UNIVERSITY OF ROCHESTER
CANCER CENTER CCOP RESEARCH BASE

A Study of the Effects of Exercise on Cancer-Related Fatigue
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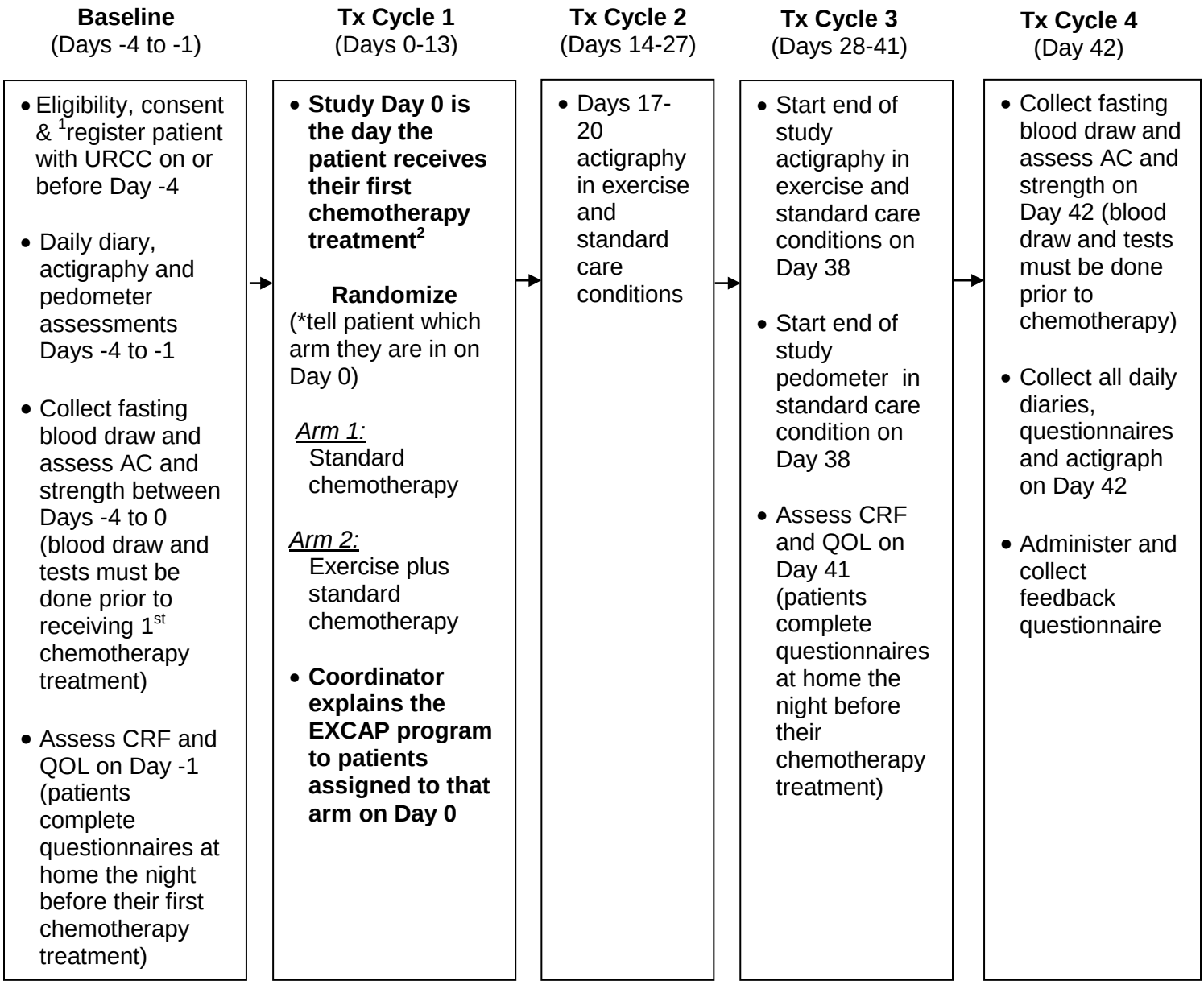
TABLE OF CONTENTS

Study Schemas

Rev 4/10; 11/10

Schema for 2-week cycle chemotherapy regimens



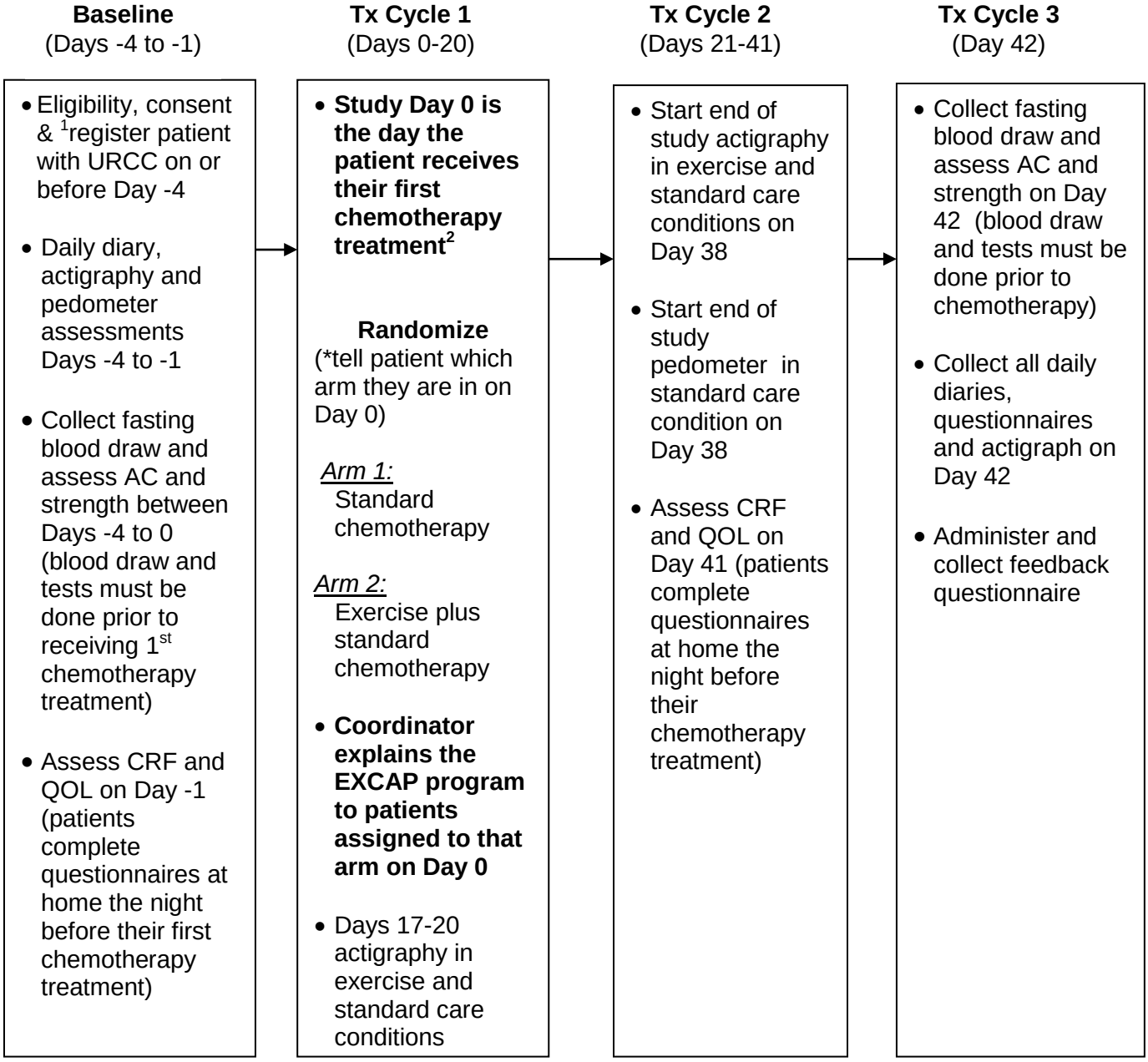
[Notes. Tx = chemotherapy treatment; CRF = cancer-related fatigue; AC = aerobic capacity; QOL = quality of life]

[1]THE COORDINATOR WILL RECEIVE THE RANDOMIZATION INFORMATION FOR EACH PATIENT WHEN THEY REGISTER THE PATIENT WITH URCC ON DAY -4. THE COORDINATOR MUST CONCEAL THE RANDOMIZATION ARM FROM THE PATIENT UNTIL DAY 0.

[2] IF CHEMOTHERAPY IS DELAYED, THE PARTICIPANT SHOULD CONTINUE WITH STUDY REQUIREMENTS IN THE SAME MANNER AS IF CHEMOTHERAY HAD STARTED.

Schema for 3-week cycle chemotherapy regimens

Rev 4/10; 11/10



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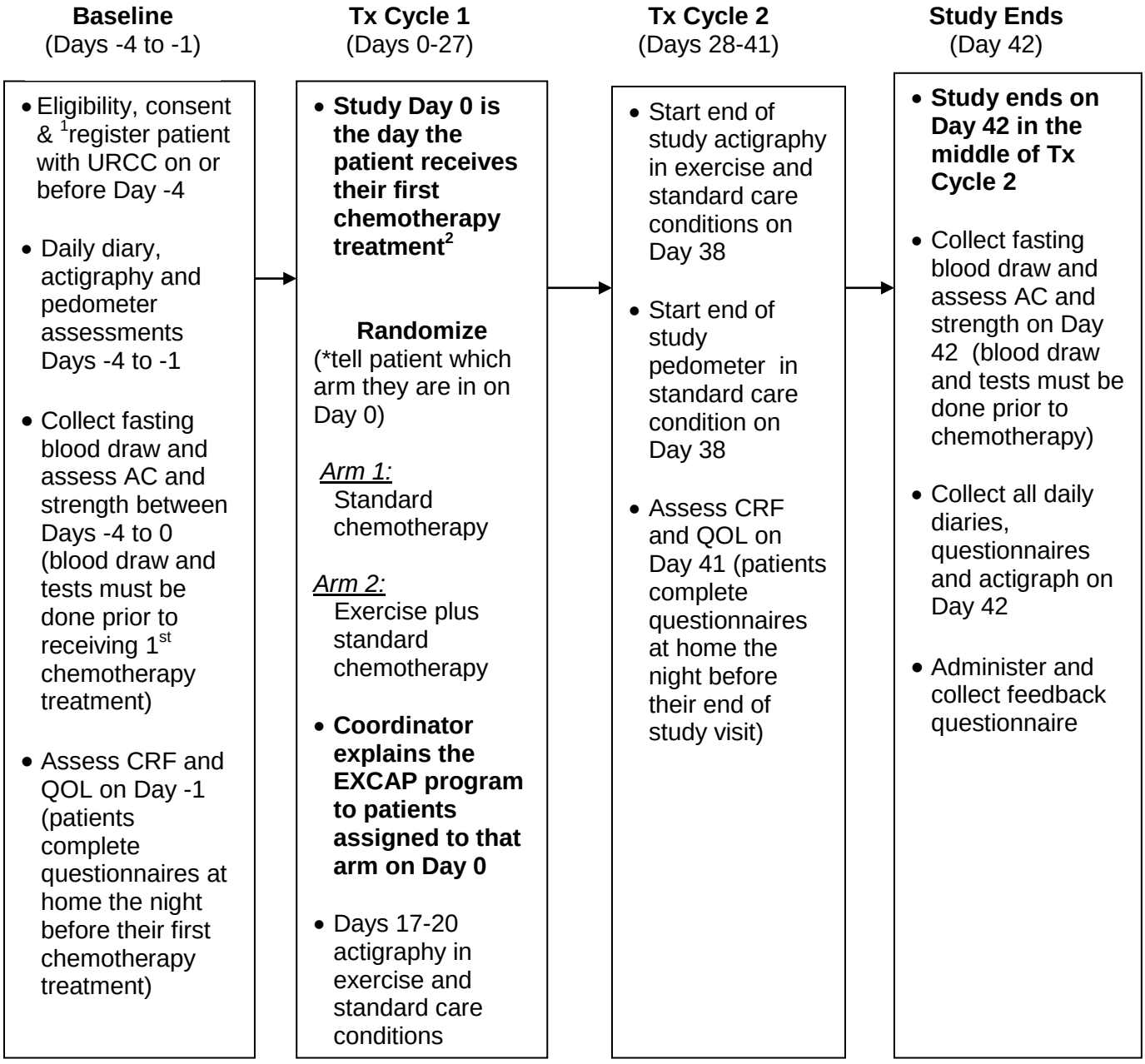
[1]THE COORDINATOR WILL RECEIVE THE RANDOMIZATION INFORMATION FOR EACH PATIENT WHEN THEY REGISTER THE PATIENT WITH URCC ON DAY -4. THE COORDINATOR MUST CONCEAL THE RANDOMIZATION ARM FROM THE PATIENT UNTIL DAY 0.

[2] IF CHEMOTHERAPY IS DELAYED, THE PARTICIPANT SHOULD CONTINUE WITH STUDY REQUIREMENTS IN THE SAME MANNER AS IF CHEMOTHERAY HAD STARTED.

[3] PATIENTS RECEIVING ORAL CHEMOTHERAPY SUCH AS XELODA WILL MOST CLOSELY FOLLOW THIS SCHEMA; ALL PATIENTS RECEIVING ORAL CHEMOTHERAPY MUST BE CONSENTED AND ENROLLED PRIOR TO RECEIVING ANY CHEMOTHERAPY TREATMENT.

Rev 4/10; 11/10

Schema for 4-week cycle chemotherapy regimens



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1.0 Introduction

Cancer-Related Fatigue During Chemotherapy. The most common source of distress and quality of life (QOL) impairment during chemotherapy is cancer-related fatigue (CRF).[1-11] CRF is a multi-faceted, subjective, physiological state characterized by persistent and overwhelming exhaustion along with a decreased capacity for physical and mental work.[1-4,7,8,12] The experience of CRF involves physical symptoms (weakness, tiredness, shortness of breath), mood symptoms (depression, anxiety), motivational symptoms (lack of initiative or motivation), cognitive symptoms (impairment of cognitive function), and social symptoms (reduced social interaction).[1,2,13-15] Data from multiple studies indicate that the frequency of CRF in patients with a variety of cancer diagnoses receiving chemotherapy ranges from 70% to 100%[1,2,14,16] and that CRF interferes significantly with QOL.[1,2,13,14,17-19] Results from a prospective "Patient Needs Assessment Survey" of 458 patients conducted by the University of Rochester Cancer Center Community Clinical Oncology Program (URCC CCOP) Research Base suggest that virtually all patients (98%) experience CRF during chemotherapy. In this study, 458 patients completed questionnaires assessing CRF with an 11-point scale (0 = symptom not present to 10 = as bad as you can imagine) prior to and after completion of chemotherapy. The mean level of CRF rose from 2.7 (SE = 0.11) during the week prior to the first chemotherapy cycle to 6.8 (SE = 0.12) during chemotherapy. 61% of these patients experienced severe CRF of 7 or above during the course of their treatment. Cancer patients report that CRF begins with the onset of treatment, continues during the course of chemotherapy, and declines somewhat but persists at a higher-than-baseline rate after treatment is completed.[1,2,20-22]

Patients who report CRF concurrently experience additional side effects such as sleep disruption, reduction in aerobic capacity, muscle weakness, anemia, hypothyroidism, depression, anxiety, pain and cognitive problems.[1-8,13,14,23-32] CRF reduces cancer patients' ability to participate in leisure activities,[33] their capacity to sustain meaningful relationships and activities with their families,[34] their ability to work, and their capacity to engage in social and other activities during and after treatment.[35,36] CRF places patients in a position of dependence on others for home management, transportation, and even simple self-care activities such as preparing food and bathing.[36,37] This change in daily activity and self-sufficiency is demoralizing and discouraging. In addition to the activities in which fatigued patients are unable to participate, patients must engage in unwanted activities such as lying down or taking naps in an attempt to cope with their CRF.[38] CRF is more distressing and has a greater impact on patients' daily activities and QOL than other cancer-related symptoms such as pain, depression, and nausea.[39] This impact is magnified by the increasing life expectancy of people with cancer and by the persistence of CRF for months or even years after the completion of cancer treatment.[40-44] **Indeed, abundant evidence shows that CRF has a pervasive deleterious influence on QOL and it may also interfere with a patient's ability to complete her or his prescribed chemotherapy regimen.**[1-8,13,14,23,24]

2.0 Background

Despite the frequency of CRF, only a few large phase III randomized controlled trials examining interventions for CRF exist in the current research literature. Therefore, little evidence is available to direct clinical practice or to develop guidelines for standard care.[3-8] Several reasons are posited for this lack of attention to the management of CRF: 1) CRF is viewed as a normal, expected, and only temporary effect of a cancer diagnosis and treatment, 2) CRF is viewed as a secondary effect related to anemia, hypothyroidism, sleep disturbance, depression, anxiety and other clinically diagnosable conditions and is expected to resolve with adequate treatment of these side effects, 3) CRF is expected to resolve with increased rest and energy conservation, 4) the CRF experienced by cancer patients is considered no more prevalent or debilitating than the fatigue experienced by individuals without cancer, 5) patients and clinicians may fail to adequately communicate regarding the prevalence and severity of CRF, and 4) oncology professionals may not possess adequate knowledge of diagnostic and management options regarding CRF.[3-8,13]

Current Methods for Managing Cancer-Related Fatigue. The established guidelines for the management of CRF currently proposed by the National Comprehensive Cancer Network[45] suggest that clinicians frequently screen for CRF in cancer patients and, when CRF is present, screen for possible contributory factors (e.g., pain, emotional distress, sleep disruption, anemia, poor nutrition) and organ system dysfunctions. When contributory factors are identified, clinicians treat them via pharmacological means: colony stimulating factors, antidepressants, steroids, benzodiazepines, benzodiazepine-receptor agonists, thyroid hormones and psychostimulants.[1,2,13,14,24,46] CRF is expected to resolve with these treatments.[1,2,13,14,24] Unfortunately, many cancer patients continue to experience CRF even after successful treatment of these contributory factors with pharmacological therapies.[1,2,13,14,24,47,48] Clinicians often encourage patients who experience CRF to rest and conserve energy, but CRF and its associated detrimental effects on QOL are not alleviated by periods of rest, as is the case with fatigue induced by other causes.[1,2,13,14,23,24,38] In fact, preliminary research suggests that increasing physical activity helps reduce CRF by preventing deconditioning.[13]

Physical deconditioning refers to a generalized physiological deterioration resulting from a simple reduction in physical activity or exercise. This deconditioning occurs fairly rapidly and is often first recognized clinically by patient reports of shortness of breath, weakness, and fatigue. Objective assessment reveals reduced aerobic capacity, strength, and muscle mass. Deconditioning as a consequence of diminished physical activity resulting either from the cancer itself or its treatments produces these reductions in aerobic capacity, strength, and muscle mass and, ultimately, causes CRF.[13,23] Many patients begin chemotherapy with decreased levels of physical activity as a result of their cancer diagnosis and/or surgical treatment, and their physical activity declines further during chemotherapy.[49,50]

Rationale for an Exercise Intervention to Reduce Cancer-Related Fatigue During Chemotherapy. In 5 recent reviews of more than 55 studies, Mustian and colleagues,[13] Cramp and colleagues,[51] Galvao and Newton,[52] Stevinsen and colleagues,[53] and Knols and colleagues[53,54] report on the benefits of exercise among cancer survivors during and after treatment. Exercise improved 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.

In early studies, MacVicar and colleagues[55,56] reported that breast cancer patients receiving chemotherapy and completing a moderately intense progressive 10-week interval-training cycle ergometer program (60-85% of heart rate reserve, 3x/week) demonstrated significantly reduced CRF, improved aerobic capacity (VO_2 maximum, heart rate, maximum test time, maximum workload), and improved mood compared with patients in a flexibility and stretching placebo condition and patients in a usual care control condition.

Mock and colleagues[57-59] demonstrated improvements in CRF, aerobic capacity (walking ability), QOL, depression and nausea among breast cancer patients during chemotherapy with home-based walking programs of moderate intensity (self-paced intensity) ranging from 3-5 days/week for 10–45 minutes compared with non-exercising controls.

Schwartz and colleagues[60-62] showed that low to moderately intense home-based aerobic exercise programs (walking or activities of patient choice) performed 3-4 days/week for 15–30 minutes resulted in less CRF and better aerobic capacity and QOL among breast cancer patients during chemotherapy.

Dimeo and colleagues[63] reported that mixed cancer patients receiving high-dose and conventional chemotherapy in addition to autologous peripheral blood stem cell transplantation maintained aerobic capacity when completing a moderately intense interval walking program (alternating between 70% of heart rate maximum and half speed for 3 minutes each) 7 days/week for a total of 33 minutes during hospitalization. In a second study Dimeo and colleagues [64] reported less CRF and psychological distress among mixed cancer patients participating in a moderately intense interval bed cycle-ergometer program (alternating between 50% of heart rate reserve and rest pauses for 1 minute each) 7 days/week for a total of 30 minutes while hospitalized during high-dose and conventional chemotherapy in addition to autologous peripheral blood stem cell transplantation when compared with patients in a usual care control condition.

Segal and colleagues[65] showed that breast cancer patients undergoing chemotherapy demonstrated improved aerobic capacity and self-report physical function when completing a self-directed (home-based, 5x/week for 26 weeks) or a supervised (3x/week supervised with 2x/week home-based exercise for 26 weeks) moderately intense (50-60% of maximum oxygen uptake) walking program compared with usual care controls.

Adamsen and colleagues[66] reported that patients undergoing high-dose or conventional chemotherapy and completing a 6-week intervention that included physical exercise, relaxation, massage, and body awareness showed significant increases in aerobic capacity and strength, as well as additional improvements in CRF, QOL domains, anxiety, and pain. The exercise component of the program consisted of 90-minute sessions 3x/week and included warm-up, aerobic (60-100% of maximum heart rate, stationary cycling), and heavy resistance (85-95% of 1 repetition maximum, 3 sets of 5-8 repetitions) exercise.

Courneya and colleagues[67]also demonstrated improvements in CRF, aerobic capacity, QOL, several domains of emotional well-being, and flexibility among colorectal cancer patients undergoing chemotherapy with a moderately intense (65-75% maximal heart rate) walking and flexibility program 3-5 days/week for 20-30 minutes compared with patients in a waitlist control condition.

Headley and colleagues[68] found less CRF and better QOL among metastatic breast cancer patients receiving chemotherapy participating in a home-based low intensity, seated exercise program 3 days/week for 3 months compared with patients in a usual care control condition.

Campbell and colleagues[69] demonstrated greater improvements in CRF among participants in a supervised mixed mode exercise program 2 days a week for 10-20 minutes at a moderate intensity for 12 weeks compared to non-exercising participants in a small pilot study.

Collectively, the results of these studies provide **preliminary** evidence that exercise is safe and well tolerated by cancer patients undergoing chemotherapy. This research also suggests that exercise interventions that involve moderately intense (60-75% of heart rate maximum) aerobic exercise (e.g., walking and cycling) ranging from 10-90 minutes in duration, 3-7 days/week are effective at reducing CRF and improving aerobic capacity and QOL in patients receiving chemotherapy. One study that was not a randomized controlled design showed that progressive resistance training (3x/week; 85-90% of 1-repetition maximum; progressively increasing sets and repetitions) was effective at maintaining strength, reducing CRF, and improving QOL among cancer patients receiving chemotherapy.

Although the extant exercise and cancer control literature provides support for the beneficial effects of exercise interventions among cancer survivors during and after treatment and suggests consistent reductions in CRF during chemotherapy, these studies have several scientific limitations. Limitations include non-randomization, a lack of controlled comparisons, small sample sizes, and additional methodological concerns.[52] For example, many of these studies use quasi-experimental designs with one treatment arm and no randomization resulting in a lack of appropriately controlled comparisons. Sometimes the patients who complied with the exercise intervention were compared with the patients who did not comply with the exercise intervention. Therefore, it is impossible to determine whether the patients who experienced CRF did not exercise because of CRF or if the exercise intervention actually reduced the CRF in these studies. These studies also have small sample sizes ranging from 9 to 123, with the most common sample sizes between 30 and 70. There is a lack of consistency with regard to the dose of exercise (frequency, intensity, mode and duration) in these interventions, which makes it impossible to draw conclusions or to effectively tailor specific exercise prescriptions that are cost and time efficient. The studies that examined aerobic exercise used various modes such as walking, stationary upright cycling, bed ergometer cycling, and activities of patient choice at various frequencies (3-7 days/week) and various durations (10-90 minutes). Only one study examined the influence of resistance training as a mode of physical exercise, providing only limited evidence of efficacy. Additional methodological concerns include the variability in measures used to assess study outcomes; for example, several different self-report instruments with varying degrees of dimensionality were used to assess CRF and QOL, and different methods were used to assess aerobic capacity (e.g., walking tests and graded exercise sub-maximal testing).[52-54]

Despite these limitations, this growing body of research supports the safety of exercise interventions for cancer patients during chemotherapy as well as the need for a large, multi-center, phase III, randomized clinical trial to substantiate the efficacy of physical exercise for reducing CRF and to provide information necessary to guide standard clinical practice.

Rev 11/10 A multi-factorial combination of psychological and physiological processes is most likely involved in any exercise-related experience of reductions in or amelioration of CRF. These changes in CRF may be influenced by the type of cancer, the type of treatment, the timing of the intervention, and a plethora of individual characteristics. Therefore, it is unreasonable to expect to design a study capable of examining all of these potential relationships effectively. For the

purpose of this investigation, we will focus our efforts on further delineation of a conceptual model of exercise and CRF based on deconditioning effects and doses of exercise that result in changes in aerobic capacity, strength and cytokines.

Psychological Mechanisms: A growing body of theoretical literature points to plausible psychosocial mechanisms that may influence the effect of exercise on CRF. Social cognitive theory hypothesizes that self-efficacy (the central component of social cognitive theory and defined as an individual's belief in her or his capability to exercise control over specific events that affect her or his life) is reciprocally related to participation in exercise. In other words, self-efficacy influences exercise behavior and is influenced by the exercise behavior.[70,71]

Research also suggests that additional psychosocial factors such as depression, anxiety, quality of sleep, and QOL may play a substantial role in the relationships between CRF and physical exercise.[52,72-76] These psychosocial factors often change concurrently in cancer patients and may, in fact, be causally related to CRF.[1,2,13,14,23]

While a full examination of these relationships will eventually determine for whom and when exercise interventions will be effective, such an examination is beyond the scope of this investigation which seeks first to determine the efficacy of the current exercise intervention for mitigating CRF and improving aerobic capacity, strength, and QOL. However, the proposed exercise intervention has been theoretically designed and piloted to promote adherence through targeted efforts to increase exercise self-efficacy via active mastery, vicarious modeling, verbal persuasion, and improving physiological and affective states.[77] Efforts to increase exercise self-efficacy include providing direct and immediate feedback regarding successful completion of the prescribed exercise by using a pedometer and having the participants record the number of steps and amount of resistance exercise completed in a daily diary. This allows participants to see for themselves that they are able to actively master the prescribed exercise program. Vicarious modeling is accomplished by providing the participants with a detailed manual that demonstrates each type of exercise to be performed. The manual uses models that are representative of the population being targeted. Verbal persuasion is accomplished through the project CRA and staff who provide the exercise intervention kit to the participants, explain it, and encourage them to complete the prescribed exercise. The CRAs also complete follow-up phone calls to remind participants to continue their exercise and continue completing the study forms. Feedback regarding improved physiological and affective states is provided for participants through completing the daily diary. In the diary, participants record the number of steps walked, the amount of resistance exercise completed, and ratings of fatigue and quality of life. Additionally, depression, anxiety, and quality of sleep will be assessed and included in the exploratory statistical analyses in order to assess their interrelationships as potential mediators and moderators of exercise-CRF relationships.

Rev 11/10

Physiological Mechanisms: Fatigue is both a centrally and peripherally mediated physiological process. Although, central and peripheral mechanisms have been proposed in the etiology of CRF, neither has been systematically investigated in a clinical population of cancer patients. Given the focus of this study, discussion is restricted to the potential mechanisms that are affected by deconditioning resulting from reduced physical activity and conditioning resulting from increased physical activity: cardiorespiratory function, muscle metabolism, inflammation and energy expenditure. One probable physiological mechanism that may affect the influence of exercise on CRF is cardiorespiratory function, which affects aerobic capacity, shortness of breath, tiredness, and ability to perform aerobic activities of daily living, such as walking.[23] A second probable physiological mechanism that may affect the influence of exercise on CRF is muscle mass metabolism, which affects strength, weakness, and ability to perform anaerobic activities of daily living such as getting up out of a chair or lifting grocery bags.[23]

Rev 11/10 Inflammation is a third physiological mechanism that may affect the influence of exercise on CRF. Cardiorespiratory function and muscle mass metabolism are affected by inflammatory cytokine responses stemming from the cancer and/or its treatments. Healthy cardiorespiratory function and muscle metabolism require a delicate and dynamic balance of pro- and anti-inflammatory cytokine production as part of normal physiological processes. Cancer and its treatments result in a dysregulation of this balance between pro- and anti-inflammatory cytokine production. This dysregulation is often prolonged and does not automatically return to normal after completion of treatments in all cases.[13,23,78-83] Studies have shown that CRF is also associated with a systemic dysregulation of inflammatory responses that includes an upregulation of pro-inflammatory cytokines.[23,80,84,85] These dysregulated responses affect cardiorespiratory function and muscle metabolism, which, in turn, affect aerobic capacity and strength, respectively.

Rev 11/10 Fatigue is both a centrally and peripherally mediated physiological process. A growing body of preliminary research suggests that systemic dysregulation of inflammatory responses stemming from cancer and its treatments, specifically a chronic up-regulation of pro-inflammatory cytokines, is one of the mechanistic pathways through which CRF is proposed to arise.[21-24,31] **Physical exercise produces a self-regulating inflammatory response by signaling the production of both pro- and anti-inflammatory cytokines as part of a physical conditioning response. This exercise-induced self-regulating inflammatory response may explain, at least in part, the mechanism through which exercise helps to reduce CRF. A better understanding of mechanisms of action will provide important data to guide clinical care in prescribing the amount and type of exercise necessary to achieve optimal reductions in CRF. We were unable to find any large phase III clinical trials that have systematically investigated the mechanistic pathways, specifically inflammatory pathways, through which physical exercise exerts its positive influence on CRF among patients receiving chemotherapy.**

Rev 11/10 Energy expenditure is a fourth physiological mechanism through which exercise may influence CRF. A reduction in physical activity leads to a reduction in energy expenditure and ultimately physical deconditioning, which is a generalized physiological deterioration. Skeletal muscle atrophy and dysregulated inflammatory processes are components of this physiological deterioration, which further reduce energy expenditure and contribute to a vicious cycle of physical deconditioning. This deconditioning occurs fairly rapidly and is often first recognized clinically by patient-reported shortness of breath, weakness, and fatigue. Objective assessments reveal reduced aerobic capacity, strength, and muscle mass. Deconditioning as a consequence of diminished physical activity resulting either from the cancer itself or its treatments produces these reductions in aerobic capacity, strength, and muscle mass and, ultimately, causes CRF.[14,29] Many patients begin chemotherapy with decreased levels of physical activity as a result of their cancer diagnosis and/or surgical treatment, and their physical activity declines further during chemotherapy.[30,31]

Physical activity is defined as any skeletal muscle movement that causes an increase in energy expenditure above a resting rate. This increased energy expenditure demands that the human body use more calories to meet the increased demand for adenosinetriphosphate (ATP; the body's basic source of usable energy). Physical exercise is defined as physical activity performed in a regular and systematic manner for the purpose of producing physical or mental health effects. Physical exercise performed in a repeated and prolonged manner that causes increases in net caloric energy expenditure produces conditioning effects that improve cardiovascular and muscular function by increasing aerobic capacity, strength and muscle mass. The relationship between energy expenditure and conditioning effects generally follows a linear pattern in which it is necessary to achieve a minimum dose of physical exercise in order

produce the desired conditioning effects. Greater doses of physical exercise above the minimum threshold produce greater conditioning effects up to a critical point at which conditioning effects are compromised and over-training occurs.[21,22] The net caloric expenditure of physical exercise is determined by the exercise dose. Exercise dose is defined by four components: mode, frequency, duration, and intensity.[21] **Collectively, this suggests that there may be an optimal dose of physical activity that will maximize reductions in CRF, particularly if improvements in cardiovascular and muscular function are necessary for reductions in CRF to occur.**

Rev 11/10 **We hypothesize, based on promising preliminary research, that increasing physical activity will help reduce CRF by preventing deconditioning.[14] Specifically, we propose that it is necessary for exercise interventions to achieve a specific dose of physical activity/exercise to produce a net caloric energy expenditure that is sufficient to elicit conditioning effects that would improve CRF either directly or indirectly by improving cardiovascular and muscular function, as well as inflammatory processes.**

Preliminary Studies

Rev 11/10 **Study 1:** Knowing that preliminary research suggests that exercise interventions for cancer patients are associated with demonstrated improvements in CRF, aerobic capacity, strength and QOL, and in anticipation of this proposed CCOP protocol, Drs. Mustian, Morrow and Roscoe conducted a local randomized two-arm phase II clinical trial to examine the influence of a 4-week, home-based walking and progressive resistance exercise program on CRF, aerobic capacity, strength, muscle mass and QOL among breast and prostate cancer patients during radiation treatments. Our intervention was specifically designed for ease of implementation in the home environment for patients and ease of exportability to community clinical oncology practices. In fact, Dr. Mustian, the study chair, designed the piloted exercise intervention using the direct feedback received from the CCOP PIs affiliated with the URCC CCOP Research Base. Our piloted exercise intervention has now been formally named the Exercise for Cancer Patients (EXCAP) program (see accompanying EXCAP manual sample). Dr. Mustian presented the preliminary results along with this exercise protocol to the URCC CCOP Research Base CCOP affiliate PIs at the 2006 Annual URCC CCOP meeting, and the protocol received unanimous support.

Also, knowing that the greatest obstacle to the success of any exercise intervention is compliance, we designed our piloted exercise program (EXCAP) to promote adherence based on theory, previous research, simplicity and ease of use by cancer patients with very busy lives. Even though the proposed study will be conducted with patients receiving chemotherapy, we chose patients receiving radiation therapy for the pilot study because their daily schedule of treatments allowed for careful monitoring of the EXCAP intervention. We thought this monitoring was important during the piloting of the exercise intervention in case unanticipated implementation or safety issues appeared *(N.B., no such issues arose)*. The proposed phase III clinical trial will be conducted with patients receiving chemotherapy rather than radiation treatments because of the higher prevalence and severity of CRF in the former group. The exercise intervention (EXCAP) will not change with this change in study population. We anticipate no problems with implementation or safety based on our URCC CCOP Research Base's previous extensive experience conducting large, randomized phase III clinical trials in patients receiving chemotherapy with our CCOP affiliates and our very promising pilot study.

Home-Based Walking and Progressive Resistance Exercise Intervention (Exercise for Cancer Patients; EXCAP Program). The exercise intervention (EXCAP) we piloted consisted of two components: aerobic conditioning through walking and strength conditioning through the

use of therapeutic resistance bands. The intent of the EXCAP intervention was to ensure that cancer patients' general level of physical activity did not decrease and, when possible, increased during the course of treatment.

The first component of EXCAP was a walking prescription and was intended to provide moderately intense aerobic exercise (60-85% of heart rate reserve, 3-5 exercise rating of perceived exertion on the ACSM revised rating scale, which is a visual analog scale ranging from 0 = no exertion at all to 10 = very, very strong, maximal exertion) 7 days a week for the entire 4-week intervention period. Monitoring patient compliance with the walking prescription was accomplished with the aid of a pedometer, which was given to all patients in both study arms (exercise and control conditions) following their consent to enter the study. We asked patients to record the number of steps they walked daily for 1 full week (7 days) using the pedometer, and then we calculated the average number of steps they walked daily during this period of time at baseline. Patients were then randomly assigned to the control or exercise intervention arms. Using the baseline average number of steps walked daily, we instructed patients in the exercise condition to walk at least as many steps every day during the 4-week exercise intervention while receiving their treatments for cancer. Patients were also strongly encouraged to increase the total number of steps walked daily, if they could, by a minimum of 5% and a maximum of 20%, stressing a 15-20% increase each week. As an instructional and motivational tool, at the start of the exercise intervention, patients in the exercise condition were provided with a table including the average number of steps they walked at baseline, as well as the number of steps that would represent increases of 5%, 10%, 15%, and 20% over this baseline amount for each of the 4 weeks of the intervention period (see accompanying EXCAP manual). Patients in the exercise condition were informed of the ACSM and CDC recommendations to walk 10,000-12,000 steps a day to decrease health risks. The EXCAP intervention encourages patients to increase the total number of steps they walk each day in an individually tailored manner with the ultimate goal of achieving the recommended 10,000-12,000 steps per day to reduce health risks.

The second component of the exercise program consisted of a therapeutic resistance band exercise prescription and was designed to provide low to moderately intense progressive resistance exercise (3-5 exercise rating of perceived exertion on the ACSM revised rating scale) 7 days a week for the entire 4-week intervention period to maintain muscular strength. Patients were given a set of 3 color-coded therapeutic resistance bands, representing varying levels of resistance and an instruction manual describing exercises. The study coordinator explained the proper use of the resistance bands, safety and the appropriate mechanics for performing the resistance training exercises. Patients were instructed to begin with 1 set of 8-15 repetitions for each of the exercises at a low to moderately challenging level. Patients were instructed to use these bands 7 days a week and to increase the intensity (change color of band or shorten length for increased resistance) and/or number of repetitions/sets (encouraged to reach 4 sets of 15 repetitions) for each of these exercises throughout the 4-week intervention period (see accompanying EXCAP manual). 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. If the resistance exercise prescription were for doses and modes of resistance training in the vigorous range it would be advisable to have at least one day of rest in between the resistance exercise sessions and to begin with 3 days a week.

Patients randomized to the control group completed all study assessments and were followed by study staff in the exact same manner as were participants in the exercise group, but did not receive any portion of the exercise intervention during the 4-week study period while receiving their cancer treatments. Assessments of CRF (Brief Fatigue Inventory: BFI), QOL (QOL; Functional Assessment of Chronic Illness Therapy-Fatigue: FACIT-F), aerobic capacity (6-minute walk test), strength (handgrip dynamometry), muscle mass (bioelectrical impedance, BIA; using an established algorithm that incorporated the resistance measure from the BIA[86]) and physical exercise (pedometer and daily diary) were made during the 7 days prior to the intervention (baseline), during the 7 days of the week following the intervention (post-intervention), and for a 7-day period 3 months following the conclusion of the intervention (3 month follow-up). Aerobic capacity and muscular strength were assessed according to the American College of Sports Medicine Guidelines for Exercise Testing.[87]

Results. One-hundred twenty patients were initially screened, and 82 were potentially eligible. Study coordinators approached 61 patients; 40 of those patients were eligible and agreed to participate. The remaining 21 patients were not enrolled because they were ineligible due to maintaining a regular exercise program, or because they declined to participate. 40 patients agreed to participate in the study and were enrolled; of the 40 patients accrued, 2 (5%) did not complete any of the study materials and were not included in the analysis. Both patients felt too busy to complete the study requirements in addition to radiation therapy requirements. The analyses presented are based on 38 fully evaluable patients.

Patients ranged in age from 36 to 82 years, with an average of 60.0 years (SD = 12.1 years). The majority of the patients were diagnosed with breast cancer, (N = 27, 71%), and all of the patients diagnosed with breast cancer were female. The remaining patients were diagnosed with prostate cancer (N = 11, 29%) and were male. The average weight and height were 179.3 pounds (SD = 44.8) and 64.8 inches (SD = 3.65), respectively. The average BMI was 29.8 (SD = 5.87). The study sample was mostly Caucasian (N = 34, 90%). Two (5%) of the patients identified themselves as Asian, and two (5%) identified themselves as Black or African American. Additionally, 23 (62%) of the patients were married, 7 (18%) were divorced, and the remaining patients were either single (N = 4, 10%) or widowed (N = 4, 10%). Most of the patients (N = 30, 79%) reported that they were working at the time of the study, with an average work week of 28.8 hours (SD = 13.0). 32 (84%) of the patients previously had surgery, and 19 (50%) previously had chemotherapy prior to starting radiation therapy and enrolling in the study.

Exercise Adherence and Compliance

Aerobic Exercise (Walking)

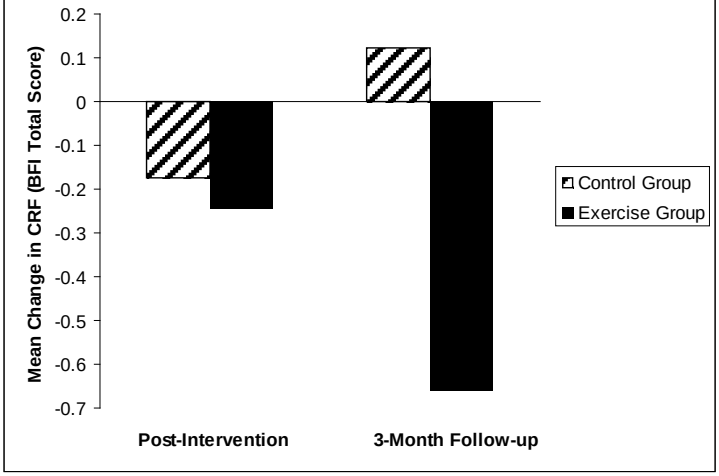
Fifteen of the 19 patients assigned to the exercise condition reported increasing their daily steps walked (DSW), with a mean increase of 5,959 steps from baseline to post-intervention and 7,095 steps from baseline to the 3-month follow-up. The DSW rose from an average of 7,222 (SD = 2,691) at baseline to 11,200 (SD = 5,851) at post-intervention, and finally, to 12,878 (SD = 7,570) at the 3-month follow-up (above the ACSM recommended 10,000 steps a day for health-related benefits). In contrast, patients assigned to the no-exercise control condition reported decreasing the DSW, with a mean decrease of 572 steps from baseline to post-intervention, and a mean decrease of 64 steps from baseline to the 3-month follow-up. The DSW for the control group declined from 5,544 steps at baseline to 4,796 steps at post-intervention and rose slightly to 5,180 at the 3-month follow-up (below 5,000 steps per day is considered sedentary and between 5,000 and 7,499 is very low active according to ACSM recommendations). Analyses of covariance (ANCOVA) comparing the means between the two groups with baseline DSW as the covariate showed statistically significant differences in DSW

at post-intervention and the 3-month follow-up (all p-values < .05).

Resistance Exercise (Therapeutic Resistance Bands)

At post-intervention, 12 patients (79%) assigned to the exercise condition reported doing resistance training during the intervention period. These 12 patients reported an average of 17 minutes 3 days a week with an exercise rating of perceived exertion (RPE) of 4 out of 10 indicating moderate intensity. At the 3-month follow-up, 8 patients (42%) in the exercise group reported doing resistance exercise. These 8 patients reported an average of 18 minutes 1.5 days a week, with 4 of these patients (21%) reporting resistance exercise 3 or more times a week at an average exercise RPE of 4 out of 10. The mean change in daily minutes spent in resistance exercise from baseline to post-intervention was 9.4 minutes (SD = 11.4), and the mean change in daily minutes spent in resistance exercise from baseline to the 3-month follow-up was 6.81 minutes (SD = 9.94) for the entire exercise group. None of the patients in the control group reported doing resistance exercise post-intervention, and only one patient (5%) reported doing resistance exercise for an average of 13 minutes 3 times a week at the 3-month follow-up in the control group. The mean change in daily minutes spent in resistance exercise from baseline to post-intervention was -1.6 minutes (SD = 4.73), and the mean change in daily minutes spent in resistance exercise from baseline to the 3-month follow-up was -1.0 minutes (SD = 6.06) for the entire control group. ANCOVAs, with baseline minutes of resistance exercise (MRE) and days of resistance exercise (DSE) as the covariates, showed statistically significant differences in MRE and DRE at post-intervention and the 3-month follow-up (all p-values < .05).

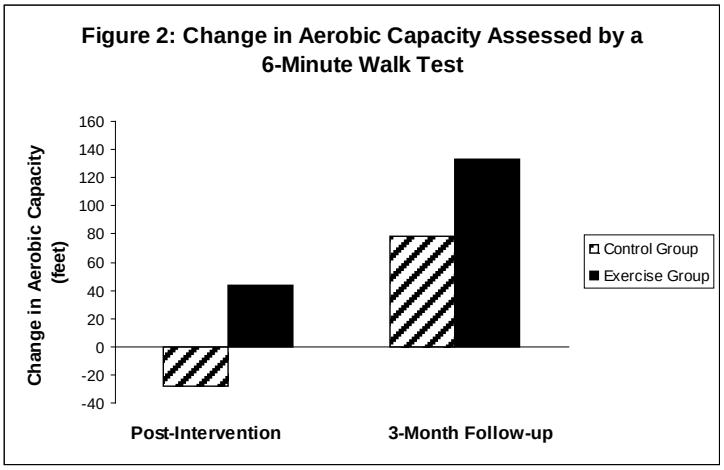
Figure 1: Change in Cancer-Related Fatigue Assessed by the BFI



Cancer-Related Fatigue (CRF)

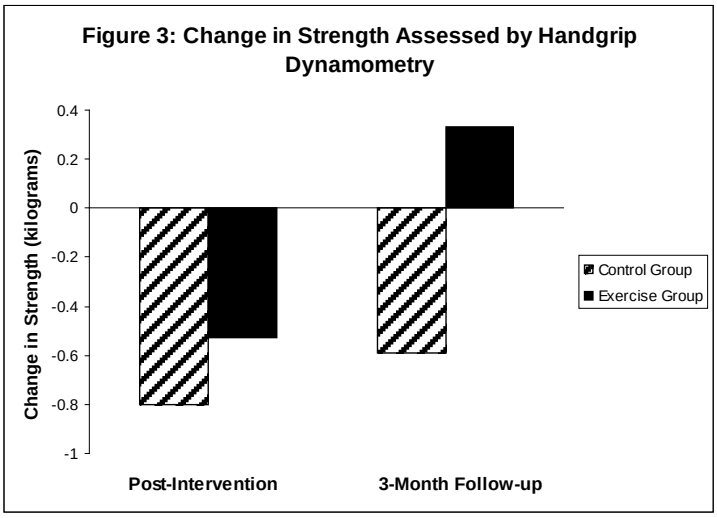
CRF was evaluated using the Brief Fatigue Inventory total score[88] (Figure 1). A noticeable improvement in CRF was noted in patients in the exercise group compared with patients in the control group. Participants in the exercise condition demonstrated improvements in CRF from baseline to post-intervention (Cohen's d = -0.15) and continued to improve from baseline to the 3-month follow-up (Cohen's d = -0.58). In contrast the control group exhibited a smaller improvement in CRF from baseline to post-intervention (Cohen's d = -0.08), but CRF worsened from baseline to the 3-month follow-up (Cohen's d = 0.04). ANCOVA,with baseline CRF as the covariate, showed a trend toward statistically significant differences at post-intervention (p = 0.07) with significant differences at the 3-month follow-up (p < 0.05). The actual means (standard deviation) were: $exercise_{baseline}$ = 1.84(1.87), $exercise_{post\text{-}intervention}$ = 1.60(1.36), $exercise_{follow\text{-}up}$ = 1.16(0.98), $control_{baseline}$ = 2.62(2.13), $control_{post\text{-}intervention}$ = 2.44(2.07), and $control_{follow\text{-}up}$ = 2.73(2.60).

Aerobic Capacity



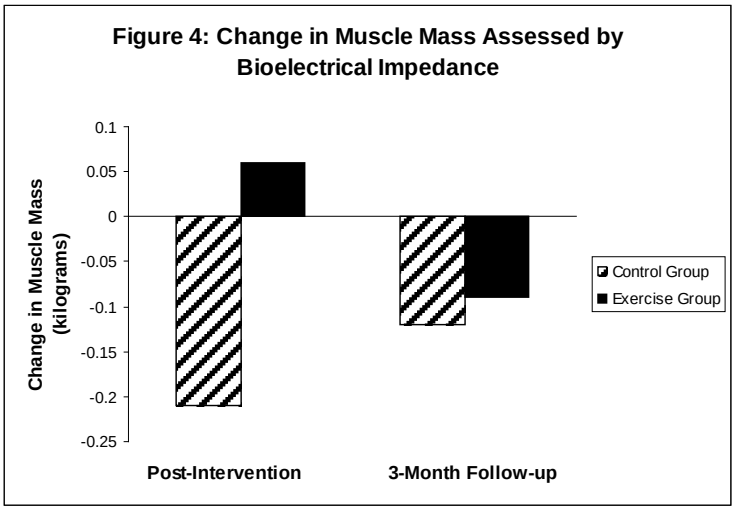
Aerobic capacity was evaluated based on the total distance walked in a 6-minute walk test[87] (Figure 2). The results paralleled the trends previously described for CRF. Participants in the exercise condition demonstrated improvements in aerobic capacity from baseline to post-intervention (Cohen's d = 0.16) and continued with improvements from baseline to the 3-month follow-up (Cohen's d = 0.37). In contrast the control group exhibited a worsening of aerobic capacity from baseline to post-intervention (Cohen's d = -0.13) but showed small improvements from baseline to the 3-month follow-up (Cohen's d = 0.28). ANCOVA, with baseline aerobic capacity as the covariate, revealed no statistically significant differences in aerobic capacity at post-intervention or the 3-month follow-up. Although these results were not statistically significant in this small pilot sample, they suggest a direct positive relationship between the average steps walked each day and aerobic capacity during treatment. The means (standard deviation) were: $exercise_{baseline}$ = 1894.37(296.78), $exercise_{post\text{-}intervention}$ = 1937.95(261.99), $exercise_{follow\text{-}up}$ = 2020.59(386.36), $control_{baseline}$ = 1478.21(401.02), $control_{post\text{-}intervention}$ = 1425.28(438.27), and $control_{follow\text{-}up}$ = 1600.33(468.86).

Strength

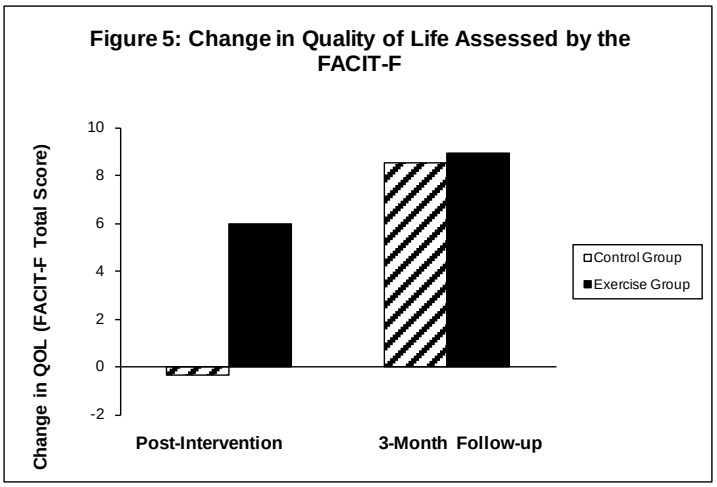


Strength was evaluated based on the force applied in pounds using a handgrip dynamometer test[87] (Figure 3). Patients in both treatment conditions demonstrated declines in muscle strength from baseline to post-intervention. Participants in the exercise condition demonstrated small declines in strength from baseline to post-intervention (Cohen's d = -0.07) but conversely exhibited improvements from baseline to the 3-month follow-up (Cohen's d = 0.11). In contrast the control group exhibited declines in strength from baseline to post-intervention (Cohen's d = -.10) and declines from baseline to the 3-month follow-up (Cohen's d = -0.06). Patients in the exercise group declined less in strength from baseline to post-intervention than patients in the control group. Although ANCOVA, with baseline strength as the covariate, revealed no statistically significant differences in strength at post-intervention or the 3-month follow-up in this small pilot sample, these results suggest a positive direct relationship between the total amount of resistance exercise completed during the intervention period and strength at post-intervention and 3-month follow-up. The means (standard deviation) were: $exercise_{baseline}$ = 26.02(7.16), $exercise_{post\text{-}intervention}$ = 25.49(7.29), $exercise_{follow\text{-}up}$ = 26.89(8.71), $control_{baseline}$ = 24.92(7.89), $control_{post\text{-}intervention}$ = 24.12(8.74), and $control_{follow\text{-}up}$ = 23.87(7.79).

Muscle Mass



Another important indicator of the efficacy of the exercise intervention was the favorable change in muscle mass in the exercise group compared with the control group (Figure 4). Muscle mass was assessed using bioelectrical impedance analysis (BIA). Prediction of lean body mass from BIA is as reliable as skin-fold measurements and hydrostatic weighing.[87] Muscle mass in pounds was calculated from the resistance measured.[86] Participants in the exercise condition demonstrated a maintenance of muscle mass from baseline to post-intervention (Cohen's d = 0.00) with improvements from baseline to the 3-month follow-up (Cohen's d = 0.10). In contrast, the control group exhibited reductions in muscle mass from baseline to post-intervention (Cohen's d = -0.04) and from baseline to the 3-month follow-up (Cohen's d = -0.02). ANCOVA, with baseline muscle mass as the covariate, revealed no statistically significant differences in strength at post-intervention or the 3-month follow-up in this small pilot sample, but these results do suggest a positive direct relationship between the total amount of resistance exercise completed during the intervention period and muscle mass. The means (standard deviation) were: $exercise_{baseline}$ = 24.48(8.78), $exercise_{post\text{-}intervention}$ = 24.54(8.96), $exercise_{follow\text{-}up}$ = 25.32(8.12), $control_{baseline}$ = 23.56(5.63), $control_{post\text{-}intervention}$ = 23.35(5.43), and $control_{follow\text{-}up}$ = 23.42(6.22).



Quality of Life (QOL)

QOL was evaluated using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) total score [89-91] (Figure 5). Participants in the exercise condition demonstrated improvements in QOL from baseline to post-intervention (Cohen's d = 0.26) and continued improvements from baseline to the 3-month follow-up (Cohen's d = 0.41). In contrast the control group demonstrated declines in QOL from baseline to post-intervention (Cohen's d = -0.02), but then showed improvements from baseline to the 3-month follow-up (Cohen's d = 0.28). ANCOVA, with baseline QOL as the covariate, showed a trend toward statically significant differences at post-intervention (p = 0.06) with statistically significant differences at the 3-month follow-up (p = 0.05). The means (standard deviation) were: $exercise_{baseline}$ = 124.19(25.12), $exercise_{post\text{-}intervention}$ = 130.19(20.13), $exercise_{follow\text{-}up}$ = 132.96(16.41), $control_{baseline}$ = 117.59(29.65), $control_{post\text{-}intervention}$ = 116.92(30.58), and $control_{follow\text{-}up}$ = 126.13(31.81).

Rev 11/10 Cytokines

As part of this same pilot study, Dr. Mustian and her team assessed the preliminary efficacy of the EXCAP intervention for eliciting favorable changes in inflammation-related biomarkers. These data are presented in Table 1. Blood was collected at two time-points: pre-intervention and post-intervention. IL-6, IL-1β, Il-8, IFN-γ, TNFα□and TNFr1 were measured using appropriate ELISAs.

Table 1: EXCAP Pilot Study Raw Means for Cytokines and Cytokine Receptor

	Raw Mean Levels (pg/mL; (SEM))				
	Pre-Intervention		Post-Intervetion		
Variable	EXCAP	Control	EXCAP	Control	ANCOVA P-Value
IL-6	5.74 (2.56)	6.28 (2.91)	6.33 (1.95)	9.26 (2.17)	0.04
IL-1β	2.24 (0.356)	7.25 (4.91)	3.19 (0.61)	6.75 (0.64)	0.62
IL-8	6.27 (0.63)	8.094 (1.18)	7.08 (0.46)	7.74 (1.07)	0.07
IFN-γ	2.00 (0.02)	2.15 (0.15)	2.00 (0.02)	2.13 (0.02)	0.01
TNFR1	760.60 (69.84)	766.30 (79.43)	680.50 (46.13)	784.00 (55.35)	0.08

SEM= Standard Error of the Mean

Raw means and standard errors of the mean are depicted for each molecule, as well as p-values for ANCOVA comparing post-intervention means, controlling for baseline values, for each cytokine and receptor. The primary purpose of this study was to provide pilot data on the raw means to help refine our hypotheses and appropriately design and power future studies examining these biomarkers. As such, the data are hypothesis generating and are not considered definitive. Our analyses revealed the level of TNFα to be below 1.0. This suggests TNFα levels may actually fall below detectable limits. We have not included these data in the summary table for this reason. Analyses revealed that the exercise group had lower levels of IL-6, IL-1β, IL-8, IFN-γ,and TNFr1 post-intervention. ANCOVAs, incorporating baseline values as the covariate, revealed significantly ($p < 0.05$) lower mean levels of IL-6 and IFN-γ, with statistical trends ($p<0.10$) for lower mean levels of IL-8 and TNFr1 in the exercise group compared to the control group post-intervention. This is suggestive of an overall reduction in inflammation in the exercise group and supports our hypothesis that exercise helps to reduce CRF by regulating inflammatory processes.

Assessing cytokines and cytokine receptors will help clarify how exercise reduces inflammation through alterations in cytokine and cytokine receptor expression and, ultimately, reduces CRF. Once we understand this, more appropriate exercise interventions can be developed to target optimal reductions in CRF and improve standard clinical care.

Rev 11/10 **Study 2:** Our recently closed URCC CCOP Research Base study, a phase III clinical trial comparing the YOCAS yoga intervention to standard care among cancer survivors, provides support for adding actigraphy to this study. The YOCAS study accrued 410 cancer survivors; all participants wore actigraphs on their wrists for 7 days at baseline and 7 days post-intervention. The actigraph team (exercise physiologist, research coordinator and data manager) at the URCC CCOP Research Base standardized all aspects of the entire process for acquiring and analyzing objective data on sleep using actigraphs in the CCOP network. The actigraphs were initialized at the Research Base, then shipped in batches using priority mail to the research coordinators at the CCOPs. The CCOP coordinators inventoried the actigraphs and logged the date and study participant to whom the actigraph was assigned. The study participants were provided with instructions for wearing and returning the actigraphs. The CCOP coordinators retrieved the actigraphs from the participants, and shipped them back to the URCC CCOP Research Base. Data from the actigraphs were downloaded to a dedicated computer, then trimmed, audited, and analyzed. We examined typical sleep outcomes such as sleep latency

and sleep efficiency and daytime napping as well as circadian rhythms. These objective assessments of sleep demonstrated significant improvements and supported patient-reported outcomes on the Pittsburgh Sleep Quality Index recently presented at the 2010 ASCO Annual Meeting.

Rev 11/10 These two preliminary studies demonstrate that: 1) physical activity as assessed by actigraphy may predict patient-reported levels of CRF, 2) the URCC CCOP Research Base can effectively implement actigraphy in a large nationwide clinical trial and analyze the data, 3) cancer patients are willing to wear actigraphs, and 4) meaningful data can be extracted from the actigraphs that may provide important scientific information to aid in the effective treatment of CRF.

Summary and Hypotheses

In summary, CRF is a serious problem for cancer patients undergoing chemotherapy. There is limited research examining the effectiveness of non-pharmacological interventions for reducing CRF. This lack of research hinders development of standard care options for oncology professionals, particularly after available pharmacological interventions have been exhausted. Existing data from our own URCC CCOP survey of 458 cancer patients provide persuasive evidence that CRF is a persistent problem among cancer patients, especially during chemotherapy. Similarly, our own pilot data and data from other researchers make it clear that cancer patients are amenable to participation in a home-based exercise intervention while receiving treatment for cancer.

Rev 11/10 Our pilot data showed that patients in the exercise condition increased their total steps walked from 7222 at baseline to 11,200 at post-intervention, while the patients in the standard care (no exercise) condition decreased their total steps walked from 5544 at baseline to 4796 at post-intervention. Although Americans are estimated to walk 5310 steps a day on average, according to the standards outlined by the American College of Sports Medicine these Americans and the patients in both study groups at baseline are classified as very low active—a classification that is associated with increased health risks. Research has shown that a diagnosis of cancer and the treatments for cancer lead to an individual decreasing physical activity regardless of their physical activity level prior to diagnosis and that physical activity level does not return to prediagnosis levels for most of these individuals. This decrease in physical activity among cancer patients who are very low active to begin with would lead to a classification as sedentary and would portend even greater health risks. Our pilot data supports this by demonstrating that patients in the standard care (no exercise) condition decreased to walking 4796 steps per day during the time they were receiving standard care resulting in a classification of sedentary with increased health risks, while patients in the exercise condition increased to walking 11,200 steps per day resulting in a classification of active with decreased health risks. The EXCAP program is safe and, potentially, effective for improving CRF, aerobic capacity, strength, and QOL while improving inflammatory profiles. The summarized studies and our very promising pilot data provide strong preliminary evidence that exercise interventions are well-accepted by cancer patients and are associated with significant improvements in a variety of cancer treatment-related side effects in addition to CRF.

Given the positive preliminary results of our pilot studies and the noted limitations in existing research, further research is warranted to provide solid evidence that can guide the practice of evidence-based medicine and the development of standard clinical practices for the treatment of CRF. The NCI CCOP mechanism provides an excellent forum for conducting this research on a nationwide scale and in a timely, cost-effective manner among patients in community settings.

Hypothesis: A home-based walking and progressive resistance exercise program will be efficacious in reducing cancer-related fatigue during chemotherapy.

3.0 Objectives

3.1 Primary Aim

To determine the efficacy of a home-based walking and progressive resistance exercise program for reducing cancer-related fatigue among patients during chemotherapy.

3.2 Secondary Aims

3.2.1 To determine if a home-based walking and progressive resistance exercise program can improve aerobic capacity in cancer patients receiving chemotherapy.

3.2.2 To determine if a home-based walking and progressive resistance exercise program can improve strength in cancer patients receiving chemotherapy.

3.2.3 To determine if a home-based walking and progressive resistance exercise program can improve quality of life in cancer patients receiving chemotherapy.

Rev 11/10 3.3 Supplemental Aims

3.3.1 To determine if a home-based walking and progressive resistance exercise program can improve inflammatory profiles (IL-6, IL-8, IL-10, IL-1β, IFN-γ, & TNFr1) among 300 patients receiving chemotherapy.

3.3.2 To provide an initial examination of whether changes in IL-6, IL-8, IL-10, IL-1β, IFN-γ, & TNFr1 mediate the relationship between physical exercise and CRF.

3.3.3 To determine if a home-based walking and progressive resistance exercise program can increase total energy expenditure in kcal/kg/min assessed using actigraphy among 300 patients receiving chemotherapy.

3.2.4 To determine if a home-based walking and progressive resistance exercise program can increase two specific components of exercise dose: 1) duration of physical activity measured in total minutes of non-sedentary activity, and 2) intensity of physical activity measured in minutes of sedentary, low, moderate and vigorous activity using objective actigraphy assessments.

4.0 Participant Eligibility

4.1 Inclusion criteria. Study participants must:

Rev 4/10

- Have a primary diagnosis of cancer other than leukemia, with no distant metastasis.
- Be chemotherapy naïve.
- Be starting chemotherapy treatments for cancer and be scheduled for at least 6 weeks of treatments with treatment cycles of either 2 or 3 or 4 weeks. Oral chemotherapy (e.g., Xeloda) is acceptable and will usually most closely follow the 3 week cycle schema
- Have a functional capacity rating of 70 or greater on the Karnofsky Performance Scale (SECSG) when assessed by the medical oncologist (or physician's designee) at the beginning of chemotherapy treatments. (Clinical Record Information form question #3)
- Be able to read English (since the assessment materials are in printed format).
- Be 21 years of age or older.
- Give written informed consent.

4.2 Exclusion criteria. Study participants must not:

Rev 4/10; 6/10

- Have a diagnosis of leukemia
- Have metastatic disease.
- Be receiving concurrent radiation therapy.
- Have physical limitations (e.g., cardiorespiratory, orthopedic, central nervous system) that contraindicate participation in a low to moderate intensity home-based walking and progressive resistance program, as assessed by the medical oncologist (or physician's designee).
- Be identified as in the active or maintenance stage of exercise behavior as assessed by the 1-item Exercise Stages of Change Short Form (which will be assessed in the screening of patients; On Study Data/Participant Interview form question #7).

5.0 Registration and Randomization

5.1 Prior to entering participants on this protocol, the following must be on file at the URCC CCOP Research Base:

- Documentation of IRB approval in the form of an HHS Form 310, CTSU approval form or signed letter from IRB
- A copy of the institution's IRB-approved informed consent document
- Written justification for any substantive modifications made to the informed consent concerning information on risks or alternative procedures.

These documents are submitted to:

Ms. Jacque Lindke
James P. Wilmot Cancer Center
URCC CCOP Research Base
601 Elmwood Av, Box 704
Rochester, NY 14642

5.2 To enroll a participant who meets the eligibility criteria and who has signed the informed consent document, log on to the URCC CCOP Research Base website at http://urcc-ccop.org/, enter your CCOP's username and password and enter the information outlined in section 5.3 below. If you are unable to log on, call 585.275.6303 between 8.30 AM and 4.30 PM Monday through Friday.

5.3 The following information will be requested:

5.3.1 CCOP site

5.3.2 Most recent IRB approval date

5.3.3 Name and telephone number of person registering study participant

5.3.4 Eligibility verification including numerical level of KPS and exercise stage of change. Participants must meet all inclusion/exclusion criteria listed in Section 4.0.

5.3.5 Verification that consent form has been signed

5.3.6 Treatment facility (coincides with IRB approval)

5.3.7 Participant's identification

5.3.7.1 First and last names/initials
5.3.7.2 Birth date (MM/DD/YYYY)
5.3.7.3 Gender
5.3.7.4 Race
5.3.7.5 Nine-digit zip code
5.3.7.6 Payment code

5.3.8 Baseline level of cancer-related fatigue (CRF) as recorded on the On Study Data/Participant Interview form (question 8) for randomization purposes

5.4 An email confirmation of registration will be forwarded by the URCC, and if requested confirmation will be faxed to the CCOP's coordinating center.

5.5 Randomization will be stratified by CCOP site, chemotherapy cycle length (2 or 3 weeks), sex and by degree of fatigue reported on the on-study assessment questionnaire (two levels: ≤ 5, > 5).

5.6 The two treatment arms are as follows:

Arm 1 = standard care (wait list control)
Arm 2 = standard care plus a Home-Based Walking and Progressive Resistance Training Exercise intervention

Rev 4/12

5.7 A computer-generated random numbers table with equal probability of block size 4 or 6 will be used to assign participants to one of the two treatment arms. The randomization will assign participants to the two arms in the ratio 1:1. The random numbers tables will be generated centrally using Statistical Analysis System (SAS) software provided by Dr. Heckler, the project biostatistician. A total enrollment of 692 participants is planned, with 346 participants in each treatment condition.

6.0 Treatment Protocol, Study Outline

Rev 4/10

6.1 **Home-Based Walking and Progressive Resistance Exercise Intervention.** The exercise intervention used in this investigation will be the EXCAP program. This exercise program is the exact same intervention that was used in the pilot study described in the preliminary studies section of this protocol. The intervention will be provided for the patient via a pre-packaged individual Exercise Kit. The kit will contain all of the necessary instructions and materials for the patient to complete the exercise intervention, including: 1) the EXCAP manual; 2) a pedometer; and 3) therapeutic resistance bands. The manual provides information on how to use the pedometer and the resistance bands, as well as information on the exercise prescriptions and proper techniques for walking and resistance exercises. The CRA will complete the walking exercise prescription on page 6 and exercise prescription on page 8 with the patient. A copy of these 2 pages will be maintained in the CCOP's records and submitted to URCC with baseline forms.

Rev 4/10; 11/10

6.2 **Treatment Fidelity/Quality Assurance and Prevention of Drift.** Each CCOP site will be responsible for designating a clinical research associate (CRA) who will be trained to administer the exercise intervention. Each CCOP will be provided with the opportunity to send a representative to the annual URCC CCOP Research Base meeting for CRA training on all aspects of the EXCAP home-based exercise intervention (e.g., where participants should wear the pedometer, use of resistance bands, correct form for performing the exercises in the intervention). Each CCOP will be encouraged to use study personnel with educational backgrounds in exercise science/kinesiology and/or who are professionally certified through ACSM when available; however such background and/or credentials are not required. In order to ensure treatment fidelity and quality delivery of the exercise intervention, all CRAs who are designated to administer the intervention will be required to have a training interview, either in person or via telephone, with the study chair (or chair's designee) explaining the exercise intervention, administering the 6 minute walk test and handgrip dynamometer test, performing actigraphy assessments, and collecting, storing and shipping of the blood. Each CRA designated to do the intervention must be approved by URCC prior to administering the exercise program or any tests to any study participants. Additionally, in order to prevent drift in the administration of the exercise intervention during the 36 months of study accrual: 1) the study protocol and exercise intervention will be reviewed each year in detail at the annual URCC CCOP research base meeting, and 2) annual mailings will be sent approximately 6 months after the annual meeting reminding the CCOP CRAs administering the exercise intervention of the most important aspects of the intervention. Additionally, instructional videos are available to the trained CRAs on the URCC CCOP Research Base website (http://urcc-ccop.org/). These videos include detailed

instructions on how to perform the handgrip test and 6-minute walk test, how to use each piece of equipment (pedometer, Therabands and assist straps), and how to do each of the exercises, as well as videos on how to charge, wear, initialize and download the actigraphs and how to collect, aliquot and store blood. Tote bags containing all the testing equipment and CRA manuals will be forwarded upon approval of the site to conduct the intervention.

6.3 The EXCAP home-based walking and progressive resistance training program was designed by an Exercise Scientist certified by the American College of Sports Medicine (ACSM) and accords with the guidelines for exercise testing and prescription as set forth by the ACSM.[87] The EXCAP program, which was piloted and showed very promising results, consists of two components that focus on aerobic and resistance conditioning. It is designed to ensure that patients' general level of physical activity does not decrease and, when possible, increases during the course of receiving treatments.

The EXCAP program was previously described in detail in section 2.0 under preliminary studies. This is the exact same intervention that will be used in this phase III clinical trial. A sample manual for the EXCAP program accompanies this protocol proposal.

6.3.1 Participants will perform the exercises in a home-based environment during the intervention period. The Exercise Kit will contain a manual that participants can view at their leisure as often as they wish. They will also be able to discuss the intervention and have their questions answered by the local CCOP study staff.

Rev 11/10

6.3.2 **Potential risks of taking part in the exercise intervention are minimal.** 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 intensity 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 intensity home-based walking and progressive resistance program is minimal*. Every effort will be made to minimize the risks through: 1) the approval of the patient's physician (or designee) to enter the study and complete all study tests and the exercise intervention; 2) the use of standardized guidelines for exercise testing and prescription provided by the American College of Sports Medicine; and 3) the use of trained technicians. 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 procedures, trained professionals and sterile materials for blood collection at each CCOP. Each CCOP site is required to follow appropriate biosafety level II guidelines at their respective institutions. **No adverse reactions have been reported by any of the participants who have completed the current pilot intervention.**

6.4 **Adherence/Compliance.** Adherence and compliance of participants to the exercise prescription in respective study conditions (chemotherapy or chemotherapy plus the

exercise intervention) will be monitored via the use of the daily diary (see section on study measures) participants complete each morning and evening. Participants are also asked to report the number of minutes spent doing aerobic and resistance exercises. In order to facilitate consistency in the reporting of physical exercise, participants are provided with a definition of exercise to use when completing these questions as part of the daily diary. This reporting will facilitate monitoring the participants randomized to exercise regarding the actual exercise dose attained, as well as monitoring the participants not assigned to the exercise arm for exercise contamination.

Rev 4/12

6.5 The study will be available to private medical oncology practice groups who are grantees of the National Cancer Institute's (NCI) Community Clinical Oncology Program (CCOP) and are affiliated with the University of Rochester James P. Wilmot Cancer Center (URCC) CCOP Research Base. A total of 692 patients currently undergoing chemotherapy will be accrued.

Rev 11/10

6.6 During the informed consent process, the study coordinator will explain to the participant that the study lasts for approximately seven weeks, will involve completing some questionnaires, both prior to and following the intervention, completing a daily diary throughout the study period, and will involve completing the exercise prescription if assigned to the exercise arm. The study coordinator will also explain to the participant that they will complete a 6 minute walk test, a handgrip test, provide blood samples and wear an actigraph as part of the study. The study coordinator will register the patient with the URCC CCOP Research Base on the same day the patient is consented. The patient is not informed of their randomization group assignment until all baseline assessments on Days -4 to Day 0 have been completed. Reminder phone calls will be made by study personnel prior to each study assessment (baseline, mid- and post-intervention) to assist the patient in remembering to complete the study forms, wear the actigraph and pedometer, and keep her or his appointment to complete the aerobic and strength tests. Additionally, phone calls will be made bi-weekly during the study intervention period to remind participants to complete their daily diaries, wear the actigraph, charge the actigraph and comply with the study condition to which they were randomly assigned. (Permission will be obtained to leave messages on a patient's answering machine before any messages are left.) Self-addressed, stamped envelopes will be provided to each patient so they can return the completed questionnaires after each assessment if necessary. Courier services or tracked mail options (e.g., Federal Express) will be provided to each patient so they can return the actigraph if necessary.

Rev 11/10

6.7 After giving written informed consent, the participant will provide demographic and clinical data via the completion of the "On-Study Data/Participant Interview" and "Clinical Record Information" forms with the study coordinator. The study schemas on pages 4-6 outline the study flow in detail. All baseline assessments will be completed from study Day -4 through Day -1 of the study. All participants will be given a pedometer, actigraph with charger, and a daily diary to complete from Day -4 through Day -1 of the study. They will be given their first packet of questionnaires (e.g., FACIT-F with additional FACIT cognitive subscale, Brief Fatigue Inventory, CESD, MFSI, STAI, Pittsburgh Sleep Quality Inventory, Profile of Mood States, Medication and CAM Form, ACLS, and Symptom Inventory) to complete on the evening of Day -1. The packet of questionnaires takes about 30 minutes to complete. All participants will be administered the 6-minute walk test and the handgrip dynamometer test between Day -4 and Day 0 prior to receiving their first chemotherapy treatment and prior to being told which study condition they are randomized to.

Rev 11/10

A fasting blood draw will be collected between Day -4 and Day 0 from all participants prior to their first chemotherapy treatment and prior to being told which study arm they are randomized to. CCOPs will schedule all blood draws for each participant and all blood draws will occur at the sites designated by the CCOPs. Patients will fast at least 9 hours prior to blood draws. The time of day will be noted, with future assessments done at approximately the same time of day during post-testing. Morning blood draws are preferred, if possible, but not required. The study participants will have their blood drawn one time at baseline on either study Day -4, -3, -2, -1 or 0. If the blood draw is performed on Day 0, it must be drawn before the participant performs the tests for aerobic capacity and strength, receives chemotherapy or is told which study arm they are randomized to.

Rev 11/10

All participants will be told their randomization arm on Day 0, prior to beginning chemotherapy on 2-, 3- or 4-week cycles. Additionally, on Day 0 participants receiving the exercise intervention will be given the Exercise Kit and instructions on the intervention. All participants will complete a daily diary each day for the 6-week intervention period. All patients will complete 4 days of actigraphy monitoring on Days 17-20. During the last week of the 6-week intervention, all participants will complete 4 days of pedometer and actigraphy monitoring (Days 38-41), as well as the exact same questionnaires, 6-minute walk test, handgrip dynamometer test and feedback questionnaire post-intervention (standard care or intervention arm) on Days 41-42 of the study. Study participants will also have a fasting blood draw on study Day 42. Blood must be drawn before the participant performs the tests for aerobic capacity and strength, or receives chemotherapy on Day 42. Arrangements will be made for the study materials and questionnaires to be returned by the participant to the CCOP via prepaid shipping (e.g., stamped envelopes, courier, Federal Express) following the conclusion of the study, if necessary. All participants, regardless of randomization group, will complete all study measures.

Rev 11/10

6.7.1 **Standard Care Condition.** All participants assigned to the non-exercise (standard care) condition will receive the exact same time and attention (e.g., testing sessions, phone calls) as the participants assigned to the exercise intervention arm. The patients in the non-exercise arm also complete all of the same study measures including the daily diary, blood draws, actigraphy, pedometer, 6-minute walk and handgrip assessments. The patients in the non-exercise arm do not receive the Exercise Kit and instructions at the beginning of the study, however these participants will be given the same Exercise Kit and instructions at the end of the study. The exercise intervention is delivered via a self-contained Exercise Kit and requires limited interaction with the CRA to deliver it (less than 30 minutes). Participants in the standard care group are given pedometers to wear for assessment purposes during the baseline (Day -4 to Day -1) and post-intervention (Days 38-42) assessment periods. The pedometers are retrieved from the patients in the standard care arm during the intervention period because it is well established that the simple act of giving a pedometer to someone will result in an increase in the total number of steps walked each day. Participants in the standard care condition will keep their pedometer at the end of the study and they will be given the rest of the Exercise Kit that accompanies the EXCAP program along with instructions.

Rev 4/10

6.7.2 **If Chemotherapy is Delayed.** In the event that chemotherapy does not start on Day 0, study participants will continue their participation as though it did. Day 0

will still be the day that chemotherapy was originally planned to begin. Any delays in treatment should be noted on the Case Summary form.

The study ends on Day 42.

6.8 In order to improve study retention in the non-exercise arm, participants will be offered the exercise intervention materials, gratis, and the option to begin an exercise program on their own after the final post-intervention assessments (Day 42 of the study). No data will be collected on these participants regarding their exercise during this time period. This offer is simply a tool to increase study accrual and retention.

6.9 Adverse Event Reporting Requirements

6.9.1 Adverse event reporting will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse event toxicity grading. Information regarding the CTCAE can be found on the CTEP website: http://ctep.cancer.gov/.

6.9.2 Adverse events will be reported using the URCC Adverse Event form. This form can be found on the URCC CCOP Research Base website.

6.9.3 Adverse events will be reported in accordance with the following guidelines:

	Grade 1	Grade 2			Grade 3				Grade 4		Grade 5	
	Unexpected and Expected	Unexpected		Expected	Unexpected		Expected		Unexpected	Expected	Unexpected	Expected
		with hospital-ization	without hospital-ization		with hospital-ization	without hospital-ization	with hospital-ization	without hospital-ization				
Unrelated Unlikely	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	Not Required	10 Calendar Days	10 Calendar Days	Not Required	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, due to adverse event.

6.9.4 Submit written adverse event reports in one of the following ways:

(1) PDF by email:	Jacque_lindke@urmc.rochester.edu
(2) By mail:	Jacque Lindke James P. Wilmot Cancer Center URCC CCOP Research Base 601 Elmwood Avenue, Box 704 Rochester, NY 14642
(3) By fax:	Jacque Lindke 585-461-5601

6.9.5 An unexpected adverse event is defined as any adverse experience, the specificity or severity of which is not consistent with the risk information described in section 6.3.2.

6.9.6 A serious event refers to any event in which the outcome results in any of the following: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability, incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

6.9.7 Adverse events should be reported to the local IRB as per their requirements

6.10 Data Safety and Monitoring

6.10.1 All adverse events requiring reporting will be submitted to Jacque Lindke as described in section 6.9. Serious adverse event reports will be forwarded to the study chair and the URCC Data Safety and Monitoring Committee (DSMC). Adverse events are entered into a protocol-specific spreadsheet.

6.10.2 Adverse event rates are monitored utilizing the spreadsheet. If a serious adverse event is being reported frequently, the study chair will conduct a detailed review. The DSMC Committee Chair will be notified and will determine if further action is required.

6.10.3 The URCC Data Safety Monitoring Committee (DSMC) will review study progress and cumulative reports of adverse events at annual meetings. An overall assessment of accrual and adverse events will enable the committee members to assess whether significant benefits or risks are occurring that would warrant study closure.

6.10.4 The URCC will notify the CCOPs immediately of any serious safety concerns identified by the DSMC.

7.0 Measures

7.1 The **On Study Data/Participant Record** is used to record demographic and clinical information as well as problems with fatigue and sleep. Diagnostic, treatment and other clinical information will be abstracted from the participant's chart and recorded on the **Clinical Record Information** form. These data will be used for descriptive purposes, to aid in participant monitoring, for moderator analyses and for exploratory analyses.

7.2 The **Medication and CAM Usage** form will track the participant's use of prescription and non-prescription fatigue and sleep medication, as well as any other fatigue and sleep aids used during the baseline and post-intervention assessments conducted during the study. This form will also specifically ask participants to report the use of any CAM modalities for any reason.

7.3 Fatigue Assessments

7.3.1 CRF will be assessed subjectively via the revised **Brief Fatigue Inventory (BFI)**, which is a 9-item, patient-report instrument with established reliability and validity that we have used in previous studies.[92] The BFI allows for the rapid assessment of fatigue level in cancer patients and identifies those patients with severe fatigue. The reliability and validity of the BFI were demonstrated in a study of 305 cancer patients and 290 community-dwelling adults. An internal consistency coefficient (Cronbach's alpha) of 0.96 was demonstrated when the BFI was administered to 305 patients with cancer.[93] This measure was used in the previously mentioned pilot study of the proposed exercise intervention.

7.3.2 CRF will also be assessed using the **Functional Assessment of Chronic Illness Therapy-Fatigue Subscale (FACIT-F).** The FACIT-F subscale is a 13 item scale that asks questions directly related to the impact of CRF on daily activities.[90] It was developed by Cella and his group through extensive interviews with oncology professionals and patients experiencing symptoms of cancer, and it has been validated in a series of studies. The basic measure has shown very good test/retest reliability as well as validity.[94,95] It has become one of the most commonly used measures in oncology, and we have used this scale in our previous studies including the pilot study designed for this protocol.

7.3.3 In addition, CRF will be assessed subjectively via the **Multidimensional Fatigue Symptom Inventory (MFSI)**. The MFSI is a 30-item fatigue scale developed specifically for documenting CRF. In addition to a fatigue total score, the instrument includes subscales for assessing general, physical, emotional, mental and vigor domains of fatigue. The self-report instrument was psychometrically validated among a sample of 304 cancer patients and has been shown to have good fit via confirmatory factor analysis, reliability and validity.[96-98]

7.4 Aerobic capacity will be assessed using the **6-Minute Walk Test,** which is a sub-maximal measurement using a 6-minute walk protocol. A recent systematic review has concluded that this method possesses excellent measurement properties, was better tolerated, and was more reflective of activities of daily living than any other walk test in use.[99] Participants are directed to a specific area designated for walking. Participants walk for a total of 6-minutes and cover as much distance as they can during this time. The walk test is optimally performed in a flat, well lit area that allows for a minimum of 100 feet of walking before the participant needs to make a turning motion. For example, the test may be conducted in a hallway (walking back and forth) or a larger room that allows for a circular/square walking pattern. Upon completion of the test, the total distance walked (in feet), exercise heart rate (in beats per minute), and exercise rate of perceived exertion (using the ACSM revised rating of exertion scale) are recorded. This test was easy to implement, and well received in a busy clinical setting in the pilot study of the proposed exercise intervention. The total distance walked in six minutes can be used to estimate gross VO_2 (oxygen consumption).[87] Gross VO_2 = Resting VO_2 + Exercise (or net) VO_2. The formula used to estimate gross VO_2 is

VO_2 (mL *kg^{-1} * min^{-1}) = [0.1 mL *kg^{-1} * $meter^{-1}$ * S (m * min^{-1})] + [1.8 mL * kg^{-1} * $meter^{-1}$ * S (m * min^{-1}) * G] + 3.5 mL *kg^{-1} * min^{-1}

Where S is speed in meters per minute and G is the percent grade expressed as a fraction. [87]

7.5 Strength will be assessed using **The Handgrip Dynamometer Test**, which 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. Trials will be performed in an alternating bilateral sequence for a total of six attempts (three with each arm). The average 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.[87] This test was also easy to implement and well received in the clinic in the pilot study of the proposed intervention.

7.6 Quality of life (QOL) will be assessed subjectively via the **Functional Assessment of Chronic Illness Therapy (FACIT). The FACIT** is a 28-item QOL scale developed specifically for use in cancer clinical trials.[90] It was developed by Cella and his group through extensive interviews with oncology professionals and patients experiencing symptoms of cancer, and it has been validated in a series of studies of 542 cancer patients. The basic measure has shown very good test/retest reliability as well as validity.[90,94,95] Along with a total score representing QOL, there are psychometrically validated subscales of physical, functional, social, and cognitive-emotional status. It is one of the most commonly used measures in oncology, and we have used this instrument in our previous studies, including the pilot study designed for this protocol.

7.7 Physical exercise/activity will be assessed subjectively using the **Aerobic Center Longitudinal Study Physical Activity Questionnaire (ACLS)** and a **Daily Diary.**

7.7.1 The **Aerobic Center Longitudinal Study Physical Activity Questionnaire (ACLS)**,[100] is an assessment of lifestyle physical activity. Participants report their engagement in fourteen different physical activities (frequency, intensity and duration) over the last month. Estimates of energy expenditure are calculated using the following equation: (sessions/week) * (min/session) * (hour/min) * MET [Note: MET = metabolic energy expenditure rate] for each activity and then summed to provide total MET hours of energy expenditure for a week. The index of walking, jogging, and running predicted treadmill performance time r = .31 and there is a moderate relationship between energy expenditure estimates and treadmill performance (r = .41). Additionally, this instrument has been effectively used to predict the relative risk of prostate cancer based on cardiorespiratory fitness,[101] and we have used it in previous studies as well.

7.7.2 The **Daily Diary** is designed to track compliance and participation in the exercise intervention, additional daily activities, and hot flashes. The participant will be asked to take 1-2 minutes and complete the journal each morning upon wakening and each evening immediately prior to sleeping. This daily diary was used in the piloted version of the proposed study, and participants completed the forms without any problems.

7.8 General symptomatology will be measured with a **Symptom Inventory,** a list of 19 symptoms modified from measures created at M.D. Anderson and Memorial Sloan-Kettering Cancer Centers. It is a series of uniscales where the severity of each symptom is indicated by filling in the appropriate circle on an 11-point scale, anchored by 0 = “Not Present” and 10 = “As Bad as You Can Imagine.” An additional eight questions assess the degree that the symptoms interfere with the participant’s quality of life, with 0=”Did not interfere” and 10=”Interfered completely.” Medical oncologists at our Cancer

Center use the measure in clinical care, and we have used it in numerous studies. It will serve as a concurrent self-report measure of symptoms that will be used in exploratory analyses.

7.9 Because CRF, depression, anxiety, mood disruption, sleep disturbance and cognitive problems are often present as symptom clusters, measures of depression, anxiety, mood, sleep and cognitive problems have been carefully selected to minimize potential confounding and enable assessment of possible confounds between these concepts.

7.9.1 Depressive *symptoms* will be measured with the **Center for Epidemiological Studies Depression Scale (CES-D).** The CES-D[56] 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,[102] and we have successfully used this measure in previous studies.

7.9.2 Anxiety will be measured using the **Spielberger State/Trait Anxiety Inventory (STAI Form Y-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 indicate the degree to which they generally experience each 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.[103,104] We have successfully implemented this measure in previous studies.

7.9.3 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.[105,106]

7.9.4 Quality of sleep will be assessed subjectively using the **Pittsburgh Sleep Quality Inventory (PSQI)** and a **Daily Diary**.

7.9.4.1 The **Pittsburgh Sleep Quality Inventory (PSQI**), a commonly used, 24-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).[107] This measure has been implemented in other CCOP studies conducted by our group.

7.9.4.2 Number of hours of sleep will be calculated from the daily diary. For each day of the entire study period, participants will indicate time to bed at night and time arose in the morning.

7.10 Cognitive problems will be assessed using the **Functional Assessment of Chronic Illness Therapy-Cognitive Well-being Subscale (FACIT-Cog).** The FACIT-Cog subscale is a 50-item scale that asks questions directly related to cognition.[90] It was developed by Cella and his group through extensive interviews with oncology professionals and patients experiencing symptoms of cancer, and it has been validated in a series of studies. The basic measure has shown very good test/retest reliability as well as validity.[90,94,95] It has become one of the most commonly used measures in oncology, and we have used this instrument in our previous studies (e.g., the pilot study designed for this protocol).

7.11 **The Feedback Questionnaire,** concerning participants' views on the experimental treatment they received, will be completed at the conclusion of the seventh week on study. The information in the feedback questionnaire will allow us, for future studies, to obtain information needed to alter aspects of the intervention with which participants were displeased and determine participants' reactions to the intervention.

Rev 11/10 7.12 **Cytokines** (IL-6, IL-8, IL-10, IL-1β, IFN-γ, & TNFr1) in the blood at baseline and post-intervention and additional blood will be collected for banking of serum and plasma and whole blood for future DNA and RNA analysis. A fasting blood draw will be performed on all patients at baseline and post-intervention. Six tubes of blood (approximately 50ml) will be collected including: two red top tubes for serum, two purple top EDTA-heparin tubes (1 for plasma and 1 for DNA) and 2 Paxgene tubes for RNA. All CCOPs will handle all human biological materials and disposal of biohazard waste in accordance with biosafety level II guidelines at their respective institutions for blood collection, handling, disposal, storage and shipping. All CCOP personnel handling human biological materials and laboratories used by CCOPs must have received appropriate biosafety certifications and meet routine inspection guidelines.

7.12.1 All requisitions, blood tubes, microfuge tubes, freezer boxes, pipettes, and labels for blood draws are provided by the URCC CCOP Research Base in the form of barcoded and pre-labeled patient kits. All patients kits are study specific.

DO NOT MIX REQUISITIONS, BLOOD TUBES, MICROFUGE TUBES OR PIPETTES ACROSS PATIENT BLOOD DRAW KITS EVEN IN THE SAME STUDY BECAUSE THE BARCODES AND LABELS ARE KIT SPECIFIC.

DO NOT MIX THE FREEZER BOXES, LABELS OR EXTRA SUPPLIES PROVIDED ACROSS STUDIES EVEN URCC CCOP RESEARCH BASE STUDIES, BECAUSE THEY ARE STUDY SPECIFIC.

All CRAs will fill in the appropriate patient information on the requisition form in each kit when it is assigned to the patient. Every time a patient blood draw is performed (baseline and post-intervention) a separate new patient kit is used and assigned to the study participant. Each CCOP is responsible for designating an individual that is certified and a lab or facility that meets the biosafety level II criteria to perform the blood draws and to handle, dispose, store and ship the blood samples appropriately. The individual designated to perform the blood draws, handle, dispose, store and ship the samples must participate in the training provided by the URCC CCOP Research Base, previously described in the methods section, and be approved by the study PI (or PI's designee) prior to any blood collection at each CCOP site.

7.12.2 Serum will be extracted from the two red top tubes for estimation of cytokines (IL-6, IL-8, IL-10, IL-1β, IFN-γ, & TNFr1). Plasma will be extracted from one of the purple top EDTA-heparin tubes for estimation of cytokines (IL-6, IL-8, IL-10, IL-1β, IFN-γ, & TNFr1). To extract the serum and plasma, the tubes will first sit upright for 30 minutes at room temperature after blood collection. Second, thetubes will then be put into a centrifuge (note temp) and spun for 15 minutes at 1600 x g. After 15 minutes, there should be a clear separation of the serum or plasma (yellowish liquid on top) from the other cells. If this is not evident, then centrifuge for 15 additional minutes. The upper layer of serum (red top tubes) and plasma (purple top tube) is then gently aliquotted into the 2.0ml microfuge tubes provided in each URCC CCOP patient blood draw kit. Serum from the red top blood tubes is to be placed into the pre-labeled pink microfuge tubes. Plasma from the purple top tube is to be placed in the pre-labeled purple microfuge tubes. All microfuge tubes are then placed in the pre-labeled freezer boxes provided by the URCC CCOP Research Base and the freezer box is then placed in either a -20 C or a -80 C degree freezer (-80 C is preferred if available but not required) for storage until shipped to URCC CCOP Research Base. Cytokines (IL-6, IL-8, IL-10, IL-1β, IFN-γ, & TNFr1) will be assessed using Multiplex and ELISA methods as appropriate. The remaining serum and plasma will be stored and banked for use in future research by Dr. Mustian and her research team at the URCC CCOP Research Base.

7.12.3 One purple top EDTA-heparin tube and two Paxgene tubes will be prepared and stored for future DNA and RNA extraction. The EDTA-heparin tube will be rocked 10 times and then placed upright in a -20 C freezer for a minimum of 24 hours. After 24 hours, the EDTA-heparin tube can then be transferred to a -80 C freezer if available. The two Paxgene tubes will be rocked 10 times, stored upright for minimum of 2 hours and a maximum of 24 hours at room temp and then placed upright in a -20 C freezer for a minimum of 72 hours. After 72 hours, the Paxgene tubes can be transferred to a -80 C freezer if available. After the tubes have been frozen upright for their designated time above, they can then be placed on their side in the pre-labeled freezer boxes provided by the URCC CCOP Research Base. (Storage in a -80 C freezer after 4 days is preferred if available but not required.) The whole blood in these tubes will be stored and banked for use in future research by Dr. Mustian, the study PI, and her research team at the URCC CCOP Research Base.

7.12.4 **Shipping Supplies to CCOPs and Inventory Tracking:** Upon notification of the URCC CCOP Research Base that a CCOP has obtained IRB approval for this study, a starter blood drawing package, operations manual, and an initial supply of barcoded and pre-labeled blood draw kits will be shipped to the CCOP for distribution and use.

Each CCOP site will be responsible for designating someone on the research staff to be responsible for receiving the blood draw supplies and kits. The staff member will verify that the shipment contains the correct number of supplies and kits and that the supplies and kits are in good condition. The identification numbers need to be verified for accuracy and recorded. The Investigational Device Accountability Record (DARF) will be used to track supplies and kits arriving from the URCC CCOP Research Base, kits given to participants, samples stored, and samples shipped to the URCC CCOP Research Base.

7.12.5 **Shipping Frozen Blood Samples to URCC CCOP Research Base:**

THE URCC CCOP RESEARCH BASE MUST BE NOTIFIED AND ARRANGEMENTS MADE TO RECEIVE SAMPLES AT THE URCC CCOP RESEARCH BASE 24 HOURS IN ADVANCE PRIOR TO SHIPPING ANY SAMPLES

Call:
Jennifer Yates
585-275-6303

Ship Samples To:
ATTN: Jennifer Yates
University of Rochester Medical Center
Wilmot Cancer Center, PEAK Laboratory (B-5035)
601 Elmwood Avenue, Box 704
Rochester, NY 14642

If samples are stored frozen at -20 C, each CCOP must ship the frozen samples to the URCC CCOP Research Base PEAK Lab every 3 months. Samples cannot be kept at the CCOP location and stored frozen at -20 C for longer than 3 months total. Samples can be shipped sooner if storage space is limited.

If samples are stored frozen at -80 C, each CCOP must ship the frozen samples to the URCC CCOP Research Base PEAK Lab every 12 months. Samples cannot be kept at the CCOP location and stored frozen at -80 C for longer than 12 months. Samples can be shipped sooner if storage space is limited.

The CCOPs are responsible for shipping all samples to the URCC CCOP Research Base. All samples must be shipped priority overnight and frozen on dry ice. Each CCOP is responsible for adhering to URCC CCOP Research Base biosafety level II guidelines (outlined in the operations manual provided), their CCOP instituitional biosafety level II guidelines and the shipping company guidelines when packing and shipping the frozen blood samples to URCC CCOP Research Base.

Rev 11/10 7.13 **Total Energy Expenditure and Exercise Dose** will be measured using actigraphy. Actigraphs record data on movement using accelerometers. The accelerometer detects movement in space which is recorded in the form of "counts."[32] As the speed of movement becomes faster, ultimately resulting in a larger distance being covered in a set amount of time or an epoch (i.e., 1 minute) the number of activity counts recorded also increases.[32] A more complex and more accurate type of actigraph uses a triaxial accelerometer capable of measuring movement in all three planes of motion: forward (sagittal), sideward (coronal) and up/downward (transverse).[32] Data is aggregated and also recorded in the form of "counts" per epoch in these units.[32] These actigraphs can be used to measure the duration and intensity of free-living physical activity/exercise and to provide accurate estimates of the rate of energy expenditure using validated and published algorithms.[32] The gold standard for estimating energy expenditure under free-living conditions, a technique called doubly labeled water (DLW),[33] is expensive and places a heavy burden on patients, which practically precludes its use in most clinical

trials.[34] Actigaphs, on the other hand, which have been validated against DLW, are cost effective, easy for patients to wear and can be used effectively in large clinical trials to provide objective assessments of physical activity/exercise duration and intensity. The CSA/MTI/Actigraph brand is one of the most extensively validated accelerometers and will be used in this study.[33]

7.13.1 Each CCOP site will be responsible for designating someone on the research staff to be responsible for receiving the actigraphs. The staff member will verify that the shipment contains the correct number of actigraphs, waist belts, USB cables and wall chargers, and that the actigraphs are in good condition. The identification numbers on the actigraphs will be verified for accuracy and recorded. The Investigational Device Accountability Record (DARF) will be used to track actigraphs arriving from the URCC CCOP Research Base, actigraphs given to participants, actigraphs returned from participants, and actigraphs returned to the URCC CCOP Research Base.

7.13.2 When the CCOP has obtained IRB approval, the URCC will send each CCOP site a starter package of actigraphs containing an operations manual, wall chargers, USB cables, actigraphs, waistbands and software keys. The number sent to each site will be determined based on accrual rates to the study. The actigraphs will be shipped from URCC with a full charge, but the CCOP staff will need to keep the actigraphs plugged in and charging prior to distributing them to a patient.

7.13.3 Each CCOP site will be responsible for designating someone on the research staff to be responsible for installing the actigraph software on a computer, managing the actigraph inventory and all associated supplies, initializing actigraphs, downloading data from the actigraph, saving the data at the CCOP site electronically and sending the data to the URCC CCOP Research Base electronically. All procedures for installing the actigraph software as well as charging and cleaning the actigraph, initializing and downloading the actigraph for data collection, storing the data and electronically sending the data to the URCC CCOP Research Base are described in detail in the operations manual provided.

7.13.4 The research staff will make sure the actigraph is fully charged before assigning the unit to the study participant. The staff will initialize the actigraph to start data collection on the morning of study Day -4 at 12:01 am. The research staff will distribute the actigraph, waist belt, USB cable, wall charger, and actigraph instructions to each participant prior to Day -4, at the same time the patient is consented. If patients provide consent way in advance, the actigraph can be given to the patient later, but the patient must have the actigraph and must be able to start wearing it when they get up on the morning of study Day -4. The participant will wear the actigraph from the time they get up until they go to bed, throughout the entire day on Day -4 to Day -1, Day 17 to Day 20, and Day 38 to Day 41. Participants will take the actigraph off if they shower, swim or do anything where the actigraph would be submerged in water; they will put the actigraph back on immediately upon finishing these activities.

7.13.5 The research staff will explain the procedures for wearing, charging and cleaning the actigraph as outlined in the operations manual. Participants will put the actigraph on immediately upon getting out of bed on Day -4 and wear it

throughout each day until going to bed on Day -1. The participant will be instructed to plug the actigraph in and keep it charging at all times when they are not wearing it. The actigraph will remain in the possession of the participants until the end of the study period (Day 42). The research staff will call the participants and remind them to wear the actigraphs on study Day -4. The research staff will call the participants on Day 16 to ensure that the actigraph is fully changed and to remind the participants to wear the actigraph on Days 17 through 20. The research staff will call the participants on Day 37 to ensure that the actigraph is fully changed and to remind the participants to wear the actigraph on Days 38 through 41.

7.13.6 The research staff will collect the actigraph, waist belt, USB cable, and wall charger from the participants on Day 42 and inventory them.

7.13.7 The research staff will download the data from the actigraph within 24 hours of study completion when it is returned from the patient. To download the data, the research staff will connect the actigraph to the computer that has the ActiLife5 software using the provided USB cable and follow the steps outlined in the operations manual. Once downloaded, the file will be saved in a HIPPA secure electronic file at the CCOP site and emailed to the URCC CCOP Research Base within 72 hours of study completion by a patient.

Email files to: URCC_EXCAP@urmc.rochester.edu

7.13.8 Once confirmation is received by the CCOP site that the URCC has successfully received and saved the data, that actigraph can be charged, reinitialized and used for the next patient accrued to the study.

7.13.9 Following the completion of the study, the research staff at the CCOP site will be responsible for shipping all of the actigraphs, waist belts, USB cables, wall chargers and any remaining actigraphy supplies and data back to the URCC CCOP Research Base.

8.0 Design Considerations

8.1 One of the strengths of our repeated-measures design which includes two important assessment time points (baseline and post-intervention) is that each subject provides data on their level of CRF prior to initiation of both chemotherapy and the exercise intervention. This type of design allows us to address several important questions about within-group and between-group changes and differences because participants are randomized to continue with standard chemotherapy alone or standard chemotherapy plus the exercise intervention after baseline assessments. This type of design also allows baseline levels of CRF to be entered as a covariate in the proposed statistical analyses to control for baseline differences between the two study conditions.

8.2 The decision to provide a moderately intense, home-based walking and progressive resistance exercise intervention that participants perform daily in the current study was based on the typical course structure of exercise interventions used in previous studies with patients receiving chemotherapy and the positive results of the local pilot study

conducted by our group using the proposed exercise intervention, as well as ACSM recommendations for exercise prescriptions to maintain or improve aerobic capacity and strength.

Rev 4/12

8.3 The 6-minute walk test and the handgrip dynamometer test were chosen to assess aerobic capacity and strength, respectively. These tests were chosen because of their simplicity, low cost, and ease of administration in a large multi-site research study in community clinical oncology practices (CCOPs). CCOPs also do not generally have access to measures that are traditionally considered "gold standards," such as graded exercise testing or repetition maximum testing. Furthermore, the cost and practicality of administering graded exercise testing and appropriate repetition maximum testing to the large proposed sample (N=692) would be extremely high and beyond the resources of the current CCOP research mechanism. Moreover, these measures were sensitive and showed good results in our pilot study. Given the large sample in the currently proposed study, the selected tests should provide an appropriate measure of aerobic capacity and strength.

8.4 The current study is based on a randomized controlled pilot study that used the EXCAP intervention in its entirety. The current study is also designed to examine the EXCAP program in its entirety. We are collecting detailed information on exercise that may allow us to post hoc begin exploring the specific role of walking and resistance training separately, however the study is not designed to accurately address these questions and we will not have the statistical power to make definitive statements. Post hoc analyses of this nature will be purely exploratory for the purpose of designing future clinical trials. If this initial clinical trial is positive, one of the next logical follow-on studies we would conduct is a three-arm trial comparing the EXCAP program to a program of walking alone and a program of resistance exercise alone.

9.0 Data Handling and Statistical Considerations

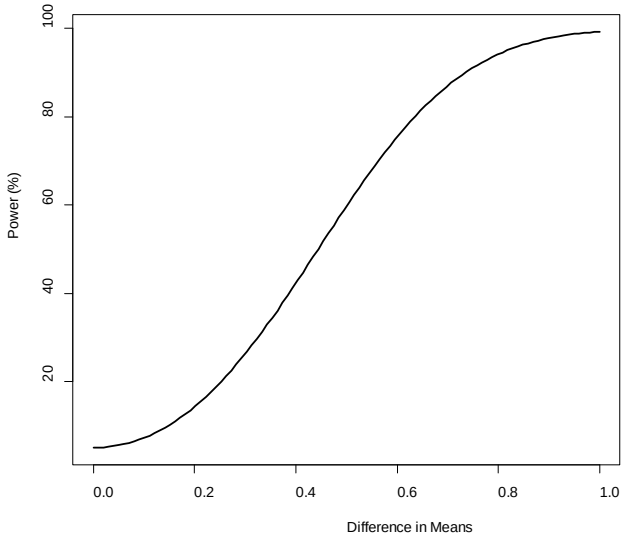
Rev 4/12

9.1 **Sample Size**: A total of 692 participants will be enrolled in this study with 346 patients in each study group. Actigraphy and cytokine assessments will be performed on a subset of 300 participants. Allowing for 30% of participants who may not provide complete data, we expect to have 484 evaluable participants total with 242 evaluable patients in each of the two treatment arms. This is an average size for our symptom management interventions because it generally provides the ability to detect a 15% -20% improvement in symptoms in the treatment group compared to the control group with an 80% - 95% power. A 15% - 20% improvement in symptoms is generally considered the minimum amount for determining clinical significance of a symptom control intervention.

The primary aim of this study is to evaluate the influence of the exercise intervention on CRF as assessed by the BFI total score at Day 41, post-intervention. Using data from the 38 cancer patients in our initial phase II pilot study, a sample size of 242 evaluable patients in each group will have 90% power to detect a difference in means of 0.7 (the difference observed in the mean of the exercise intervention group and the mean of the control group) using a two group ANCOVA with baseline CRF as the covariate and assuming a 0.050 two-sided significance level, a common standard deviation at or below 2.60 (upper 95% confidence bound) and a correlation coefficient of R = .40 for baseline CRF and post-intervention CRF. The upper 95% confidence bound for the standard

deviation was used because of the high uncertainty in the estimation due to the small sample size in the pilot study. The method published by Borm et al.[108] was used as the basis for modifying the sample size estimate to account for the increased power of the ANCOVA when using a correlated covariate. The formula starts with the sample size required by a two-sample t-test or ANOVA then multiplying the sample size by (1 – R^2) where R is the correlation between the baseline and the dependent variable. The correlation coefficient of .40 was used as the basis for converting the sample size requirement. This sample size will also be sufficient to test our secondary aims. The power curve in Figure 9 shows the statistical power we have to detect relative difference between the two treatment arms in means post-intervention on the BFI total score should the currently proposed study yield smaller mean differences.

Figure 9. Estimated Statistical Power Post-Intervention Between Treatmen



Rev 4/12 9.2 Study Timeline: Enrollment of the 692 participants is expected to take 24 to 36 months.

9.3 Representation of Women and Minorities: None of the eligibility criteria for the study involve gender or ethnicity. Past enrollment in our CCOP studies has closely paralleled the gender and ethnic composition of the available population.

9.4 The same protocols and procedures for data quality and control that we have used for our previous URCC CCOP Research Base protocols will be used for this study. Data will be entered on scannable forms (Teleform) and electronically sent to a Microsoft Access database. After scanning, data are audited visually for errors, then the entire database is re-audited. SPSS and SAS statistical packages will be used for the analyses.

9.5 Unless otherwise stated, all statistical tests will be performed at the two-tailed 5% level of significance. Likewise, 95% confidence intervals will be constructed for estimation of effects (e.g., difference in mean CRF, aerobic capacity, strength and QOL between the active treatment group and the control group). Data will be analyzed on an "intent-to-treat" basis; participant data will be included in the treatment group to which the participant was randomized, regardless of any subsequent changes to the treatment (treatment in this study is considered the study intervention, i.e., exercise intervention or standard care).

9.5.1 *Assumptions*: The assumptions underlying all statistical analyses will be thoroughly checked using appropriate graphical and numerical methods.[109,110] In the case of violations of the assumptions, appropriate nonparametric methods will be attempted.[111,112] If distributions are markedly skewed, we will apply transformations as appropriate. If outliers or influential data are detected, the accuracy of the data will be investigated. If no errors are found, analyses may be

repeated after removing these cases to evaluate their impact on the results. However, the final analyses will include these data points. If heteroscadistic variance is found in the data a Box-Cox transformation will be applied to the data.

Rev 4/12

9.5.2 *Missing Values*: Every effort will be made to encourage and facilitate participants' completion of questionnaires. In the event that missing data occur, all analyses will be performed using the predictive model-based multiple imputation method.[113] Such analyses provide more accurate estimates of treatment effects and an indication of the sensitivity of analyses to missing data.

9.6 Statistical Analyses

9.6.1 The primary outcome measure for this study is CRF assessed at the end of the study on Day 41, as assessed by the BFI total score.

9.6.2 To assess the **Primary Aim** (e.g., to examine the efficacy of the exercise intervention for improving CRF, as assessed by the BFI total score) we will perform an ANCOVA to compare means in CRF between the two treatment groups on Day 41 (post-intervention). The ANCOVA will include baseline CRF as a correlated covariate to increase the efficiency of the ANCOVA, and this analysis will also include an interaction term (baseline value with treatment arm) to understand possible interactions. The other stratification factors, CCOP site, chemotherapy cycle length, and sex will also be included in the ANCOVA model as covariates; any that are insignificant will be removed from the model used to report the results.

9.6.3 *Secondary Aims*: The secondary outcome measures for this study are aerobic capacity, strength and QOL at the end of the study on Days 41-42, as assessed by the 6-minute walk test, handgrip dynamometry and the FACIT-F total score, respectively. To assess the **Secondary Aims** (e.g., to examine the efficacy of the exercise intervention in improving aerobic capacity, strength and QOL, as assessed by the 6-minute walk test, handgrip dynamometry and FACIT-F), three ANCOVAs to compare means in aerobic capacity, strength and QOL between the two treatment groups on Days 41-42 will be performed. These three ANCOVAs will include baseline values as correlated covariates to increase the efficiency of the ANCOVA, and these analyses will also include interaction terms (baseline value with treatment arm) to understand possible interactions. The other stratification factors, CCOP site, chemotherapy cycle length, sex and baseline fatigue will also be included in the ANCOVA models as covariates; any that are insignificant will be removed from the model used to report the results.

Rev 4/12

9.6.4 Potential moderators and/or mediators of the intervention will be investigated through a series of hierarchical regression and correlational analyses. A moderator variable precedes and is not correlated with treatment. It affects the strength and direction of relationship between treatment and clinical outcome, providing information about *when* and *for whom* a treatment will be effective. A mediator, by contrast, occurs during and is correlated with treatment, and accounts for the relationship between the treatment and clinical outcome, defining *how* or *why* a treatment works and possible causal mechanisms.[114,115] Establishing moderators and mediators of treatment outcomes are essential to understanding treatment mechanisms and are of considerable benefit in guiding clinical practice as well as the design of future studies.[114] We will follow

procedures set forth by Kraemer[114] and MacKinnon et al. (2002)[52] for these analyses Specifically, we will use the joint significance method described by MacKinnon, and implemented in structural equation modeling software (MPlus).

Potential clinically meaningful **moderators** of the efficacy of the intervention for improving CRF at the end of the study (Days 41-42), as assessed by the BFI total score, that meet the assumption of precedence (e.g., moderators must precede the intervention)[114] include: age, gender, exercise stage of change at baseline, baseline level of physical activity, baseline CRF, baseline aerobic capacity, baseline strength, baseline QOL, baseline anxiety, baseline depression, baseline mood, baseline quality of sleep and baseline cognitive well-being. Exercise stage of change will be assessed using the Exercise Stages of Change question on the On-Study Form, and physical activity history will be assessed using the ACLS total score at baseline. CRF will be assessed using the baseline BFI total score and MFSI total score, aerobic capacity using the baseline 6-minute walk test, strength using the handgrip dynamometry, QOL using the baseline FACIT-F total score, anxiety using the baseline STAI score, depression using the baseline CES-D score, mood using the baseline POMS score, sleep quality using the baseline PSQI score and cognitive well-being using the baseline FACIT Cognitive Subscale. Statistically speaking, a moderator of a treatment intervention must meet two criteria: 1) it must be **uncorrelated** with treatment condition, and 2) the interaction of the treatment condition(s) and the putative moderator must be a statistically and/or clinically significant predictor of treatment outcome.

- To determine whether or not the first criterion is satisfied, bivariate analyses (Spearman's rho) and/or Chi-square analyses, as appropriate, will be used to examine whether the variables are correlated ($p \leq .05$) with treatment condition. Only those variables established as uncorrelated with either of these treatment vectors will be further analyzed for moderator status.[114] (Note: Since this is a randomized trial, treatment condition would not be expected to correlate with any of these variables.) Any of these variables that are found to correlate with treatment outcome will be used as an additional covariate in the analyses testing both the Primary and Secondary Aims described earlier, instead of examined as a potential moderator of treatment outcome.

- To determine whether or not the second criterion (e.g., there being a significant interaction between the putative moderator and treatment condition on the treatment outcome) is satisfied, the above-mentioned variables that are uncorrelated with treatment condition will each be further examined through hierarchical regression analyses. As in the analysis for the Primary Aim, described earlier, the dependent variable in each of these regression equations will be CRF at the end of the end of the study on Day 42 as assessed by the BFI total score. CRF severity at baseline will be controlled by entering it at the first step in each equation. A coded variable for treatment condition will be entered at the second step. The putative moderator will be entered at the third step and the interaction terms (created by multiplying the putative moderator score by the coded treatment variable at the second step) will be entered at the fourth and final step. The examined variable, whether or not it has a significant main effect, will be considered a

moderator only if one or both of the interaction terms are a statistically and/or clinically significant predictor of treatment outcome.[114]

The potential **mediators** of the exercise intervention in reducing CRF at the end of the study on Days 41-42 (as assessed by the BFI total score) that we will examine include changes in aerobic capacity, strength, QOL, level of physical activity, anxiety, depression, mood, sleep quality and/or cognitive well-being from baseline at Days -1 to 0 to the end of the study at Days 41-42. These potential mediators meet the assumption of precedence (e.g., mediators do not precede the intervention).[114] Aerobic capacity, strength, QOL, level of physical activity, anxiety, depression and sleep quality for these analyses will be assessed using the 6-minute walk test, the handgrip dynamometer, the total score from the FACIT-F, the total score from the ACLS, the STAI score, the CES-D score, the POMS score, the PSQI score, and the FACIT Cognitive Subscale score, respectively. Changes in potential mediators will be determined by calculating simple change scores (e.g., subtracting the score of the variable measured at Days 41-42 post-intervention from the corresponding score measured at baseline on Days -1 to 0). A mediator of a treatment intervention must meet two criteria: 1) it must be **correlated** with treatment condition, and 2) the putative mediator and/or the interaction of the treatment condition(s) and the putative mediator must be a statistically and/or clinically significant predictor of treatment outcome.

- To determine whether or not the first criterion is satisfied, bivariate analyses (Spearman's rho) will be used to examine whether the above variables are correlated ($p \leq .05$) with treatment condition. Only those variables established as correlated with treatment condition will be further analyzed for mediator status.[114]

- To determine whether or not the second criterion (e.g., there being a significant main effect and/or interaction between the putative mediator and treatment condition on treatment outcome) is satisfied, the above variables that are correlated with treatment condition will each be further examined through hierarchical regression analyses. These regression analyses will be identical in construct to those described in the second bullet under moderators (directly above), although the interpretation of findings will be slightly different. The examined variable will be considered a treatment mediator if it is a statistically and/or clinically significant predictor of treatment outcome or if one or both of the interaction terms are a statistically and/or clinically significant predictor of treatment outcome.[114]

These analyses of potential moderators and mediators of the efficacy of the intervention in reducing CRF are numerous. At present, findings from these analyses would not be considered anything other than information to be used in the design of further randomized controlled investigations.

9.6.5 *Additional Exploratory Analyses*: The data analytic techniques described above for analysis of the Primary Aim and the Secondary Aims will also be used to determine if there are any observed positive benefits of the intervention on CRF as assessed by the FACIT-F fatigue subscale and the MFSI, physical activity as assessed by the ACLS, symptoms using the symptom inventory, depression using the CES-D, anxiety using the STAI, mood using the POMS, sleep using the PSQI and daily diary, and cognition using the FACIT Cognitive Well-being

subscale. **Because of the large number of additional exploratory analyses that will be conducted, positive findings, if any, will be interpreted cautiously.**

9.6.5. Supplemental Aims:

Supplemental Aim 1: The purpose of supplemental aim 1 is to determine the influence of our EXCAP intervention on five cytokines and one cytokine receptor (IL-6, IL-8, IL-10, IL-1β, IFN-γ, & TNFr1). To assess this aim we will perform an ANCOVA to compare means in each response between the two treatment groups on Day 41 (post-intervention). The ANCOVA will include baseline response as a correlated covariate to increase the efficiency of the ANCOVA, and this analysis will also include an interaction term (baseline value with treatment arm) to understand possible interactions. If the interaction is not significant, it will be removed to obtain a more interpretable model. The other stratification factors, CCOP site, chemotherapy cycle length, and sex will also be included in the ANCOVA model as covariates; any that are insignificant will be removed from the model used to report the results.

Supplemental Aim 2: The purpose of this aim is to provide an initial examination of whether changes in IL-6, IL-8, IL-1β, IFN-γ, & TNFr1 mediate the relationship between physical exercise and CRF. To assess this aim, we will use the techniques of mediation analysis, popularized by Baron and Kenny (1986),[50] described by Kraemer (2002)[51] in clinical trials contexts, and methodologically updated by MacKinnon et al. (2002).[52] Specifically, we will use the joint significance method described by MacKinnon. These analyses are numerous. **Findings from these analyses would not be considered anything other than information to be used in the design of further randomized controlled investigations.**

Supplemental Aim 3: The purpose of supplemental aim 3 is to determine the influence of our EXCAP intervention on total energy expenditure as assessed by actigraphy. To assess this supplemental aim we will perform an ANCOVA to compare mean change in energy expenditure between the two treatment groups from baseline to post-intervention. The ANCOVA will include baseline response as a correlated covariate to increase the efficiency of the ANCOVA, and this analysis will also include an interaction term (baseline value with treatment arm) to understand possible interactions. If the interaction is not significant, it will be removed to obtain a more interpretable model. The other stratification factors, CCOP site, chemotherapy cycle length, and sex will also be included in the ANCOVA model as covariates; any that are insignificant will be removed from the model used to report the results.

Supplemental Aim 4: The purpose of supplemental aim 4 is to determine the influence of our EXCAP intervention on total minutes of non-sedentary physical activity (exercise duration) intensity of physical activity assessed using actigraphy. To assess total energy expenditure we will perform an ANCOVA to compare mean change in total minutes of non-sedentary physical activity between the two treatment groups from baseline to post-intervention. The ANCOVA will include baseline response as a correlated covariate to increase the efficiency of the ANCOVA, and this analysis will also include an interaction term (baseline value with treatment arm) to understand possible interactions. If the

interaction is not significant, it will be removed to obtain a more interpretable model. The other stratification factors, CCOP site, chemotherapy cycle length, and sex will also be included in the ANCOVA model as covariates; any that are insignificant will be removed from the model used to report the results.

To assess the effect of the EXCAP intervention on the intensity of physical activity measured in minutes of sedentary, low, moderate and vigorous activity. We will use a multivariate ANCOVA with the four outcome variables as the response, arm as the factor, and the four baseline values as covariates. Wilk's Lambda will be used to test the significance of the EXCAP intervention. Plots of the means will be used to help interpret the effects in terms of each outcome, and a principal components analysis will be performed on the response change score data in each arm separately and displayed as a biplot for each arm. These plots will give insight into changes in the correlation structure of the responses due to the intervention.

Exploratory Analyses for Supplemental Aims:

Supplemental Aims 1 and 2: To gain greater insight into the change in the cytokines and the receptor induced by the exercise intervention, we will apply to the post-pre intervention change scores multivariate ANOVA to test for changes overall, followed by principal components analysis and biplot displays for each arm separately. These should provide considerably more insight about the nature of the exercise induced changes than separate univariate analyses. A by-product of this analysis will be correlations amongst the cytokines/receptors for each treatment group. As an alternative approach to separate mediation analyses, we will use structural equation modeling on change scores to further explore the role of the cytokine/receptor levels and exercise variables in the development of CRF. **The purpose of these analyses is hypothesis generation, and will be subject to confirmation with new studies.**

Supplemental Aims 3 and 4: We will perform exploratory analyses to examine whether changes in energy expenditure (kcal/kg/min), or duration (total minutes) and intensity (minutes in sedentary, low, moderate or vigorous activity) of physical activity mediate the relationship between physical exercise and CRF. To assess this we will use the techniques of mediation analysis, popularized by Baron and Kenny (1986)[42], described by Kraemer (2002)[43] in clinical trials contexts, and methodologically updated by MacKinnon et al. (2002)[44]. Specifically, we will use the joint significance method described by MacKinnon. *These analyses are numerous.* **Findings from these analyses would not be considered anything other than information to be used in the design of further randomized controlled investigations.** As an adjunct approach to separate mediation analyses, we will use structural equation modeling on change scores to further explore the role of energy expenditure, duration and intensity of physical activity and exercise variables in the reduction of CRF. **The purpose of these exploratory analyses is hypothesis generation, and will be subject to confirmation with new studies.**

9.6.6 *Interim Analyses*: No interim analyses of efficacy data from the trial are planned.

10.0 Records To Be Kept

Rev 4/10

10.1 Study forms and assessment times:

FORM	On Study (At time of consent)	Baseline Assessment (Days -4 - 0)	End of Study Assessment (Days 38-42)
URCC Clinical Trial Patient Registration Form, Eligibility Checklist, Consent Form	✓		
Participant Contact Form for Future Research	✓		
On-Study Data/Participant Form (Demographic, sleep history, etc)	✓		
Clinical Record Information (clinical data)	✓		
Chemotherapy Flow Sheet and/or RT Treatment Summary (copy from chart)	✓		
Lab Tests (if within last 3 mos)		✓	✓
Medication and CAM Usage		✓	✓
Brief Fatigue Inventory		✓	✓
Multidimensional Fatigue Symptom Inventory (MFSI)		✓	✓
Fitness Testing (6-Minute Walk Test, Handgrip Dynamometer Test)		✓	✓
Pedometer		✓[1]	✓[1]
Functional Assessment of Chronic Illness Therapy, -Fatigue, -Cognition (FACIT, -F, -Cog)		✓	✓
Aerobic Center Longitudinal Study Physical Activity Questionnaire (ACLS)		✓	✓
Daily Diary (including Hot Flashes)		✓[2]	✓[2]
Center for Epidemiological Studies Depression Scale (CES-D)		✓	✓
State Trait Anxiety Inventory (STAI X-1)		✓	✓
Profile of Mood States (POMS)		✓	✓
Pittsburgh Sleep Quality Inventory (PSQI)		✓	✓
Symptom Inventory		✓	✓
Walking and Resistance Exercise Prescription Sheets (EXCAP Patient Manual)	✓		
Feedback Questionnaire			✓
Participant Contact Sheets (3)			✓

[1]Assessed for 4 consecutive days during baseline (Days -4 to -1), which is immediately prior to beginning the study intervention (Day 0) and again for 4 consecutive days immediately prior to the study end (study Days 38-41).

[2]Begin on the same day that pedometer commences during baseline and continue for the entire study period ending on the last day of pedometer at the end of the entire study period.

10.2 All written materials will be kept confidential, locked in the private office of the research coordinator and identified by ID numbers. Electronic databases are password protected with limited access.

10.3 The Case Summary should accompany ALL data submissions. Completed On-Study and Baseline forms must be submitted within 30 days of randomization and End of Study Assessment should be submitted within 30 days of going off study. Data should be sent to:

Diane Malone
URCC CCOP Research Base
601 Elmwood Avenue, Box 704

Rochester, NY 14642

11.0 Participant Consent and Peer Judgment

11.1 All investigational, FDA, NCI, state, federal and institutional regulations concerning informed consent and peer judgment will be fulfilled.

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Appendix A: Study Measures

1. **Eligibility Checklist**
2. **On-Study Data/Participant Interview**
3. **Clinical Record Information**
4. **Lab Tests**
5. **Medication and CAM Usage**
6. **Brief Fatigue Inventory (BFI)**
7. **Multi-dimensional Fatigue Symptom Inventory (MFSI-SF)**
8. **Functional Assessment of Chronic Illness Therapy-Fatigue, -Cognition (FACIT-F, -Cog)**
9. **Aerobic Center Longitudinal Study Physical Activity Questionnaire (ACLS)**
10. **Center for Epidemiological Studies-Depression Scale (CES-D)**
11. **State-Trait Anxiety Scale form Y-1 (STAI)**
12. **Pittsburgh Sleep Quality Inventory (PSQI)**
13. **Symptom Inventory**
14. **Daily Diary (activity, sleep, hot flashes)**
15. **Feedback Questionnaire**
16. **URCC Clinical Trial Patient Registration Form**
17. **Profile of Mood States**
18. **Case Summary Form**
19. **Fitness Testing**
20. **Participant Contact Forms:**
    - **for Future Research**
    - **Baseline**
    - **Intervention: Day 4-6, 18-20**
    - **Intervention: Day 32-34, 38-40**

Appendix B: EXCAP: Exercise for Cancer Patients Manual