

Biobehavioral Effects of Tai Chi Qigong for Male Cancer Survivors with Fatigue (HERO)

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STUDY INFORMATION

- **Title of Project:**
Biobehavioral Effects of Tai Chi Qigong for Male Cancer Survivors with Fatigue

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1.0 Research Design

1.1 Purpose/Specific Aims

Although men with a history of prostate cancer are a group that is nearly as large as breast cancer survivors are, they are not studied as extensively, especially with regard to testing behavioral interventions designed to ameliorate cancer-related symptoms.^{1,2} Research on exercise interventions (e.g., aerobic exercise, resistance exercise, walking, or a combination) has shown some benefits in treating fatigue and improving QOL in cancer patients.³⁻⁸ However, a recent meta-analysis of the effects of exercise in modulating CRF reported that only 11% of studies (n = 4) enrolled prostate cancer survivors exclusively.⁹⁻¹¹ Recent recommendations from the American Society of Clinical Oncology and the National Comprehensive Cancer Network for the management of CRF advise the tailoring of exercise interventions to the tolerance of the individuals.^{1,12} For elderly prostate and other cancer survivors suffering from fatigue, body-mind training (BMT), such as Tai Chi Qigong may be more appealing because they are not overly physically exertive and they are safe for elderly populations.¹³ We will use BMT to refer to the Tai Chi Qigong intervention throughout this protocol. BMT differs from pure exercise interventions with the inclusion of a focus on deep breathing techniques, synchronized rhythmic movements, specific postures, and meditation to induce relaxation.¹⁴ If proven effective, our manualized BMT intervention can contribute to a needed evidence base for prostate and other cancer survivorship care, being broadly disseminated to the elderly population who suffer extensively from fatigue. Although prostate cancer accounts for 20% of men diagnosed with cancer, fatigue is not limited to this cancer exclusively. Men are an understudied population as a whole, especially in cancer-related fatigue research.

BMT provides a unifying, short-hand label for the many types of Qigong and Tai Chi (including Tai Chi Chih) that have been used, as these practices have similar theoretical foundations, proposed mechanisms of action, and expected benefits.¹⁵ BMT includes Tai Chi practices with a primary Qigong focus, and most Qigong has a Tai Chi component. The different types of Tai Chi Qigong vary in the amount of Qigong (i.e., relatively static moves making them generally simple to perform) vs. Tai Chi (i.e., dynamic moves that can take months to learn, years to master, and are more cognitively demanding). Hence, we have manualized a BMT intervention that incorporates Qigong and simplified forms of Tai Chi (e.g., Tai Chi Ruler, Cloud Hands and Wild Goose). This manualized BMT can be learned quickly because they involve repeating a single movement or small number of movements. Further, BMT is also very adaptive to different levels of physical functioning making it well suited for sedentary senior men with cancer with fatigue.¹⁴

For participant recruitment and research materials such as the participant consent forms, recruitment letters, advertisements, intervention implementation etc., we will avoid the use of the term Tai Chi Qigong specifically and will refer to the intervention groups as follows: Tai Chi Qigong intervention is referred to as body-mind training (BMT) and the intensity-matched condition is body training (BT). This will help to reduce bias by minimizing participants' expectations or perceived differences between the groups.

Application of the Biopsychosocial and Psychoneuroimmunology Models to BM

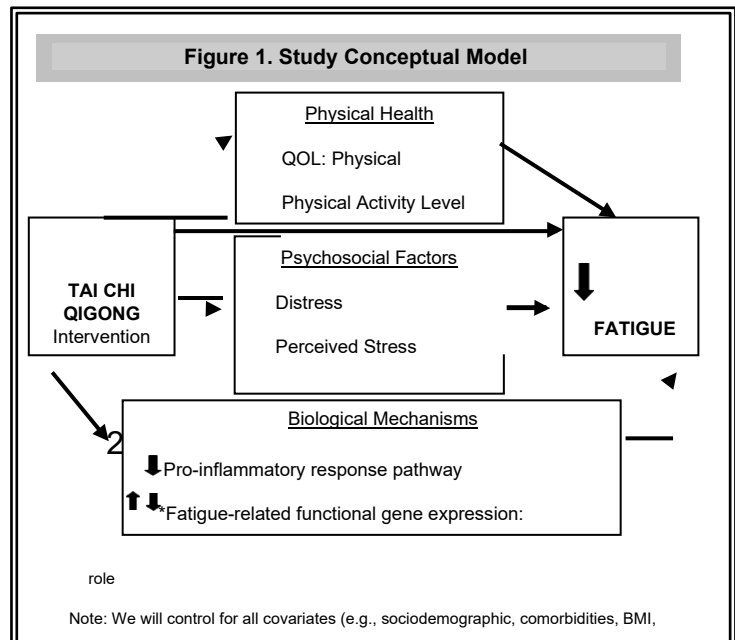
Psychosocial Mechanisms: It is thought that biological, psychological and social factors may interact to have an effect on health and illness through neuroendocrine (hypothalamic-pituitary-adrenal and sympathetic-adrenal-medullary axes) and biologic (e.g., immune) pathways.¹⁶⁻²¹ Consistent with the

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biopsychosocial model^{16,22} and the model of psychoneuroimmunology,²³⁻²⁵ movement-based body-mind interventions combine deliberate movements, diaphragmatic breathing, meditation, and deep relaxation in a group-based class to influence psychological, social, and physical health components and biological processes.^{14,21,26,27} BMT targets stress effector mechanisms, and can exert benefits on fatigue directly through effects on psychological distress and stress, social well-being, QOL, physical well-being, and biological processes in cancer survivors and older adults as delineated in Figure 1.^{14,15,21,27-32}

Biological Mechanisms of Fatigue - Pro-inflammatory Cytokines and Gene Expression: Basic research on neural-immune signaling indicates that pro-inflammatory cytokines can signal the central nervous system to generate symptoms of fatigue and other behavioral changes,³³ and there is growing evidence for a role of pro-inflammatory cytokines in CRF.³⁴ We have also documented elevations in systemic, cellular, and genomic markers of inflammation in women who experience persistent post-treatment fatigue,³⁵⁻³⁷ consistent with findings from other research groups.³⁸ In randomized controlled trials, we have found that body-mind interventions are associated with robust and sustained (i.e., one-year follow-up) decreases in markers of systemic inflammation such as C-reactive protein (CRP) and interleukin-6 (IL-6), decreases of TLR-4 stimulated production of pro-inflammatory cytokines, and decreases in the expression of genes regulated by the transcription factor NFκB.^{21,39-41} Specifically, BMT treatment is also associated with decreased blood pressure, cortisol, and CRP.^{14,15,42-46} Whereas some studies do not find effects of body-mind interventions on pro-inflammatory cytokines,^{46,47} we have recently conducted a meta-analysis²⁷ and showed that body-mind interventions reduce markers of inflammation such as CRP and possibly IL-6, and reverse inflammatory gene expression profiles.^{39,40} Nevertheless, there are inconsistent findings which may be due to variation in selection of the control condition,^{21,40,41} sample population, control for confounding, and length of treatment and follow-up, all of which are addressed in this study design.^{48 21,40,41} Overall, available literature provides compelling evidence that pro-inflammatory cytokines and the signaling pathways associated with inflammatory activation contribute to fatigue during and particularly after cancer treatment.^{21,39-41,49} However, the effects of BMT on these mechanisms in elderly, inactive fatigued prostate and other cancer survivors are unknown, further underscoring the significance of our study.

Although a growing body of work supports a role of inflammation pathways as a biological mechanism associated with fatigue in cancer patients and survivors, other work has suggested that multiple neural and immune pathways may be involved.^{48,50} It has been hypothesized that the etiology of CRF likely involves the dysregulation of several physiological and biochemical systems including 5-HT neurotransmitter dysregulation, vagal afferent activation, alterations in muscle and ATP metabolism, hypothalamic-pituitary-adrenal axis dysfunction, circadian rhythm disruption, and cytokine dysregulation.⁵¹ The specific fatigue-related neurological, energy metabolism and immune pathways that are functionally altered by cancer, its treatment, and body-mind therapies such as BMT have not been established. One advantage of examining the complex mechanisms of fatigue through leukocyte gene expression (mRNA) is that multiple pathways can be examined efficiently from a single blood sample. Testing of mRNA outcomes could confirm some of these previously suggested genes as biomarkers for CRF in prostate cancer survivors, or as genes that predict successful response to our treatment (i.e., BMT), including reductions in fatigue.^{13,50} Genes that track improvement could also be clues as to the mechanisms of fatigue and the mechanisms of improvement caused by our BMT intervention.

A. Objectives

Primary Objective:

Specific Aim 1: Test the hypothesis that BMT, as compared to body training (BT) or usual care (UC), will reduce fatigue (primary outcome) in inactive, elderly, prostate and other cancer survivors.

Secondary Objective:

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Specific Aim 2: Test the hypothesis that BMT, as compared to BT or UC, will reduce inflammation as indexed by a vertically integrated approach: systemic levels of pro- and anti-inflammatory cytokines, Toll-like receptor (TLR)-4 stimulated monocyte production of inflammatory cytokines, inflammatory signaling (e.g., nuclear factor, NF-κB) and promoter-based bioinformatics inflammatory transcriptional profiling.

Specific Aim 3: Test the hypothesis that BMT, as compared to BT or UC, will alter expression of two major fatigue-associated functional clusters of genes: 1) inflammation, vasodilation and metabolite sensing and 2) energy and adrenergic activation.

Specific Aim 4: Examine potential underlying theoretical mediating (changes in distress, perceived stress, sleep quality, functional and social well-being, physical activity, inflammation pathway markers, and gene expression) and moderating mechanisms (sociodemographic and clinical factors; body mass index (BMI), and participation of a companion in intervention classes) that are related to improvements in fatigue, which will further specify and elucidate intervention effects.

B. Hypotheses / Research Question(s)

We predict that BMT will reduce cancer-related fatigue and that this type of intervention can be integrated into survivorship care plans. The study's findings will also provide novel information about underlying bio behavioral mechanisms.

1.2 Research Significance

Cancer survival rates have been increasing over the past several decades, due to earlier detection of the disease and more effective cancer treatment.^{52,53} The number of survivors is expected to continue to rise, with a prediction of 70 million survivors in 2030.^{52,54,55} Notably, there are an estimated 9 million survivors that are 60 years of age or older.⁵² Elderly cancer survivors have unique challenges in that they are coping with late and long-term effects of having had a cancer diagnosis and treatment, coupled with age-related declines and comorbidities.⁵⁵⁻⁵⁸ This may influence their ability to engage in behavioral interventions because of slower post-treatment recovery, increased functional limitations, and other quality of life (QOL) impairments.

Prostate cancer is the most common cancer among male survivors, representing 20% of all cancer survivors.⁵⁹ Survival rates are high for men diagnosed with prostate cancer, with nearly 3 million men in the U.S living with this diagnosis. The median age of diagnosis is 67 years (for all races combined).⁶⁰ Surgery and radiation are common treatments for prostate cancer and androgen deprivation therapy (ADT) is often used as an adjunct to surgery or used as a primary treatment for advanced disease, and for men who have a biochemical recurrence (elevated PSA) and no other detectable metastatic disease. ADT side effects can significantly impair patients' QOL⁶¹⁻⁶³ including increased fatigue⁶⁴⁻⁶⁶ and psychological distress.⁶⁷ Since the majority of prostate cancer survivors are elderly, both short- and long-term treatment-related side effects are often compounded with physiological declines and comorbidities associated with aging.^{55,56} Although prostate cancer is the most common, fatigue is associated with other cancers as well.

The National Comprehensive Cancer Network (NCCN) defines cancer related fatigue (CRF) as "a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning".¹² Fatigue is one of the most commonly reported symptoms by elderly cancer patients (i.e., 60-90%), including senior prostate cancer patients.^{12,58,68-71} Furthermore, it is one of the least understood cancer-related symptoms by patients and healthcare providers.⁷² Many prostate cancer patients report fatigue lasting 6 months or more after completion of treatment.^{73,74} Fatigue is common, under-recognized, undertreated and correlated with impairments in psychological distress, social and functional well-being and health-related QOL in cancer survivors, including men with prostate cancer.^{12,75,76} Limited published evidence exists to inform health promotion survivorship guidelines for reducing fatigue in men who have been treated for prostate cancer.^{77,78} Although several randomized controlled trials are underway that target fatigue in breast cancer survivors, there is a relative absence of randomized efficacy

trials that have focused on fatigue symptoms as a primary outcome in men with prostate cancer and even fewer have studied this in the context of elderly prostate cancer survivors.⁷⁹

1.3 Research Design and Methods

This parallel 3-arm, randomized clinical superiority trial will adhere to the CONSORT guidelines for conducting and reporting clinical trial results. The rationale for this study is that it will establish the efficacy of a 12-week manualized BMT for reductions in fatigue, the primary outcome. Secondary outcomes include changes in the biomarkers of inflammation, including genome wide transcriptional factors, and expression of fatigue-related genes.

A. Research Procedures

After obtaining informed consent and baseline assessments, 166 elderly, fatigued cancer survivors age 55 years and older will be randomized to the BMT arm, the intensity-matched body training (BT) arm, or the usual care (UC) arm. Patient-reported assessments (surveys) will occur at baseline (within 1-week pre-intervention), mid-intervention (6 weeks), 1-week post-intervention (13 weeks), as well as at 3 months and 12 months post-intervention. Bio specimen collection will occur at baseline, 13 weeks, 3 months, and 12 months post-intervention. Due to COVID-19, a one-time “Assessment survey” will be given to the participants who were enrolled during the Coronavirus Pandemic of 2020. Phlebotomy and stool collection will occur at baseline, 1-week post intervention (13 weeks), and 3 months and 12 months post intervention. The food and activity questionnaire will be given at the 6-week mid-intervention time point only.

Interventions

Eligible participants will be assigned to a study arm, body-mind training (BMT), body training (BT) or usual care (UC), according to the randomization procedure. Classes for the two intervention arms will be conducted on Rutgers campus or at a community site by trained instructors. Classes may also be conducted via Webex or a similar videoconferencing platform. All interventionists will be trained regarding the importance of adhering to the intervention protocol. For Newark participants, intervention will be held at Newark Public Library – Weequahic branch in a private room on the second floor. Library staff will not be involved in any research procedures or interaction with any study participants. CINJ trained study staff will be responsible for all study related procedures at the library during intervention. In addition, study staff may provide a bagged lunch to study participants at Newark and New Brunswick sites before or after intervention. The meal may help with retention and overall study satisfaction.

For all classes, instructors and study staff who observe each class will complete intervention fidelity checklists used in our prior research^{13,80-84} to ensure that the intervention is being administered as intended. To assess the perceived intensity of the two exercise interventions, self-reported Borg Rating of Perceived Exertion scale measures⁸⁵ will be collected following class on a regular basis and reviewed to ensure that both interventions are perceived to be of mild-to-moderate intensity. In addition, to ensure that the BMT and BT interventions are intensity-matched, an objective measure, heart rate, will be measured with heart rate monitors worn by participants on a weekly basis and pedometers (which will be worn over the course of the 12-week intervention period and into week 13-post intervention). Data will be reviewed regularly by the PIs and project director, and compared across intervention arms to ensure that the two exercise interventions are intensity-matched. An additional survey will be asked following both the BMT and BT Webex/Videoconference classes to assess their thoughts and feelings regarding moving to an online platform. These survey results will be stored in a HIPAA compliant database and paper copies will be stored in a locked cabinet.

Body Mind Training (Tai Chi Qigong): The BMT sessions will be led by trained BMT instructors who have

prior training in Qigong or Tai Chi, a form of Qigong, and training in the HERO Project's manualized BMT intervention. During the first session, the instructor will explain the underlying BMT theory and orient participants to the procedures of BMT. In all subsequent sessions, participants will practice BMT under the instruction of a BMT instructor. The rationale that will be communicated to participants randomized to this arm is that BMT is a health promotion intervention that incorporates meditation, body training, and repetitive movements to promote health and well-being. Each session will include: 1) warm up and a review of BMT principles; 2) meditation with BMT movement; 3) breathing techniques; and 4) relaxation procedures. Eccentrically-biased movements that can be completed while seated or standing (depending on participants ability) were chosen for the intervention (e.g., rocking chair, Tai Chi ruler, etc.) to increase the intensity of the intervention while maintaining a level of safety.⁸⁶ Based on our feasibility study, the classes will last 60 minutes, take place twice per week, and supplemented with home-based practice using an instructional DVD and handouts illustrating the specific poses to help with their independent practice. Participants will be instructed to practice at least 30 minutes a day (at least 3 days per week) throughout the intervention and post-intervention follow-up period. The BMT instructor will be trained by Dr. Kinney. The BMT instructor will then practice the intervention protocol by leading three classes with elderly male cancer survivors not enrolled in the study. Practice classes will be videotaped and the BMT expert will provide feedback to the instructor by phone or Skype. All BMT classes will be delivered according to an instructor manual.¹³

Body Training (BT): The rationale for the BT condition is that it will serve as a movement-based, intensity-matched and attention control arm and will match the BMT classes in non-specific factors such as contact time, getting out of the home a couple of times a week, experiencing a therapeutic environment, types of interactions with trained instructors and research participants that are possible in an exercising arm, attention and expectation of therapeutic benefit. In addition, this intervention controls for flowing, stretching (e.g., extending arms upward and outward) and eccentric (e.g., bending and moving back and forth) movements and physical activity intensity, and home practice with a DVD. The therapeutic benefit of participation in this arm will be emphasized by both study staff and the instructor to support retention of participants and control expectancy effects.⁸⁷ The rationale that will be communicated to participants is that this exercise program incorporates repetitive movements to promote health and well-being. Like the BMT classes, the 60-minute BT classes will meet twice a week for 12 weeks, and participants will be provided with an instructional DVD and handouts illustrating the specific movements to help with their independent practice and given the same expectations for home practice (minimum of 3 days per week).

Usual Care (UC): Participants in the usual care arm will receive care as normal and will not attend classes but will complete the same assessments as participants in the BMT and BT classes. They will be asked to mail back a survey at the mid-intervention point or to complete a survey by telephone, if they prefer.

B. Data Points

See table below for study schedule of assessments and data points to be collected.

Schedule of assessments. CINJ = Rutgers Cancer Institute of New Jersey; PHS = Project HERO Staff; Clinical Measures = CLINIC. Assessments will take place at a Rutgers University, an outpatient clinical space in Newark or RBHS clinic.

Assessment	Responsible Party	Baseline	6week midpoint	13 weeks	3 months	12 months
Informed Consent	PHS	X				
List of Medications	PHS	X	X	X	X	X
Survey	PHS	X	X	X	X	X
Sleep Diary (7 days)	PHS	X	X	X	X	X
Food Diary (3 days)	PHS	X		X	X	X
Food Frequency Questionnaire	PHS		X			
Stool	CLINIC	X		X	X	X
Clinical Measures:	CLINIC/PHS	X		X	X	X

Assessment	Responsible Party	Baseline	6week midpoint	13 weeks	3 months	12 months
Height, weight, blood pressure, hip : waist ratio						
Heart Rate Variability	CLINIC/PHS	X		X	X	X
Blood Tube Collection	CLINIC	X		X	X	X
Timed Up & Go (TUG) Test	CLINIC	X		X	X	X
Chair Stand Test	CLINIC/PHS	X		X	X	X
Credibility/Expectancy Questions	PHS	X	X	X		
Satisfaction Questions	PHS			X		
Adherence Questions	PHS				X	X

C. Study Duration

- The duration of an individual subject's participation in the study will be approximately 15 months.
- The subjects will be enrolled on an ongoing basis in years 1-4.
- The duration estimated for the investigators to complete the study is approximately 60 months. Primary analysis will occur in years 4 and 5 upon completion of post-intervention assessments.

Month 1-6:	Protocol development/hiring staff, training instructors, finalizing measures, crafting and testing database, recruiting first cohort
Month 6-48:	Recruitment and Follow-up
Months 3-6:	Intervention implementation and 1-month follow-up
Months 12-54:	Biomarker assays
Months 48-60:	Analyze data; generate reports and manuscripts

D. Endpoints

Primary Objective: To assess the effects of BMT, as compared to body training (BT) or usual care (UC), in reducing fatigue (primary outcome) in inactive, elderly, cancer survivors.

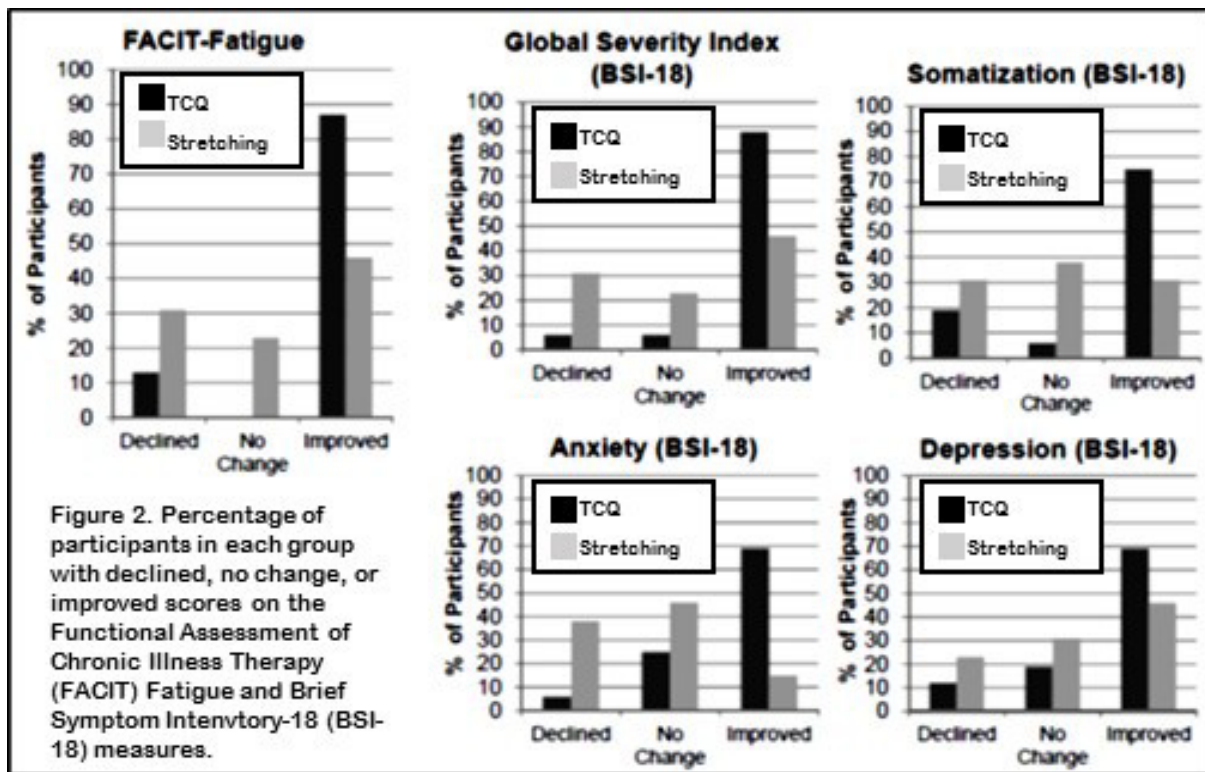
Primary Endpoints: Measures of fatigue collected at baseline, 6-weeks, 13-weeks and 3-months.

Secondary Objective: Assess the effects of BMT, as compared to BT or UC, on the reduction of inflammation as indexed by a vertically integrated approach: systemic levels of pro- and anti-inflammatory cytokines, Toll-like receptor (TLR)-4 stimulated monocyte production of inflammatory cytokines, inflammatory signaling (e.g., nuclear factor, NF-κB) and promoter-based bioinformatics inflammatory transcriptional profiling. On the expression of two major fatigue-associated functional clusters of genes: a) inflammation, vasodilation and metabolite sensing, b) energy and adrenergic activation. Examine potential underlying theoretical mediating (changes in distress, perceived stress, sleep quality, functional and social well-being, physical activity, inflammation pathway markers, and gene expression) and moderating mechanisms (sociodemographic and clinical factors; body mass index (BMI), and participation of a companion in intervention classes) that are related to improvements in fatigue, which will further specify and elucidate intervention effects.

Secondary Endpoints: Biological measures of inflammation and fatigue from biological specimens collected at baseline (prior to random assignment) and at one week, three months and 12 months post-intervention. Measures of fatigue, psychological distress, sleep, perceived stress, well-being and quality of life measured by survey at baseline, post-intervention at 6-weeks, 13-weeks and 3-months.

1.4 Preliminary Data

The investigative team has extensive experience directing, implementing and analyzing both relatively large (400 to >1,000 participants) to modest size randomized controlled trials including the delivery of body-mind exercise interventions.^{27,41,50,82,83,88-100} Furthermore, the team has extensive experience assessing the patient-reported outcomes used in this study and collecting, processing and analyzing the proposed bio specimens according to established laboratory procedures and employing the necessary quantitative techniques to address the study's aims.



Feasibility and Preliminary Efficacy of BMT. The feasibility of this manualized 12-week BMT intervention was established in a randomized controlled trial led by Dr. Kinney and in collaboration with Dr. Light (clinicaltrials.gov: NCT01564394).¹³ It used an attention-matched stretching movement condition (referred to in this protocol as body training) of similar intensity as measured by heart rate monitors. The majority (76%) of study participants met the FACIT-Fatigue cutoff (≤ 43) at baseline.¹⁰¹ Participation was facilitated by use of social marketing and other strategies (flyers designed with help from prostate cancer survivors, newspaper ads, face-to-face clinic recruitment, and

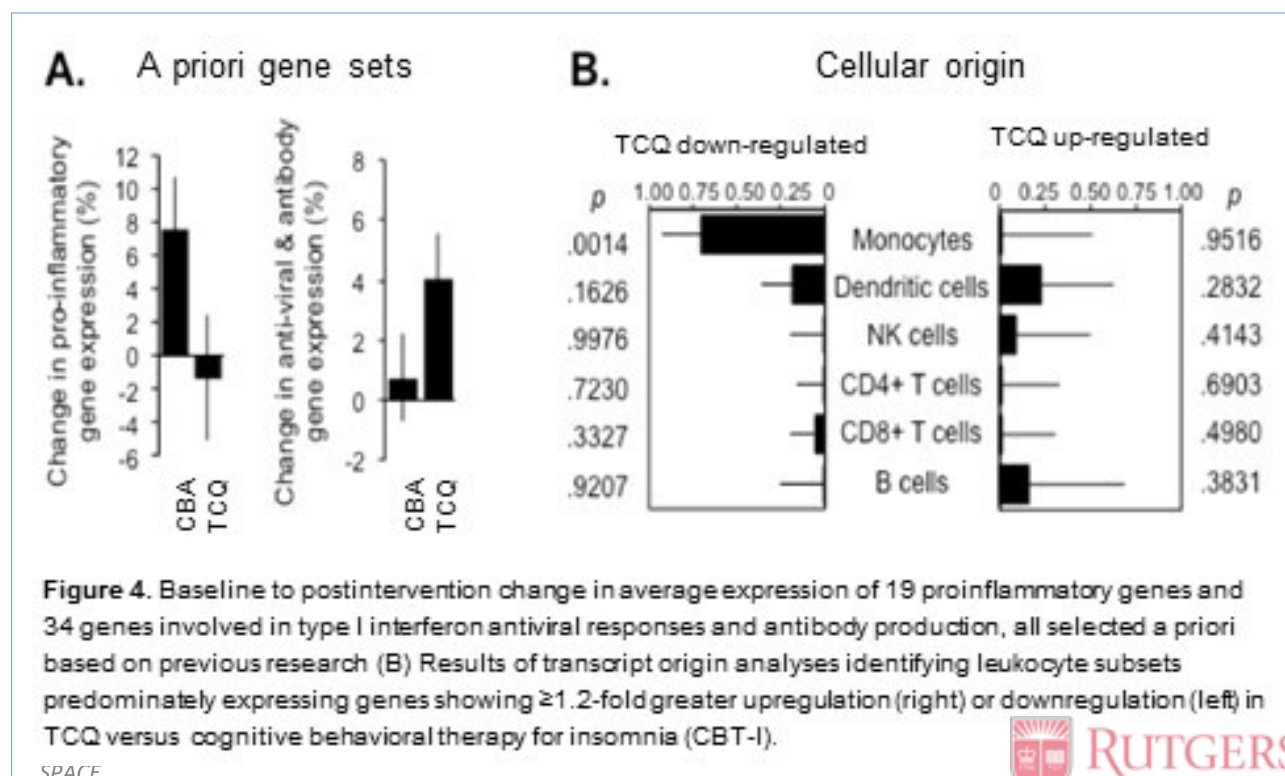
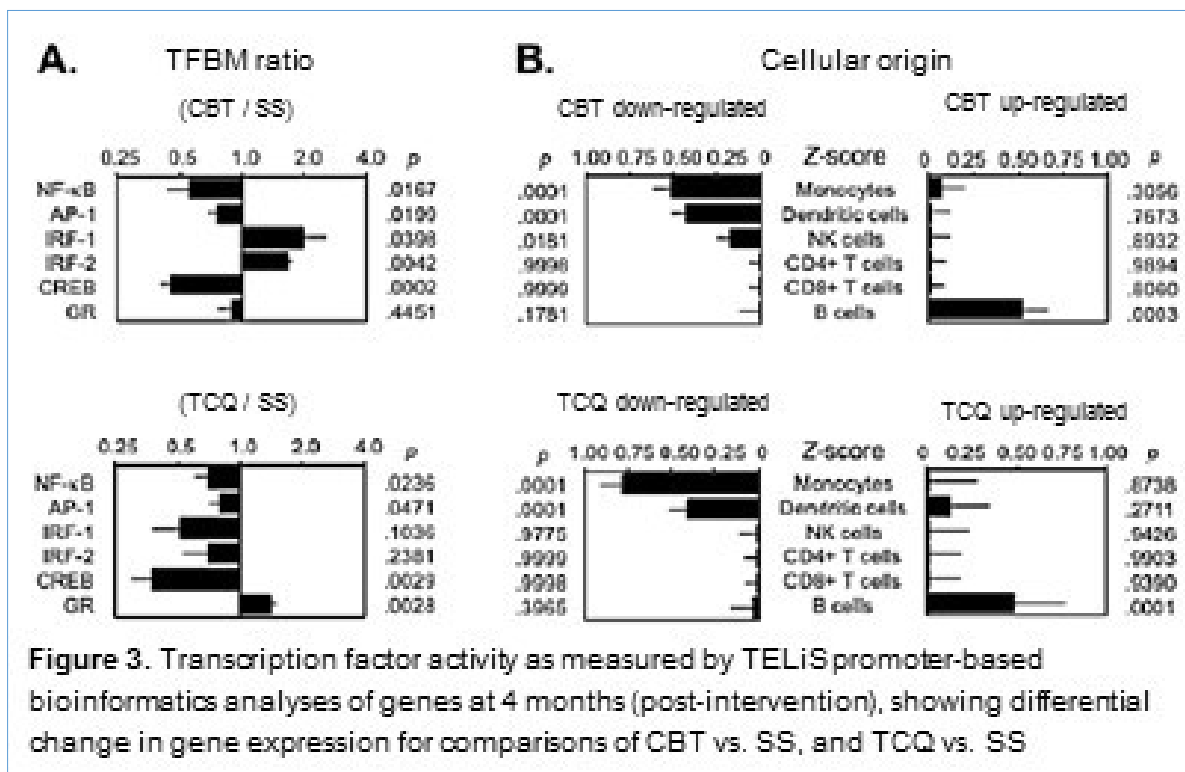
inviting social network members (e.g., family members, caretakers, significant others) to the interventions as a recruitment strategy. Classes were conducted twice a week for 12 weeks. Although our BMT intervention was perceived by participants to be of higher intensity, mean heart rate changes indicated that both study arms were of light intensity physical activity. Although not a goal of our pilot work we found that we could match, if desired, the intensity of the two exercise conditions by increasing the eccentric movements and the type and amount of flowing movements (e.g., arms over head) in the BT (which we plan to do in the current study). Improvement in fatigue and distress were more pronounced in the BMT arm than in the BT arm. We compared the proportions of participants showing improvement, no change or decline. As shown in Figure 2, more BMT than BT participants had a minimally important clinical difference in improvements of three points or more in fatigue score.¹⁰² Mean (M), FACIT-Fatigue scale scores significantly improved from baseline to post-intervention for the the BMT arm ($p = 0.02$; M change = 7.5; SD = 8.1) but not the SMC arm (M change = -0.9; $p = 0.002$; SD = 8.0), an effect size (ES) of $d=0.78$. We also observed statistically and clinically meaningful improvements in distress levels as measured by the Brief Symptom Inventory (BSI)¹⁰³ in the BMT arm ($p = 0.002$, M change = 7.4 point improvement) but not the BT arm (M change = -0.6; SD = 7.6), an ES of $d=1.18$. Ninety-five percent of men reported doing some BMT or BT home practice.

Inflammation Biology Pathways, Fatigue and BMT. CRF has been linked to the release of pro-inflammatory cytokines during cancer and in response to cancer treatment.^{20,34} In a study of women who had recently completed therapy for breast cancer, fatigue severity was correlated with plasma levels of the inflammatory marker soluble tumor necrosis factor receptor II (sTNF-RII) for those who had undergone chemotherapy, suggesting that inflammatory signaling may contribute to post-treatment fatigue.¹⁰⁴

Body-Mind Therapies: Impact on Systemic Markers of Inflammation. Dr. Irwin and colleagues conducted the first comprehensive meta-analysis of 34 studies to evaluate the effects of body-mind therapies including Tai Chi and Qigong on markers of inflammation.²⁷ This meta-analysis demonstrated a moderate effect on reduction of C-reactive protein (CRP; ES, 0.58; 95% confidence interval [CI], 0.04 to 1.12) after 7 to 16 weeks of body-mind interventions, small but not significant reduction of interleukin-6 (IL-6; ES 0.35; 95% CI, -0.04 to 0.75). Stratified by clinical populations, the subgroup meta-analysis showed that studies in healthy individuals were homogeneous and showed an insignificant effect on CRP (ES 0.20, 95% CI. 20.13 to 0.53), whereas studies in populations with disease conditions such as cancer showed significant reductions in CRP levels (ES 0.74, 95% CI. 0.00 to 1.48). Moreover, studies of BMT had larger mean effect sizes (ES 0.78, 95% CI. -0.24 to 1.80; $I^2 = 96\%$) compared with studies of meditation (ES 0.40, 95% CI. 0.02 to 0.77; $I^2 = 41\%$). Together, these meta-analytic results support the conceptual rationale to test the impact of BMT on circulating markers of inflammation in senior, fatigued cancer survivors for which there are not data.

CBT and Tai Chi Chih (TCC, a form of BMT) Reverse Cellular and Genomic Markers of Inflammation. Irwin and colleagues studied 123 older adults with chronic and primary insomnia who were randomized to Cognitive Behavior Therapy (CBT), BMT, or Sleep Seminar (SS) 2-hour group sessions weekly over 4 months with follow-up at 7 and 16 months.⁸⁹ Change in mean levels of CRP in the three intervention arms from baseline to month 4 (i.e., post-intervention) and month 16 was determined. As compared to SS, BMT resulted in lower levels of CRP at month 4 ($p = 0.06$). CBT and BMT showed similar levels of CRP at month 4 ($p = 0.56$). As compared to SS and CBT, BMT resulted in lower levels of percentage of monocytes co-expressing TNF and IL-6 ($p < 0.001$), with significant differences at month 2 ($p = 0.001$), month 4 ($p = 0.001$), month 7 ($p = 0.02$) and month 16 ($p = 0.03$). Genome-wide transcriptional profiling was carried out using blood samples in a random subsample at post-treatment 4 month ($n = 78$), with

evaluation of the number of genes showing a 1.2 fold up- or down regulation in BMT vs. SS. For BMT vs. SS, results (see Figure 3) indicated a near-significant trend toward reduced activity of NF- κ B (0.61 ± 0.14 , $p = .0561$) and significantly reduced activity of AP-1 (0.76 ± 0.09 , $p = 0.0221$) and CREB (0.33 ± 0.09 , $p = .0009$).



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Expiration Date: 11/30/2021

BMT, Cellular Inflammation, and Transcriptome Dynamics in Breast Cancer Survivors with Insomnia: A Randomized Controlled Trial.⁴⁹ Irwin and colleagues have also previously shown that BMT augments viral specific immune responses, boosts immune response to the zoster vaccine, improves sleep, reduces sympathetic stress activity, and reduces inflammation as indexed by IL-6 and CRP.^{83,105} In a study of 90 breast cancer survivors with insomnia, they used genomics-based methods to assess whether BMT can reverse the pattern of leukocyte transcriptional alterations.⁴⁰ As compared to CBT-I, levels of TLR-4 activated monocyte for the production of IL-6 and TNF showed an overall reduction in BMT ($p < 0.02$), similar to the findings in older adults with insomnia. For genome-wide transcriptional profiling of circulating PBMC, expression of genes encoding pro-inflammatory mediators showed an overall reduction in BMT vs. CBT-I ($p = 0.001$) (Figure 4). The study suggested that 3 months of BMT reduced cellular inflammatory responses, and reduced expression of genes encoding pro-inflammatory mediators. These findings provide an evidence-based molecular framework to understand the potential salutary effects of BMT on chronic conditions.

Unique Gene Expression Clusters Associated with Fatigue in Patients with Prostate Cancer. Drs. Light and Kinney recently published a study of the relationship between 46 candidate genes and self-reported fatigue scores in 30 prostate cancer patients on ADT as compared to controls.⁵⁰ We found that the expression of DBI (diazepam binding inhibitor) and P2RY1 (purinergic receptor-P2Y) provided the best predictive model of fatigue scores for prostate cancer patients. The intercorrelation of mRNA levels yielded two gene clusters with P2RY1 and DBI as the strongest predictors 1) Inflammation and Vasodilation/Metabolite Sensing (DBI) and 2) Energy and Adrenergic Activation (P2RY1). Activation of DBI is involved in energy regulation through lipid metabolism; it was negatively correlated with fatigue scores. The intercorrelation of mRNA levels showed that DBI clustered with 10 genes related to inflammation (TNF, LTA, NR3C1, SIRT1) and vasodilation/metabolite sensing (ADBR2, VIPR2, OXT, ASIC3, P2RX4, P2RX7). Six of these genes were down regulated in the prostate cancer survivors with fatigue compared to controls. P2RY1 is part of a class of G protein coupled receptors that binds catecholamine and can stimulate the sympathetic nervous system. Activation of P2RY1 increases mobilization of intracellular calcium ions, and influences immune function and sensory signaling of inflammation-related pain and fatigue by activating thermal polymodal receptors, other nociceptors and microglial activity.¹⁰⁶ P2RY1 was positively correlated with fatigue and clustered with 8 other genes related to mitochondrial energy and adrenergic activation (ADRB1, ADRA2a, ADRA2c, HSPA2, ATP5E, NDUFS5, TLR4, CXCR4). These functional clusters may represent distinct biological pathways by which BMT impacts fatigue, providing support to the biopsychosocial model for the complex interactions of biological, psychological and social factors on health and illness and psychoneuroimmunology via neuroendocrine (HPA) and sympathetic-adrenal-medullary axes) and immune pathways. In the proposed study, these pathways⁵⁰ will be evaluated separately and we expect to see differential gene expression for fatigue-related genes due to the BMT intervention. To minimize confounding from other types of exercise, enrollees will be asked to refrain from exercise 48 hours prior to sample collection.

1.5 Sample Size Justification

The primary goal of the statistical analyses is to assess the efficacy of the BMT intervention in reducing fatigue (primary outcome), compared to the BT and UC arms. Fatigue is measured at baseline, followed by three additional measurements: 6 weeks as an interim, 13 weeks, and 3 months post-intervention. We want to be able to detect a minimum 15% difference in fatigue score among the groups and within a subject across time. We also want to reduce the total subjects of the UC group and allocate twice the other two intervention groups, with a 1:2:2 allocation ratio. This is a more efficient study design, especially given the NCI budget cuts to all active grants.

Ours' and others' prior published work^{22,25,28,46,68} and our TCQ feasibility trial³¹, have found an average fatigue score for the target population of 32.4, a standard deviation of 8.5, and an autocorrelation between adjacent measurements on the same subject of 0.7. We assume that first-order autocorrelation (AR1) adequately represents the autocorrelation pattern.

We assume the UC, BT, and BMT group fatigue average score means of 32.4, 34.4, and 39.9 after the immediate post-intervention (3 months post-intervention) for UC, BT, and BMT, respectively. From a fatigue score of 32.4, 0%, 6%, and 23% increase from the baseline for the corresponding group. Similarly, a 23% increase within a subject for the BMT group would result in a fatigue score of 39.9.

A repeated measures design with 1 between factor (group) and 1 within factor (time) has 3 groups with a total of 123 subjects (25, 49, 49 subjects with 1:2:2 allocation ratio for UC, BT, and BMT groups, respectively). Each subject is measured 4 times. This design achieves at least 69%, > 85%, > 80% power to test group, time, and their interaction factors, respectively, if a Hotelling-Lawley Test is used with a 2.5% significance level and an actual effect size is 0.3, 0.45, and 0.46 for group, time, and interaction, respectively. The sample size and its dropout (25% assumption) inflated sample size by the group are below Table:

Average group sample size	Group	Dropout Rate	Sample size achieving the pre-specified power	Dropout Inflated Enrollment Sample Size
28.3	UC	25%	25	34
	BT	25%	49	66
	BMT	25%	49	66
	Total		123	166

Based on t-test evaluation, group sample sizes of 40 and 20 achieve 81% power to reject the null hypothesis of equal means when the population mean difference is 7.5 (39.9 vs. 32.4 post-intervention) with a standard deviation for both groups of 8.5 and with a significance level of 0.025 using a two-sided two-sample equal-variance t-test.

1.6 Study Variables

A. Independent Variables, Interventions, or Predictor Variables

The primary goal of the study is to assess the efficacy of the BMT intervention in reducing fatigue (primary outcome), compared to the BT and UC arms. Please review Research Design and Methods (section 1.3 above) for a more detailed description of the different study interventions.

B. Dependent Variables or Outcome Measures

The primary outcome of this study is fatigue. Secondary outcomes include changes in the biomarkers of inflammation, including genome wide transcriptional factors, and expression of fatigue-related genes.

1.7 Drugs/Devices/Biologics

N/A

A. Drug/Device Accountability and Storage Methods

N/A

1.8 Specimen Collection

A. Primary Specimen Collection

Bio specimens: Participants will receive oral and written instructions about all testing procedures. Blood and stool samples will be collected at baseline (prior to random assignment) and at one week, three months, and 12 months post-intervention using standardized procedures. Blood and stool collection dates may be within two weeks of each time point, and late collections (not within two weeks but within 1 month) will be allowed, noted and controlled for in the analysis. If there is a delay in blood and stool collection due to the COVID-19 lab closures, it will be thoroughly documented and controlled for in a sensitivity analysis. A trained phlebotomist will draw blood 30 minutes after arrival to the lab,¹⁰⁷ and collection of samples will be done at the same time of day to ensure comparability of measures across participants and across repeated measures (time-points). Participants will also submit a stool sample at clinic visit using a kit and instructions mailed or given to them prior to their scheduled appointment. Specimens will be logged into the CINJ bio specimen-tracking databases stored at the appropriate temperature, and de-identified biospecimens will be shipped according to each of the protocols for the Irwin Lab.

Microbiome: Stool will be collected and processed for gut microbes (microbiome analysis), including DNA and RNA sequencing.

Blood and stool samples will be stored for future research. For more details, please see Section 7.0 Data and Specimen Banking.

- **Types of Specimens:** The table below provides details about the specimens that will be collected in the clinic, de-identified and shipped to UCLA for analysis; remaining specimens will be stored in the analyzed, and stored for the study:

		Collection Time Points				Analysis	Storage
		Baseline	1-wk post-intervention	3-mo post-intervention	12-mo post-intervention		
Blood	Proinflammatory Cytokines (IL-1, IL-6, TNF, IL-8, IL-10)	X	X	X	X	UCLA	CINJ
	Fatigue-related Gene Expression: Inflammation, Vasodilation and Energy/Adrenergic Activation	X	X	X	X	UCLA	CINJ
	TELiS Promoter-based Bioinformatics for Activation of Transcription Factors	X	X	X	X	UCLA	CINJ
	Nuclear Protein Extraction	X	X	X	X	UCLA	CINJ
Stool	Microbiome	X	X	X	X	TBD (future research)	CINJ

As noted in the table directly above, deidentified blood samples will be sent to UCLA for analysis; however, extra aliquots of blood samples and stool samples will be stored at Rutgers CINJ Biospecimen Repository Service (BRS) for future processing and/or analysis, including RNA and DNA extraction and sequencing of gut microbes (stool sample).

- **Transport:** The CINJ Biospecimen Repository Service (BRS) will receive the processed specimens from the Rutgers Institute for Translational Medicine and Science or Infinity Biologix (IBX) and pack the deidentified biospecimens and ship them in dry ice via FedEx to UCLA. Samples will be transported by trained staff, who have all received mandatory biosafety training.
- **Processing:** The samples will be processed at Infinity Biologix (IBX).
- **Storage:** Specimens will be kept until all data analyses are complete and the study is complete.
- **Disposition:** Specimens will be destroyed in accordance with CINJ and protocols.

1.9 Data Collection

A. Primary Data Collection

- **Location:** Research activities will take place on the Rutgers New Brunswick campus in closed-door offices and research cubicles within the Rutgers Cancer Institute of New Jersey (CINJ) and health assessments and biological specimens will be collected in private rooms at CINJ, an outpatient clinical space in Newark, or the Environmental Occupational Health Sciences Institute (EOHSI). Biological assays and data analysis of de-identified data biospecimens be performed at the University of California Los Angeles, UCLA campus under the direction of Dr. Michael Irwin.
- **Process of Data Collection:** Surveys will be sent to participants prior to study visits. Study staff will review surveys for completeness. Participants in the UC arm will be asked to mail their 6-week mid-intervention survey back in a pre-paid envelope or complete a survey by telephone because they will not attend an intervention class. Surveys will be de-identified and labeled with only a study ID. All participants will be given the option to mail in their questionnaire, or complete a questionnaire by telephone if the need arises, such as if they forget their questionnaire at home or prefer this option for other reasons. If surveys are incomplete or if clarification is needed, participants will be asked the items during clinic assessments or be called by telephone by study staff to ask the participant if he would like to complete his answers or make any clarifications.
- **Timing and Frequency:** Patient-reported assessments (surveys) will occur at baseline (within 1-week pre-intervention), mid-intervention (6 weeks), 1-week post-intervention (13 weeks), as well as at 3 months and 12 months post-intervention. Bio specimen collection will occur at baseline, 13 weeks, 3 months, and 12 months post-intervention. Phlebotomy and stool collection will occur at baseline, 1-week post intervention (13 weeks), and 3 months and 12 months post intervention. The food and activity questionnaire will be given at the 6-week mid-intervention time point only.
- **Procedures for Audio/Visual Recording:** N/A – There will be no audio or visual recording of participants at any point during this study.
- **Study Instruments:**
Cancer enrollees will complete all measures outlined below.

Diet: *The Block Food Frequency and Activity Questionnaire and Diet Log* is a validated questionnaire (NutritionQuest.com) that will be used to assess participants' food intake over the previous year. The purpose of this is to assess general dietary patterns and control for this factor in relevant biomarker analysis (inflammation and but microbiome). Participants will complete this questionnaire at the 6-week mid-intervention time point only. Participants will also complete a 3-day food diary for the 3 days prior to each of their Rutgers CINJ visits to control for dietary patterns that may affect inflammatory biomarkers and gut microbiome.

Psychological and Health Assessments: Survey measures were selected based on their established validity and reliability, and appropriateness for use in elderly and prostate as well as other cancer populations.

Fatigue: Fatigue, our primary outcome, will be assessed with the *Functional Assessment of Chronic Illness (FACIT)-Fatigue Scale*,¹⁰¹ the measure used in our feasibility study, and frequently used with cancer survivor populations because it has established minimally important differences. This 13-item scale assesses level of fatigue during usual activities over the past 7 days, with higher scores indicating less fatigue (score range=0-52; Cronbach's alpha=0.86).

Psychological Distress, Sleep, Perceived Stress, Well-Being and QOL: We will also examine whether intervention effects might extend to behavioral symptoms and health-related measures associated with fatigue and serve as mediators of these effects. We will assess: 1) psychological distress (depression and anxiety) using the Brief Symptom Inventory-18 (BSI-18; $\alpha = 0.79-0.91$);¹⁰⁸ 2) stress perceptions using the Perceived Stress Scale ($\alpha = .78$);¹⁰⁹ 3) sleep quality and amount using the *Pittsburgh Sleep Quality Index*

($\alpha = .83$) and *Berlin Sleep Questionnaire and Consensus Sleep Diary*; 4) social well-being will be assessed with validated PROMIS 2 Version 2 measures:¹¹⁰ SF4a Satisfaction with Participation in Social Roles and activities, SF4a Emotional Support, SF4a Ability to Participate in Social Roles, and SF4a Social Isolation; 5) Functional Well-being will be assessed with the Functional Well-being Scale;¹¹¹ 6) health-related QOL (mental and physical) will be assessed using the SF-36v2™ Health Survey;¹¹² 7) and spirituality will be measured using the FACIT-Sp-12 Spiritual Well-Being Scale. Follow-up questions will be asked of all participants at 1-week post intervention. These new questions are to briefly assess their experience during the intervention period. Please see survey for complete measures.

Current major depression will be assessed by using the 9-item Patient Health Questionnaire (PHQ-9) as a final screening measure before the patient is consented to the study and the baseline assessment is administered.¹¹³ A score of 10 or above has a sensitivity of 88% and a specificity of 88% for detecting major depression. In the event that a participant scores ≥ 12 (a score of 10-12 could also be due to fatigue and cancer-related effects), study staff will immediately follow the HERO Crisis Protocol. Please see Appendix for the study's Crisis Protocol.

Clinic Physical Assessments: Participants will be asked to attend appointments at the Rutgers Cancer Institute of New Jersey or EOHSI at baseline, at one week, three months, and 12 months post-intervention. During these appointments, participants will receive a brief physical assessment that will include blood pressure, height, weight, waist/hip ratio measurements, heart rate variability, the Timed Up and Go (TUG) test, and a chair stand test. These appointments will coincide with the collection of bio specimens and collection of surveys by study staff.

Inflammation Biology Measures: Specimens for inflammation biology and gene expression measures will be collected at Rutgers, CINJ or EOHSI, prepared and shipped to Dr. Irwin's (Co-I) laboratory for analysis using methods previously found to be highly reliable.^{21,39-41} The CINJ Biospecimen Repository staff have completed required IATA shipping training.

Fatigue-related Functional Cluster Gene Expression: As discussed in the Preliminary Work section, Drs. Light and Kinney previously identified differentially expressed genes associated with fatigue in prostate cancer patients compared to healthy controls.⁵⁰ These genes grouped into two major functional gene clusters by mRNA level intercorrelations: 1) Inflammation, Vasodilation, and Metabolite Sensing and 2) Energy and Adrenergic Activation. To test the hypothesis that genes within these defined functional clusters are impacted by BMT and associated changes in fatigue, we will target our analysis of gene expression for these. Following these *a priori* tests, we will use more conservative analytic approaches (controlling for multiple comparisons) to examine expression of additional genes/pathways from the full genomic data yielded by the gene expression assays.

Genetic, Genomic, Health-related and Aging Markers: As part of this study, blood and stool will be stored for analysis of health, aging, and cancer biomarkers, including genetic and genomic analysis (e.g., cellular assays, telomere length, gene expression, genetic variants (e.g., SNPs), epigenetic markers, DNA/RNA sequencing). Whole genome sequencing will not be done.

Additional measures of covariates, moderators and mediators: Participants will complete demographic questions including self-reported age, race, ethnicity, income, education, stage of diagnosis, types of cancer treatment, date of diagnosis, and date of primary cancer treatment. Comorbidity, BMI, and other medication information will be collected at each survey time point, including current prescription and non-prescription medications and over-the-counter supplements. Body-mass index (BMI) will be assessed during the phlebotomy visits.

Physical Activity Level and Home Practice Logs: Differences in physical activity outside the intervention will be assessed at all survey time points with the *Godin-Shephard Leisure-Time Physical Activity Questionnaire* and the *Measurement of Older Adults Sedentary Time (MOST) Questionnaire*. In addition, participant activity levels throughout the intervention period will be recorded with weekly activity logs of home performance of the interventions and other forms of physical activity. The log will include a measurement of perceived exertion using the Borg scale for each of the activities performed and times a specific activity was performed.⁸⁵

Participants will also be asked to wear a pedometer and will be trained on how to use the pedometer to record the number of steps they take each day.¹¹⁴ Activity and home practice logs will be collected once a week at class check-in and at the 3-month and 12-month follow-ups. At the end of the 12-week intervention, participants will be encouraged to continue practicing what they learned during their classes, BMT and BT, ideally 5 times a week, using the DVDs provided to them. UC participants will be asked to continue with their normal daily activities. All participants will also be asked to turn in weekly logs to capture activity and capture frequency and duration of engagement (DVD, handouts, and non-aerobic BT and Borg scale for BMT and BT) for their respective arm. UC participants will be called weekly by study staff to collect their activity log and pedometer readings because they will not attend classes. Logs will be collected once a week at class check-in, or by telephone and at the 3-month and 12-month follow-up. After the 13-week follow-up, BMT and BT participants will receive monthly mailed reminders, phone calls, text messages, or other social media contact (as preferred by the participant) to complete their home practice logs.

Treatment credibility and expectations will be assessed during the first week of class, mid-intervention and post-intervention using the 6-item credibility/expectancy scale modified for a class-based intervention with health and well-being as outcomes.¹¹⁵ This scale assesses both an expectancy and credibility factor and includes items about participants' thoughts and feelings about the likelihood that the intervention will have the desired effect (i.e., on health and well-being), as well as expectations about the size of the effects. Across several different treatment populations the scale demonstrated high internal consistency ($\alpha = 0.79-0.81$) and high test-retest reliability (0.75-0.82).¹¹⁵

Data Accuracy and Protocol Compliance: Several strategies will be used to assure data accuracy and protocol compliance. The database will use logic and range checks to minimize data entry errors. The project director will utilize double data entry strategies to detect data entry errors. The project director will regularly assess for errors and generate reports to discuss data entry accuracy and quality improvement measures. Completion of surveys and blood draws will be monitored by study staff. Reminder letters and phone calls will be made to participants. Individuals who do not turn in surveys or complete blood draws will be reminded by phone calls and scheduled for biological assessments at a convenient time for the participant.

A standard protocol will be used, and all study staff will receive extensive training under the supervision of the PIs and project director. Procedures have been established in our preliminary work. The protocol will be modified if safety concerns are raised. Intervention fidelity will be assessed at each class session by study staff and reviewed biweekly by the PIs and the project director. The BMT instructor will be trained by a Master BMT practitioner in the manualized protocol. Practice tapes will be reviewed by the Master BMT practitioner and feedback will be provided. All instructors will be trained on the study's protocol. The body training classes will be manualized as in our prior research.

1.10 Timetable/Schedule of Events

Study Timeline

- The duration of an individual subject's participation in the study will be approximately 15 months.
- The subjects will be enrolled on an ongoing basis in years 1-4.
- The duration estimated for the investigators to complete the study is approximately 60 months. Primary analysis will occur in years 4 and 5 upon completion of post-intervention assessments.

Months 1-6:	Protocol development/hiring staff, training instructors, finalizing measures, crafting and testing database, recruiting first cohort
Months 6-48:	Recruitment and Follow-up
Months 3-6:	Intervention implementation and 1-month follow-up
Months 12-54:	Biomarker assays
Months 48-60:	Analyze data; generate reports and manuscripts

2.0 Project Management

2.1 Research Staff and Qualifications

Anita Y. Kinney, PhD, RN, Principal Investigator. Dr. Kinney is Professor, Department of Epidemiology and Director, Center for Cancer Health Equity, School of Public Health, Rutgers University, Associate Director for Cancer Health Equity, Cancer Institute of New Jersey. Dr. Kinney will have primary responsibility for directing all scientific and administrative activities associated with this project. She will lead and organize the collaborative team, supervise and train study staff, and oversee data collection activities, recruitment and retention of participants, intervention implementation and adherence to the timeline of this randomized clinical trial. She will also serve as the contact PI, oversee data analysis for Aims 1 and 3, and the exploratory aim and oversee dissemination of the study findings related to these aims working closely with Dr. Irwin.

Dr. Michael Irwin, Co-Investigator. Dr. Irwin is Distinguished Professor in the Department of Psychiatry and Biobehavioral Sciences at the University of California Los Angeles Medical Center. Dr. Irwin has more than 2 decades of experience analyzing the inflammatory biology mechanisms in relation to behavior and a decade of experience in the delivery and testing of efficacy of body-mind interventions in various populations such as cancer survivors and the evaluation of body-mind interventions on biological processes. Dr. Irwin will provide scientific, administrative, and budgetary oversight of the plasma and cellular measures of inflammation and immune activation. He will advise on design and implementation strategies including recruitment and retention, questionnaire items and data collection procedures, experimental and control condition content and protocols, strategies to maintain intervention fidelity, analysis, and interpretation of the study's immunological data. He will participate in the dissemination of the study's findings in scientific journals.

Co-Investigators

Co-Investigators will provide general guidance and expertise, participate in team meetings, increase recruitment efforts and aid in the dissemination of research findings.

Wadih Arap, MD, PhD, Co-Investigator. Dr. Arap is the Director of the Cancer Institute of New Jersey at University Hospital and Chief Division of Hematology/Oncology Rutgers New Jersey Medical School Medical Oncology. Dr. Arap has clinical expertise in the area of genitourinary (GI) cancers with a specialty in prostate cancer.

Cindy Blair, PhD, Co-Investigator Dr. Cindy Blair is the Assistant Professor in Department of Internal Medicine at the University of New Mexico. Dr. Blair is a cancer epidemiologist with research experience in cancer

epidemiology, and cancer survivorship and intervention development and implementation. She strives to improve both the quality and quantity of years lived beyond the cancer diagnosis and treatment and has special interest in programs like HERO that strives to reach the underserved and understudied populations.

Isaac Kim, MD, PhD, MBA, Co-Investigator Dr. Kim is the Chief of the Urologic Oncology, Executive Director of the Prostate Cancer Program at the Rutgers Cancer Institute and the Medical Director of Robotic Surgery at Monmouth Medical Center. Dr. Kim has helped thousands of patients navigate and better understand their urologic cancer. Dr. Kim is a strong advocate for clinical trials that challenges and improves current guidelines to continue helping patients.

Yong Lin, PhD, Co-Investigator Dr. Lin is a Professor in the Department of Biostatistics and Epidemiology at the Rutgers School of Public Health. His research interests include statistical methodologies and applications. The methodological research has mostly been on the designs of clinical trials, especially on Phase I, II, and III. Dr. Lin will contribute to interpreting and analyzing data as well as reporting findings.

Rita Musanti, PhD, APN-BC, Co-Investigator Dr. Musanti is the Co-Director of ScreenNJ and Assistant Director for Community Outreach and Engagement at the Rutgers Cancer Institute of New Jersey, Rutgers, The State University of New Jersey. She has a strong interest in working with vulnerable populations and the intersections of community health. Dr. Musanti has studied the link between exercise and the benefit it may provide to patients with cancer, and will contribute her expertise on the topic.

Anupama Nehra, MD, Co-Investigator is the Clinical Director of Hematology/Oncology at the Rutgers Cancer Institute at University Hospital. She is responsible for overseeing delivery of clinical services for Hematology/Oncology in Newark and will provide support in recruiting patients.

Biren Saraiya, MD, Co-Investigator Dr. Saraiya is a Medical Oncologist at the Rutgers Cancer Institute of New Jersey in the Genitourinary Oncology Program. Dr. Saraiya has clinical expertise in prostate cancer, kidney cancer, bladder cancer and palliative care. He not only provides clinical care, but acts as a source of support helping patients navigate their cancer diagnosis. Dr. Saraiya believes in survivorship care and strives to remain abreast of the latest treatments, technologies and communication aspects.

Research Staff Training

All staff will be properly trained with CITI as well as full protocol training.

2.2 Resources Available

Facilities:

Project/Performance Site Primary Location – CINJ Rutgers University

All study personnel have adequate space for secure data storage, office support (photocopy machines, fax, etc.), and conference rooms at Rutgers University CINJ has sufficient space to hold team meetings. All study personnel have personal computers with word processing and high-speed internet connections. The computers are connected to the high-speed network at the Rutgers University and are installed with necessary software needed to carry out this study, including Microsoft Office, R, SPSS and SAS statistical software, Adobe Acrobat 9 pro, and EndNote. Study data are stored in a secure network supported by well-established institutional and national best practice guidelines.

UCLA Cousins Center and Inflammatory Biology Core

The UCLA Semel Institute for Neuroscience has assigned the Cousins Center and Inflammatory Biology Core laboratory over 2000 sq. ft. of laboratory space for the conduct of the proposed inflammatory biology assays. All the equipment infrastructure is available in this laboratory with the exception of the multiplex instrument, which is housed in a nearby laboratory on the medical campus. Dr. Irwin has an office adjacent to the Inflammatory Biology Core laboratory making it readily possible for the investigators to oversee all aspect of sample processing and assay. Finally, this team of investigators have contributed to the success of over a dozen different R01 type awards and have published extensively and collaboratively based on their shared expertise. This kind of day-to-day interaction

of a team of investigators will ensure that integrity of the research is maintained, and that new knowledge that contributes to innovative approaches to the proposed measures will be rapidly translated into the current project.

UCLA Social Genomics Core Laboratory

Genomic, and bioinformatic studies will be carried out in Dr. Irwin's 325 sq. ft. laboratory in UCLA's Factor Building (Jonsson Comprehensive Cancer Center), which includes a BSL-3 laboratory for primary tissue culture and a separate molecular biology laboratory including a BSL-2 tissue culture hood, a PCR-clean sample preparation cabinet, real-time PCR equipment, molecular biology bench stations, electrophoresis and imaging stations, and associated computers. All techniques and procedures proposed for this research have been successfully carried out previously in this laboratory (as indicated in our published research cited in the Research Plan). Dr. Irwin also maintains an additional 200 sq. foot molecular biology research laboratory in the UCLA Semel Institute for Neuroscience and Behavior 300 Medical Plaza Building, including molecular biology desk- and benchspace suitable for 4 full time molecular biology staff and 2 bioinformatics programmers as needed, a separate BSL2 cell culture facility, and a PCR-clean sample preparation cabinet adjacent to real-time PCR equipment.

2.3 Research Sites

The study is based at the Rutgers Cancer Institute of New Jersey. Participant clinic visits, specimen collection, processing, analysis, and storage will take place at the Rutgers Cancer Institute of New Jersey, , Rutgers Environmental and Occupational Health Sciences Institute (EOHSI, Infinity Biologix (IBX) and the Biospecimen Repository. Additional specimen analysis and storage will take place at UCLA Cousins Center and Inflammatory Biology Core and the UCLA Social Genomics Core Laboratory. Participants will be recruited through Rutgers and RWJ Barnabas sites and referrals from other community sites. Intervention classes will be held in an appropriate private space at Rutgers University, at a similar space at a community site, or via Webex, or another videoconferencing platform if necessary.

3.0 Multi-Center Research

N/A

4.0 Subject Considerations

4.1 Subject Selection and Enrollment Considerations

A. Method to Identify Potential Subjects

Men who have fatigue scores that meet study criteria for fatigue: Medical Health Outcome Study Short Form Vitality/Fatigue subscale (SF-36 Vitality scale) using a fatigue cut-off value of ≤ 13 ; or the Patient-Reported Outcomes Measurement Information System Fatigue scale (PROMIS Fatigue scale) using a cut-off value of ≥ 9 and are inactive (< 150 minutes of vigorous exercise/week per CDC guidelines will be eligible. Such inactive and fatigued individuals may stand to benefit most from the BMT intervention by reducing fatigue and related symptoms and improving QOL and well-being. Cancer patients and survivors will have completed therapy (surgery and radiation) at least 3 months earlier with the exception of ADT and hormonal resistant therapy for which they must be on therapy for at least four months. Metastatic disease may include biochemical detectable disease (i.e., abnormal PSA) or metastasis to other sites with the exception of brain or liver metastasis.

Participants who have been told they may have a condition that interferes with exercise will be cleared by their primary care or oncology physician to participate in light to moderate intensity exercise; a form signed by their physician/primary care provider allowing them to participate in light to moderate intensity exercise will be required prior to enrollment. Medical and medication history will be collected during the screening call, Rutgers Cancer Institute of New Jersey assessments and surveys. We will control for medication use in the analysis.

Current major depression will be assessed by using the 9-item Patient Health Questionnaire (PHQ-9) as a final screening measure before the patient is consented to the study and the baseline assessment is administered.¹¹³ A score of 10 or above has a sensitivity of 88% and a specificity of 88% for detecting major depression. In the event that a participant scores ≥ 12 (a score of 10-12 could also be due to fatigue and cancer-related effects), study staff will immediately follow the HERO Crisis Protocol. Please see Appendix for the study's Crisis Protocol.

B. Recruitment Details

Recruitment will occur through 1) invitation letters to patients and clinician referrals from health care providers at Rutgers University, community sites, and other community partners; 2) clinics (face-to-face) at the Rutgers CINJ; 3) clinicians will refer patients from other private and public clinics and healthcare settings to the study or will obtain patient permission to pass on contact information (name, telephone, email, address or other contact information as preferred by the patient) to study staff in order to be contacted about the study; 4) through the Rutgers RWJ Barnabas Health System community sites (via Rutgers IRB approved protocol); 5) community-based recruitment strategies; and 6) through utilization of a testimonial video from past HERO participants shared on various approved platforms.

As a recruitment strategy we will permit participants to have a social network member (e.g., family member/caretaker/significant other) accompany them to classes as was done in our feasibility trial.¹³ We will evaluate this possible design effect in the analysis (although we did not observe appreciable subgroup differences in our feasibility trial).

Several additional strategies will be used to promote retention and adherence to the interventions: 1) Dr. Kinney will greet and meet with all participants at the first class (and monthly) and project staff will meet and greet each participant prior to every class and collect/distribute study-related surveys and logs/diaries; 2) weekly phone calls to non-adherent participants to promote adherence using motivational strategies and barriers counseling; 3) reminder postcards, phone calls, and/or letters will be sent to participants about appointments or class schedules; 4) monetary incentives (in the form of clincards or SVM gift card : \$75 per completion of each assessment and \$150 for completion of all of the assessments at baseline, 6 weeks mid-point, and 1-week, 3 months and 12 months post intervention classes.; 5) continued emphasis on the importance of the study and the potential benefits of the results for other survivors at the beginning or end of classes; 6) class instructors emphasize the importance of attendance for personal benefit and the scientific integrity of the study at the end of each class; and 7) for cohorts with low enrollment, previous HERO participants who have completed all study responsibilities will be given the opportunity to attend additional intervention classes to encourage retention and emphasize social support.

C. Subject Screening

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Screening will be done in person or by telephone by research study staff.

■ Inclusion Criteria

- Age ≥ 55 years
- Local or regional stages of the following cancers: prostate, colon, rectum, lung, oral/pharynx, small intestine, soft tissue, thyroid, non-muscle invasive bladder cancer, kidney, and renal pelvis.

- Previous diagnosis of local, regional, or metastatic cancer in which patients have at least a 1 year life expectancy.
- If treated for cancer, cancer therapy completed, except for oral therapy 3+ months
- If on ADT/ hormone manipulation, must be for 4 or more months
- Meet study criteria for fatigue: Medical Health Outcome Study Short Form Vitality/Fatigue subscale (SF-36 Vitality scale) using a fatigue cut-off value of ≤ 13 ; or the Patient-Reported Outcomes Measurement Information System Fatigue scale (PROMIS Fatigue scale) using a cut-off value of ≥ 9
- Inactive (<150 minutes of vigorous exercise/week within the past 3 months)
- Has transportation to attend on-site classes and assessments
- **Exclusion Criteria**
 - Men treated for hematological malignancies would be ineligible because of possible confounding between disease features, treatment, and immune measures
 - Patient Health Questionnaire PHQ-9 Score ≥ 12
 - Indication of suicidality from PHQ-9, reports that he has several or more days of “thoughts that you would be better off dead, or of hurting yourself”
 - Karnofsky performance status score of 50 or below
 - Current regular practice within the past year (2-3 times a week over a period of two months that is not interrupted) of BMT or other complementary and alternative medicine that shares similar principles of BMT.
 - Inability to speak and read English proficiently
 - Unable to understand informed consent
 - Current health conditions that may interfere with the intervention: respiratory, cardiovascular, or neurological problems unless released by physician
 - Medical conditions or activities that can cause severe fatigue: Severe hearing loss that would cause difficulty following an instructor in a group setting, chronic fatigue syndrome, current major depression, alcohol use disorder, shift work
 - Cancer that has metastasized to the liver, brain, or lungs
 - Currently receiving chemotherapy with VePesid, Cytosan, intravenous chemotherapy or radionucleotides (Strontium-89, Samarium (Quadramet®), Radium-223 (Xofigo®)), or other therapy (as confirmed by study team)
 - Unwilling to be randomized to study arms and/or commit to 12 weeks of classes and assessments
- Some individuals may be deferred if they were ineligible due to the fatigue scores or a health condition. Potential participants may be screened during a later cohort to determine if they are eligible.
- During screening, men who have had prostate cancer will be asked if they are willing to be contacted about a one-time survey study for men with prostate cancer, being conducted at the University of New Mexico. Individual’s willingness to be contacted will have no impact on their eligibility for the HERO study. For men already screened in the HERO database, and who may be eligible for the one-time survey, they will be sent an opt-out letter informing them of the additional research opportunity.
 - Men will be offered this option of being contacted about a survey if they:
 - Refuse the HERO study
 - Are ineligible to participate in HERO due to being within 3 months of time of cancer treatment, on Hormone manipulation less than 4 months, do not have transportation to attend on-site classes distances, have a current regular practice of BMT, unwillingness to participate in the intervention or unwillingness to be randomized.
 - Are eligible for HERO but are not able to participate until a future cohort.

4.2 Secondary Subjects

N/A

4.3 Number of Subjects

A. Total Number of Subjects

After obtaining informed consent and baseline assessments, 166 elderly, fatigued cancer survivors age 55 years and older will be randomized with an allocation ratio of 1:2:2 to the UC, BT, or BMT arms, respectively. Thirty-five men were recruited to the study at the University of New Mexico prior to the transition of Dr. Kinney and Dr. Arap to Rutgers University and CINJ. Thus, 131 participants will be enrolled at CINJ.

B. Total Number of Subjects If Multicenter Study

Yes this is a multicenter study. 35 participants have already been recruited and enrolled for this study in New Mexico. No additional participants will be recruited from New Mexico. Moving forward, all remaining participants (n=131) will be recruited from New Jersey.

C. Feasibility

Our team has substantial experience recruiting survivors to behavioral intervention trials, including body-mind interventions.^{13,81-83,105,117} It is estimated that at the time of our study there will be approximately over 4,500 prostate cancer survivors within 75 miles of the study intervention site and that at least 2,000 will meet our eligibility criteria. As in our prior feasibility trial, we will enhance enrollment by encouraging companions to join the survivors in the classes. As reported in the literature, recruitment of men to exercise and other group-based interventions can be a momentous challenge. We face significant recruitment challenges in this study. The most common patient reported barrier to recruitment is respondent burden related to the expectation of attending a class twice a week for 12 weeks, especially because of fatigue and poor health. We have implemented myriad recruitment strategies such as newspaper, social media and radio ads, flyers in clinic and community settings, referral by health care providers, and electronic health record messaging. Recruitment sources include oncology and primary care clinics, statewide cancer registries, cancer center registries, and physician letters. The most effective strategy is face-to-face clinic-based recruitment by study staff working closely with clinicians. However, this is also the most labor-intensive and costly form of recruitment. To date, we have contacted and screened hundreds of prostate cancer survivors and have enrolled approximately 51 men.

Given these challenges, we propose to expand the pool of available subjects for entry into this study by including male cancer survivors who have undergoing diagnosis and treatment of prostate cancer as well as other solid tumors as noted below. Although prostate cancer accounts for 20% of men diagnosed with cancer, fatigue is not limited to this cancer. Men are an understudied population, especially in cancer related fatigue research. Furthermore, we recently published a meta-analysis in the Annals of Behavioral Medicine (CG Ford et al.) showing that male cancer survivors are appreciably under-represented in mindbody intervention research. To reach our accrual goal and improve the generalizability of the study's findings we will expand to all cancers, not just prostate. Men will only be enrolled because this is an understudied population.

4.4 Consent Procedures

A. Consent Process

▪ Location of Consent Process

The consent form will initially be sent to participants in the mail prior to enrollment at their baseline clinic visit. This will allow participants to review the consent form and formulate any questions or concerns prior to meeting with study staff, consenting in person, and enrolling in the study. Participants are asked to bring their signed consent form with them at their baseline assessment. The in-person consent process facilitated by study staff will take place in a closed-door private room during the participant's baseline clinical visit.

- **Ongoing Consent**

Participants will be consented once. If there is a need to modify the consent form in any way during the course of a participant's enrollment, study staff will notify them of the changes and ask them to review and sign the modified/updated consent form in order to continue with study participation.

- **Individual Roles for Researchers Involved in Consent**

- Research Assistants will complete consents.

- **Consent Discussion Duration**

Project staff will spend as much time discussing the consent with the participant as necessary. The expected duration of the consent discussion, not including extensive questions or concerns presented by the participant, is approximately 25 minutes.

- **Coercion or Undue Influence**

The consent form will abide by IRB and HIPAA regulations. The consent form will be mailed to participants with the study surveys prior to the initial baseline clinic visit in order to give the participants the opportunity to review the consent and discuss with family and/or friends if necessary prior to meeting with project staff. This will provide time for participants to prepare questions or concerns they might have about the consent and their participation in the study. During the consent process at the clinic, project staff will emphasize that participation in the study is completely voluntary and a decision not to participate would in way influence the medical care that they currently received. Project staff will also make clear to participants that upon consenting to participate in the study, they will be able to withdraw from the study at any time and for any reason.

- **Subject Understanding**

During the consent process project staff will ask open-ended and non-directed questions about the consent form to ensure participant comprehension. Such questions may facilitate discussion about the consent with the participant, elicit questions from the potential subject, and prompt the potential subject to think more carefully about the study. This approach can help project staff assess if the potential participant has sufficiently understood the consent form, the study, and their potential participation in it. Furthermore, participants will be mailed the consent form prior to enrolling in order to provide them with ample time to review it and prepare any questions or concerns to discuss with study staff upon meeting with them in person to enroll in the study.

B. Waiver or Alteration of Consent Process

- **Waiver or Alteration Details**

N/A

- **Destruction of Identifiers**

N/A

- **Use of Deception/Concealment**

N/A

- a. **Minimal Risk Justification**

N/A

- b. **Alternatives**

N/A

- c. **Subject Debriefing**

N/A

C. Documentation of Consent

- **Documenting Consent**

Consent is documented in writing. We have submitted the consent form to Rutgers IRB.

- **Waiver of Documentation Of Consent (i.e., will not obtain subject's signature)**

N/A

4.5 Special Consent/Populations

A. Minors-Subjects Who Are Not Yet Adults

- **Parental Permission**
N/A
- **Non-Parental Permission**
N/A
- **Assent Process**
N/A
- **Documentation of Assent**
N/A
- **Reaching Age of Majority During Study**
N/A

B. Wards of the State

- **Research Outside of NJ Involving Minors**
N/A

C. Non-English-Speaking Subjects

- N/A
- **Process for Non-English-Speaking Subjects**
N/A
- **Short Form Consent for Non-English Speakers**
N/A

D. Adults Unable to Consent / Cognitively Impaired Adults (for interventional studies)

- N/A
- **NJ Law-Assessment of Regaining the Capacity to Consent**
N/A
- **Capacity to Consent**
N/A
 - a. **NJ Law-Selecting A Witness**
N/A
 - b. **Removing a Subject**
N/A

4.6 Economic Burden and/or Compensation for Subjects

A. Expenses

Participants will not have an economic burden to participate because they will not be charged to participate in this study and they will receive a self-addressed, pre-paid return envelope to return all research-related materials. Additionally, they'll be reimbursed for their time a various time points with prepaid merchandise cards. If participants express concern with costs related to transportation getting to and from assessments and class, they will be provided up to \$60 per week to cover those costs but must show proof of a receipt.

B. Compensation/Incentives

We will offer participants compensation for completing each assessment (\$75/assessment) and an additional \$150 if the participant completes all assessments: at (1) baseline, (2) 6 weeks - intervention mid-point, and (3) 1 week post intervention (13 weeks), and (4) 3 months and (5) 12 months post intervention. Thus, participants who complete all time point assessments will be compensated a total

of \$525.

C. Compensation Documentation

Participants are provided compensation at each assessment time point. For all of these time points except the midpoint, the participants visit the Rutgers CINJ. During this visit project staff maintain a checklist of activities required for each participant. Among the items on the checklist is one to ensure that they received their compensation (via a merchandise card). To confirm participants have received an SVM gift card, a participant receipt form will be sent for the subject to sign and return back to the Project HERO staff. This information is also input by project staff into a participant tracking database. For the midpoint time point (when participants do not visit the clinic), project staff will keep track of completed assessments submitted by participants and similarly enter into a tracking database if they were provided compensation for their efforts. The merchandise cards for the midpoint time point will be loaded by the Rutgers CINJ remotely.

4.7 Risks of Harm/Potential for Benefits to Subjects

A. Description of Risks of Harm to Subjects

▪ Reasonably Foreseeable Risks of Harm

There are minimal risks involved in participating, as the BMT procedures have been safely implemented with other elderly, frail populations. A potential but minimal risk in this study is the breach of participant confidentiality. There is the potential that cancer communication may produce adverse psychological effects such as increased anxiety. Staff will be trained in recognizing clinically significant psychological distress and will be instructed to report such an event immediately to the PI. The risks of injury during blood draw are minimal and include superficial bruises, discomfort and bruising at the site of the needle insertion, bleeding from the site of puncture, and uneasiness associated with needles. Small risks associated with physical activity, especially in elderly populations, may include musculoskeletal injuries such as muscle pain, joint pain/injury, falls and/or cardio-pulmonary complications. However, the BMT and BT interventions that we will employ have been safely used in elderly populations with cardiovascular disease, cancer, those at risk of falls, and those with other chronic diseases or health impairments. Any physical or mental complaint will be documented and the BMT and BT moves will be adjusted accordingly with the assistance of the trained and certified BMT and BT instructors.

▪ Risk of Harm from an Intervention on a Subject with an Existing Condition

Study staff, including intervention instructors, will, to a reasonable extent possible, adapt intervention exercises to accommodate any physical limitations that participants may have in order to ensure their safety while matching intensity of other study participants. The investigators retain the right to end participant involvement in the study if they determine that the requirements of the study impose unreasonable risk to the participant's well-being due to any physical/psychological condition or disorder.

▪ Other Foreseeable Risks of Harm

N/A

▪ Observation and Sensitive Information

Observation will occur during intervention for the BT and BMT arms of the study; however, this observation will be limited to reviewing attendance and the exercise schedule/checklist for each intervention arm and will not include observation or disclosure of sensitive information.

Data analysis will occur in closed offices using de-identified data. Telephone calls will take place in closed door offices or cubicles in the CRF to ensure privacy. Each person contacted for the study and each study participant will receive a Participant Identifier. Data will be linked by this participant ID. Names and birthdates (and other PHI) that could be used to identify individuals will not be entered into the main study database. These data will be stored in a 'registry' which will be kept separate from research data. Randomization lists, assignments and decoding data will be stored on a secure server. To help us protect participant privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health.

B. Procedures which Risk Harm to Embryo, Fetus, and/or Pregnant Subjects

N/A

C. Risks of Harm to Non-Subjects

N/A

D. Assessment of Social Behavior Considerations

N/A

E. Minimizing Risks of Harm

There are minimal risks involved in participating, as the BMT procedures have been safely implemented with other elderly, frail populations. A potential but minimal risk in this study is the breach of participant confidentiality. There is the potential that cancer communication may produce adverse psychological effects such as increased anxiety. Staff will be trained in recognizing clinically significant psychological distress and will be instructed to report such an event immediately to the PI. The risks of injury during blood draw are minimal and include superficial bruises, discomfort and bruising at the site of the needle insertion, bleeding from the site of puncture, and uneasiness associated with needles. Small risks associated with physical activity, especially in elderly populations, may include musculoskeletal injuries such as muscle pain, joint pain/injury, falls and/or cardio-pulmonary complications. However, the BMT and BT interventions that we will employ have been safely used in elderly populations with cardiovascular disease, cancer, those at risk of falls, and those with other chronic diseases or health impairments. Any physical or mental complaint will be documented and the BMT and BT moves will be adjusted accordingly with the assistance of the trained and certified BMT and BT instructors.

▪ **Certificate of Confidentiality**

To help us protect participant privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. The researchers can use this Certificate to legally refuse to disclose information that may identify participants in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify participants, except as explained below.

Study staff will make clear to participants that a Certificate of Confidentiality will not prevent participants or a member of their family from voluntarily releasing information about participants or their involvement in this research. If an insurer, employer, or other person obtains a participant written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality will not be used to prevent disclosure to state or local authorities of harm to self or others.

▪ **Provisions to Protect the Privacy Interests of Subjects**

Telephone interviews will take place in closed door CRF offices to ensure privacy. Data analysis will occur in closed offices using de-identified data.

F. Potential Benefits to Subjects

Personal benefits include interacting with other similar cancer survivors and receiving free BMT and BT classes that may improve fatigue and overall well-being.

5.0 Special Considerations

5.1 Health Insurance Portability and Accountability Act (HIPAA)

We will request a list of potential participants including names, mailing addresses, telephone numbers, and email address so that we can contact potential participants by telephone, email or regular mail to invite them to be part of this study. Trained study staff will make a screening telephone call to participants to provide study information, obtain verbal consent for screening, and to screen for eligibility to participate. Recruitment for this study depends on the contact information of the physicians and eligible subjects. The initial identification and notification of eligible subjects could not be reasonably accomplished without a waiver of HIPAA Authorization due to limited resources.

Eligibility cannot be determined without access to protected health information. The physicians and eligible subjects cannot be contacted without knowledge of this information.

Identifiers will be destroyed at the end of the study. If more time is needed to complete this research, the investigators will apply for an extension through an amendment with the HRRC.

The study team will obtain participant signed informed consent and HIPAA release prior to data collection as outlined in the section above, 4.6 B.

5.2 Family Educational Rights and Privacy Act (FERPA)

N/A

5.3 NJ Access to Medical Research Act (Surrogate Consent)

N/A

General Data Protection Regulation (GDPR)

N/A

5.4 Code of Federal Regulations Title 45 Part 46 (Vulnerable Populations)

N/A

A. Special Populations

- Prisoners: N/A
- Neonates: N/A
- Neonates of Uncertain Viability: N/A
- Children: N/A
- Individuals with Impaired Decision-Making Capacity: N/A

6.0 Data Management Plan

6.1 Data Analysis

The screening and study questionnaire data will be entered and stored in a database on a designated HIPAA compliant, password-protected network drive. The database will reside on servers maintained and fully protected by a firewall. All data stored on the server will be backed up daily. Access to the study database will be limited to specific study staff users at the discretion of the study Principal Investigator and Co-I, Drs. Kinney and Irwin, and in accordance with institutional review board policies. Data generated during the course of the study will be managed in compliance with the general guidelines for the Use of Confidential Data used by our IRB. Unique identification numbers will replace all names whenever a name is not essential for research purposes and will be kept separate from subject identifiers, except in the case of a password protected subject master file created by the PI approved study staff member. Electronic access to all personally identifiable data will be kept to the minimum necessary to accomplish the project and will require a password. All copies of files containing personally identifiable data will be

stored in separate, locked cabinets in rooms where unauthorized persons do not have access. All personnel will be trained in appropriate security measures for handling personally identifiable data they will not disclose any such information to any person or agency.

Data analysis will occur in closed offices using de-identified data. Telephone calls will take place in closed door offices or cubicles in the CRF to ensure privacy. Each person contacted for the study and each study participant will receive a Participant Identifier. Data will be linked by this participant ID. Names and birthdates (and other PHI) that could be used to identify individuals will not be entered into the main study database. These data will be stored in a 'registry' which will be kept separate from research data. Randomization lists, assignments and decoding data will be stored on a secure server. To help us protect participant privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health.

A. Data analysis plan

Outcome variables, along with sociodemographic, psychological, and clinical factors, and biomarker data, will be summarized by study arm and the enrollment time block, using the standard descriptive statistics such as means (standard deviation) for continuous variables and tabulations for categorical variables. If the deviation from normality/equal variances is significant for raw outcome variables, alternative approaches including log or square root transformations will be utilized. *Multiplicity* will be legitimately adjusted as needed for this study.

For Aim 2 and Aim 3 with multiple target genetic and other biomarkers, the multiple comparisons will be controlled using a false discovery rate (FDR) that has less stringent control over other methods and is designed to control the expected proportion of incorrectly rejected null hypotheses.¹¹⁸ *Non-compliance and missing data* will be handled by intention-to-treat (ITT) analysis for the primary and secondary outcomes. To manage missing data, multiple imputation under the Missing at Random assumption will be applied using a Markov Chain Monte Carlo method^{119,120} via PROC MI in SAS, given the expected pattern of non-monotonic missing data. A post hoc approach¹¹⁹ will address the influence of Missing Not at Random (MNAR) on fatigue. Sensitivity analyses will be performed to assess alternative multiple imputation techniques upon the extent of MNAR influences.

All analyses will be conducted with SAS and R Statistical Software. All tests will be two-sided. The effect sizes and 95% confidence intervals of the primary and secondary outcomes will be reported regardless of the statistical significances.

B. Power analysis

The primary goal of the statistical analyses is to assess the efficacy of the BMT intervention in reducing fatigue (primary outcome), compared to the BT and UC arms. Fatigue is measured at baseline, followed by three additional measurements: 6 weeks as an interim, 13 weeks, and 3 months post-intervention. We want to be able to detect a minimum 15% difference in fatigue score among the groups and within a subject across time. We also want to reduce the total subjects of the UC group and allocate twice the other two intervention groups, with a 1:2:2 allocation ratio. This is a more efficient study design, especially given the NCI budget cuts to all active grants.

Ours' and others' prior published work^{22,25,28,46,68} and our TCQ feasibility trial²¹, have found an average fatigue score for the target population of 32.4, a standard deviation of 8.5, and an

autocorrelation between adjacent measurements on the same subject of 0.7. We assume that first-order autocorrelation (AR1) adequately represents the autocorrelation pattern.

We assume the UC, BT, and BMT group fatigue average score means of 32.4, 34.4, and 39.9 after the immediate post-intervention (3 months post-intervention) for UC, BT, and BMT, respectively. From a fatigue score of 32.4, 0%, 6%, and 23% increase from the baseline for the corresponding group. Similarly, a 23% increase within a subject for the BMT group would result in a fatigue score of 39.9.

A repeated measures design with 1 between factor (group) and 1 within factor (time) has 3 groups with a total of 123 subjects (25, 49, 49 subjects with 1:2:2 allocation ratio for UC, BT, and BMT groups, respectively). Each subject is measured 4 times. This design achieves at least 69%, > 85%, > 80% power to test group, time, and their interaction factors, respectively, if a Hotelling-Lawley Test is used with a 2.5% significance level and an actual effect size is 0.3, 0.45, and 0.46 for group, time, and interaction, respectively. The sample size and its dropout (25% assumption) inflated sample size by the group are below Table:

Average group sample size	Group	Dropout Rate	Sample size achieving the pre-specified power	Dropout Inflated Enrollment Sample Size
28.3	UC	25%	25	34
	BT	25%	49	66
	BMT	25%	49	66
	Total		123	166

Based on t-test evaluation, group sample sizes of 40 and 20 achieve 81% power to reject the null hypothesis of equal means when the population mean difference is 7.5 (39.9 vs. 32.4 post-intervention) with a standard deviation for both groups of 8.5 and with a significance level of 0.025 using a two-sided two-sample equal-variance t-test.

Primary Objective: The analytical goal of **Aim 1** is to test if a BMT intervention will reduce fatigue in inactive, elderly, cancer survivors, compared to BT or UC. The primary outcome for this study is fatigue as measured by the FACIT. Generalized linear mixed effects model (GLMM) with an appropriate link function (e.g., identity for continuous and logit for binary outcomes) will be fitted to examine effects of intervention assignment on the longitudinally measured primary outcome (at baseline, 6 weeks, 13 weeks and 3 months post intervention) with the main covariates of intervention condition, time (in weeks), and their interaction between condition and time. The interaction term will be the main test of interest as it tests for the average departure from the slope due to the intervention. The potential correlations within the same subjects due to the repeated measurements will be accounted for in the GLMM using unstructured, AR(1) or compound symmetric correlation structures. In the event that baseline values of potential confounders (e.g., medications, BMI, age, stage, prior treatment, co-morbidities, psychosocial factors, presence of a companion and companion dose) are not balanced across the 3-study arms, their influence on outcomes of interest will be assessed by adjustment in

multivariable models. We will explore intervention effects on patient-reported outcomes 12 months after completion of the group classes.

Secondary Objective: For **Aim 2** testing the hypothesis that BMT will decrease biomarkers associated with inflammatory mechanisms such as levels of CRP, IL1 β , IL6, IL8, IL10, and TNF α ; decrease TLR-4 stimulated production of inflammatory cytokines (all baseline, 13-week, and 3-month specimens), and decrease expression of a number of genes regulated by NF- κ B pathways (all baseline and 13-week specimens), GLMM will be used to handle each of the biomarkers with the main covariates of intervention conditions, time, and their interaction between condition and time, as described above. We will also test the hypothesis (**Aim 3**) that for male cancer survivors, BMT will regulate the expression of genes from two major functional clusters: 1) inflammation, vasodilation and metabolite sensing and 2) energy and adrenergic activation. Descriptive statistics will be summarized for each gene at baseline and 1-week post intervention (Week 13) and for the change over time by intervention arms. Then, general linear model/ANOVA or the corresponding non-parametric methods, as appropriate, will be used to determine the difference in each gene expression across arms. For the separate functional clusters GLMM will be utilized, while accounting for the correlation among the genes within the cluster by including a random effect of gene and specifying a correlation structure. Multiple comparisons adjustment will be done using FDR as described above. To explore the impact of potential mediators and moderators of BMT's effect on fatigue (**Aim 4**), we will use multiple generalized linear regression models. Specifically, based on the pattern of observed results and the study's conceptual model depicted in Figure 1, mediation analysis¹²¹ will be conducted to examine whether psychosocial (changes in distress, perceived stress, sleep, mental QOL, physical QOL, social well-being, functional well-being, presence of a companion) and/or biological mechanisms (inflammation biology pathways, treatment expectations, fatigue-related gene expression) mediated or explained intervention effects on the fatigue outcome. Adjusted analysis for all aims will control for these factors and will also control for dose (physical activity level, class attendance level, dose of home practice, and dose of companion involvement) as well as sociodemographics and clinical factors. Path coefficients for the mediator model and 95% bootstrap confidence intervals for effects will be estimated to determine the significance of a potential mediator.¹²¹ Further investigation with possible exposure-mediator interactions and causal interpretation will be investigated using VanderWeele methods.¹²² Subgroup analyses (e.g., age <75 vs. $\geq$ 75, companion participation, co-morbidity index, ADT status and intervention dose) will be conducted as sensitivity analyses for the primary and secondary outcomes, although there is no scientific evidence that the intervention effect varies across subgroups in this population. Potential moderators including ADT status, class attendance dose, home practice dose, and co-morbidity index will be explored using a multivariable modeling approach in a similar way above. All these subgroup and interaction analyses will be interpreted cautiously as the Type I error rates are unknown.

C. Steps to secure data

The screening and study questionnaire data will be entered and stored in a database on a designated HIPAA compliant, password-protected network drive. The database will reside on servers maintained and fully protected by a firewall. All data stored on the server will be backed up daily. Access to the study database will be limited to specific study staff users at the discretion of the study Principal Investigator and CO-I, Drs. Kinney and Irwin, and in accordance with institutional review board policies. Data generated during the course of the study will be managed in compliance with the general guidelines for the Use of Confidential Data used by our IRB. Unique identification numbers will replace all names whenever a name is not essential for research purposes and will be kept separate from

subject identifiers, except in the case of a password protected subject master file created by the PI approved study staff member. Electronic access to all personally identifiable data will be kept to the minimum necessary to accomplish the project and will require a password. All copies of files containing personally identifiable data will be stored in separate, locked cabinets in rooms where unauthorized persons do not have access. All personnel will be trained in appropriate security measures for handling personally identifiable data they will not disclose any such information to any person or agency.

D. Procedures that will be used for quality control of collected data.

Data sources include 1) observational data collected from intervention classes, 2) clinical and physical assessment data collected at the Rutgers CINJ, 3) bio specimens (blood and stool samples) collected at Rutgers CINJ, and 4) participant-reported survey data.

Study staff will ensure accuracy and completeness of observational data in intervention exercise classes by documenting a “fidelity checklist” of specific exercises required for each class. Similarly, study staff will maintain a checklist of required tests, assessments, procedures, and bio specimen samples to be completed at each clinic visit to ensure accuracy and completeness of data that needs to be collected for the study. Study staff will review this checklist prior to the participant leaving the clinic, so any missing or outlier data can be followed up with or explained by the collaborating lab staff. For four of the five time points in the study (baseline, 1 week post, 3 month post, and 12 month post) participants will provide self-reported data in the form of diaries and surveys at the clinic visit. During the clinic visit while the participant is with lab staff, two study staff will review each of the surveys and diaries to document any missing, incomplete, unclear, or outlier responses. At the end of the visit study staff will review any such discrepant data with the participant in order to resolve questions and ensure completeness. At the midpoint time point participants will mail their self-reported survey and diary data to study staff in pre-paid envelopes. Upon receipt study staff will review these forms and follow-up with participants via phone about any missing, incomplete, unclear, or outlier responses.

All data collected from participants and digitally captured will be checked via double data entry.

Furthermore, Project HERO Staff will conduct regular quality checks on missing data and out of range values.

E. Data handling study-wide

▪ *What information will be included in that data?*

Data sources include 1) observational data collected from intervention classes, 2) clinical and physical assessment data collected at , CINJ, or EOHSI. 3) bio specimens (blood and stool samples) collected at the, CINJ or EOHSI, and 4) participant-reported survey data. All participant data collected for the study will be de-identified and securely stored.

▪ *Where, how, and for how long will the data will be stored?*

The screening and study questionnaire data will be entered and stored in a database on a designated HIPAA compliant, password-protected network drive. The database will reside on servers maintained and fully protected by a firewall. All data stored on the server will be backed up daily. All hard copies of files containing personally identifiable data will be stored in separate, locked cabinets in rooms where unauthorized persons do not have access. All personnel will be trained in appropriate security measures for handling personally identifiable data they will not disclose any such information to any person or agency.

▪ *Who will have access to the data?*

Access to the study database will be limited to specific study staff users at the discretion of the study Principal Investigator and CO-I, Drs. Kinney and Irwin, and in accordance with institutional review board policies.

- *Who is responsible for receipt or transmission of the data?*
Principal Investigators will delegate responsibility for receipt and transmission of data as appropriate to trained study staff.
- *How will the data will be transported/shared?*
The proposed research will include data from approximately 166 male cancer survivors completing a Tai Chi Qigong, stretching movement, or health education class intervention. The final dataset will include self-reported demographic and behavioral data from surveys with survivors and their companions and laboratory data from collected blood samples. The final dataset will be stripped of identifiers prior to release for sharing and will not contain information that could identify individuals.

6.2 Data Security

The screening and study questionnaire data will be entered and stored in a database on a designated HIPAA compliant, password-protected network drive. The database will reside on servers maintained and fully protected by a firewall. All data stored on the server will be backed up daily. Access to the study database will be limited to specific study staff users at the discretion of the study Principal Investigator and Co-I, Drs. Kinney and Irwin, and in accordance with institutional review board policies. Data generated during the course of the study will be managed in compliance with the general guidelines for the Use of Confidential Data used by our IRB. Unique identification numbers will replace all names whenever a name is not essential for research purposes and will be kept separate from subject identifiers, except in the case of a password protected subject master file created by the PI approved study staff member. Electronic access to all personally identifiable data will be kept to the minimum necessary to accomplish the project and will require a password. All copies of files containing personally identifiable data will be stored in separate, locked cabinets in rooms where unauthorized persons do not have access. All personnel will be trained in appropriate security measures for handling personally identifiable data they will not disclose any such information to any person or agency.

6.3 Data and Safety Monitoring

A. Data/Safety Monitoring Plan

This is a minimal risk study.

Rutgers University places a high priority on ensuring the safety of patients participating in clinical trials. All clinical trials require monitoring commensurate with the degree of risk involved in participation of studies. Standard Operating Procedures (SOPs) detail functions and processes found in this plan.

In addition to complying with NIH/NCI guidelines, the data safety monitoring plan (DSMP) complies with, Rutgers University Office of Research Regulatory Affairs (ORRA guidelines for safety and data monitoring. The DSMP is distinct from, and complements, the activities of the Scientific Review Committee at CINJ and the clinical protocol and management functions of CINJ.

- **Periodic Data Evaluation**

Data and safety monitoring activities continue until all patients have completed their participation and all patients are beyond the time point at which study-related adverse events would likely be encountered. Rutgers University has implemented a process for routine real time data monitoring and safety review of Investigator Initiated trials which takes into account the Essential Elements of the National Cancer Institute (NCI) guidelines, Good Clinical Practice Guidelines and other DSM plans and programs approved by the NCI.

- **Type of Data Evaluated**

Protocol violations and untoward events will be reviewed.

- **Collection of Safety Information**

- The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study
- Investigators must report events to the Rutgers IRB as soon as possible but no later than 5 days from the event date or “site awareness date.”
- The Rutgers IRB must be notified within 10 business days of “any unanticipated problems involving risk to subjects or others.”
- All other adverse events, such as those that are expected, or are unlikely or definitely not related to the study participation, will be reported at least annually as part of regular Data Safety and Monitoring Committee (DSMC) and IRB review.

- **Frequency of Data Collection**

Data will be collected from enrollment through the participant’s last follow-up clinic visit, which is scheduled for 12 months after the intervention ends.

Please refer to the table in section “1.3 B” above for the schedule of data collection.

Adverse events will be reported in a timely manner, as noted above in section “6.3 C”.

All other adverse events, such as those that are expected, or are unlikely or definitely not related to the study participation, will be reported at least annually as part of regular Data Safety and Monitoring Committee (DSMC) and IRB review.

- **Reviewer of Data**

Since this is a low risk study, monitoring will be conducted primarily by the principal investigator and the research staff according to the most current version of the Rutgers University data and safety monitoring plan (DSMP). Central elements (i.e. informed consent, subject eligibility, and data quality) will be monitored and reviewed on an annual basis by the PI and research staff. The conduct of the study and any observed adverse events are reported in annual documentation to the IRB of record. This same documentation is also submitted to the Data and Safety Monitoring Committee (DSMC) for review.

The project director will oversee day-to-day study activities and have daily contact with the Rutgers PI (Dr. Kinney). The project director and other project staff will support regular communication among the research team. There will be 1) regular meetings with project staff and Rutgers investigators to discuss study progress, adverse events, or other research related issues, and regular meetings with Dr. Irwin (co- investigator); 2) direct supervision of BMT and body training instructors during each class to ensure that they adhere to the intervention protocols – fidelity checklists will be used; 3) presence of staff/instructors in each class session that assist participants in performing movements and monitoring

participants for adverse reactions and 4) twice-weekly contact with study participants and follow up contact to participants who do not attend class (to promote retention).

- **Schedule of Review of Cumulative Data**

Study data is reviewed for completeness and outliers at least monthly.

- **Tests for Safety Data**

N/A

- **Suspension of Research**

We do not expect to encounter serious safety issues based on the literature and our considerable experience establishing the feasibility and safety of BMT for frail elderly individuals; however, we would consider early termination if these occur. If during the intervention, the staff or instructors believe that a participant is expressing significant physical or emotional issues, this will be reported. Medical emergency help will be obtained if and when it is needed.

B. Data/Safety Monitoring Board Details

N/A

6.4 Reporting Results

A. Individual Subjects' Results

Current major depression will be assessed by using the 9-item Patient Health Questionnaire (PHQ-9) as a final screening measure before the patient is consented to the study and the baseline assessment is administered.¹¹³ A score of 10 or above has a sensitivity of 88% and a specificity of 88% for detecting major depression. In the event that a participant scores ≥ 12 (a score of 10-12 could also be due to fatigue and cancer-related effects), study staff will immediately follow the HERO Crisis Protocol. Please see Appendix for the study's Crisis Protocol.

Otherwise, participants will be informed that no individual results will be shared. Bio specimens provided by participants for the study will be analyzed in a research lab to provide research-grade results/data; they will have no clinical meaning to participants.

B. Aggregate Results

Results will be disseminated in scientific presentations and published in scientific journals. No identifying information will be shown in any of these presentations, abstracts, or manuscripts

C. Professional Reporting

The aggregate results of the questionnaire/survey will be published in peer-reviewed journals or presented at academic conferences.

D. Clinical Trials Registration, Results Reporting and Consent Posting

This study is registered with ClinicalTrials.gov per NIH regulations. The ClinicalTrials.gov registration number is: NCT03345563.

Per ClinicalTrials.gov requirements, the ClinicalTrials.gov record for Project HERO will be updated within 30 days of any changes to any of the following: recruitment status, overall recruitment status, and completion date. These updates will be made by the study's principal investigator or delegated to a study staff member by the principal investigator.

Per ClinicalTrials.gov requirements, other changes or updates to the record, such as protocol amendments, will be made at least every 12 months. The Record Verification Date will be updated every 6 months until the study is complete. These updates will be made by the study's principal investigator or delegated to a study staff member by the principal investigator.

6.5 Secondary Use of the Data

The proposed research will include data from approximately 166 cancer survivors completing a Tai Chi Qigong, stretching movement, or health education class intervention. The final dataset will include self-reported demographic and behavioral data from surveys with survivors and their companions and laboratory data from collected blood samples. The final dataset will be stripped of identifiers prior to release for sharing and will not contain information that could identify individuals.

7.0 Research Repositories – Specimens and/or Data

Data will be stored on a secure, password-protected server. Only approved staff with CITI training will have access to the data under the direction of the PI. Direct identifiers will be destroyed when the study is completed. De-identified data will not be destroyed.

All blood draws and stool collection will be conducted by , CINJ, an outpatient clinical space in Newark or EOHSI according to university and national guidelines. Samples will be labeled with the participant's ID number. Personally identifiable information will not be stored with the samples. Following collection, samples will be initially processed by the Rutgers CINJ lab or IBX and stored in a secure laboratory. The ID and personal information will be stored in a protected file separately from the samples. The file will be stored in a secure folder on a secure, password-protected computer server. Only authorized research staff will be able to link personal information with the ID.

This study will store extra blood and stool samples (including processed samples) in The CINJ Biospecimen Repository Service (BRS) for future biological analysis including cellular, genetic and genomic markers of health, and DNA/RNA sequencing if the participant provides appropriate consent for this part of the study. Genetic and genomic analysis will include cellular assays, telomere length, gene expression, genetic variants (SNPs) and epigenetic markers. Whole genome sequencing will not be done. Samples may be shared with research collaborators at Rutgers or other institutions with the permission of the PIs. Names and any other personal identifiers will not be shared; the samples and any data collected during the study will only be labeled with ID numbers. Other investigators will not be able to link any personal information with participant data. Participants will be able to request that their samples be removed from the biobank and their samples will be destroyed. Samples will be used in accordance with established institutional policies. We will submit the appropriate applications before collection and use of these biobanked samples. Participants will be provided the opportunity in the Informed Consent form to document their decision regarding storage of their samples for future research. They will also be informed that they may change their mind and revoke their permission at any time.

8.0 Approvals/Authorizations

Approval will be obtained from CINJ SRC and Rutgers IRB. This study is funded by NIH.

9.0 Bibliography

Version Number:

Protocol Number: Pro2018002020

PI Name: Anita Kinney, PhD, RN

Protocol Title: Biobehavioral Effects of

Tai Chi Qigong for Male Cancer

Survivors with Fatigue

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