 2)

Figure 2: Proposed model for chemotherapy-related cognitive difficulties and interventions to inhibit inflammation.



Model: Chemotherapy likely leads to heightened peripheral blood levels of cytokines causing sustained inflammation which, in turn, activates the blood brain barrier and causes CNS inflammation. Chronic CNS inflammation leads to neurotoxicity and cognitive difficulties. Interventions that reduce inflammation, such as exercise and ibuprofen, can dampen the inflammatory response caused by chemotherapy leading to an improvement in cognitive functioning.

1.3 Exercise as an intervention to reduce inflammation and treat cognitive impairment

Increasing evidence suggests that exercise improves functional capacity and quality of life (QOL) in cancer survivors [25-27] and may provide a useful intervention for reducing symptom burden resulting from treatment in this population. These positive outcomes may be linked in part to the overall anti-inflammatory effects of exercise. For example, exercise may help to maintain or reduce body fat, a source of highly inflammatory adipose tissue.[28, 29] Regular aerobic exercise can reduce levels of circulating cytokines (e.g. IL-6, CRP) and both aerobic exercise and resistance training each can reduce TNF-alpha [30] in older adults. A ten-week walking program also demonstrated a reduction in IL-6 and psychological stress.[31]

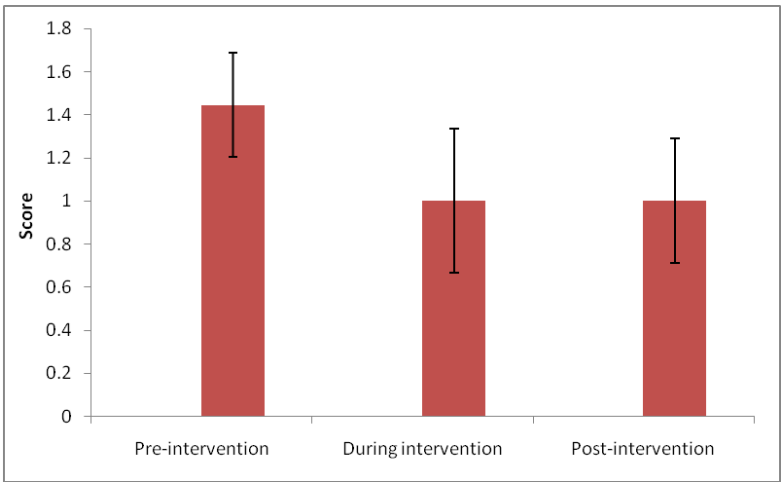
Exercise may particularly be a good intervention to reduce inflammation in women receiving chemotherapy. These women tend to gain weight, which is largely attributed to an increase in fat mass (adiposity) [32-34]. Increases in adiposity lead to increases in inflammation within the body that we hypothesize contribute to cognitive difficulties in cancer patients.

Studies have shown the beneficial effects of aerobic exercise and strength training on cognitive functioning in older adults with and without cognitive decline, as reviewed in a recent meta-analysis. [35] Moreover, physical activity may be related to decreased risk of developing cognitive problems. A recent randomized controlled trial examined the effects of a 6-month home-based exercise intervention in 170 subjects on problems in memory and found improvements in memory which persisted for one year post-intervention. [36]

Exercise interventions in cancer patients are feasible and safe. Mustian and colleagues,[37] Cramp and colleagues, [38] Galvao and Newton,[39] Stevinsen and colleagues, [40] and Knols and colleagues [41] report on the benefits of exercise among cancer survivors during and after treatment. Exercise has been shown to improve Cancer-Related Fatigue (CRF), QOL, emotional distress, immunological parameters, aerobic capacity, strength, flexibility, and body composition in these studies. Fourteen of these studies by nine different research groups assessed the beneficial effects of exercise interventions specifically during chemotherapy.

We performed secondary analyses on a pilot RCT originally conducted by Dr. Mustian, a Co-Investigator on this study, that compared the effects of a 12-week exercise (Tai Chi Chuan) intervention to a non-exercise control group on functional capacity and quality of life in 21 breast cancer survivors.[25] In this study, subjects were also asked about forgetfulness on a 5-point scale (0 = not at all to 4 = extremely) prior to the intervention, halfway through the intervention, and post-intervention. While significance was not reached, a trend toward improvement (p=0.12) was observed from the pre-intervention to post-intervention time-points (see Figure 3 below) for the exercise group.

Figure 3



1.3.1 The home-based exercise program, EXCAP, used in the proposed study, and developed by Dr. Mustian, has been validated and safety-tested in cancer patients undergoing radiation treatment and is associated with improved functional capacity, reduced fatigue, and altered cytokine levels

[42-45] compared to standard care. This intervention is now being tested in a multi-center clinical trial for effects on fatigue in cancer patients undergoing chemotherapy through the URCC NCORP and affiliates.

1.4 Ibuprofen as an intervention to reduce inflammation and treat cognitive impairment

Ibuprofen is a non-selective non-steroidal anti-inflammatory agent (NSAID) that is FDA-approved for treatment of numerous conditions including pain, headache, fever, and inflammation. Ibuprofen inhibits cyclooxygenase 1 and 2 activity, thereby inhibiting the synthesis of prostaglandins (e.g. PGE2) and consequently down-regulating inflammatory pathways involving IL-1β, TNF-α, MCP-1 and other pro-inflammatory signaling pathways.

NSAIDs have been associated with reduced odds of cognitive problems, especially with long-term usage. Low-dose ibuprofen also may have positive effects on cognitive functioning in the setting of neurodegenerative disease. A recent case-control study assessing the effects of anti-inflammatory medication on risk of Alzheimer's disease revealed a 44% reduction in risk with long-term usage (> 2 years), although prospective studies have been inconsistent. [46]

Long-term NSAID usage, particularly ibuprofen, also has been associated with better cognitive performance and lower rates of cognitive decline in a study of healthy older adults. [47]

1.4.1. The value of low-dose, short-term usage of an anti-inflammatory on cognitive function has not been investigated, and assessing such usage for preliminary effectiveness in cancer patients is the primary goal of this study.

1.5 Summary

Exercise and ibuprofen usage have been associated with the maintenance of proper cognitive functioning among the general population compared to non-users. Little research has been done on the effects of exercise on cognitive functioning in cancer patients undergoing treatment and no research has been done to test ibuprofen for effects on cognitive functioning in cancer patients undergoing treatment. This pilot study serves as a feasibility trial for ibuprofen, exercise, and combined intervention arms in cancer patients undergoing chemotherapy. Both the ibuprofen and exercise interventions are aimed at maintaining cognitive functioning by reducing inflammation within the body and brain, thereby reducing cognitive difficulties due to chemotherapy.

We propose to conduct a feasibility pilot to assess preliminary efficacy of a 6-week course of ibuprofen (200 mg BID with doses 8 hours apart) and a

structured home-based walking/progressive resistance exercise program, EXCAP, alone or together, on cognitive function and levels of inflammatory molecules (MCP-1, TNF-α, IL-1β, IL-6, IL-8, PGE2) among cancer patients receiving chemotherapy. If these interventions prove to be useful and have a potential benefit, they could have a substantial impact on treating cognitive difficulties experienced by cancer patients ultimately leading to improved performance in activities of daily living, at work, and in interpersonal relationships. Moreover, if there is an effect of these interventions on cognitive functioning and inflammation, we will gain more knowledge of a possible mechanism of chemotherapy-related cognitive difficulties.

2.0 Objectives

2.1 Study hypotheses

A combination of low-dose ibuprofen (200 mg BID with doses 8 hours apart) along with a structured home-based walking and progressive resistance exercise program, EXCAP, will be efficacious in reducing cognitive difficulties among cancer patients receiving chemotherapy, as assessed 1) objectively by a validated computerized cognitive (memory) test (CANTAB), 2) subjectively by a psychometrically validated self-report instrument (FACT-COG) and 3) biologically by cytokine and receptor levels (e.g. MCP-1, TNF-α, IL-1β, IL-6, IL-8, PGE2).

2.1.1. Primary Objective

To collect preliminary efficacy data on a 6-week course of ibuprofen (200 mg BID) and a structured home-based walking/progressive resistance exercise program, EXCAP, combined or alone, for improving cognitive functioning in cancer patients receiving chemotherapy, as assessed objectively by a validated computerized cognitive (memory) test (CANTAB).

Hypothesis 1: Exercise and ibuprofen (combined or alone) will lead to higher memory performances (percent correct across delays) as assessed by the objective CANTAB delayed matching to sample task in cancer patients receiving adjuvant chemotherapy.

2.1.2 Secondary Objective

To collect preliminary efficacy data on a 6-week course of ibuprofen (200 mg BID) and a structured home-based walking/progressive resistance exercise program, EXCAP, combined or alone, for

improving cognitive functioning in cancer patients receiving chemotherapy, as assessed subjectively by a psychometrically validated instrument (FACT-COG).

Hypothesis 2: Exercise and ibuprofen (combined or alone) will lead to higher cognitive functioning score as assessed subjectively by a psychometrically validated instrument (FACT-COG).

2.1.3 Tertiary Objective

To collect preliminary data on the effect of a 6-week course of ibuprofen (200 mg BID) and a structured home-based walking/progressive resistance exercise program, EXCAP, combined or alone, on cytokines and their receptors (e.g. MCP-1, TNF-α, IL-1β, IL-6, IL-8, PGE2) in cancer patients receiving chemotherapy.

Hypothesis 3: Exercise and ibuprofen (combined or alone) will lead to reduced levels of inflammatory cytokines and their receptors ((e.g. MCP-1, TNF-α, IL-1β, IL-6, IL-8, PGE2).

3.0 Subject Eligibility

Inclusion Criteria:

3.1 Must report cognitive difficulties of 3 or higher (on a scale of 0 = “Not Present” to 10 = “As Bad As You Can Imagine”) on our adapted Symptom Inventory question, “Are you currently experiencing any cognitive (e.g. in memory, attention, concentration) problems since your cancer diagnosis?” at the start of or after their first cycle of chemotherapy.

3.2 Must provide informed consent.

3.3 Be able to read English (since the assessment materials are in English).

3.4 Have a primary diagnosis of cancer.

3.5 Be able to swallow medication.

3.6 Women of child-bearing potential (i.e. women who are pre-menopausal or not surgically sterile) must not be pregnant or become pregnant during the 6-week study.

3.7 Agree not to take a daily dosage of an NSAID over 200 mg during the 6-week intervention period. (Higher doses of an NSAID on an ‘as needed’

basis are OK but should not exceed more than 1000 mg for one day per week; higher doses of acetaminophen are OK for pain management.)

3.8 Be scheduled to receive at least 2 additional cycles of oral or IV chemotherapy over the 42-day study period.

3.9 Must have the approval of their treating physician (or physician's nurse practitioner or physician's assistant) to participate in exercise testing (i.e.VO2max test and handgrip test) and a low to moderate home-based walking and progressive resistance exercise program.

3.10 Must have the approval of their treating physician (or physician's nurse practitioner or physician's assistant) to receive the 6 week ibuprofen/placebo regimen (200 mg BID and doses 8 hours apart).

3.11 Must be at least 18 years of age.

Exclusion Criteria:

3.12 Currently taking a consistent dosage (at least 3 days a week) of a NSAID for the last 3 months that is over 400 mg daily.

3.13 Have an allergy to ibuprofen.

3.14 Be identified as in the active or maintenance stage of exercise behavior as assessed by the single-item Exercise Stages of Change Short Form.

3.15 Have physical limitations (e.g. cardiorespiratory, orthopedic, central nervous system) that contraindicate participation in sub-maximal physiological fitness testing or a low to moderate home-based walking and progressive resistance program, as assessed by the oncologist (or physician's designee).

3.16 Have a history of peptic ulcer disease within the last 12 months unless adequately treated, as assessed by the patient's primary care physician or medical oncologist.

3.17 Diagnosed with a neurodegenerative disease.

3.18 Had a myocardial infarction within the past 6 months.

3.19 Patients with a neutropenic episode (characterized by neutropenic fever) during the first cycle of chemotherapy or at high risk for a neutropenic episode during future chemotherapy cycles at the treating physician's discretion.

3.20 Have confirmed metastatic disease to the central nervous system.

3.21 Have been diagnosed with a major psychiatric illness within the last five years.

4.0 Treatment Assignment

4.1 All patients who meet the eligibility criteria, sign the patient informed consent form, obtain physician consent, and complete baseline assessments will be randomized to one of four treatment arms. Randomization will be determined by means of a computer-generated random number table.

4.1.1 This study will use a permuted block-randomized scheme with block sizes of 4 or 8 with equal probability to ensure an equal distribution among the four arms.

4.1.2 Participants will be stratified by gender (female, male) and tumor site (Breast, GI, Other).

4.1.3 A total enrollment of 116 patients is planned (29 in each treatment arm).

4.1.4 All patients will receive usual care monitoring.

4.1.5 Treatment sequence in the four trial arms will be as follows:

Treatment Arm	**Condition**
1	*Placebo:* Patients will be given a 200 mg placebo to be taken BID by mouth and 8 hours apart, beginning on Day 1 of the next on-study chemotherapy cycle for a period of 6 weeks.
2	*Ibuprofen 200 mg BID:* Patients will be given 200 mg of ibuprofen to be taken BID by mouth and 8 hours apart, beginning on Day 1 of the next on-study chemotherapy cycle for a period of 6 weeks.
3	*Placebo and Home-Based Exercise (EXCAP):* Patients will be given 200 mg placebo to be taken BID by mouth and 8 hours apart beginning on Day 1 of the next on-study chemotherapy cycle for a period of 6 weeks along with a progressive walking and resistance band exercise treatment for a period of 6

weeks.

4 *Ibuprofen 200 mg BID and Home-Based Exercise (EXCAP):* Patients will be given 200 mg of ibuprofen to be taken BID by mouth along with a progressive walking and resistance band exercise treatment beginning on Day 1 of the next on-study chemotherapy for a period of 6 weeks.

5.0 Treatment Protocol

5.1 This will be a four-arm feasibility clinical trial of an intervention examining the preliminary efficacy of ibuprofen 200 mg BID alone, a structured home-based walking/progressive resistance exercise program alone, and the combination of ibuprofen 200 mg BID and a structured home-based walking/progressive resistance exercise program for reducing cognitive difficulties during chemotherapy.

5.2 Recruitment, Screening, and Eligibility

5.2.1 Potentially eligible subjects at the University of Rochester Medical Centers will be identified by their physician or other physician-designated clinical personnel. The study coordinator can contact the physician or physician-designated clinical personnel about potentially eligible subjects and the physician or physician-designated clinical personnel can verify that they are ok to approach.

Subjects may also be recruited through the use of study posters, flyers, and brochures. The URMC PEAK Laboratory staff will share information about this study on the laboratory's social media page located at www.facebook.com/URMCPEAKLAB. All study related information posted on the PEAK Lab social media page will be obtained from IRB approved study recruitment materials.

The initial contact will assess whether the patient has any interest in participating in a clinical trial to reduce cognitive difficulties at the start of or after their first chemotherapy treatment. If interested, patients will be screened to determine their eligibility for the study. Screening will be done in a closed room or private area at Wilmot Cancer Institute locations or in our Cancer Control Research Department. Recruitment and screening will be carried out at Wilmot Cancer Institute sites including, but not limited to, Wilmot Cancer Center, Wilmot Cancer Institute's Pluta Cancer Center, Wilmot Cancer Institute at Highland Hospital, Wilmot Cancer

Institute at Park Ridge, and the Wilmot Cancer Institute at Strong West. During screening a patient must report cognitive difficulties of 3 or higher (on a scale of 0 = “Not Present” to 10 = “As Bad As You Can Imagine”) adapted from a similar Symptom Inventory question, “Are you currently experiencing any cognitive (e.g. in memory, attention, concentration) problems since your cancer diagnosis?”

If the patient then meets eligibility criteria, study personnel will explain the details of the study and obtain informed consent from patients who agree to participate. For subjects that are recruited and enrolled, study personnel will complete basic medical history questionnaires with the subjects, show them how to use the pedometer and how to correctly record their steps. Study coordinator will verify at this time that the study subject is not pregnant from their medical record.

Ideally, screening will occur by in-person contact. Screening may also occur by answering to a score of 3 or higher on a written form containing the screening question that has been provided to the patient (e.g. at appointment check-in given by the secretary/administrator or in person with study staff) at the start of or after their first chemotherapy treatment. Only patients that are to be receiving chemotherapy will be provided with this form. The coordinator will follow-up with interested participants to tell them about the study after physician or physician designee approval is granted for study personnel to approach the patient.

5.3 Consent Process, Baseline Assessments, Co-Enrollment, and Participant Compensation

5.3.1 Cancer patients who are scheduled to receive at least 2 additional cycles of chemotherapy or 6 weeks of active chemotherapy treatment who meet the eligibility criteria including approval from their physician will be invited to participate in the trial.

Upon consent, with help from the study coordinator, the patient will complete an On-Study Data Form and a Medication Form to provide clinical and demographic data. Questions concerning the patient’s medical history, supplement and prescription drug usage history, and exercise history are included.

The study coordinator will obtain information necessary to complete these forms from the patient’s medical records when the patient is unable to provide this information in sufficient detail (e.g., staging, Karnofsky Performance Scale or ECOG Performance Status, surgical procedures, types and doses of treatments).

5.3.2 Co-Enrollment in RSRB 54027 and RSRB 31416

Patients receiving cancer treatments at Wilmot Cancer Institute sites that meet inclusion and exclusion criteria for RSRB 54027 and RSRB 31416 are eligible to co-enroll in both RSRB 54027 and RSRB 31416.The principal investigator and study team have determined co-enrollment will not compromise the scientific merit or integrity of the observational study RSRB 54027 or the interventional study RSRB 31416. RSRB 54027 participants that meet all eligibility criteria for RSRB 31416 will be screened and offered the opportunity to co-enroll.

To minimize the burden on study participants co-enrolled in RSRB 54027 and RSRB 31416 redundant study assessments will be not be duplicated for overlapping time points. Study assessments required at both Assessment 5 in RSRB 54027 and the Baseline visit in RSRB 31416 will be completed one time and the data utilized in both studies. Study assessments scheduled at Assessment 5 in RSRB 54027 and at the Baseline assessment for RSRB 31416 are shaded in the Co-Enrollment Assessments Table.

Co-Enrollment Assessments Table		
Procedure/Form	**RSRB 54027 Assessment 5**	**RSRB 31416 Baseline Visit**
On Study Data	Done at Assessment 1	X
Medication Form	X	X
Blood Draw	X	X
PBMC Collection	X	
FACT-G	X	X
FACT-COG	X	X
Computerized CANTAB Tests	X	X
WRAT-4	Done at Assessment 1	X
HVLT-R Form 3	X	X
CTMT	X	X
COWA	X	X
POMS	X	X
FSCL	X	X
PSQI	X	X
CES-D		X
MFSI	X	
ACLS	X	
Symptom Inventory	X	
Cancer Treatment Dosage Form	X	
Toxicity Outcome Form	X	

Cancer Therapy Treatment Notes	X	

5.3.3 Baseline measures of physical activity involve fitting each participant with a Pedometer for a 3-day baseline assessment prior to their next on-study chemotherapy. At baseline, patients will also complete brief and validated measures of cognitive functioning (FACT-COG), quality of life (FACT-G), sleep (PSQI), fatigue (FSCL), anxiety (STAI), mood (POMS), and depression (CESD). These forms will take approximately 15-20 minutes for the patients to complete.

Fasted blood samples (4-6 hours prior to blood draw with encouragement to maintain hydration) will be drawn by URMC-approved phlebotomists (URMC Labs) or by a Wilmot Cancer Institute phlebotomist or nurse. Blood samples may also be obtained at the Clinical Research Center (CRC) located in Strong Memorial Hospital by a CRC phlebotomist or nurse. If the blood sample is not fasted, we will still collect the blood sample and note the last time the person ate in the research record. All subjects will be offered a light snack upon completion of the blood draw and provided with a $5 gift card for a café at URMC.

In a cancer control designated laboratory (e.g. Dr. Mustian's Physical Exercise, Activity and Kinesiology laboratory), patients will complete computerized and paper-based cognitive tests of memory, executive function and processing speed/attention that will total 60 minutes of time.

Patients will then be evaluated on vitals (Resting Heart Rate, Height, Weight & Blood Pressure), aerobic capacity (VO2max Treadmill Test), muscular strength (Handgrip Dynamometry test and upper and lower body fitness testing), body composition (bioelectrical impedance) and physical activity. All exercise testing will be conducted in the Physical Exercise, Activity, and Kinesiology (PEAK) Laboratory. The Physical Activity Readiness Questionnaire (PAR-Q) will be used by the clinical exercise physiologist prior to fitness testing to make sure that patients are ready to perform fitness tests and to guide any modifications.

5.3.4 Participants will be paid for participating in this study. Each participant will receive $40.00 upon completion of the baseline study visit assessments, $50.00 upon the completion of the post-intervention visit assessments, and will be provided with a $5 gift card for a café at URMC upon completion of each study blood draw. Participants will not be paid for visits that they do not complete. Participants can be paid up to $100.00 for taking part in

this study.

If participants will be traveling greater than 25 miles round trip to attend the Baseline and Post-Intervention office visits at the PEAK Laboratory (located at 250 Crittenden Boulevard, Rochester, NY 14642), they will be provided with travel compensation. Distance based compensation will be provided as follows:

- Less than 25 miles round trip = $0
- Between 25-50 miles round trip = $10
- Greater than 50 miles round trip = $20

Participants will be reimbursed for travel expenses up to a maximum amount of $40 during the study. Distance based compensation will not be provided if a participant's research study visit corresponds with a clinic visit. Travel compensation and participant payment costs will be paid from funds from Dr. Janelsins' NCI K07 Award and her other research funds. Participants that are co-enrolled in RSRB 54027 and RSRB 31416 will receive compensation as scheduled for the Baseline study visit in RSRB 31416 in addition to the compensation scheduled for Assessment 5 in RSRB 54027.

5.3.2 Patients will be randomized to one of four treatment arms. Study medication (provided by the University of Rochester Investigational Drug Service (IDS)) and instructions for ibuprofen/placebo 200 mg BID will be given and reviewed with all patients in a cancer control designated laboratory. Study personnel will bring the medication to the cancer control laboratory at the time of randomization. Drug provided by the IDS is stored in a secured location within the Cancer Control Unit at URMC that is locked at all times and only accessible by approved study personnel. Ibuprofen/placebo pills will be over encapsulated in gelatin capsules so that patients will not know whether they have ibuprofen or placebo. Arm 3 and arm 4 patients will also receive instructions and an Exercise Kit for the home-based walking and progressive resistance exercise program. (Note: Patients not randomized to an exercise arm will receive the exercise kit at the end of the study at no cost.)

5.3.2.1 Patients assigned to Treatment Arm 1 will receive a 6-week supply of placebo, which consists of 84 pills of placebo to be taken twice daily (BID) and at least 8 hours apart.

5.3.2.2 Patients assigned to Treatment Arm 2 will receive a 6-week supply of ibuprofen, which consists of 84 pills of ibuprofen to be taken twice daily (BID) and at least 8 hours apart.

5.3.2.3 Patients assigned to Treatment Arm 3 will receive a 6-week supply of placebo, which consists of 84 pills of placebo to be taken twice daily (BID) and at least 8 hours apart and a home-based walking and progressive resistance exercise regimen to follow for a total duration of 6 weeks. Participants assigned to Treatment Arm 3 will wear the pedometer and Garmin DAT and pedometer daily during the study intervention period.

5.3.2.4 Patients assigned to Treatment Arm 4 will receive a 6-week supply of ibuprofen, which consists of 84 pills of ibuprofen to be taken twice daily (BID) and at least 8 hours apart and a home-based walking and progressive resistance exercise regimen to follow for a total duration of 6 weeks. Participants assigned to Treatment Arm 3 will wear the pedometer and Garmin DAT and pedometer daily during the study intervention period.

5.4 Physiological and Psychological Assessments

5.4.1 Baseline assessments will be completed prior to the initiation of the next chemotherapy cycle. Post assessments will occur most often on Day 42 of the intervention. Because scheduling issues can occur, the post assessment may not always be completed on Day 42, and therefore, the post assessment may be performed during the last week on study up until the subject's last on-study chemotherapy.] In the instance of an adverse event, assessments may be delayed.

5.4.2 Fasting blood draws at 2 time-points (baseline and post-intervention) will be done to measure cytokine, chemokine and receptor levels by appropriate ELISA/multiplex methods. These time-points coincide with baseline and post-intervention assessments but are not always on the same day. We often, at the request of the patient, will collect blood along with pre-chemotherapy labs.

Blood draws will be performed by a nurse or phlebotomist in the Wilmot Cancer Institute and or by a nurse from the Clinical Research Center (CRC) at Strong Memorial Hospital prior to the patient's chemotherapy appointment (within 5 days before or the morning/afternoon of). The time of day will be noted, with future assessments at approximately the same time of day during post-testing.

The blood sample (35 ml) for cytokine measurements will be drawn in 2 red (for serum), 2 paxgene (for RNA), and 1 purple EDTA tube (for whole blood) vacutainers and will be transported by a member of the research team to Dr. Janelsins' Laboratory in the Department of Surgery for immediate spinning, processing, and storing (at -20° or -80° C) of serum/whole blood/RNA. All human biological materials will be handled in adherence with the University of Rochester Office of Environmental Safety Biosafety Level II requirements. Dr. William's laboratory is a back-up site should that laboratory be needed for any processing. Dr. William's and Dr. Janelsins' laboratories have received appropriate biosafety certifications by the University of Rochester Institutional Biosafety Committee and undergoes routine inspections. Samples not included in the immunological analyses of this project will be stored for future research by Dr. Janelsins and her team (if the patient has consented that we can use their samples for future research).

5.4.3 Blood Samples for Participants Co-enrolled in RSRB 31416

For participants co-enrolled in RSRB 54027 and RSRB 31416, blood sample collection will occur once for Assessment 5 in RSRB 54027 and the Baseline visit in RSRB 31416. After processing, blood samples will be split equally between the two studies. The total volume of blood collected from participants co-enrolled in RSRB 54027 and RSRB 31416 for both RSRB 54027 Assessment 5 and RSRB 31416 Baseline assessment will be approximately 50 mL.

BLOOD COLLECTION FOR PARTICIPANTS CO-ENROLLED IN RSRB 31416 and RSRB 54027			
	RSRB 54027 Assessment 5	**RSRB 31416 Baseline Visit**	**Co-Enrolled**
Serum (Red Top)	2 tubes (20mL)	2 tubes (20mL)	2 tubes (20mL)
Whole Blood (Purple Top)	1 tube (10 mL)	1 tube (10 mL)	1 tube (10 mL)
Paxgene	1 tube (2.5 mL)	2 tubes (5 mL)	2 tubes (5 mL)
PBMC (Green top)	2 tubes (10mL + 5mL)	Not collected	2 tubes (10mL + 5mL)
Approximate Total Volume	**48 mL**	**35 mL**	**50 mL**

5.4.3 Blood counts measured by standard CBC with differential procedures will be abstracted from the patient's medical record.

5.4.4 All patients will be given a measure of cognitive functioning (Functional Assessment of Cancer Therapy with Cognition (FACT-

Cog)), Functional Assessment of Cancer Therapy (FACT-G), Pittsburgh Sleep Quality Index (PSQI), Fatigue Symptom Checklist (FSCL), Spelberger State/Trait Anxiety Inventory (STAI), Profile of Mood States (POMS), and Center for Epidemiological Studies Depression Scale (CES-D), to complete at home at the appropriate times (i.e. during baseline, and at post-intervention). FACT-COG and FACT-G will be completed at pre- and post-intervention and at week 3 (during the intervention). Additionally, each patient will complete a daily diary which includes questions about symptoms, daily exercise, and drug usage. The exercise daily diary will also be used to measure adherence and compliance to the exercise intervention (if randomized to those arms). Participants assigned to the exercise program will wear the Garmin DAT and pedometer daily during the study intervention period. Participants assigned to non-exercise treatment arms will receive a Garmin DAT at the post-intervention visit.

5.4.5 All patients will be evaluated on aerobic capacity (VO2max Treadmill Test and Resting Metabolic Rate Test), and muscular strength (handgrip dynamometry). All physiological fitness testing will be administered according to the Guidelines for Exercise Testing and Prescription (GETP) as outlined by the American College of Sports Medicine (ACSM).

5.4.6 All patients will be evaluated for cognitive performance on the CANTAB computerized neuropsychological assessment of memory performance on a delayed matching to sample task. This assessment measures memory across delay times (0, 4, 12 seconds) as well as reaction time. This assessment is non-invasive and only requires touching a computer screen. This assessment takes less than 10 minutes to complete. Three other CANTAB tests will be included for secondary/exploratory analyses: Verbal Recognition Memory (Immediate and Delayed memory; ten minutes), Rapid Visual Information Processing (a short 10 minute test of attention and working memory) and One Touch Stockings of Cambridge (OTS) (a short ten-minute test of frontal lobe executive functioning). Paper-based assessment with the WRAT, HVLT-R, COWA, and TMT A/B will also be conducted for secondary analyses.

5.5 Ibuprofen 200 mg (Arms 2 & 4) or placebo 200 mg (Arms 1 & 3)

5.5.1 The ibuprofen arms 2 & 4 will follow the guidelines listed below:

5.5.1.1 The ibuprofen 200 mg pills will be supplied by the University of Rochester Medical Center Investigational Drug

Service and will be over-encapsulated. The pills will be given to the subjects in a plastic vial by the study coordinator and will receive a full 6-week supply as prepared by the IDS. Research subjects will be instructed to take the ibuprofen once in the morning and once in the evening as long as the doses are at least 8 hours apart. Subjects will take 2 capsules /day for duration of 6 weeks. (Note: Study medication is prepared by the IDS and stored in the Cancer Control Unit per section 5.3.2).

5.5.1.2 The placebo 200 mg pills will be supplied by the University of Rochester Medical Center Investigational Drug Service and will be over-encapsulated and given to the subjects in a plastic vial with a six week supply by the study coordinator. Research subjects will be instructed to take the ibuprofen once in the morning and once in the evening as long as the doses are at least 8 hours apart. Subjects will take 2 capsules/day for a duration of 6 weeks. Note: Study medication is prepared by the IDS and stored in the Cancer Control Unit per section 5.3.2).

5.5.1.3 The study coordinator will contact each subject weekly. The study coordinator will use this opportunity to assess any potential complications or toxicities due to the intervention.

5.6 Walking and Progressive Resistance Exercise Arms 3 & 4

5.6.1 The Home-Based Walking and Progressive Resistance Exercise Program, EXCAP, is designed by an Exercise Scientist certified by the American College of Sports Medicine (ACSM) and is in accordance with the guidelines for exercise testing and prescription as set forth by the ACSM. EXCAP has been tested by Dr. Mustian in a pilot study with cancer patients receiving radiation treatment. A large randomized controlled trial of EXCAP is currently being conducted by Dr. Mustian with URCC NCORP and affiliates in patients receiving chemotherapy.

5.6.2 The Home-Based Walking and Progressive Resistance Exercise Program, EXCAP, will follow the guidelines listed below.

5.6.2.1 The Home-Based Walking Prescription will be based on a patient's baseline pedometer assessment. Subjects will be encouraged to increase their total steps walked by a minimum of 5% a week, while maintaining a moderate intensity, during the 6-week intervention. [Note: Walking

intensity will be monitored via the Revised Rating of Perceived Exertion (RPE) Scale, which is a visual analog scale ranging from 0 = No exertion to 10 = Maximal exertion; and part of the daily diary that participants will keep. An RPE between 3-7 corresponds to a heart rate reserve of 40-70%]

5.6.2.2 The Home-Based Progressive Resistance Prescription will be based on a patient's optimal level of challenge. Subjects will be instructed on the proper use of resistance bands. Subjects will then be instructed to choose a resistance band with which they can perform 8-15 repetitions of various upper body resistance exercises (bicep curl, tricep extension, chest press, rows, overhead press) and lower body resistance exercises (leg curl, leg extension, squat, toe raises, side bends). The resistance will be determined via the Revised Rating of Perceived Exertion (RPE) Scale. Participants will choose a resistance level that corresponds to an RPE between 3-7. Subjects will be instructed to begin with 1 set of 8-15 repetitions at a moderately challenging level daily. Patients will be instructed to progressively increase to four (4) sets for each exercise daily with 15 repetitions. Participants will be instructed to use a 3-4 second eccentric movement and a 3-4 second concentric movement. Each resistance training session will last between 30 – 45 minutes. (Note: Patients will be instructed in the proper methods for performing each exercise and will be able to call the coordinator or exercise trainer if questions arise). The resistance band training program is a mild to moderate progressive resistance program designed to maintain strength, muscle mass and function, not a vigorous weight training program designed to substantially increase strength and muscle mass. The dose of resistance exercise is very similar to programs used in rehabilitation. It is common and safe to prescribe resistance exercises like these on a daily basis to maintain strength, muscle mass and function.

5.6.2.3 The study coordinator will talk with each patient on a weekly basis. He/she will answer any questions the patient may have regarding the exercise program in order to facilitate proper adherence and compliance to the exercise intervention.

5.6.3 All Walking and Progressive Resistance Exercises will be performed off-site from the University of Rochester Cancer Institute

in a home-based patient-selected environment.

5.6.4 There will be no costs to the patient for the physiological assessments (e.g. serum collection and muscular strength), resistance bands, pedometer, Garmin digital activity tracker, or Home-Based Walking and Progressive Resistance Exercise Prescription. All costs will be paid from funds from Dr. Janelsins' NCI K07 Award and her other research funds.

5.7 Toxicity Monitoring:

Removal from study: Patients can be removed from the study for any of the following reasons:

1. Any grade ≥ 3 toxicity related to the study drug.
2. A grade 2 toxicity that persists for more than 2 weeks.
3. Withdrawal of consent.

For any clinically adverse event, the toxicity grading scale established by the FDA will be used. It is as follows:

Grade 1 toxicity (Mild): No interference with activity
Grade 2 toxicity (Moderate): Some interference with activity not requiring medical intervention.
Grade 3 toxicity (Severe): Prevents daily activity and requires medical intervention.
Grade 4 toxicity (Potentially Life Threatening): ER visit or hospitalization.

5.7.1 Any grade 3 toxicity or persistent grade 2 toxicity reported to Dr. Janelsins and Dr. Janelsins' research team will be reviewed immediately by one of the medical monitors (Dr. Mohile (primary), Dr. Tejani (secondary), all other protocol oncologists (tertiary)) to determine whether the toxicity is related to the study interventions or to chemotherapy. If the toxicity is <u>at least possibly</u> due to the study interventions, the participant will be removed from the study.

If a study participant is removed from the study, the research team may continue to follow the study participant for assessment data if the participant agrees and medical monitors feel it is safe for the participant to perform study assessments.

5.7.2 Ibuprofen

The potential risks and side effects of ibuprofen include:

Side effects can include headaches, dizziness, drowsiness, rash, abdominal pain, nausea, diarrhea, constipation, and heartburn. Since ibuprofen reduces the ability of blood to clot, bleeding may be increased after injury. Studies of high doses of ibuprofen (800 mg 3 times per day) have been associated with low incidence of gastroduodenal and gastric ulcers.[48, 49] The low dose for the proposed studies is not likely to cause ulcers; as a precaution, we are excluding those who have a history of ulcer disease during the past year.

NSAIDs (e.g. ibuprofen) have been used in clinical studies in cancer patients receiving chemotherapy and have been safe and have not altered chemotherapy pharmacokinetics[50]. The doses of ibuprofen and time-frame of ibuprofen that we have chosen are similar to other ongoing studies of NSAIDs given in combination with chemotherapy (clinicaltrials.gov identifiers: NCT00520091, NCT00300729, NCT00064181, NCT00135018).

5.7.3 Exercise

Commencement of a low to moderate walking and progressive resistance exercise program is not associated with any severe side effects, and risks are minimal for individuals with no cardiopulmonary, orthopedic, or age-identified high risk factors as determined by the patient's treating physician (or designee).

The chance of a cardiac event is rare once coronary disease has been excluded with reasonable certainty. Approximately 1 death per 15,000-20,000 healthy men per year occurs during jogging; this risk is much lower in women. A transient increase in blood pressure may occur with all types of exercise. Although unlikely, the risks involved in a low to moderate walking and progressive resistance exercise program are musculoskeletal— possibly mild muscle soreness, a muscle strain, or related injuries such as tripping. Overall, the risk level for participation in a low to moderate Home-Based Walking and Progressive Resistance program is minimal.

Risks associated with a VO2max test or 6-minute walk test are similar to participation in a low to moderate walking exercise program and are minimal for individuals with no cardiopulmonary, orthopedic, or age-identified high risk factors as determined by the patient's doctor. The nature of these assessments will require a level of exertion causing temporary changes such as an increase in heart rate and blood pressure, both of which are normal responses to moderate exercise. Seven-to-ten Repetition Maximum Tests for

strength may cause minor stiffness and/or tenderness in muscles for a couple of days following testing. The nature of these assessments will require a level of exertion causing temporary changes like an increase in heart rate and blood pressure, both of which are normal responses to moderate exercise. There is a small risk of irritation to the skin from the electrodes used for the BIA analysis.

Every effort will be made to minimize the risks for all study procedures through the approval of the treating physician to enter the study, supervision of all testing and exercise prescription by an American College of Sports Medicine certified Health and Fitness Instructor or a physician (or physician's designee) when necessary according to American College of Sports Medicine Guidelines, the use of standardized guidelines for exercise testing and prescription provided by the American College of Sports Medicine and resting metabolic rate testing. Risks will also be minimized by following the documented and approved procedures for the tests that are performed in the NIH-funded and approved University of Rochester Clinical Research Center, and trained staff will perform these tests.

Dr. Mustian has found the intervention to be safe in breast and prostate cancer patients undergoing radiation treatment [45]; additional approved study with EXCAP in cancer patients receiving chemotherapy and/or radiation therapy is being conducted at the University and through the University of Rochester NCORP program.

5.7.4 There is a chance of bruising and a very slight chance of infection with blood collection. This will be minimized through the use of standardized hospital procedures for blood collection, use of a trained phlebotomist and sterile materials.

5.8 **Adverse Events**

5.8.1 A research coordinator will call each patient weekly to assess side effects. The coordinator will record any adverse events (AE) and/or serious adverse events (SAE). All patients are routinely undergoing close supervision by their oncologist and medical team and often, these AEs and SAEs are addressed during the patients clinic visit as part of the standard of care. If any follow-up appointment is needed regarding the AE or SAE, the patient will follow-up as directed by their oncologist and this will be documented in the research record. Reports regarding potential toxicities, patient safety, and outcomes will be submitted to the University of Rochester Medical Center Research Subjects Review

Board (RSRB).

5.8.1.1 An **adverse event (AE)** is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (eg, including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug, whether or not it is considered to be drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

5.8.1.2A **serious adverse event** (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in **death**.
- Is **life-threatening**. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires inpatient **hospitalization or prolongation of existing hospitalization**. Hospital admissions and/or surgical operations scheduled to occur during the study period but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (eg, surgery performed earlier than planned).
- Results in **persistent or significant disability/incapacity**. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is an **important medical event**. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. 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.

5.8.1.3 An **unexpected adverse event** is any drug/intervention experience, the specificity or severity of which is not consistent with the risk information described in the investigators brochure or general investigational plan. Unexpected as used in this definition refers to an adverse drug event that has not been previously observed rather than from the perspective of such experience not having been anticipated from the pharmacological properties of the drug/intervention.

5.8.2 Adverse Event Reporting

Serious adverse events that are associated with the study and occur while a subject is on study until 14 days after the date the subject goes off study must be reported in writing to the Strong Memorial Hospital IRB within 10 working days. They are also reported to the Data Safety Monitoring Committee within the same time frame. Adverse events that are both **unexpected fatal or life-threatening events** must be reported immediately to the IRB.

5.8.3 Data Safety Monitoring Plan

Investigators will conduct continuous review of data and patient safety. The review will include for each treatment arm level: the number of patients, significant toxicities as described in the protocol, dose adjustments, and responses observed. The Investigator will submit twice yearly summaries of this data to the Clinical Trials Monitoring Committee for review.

Clinical Trials Data Safety Monitoring Committee: The Director of the Cancer Institute delegates responsibility for continued review and monitoring of all clinical trials conducted by the URCC to the Clinical Trials Data Safety Monitoring Committee. This committee provides oversight of study progress and safety by review of accrual and adverse events at biannual meetings. Any adverse event requiring expedited review per protocol will be submitted to the Data Safety Monitoring Committee (DSMC) for determination as to whether further action is required. The study PI and the study medical monitor determine if the adverse event requires expedited review. Interim meetings are scheduled, as needed, to address specific issues that require immediate attention to assure patient safety.

The Committee:

a) Reviews assigned clinical trials conducted at the URCC for progress and safety.

b) Reviews all adverse events requiring expedited reporting as defined in the protocol.

c) Reviews reports generated by the URCC data quality control review process.

d) Submits recommendations for corrective actions to the Protocol Review Committee and the PI

e) In general, outcome data is not made available to individuals outside of the DSMC until accrual has been completed and all patients have completed their treatment. At this time, the DSMC may approve the release of outcome data on a confidential basis to the trial PI for planning the preparation of manuscripts and/or to a small number of other investigators for purposes of planning future trials. Any release of outcome data prior to the DSMC's recommendation for general dissemination of results must be reviewed and approved by the DSMC.

Safety Coordinator: The Medical Director of the Cancer Center Clinical Trials Office appoints the Safety Coordinator. The Safety Coordinator monitors adverse event rates utilizing the URCC Clinical Trials database. If any assigned study has had two or more of the same SAEs reported in a month or more than six of the same SAEs in six months, the DSMC will review the summary of SAEs, discuss events with the Study Chair, and conduct a more detailed review with the Study Chair. The Data Safety Monitoring Chair will determine if further action is required.

5.8.4 All study drugs will be dispensed and all biological specimens will be collected at the University of Rochester Medical Center locations.

6.0 Treatment Evaluation

6.1 Measures

6.1.1 Cognitive Assessments – Computerized (~35 minutes)

6.1.1.1 CANTAB was developed for assessment and evaluation of **cognitive function**. CANTAB tests are reliable and validated and have been reported in over 600 publications, including those by Co-Investigator on this protocol, Dr. Deborah

Cory-Slechta.

The administrator will closely follow the provided script. The primary outcome measure will be **short-term memory** (percent correct) performance across a delay series as assessed by the delayed matching to sample task. This test takes approximately 10 minutes to complete, and a total of three data points is obtained (at 0, 4, and 12 seconds). A subject is shown a complex visual pattern and then, after a brief delay (4 and 12 seconds), is shown four similar patterns. The subject is instructed to touch the pattern on the computer screen which exactly matches the sample. Speed to complete the task (latency in ms) is also assessed within the same measure which may indicate attention/motivation contributions to performance on the task.

6.1.1.2 **Memory (verbal)** will also be assessed by the Verbal Recognition Memory (**VRM**) Task. In this task, the subject is asked to remember a list of words (presented to them on a screen) and then immediately recall them verbally. The subject is then asked to recall from a list if they previously saw the word (pressing yes or no). Following the next two tasks (i.e. the executive function and attention task) approximately 20 minutes later, the subject is then asked to recall whether or not they recognize the word (pressing yes or no) from the original list of words.

6.1.1.3 **Attention** will be assessed by the Rapid Visual Information Processing (**RVP**) task. The second **secondary outcome measure** will be **total latency (ms)**. Errors will also be recorded. A white box is displayed in the center of the computer screen, inside which digits, from 2 to 9, are displayed in a pseudo-random order, at the rate of 100 digits per minute. The subject must detect consecutive odd or even sequences of digits (for example, 2-4-6) and respond by pressing the touch pad.

6.1.1.4 **Executive function** will be assessed by the One Touch Stockings of Cambridge (**OTS**) planning task (**total percent correct)**. Percent correct based on the number of necessary moves involved will also be assessed. The subject is shown two displays containing three colored balls. The displays are presented in such a way that they can easily be perceived as stacks of colored balls held in stockings or socks suspended from a beam. There is a row of boxes containing numbers at the bottom of the screen, from one upwards. The test administrator first demonstrates to the subject how to use the balls in the lower display to copy the pattern shown in the upper display. The balls may be moved one at a time by touching the required ball, then touching the position to which it

should be moved. The subject is shown one demonstration problem, then must solve three further problems. These problems increase in complexity, from one move to four moves. Next the subject is shown more problems and must work out how many moves the solutions require in his/her head, then touch the appropriate box at the bottom of the screen to indicate the number of moves required.

6.1.1.5 All patients will complete the 50-item Functional Assessment of Cancer Therapy with Cognition (FACT-Cog) questionnaire. The FACT-Cog addresses a wide range of cognitive functioning domains which allows one to separate specific domains of cognition. It was developed by Wagner and colleagues[6] and is currently undergoing validation in studies with cancer patients.[51]

6.1.2 Cognitive Assessment – Paper Based (~25 minutes)

6.1.2.1 Basic academic skills/cognitive reserve will be measured with the **Wide Range Achievement Test-Third Edition (WRAT-4).** This test has been validated for individuals aged 5-75.[49] Three subtests are included: reading, spelling, and arithmetic. The reading test includes the recognition and naming of letters and pronunciation of words out of context. The spelling test includes the subject writing his/her name and then writing letters and words as dictated. The arithmetic involves counting, reading number symbols, solving oral problems, and doing written computations.

6.1.2.2 Short-term memory will be assessed by the **Hopkins Verbal Learning and Memory Test-Revised (HVLT-R)**.[50, 51] In this test, the administrator reads a list of 12 words to the subject three times. Immediate recall is assessed after each time. After 20 minutes, the participant is asked to recall the 12 words. The administrator records the number of correct and incorrect words. The score is the number of correct words in both the immediate (3 trials) and delayed recall (after 20 min). For the delayed recall, the number of correct words minus the number of incorrect words will also be recorded.

6.1.2.3 Attention/scanning, speed/sequencing, and executive function will be assessed by the **Trail Making Test (Comprehensive Trail Making Test Trails 1 and 5**).[52, 53] In part A/Trail 1, participants draw a line connected to each number in sequential order. In part B/Trail 5, participants draw a line to connect numbers and letters in sequential order. Time to complete

the test (in seconds) is recorded for both parts A and B. Part A is stopped after 3 min, and Part B is stopped after 5 minutes.

6.1.2.4 Verbal fluency/executive function will be assessed by the **Controlled Oral Word Association Test (COWA)**.[54] Designed by Benton and colleagues, this test assesses fluency with naming words with C, F, and L. Subjects are asked to tell the administrator as many words as possible beginning with the letter C, excluding proper nouns, numbers, and the same word with a different suffix. The subject has 60 seconds to list as many words as possible. The number of correct words, incorrect words, and the number of repeats will be recorded. This test takes less than five minutes to administer. Trials are repeated for the letter F and L.

6.1.3 Inflammation markers

Cytokines and their receptors (e.g. IL-1β, TNF-α, IL-6), Chemokines (e.g. MCP-1 and IL-8) prostaglandins (i.e. PGE2) can be easily measured in the serum with reliable results. Serum is aliquoted into microfuge tubes to minimize freeze/thaw cycles that could result in protein degradation. Cytokine levels will be assessed using a colorimetric ELISAs from R & D Systems in Dr. Janelsins' Laboratory or by Luminex at the URMC Human Immunology Center Core. Inflammation marker RNA levels and genotyping will be analyzed by qRT-PCR at the URMC Genomics Core.

6.1.4 Physical Activity

Physical activity will be assessed by questions on the daily journal. In addition, objective assessments of physical activity will be obtained via the pedometer.

The **Pedometer** devices will be used to assess duration of physical activity via steps walked during the time out of bed. Participants NOT assigned to the exercise arm will give back their pedometer after the 3-day baseline measure and will have the pedometer and reissued for the 3-day measure at the end of the trial. Permission will be obtained to mail the pedometer to the subject if necessary.

The **Garmin Digital Activity Tracker** will be used to evaluate the feasibility and preliminary efficacy of a wrist-worn digital activity tracker for assessing the duration of physical activity via steps walked during the time out of bed. Participants assigned to the exercise intervention will wear the Garmin DAT daily during the study intervention period. Participants not assigned to the exercise

intervention will receive a Garmin DAT at the post-intervention visit.

6.1.5 Aerobic Capacity

Aerobic capacity will be assessed using a **VO2max Treadmill Test** as a measure of compliance using a modified "Branching Treadmill Protocol". Participants begin at a normal walking speed (2.5 mph) and 0% grade. After 2 min. the speed is increased to a faster walking speed (3.0 mph) and 0% grade. After 2 min, the speed is increased to 3.5 mph and 2% grade. Thereafter, only the grade is increased by 2% every 2 min. Oxygen consumption (VO2), carbon dioxide production (VCO2), and flow rate will be measured continuously. The test is ended when the participant wants to stop. An MD is available onsite in the hospital during all tests as outlined by the ACSM fitness testing guidelines. In preparation for the exercise treadmill test, subjects have the option to fast for 4 hrs prior to the test and they will be asked to rest quietly on a bed in a quiet room for 30 minutes under a clear canopy which is placed over their head. During this 30 minute period, they will have their **resting metabolic rate** measured for 30 minutes using continuous, computerized open-circuit indirect calorimetry (Sensormedics® Vmax). A 6-Minute walking test may be substituted for the treadmill test in the event the person is not able to complete it. This is a sub maximal measurement using a 6 minute walk protocol. Participants are given a short warm up and cool down walking protocol in the test walking area in the University of Rochester. Participants walk for a total of 6 minutes and cover as much distance as they can during this time. Upon completion of the test, the total distance walked is used to calculate an estimate of aerobic capacity (VO2max:Maximal Oxygen Consumption).

6.1.6 Muscular Fitness

Muscular fitness will be assessed using a handgrip dynamometer test and the 7-10 repetition maximum dynamic strength testing protocol.

The **Handgrip Dynamometer Test** is a grip strength test used to assess the maximal voluntary contraction generated by the arm muscles. The test is administered with the patient standing in anatomical position; the elbow joint angle will be held constant at 180 degrees with the medial distal humeral epicondyl held 2 inches from the torso. Trials will be performed in an alternating bilateral sequence for a total of six attempts (three with each arm). The best score of the three trials will be used for right and left limbs to calculate static strength. The surgically involved arm(s) will be

noted for data analysis. The handgrip dynamometer test has been previously used in a number of URCC NCORP protocols and has shown to be a reliable clinical method of assessing strength. [52]

The standard **7-10 Repetition Maximum Dynamic Strength Testing Protocol** will be used to estimate patients' 1-repetition maximums for the **leg extension (quadriceps) and bench press (pectoralis and deltoid)**. The patients will receive a full orientation to the fixed resistance machines and proper lifting form by a certified (e.g., ACSM) exercise testing professional. Participants will perform a light warm up consisting of 8 lift repetitions employing the lightest weight on the machine. After the warm up, patients will be given a 2-3 minute rest break. A weight will be selected by the exercise testing staff based on the ease or difficulty of completing the warm up for each patient and this weight will be lifted until subjective fatigue. Alternating rest breaks (2-3 minutes) and lifting bouts will continue with the resistance weight being adjusted by the exercise testing staff until the patient reaches a level of resistance that results in subjective fatigue between 7-10 repetitions. Established algorithms employing the weight lifted and the number of repetitions completed will then be used to estimate the patients' 1-repetition maximum.[53]

6.1.7 Muscle Mass

The **RJL Bioelectrical Impedance System** is a non-invasive, easy-to administer and safe method of assessing **lean body mass**. BIA involves passing a small electrical current through the body and evaluating the reactance and resistance to flow, which are related to fat-free mass (FFM) and total body water. Prediction of lean body mass from BIA is as reliable as skin-fold measurements and hydrostatic weighing. Participants have the option to be 4 hours fasted, although it is not required. Participants need to be abstained from alcohol and diuretics (unless prescribed) for 48 hours, well hydrated (water only), and voided completely prior to assessment. We will also document whether participants exercised within the last 12 hours or not. Participants lie supine on a flat surface for approximately 5 minutes prior to the test, to ensure a resting metabolic state. Electrodes are attached to the right hand (distal end of the 3rd and 4th metacarpal and distal end of the ulnar and radius), and the right foot (distal end of the 3rd and 4th metatarsal and distal end of the tibia and fibula). Skeletal muscle mass will then be calculated from the lean body mass. [54]

6.1.8 Daily Diaries

Participants will be asked to complete daily diaries each night. All participants will complete the Daily Symptom Diary. Participants assigned to the exercise intervention will be asked to record step counts measured via pedometer and Garmin digital activity tracker, number of minutes they exercised that day (aerobic and resistance training), perceived exertion during exercise, and severity of eight symptoms assessed on 11-point scales anchored by 0 = "Not Present" and 10 = "As Bad As You Can Imagine" on the Exercise Daily Diary. The symptoms queried about at their worst on a daily basis are fatigue, sleep, stress, depression, concentration, memory, pain and anxiety. The diary takes 2-3 minutes to complete. Questions about daily exercise and daily NSAID usage are also included. Note: When patient diaries are returned to us they the symptom section will be reviewed for indications of problems and the patient's medical team will be notified if any symptom is consistently scored as 4 or higher throughout the study period. The study coordinator will ask about symptoms during weekly phone calls and will contact the subject's medical team if a severe complaint (scored as 8 or greater and out of the ordinary for the patient) is made.

6.1.9 Quality of Life

The Functional Assessment of Cancer Treatment-General (FACT-G) is a 27-item assessment of **four domains of well-being**: physical, social/family, emotional, and functional. Subjects are asked questions related to domains of well-being on a five point scale (0-4) with 0 being a score of "not at all" and 4 being a score of "very much". This questionnaire is a well-validated test for assessment of quality of life for cancer patients receiving treatment.[55, 56]

6.1.11 Mood

General mood will be assessed using the short form of the **Profile of Mood States (POMS)**. The POMS consists of 30 adjectives in 6 subscales (e.g., anxiety, depression), which subjects rate on a five-point scale with "1" = "Not at all" and"5" = "Extremely" to describe their moods over the past week. The POMS has been used extensively in research with cancer patients and has demonstrated reliability and validity. [57, 58]

6.1.12 Fatigue

The **Fatigue Symptom Checklist (FSCL)**[59] will be administered to measure **fatigue**. This instrument consists of 30 items in three

subscales that have been associated with fatigue: drowsiness and dullness, difficulty of concentration, and projection of physical impairment. Subjects are asked to indicate the presence and intensity of each item on a five-point scale. Both the number and intensity of fatigue symptoms can be calculated for this scale.

6.1.13 Anxiety

Anxiety will be measured using the **Spielberger State/Trait Anxiety Inventory (STAI Form X-1).** In order to reduce the overall patient burden, we will use only the state portion of the questionnaire. This one-page, self-administered questionnaire consists of 20 short statements which people may use to describe their feelings. Participants are asked to fill in a numbered circle to indicate the degree to which they generally experience the particular feeling, ranging from 1 = “Not at all” to 4 = “Very much so” at that time. It is one of the most widely-used assessments of anxiety. Internal consistency coefficients > 0.90 have been shown, along with test/retest reliability coefficients > 0.70. Concurrent, construct, convergent and divergent validity have also been demonstrated. [63] We have successfully implemented this measure in previous studies.

6.1.14 Sleep

The **Pittsburgh Sleep Quality Inventory (PSQI**), a commonly used, 25 item psychometrically sound measure scored for both global severity and subscale scores, will assess sleep initiation and maintenance problems and possible etiologic factors (e.g., pain, nightmares, hot flashes).[64] This measure has been implemented in other NCORP studies conducted by our group.

6.1.15 Depression

Depressive *symptoms* will be measured with the **Center for Epidemiological Studies Depression Scale (CES-D).** The CES-D is a 20-item depression scale developed and validated for use with a variety of populations. It is in a format similar to that of the Beck Depression Inventory, but with less emphasis on physical symptoms of depression that may be confounded with disease symptoms or treatment side effects. It has been shown to reliably and validly measure depression in cancer populations,[65] and we have successfully used this measure in previous studies.

Note: Because cognitive difficulties, depression, anxiety, mood disruption, sleep disturbance and fatigue are often present as

symptom clusters, measures of depression, anxiety, mood, sleep and fatigue have been carefully selected to minimize potential confounding and enable assessment of possible confounds between these concepts.

6.1.16 Feedback Questionnaire

At the post-intervention assessment, we will ask patients to complete a 3-item questionnaire about the usefulness and acceptability of the study treatments.

6.1.17 Disclosure of Physical Activity Results

After completion of study participation and upon request, results of physical activity testing may be shared with the patient by the coordinator and exercise physiologist. If requested, A Summary of Physical Activity Testing sheet will be completed by the study coordinator and mailed to the patient. The sheet will contain results of the patient vitals (pulse, blood pressure, height, weight), body composition, and metabolic, strength, and cardiopulmonary assessment results. The study coordinator or exercise physiologist will discuss the results provided on the Summary of Physical Activity Testing sheet over a follow-up phone call with the subject or in person in the PEAK lab.

7.0 Statistical Considerations

7.1 Primary analyses: The primary purpose for conducting this Phase II pilot study is to gather preliminary efficacy data for the development of a larger R01-level investigator-initiated grant submission of efficacy. The primary analyses will consist of calculating means, standard deviations and effect sizes for each of the objectives at pre-intervention and post-intervention in each of the 4 study arms.

These analyses will be interpreted as providing preliminary effect size estimates for an R01 submission. The main analyses are described individually below for each of the study hypotheses.

Stratification: All models will have gender and site as additional covariates.

7.1.1 Hypothesis 1 (Primary Objective): Exercise and ibuprofen (combined or alone) will lead to higher short-term memory performances (percent correct across delays) as assessed by the objective CANTAB delayed matching to sample task in cancer patients receiving adjuvant chemotherapy. The mean effect of

treatment arm scores will be assessed by ANCOVAs, using the longest delay on this task (1200 ms), with baseline as a covariate. Interaction terms may be included but removed if not significant. We will also assess other covariates that may influence cognitive function, including age, education level, menopausal status (if applicable), and WRAT-4 reading score. Additionally, repeated measures ANOVAs using mixed modeling across sessions (0,4,12 second delays) will be used. To model the response (Post-intervention – Baseline), the fixed effects will be delay, arm, and delay x arm interaction. Random effects will be patient to patient and within patient variability. All main effects will be studied by post-hoc tests. In all cases, p values of ≤ 0.05 will be considered statistically significant.

7.1.2 Hypothesis 2 (Secondary Objective): At post-intervention, the effects of exercise and ibuprofen (combined or alone) on quality of life as assessed by the FACT-COG self-reported cognitive performance after completion of all chemotherapy compared to the control. The mean effects of treatment arm scores will be assessed by ANCOVA incorporating baseline as a covariate. Interaction terms will be incorporated initially but removed if not significant. We will also assess other covariates that may influence cognitive function, including age, education level, menopausal status (if applicable), and WRAT-4 reading score.

7.1.3 Hypothesis 3 (Tertiary Objective): At post-intervention assessment, exercise and ibuprofen (combined or alone) will lead to reduced immune marker levels compared to standard care in cancer patients receiving adjuvant chemotherapy. The mean effects of treatment arm scores will be assessed by ANCOVA incorporating baseline as a covariate. Interaction term between baseline and arm will be included initially, but removed from the model if not significant. We will also assess other covariates that may influence cognitive function, including age, education level, menopausal status (if applicable), and WRAT-4 reading score.

7.1.4 Exploratory Hypotheses: Additional analyses will examine between group differences in the other outcome measures. These will include performance on CANTAB attention and executive functioning tests, paper-based tests of attention, reading, executive function and verbal memory, Physical Activity (Pedometer), aerobic capacity (VO2max treadmill test, Resting metabolic Rate), muscular strength (handgrip dynamometry and 7-10 Rep. Max Tests), body mass (BIA), other disease or cognitively related biomarkers, and self-reported measures (i.e. cognitive functioning, quality of life, fatigue, anxiety, depression, sleep, mood). These exploratory

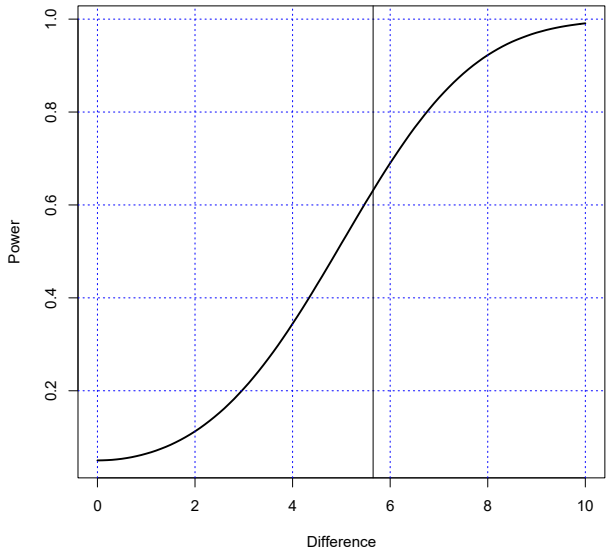
analyses may be useful in refining or adding to the follow-up larger study. Preliminary analyses of the relationships to these outcomes and biomarkers will be conducted.

7.2 Sample Size

7.2.1 116 is the target accrual for this Phase II study and was selected as an adequate size to provide pilot data for effect size determination for subsequent R01-level studies.

7.2.2 It is possible that 20% of patients will not provide evaluable data leaving approximately 23 evaluable patients per treatment condition. This number of patients will be adequate to meet our primary objective of ascertaining the appropriateness of our procedures and methods and to provide data to generate a sample-size estimate for a R01-level investigator-initiated grant, especially considering that we will be able to take advantage of the 2x2 factorial design in determining the intervention effectiveness. We have been able to determine preliminary power based on Dr. Janelsins' feasibility research with the CANTAB cognitive battery. Using our preliminary CANTAB DMS data, the standard deviation of percent correct for all delays was 11.3. Assuming 23 evaluable subjects per arm (21% attrition), alpha=0.05, and 80% power, ANCOVA should be able to detect a change of 7%. This assumes a correlation of about 0.8 between baseline and post-intervention. This is based on the effect size for the most conservative pattern of four means: (0, d/2, d/2, d) where d is the largest difference existing among the means. The power curve is shown in the figure, with a vertical line marking ½ SD.

Power Across Possible Detectable Differences of Primary Outcome Measure



7.2.3 Based on Dr. Janelsins' preliminary research with co-investigators and oncologist collaborators on this project, it will take approximately 4 years to enroll 116 participants

8.0 Schedule of Activities

Procedure	**Time Since Randomization**		
	0	21 Days	42 Days
Eligibility Interview	X		
Informed Consent	X		
Clinical Record Information	X		X*
On Study Data	X		X*
Medication Form	X		X*
Blood Collection Information (e.g. Date, Time, Volume)	X		X
Blood CBC Levels	X		X
Inflammation Markers (Protein, RNA, DNA)	X		X
Phone Calls	Weekly	Weekly	Weekly
Daily Diary	Daily	Daily	Daily
FACT-G	X	X	X
FACT-COG	X	X	X
CANTAB Cognitive Tests	X		X
Paper-Based Cognitive Tests	X		X
Resting Metabolic Rate	X		X
VO2max Treadmill Tests	X		X
Pedometer	X		X
Handgrip Dynamometer	X		X
BIA	X		X
7-10 Repetition Maximum Test	X		X
POMS	X		X
FSCL	X		X
PSQI	X		X
CES-D	X		X
*Update			

8.1 All hardcopy research records will be stored onsite in the University of Rochester Medical Center, in the Behavioral Medicine Unit of the Saunders Research Building and the Wilmot Cancer Institute. The Cancer Institute is secured by electronic key cards. Offices within the Cancer Institute are again secured by key and data is kept in locked file cabinets. Electronic research records are stored on the University of Rochester Medical Center's password secured and firewall protected networks. These are the same methods of security used for patient medical records. Human serum samples and biopsy samples are stored in locked freezers, within locked and alarmed laboratories that are accessible by key codes and electronic card swipes. All final files, databases and blood samples that are stored after study completion will remain on secured servers or in locked freezers, respectively, and all information will be de-identified.

8.2 All data (information, human blood samples, and human tissue samples) collected for the current study will be used in post hoc analyses as appropriate. The patient indicates on the consent form whether their blood is allowed to be used for future research. If a patient does not allow their blood to be used for future research, their blood will not be banked. Patients also are provided the opportunity to be contacted for future research studies in the informed consent. The patient's individual research record will not be shared with their treating physician, unless they provide consent or the patient's treating physician is a study physician, in which case they will have access to study data as a study co-investigator. A short letter with feasibility findings and notice of extension of the study due to federal grant funding will be provided to the 36 participants accrued before 2/2013. Overall study results will be presented to participants, faculty and staff at the University of Rochester Medical Center. Study results will be presented at professional meetings and published.

8.3 The study coordinator will assign a numerical Study ID to each participant once they have signed the consent form. Questionnaires will use this number and the participant's first, middle, and last initials as identifiers, to ensure data integrity. Other identifying information will not exist on these forms. A complete list of study participants with study ID, name, and contact information will be maintained separately. This linkage information will only be accessible to the study coordinator, study investigators, and the individual responsible for maintaining the database.

9.0 Patient Consent and Peer Judgment

9.1 Current, state, federal, and institutional regulations concerning informed consent will be followed. Participation in this study is voluntary. Participants are free not to take part or to withdraw at any time, for whatever reason, without risking loss of present or future care they would otherwise expect to receive. In the event that a patient does withdraw

from the study, the information they have already provided will be kept in a confidential manner. Participants may discontinue participation in the study at any time if they decide they do not wish to take part any longer. Participants may be withdrawn from the study by research personnel if it is deemed in their best interest to no longer participate.

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