Protocol and Analysis

Project Title: The impact of inspiratory muscle strength training and personalized exercise prescription on metabolism, cardiovascular function, and cardiorespiratory fitness in lymphoma survivors

NCT: NCT05938127

Version Date: 8/28/2024

Project Title: The impact of inspiratory muscle strength training and personalized exercise prescription on metabolism, cardiovascular function, and cardiorespiratory fitness in lymphoma survivors

Protocol #: 22-1216

Principal Investigator: Ryan Marker, PT, PhD

Co-investigators: Travis Nemkov, PhD
Lavanya Kondapalli, MD

Study MD: Lavanya Kondapalli, MD

Version Date: 8.28.24

PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

Contents

1. STATEMENT OF COMPLIANCE 3
2. LIST OF ABBREVIATIONS 4
3. SYNOPSIS....4
4. RATIONALE AND BACKGROUND 6
5. RESEARCH METHODS....7
5.1 Outcome Measures 7
5.2 Description of Population to be Enrolled 9
6. STUDY DESIGN AND RESEARCH METHODS 11
6.1 Experimental Design 11
6.2 Screening and Recruitment 12
6.3 Study Procedures 12
6.4 Summary of Knowledge to be Gained....15
6.5 Potential Obstacles....15
7 STATISTICAL CONSIDERATIONS....16
8. RISKS AND JUSTIFICATION OF PROCEDURES AND DATA COLLECTION TOOLS 16
8.1 Potential Risks and Risk Mitigation 16
8.2 Potential Benefits....18
8.3 Assessment of Potential Risks and Benefits 19
9 STUDY DISCONTINUATION 19
9.1 Discontinuation of Study....19
10 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM STUDY 19
11 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS....20
11.1 Definition of Adverse Events (AE) 20
11.2 Definition of Serious Adverse Events (SAE) 20
11.3 Classification of an Adverse Event 20
12 UNANTICIPATED PROBLEMS....21
12.1 Definition of Unanticipated Problems (UAPs)....21
12.2 Reporting of Unanticipated Problems....21
13 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS 22
13.1 Informed Consent Process 22
13.2 Confidentiality and Privacy 22
13.3 Future Use of Stored Specimens or Data 23
13.4 Data Safety Monitoring 23
13.5 Quality Assurance and Quality Control 24
13.6 Data Handling and Record Keeping 24
13.6 Protocol Deviations....24
13.7 Publication and Data Sharing Policy 25
13.8 Conflict of Interest Policy 25
14 REFERENCES 25

1. STATEMENT OF COMPLIANCE

This is an investigator-initiated study. The principal investigator (PI), Dr. Ryan Marker, is conducting the study and acting as the sponsor. As the sponsor-investigator, both the legal/ethical obligations of a PI and those of a sponsor will be followed.

The trial will be carried out in accordance with Good Clinical Practice as required by applicable United States (US) laws and applications, including but not limited to United States (US) Code of Federal Regulations applicable to clinical studies (45 Code of Federal Regulations Part 46).

The PI will assure that no changes to the protocol will take place without documented approval from the Colorado Multiple Institutional Review Board (COMIRB). All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Sponsor-Principal Investigator: Ryan J Marker, PT, PhD
Print/Type Name

Signature: _____ **Date:** 1-17-2023

2. LIST OF ABBREVIATIONS

AE	Adverse event
CRF	Cardiorespiratory fitness
VO_2max	Maximal uptake of oxygen
CTRC	Clinical and Translational Research Center
QC	Quality control
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
UAP	Unanticipated Problem
BMI	Body mass index
AHWC	Anschutz Health and Wellness Center
IMST	Inspiratory muscle strength training
6MWT	6-minute walk test
SBP	Systolic blood pressure
NO	Nitric Oxide
ROS	Reactive Oxygen Species
CVD	Cardiovascular disease

3. SYNOPSIS

Protocol title: The impact of inspiratory muscle strength training and personalized exercise prescription on metabolism, cardiovascular function, and cardiorespiratory fitness in lymphoma survivors

Objectives & hypotheses: Cancer survivorship has been steadily improving as a result of earlier detection and improved therapies. Behind cancer recurrence, the primary cause of morbidity and mortality among survivors stems from the onset of cardiovascular disease that arises in part due to cardiotoxic chemo and radiation therapies. The increased risk of cardiovascular disease is particularly high in specific survivor populations, such as lymphoma survivors. Although exercise has been demonstrated to improve both recovery after cancer therapy and quality of life, both physical and logistical hurdles may prohibit certain patients from accessing this intervention. High-resistance inspiratory muscle strength training (IMST) is a time-efficient (~5 minutes/day) form of exercise that employs an affordable, handheld device which impedes inspiratory breathing to train the diaphragm and accessory respiratory muscles and has demonstrated improvements in both cardiovascular health (9 mmHg reduction in systolic blood pressure, 45% improvement in vascular endothelial function) and improve exercise tolerance (12% increase in treadmill exercise time) in generally healthy midlife/older adults. Therefore, this approach may circumvent preventative

hurdles to exercise, and augment the effects of exercise for capable survivors.

Primary Objectives:
Aim 1: **Assess the feasibility of recruitment, assessment, and delivery of the proposed investigation.**
Objective: Measure the recruitment rate of eligible participants (total recruitment, enrolled participants/month), assessment completion (number of valid assessments/participant), and intervention delivery (session attendance/participant, total participants completing intervention and control intervention), in order to inform a robust subsequent efficacy trial.

Aim 2: **Determine the impact of 6 weeks of IMST alone and combined with a 12-week individualized exercise program on improving systolic blood pressure in lymphoma survivors.**
Hypothesis: Participants receiving IMST, compared to those receiving sham (low-resistance) IMST, will demonstrate significantly greater improvements in systolic blood pressure (SBP) after IMST alone and combined with a 12-week exercise program.

Secondary Objective:
Aim 3: **Determine the impact of 6 weeks of IMST alone and combined with a 12-week individualized exercise program on improving measures of cardiorespiratory fitness, physical performance, and cardiovascular health in lymphoma survivors.**
Hypothesis: Participants receiving IMST, compared to those receiving sham IMST, will demonstrate significantly greater improvements in cardiorespiratory fitness (estimated VO_{2max}), physical performance (6 minute walk test [6MWT]), and molecular markers of cardiovascular health (nitric oxide and reactive oxidative species production) after IMST alone and combined with a 12-week exercise program.
Aim 3: **Identify molecular signatures of cardiovascular fitness in lymphoma survivors using mass spectrometry-based metabolomics and quantify impact of BfitBwell and IMST interventions.**

Endpoint:

Primary Endpoints:
Feasibility: Total participants recruited, enrolled participants per month, valid assessments per participant, session attendance per participant, total participants completing the intervention (and control intervention).

Efficacy: SBP at baseline, post-IMST, and post-IMST+BfitBwell

Secondary Endpoints:
Metabolomic exercise profiles at baseline, post-IMST, and post-IMST+BfitBwell
6MWT at baseline, post-IMST, and post-IMST+BfitBwell

	Estimated VO_{2max} at baseline, post-IMST, and post-IMST+BfitBwell Molecular markers of cardiovascular health (nitric oxide [NO] and reactive oxygen species [ROS] production) at baseline, post-IMST, and post-IMST+BfitBwell
Population:	**Sample size** Maximum number of participants that can be enrolled is 24. Minimum number of participants to be enrolled is 18.
Participating sites:	University of Colorado – Anschutz Medical Campus University of Colorado at Boulder
Description of study intervention:	18-week intervention (6-week IMST or sham alone + 12-week personalized exercise and IMST or sham)
Study duration:	2 years
Participant duration:	5 months

4. RATIONALE AND BACKGROUND

4.1 Rationale

Cancer survivorship has been steadily improving as a result of earlier detection and improved therapies. Behind cancer recurrence, the primary cause of morbidity and mortality among survivors stems from the onset of cardiovascular disease that arises in part due to cardiotoxic chemo and radiation therapies. The increased risk of cardiovascular disease is particularly high in specific survivor populations, such as lymphoma survivors. Although exercise has been demonstrated to improve both recovery after cancer therapy and quality of life, both physical and logistical hurdles may prohibit certain patients from accessing this intervention. High-resistance inspiratory muscle strength training (IMST) is a time-efficient (~5 minutes/day) form of exercise that employs an affordable, handheld device which impedes inspiratory breathing to train the diaphragm and accessory respiratory muscles and has demonstrated improvements in both cardiovascular health (9 mmHg reduction in systolic blood pressure, 45% improvement in vascular endothelial function) and improve exercise tolerance (12% increase in treadmill exercise time) in generally healthy midlife/older adults. Therefore, this approach may circumvent preventative hurdles to exercise, and augment the effects of exercise for capable survivors. The goal of this proposal is to determine the effects of 6 weeks of low-barrier, time-efficient IMST on physical fitness and cardiovascular (CV) health in lymphoma survivors and identify cooperative effects in combination with a 12-week individualized exercise training program (BfitBwell). Mechanisms of IMST and exercise response will be further elaborated using metabolomics to define metabolic pathway utilization as a function of endurance and cardiorespiratory fitness.

4.2 Background

As the quality of cancer diagnosis and treatment improves, 14 million cancer survivors are alive in the United States today and 19 million are expected by 2024.[1-3] Among current survivors, 2 in 3 will survive beyond 5 years after diagnosis, though this number decreases to 2 in 5 for 10-year survivorship.[1-3] Exercise within this population is a demonstrated intervention to improve both recovery after therapy and quality of life.[4] As such, the BfitBwell program was established between the CU Cancer Center and the Anschutz Health and Wellness Center to provide 12-week personalized exercise prescriptions for ~150 cancer survivors each year to maximize survivorship.[5,6] Focusing on specific treatment-related causes of morbidity and mortality will further improve outcomes for cancer survivors. The 2nd highest cause of death in survivors behind cancer recurrence is cardiovascular disease (CVD; ischemic heart disease, stroke, or heart failure). Lymphoma patients have high incidence rate ratio of CVD compared to common cancers,[7] which is attributed to cardiotoxic therapies such as anthracycline chemotherapy and radiation to the heart and vasculature.[8-11] Ultimately, CVD diagnosis in cancer survivors results in a ~4-fold increased risk for all-cause mortality[7] and therefore **prevention or mitigation of CVD offers a therapeutic opportunity to improve lymphoma survivorship.**

CVD results from impaired CV function including increased blood pressure (BP), decreased vascular endothelial (VE) function, and arterial stiffening[12] mediated by increased oxidative stress[13] and decreased nitric oxide (NO) bioavailability.[14] Aerobic exercise training is one of the most well-characterized interventions for improving CV function.[6-9] However, only 14% of cancer survivors[15] are able to adhere to current aerobic exercise guidelines of 75-150 minutes per week[16,17] due to time constraints, physical limitations, cost, and transportation requirements. Inspiratory muscle strength training (IMST) offers an alternative CV intervention that circumvents many of these issues. IMST employs an affordable handheld device which impedes inspiratory breathing to train the diaphragm and accessory respiratory muscles.[18] Previous work has demonstrated that repeated inhalations using an IMST device for as little as **5 min per day**, 6 days/week over 6 weeks, has significant benefits for CV health (improved inflammatory and oxidative stress profiles, decreased BP and increased VE function), and increased time to exhaustion (TTE) during a standardized treadmill test.[19]

Enhanced monitoring of exercise and IMST interventions also holds promise to improve survivorship. Physiological parameters such as VO_2max and heart rate have been used as quantitative measures of physical fitness and performance underlying TTE, but they lack mechanistic resolution (i.e., utilized substrates and pathways). Mass spectrometry-based metabolomics, however, offers the ability to measure the levels of thousands of molecules that can contribute to these fitness parameters in a single analysis and requires minimal sample input. Changes in blood derived metabolic signatures are seen in healthy human subjects after IMST, such as correlations between fitness improvement (TTE) and increased acylcarnitines (functional in fat burning capacity) as well as decreased basal levels of succinate (a marker of improved tissue oxygenation)[20].

5. RESEARCH METHODS

5.1 Outcome Measures

Feasibility measures. A **primary outcome** of this investigation is the feasibility of recruiting, assessing, and delivery the intervention to inform the design of a subsequent larger efficacy trial. These measures are total participants recruited, enrolled participants per month, valid assessments per participant, session attendance per participant, total participants completing the intervention.

Adherence to 75% of the program (i.e. 75% of participants complete both pre and post assessments) and its components (i.e. participants complete 75% of prescribed exercise sessions, on average) will be deemed acceptable, as it is similar to adherence in the BfitBwell Program and other effective exercise interventions.

Cardiovascular Health: Systolic blood pressure will be a **primary outcome** of this investigation. *Molecular markers* of cardiovascular health will be **secondary outcomes.**

Casual blood pressure: Following 5 minutes of seated rest, systolic and diastolic blood pressure will be measured in triplicate under quiet, comfortable ambient laboratory conditions using a standard blood pressure cuff around the upper arm, following current recommendations for blood pressure evaluation.[21] This will be performed by trained personnel at the University of Colorado Clinical and Translational Research Center (CTRC).

Molecular markers: Serum will be used to perform experiments in which purchased cultured endothelial cells will be exposed to 10% serum from human subjects for 24 hours. We will measure acetylcholine-stimulated production of nitric oxide (NO) and basal reactive oxygen species (ROS) production in endothelial cells following serum incubation. Serum will be collected via venipuncture performed at the CTRC and stored at -80°C until analysis. Samples will be transferred to the Integrative Physiology of Aging Laboratory at the University of Colorado Boulder for analysis.

Cardiorespiratory Fitness (CRF): CRF will be assessed via *estimated* VO_{2max} and is a **secondary outcome**. This will be measured by the *Tecumseh Step Test*. This is a valid, submaximal step test[22] that has been used in cancer survivors previously[23,24]. Participants step on and off an 8" step for 3 min, at a metronome-controlled pace of 24 steps/min. Afterward, they immediately sit down, and heart rate is recorded at 30 s and 1 min after completion (using Polar H10 heart rate monitors). These recovery heart rates are then entered into a predictive formula, along with patient biometric information (age, weight, gender), to calculate an estimated VO_2max[25]. This assessment is regularly performed by the BfitBwell Program with no adverse events. Participants will be asked to refrain from drinking caffeine for 4 hours prior to the test.

Physical function. This will primarily be assessed by the 6MWT, routinely performed by BfitBwell Program staff at the Anschutz Health and Wellness Center (AHWC). Participants will be instructed to walk as far as possible in a six minute period on an indoor track. **This is a secondary outcome**. Other secondary measures of physical function will be collected by the BfitBwell Program, including grip strength, gait speed, timed up and go test, and 30 s sit-to-stand. These measures will be collected as potential moderators or confounders of study outcomes (e.g. the influence of baseline fitness), inform the personalized exercise program, and provide insight on other benefits of the intervention.

Metabolomics analyses will be performed on blood samples collected during a standardized aerobic exercise session. Samples will be collected before exercise, immediately after, and after 30 min of recovery. *Samples will be collected with patient-centric Tasso+ devices (Tasso, Inc)* which minimize the discomfort of collection. Approximately 0.3 mL of blood will be collected per sample, totaling approximately 1 mL per visit. These devices have been used with similar methodology in several previous investigations[26]. Samples will be centrifuged to isolate plasma and red blood cell fractions prior to storage in a -80°C freezer at the Anschutz Health and Wellness Center. Samples will be transferred for processing in the University of Colorado Cancer Center Metabolomics Core. **This is a secondary outcome.** Lipidomic and proteomic analyses will also be performed to supplement the metabolomic profiles and create hypothesis-generating data for future trials.

Other secondary outcome measures

- *Patient reported outcomes* will collected similar to the BfitBwell Cancer Exercise Program and include the Functional Assessment of Cancer Therapy – General (FACT-G, assessing quality of life), Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue), the Godin Leisure Time Physical Activity Questionnaire, and the Hospital Anxiety and Depression Scale (HADS). These outcomes will be collected using REDCap, a secure, university supported and approved data collection tool. These measures have been shown to be related to program adherence and outcomes[27] and will be collected as potential confounders or moderators of the exercise program response and to inform on other benefits of the exercise program.
- *Cardiac risk factors* will be collected from medical history forms regularly administered by the BfitBwell Program, which include: history of heart attack or surgery, history of cardiac catheterization, angioplasty, or pacemaker, history of valve disease or heart failure, current cardiac medications, history of recent smoking, high cholesterol (>200 mg/dL). These risk factors will be included in secondary analyses to assess if participants at higher known risk of cardiac disease differ in their response to the intervention.

All assessments will be done by study personnel who will be blinded to IMST vs sham randomization.

5.2 Description of Population to be Enrolled

We will enroll 24 lymphoma survivors who meet the below inclusion and exclusion criteria. The primary outcome of this study is a decrease in SBP. Power calculations were performed using previously published data from the research team, which suggested an expected effect size of 1.5.[3] A priori power analysis determined that, using a two-tailed t-test with alpha=0.05, beta=0.8, and Cohen's d=1.5, a sample size of 18 participants (9 per group) is required to compare the change in SBP between groups (IMST vs sham). To account for 25% dropout, we will recruit 12 subjects per group and plan to enroll an equal number of women and men per group.

5.2.1 Major Inclusion Criteria

In order to be eligible to participate, an individual must meet all of the following criteria:

- Age 18 - 80
- Primary cancer diagnosis of lymphoma

- Able and willing to participate in a supervised exercise program at the Anschutz Health and Wellness Center
    - Provides a signed physician exercise clearance form
- SBP > 120 mmHg
- Completion of curative cancer treatment over 12 months prior (individuals on maintenance therapy will be included)
- Possession of a smartphone compatible with the IMST training application (available on both Android and Apple).

5.2.2 Major Exclusion Criteria

Participants will be excluded if they meet any of the following criteria:

- Second active cancer diagnosis
- Planned active cancer treatment or change in current treatment in the next 6 months
- Severe obesity (BMI > 40 kg/m^2) or underweight (BMI < 18.5 kg/m^2)
- Unstable weight (> 3 kg change in body mass in last 3 months)
- Significant metabolic disorder (e.g. diabetes type II)
- Uncontrolled thyroid disease
- Recent changes in hypertensive medication (within last 3 months)
- Any medical condition that would impact the safety of, or participation in, an exercise program, including:
    - Significant pulmonary conditions such as chronic obstructive pulmonary disease, emphysema, or interstitial lung disease
    - Known cardiovascular disease, significant hypertension (> 180/120), or a recent cardiac event (within past 6 months)
    - Orthopedic conditions such as advanced osteoarthritis, mobility-limiting amputations or chronic injuries, or mobility-limiting acute orthopedic injuries
    - Advanced rheumatoid arthritis or chronic widespread pain conditions such as fibromyalgia

Enrolled participants will undergo a version of the BfitBwell Cancer Exercise Program physical assessment, which assesses physical fitness and function (see Outcomes). This assessment has been used to determine exercise safety for over 600 BfitBwell participants. Any enrolled participant with assessment results indicating unsafe exercise participation will be withdrawn and referred to their primary care provider or oncologist.

The BfitBwell Program employs a Spanish-speaking cancer exercise specialist who will be trained in all necessary study protocols to facilitate the inclusion of Spanish-speaking participants. We anticipate ≤ 3 Spanish-speaking participants to enroll in this pilot and will use IRB approved and available short forms for informed consent. We will use available and validated translations of patient reported outcomes and translate other study material as needed for this pilot. If a fourth Spanish-speaking participant is enrolled (or before a subsequent efficacy trial) we will fully develop Spanish language materials for the protocol.

6. STUDY DESIGN AND RESEARCH METHODS

6.1 Experimental Design

This is a prospective, randomized clinical trial of IMST vs sham IMST in isolation (6 weeks) and in combination with an individualized exercise program (12 weeks). Following the ORBIT Model[28], this is a Phase IIb Feasibility Trial, determining feasibility and design of a robust Phase III Efficacy Trial. **Figure 1** shows the study protocol.

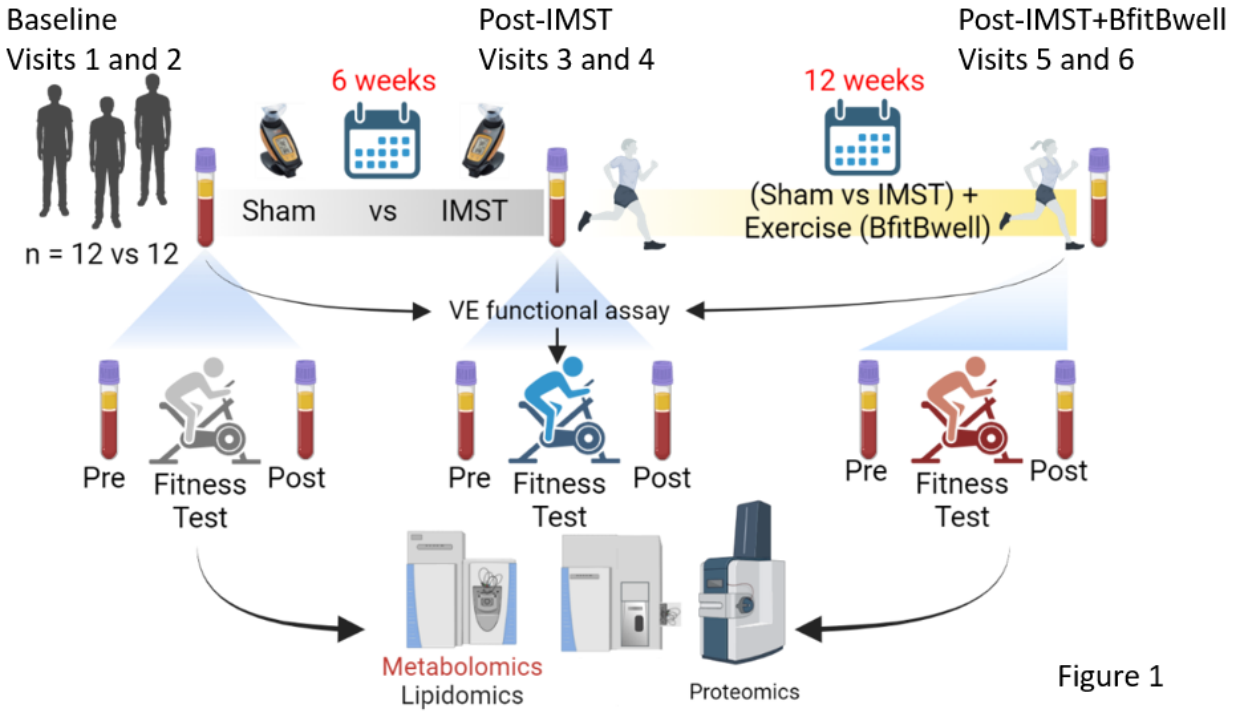

Figure 1

6.2 Screening and Recruitment

We will recruit using several mechanisms. BfitBwell maintains an IRB approved recruitment registry as a part of the BfitBwell Research Database (COMIRB# 16-0692). Participants in the registry will be screened for major inclusion/exclusion criteria (e.g. cancer diagnosis, completion of treatment, age, etc.). All eligible participants will be contacted by study personnel by email or phone. A series of screening questions will be emailed via REDCap or administered over the phone (and entered into REDCap by study personnel). Separate REDCap forms will collect identifying information and inclusion/exclusion information. After reviewing the inclusion/exclusion criteria, study personnel will decide whether a patient qualifies or not or contact the patient with clarifying questions. The patient will be contacted to explain their inclusion (and next steps) or why they were excluded. Once the inclusion/exclusion decision is made, this will be recorded in the de-identified screening question form, along with reason for exclusion if excluded. The identifying information will be deleted for excluded participants or those choosing not to enroll. Any participant excluded from the study will be given information on potential exercise resources for them, if safe and applicable (BfitBwell alumni programming, or other local online or in-person programs found in https://www.exerciseismedicine.org/eim-in-action/moving-through-cancer/).

Participants will also be recruited through the clinical practice of study co-investigator Dr. Lavanya Kondapalli, director of Cardio-Oncology, using multiple methods. Dr. Kondapalli will review the medical records of recent patients, identifying those who may be eligible. Research personnel and Dr. Kondapalli will then reach out to these participants via the above described process. Additionally, upcoming patient visits will also be reviewed. Study personnel will be available during identified appointments. Dr. Kondapalli will discuss the study with patients and introduce them to study personnel who will continue a discussion of the study and ask screening questions. Participants recruited in-person like this may provide informed consent during this initial meeting, if eligible and willing. Fliers advertising the study will be created and given to providers who have clinical relationship with lymphoma survivors and placed in clinical spaces frequented by lymphoma survivors.

Participants will be incentivized to enroll and complete the investigation by offering the required participation in the BfitBwell Program for free (typical cost to participants is $177 and the approximate true value of the program is $1800). All participants, whether randomized to IMST or sham IMST, participate in the BfitBwell Program.

6.3 Study Procedures

Consent. Informed consent will be obtained in an in-person meeting in a private space at the AHWC or UCH facility (for those following an appt with Dr. Kondapalli) or virtually, utilizing Zoom, depending on participant availability and preference. All participants will be required to obtain the necessary physician exercise clearance form prior to consent. Study personnel will review all aspects of the consent form with the participant, asking questions to ensure comprehension and eliciting questions from the participant. If the potential participant chooses to enroll in the study, the consent form will be signed. The preferred method of signing the informed consent will be through the REDCap e-consent

framework, on provided tablets if consent performed in-person. Participants will be walked through each stage of reviewing and signing the consent in this format. Participants will be emailed a copy of the signed consent form when it is presented to them at the end of the consent survey or a pdf of the signed copy will be automatically emailed to them. Paper versions of the consent will be made available for participants who request this, with copies of the signed version made and given to the participant. This session will last approximately 45 minutes.

Visits: Each timepoint (baseline[visits 1 and 2], post-IMST[visits 3 and 4], post-IMST+BfitBwell[visits 5 and 6]) will consist of two study visits. The first visit of each time point (1, 3, and 5) will be performed at the University of Colorado Anschutz Medical Campus CTRC and AHWC. This visit will be scheduled in the morning and participants will be instructed to fast at least 5 hours prior to the visit (preferably an overnight fast). It will begin at the CTRC, where blood pressure and a blood draw (for molecular markers of cardiovascular health) will be performed. Participants will then walk or be transported to the AHWC where they will perform the BfitBwell physical assessment, consisting of the measures of physical fitness and function described in the Outcomes (including estimated VO_{2max} and 6MWT), as well as patient reported outcomes. Participants will be told to bring preferred snacks or provided snacks (e.g. Cliff bars) and water prior to the BfitBwell assessment. This session will last approximately 2 hours.

The second visit (2, 4, and 6) will include the below described exercise response session for metabolomic analyses (**Figure 2**). These sessions will be scheduled in the morning (before 12PM) and participants will be told to eat a 'typical breakfast', which will be recorded. These sessions will last approximately 1-1.5 hours. Session 2 will last an additional 30 min to allow for IMST training.

Exercise Response Sessions. The exercise performed in these sessions will be similar to aerobic exercise sessions performed during the exercise program, with all sessions performed on a treadmill. This should be obtainable for participants beginning the program, as the intensity is low-to-moderate. Blood draws will be performed three times: prior to initiating exercise, immediately after (within 5 min) and at 30 min of seated rest after exercise. Sample collection with the Tasso+ device is patient-centric, minimizing discomfort, and described in the Outcomes Measures section.

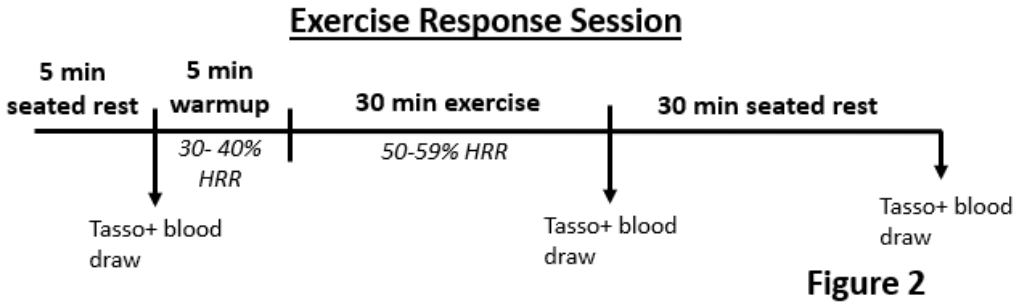

Figure 2

HRR = heart rate reserve

IMST Intervention. Participants will be randomized to IMST or sham following the exercise response protocol in Visit 2 (prior to IMST training). Participants will then complete Visit 2. Receiving either IMST training or sham training by study personnel who will remain unblinded for the trial duration. Investigative team members not involved in outcome measure data collection and analysis will oversee IMST and sham training, as these duties inherently necessitate unblinding. Participants in the IMST group will train 6 days/week for 18 weeks (6 weeks of IMST only, 12 weeks of exercise+IMST). Each training session will involve 30 breaths in against resistance Airofit Pro2 inspiratory muscle strength training device, consisting of 5 sets of 6 inspiratory efforts. Each effort will last approximately 2 s, with an additional 4 s between each effort for expiration. An inspiratory effort begins after a subject has fully exhaled, they then breathe in as powerfully and deeply as possible. Approximately 1 min will elapse for rest between each set. During week 1, participants in the IMST group will train at 55% of their maximum inspiratory pressure (PI_{MAX}). Resistance will then be increased to 65% PI_{MAX} for week 2 and to 75% PI_{MAX} starting week 3; resistance will remain at 75% PI_{MAX} throughout the rest of the intervention. The sham group will follow an identical training plan, except resistance will be set to 15% PI_{MAX} throughout the entire intervention. PI_{MAX} is determined weekly as the peak pressure achieved during a maximal inspiratory maneuver (i.e., inhaling against near-infinite resistance) performed with the Airofit Pro 2. Training is facilitated by the Airofit research app that will be provided to each participant. The research app walks participants through each training session with the appropriate timing and intensity. Adherence will be monitored remotely by the expert research module associated with the Airofit devices. Realtime feedback is displayed through the Airofit research app, helping to facilitate inspiratory muscle strength training by providing a count of the inspiratory maneuvers performed during a training session and by providing auditory feedback (a quiet verbal prompt) when it is time to perform the next inspiratory maneuver. All volunteers are provided in-person training for device operation and given written instructions.

The Airofit Pro2 inspiratory muscle strength training device meets FDA guidelines for a Nonsignificant Risk Device because it is **not**: a) intended as an implant; b) purported to support or sustain human life; c) for a use of substantial importance in diagnosing, curing, mitigating, or treating disease; or d) otherwise present a potential for serious risk to health, safety, or welfare of a subject. The Airofit Pro2 consists of a body with an adjustable valve, an electronic control unit, and a mouthpiece. The body serves to regulate inspiratory resistance. The electronic control unit stores training information, and serve as a subject/investigator interface for controlling the device via the associated smartphone app. The valve head is a mechanical component that generates resistance to inspiration and is controlled by the handset. The mouthpiece is a plastic attachment to the valve head that subjects breathe through to facilitate inspiratory muscle strength training. No changes to the device are anticipated during the course of this clinical study.

The Exercise Intervention will provided by the BfitBwell Cancer Exercise Program and will follow the standard clinical protocol of the program. The BfitBwell Cancer Exercise Program is a 12 week supervised exercise program for survivors of cancer treated at the University of Colorado Cancer Center. It provides tailored exercise training for individual

participants based on National Comprehensive Cancer Network (NCCN) guidelines for survivorship [29] and other national recommendations [30]. The program has been shown to be effective at improving fitness and other well-being related [5,31]. In brief, exercise prescription takes a 'whole-body' approach, targeting increased aerobic endurance and increased strength and flexibility of large upper and lower body muscle groups. Content is tailored to a given individual's preferences, goals, and health status. Aerobic exercise is typically performed by walking on a treadmill or indoor track, or stationary cycling, and resistance exercises typically consist of multi-joint exercises using free weights or body weight. Exercise intensity is regularly adjusted based on participants' current health status, symptom experience, and ability, with the goal of maintaining a rate of perceived exertion (RPE, 0-10 scale) of 6-7 out of 10. Participants receive one 50 min, one-on-one exercise sessions per week for the first month, and one 50 min, small group (≤ 4 participants, each receiving an individual workout plan) session per week for the second and third months. Exercise sessions take place in the AHWC Fitness Center or are virtually supervised (using University-supported Zoom software). Programs are supplemented by at least one additional personalized exercise session provided by a smartphone/internet personal training application. Sessions are led by trained exercise physiologists with certifications as cancer exercise specialists. Participants receive a membership to the AHWC Fitness Center for the duration of the study and are able to use the facility in addition to their prescribed exercise. Behavioral strategies will be employed in the exercise intervention to promote participant adherence including: social support during supervised sessions, structured plans for unsupervised sessions delivered via a personal training smartphone application, individualized goal setting, and regular symptom monitoring with appropriate exercise adjustment.

6.4 Summary of Knowledge to be Gained

IMST offers an alternative intervention that circumvents many issues impacting a cancer survivor's ability to experience the benefits of an exercise intervention. Repeated inhalations using an IMST device for as little as 5 minutes per day, 6 days per week, has shown significant benefits for cardiovascular health and increases the amount of time to exhaustion during a standardized treadmill test. This proposal is to determine if lymphoma survivors benefit from using IMST and if these benefits augment the improvements that exercise has on cardiovascular health. Improving how exercise and IMST are monitored also holds promise to improve survivorship. Physiological parameters such as VO_2max and heart rate have been used as measurements of physical fitness and performance, but they lack the resolution on the molecular level that can provide key biological insights such as which fuel sources are preferred to generate energy during exercise. This investigation will identify new molecular signatures in blood that can help to better describe the current physical fitness of an individual. If successful, this approach will allow for improved patient care and management for lymphoma, but furthermore, the success of this proposal can be adapted for a wide variety of patients where the health of the cardiovascular system impacts disease.

6.5 Potential Obstacles

Recruitment: The recruitment of survivors meeting eligibility criteria may prove difficult within the study time frame. If recruitment is not progressing as planned after approximately 2 months, inclusion criteria will be expanded, specifically dropping the requirement of SBP > 120 mmHg, as IMST and exercise improve cardiovascular health regardless of baseline blood pressure, benefiting lymphoma survivors who are at an increased risk of developing CVD.

Intervention adherence: Participants may struggle to adhere to the exercise prescription. If this occurs in a large portion of participants (>50%) strategies will be implemented to increase adherence based on participant feedback. Intensity can be adjusted to make the exercise more tolerable, or several supervised sessions could be converted to unsupervised sessions to reduce travel and scheduling burdens on participants. Historically, adherence to BfitBwell has been good (>75%) and even better when performed as part of a research study (>90%).

Study power: The anticipated effect size of the intervention is large, possibly leading the study to be underpowered in the event the actual effect size is less. This pilot investigation will provide the necessary data to determine the sample size of a more robust subsequent efficacy trial.

7 STATISTICAL CONSIDERATIONS

Statistical significance will be defined as $\alpha \leq 0.05$. Change scores for all outcomes will be calculated for each participant for the post-IMST and post-BfitBwell+IMST timepoints. These scores will be compared between the IMST and sham IMST groups using paired t-tests at each timepoint. For the exploratory omics investigations, datasets will be generated using the metabolomics, lipidomics, and proteomics platforms. Analysis of these datasets will include standard uni- and multivariate, hierarchical clustering, principal component analyses, partial least-square discriminant analyses, uMAP, tSNE, repeated measure ANOVA for longitudinal experiments. In-house (Compound Discoverer, GraphPad Prism) or freely available (MetaboAnalyst, R) tools will be used. We will perform post-hoc corrections for multiple measurements (e.g. Benjamini-Hochberg adjustment to False-Discovery Rate less than 5%) and adjustment for biological or technical statistical confounders. Static (single timepoint) and dynamic (longitudinal time points) molecular profiles will be compared to other outcomes (cardiovascular health, CRF, and physical function) to generate novel hypotheses.

8. RISKS AND JUSTIFICATION OF PROCEDURES AND DATA COLLECTION TOOLS

8.1 Potential Risks and Risk Mitigation

Risks of exercise and fitness assessments: Certain risks are associated with performing exercise in any population, as well as specifically in cancer survivors. The likely risks of exercise include muscular fatigue and/or soreness, acute increase in fatigue, joint stiffness

or soreness, and possible acute increase in treatment- or cancer-related symptoms. The more serious risks include fracture associated with unknown bone metastases, development of ventricular arrhythmia, myocardial infarction, cardiac arrest, and death.

For adults in the general population and for cancer survivors in particular the benefits of exercise training outweigh the risks. Exercise interventions have been shown to be safe in multiple cancer survivor populations[33]. The discomforts of exercise training and testing will be explained to the participants. Participants will be informed that they can choose to withdraw or not participate in some or all portions of the study at any time for any reason (though this may result in their withdrawal from the study). Before, during, and at the conclusion of each exercise training and testing session, study personnel will ask participants about new or worsening signs and symptoms. Every exercise session will be supervised by qualified study personnel who are versed in exercise training for clinical populations and BLS-certified. Exercise intensity will be monitored by study personnel to decrease likelihood of an acute cardiac event, and participants will be monitored for symptoms including chest pain, acute shortness of breath at rest, or dizziness. Patients will be instructed to stay well-hydrated, and will be monitored for symptoms of dehydration including headache, confusion, tachycardia, significantly increased respiratory rate, and changes in skin elasticity.

After providing written informed consent, each participant will be asked to provide clinical provider contact information. In the event of an emergency, study personnel will call 9-1-1, according to the protocol of the AHWC and outpatient clinics on the AMC. AEDs are available throughout the AHWC. The PI will contact the designated clinical provider if an emergency arises (after first responders are summoned) or a participant exhibits or reports exacerbation of symptoms. In the case of a medical emergency, the participant must be cleared for exercise by their clinical provider before resuming exercise training or testing.

The BfitBwell Program has emergency protocols established for virtually supervised exercise sessions:

- Prior to each exercise session the physical address of where the participant is located will be collected/confirmed and the name and contact information of a close by individual will be collected and confirmed (local support person).
- Non-emergent event protocol: In response to a non-emergent event (e.g. non-life threatening injury in which the participant remains conscious and is able to communicate) study personnel will stay online with the participant and contact the local support person. A plan of action will be created and executed, with periodic follow up by study personnel.
- Emergent event protocol: In response to an emergent event (e.g. participant loses consciousness or shows signs of a serious health event [heart attack or stroke]) study personnel will call 911 and provide the physical address of the participant. If possible, personnel will then contact the local support person. Personnel will stay in touch with all involved until emergency support arrives at the participant's location. Study personnel will then follow up with the participant or local support person.

Risks of IMST - While performing spirometry and breathing maximally, it is possible that participants may begin to feel light-headed or dizzy, or experience a brief headache or momentary shortness of breath. To minimize the likelihood of these events participants will be allowed recovery time between each task and will be instructed to perform training while seated in a safe location. Participants will be warned of these risks and told to report any experiences of these risks.

The risks of the venipuncture (molecular markers) are momentary discomfort from the needle stick, excessive bleeding, light-headedness with insertion of needle, and infection or hematoma at the site of the blood draw. The risks of hematoma and infection will be minimized by having trained clinical personnel perform the procedures using sterile techniques at the CTRC.

Risks of Tasso+ blood sample collection: The Tasso+ device sticks to the skin with a light adhesive. When the button is pressed, a vacuum forms and a lancet pricks the surface of the skin. The vacuum draws blood out of the capillaries and into a tube attached to the bottom of the device. There is a slight risk of an allergic reaction to the adhesive, which will be monitored for and the device removed immediately if this occurs. There is risk of bruising or soreness at the site where blood is drawn. There is also a slight possibility of infection, and a rare risk of fainting. These risks are minimized by having trained personnel perform the sample collection. The area of collection will be cleaned with alcohol prior placement of the device. The Tasso+ is an FDA approved Class I device, presenting minimal potential harm to the user.

Risk of data collection and confidentiality: The primary risk of data collection in the study is a breach of confidentiality and privacy. Overall, no stigmatizing information is collected in the study, minimizing risk. This risk will be explained to participants prior to enrolling in the study. Study data will be stored on University servers and/or REDCap, a secure, university approved data collection tool. Only study personnel will be given access to the REDCap project.

8.2 Potential Benefits

All participants, whether in the IMST or sham group, will receive free participation in the BfitBwell Cancer Exercise Program. The benefits of exercise in cancer survivors are numerous and well documented, including improved quality of life, reduced fatigue, improved physical fitness and function, and potential reductions in risk of recurrence.

The outcomes and results of this investigation will not be utilized to inform the exercise prescription in the study and will not impart any direct benefit to the participant.

8.3 Assessment of Potential Risks and Benefits

The risks to participants are reasonable in relation to the anticipated benefits to participants and/or society, and in relation to the importance of the knowledge that may reasonably be expected to result, thereby falling in favor of performing the study:

- *To Participant*: Minimal risks with possible significant benefit. The risks of exercise, IMST, fitness assessment, and blood sample collection are minimal for these standard procedures and activities. The potential benefit of exercise and IMST in the participant can be substantial, though individual results are variable.
- *To Society:* As the number of cancer survivors continues to grow, effective supportive care programs, such as exercise programs will grow. This investigation will inform adaptations and modifications of these programs to improve exercise prescription to maximize potential benefits of exercise in each individual patient.
- *Justify the importance of the knowledge gained:* IMST is a novel, accessible, and potentially effective tool to reduce CVD risk in cancer survivors instead of or alongside a personalized exercise program. Increased knowledge of this intervention and its mechanisms are necessary to maximize its benefit in each individual cancer survivor.

9 STUDY DISCONTINUATION

9.1 Discontinuation of Study

The investigative team has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory, despite efforts to increase enrollment.

10 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM STUDY

Participants are free to withdraw from participation in the study at any time upon request. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the Sponsor-Investigator determines may jeopardize the patient's safety if he or she continues in the study.
- Sponsor-Investigator determines it is in the best interest of the patient
- Patient non-compliance

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate case report form.

11 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

11.1 Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

11.2 Definition of Serious Adverse Events (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the PI or investigative team, it results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/ birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.3 Classification of an Adverse Event

11.3.1 Severity of event

For AEs, the following guidelines will be used to describe severity.

- *Mild* – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- *Moderate* – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- *Severe* – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

11.3.2 Relationship to study intervention

Only AEs directly related to study intervention will be recorded.

11.3.3 Expectedness

Expectedness will only be documented for SAEs. The study PI and MD will be responsible for determining whether an SAE is expected or unexpected. An SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

11.3.4 Time period and frequency for event assessment and follow-up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form. Information to be collected includes event description, time of onset, clinician's assessment of severity, (if applicable) relationship to study intervention (assessed only by those with the training and authority to make a diagnosis), and time of resolution/

stabilization of the event. All AEs occurring while on study must be documented appropriately. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. Unanticipated problems (UAPs) will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 30 days after the last day of study treatment or until initiation of new treatment, whichever comes first. SAEs will be followed until resolution or stabilization. At each study visit, the investigator will inquire about the occurrence of AE/ SAEs since the last visit.

11.3.5 Adverse event reporting

The investigator will record non-serious adverse events in a case report form. Adverse events will be reported to COMIRB according to their policy.

11.3.6 Serious adverse event reporting

The PI will record all SAEs and report to COMIRB within five days, in accordance with their policy. All deaths and immediately life-threatening events, (if applicable, whether related or unrelated) will be recorded on a SAE Form and submitted to COMIRB within 24 hours of site awareness. SAE will also be reported to the University of Colorado Cancer Center Data Safety Monitoring Committee within five business days.

12 UNANTICIPATED PROBLEMS

12.1 Definition of Unanticipated Problems (UAPs)

This study will use the COMIRB definition of UAP. An UAP is any event or information that was unforeseen and indicates that the research procedures caused harm (including physical, psychological, economic, or social harm) to participants or others or indicates that participants or others are at increased risk of harm than was previously known or recognized.

12.2 Reporting of Unanticipated Problems

This study will follow COMIRB's guidance for UAP reporting. AEs, noncompliance and protocol violations will be recorded and reported as required either promptly (within 5 business days of PI's knowledge) or at the time of the study's continuing review. It is the responsibility of the PI to report incidents or events that meet the criteria for UAPs reporting to COMIRB using COMIRB's standard UAP form.

13 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

13.1 Informed Consent Process

13.1.1 Consent/assent and other informational documents provided to participants

Consent forms describing in detail the study agent, study procedures, and risks will be given to the participant and written documentation of informed consent is required prior to starting the study.

13.1.2 Consent procedures and documentation

Informed consent process will be initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and - if applicable - their families.

Consent forms will be approved by COMIRB and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study.

The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.2 Confidentiality and Privacy

Participant confidentiality is strictly held in trust by the participating investigators and staff. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the PI.

The study monitor, other authorized representatives of the sponsor-investigator, or representatives of COMIRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

Hard or digital copies of the study participant's contact information will be securely stored at the Anschutz Health and Wellness Center or on REDCap for internal use

during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored through REDCap (Research Electronic Data Capture), which is a secure, HIPAA-compliant web-based application designed for data collection for research studies. REDCap is secured and password protected; login will be limited to members of the study team.

13.3 Future Use of Stored Specimens or Data

Intended Use: Data collected under this protocol may be used to investigate molecular responses to exercise and IMST in cancer survivors.

Storage: Data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers or secure laboratories. Only study investigators will have access to the data and specimens.

Tracking: Data and specimen location and status will be tracked using REDCap.

Disposition at completion of the study: Study participants who request destruction of data will be notified of compliance with such request and all supporting details will be maintained for tracking.

13.4 Data Safety Monitoring

The principal investigator will be responsible for the conduct of this study, overseeing participant safety, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and study participant safety for all trials at the CU Cancer Center. A summary of the DSMC's activities is as follows:

• Conduct of internal audits
• Ongoing review of all serious adverse events (SAEs) and unanticipated problems (UAPs)
• May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs and UAPs are reported to the DSMC, IRB and the principal investigator per protocol. All SAEs and UAPs are to be reported to the DSMC within 7 (for fatal or life-threatening events) or 15 (non-life-threatening events) calendar days of the principal investigator receiving notification of the occurrence.

Study audits conducted by the DSMC will consist of a review of the regulatory documents, consent forms, and source data verification. Documentation of the audit conducted by the DSMC will then need to be submitted to the IRB of record at the time of the IRB's continuing review of this trial.

13.5 Quality Assurance and Quality Control

Quality Control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/ resolution.

Following written SOPs, the PI will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The investigational site will provide direct access to all trial-related sites, source data/ documents, and reports for the purpose of auditing by the DSMC audit team, and inspection by local and regulatory authorities.

13.6 Data Handling and Record Keeping

13.6.1 Data collection and management responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic case report form will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the electronic case report form derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

13.6.2 Study records retention

Study documents should be retained for a minimum of 7 years per HIPAA regulations. These documents should be retained for a longer period, however, if required by local regulations or institutional policies. No records will be destroyed without the written consent of the sponsor-investigator.

13.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or good clinical practice. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be

developed by the site and implemented promptly. These practices are consistent with International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use E6, sections:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3.
- 5.1 Quality Assurance and Quality Control, section 5.1.1.
- 5.20 Noncompliance, sections 5.20.1 and 5.20.2.

All deviations will be addressed in study source documents and reported to COMIRB, per their guidelines. The PI and study staff is responsible for knowing and adhering to COMIRB requirements.

13.7 Publication and Data Sharing Policy

This study will ensure that the public has access to the published results of this research upon request.

13.8 Conflict of Interest Policy

Independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed.by the University of Colorado Denver's Office of Regulatory Compliance Conflict of Interest and Commitment Management program. Persons with a perceived conflict of interest will have such conflicts managed in a way that is appropriate to their participation in the trial. Conflict of Interest management plans are project-specific and are reviewed at least annually. University of Colorado Denver has integrated the institutional conflict of interest management program with its existing program.

14 REFERENCES

1. de Moor JS, Mariotto AB, Parry C, et al. Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care. *Cancer Epidemiol Biomarkers Prev.* 2013;22(4):561-570.
2. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010-2020. *J Natl Cancer Inst.* 2011;103(2):117-128.
3. DeSantis CE, Lin CC, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2014. *CA Cancer J Clin.* 2014;64(4):252-271.
4. Demark-Wahnefried W, Rogers LQ, Alfano CM, et al. Practical clinical interventions for diet, physical activity, and weight control in cancer survivors. *CA Cancer J Clin.* 2015;65(3):167-189.
5. Marker RJ, Cox-Martin E, Jankowski CM, Purcell WT, Peters JC. Evaluation of the effects of a clinically implemented exercise program on physical fitness, fatigue, and depression in cancer survivors. *Support Care Cancer.* 2018;26(6):1861-1869.
6. Marker RJ, Ostendorf DM, Leach HJ, Peters JC. Cancer-related fatigue mediates the relationships between physical fitness and attendance and quality of life after participation in a clinical exercise program for survivors of cancer. *Quality of Life Research.* 2022.
7. Armenian SH, Xu L, Ky B, et al. Cardiovascular Disease Among Survivors of Adult-Onset Cancer: A Community-Based Retrospective Cohort Study. *J Clin Oncol.* 2016;34(10):1122-1130.
8. McGowan JV, Chung R, Maulik A, Piotrowska I, Walker JM, Yellon DM. Anthracycline Chemotherapy and Cardiotoxicity. *Cardiovasc Drugs Ther.* 2017;31(1):63-75.

9. Yeh ET, Tong AT, Lenihan DJ, et al. Cardiovascular complications of cancer therapy: diagnosis, pathogenesis, and management. *Circulation.* 2004;109(25):3122-3131.
10. Lenihan DJ, Cardinale DM. Late cardiac effects of cancer treatment. *J Clin Oncol.* 2012;30(30):3657-3664.
11. Accordino MK, Neugut AI, Hershman DL. Cardiac effects of anticancer therapy in the elderly. *J Clin Oncol.* 2014;32(24):2654-2661.
12. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a "set up" for vascular disease. *Circulation.* 2003;107(1):139-146.
13. Pierce GL, Donato AJ, LaRocca TJ, Eskurza I, Silver AE, Seals DR. Habitually exercising older men do not demonstrate age-associated vascular endothelial oxidative stress. *Aging Cell.* 2011;10(6):1032-1037.
14. Forstermann U, Sessa WC. Nitric oxide synthases: regulation and function. *Eur Heart J.* 2012;33(7):829-837, 837a-837d.
15. Arem H, Mama SK, Duan X, Rowland JH, Bellizzi KM, Ehlers DK. Prevalence of Healthy Behaviors among Cancer Survivors in the United States: How Far Have We Come? *Cancer Epidemiol Biomarkers Prev.* 2020;29(6):1179-1187.
16. Piercy KL, Troiano RP, Ballard RM, et al. The Physical Activity Guidelines for Americans. *JAMA.* 2018;320(19):2020-2028.
17. Schoenborn CA, Stommel M. Adherence to the 2008 adult physical activity guidelines and mortality risk. *Am J Prev Med.* 2011;40(5):514-521.
18. Craighead DH, Freeberg KA, McCarty NP, Seals DR. Time-efficient, high-resistance inspiratory muscle strength training for cardiovascular aging. *Exp Gerontol.* 2021;154:111515.
19. Craighead DH, Heinbockel TC, Freeberg KA, et al. Time-Efficient Inspiratory Muscle Strength Training Lowers Blood Pressure and Improves Endothelial Function, NO Bioavailability, and Oxidative Stress in Midlife/Older Adults With Above-Normal Blood Pressure. *Journal of the American Heart Association.* 2021;10(13).
20. Nemkov T, Skinner SC, Nader E, et al. Acute Cycling Exercise Induces Changes in Red Blood Cell Deformability and Membrane Lipid Remodeling. *International Journal of Molecular Sciences.* 2021;22(2):896.
21. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Pr. *Hypertension.* 2018;71(6):e13-e115.
22. Hughes AD, Chaturvedi N. Estimation of Maximal Oxygen Consumption and Heart Rate Recovery Using the Tecumseh Sub-Maximal Step Test and their Relationship to Cardiovascular Risk Factors. *Artery Res.* 2017;18:29-35.
23. Hanssens S, Luyten R, Watthy C, et al. Evaluation of a comprehensive rehabilitation program for post-treatment patients with cancer. *Oncol Nurs Forum.* 2011;38(6):E418-424.
24. Lee MK, Kim NK, Jeon JY. Effect of the 6-week home-based exercise program on physical activity level and physical fitness in colorectal cancer survivors: A randomized controlled pilot study. *PLoS One.* 2018;13(4):e0196220.
25. Hong SH, Yang HI, Kim DI, Gonzales TI, Brage S, Jeon JY. Validation of Submaximal Step Tests and the 6-Min Walk Test for Predicting Maximal Oxygen Consumption in Young and Healthy Participants. *Int J Environ Res Public Health.* 2019;16(23).
26. Catala A, Culp-Hill R, Nemkov T, D'Alessandro A. Quantitative metabolomics comparison of traditional blood draws and TAP capillary blood collection. *Metabolomics.* 2018;14(7).
27. Leach HJ, Marker RJ, Scorsone JJ, Peters JC, Purcell WT. Predictors of attendance during an exercise program for cancer survivors. *Support Care Cancer.* 2021;29(7):3425-3428.
28. Czajkowski SM, Powell LH, Adler N, et al. From ideas to efficacy: The ORBIT model for developing behavioral treatments for chronic diseases. *Health Psychol.* 2015;34(10):971-982.

29. Denlinger CS, Ligibel JA, Are M, et al. Survivorship: healthy lifestyles, version 2.2014. *J Natl Compr Canc Netw.* 2014;12(9):1222-1237.
30. Campbell KL, Winters-Stone KM, Wiskemann J, et al. Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. *Med Sci Sports Exerc.* 2019;51(11):2375-2390.
31. Marker RJ, Kittelson AJ, Jankowski CM, Scorsone JJ, Peters JC, Purcell WT. Development of a Reference Chart for Monitoring Cancer-Related Fatigue Throughout a Supervised Exercise Program. *Rehab Oncol.* 2022;40:82-88.
32. Curran-Everett D. Explorations in statistics: permutation methods. *Adv Physiol Educ.* 2012;36(3):181-187.
33. Schmitz KH, Holtzman J, Courneya KS, Masse LC, Duval S, Kane R. Controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev.* 2005;14(7):1588-1595.