Study Protocol and Statistical Analysis Plan

NCT03576274

Combined Technology Enhanced Home Exercise Program and Other Non-pharmacological Intervention for Cancer Survivors

09/26/2024

JHM IRB - eForm A – Protocol

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Title: Effectiveness of the combined technology-enhanced home exercise program and other non-pharmacological interventions on fatigue, physical function and well-being among cancer survivors

1. Abstract

Home-based exercise interventions have a significant effect on fatigue; however, motivation and intervention compliance are the main challenges. The use of personalized exercise and immediate feedback has been found to increase motivation. We developed a 12 weeks technology-enhanced home exercise (TEHE) program using mobile technologies that provide immediate feedback and sends reminder messages to improve exercise motivation. Moreover, to enhance the effectiveness of exercise, we combine this TEHE program with techniques--acupressure and mindfulness based intervention--, which have been found to affect fatigue and physical activities. The acupressure and Mindfulness-Based Intervention (MBI) may enhance the effect of exercise on fatigue; however, the feasibility and effectiveness of this combination have not been tested. This study will examine the feasibility of the TEHE program and ascertain the effect of TEHE program alone (TEHE only), the combined acupressure and TEHE program (TEHEplus), acupressure alone (Acupressure only), the combined MBI and TEHE program and usual care on fatigue, physical function and well-being among cancer survivors. In addition, we will explore peripheral and central markers (e.g., Phosphorous levels) of cancer-related fatigue using magnetic resonance spectroscopy (MRS). This study will also investigate whether specific types of fatigue (e.g., physical fatigue, cognitive fatigue) will have different levels of these peripheral and central energy markers).

Conceptual Framework: The biopsychosocial model will be used.
Main Research Variable(s): The independent variables are (1) the 12-week program of TEHE alone, (2) the 12-week program of acupressure only, (3) the 12-week program of combined acupressure and TEHE (TEHE Plus), (4) the 12-week program of combined MBI and TEHE and (5) control (usual care). Outcome variables are fatigue, physical activity, contributing factors of fatigue (depressive symptom, anxiety, sleep, relationship with others), and biomarkers.
Design: Repeated measures randomized controlled trial design.
Setting: Participants will be recruited through the Comprehensive Cancer Center, Johns Hopkins University.
Sample: A total of 105 participants will be recruited from 2 populations

Population 1: Individuals diagnosed with solid tumor cancer; who had completed all primary cancer treatment (surgery, chemotherapy, and radiation therapy) within at least 3

months OR prostate cancer completed all primary cancer treatment and have hormone therapy for at least 6 month, aged 21 years or older, experiencing fatigue in the past 7 days on average of ≥ 3/10, self-report ability to complete the 6 min walk test with a perceived exertion of 6 or below on a scale 1 (hardly any exertion) to 10 (feels almost impossible to keep going), can communicate in English and own a smart phone.

Population 2: individuals diagnosed with solid tumor cancer; who are receiving immunotherapy for at least 3 months before enrollment, aged 21 years or older, experiencing fatigue in the past 7 days on average of ≥ 3/10, self-report ability to complete the 6 min walk test with a perceived exertion of 6 or below on a scale 1 (hardly any exertion) to 10 (feels almost impossible to keep going), can communicate in English and own a smart phone.

Methods: Participants who meet the inclusion criteria will be randomly assigned to the TEHE only or Acupressure only or combined acupressure and TEHE (TEHE plus) or combined MBI and TEHE or control (usual care) group. All exercise groups will be offered a 12-week exercise program. They will be instructed to exercise at home to achieve weekly activity/step goals. Activity/steps and symptoms will be monitored daily using the FitBit and a smart phone application. Weekly summary report of physical activity and symptoms will be sent to participants through a web-based mobile phone application. In addition to the TEHE, the TEHEplus group will receive instructions on how to locate and apply the pressure on the acupressure points and weekly recommendation for acupressure points. The acupressure only group will receive only instruction on how to apply the pressure on the acupressure points through the online training or in person training with weekly recommendation for acupressure points. The MBI+TEHE group will receive a weekly recommendation to add mindfulness based intervention including body scan mindful breathing, and mindful movement. The control (usual care) group will report their symptoms level and monitor physical activity through Fitbit and smartphone application daily. At the end of week 12, in addition to the questionnaires, participants will answer open-ended questions about their opinions on the program. Symptoms will be assessed and blood will be drawn before and after the program. Participants who enrolled in the sub-study will be scheduled for one visit for an MRS.

2. Objectives (include all primary and secondary objectives)

Purpose/Specific Aims:

The study primary aims are to (1) test the feasibility of a 12-week technology-enhanced home exercise (TEHE) program and combined technology-enhanced home exercise and Acupressure (TEHEplus) program among cancer survivors; (2) to determine the effect of the TEHE plus program on fatigue, physical activity and serum biomarkers (Heat Shock Protein 90 and Brain-Derived Neurotrophic Factor) compared to the control (usual care) group.

The secondary aims are to (3) compare the effect of the TEHE only, TEHEplus, Acupressure only, combined MBI and TEHE on fatigue and physical activity; and (4) determine the change in serum biomarkers at week 12 compared to baseline in the TEHE only, TEHE plus, Acupressure only, MBI+TEHE, and control (usual care) groups (5) explore the associations of muscle and brain energetic markers using magnetic resonance spectroscopy (MRS) with fatigue symptoms of cancer survivors.

3. Background

With the advancement of cancer diagnosis and treatment, localized cancer patients have nearly a 100% 5-year survival rate.[1] Approximately 40% of these cancer survivors experienced severe fatigue up to 2 years post-treatment, which impact the quality of life of these individuals.[2] Furthermore, 20% of patients receiving ICIs (PD-1/PD-L1 checkpoint inhibitors) report severe fatigue at the any-grade adverse event,[3] which impact the patients' quality of life and hamper the clinical benefit with ICI.[3, 4] To date, there are no US FDA approved medications to treat cancer-related fatigue (CRF). Several clinical trials have investigated medications for CRF such as psychostimulants (e.g., Methylphenidate, Modafinil) and antidepressants (e.g., nortriptyline, amitriptyline, and bupropion), however, they have shown inconsistent results on effectiveness.[5-8] [9]The National Comprehensive Cancer Network (NCCN; 2015) recommends five non-pharmacological interventions to manage CRF, physical activity is one of the most effective interventions for CRF.[10] The American cancer society recommended 150 minutes/week of moderate-intensity aerobic physical activity (exercise performed at 60-80% of maximum heart rate) for cancer survivors with no physical limitation.[11] **The aerobic moderate-intensity exercise program significantly improved fatigue among cancer patients.**[12-16] Cancer survivors are less likely to exercise due to the limitation of access to an exercise facility and scheduling conflict.[17] To overcome these barriers, a home-based exercise intervention was used. Studies suggested a significant effect of home-based exercised on fatigue severity.[14] Most home-based exercise programs were challenged by the lack of motivation and low adherence rate to the exercise regimen.[18-21] The use of technology e.g., exergaming (Wii-Fit) can increase motivation and exercise adherence.[22-24] However, the use of Wii-Fit can be limited because it required exercise equipment, television, or monitor and exercise space at home. This proposed study will use the goal-setting by using step count from the physical tracker, which will be easier to implement than exergaming and require no additional equipment and space for exercise. To enhance the effectiveness of home-based exercise on fatigue, we hypothesized combining exercise with other nonpharmacological interventions such as acupressure or mindfulness-based intervention may provide a greater effect on fatigue reduction.

Acupressure is a noninvasive complementary method, which is easy to learn. People can learn and self-administer this technique at home as needed. Studies found that relaxation acupressure on the body significantly reduce cancer-related fatigue among breast cancer patients.[25-27] The Auricular Point Acupressure (APA is the application of the pressure on the ear points. The method is to apply the pressure on the selected point through a small adhesive tape with small plant seeds, *Vaccaria segetalis,* which is easy to self-administer the technique to manage symptoms. Studies among breast cancer patients found that APA improves fatigue, pain, and sleep.[28, 29] Based on the previous study result, this technique for both body points and ear points may enhance the effectiveness of exercise on fatigue; however, it has never been tested. Moreover, studies found a significant effect on fatigue among women. The understanding of this effect of APA among men with cancer is limited.

The mindfulness-based intervention (MBI) is a method that uses the open, nonjudgmental attention to one's present moment experience. The MBI alone effectively improve symptoms such as psychological and fatigue among cancer survivors.[30, 31] The body scan, mindful movement and mindful breathing are mindfulness based techniques that trains a person to move one's attention calmly to the different parts of their body and be mindful with the movement and breathing. During the mindful practice, a person will be trained to notice and accept the

sensations they experience in an open and nonjudgmental way. This may improve the awareness of physical sensation during exercise, which may affect the fatigue. The effectiveness of the combined home-based exercise and mindfulness on fatigue is unknown.

Based on the preliminary studies, patients with chronic fatigue had a high level of Heat Shock Protein 90 (HSP90) and low brain-derived neurotrophic factor (BDNF). HSPs are known as stress proteins that maintain proper protein folding for cell growth and survival against stress.[32] BDNF is a member of the neurotrophic family of proteins that plays a significant role in neuronal survival.[33] Both BDNF and HSPs can be modulated by oxidative stress during physical and psychological stressful events (e.g., inflammation, extreme exhaustion). During stressful events, HSP90's function related to protein folding is altered leading to cell death,[34], and BDNF are activated to enhance neuroprotective mechanisms.[35] BDNF has been proposed to influence change in behaviors like depression.[36, 37] In cancer, high HSP90 is believed to support a malignant transformation and is currently a new anti-cancer treatment target. High HSP90 levels are associated with an advanced stage of cancer and poor treatment prognosis.[38] Studies in prostate cancer have shown that the HSP-based chaperone mechanism is involved in prostate cancer progression.[39] Both HSP90 and BDNF levels can be changed by interventions such as exercise.[40, 41] A study in patients with chronic fatigue syndrome (CFS) reported significantly higher blood HSP90 levels among patients with CFS than healthy control and significantly decrease 30% from baseline after the exercise.[42] No studies have investigated the effect of exercise on HSP90 and BDNF in patients with CRF. Information about the relationship between HSP90, BDNF, and CRF is highly important, for it may also trigger a discussion on the potential of CRF as a predictor of cancer prognosis and treatment outcomes.

The organizing framework for this study will be guided by the biopsychosocial model, which incorporates biological influences, social influences, and psycho-behavioral influences on CRF. We hypothesize that CRF is influenced by social (e.g., interpersonal relationships with caregivers), psycho-behavioral (e.g., depressive symptoms, anxiety, physical activity and sleep disturbance), and biological factors (HSP90 and BDNF levels) (figure 1).

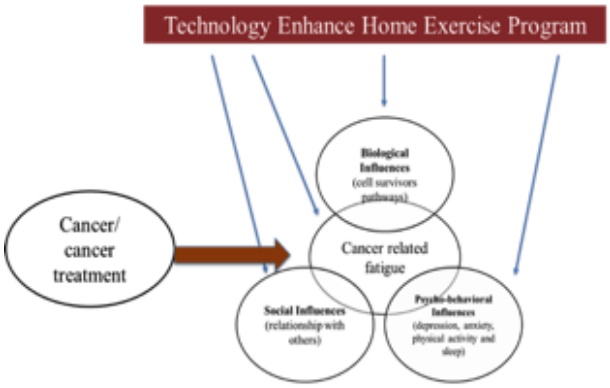


Figure 1: Conceptual Framework based on biosychosocial model of cancer related fatigue

A technology-enhanced home-based exercise program can reduce CRF by having an impact on the biological and psychological aspects of fatigue. The group training exercise

program during study visits impact on social, psycho-behavioral components of CRF experience.

Phosphorous bioenergetics in muscles and brain areas using magnetic resonance spectroscopy (MRS) has been used to estimate mitochondrial oxidative phosphorylation (i.e. oxidative stress) in vivo. For example, one study observed that peripheral fatigue in healthy men was associated with a perturbation in skeletal muscle pH and deprotonated phosphate ion. Another study found that patients with chronic fatigue syndrome have abnormal recovery of intramuscular pH following standardized exercise compared to normal controls. It has been proposed that oxidative stress explains the biologic underpinnings of cancer-related fatigue, but no study has yet to explore whether these markers are associated with fatigue symptoms in cancer survivors. The sub-study seeks to explore peripheral and central energy markers of cancer-related fatigue using magnetic resonance spectroscopy (MRS). This study will also investigate whether specific types of fatigue (e.g., physical fatigue, cognitive fatigue) will have different levels of these peripheral and central energy markers. Information derived from this study will be clinically relevant to identify potential therapeutic targets to optimize the management of this debilitating symptom.

4. Study Procedures

Design. The repeated measure randomized control trial will be used to test the study hypotheses.

Sample and Setting. Participants will be recruited from the Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University.

Data Collection Schedule and Procedures. Upon receiving approval from the Johns Hopkins University Institutional Review Board, the study flyer will be posted and distributed at the Sidney Kimmer Comprehensive Cancer Center, Maryland. The study information and link to eligibility screening survey will be posted on social media platforms (Facebook, Instagram, Twitter). The Johns Hopkins Institute for Clinical and Translational Research (JHU-ICTR) MYChart Recruitment Service will be used to send a message to potential participants through database queries that are embedded in Epic.

Recruitment, Informed Consent, and Confidentiality.

Recruitment methods for this study include

(1) distributing and posting flyers and bookmarks, with study e-mail and Recap screening survey link and/or QR code for potential participants to contact the principal investigator (PI) and research staff to inquire more information about the study or to leave contact information for the study team to reach out and send the study information. Flyers and bookmarks will be distributed to patients who come in for follow-up visits at Sibley Memorial Hospital, Johns Hopkins Bayview Medical Center, Johns Hopkins Hospital;

(2) posting study information on social media platforms;

(3) referral by co-investigators; and

(4) sending messages to potential participants through JHU-ICTR MyChart Recruitment Service.

The participants who completed the Redcap screening survey will be contacted by the principal investigator (Nada Lukkahatai) or a research team member. Potential participants will receive a verbal explanation by phone or face-to-face meetings in terms suited to their comprehension of the purpose, procedures, and potential risks of the study. During the screening for the eligibility process, an oncologist will be available for consultation. The oncologist will be notified and consulted for the appropriateness of the exercise for participants who self-report having co-morbidities. The participants and family or legal guardians will have an opportunity to carefully review the consent form and ask questions regarding this study before signing. Participants will be encouraged to consult with their primary doctor if any concerns or additional questions. Participants will be informed that they may withdraw from the study at any time without prejudice to themselves. The information of potential participants collected through the redcap survey will be kept confidential. The personally identifiable information will be kept in the password log computer. The identifiable information of participants who refuse to participate or are ineligible will be removed from the stored file.

Exercise study: In the eligibility screening process, potential participants will be approached and screened by phone for the average fatigue level within the past 7 days at the level of 3 or more on the 0 (no fatigue) to 10 (worse fatigue) Likert scale, the self-report perceived ability to walk for six-minute and the exertion level after the walk on a 0-10 numeric perceived exertion scale (0 = no exertion at all to 10 = maximal exertion). Eligible participants will be asked if they would like to participate and to sign the electronic informed consent.

Sub-study (MRS imaging): Participants who are eligible for the exercise study will be asked to answer additional screening questions by phone to assess the eligibility for the study including

1. In the last five years, have you been diagnosed as having a substance abuse disorder?
2. Do you currently drink alcohol? If yes, how many drinks per day on average? (ineligible if answer 5 or more drinks per day for male and 4 or more drinks per day for female).
3. Do you have
    a. Implanted cardiac pacemakers, metal aneurysm clips;
    b. Broken bones repaired with metal pins, screws, rods, plates;
    c. Prosthetic eye implants,
    d. Transdermal medications or infusion pumps;
    e. Bullet fragments or other metal pieces in the body from old wounds;
    f. Significant work exposure to metal particles;
    g. Clinically relevant claustrophobia;
    h. Unable to lie comfortably on the back for up to 4 hours;
    i. Being pregnant or lactating

Only the participants who eligible for the MRS (answer “No” to the above questions), will be invited to participate in the sub-study.

Recruitment for the MRS imaging

Those participants who consent to participate in the exercise study and eligible for the sub-study will have the option to enroll in the sub-study (MRS). Declining to participate in the sub-study will not affect their participation in the main study. This will be a convenience

sampling. Once the participant reviews and sign the sub-study section in the consent form. A study visit for the MRS will be scheduled before the first exercise intervention.

Data collection schedule and procedures:

Exercise study:

Once the informed consent is signed, instruction video on how to install a smartphone application and activity tracker (Fitbit), study materials will be sent to the participant. The participants will be meet with a research team member online using the participant's preferred method (e.g., FaceTime, Zoom, etc.) to review the equipment instruction, and measure cognitive function and perceived short physical performance online. If travel is feasible, participants will be meet with the research team member in person at the East Baltimore (Wald) Community Nursing Center and Outreach or Sidney Kimmel Comprehensive Cancer Center to set up the study device and measure muscle strength, physical performance and heart rate variability (table 1). Participants will be asked complete the questionnaire package through Redcap survey. The physical activity tracker (Fitbit) and the mEMA application will be installed on the participants' smartphone with written instructions on how to use both devices. Participants will be asked to wear the Fitbit on the non-dominant arm and respond to the mEMA daily for 12 weeks. Peripheral blood will be drawn at week 1 and week 12 for participants who can complete the study visit in person by a registered nurse or trained research staff at the East Baltimore (Wald) Community Nursing Center and Outreach or at the phlebotomy (research clinical blood draw) at Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University. The collection of blood samples by venipuncture in this study will include the amount of 15 mL, one time per study visit, 2 visits in 12 weeks. (Confirmation that the blood collection by venipuncture from study subjects, the amounts were drawn will be less than 550 ml in 8 weeks and collection occur less than 2 times per week). Blood will be transferred and processed at the Johns Hopkins School of Nursing biophysiological laboratory.

Sub-study (MRS imaging):

Participants enrolled in the sub-study will be scheduled for the MRS at the National Institute on Aging (NIA) located at Medstar Harbor Hospital. The MRS will be done by the NIA staff. The research assistant will accompany the participants and a registered nurse will be available for consultation throughout the MRS process. Only de-identified data will be shared with the Medstar for data analysis.

Table 1: Data collection process

Tasks	Study visit 1	Weeks											Study visit 2
	Baseline	1	2	3	4	5	6	7	8	9	10	11	12
Demographic and disease information questionnaire	X												
FACT-F and PROMIS fatigue	X												X
PROMIS Adult profile	X												X
Cognitive function (MOCA and MASQ)	X												X
Physical activity (steps) and HR (from the wearable device)*	X	X	X	X	X	X	X	X	X	X	X	X	X
Muscle strength test	X												X
Short-form survey (SF-36)	X												X

Connor-Davidson Resilience Scale	X												X
Coping self-efficacy scale	X												X
Pittsburg Fatigability Scale (PFS)	X												X
Physical performance	X												X
Heart rate variability	X												X
Blood sample for HSP90 and BDNF level	X												X
Open-ended questions about the feasibility of the program													X
MRS for the central and peripheral markers (sub-study)	X												

Randomization:
After the baseline data collection and blood draw, the participants will be stratified by type of cancer (breast cancer vs. prostate cancer), age, and treatment (completed treatment vs. receiving immunotherapy). Participants will be randomly assigned to the control and intervention (TEHE only, TEHE plus, Acupressure only, TEHE +MBI groups) groups. The participants' random group assignment will be determined using the Excel program.

Participants in the experimental groups will receive either a) 45-60 min online exercise training/consultation session only, b) an online exercise training session and online and written APA instruction (TEHE +Acupressure group), c) online and written APA instruction only or d) exercise training instructions and mindfulness relaxation instructions (TEHE + MBI groups). After the exercise training session, participants will select their preferred exercise type and their preferred follow-up methods, duration of exercise, exercise schedule, and exercise frequency for the next 12 weeks. Participants will receive weekly recommendation for physical activity goals, recommended acupressure points (for TEHEplus and Acupressure only groups) and recommended mindfulness techques (for TEHE + MBI group). Participants in the control group will continue with their daily usual physical activity.

The feasibility of the TEHE plus program includes the evaluation of the recruitment and retention, acceptability, compliance, and delivery of the intervention. This study aims to measure the feasibility of the TEHE groups (including all five intervention arms). In the data collection process, the eligible participants recruited patients, a number of participants completing the intervention program will be recorded. Adherence to the intervention will be assessed using data collected from the activity tracker on minutes of moderate-intensity or greater activity. During the weekly exercise training, participants will discuss their home-based exercise barriers and potential solutions. At the end of the 12 weeks, participants will answer open-ended questions about their satisfaction and opinion about the programs (intervention groups) and the use of physical activity trackers and mobile phone application (control group).

By participating in the study, participants will spend 12 weeks, with 2 study visits. Participants will continue to receive their routine care and current therapy. They will continue with their therapy when the study ends or if the participation end prematurely. During the study, unexpected circumstances (e.g., worsening of cancer, extreme anemia, or another late side effect of cancer treatment). Participants will be removed from the study if his/her disease and/or condition is worsening.

Participants' personal information will be kept as private as possible and participants' names will not appear on any of the data forms. Blood sample tubes will be coded but de-identified and will be stored in locked freezers at Johns Hopkins School of Nursing biophysiological laboratory freezer until analyzed. Participants' health information will only be disclosed for this research study. Data will be stored for five years using assigned codes and will be kept on a password-protected computer held at the Johns Hopkins School of Nursing. Only study investigators will have access to the study data. After five years, the data will be shredded and discarded.

5. Inclusion/Exclusion Criteria

Exercise study:

Inclusion criteria are (1) diagnosed with a) breast cancer; who had completed primary cancer treatment (surgery, chemotherapy, and radiation therapy) or b) prostate cancer, completed primary cancer treatment and have hormone therapy for at least 6 months prior to enrollment or c) diagnosed with a solid tumor cancer; who are receiving immunotherapy for at least 3 months prior to enrollment; (2) aged 21 years or older; (3) experiencing fatigue in the past 7 days on average of ≥ 3/10; (4) self-report ability to complete the 6 min walk test with a perceived exertion of 6 or below on a scale 1 (hardly any exertion) to 10 (feels almost impossible to keep going); (5) able to communicate in English; (6) own a smartphone.

Exclusion criteria are those (1) have an active infection (e.g., fever, localized redness, swelling, sinus congestion); and (2) diagnosed with a psychological disorder (e.g., suicidal or homicidal tendencies, extreme anxiety or depression).

During the screening for eligibility process, an oncologist will be available for consultation. The oncologist will be notified and consulted for the appropriateness of the exercise for participants who self-report having co-morbidities. Participants who meet the inclusion criteria will be randomly assigned to the intervention groups (TEHE only, Acupressure only, TEHEplus, TEHE + MBI) or the control group.

Sub-study (MRS imaging): participants eligible for the exercise study will be screened for the sub-study.

Additional exclusion criteria for sub-study are those 1) self-identified as a high-risk drinker (≥5 drinks/day for men, ≥4 drinks per day for women). ("Dietary Guidelines for Americans 2015-2020," U.S. Department of Health and Human Services and U.S. Department of Agriculture); or 2) have any of a) implanted cardiac pacemakers, metal aneurysm clips; b) broken bones repaired with metal pins, screws, rods, plates; c) prosthetic eye implants; d) transdermal medications or infusion pumps; e) bullet fragments or other metal pieces in the body from old wounds; f) significant work exposure to metal particles; g) clinically relevant claustrophobia; h) unable to lie comfortably on the back for up to 4 hours; and/or i) individuals who are pregnant or lactating.

6. Drugs/ Substances/ Devices

There will be no drugs or substances used in this study. The wearable device (Fitbit) is a wrist-worn commercially available device in the market, which was found to be safe for most users.

7. Study Statistics

The feasibility of the TEHE plus program includes the evaluation of the recruitment and retention, acceptability, compliance, and delivery of the intervention. This study aims to measure the feasibility of the TEHE groups (including all three intervention arms). In the data collection process, the eligible participants recruited patients, a number of participants completing the intervention program will be recorded. Compliance with the intervention will be assessed using data collected from the activity tracker on minutes of moderate-intensity or greater activity. At the end of the program (12 weeks), participants will be asked to complete open questions on their satisfaction and opinion on the intervention and delivery method.

Primary and secondary objectives

The study primary aims are to (1) test the feasibility of a 12-week technology-enhanced home exercise (TEHE) program and combined technology-enhanced home exercise and Acupressure (TEHE plus) program among cancer survivors; (2) the effect of the TEHE program and TEHE plus on fatigue, physical activity and serum biomarkers (Heat Shock Protein 90 and Brain-Derived Neurotrophic Factor) compare to the control (usual care) group.

The secondary aims are (3) compare the effect of the TEHE only, Acupressure only, TEHEplus, and combined TEHE and MBI on fatigue and physical activity; and (4) determine the change in serum biomarkers at week 12 compared to baseline in the TEHE only, Acupressure only, TEHEplus, MBI+TEHE, and control (usual care) groups

Analysis plan

Exercise study:
The mean and standard deviation of each outcome measure, recruitment rate, drop out, acceptability, tolerability will be calculated per group per study visit. The study primary aim the feasibility of a 12-week technology-enhanced home exercise (TEHE) program and TEHE plus program ***(Aim 1)*** will be analyzed using descriptive statistics of eligible participants and recruited participants, a number of participants completing the intervention program, compliance (number of participants complete the daily step goal), and participants' satisfaction and opinion of the intervention. To examine the effect of the TEHE program on fatigue, physical activity and serum biomarkers (Heat Shock Protein 90 and Brain-Derived Neurotrophic Factor) ***(Aim 2)***, the paired t-test will be used to analyze the effect of the program on fatigue, PA and biomarkers at the end of the program compared to baseline. The student t-test will be used to compare the variables among participants in the TEHE program, Acupressure only, TEHEplus, and TEHE +MBI compare to the usual care (control) group.

The secondary aims: The change of fatigue and physical activity level in week 12 compared to baseline will be calculated. Analysis of Variance (ANOVA) will be used to compare the effect of the TEHEplus, combined TEHE, and MBI with the TEHE only and Acupressure only on fatigue and physical activity ***(Aim 3)***. Change from baseline to 12 weeks will be computed for serum HSP90AA1 and BDNF levels. ANOVA will be used to examine the differences of change in serum biomarkers at week 12 compared to baseline in the TEHE only, Acupressure only, TEHEplus, TEHE +MBI and control (usual care) groups ***(Aim 4).***

Sample size justification
Sufficient information from prior studies is not available for us to conduct a sample size calculation for the proposed multilevel analyses. The purpose of this pilot project is to explore the feasibility of the program and the relationships between the trajectories of the outcome measures, and not to achieve high power. The proposed *N* of 110 (22 participants/group) will likely result in low (below 0.60) statistical power. Results obtained will inform future power analyses for full-scale studies.

Early stopping criterion for safety/futility/efficacy as needed.
The purpose of this pilot study is to examine the feasibility of the interventions. Therefore, participants may be asked to stop their participation early if there are serious complications include metastasis of the disease is found, serious injuries (broken bone, severe muscle injury) that prohibit the participants to exercise, severe infection during the 12 weeks intervention (e.g., fever, redness, swelling, etc.).

Inclusion and exclusion criterion: please see section 5.

Intervention/Independent Variables.
Technology-Enhanced Home Exercise (TEHE) Program: An online individual exercise session will be offered at the first study visit. Participants will be complete an exercise training program (45-60 min) to reach a moderate intensity using the heart rate monitor and exertion level.
The online exercise training/consultation program will include

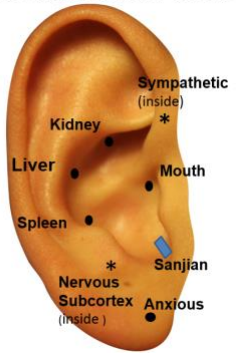
- Goal setting/discussion of the progress (25 min): Participants will spend 25 min to discuss the physical activity barriers and set up a goal for the program.
- Exercise safety and body alignment (10 min): Participants will learning about posturing and body alignment to maintain their safety during exercise and monitoring the heart rate using the wearable device.
- Review physical activity and symptoms (15 min)
- At the end of the program, participants will select follow up methods (phone or video call), reminder message scheduled time and frequency.

At home: Participants will receive a weekly recommendation through a smartphone application and be instructed to follow their physical activity/step goals. Participants will receive a summary report of their weekly physical activity and symptoms (Fitbit and mobile phone application data).

The PI (Dr. Lukkahatai) will monitor the intervention session to ensure intervention fidelity. Adherence to the intervention will be assessed by data collected from the activity tracker on minutes of moderate-intensity or greater activity. At the end of the 12 weeks, participants will answer open-ended questions about their satisfaction with the program.

The Acupressure program: Participants in this group will receive online or in person auricular point acupressure (APA) and body pressure points training at the first study visit. An online educational video and written material developed by interventionists and PI, will

Figure 3. Ear Points for Fatigue



be provided. The participants will review the instruction video. During the online study visit, participants will be asked to locate the ear point, place the seed on the ear points, and pressing the ear points.
The training information will include

1) The selection of the ear point: The points that will receive acupressure include *sympathetic, nervous subcortex, Sanjian, kidney, liver, spleen, mouth, and anxious* point (see Figure 3). [43, 44] The selection of *sympathetic* and *nervous subcortex* are for regulating the function of the central nervous system; *sanjian* is related to increase the metabolism of food; *liver, spleen and kidney* points are to help strengthen the energy; the mouth is also called speed recovered fatigue, and the anxious point is used to promote relaxation.[43, 44]
2) Placing the seeds: After the points are located, the outer ear and the earlobe will be cleaned with 75% alcohol, then place pieces of pre-prepared tape with seeds on the participant's ear. Points on both ears will be identified and used for treatment in the proposed study.
3) Applying pressure on the ear points: evenly press the tape and seeds covering each ear point without rubbing (to avoid skin damage and infection at the acupuncture point) for 10 seconds per time for 3 times/point four times daily, even if they do not experience fatigue. The optimal pressure is considered to have been achieved when the participants feel localized tingling or mild discomfort.
4) Pressure points on the body: Participants will be asked to apply pressure using thump on the following points for fatigue and energy include outer gate point (locates between 2 tendons on the backside of the arm, free finger above the wrist) Spirit Gate or Heart 7 or Shen Men body point (locates on the wrist crease in between little finger and ring finger), large intestine 4, stomach 36, liver 3 and kidney 3. Participants will be instructed to apply pressure 10 seconds per time for 3 times/point four times daily, even if they do not experience fatigue.

At home: Participants will be received a weekly recommendation for points that tailored for their weekly symptoms experience and instructed to press the tape and seeds covering each ear point for 10 seconds per time for 3 times/point four times daily (morning, afternoon, evening and before bed), even when they do not experience fatigue. The optimal pressure is considered to have been achieved when the participants feel localized tingling or mild discomfort. The tape and seeds will remain on ear points for 5 days. Participants will be instructed to remove both at the end of the 5th day and apply the new seeds.

To ensure the accuracy of the ear points, participants will be asked to send the photo of their ear after the seeds are placed for comments and suggestions.

The combined Acupressure and TEHE program (TEHE plus): In addition to the TEHE program, participants will receive Acupressure training at the first study visit and weekly recommendations that include both exercise goal and suggested pressure points.

The combined MBI and TEHE program: In addition to the TEHE program, the TEHE+MBI group will receive a 10-15 min audio-recording of a mindfulness-based body scan or mindful movement or mindful breathing. This technique is often used as an entry point to mindfulness

meditation.[45, 46] This recording guided the participants to focus on specific bodily and breathing sensations.
At home: Participants will be instructed to include mindfulness-based body scan or mindful breathing, mindful movement. The participant will be instructed to acknowledge all sensation with the non-judgemental acceptance and not attempting to change the experience. Participants will receive a weekly recommendation for the activity goals and suggested mindfulness techniques.

Control Group: The control group will receive instructions on how to use the physical activity tracker and the smartphone application. Participants will be asked to meet with a research team member on the first week to review the equipment set up instruction. Participants will be asked to monitor their physical activity daily using Fitbit and receive a daily notification to complete the short on fatigue and other symptoms from the smartphone application.

Dependent variables and instruments. The study variables will be measured as follows:
Questionnaires

- *Fatigue* will be measured by the Functional Assessment of Cancer Therapy-Fatigue subscale (FACT-F). A 13-item questionnaire with good test-retest reliability ($r = 0.90$), internal consistency ($\alpha = 0.93$ and 0.95) on initial and test-retest administration suggesting that it can be administered as an independent, unidimensional measure of fatigue.[25] and the Patient-Reported Outcome Measurement Information System short form-Fatigue (PROMIS-F) 6-items; self-reported fatigue (frequency, duration, intensity) and the impact of physical, mental, & social activities influencing one's daily lives, including work & social roles; has five response options (1 or never to 5 or always). Initial psychometric properties showed an internal consistency reliability coefficient of greater than 0.80.
- *Self-perceived cognitive dysfunctions* were measured by the 38-item Multiple Ability Self-Report Questionnaire (MASQ) in 5 domains: language, visual-perceptual ability, verbal memory, visual-spatial memory, and attention/ concentration, using a 1-5 Likert scale rating.[47] The language subscale includes items relating to speech, the ability to follow conversations, and the ability to convey thoughts. Visual perceptual ability items measure the patient's ability to follow visual directions and solve puzzles. Items in the verbal memory subscale evaluate forgetfulness with events, important information, and names, and visual-spatial memory items relate to faces, pictures, and places. The attention/concentration subscale items assess perceived difficulties with performing tasks, simple calculations, alertness, and maintaining a train of thought. The total score for each domain ranged from 8-40, except for visual-perceptual ability, which ranged from 6-30.[48] Higher MASQ scores indicate a greater perception of cognitive dysfunctions. Each MASQ subscale had high internal consistency reliability (Cronbach's coefficient alpha ranging from 0.72-0.74).[47]
- *Psychosocial factors contributing to fatigue* (e.g., physical function, anxiety, depressive symptom, sleep disturbance, pain intensity, pain interference, and ability to participate in the social activities) will be measured by the Patient-Reported Outcome Measurement Information System (PROMIS)-Adult Profile short form. The items were rated on the past seven days using a 5-point response scale from "never" to "almost always." Initial psychometric properties showed an internal consistency reliability coefficient of greater than 0.80. Disease stage, PSA, and testosterone levels will be obtained by chart review.

- *Resilience* will be measured using the Connor-Davidson Resilience Scale. This is a 10 items self-report scale ask the participant to rate their opinion on the Likert scale range from 0 (not true at all) to 4 (true nearly all the time). This instrument has good internal consistency (Cronbach's alpha of 0.85) and constructs validity.
- *Well-being* will be measured using the Short-form survey (SF-36). This is a 36-items self-report instrument measure 2 domains: physical and affective well-being. SF-36 has good internal consistency (Cronbach's alpha ≥0.70).
- *Self-efficacy* will be measured by the coping self-efficacy (CSE) scale. The 13-items measure perceived self-efficacy for coping with challenges or threats. The CSE has a good internal consistency (Cronbach's alpha ranged from 0.8-0.91
- *Sleep difficulty* will be measured by the Insomnia severity index. This 7 items questionnaire has acceptable reliability (Cronbach's alpha =0.73)
- *Fatigability or fatigue associated with specific physical activity* will be measured by the Pittsburg Fatigability Scale (PFS). The 10 items scale has strong internal consistency (Cronbach's alpha =0.88) and excellent rest-re-test reliability (interclass correlation 0.86).
- *MD Anderson Symptoms inventory* will be used to measure cancer related symptoms severity and interference. This 13-items questionnaire has acceptable reliability and validity.

Physiological and Biological Measurements

- *Physical activity (number of steps) and sleep duration* will be objectively measured by Fitbit Charge. This device can track 7 days of detailed motion, sleep, and physical activity data (e.g., steps, distance, active minutes, sleep duration, heart rate, and caloric usage) and store activity data in the Microsoft platform. Comparing the wearable devices (FitBit and Microsoft band 2) with the physical measurement gold standard (ActivPAL) in healthy participants during treadmill walking and during the free-living environment, the wearable device had an excellent agreement with the ActivPAL (Intraclass Correlation Coefficients = 0.81 and 0.96 respectively, $p < .01$).[49] When compared to the commercially available wearable devices (FitBit, Apple Watch, Garmin Vivofit and Microsoft Band 2), Fitbit has acceptable performance on the accuracy of the heart rate and precise calculation of carries burnt and distances.[50]
- *Skeletal muscle strength* will be measured with a hand-held dynamometer. Grip strength will be measured on both hands in a neutral position of the arm, forearm, and wrist. Two consecutive attempts at 1-minute intervals will be measured. Each attempt will require a participant to exert a maximum possible grip force for about 5 seconds. After a minute of rest, the third attempt will measure fatigue resistance by asking the participant to hold the maximum hand grip as long as able until the 50% maximum grip force (based on the highest maximum handgrip force obtained from the first 2 attempts) is reached, which is often reached in less than a minute. The test will be repeated on the other hand. The same dynamometer will be used for all participants.
- *Plasma HSP90 and BDNF protein levels* will be measured by ELISA. ELISA will be performed according to the manufacturer's guide by one laboratory technician.

The physical performance will be measured using the short physical performance battery assessment (SPPB) and virtual SPPB (vSPPB) at baseline, 12 weeks at the program completion.

Cognitive function will be measured by the Montreal Cognitive Assessment (MOCA) and the Multiple Ability Self-Report (MASQ) questionnaire. It is a 38-item measure that assesses 5 domains of perceived cognitive difficulties: language, visual perception, verbal memory, visual-spatial function, and attention/concentration.[64]

HRV Data Collection:

An electrocardiogram approximately 5 minutes in length will be captured using the commercially available KardiaMobile ECG device (AliveCor, San Francisco, CA, USA). Participants will place their forefingers on the touchpad while seated and resting for the reading. Data will be captured using Kubios HRV software, a software tool for heart rate variability analysis (Kubios, Inc. Kuopio, Eastern Finland). Data will be analyzed by Dr. Stavros Stavrakis (mentor for this project) who has extensive experience with both these technologies and has published on them.[9] Differences between adjacent NN intervals will be assessed. Frequency domain analysis will be used to assess low-frequency power (LF power), high-frequency power (HF power), and the LF/HF ratio.

Magnetic Resonance Spectroscopy (MRS):

Before the first exercise intervention session, the diffusion-weighted (DW) imaging and ^{31}P spectroscopy data will be collected using a 3T Philips Achieva MR scanner (Philips, Best, Netherlands) in the same imaging session. The data collection protocol and analysis will be done at NIA by Dr. Richard G. Spencer (The NIA Magnetic Resonance Spectroscopy expert) and his team.

Table 1: Data collection process

Tasks	Study visit 1	Weeks											Study visit 2
	Baseline	1	2	3	4	5	6	7	8	9	10	11	12
Screening: perceived exertion of 6MWT	X												
Demographic and disease information questionnaire	X												
FACT-F and PROMIS fatigue	X												X
PROMIS Adult profile	X												X
Cognitive function (MOCA and MASQ)	X												X
Physical activity (steps from the wearable device)*	X	X	X	X	X	X	X	X	X	X	X	X	X
Muscle strength test	X												X
Short-form survey (SF-36)	X												X
Connor-Davidson Resilience Scale	X												X
Coping self-efficacy scale	X												X
Pittsburg Fatigability Scale (PFS)	X												X
Physical performance (SPPB and vSPPB)	X												X
Heart rate variability	X												X
Blood sample for HSP90 and BDNF level	X												X
MRS for the central and peripheral markers (sub-study)	X												
Open-ended questions about the feasibility of the program													X

8. Risks

Potential Risks and Protection Against Risks. Potential risks include (1) complications during the blood draw including pain and bleeding at the drawing site, (2) complications of the APA procedure, (3) minimum discomfort might occur while wearing the Fitbit charge (worn like a bracelet), (4) complications such as fainting or injury during the exercise program may occur. The MBI and responding to the questionnaires has no medical risk. The PI and research team plan to prevent the following risks:

1. Complications during the blood draw. Participants may experience pain and discomfort during the blood draw. They may also be at risk of bleeding. All blood draws will be performed by a certified phlebotomist. After the blood draw, participants' conditions will be monitored by a registered nurse (RN).
2. Complications of APA procedure: The auricular acupuncture procedure is considered safe with minimal risk. The most frequently reported adverse events were local skin irritation and discomfort, mild tenderness or pain, and dizziness. These events were transient, mild, and tolerable. Participants will be instructed to remove the tap with the seed when adverse events occur.
3. Minimum discomfort might occur while wearing the Fitbit charge (worn like a bracelet). Participants will be asked to wear a Fitbit to measure physical activity and sleep duration during their participation in the study. Participants will be instructed to take the band off when taking a shower. This equipment may cause discomfort. The material does not contain latex; however, the clasp is made of surgical grade stainless steel and contains traces of nickel, which may cause a rash. The device can be easily removed if discomfort is experienced. Participants will be asked to record the time and reason when and why they removed the band.
4. Complications (e.g., fainting, injury) during the exercise program. Participants will be instructed to walk and exercise at their own pace in the safety of their environment. All participants will be instructed to wear tennis shoes, comfortable clothing, and to eat a light snack before exercise.
5. The MBI and responding to the questionnaire has no medical risk. Participants will be asked to spend 20-30 min completing the questionnaire and listening to the instructions on how to use the smartphone application and Fitbit. All subjects will be informed that they can stop answering questions if they feel tired; they can resume the questionnaire at a later time. Participants will spend less than 5 min responding to a short survey on fatigue level, daily, through the application. Participation in this study involves the completion of questions (4 questions) about depressive symptoms. Scores from these questions (range from 4-20) would not be a sufficient basis for clinical decisions or diagnosis, contain substantial margins of error, and are not used for diagnostic purposes in this study. This score might hint at health conditions. Therefore, participants will receive the score for this depressive symptom subscale. If the depression score is higher than 16 (T score of > 70: severe depressive symptom), a registered nurse will suggest the participant discuss this issue with his/her primary health care provider.
6. Magnetic Resonance Spectroscopy (MRS)

   There is a risk for injury from the magnetic resonance imaging (MRI) magnet if the participant has some type of metal in their body. It may be unsafe to have an MRI scan if the participant has a pacemaker or other implanted electrical device, brain stimulator, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery),

metallic prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, implanted delivery pump, or shrapnel fragments.
Welders and metal workers may have small metal fragments in the eye. Each participant will be screened for such metal before having any scan. If the participant has any metal, they will not receive an MRI scan. If the participant has a question about metal in their body, they should inform the research team.
Each participant will be asked to complete an MRI screening form before each MRI scan. All magnetic objects must be removed before entering the MRI scan room. This includes items like watches, coins, jewelry, and credit cards.
It is not known if MRI is completely safe for a developing fetus. Therefore, female participants in childbearing age will have a pregnancy test done no more than 24 hours before each MRI scan. The scan will not be done if the pregnancy test is positive.
People with a fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing protection. If the hearing protection comes loose during the scan, the participant should inform the research staff right away.

9. Benefits

There is no direct benefit to the participant from being in this study. However, the technology-enhanced home-based exercise (TEHE) program and the combination of the Acupressure and MBI with the TEHE programs proposed in this study could be used as choices for cancer survivors to manage their fatigue and improve patients' quality of life. The mEMA application and Fitbit will serve as useful tools for health care providers to monitor intervention outcomes and compliance.

10. Payment and Remuneration

Participants will receive a total of $40 incentive and a Fitbit for completing 12 weeks program with 2 study visits and phone/video calls follow up. Participants who participate in the sub-study (MRS) will receive an additional of $70 for participation.
If participants withdraw from the study before the 12week, participants will be asked to return the device through the mail and there will be no penalties for withdrawal.

11. Costs

There will be no cost for participants to participate in this study.

12. Data Safety Monitoring Plan

This proposed study intends to evaluate the feasibility and preliminary efficacy of a 12-week technology-enhanced home exercise (TEHE) program and TEHE plus program with physical

activity and fatigue; (2) explore the effect of the combined TEHE program with Acupressure and MBI on fatigue and physical activity; and (3) determine the effectiveness of the TEHE alone, TEHEplus, and MBI+TEHE programs on serum biomarkers (Heat Shock Protein 90 and Brain-Derived Neurotrophic Factor) compare to control (usual care) group. A Safety Monitoring Committee (SMC) will be formed, consisting of Johns Hopkins University clinician faculty members who are independent of this proposed feasibility study. The SMC will be responsible for overall monitoring of the safety of participants in this proposed study and overseeing the PI, Co-Is, and research assistant.

The PI will be responsible for managing all data, securing privacy and confidentiality, minimizing and identifying risks, monitoring and reporting adverse events or any safety issues, and complying with timely reporting requirements to all applicable regulatory bodies for any adverse events or unexpected problems. Monthly reports will be completed by the PI detailing participant demographics, recruitment status, treatment retention rates, protocol compliance, data gathered and accuracy, and quality assurance or regulatory issues that transpired, and summary of any adverse events. The research team (PI, Co-Is, and research assistant) will meet weekly via face to face or conference calling to discuss data and safety monitoring.

The SMC will meet annually (or more frequently if needed) and review the annual reports completed by the PI; review study safety, integrity, and progress including any adverse events; provide advice about continuing, changing, or terminating the study when necessary; require more frequent reporting as needed; audit the study for compliance and verify the authenticity of data, and assess that the research team is complying with informed consenting and other required regulations. These annual meetings will be conducted face-to-face or through conference calls.

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