Improving Exercise Capacity with a Tailored Physical Activity Intervention in Lymphoma and Breast Cancer Patients Undergoing Treatment – An addendum to NIH R01CA167821 "Early Imaging Detection of CV Injury after Cancer"

Wake Forest Baptist Comprehensive Cancer Center

CCCWFU# 99112

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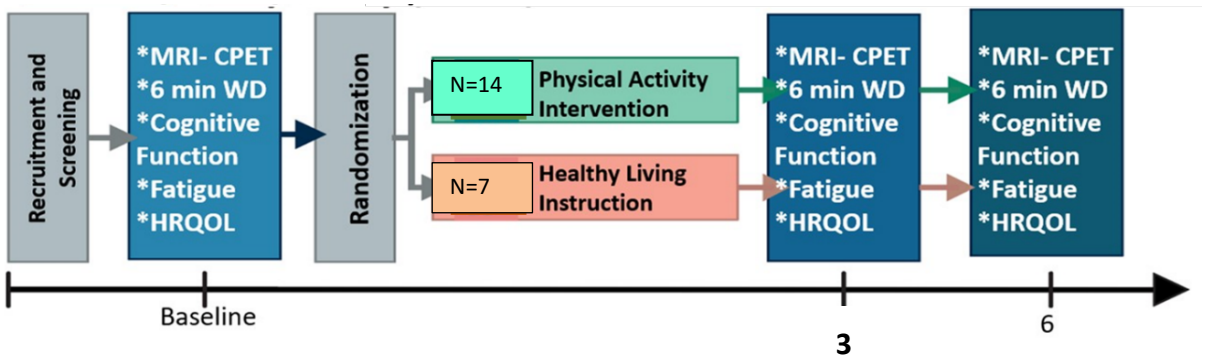
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*Cognitive Function
*Fatigue
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Physical Activity Intervention
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Healthy Living Instruction
*MRI- CPET
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Baseline
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6

1.0 Introduction and Background

Cardiovascular complications from anthracycline-based chemotherapy (Anth-bC) and other potentially cardiotoxic cancer therapies are a leading cause of morbidity and mortality for survivors of lymphoma, the 5th most common cancer in North America. The objective of this proposal is to gather pilot data for a pending NIH R01 submission that will seek to reduce this cancer treatment related CV morbidity by performing and testing a pre-chemotherapy, patient-centered, tailored physical activity intervention (PAI) designed to prevent declines in exercise capacity, cardiovascular performance, cognitive function, and quality of life in patients receiving Anth-bC and other potentially cardiotoxic cancer therapies for lymphoma or breast cancer. The novel features of this proposal include:

1) Initiation of the intervention before and/or during receipt of chemotherapy, leveraging results from animal experiments suggesting this strategy reduces Anth-bC related cardiac injury;
2) Incorporation of three modalities of exercise/activity based training: a) tailored progressive activity, b) strength training, and c) home-based activities suited to one's individual lifestyle, each facilitated and reinforced objectively using activity tracking;
3) Use of a newly developed magnetic resonance cardiopulmonary exercise treadmill test to assess, for the first time, near simultaneously and with high accuracy, the factors [e.g., cardiac output (stroke volume x heart rate)] that contribute to peak VO_2, the gold standard, objective measure of exercise capacity. This new information will provide mechanistic insight into how a tailored exercise-based physical activity intervention helps preserve exercise capacity and reduces fatigue; and
4) Measurement of cognitive function, thereby helping to unravel the association between the impact of exercise training on exercise capacity and cognitive function after receipt of Anth-bC or other potentially cardiotoxic cancer therapies for lymphoma and stage I-IV breast cancer.

This study is designed to demonstrate feasibility of performing the (PAI) and the primary outcome measures before, during and six months after initiating Anth-bC or other potentially cardiotoxic cancer therapies for treatment of non- or Hodgkin lymphoma and Stages I-IV breast cancer. This study will test the potential for a novel (lifestyle) intervention designed to improve exercise capacity, HRQOL and cardiac and cognitive dysfunction. This data will inform the development of the R33 phase of the clinical trial to determine if the (PAI) can reduce exercise intolerance in this high-risk population. In addition, cardiac MRI data from individuals within this pilot will be compared to cardiac MRI data from individuals in the parent study that did not undergo either of the two interventional arms of this study.

Anthracycline-based chemotherapy (Anth-bC) or other potentially cardiotoxic cancer therapies improves cancer-related survival in non-Hodgkin lymphoma (NHL) , but Anth-bC or other potentially cardiotoxic cancer therapies also can promote left ventricular (LV) dysfunction, exercise intolerance, fatigue, reduced health-related quality of life (HRQOL) and cognitive impairment threatening observed gains in cancer survivorship.[1-3]

- Prospective analyses show that ~20% of patients with NHL taking Anth-bC experience >10% reductions in LVEF ($p<0.0001$) and reduction in peak exercise capacity (VO_2) to <80% of pretreatment values[4-6]
- Lymphoma survivors experience marked reductions in HRQOL and often require psychosocial support interventions to perform societal activities of daily living. Routine exercise enhances both physical and mental HRQOL in survivors of lymphoma.[6-8]
- Cognitive impairment occurs after receipt of Anth-bC for NHL. Breast cancer recipients of doxorubicin experience cognitive dysfunction that improves as activity levels increase.[9]

In cancer survivors, exercise capacity – a modifiable characteristic that is strongly associated with risk of CV events – is reduced after Anth-bC or other potentially cardiotoxic cancer therapies can be enhanced through exercise training, and is associated with improved QOL and cognitive function.

- Survey data suggest that more physical activity after lymphoma is associated with decreased CV events.[10]
- In 122 participants who completed treatment for non- or Hodgkin lymphoma, 12 weeks of supervised exercise training improved peak VO_2 relative to those provided written materials ($p<0.001$). Improved peak VO_2 correlated with improved physical function ($p=0.026$). [6]
- In meta-analyses of >3,000 individuals with chronic diseases (including 480 subjects with cancer), low to high intensity exercise interventions were associated with enhanced cognitive function, independent of the disease process, or the type, frequency or intensity of the exercise regimen). [11] Proof-of-concept trials reported improved cognitive function ($p<0.01$) after exercise in breast cancer survivors treated with Anth-bC
- Among 96 breast cancer survivors, aged 58±10 years, 6-month individualized exercise interventions (2 to 3 60-minute moderate intensity episodes/week) resulted in a 20% improvement in peak VO_2, ($p=0.04$) and a 35% to 50% reduction in behaviorally related fatigue ($p=0.001$) on the Piper Fatigue Scale.[12]

In NHL patients, the feasibility, timing of initiation, mechanism of benefit, and overall utility of a tailored/progressive physical activity intervention for

preserving peak VO_2 during Anth-bC or other potentially cardiotoxic cancer therapies is unknown.

- Among 301 women being treated for breast cancer (either 90 or 180 minutes per week of non-tailored moderate-intensity continuous exercise at 75% predicted peak VO_2) did not prevent decline in peak VO_2 after completion of breast cancer treatment. [13]
- In addition, pilot data presented in Section 3.C.1. indicate that lymphoma survivors do not desire a rigid "exercise" program during receipt of Anth-bC. They are however very interested in a program that encourages activity, is tailored to their capabilities, and initiates early during their cancer treatment.[14]
- Interestingly, in 20 individuals randomized to 12 weeks of 3 individualized/tailored bicycle exercise, varying from 60% to 100% of maximum exercise capacity, peak VO_2 increased by 2.6+3.7 ml/min/kg, versus a 1.5+2.2 ml/min/Kg decline in those not exercising.[15]
- In male Sprague-Dawley rats, 10 weeks of exercise preconditioning on motorized treadmills or voluntary running wheels attenuated LV dysfunction 5 and 10 days after doxorubicin treatment; when continued through chronic administration of doxorubicin, it prevented 4-week post-treatment-related declines in LV performance.[2-4] A single bout of exercise 24 hr before doxorubicin protected against cardiac dysfunction.[1]
- How tailored exercise training preserves exercise capacity – via preservation of

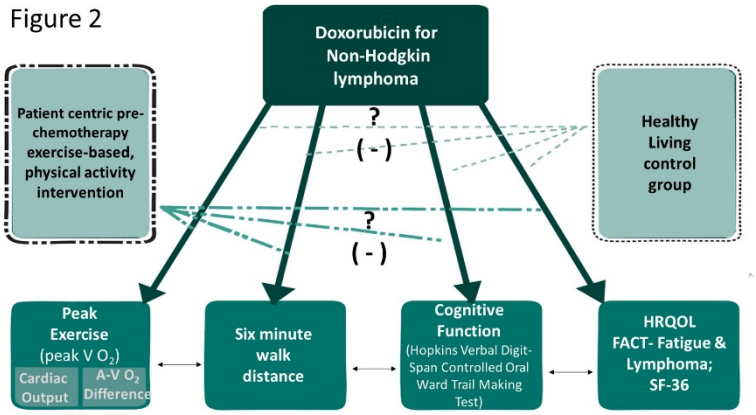
Figure 1: *Fick Equation:*

$$\underset{\text{(Exercise Capacity)}}{\text{Peak VO2}} = \underset{\text{(LV Stroke Volume X Heart Rate)}}{\text{Cardiac output}} \times \underset{\text{(Peripheral Factors Influencing Skeletal Muscle Oxygen Extraction)}}{\text{Arterio-venous oxygen difference}}$$

cardiac function and/or peripheral A-VO2 difference,– is unknown. As shown in **Figure 1**, exercise capacity is related to two components; [16] most studies have focused on the adverse effects of Anth-bC on LV stroke volume (a contributor to exercise- associated cardiac output). However, postmenopausal women before, during, and after treatment for breast cancer had decreased peak VO_2 but not necessarily a marked decrease in exercise-associated cardiac output.[17] These findings challenge the conventional paradigm that all exercise intolerance after Anth-bC or other potentially cardiotoxic cancer therapies is related solely to cardiac injury, and raise important considerations for new targets of activity-based interventions to improve exercise capacity.

We desire to propose a clinical trial to test the hypothesis that a patient-centric tailored exercise-based physical activity intervention (PAI) initiated before and continued throughout Anth-bC treatment or other potentially cardiotoxic cancer therapies will attenuate LV and cognitive dysfunction, and preserve HRQOL, reduce fatigue and maintain peak exercise capacity and 6-min WD. (Figure 2). This study would be significant because it addresses several important premises:

Figure 2



1) Exercise intolerance and LV dysfunction are important causes of morbidity and mortality in patients with NHL who receive Anth-bC.[1-3]
2) Animal data suggest that exercise before anthracyclines reduces LV dysfunction [18-20] If this premise were true in human subjects, patients with NHL may be directed to purposely avoid sedentary behavior during receipt of Anth-bC – a true paradigm shift in the management of these individuals.
3) The benefits of activity-based interventions on exercise capacity may extend beyond the heart. [17] Existing surveillance recommendations to prevent CV events focus primarily on serial measures of "cardiotoxicity", including LV ejection fraction, and global longitudinal strain. These strategies miss the potential adverse effects of Anth-bC on peripheral arterial and skeletal muscle function. Importantly, this study will evaluate the differential effects of Anth-bC or other potentially cardiotoxic cancer therapies on components of peak VO_2.
4) Activity based interventions may improve cognitive function in conjunction with increases in exercise capacity during cancer treatment. [7]
5) NHLBI and NCI mandates: a) the NHLBI goal to improve understanding of clinical mechanisms of CV disease and thereby enable better prevention, diagnosis and treatment;[21] and b) the NCI's commitment to determine actionable strategies to reduce morbidity and mortality in patients with cancer.[22]

However prior to submitting this application, we need to conduct a pilot open label intervention to determine the feasibility of conducting such a proposal. Our pilot will be innovative in that:

- We are developing **a novel integrated, comprehensive program for promoting cardiac health and preventing CV events in NHL patients.** This program addresses multiple challenges for lymphoma patients to combat exercise intolerance by enabling patients to perform both goal-

directed structured aerobic exercise and home-based physical activity after accounting for factors related to their cancer treatment (e.g., anemia, dehydration).

- The study will incorporate **new, advanced, rapid, and highly reproducible MRI combined with cardiopulmonary exercise testing (CPET) testing results to ascertain primary and secondary study aims with much smaller sample sizes than would be needed with other modalities.** Combining advanced MRI measures with the exercise variables will provide mechanistic insights into how increasing activity affects the heart versus peripheral factors associated with arteriovenous O_2 differences, impacting exercise capacity in lymphoma patients.
- This is the first study **to test whether initiating exercise-based physical activity before and/or during Anth-bC therapy or other potentially cardiotoxic cancer therapies can enhance exercise capacity and/or preserve LV function in NHL patients. Our results could challenge existing clinical practice regarding exercise & physical activity recommendations for lymphoma patients and stage I-IV breast cancer before they begin cancer treatment.**

2.0 Objectives

2.1 Primary Objective

To provide critical participant enrollment data necessary to accomplish the R01 submission, including:

2.1.1 Feasibility of screening, enrolling, and randomizing 21 Non or Hodgkin lymphoma and stage I-IV breast cancer patients including the reasons for failed randomization,

2.1.2 Identification of barriers for participating in, or adhering to the Patient ES-AI and the Healthy Living Control Group.

2.2 Secondary Objective

In these 21 patients, at study initiation then 3 and 6 months after initiating Anth-bC or other potentially cardiotoxic cancer therapies to assess the ability to ascertain: peak exercise cardiac output, calculated A-V O_2 difference and VO_2, and pre- exercise measures of LV & cognitive function, HRQOL, six-minute walk distance (6min WD) and fatigue. Ascertainment of the LV function and HRQOL will be attempted in a manner similar to ascertainment of these variables from 47 individuals with lymphoma in the parent study.

3.0 Study Population

Inclusion Criteria: We will enroll 21 eligible and consenting men and women aged 18- 85 years with non- or Hodgkin lymphoma or I-IV stage Breast Cancer patients[23-28] that expect to receive an anthracycline based chemotherapeutic regimen or other potentially cardiotoxic cancer therapies (e.g. chemotherapy regimens [anthracyclines, trastuzumab]), immuno-therapies (immune checkpoint inhibitors [ICI's]) or radiation (within 8 weeks of completion).[29-31] Potential enrollees will need the capacity to walk at least 2 city blocks on a flat surface. English-speaking participants only will be enrolled. Stage IV breast cancer participants must have a 2 year survival prognosis and approval from their physician.

Exclusion criteria: The following are relative contraindications and can be considered by the medical director of the study: Uncontrolled hypertension (systolic blood pressure >190 mm Hg or diastolic blood pressure >100 mm Hg), a recent history of alcohol or drug abuse, inflammatory conditions such as lupus or inflammatory bowel disease, or another medical condition that might compromise safety or successful completion. Other exclusions include those with contraindications to MRI such as ferromagnetic cerebral aneurysm clips or other intracranial metal, pacemakers, defibrillators, functioning neurostimulator devices or other implanted electronic devices. unstable angina; inability to exercise on a treadmill or stationary cycle; significant ventricular arrhythmias (>20 PVCs/min due to gating difficulty); atrial fibrillation with uncontrolled ventricular response; acute myocardial infarction within 28 days; moving within 12 mos. of enrollment.

Rationale for selecting patient population: Patients with lymphoma or stage I-IV breast cancer were included because their disease is potentially curable and therefore late CV effects of treatment are relevant. These individuals experience rates of CV morbidity and mortality that can exceed their cancer-related mortality. We will recruit all study participants from within the Wake Forest Comprehensive Cancer Center.

4.0 Methods

4.1 Recruitment Plan

Study team members will screen and recruit WFUCCC patients via medical record review and will attempt to contact these potential subjects via telephone for screening of eligibility. Permission is required from the attending Hematology/Oncology Physician/Fellow before potential subjects are contacted by a study team member. Interested persons will be asked a series of

questions through a telephone interview to determine if they will qualify for the study. We are requesting a "limited" waiver of HIPAA authorization to identify subjects via Medical Records Review; and the Cancer Center screening/recruiting process. We are requesting further use of our "limited" waiver of HIPAA authorization to identify subjects via Medical Records Review using patient visit schedules from the following Wake Forest Baptist Health departments and clinics: a) Nuclear Medicine/P.E.T. Department, b) Cardiac Ultrasound and Stress Testing, c) Breast Care Services at Medical Plaza-Clemmons, c) Hematology and Oncology clinics located on the main campus and in Clemmons, Lexington, Statesville, Mount Airy, Elkin and Lenoir NC.

4.2 Registration Procedures

All patients entered on any CCCWFU trial, whether treatment, companion, or cancer control trial, **must** be linked to the protocol in EPIC within 24 hours of Informed Consent. Patients **must** be registered prior to the initiation of treatment.

We will perform the following steps in order to ensure prompt registration of each patient:

1. Complete the Eligibility Checklist (Appendix B)
2. Complete the Protocol Registration Form (Appendix A)
3. Alert the Cancer Center registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.

   Contact Information:
   Protocol Registrar PHONE (336) 713-6767
   Protocol Registrar FAX (336) 713-6772
   Protocol Registrar E-MAIL (registra@wakehealth.edu)

   *Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.

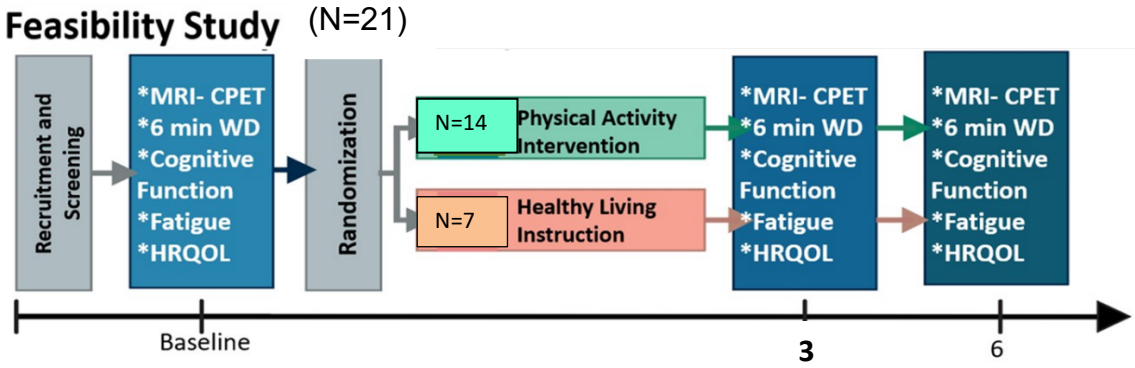
4. Fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

Note: If labs were performed at an outside institution, provide a printout of the results. Ensure that the most recent lab values are sent.

To complete the registration process, the Registrar will:

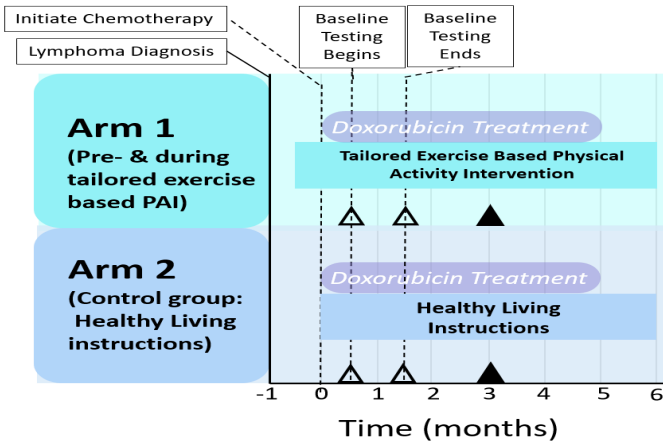
- assign a patient study number
- register the patient on the study

4.3 Summary of Study



Interventions Participants will be randomized into 1 of 2 arms. Study participants in arm 1 will receive the PAI during cancer treatment. In arm 2, participants will participate in the Healthy Living instruction group. Those randomized to each arm will undergo the MRI exam and CPET testing within 5 weeks of initiating treatment and then at 3 & 6 months (Figure 5). If there are restrictions to in person testing or if participants prefer, MRIs and CPETs may be omitted. All individuals in the PAI will participate in qualitative assessments of the physical activity intervention using our QPRO program as described in the Resources Section of the document.

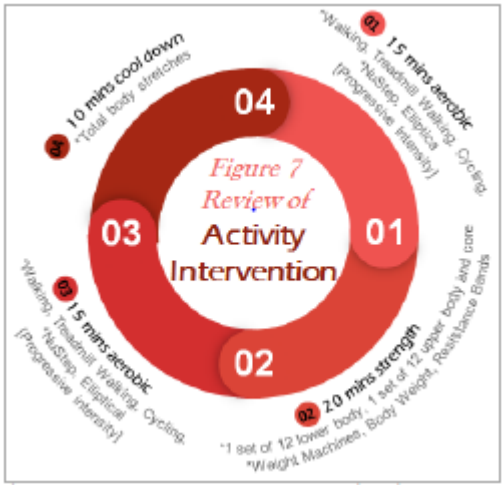
Figure 5: Study Intervention timeline: Dark triangle signifies testing for MRI-CPET, 6 minWD, HRQOL, QPRO, Cognition, Fatigue



Patient-centric pre-chemotherapy tailored physical activity intervention (Arm 1)

The PAI for this study is based on our experience with PAI in breast cancer patients during active treatment[32] with anthracyclines, findings from our recent

focus group with lymphoma patients, as well as previously reported successful exercise/PA interventions in breast, prostate, leukemia, and lymphoma patients. The exercise intervention component of our PAI will be initiated at the Health and Exercise Science Clinical Research Center near the Reynolda Campus of Wake Forest University, Wake Forest Baptist Health Sticht Center or in Cardiac Rehabilitation Facilities and under the direct supervision of a master's level clinical exercise physiologist. Three center-based PAI sessions will be offered each week (M,W,F). They will have the ability to participate in one to two training sessions per week at one of these centers and 1-2 sessions per week at home (the 4th level of our multi-level intervention). Each PAI session will consist of a slow (15min) aerobic warm-up; followed by 20 minutes of strength training; 15 minutes of progressive intensity aerobic exercise (AE); and 10 minutes of cool-down by stretching/toning with elastic bands similar to those recommended by the American Cancer Society (Figure 7).[33]



Home based activities will be offered if participants are unable to travel to the exercise center. The exercises will be constructed similarly to the center-based exercise and tailored to their access to equipment and symptoms. The study interventionist will work with participants to create an exercise session and find creative ways to complete different types of exercises. Exercises could include, but are not limited to, over ground walking, body weight exercises, or use of resistance bands.

The mode of activity for the center-based AE sessions will be over-ground walking and/or stationary cycling that is prescribed based on the "non-linear approach" described by Jones at al.[34,35] This approach adheres to the principle of progressive intensity and is designed to increase exercise capacity outcomes (peak VO2 peak and 6min walk distance), yet also permit individual "tailoring" based on each participant's daily perceived level of fatigue and disease/treatment related symptoms. Specifically, in "non-linear" prescriptions,

the AE sessions are sequenced such that the physiological "stimulus" is progressively modified with regard to the intensity and duration and in conjunction with appropriate rest and recovery sessions in order to optimize physiological adaptations. The goal for the moderate – 45-60 minute AE sessions per week is to progress the intensity from 50% to 75% of VO2peak by the end of the 6 month progressive tailored intervention.[36] Strength training will initiate at similar thresholds for core and peripheral skeletal muscles in that 50% of maximal resistance exercises at 5-8 repetitions per muscle group will occur at the initial visits and then progress to 70% of maximum resistance with the same number of repetitions toward the 6 month completion of the study. The CPET will be re-assessed after 3 months of treatment to re-calculate the AE intensity level to ensure continual increase in the physiological stimulus. During AE sessions, intensity and safety will be stressed and when at the cardiac rehabilitation facilities be continuously assessed via heart rate while blood pressure at the beginning, middle, and end of each session. Participants will be encouraged to accumulate 150 minutes (~30 minutes day) of light-moderate intensity PA per week outside the program facility. Daily and weekly targets for PA will be self-monitored by the participant and validated weekly by the intervention staff from wrist-worn Fitbit and Actigraph activity monitors. Increasing lifestyle physical activity is an important supplement to the 1-2 day/wk center-based AE and provides flexibility to the participant's schedule and disease/treatment related side effects. [37]

To enhance safety, each subject will be instructed to participate at an individually prescribed level of exertion, report any symptoms or problems during PA, and to rest as needed. The interventionist will take time to communicate with participants during the center-based AE sessions to determine whether PA prescriptions are appropriate, to ask how participants are feeling, and to answer questions regarding the PA prescription.

Adherence, Retention & Barriers to Patient PAI. All interventionists will receive training and ongoing supervision from Dr. Mihalko in validated behavioral techniques developed from social cognitive theory (SCT) to enhance intervention adherence. SCT provides a strong conceptual framework for understanding the pathway from physical activity to health outcomes, with self-efficacy identified as a consistent outcome of physical activity with strong potential for modification. Techniques include frequent contact during the intervention; positive feedback; incentives to reach attendance and performance goals; establishing personal commitment to the project; promoting a sense of community via study logo and incentives; and targeted mechanisms for behavioral adherence, including self-efficacy, outcome expectations, and self-regulatory skills. From the outset, the importance of regular attendance will be emphasized. Adherence data will be reviewed regularly to identify any

participants who need additional reminders and/or counseling, and gain insight to difficulty with participation in PAI. Interventionists first meet with each participant to discuss expectations and negotiate participant goals. Interventionists then use a flexible "toolbox" approach to tailor interventions to each participant's needs. Using a social problem-solving framework, a problem is identified (e.g., fatigue), and a solution is found (e.g., negotiate alternate time when energy is higher) and tested for a specific period of time (e.g., 2 sessions). Participants have input on options that are selected. If the solution effectively resolves the problem, the strategy is continued until consistent behavior change is observed. If the solution is unsuccessful, a new option for solving the problem is selected (e.g., decrease intensity of physical movements) and tested. Collectively, these strategies will increase social cognitive mechanisms for regular participation and enhanced adherence in both groups. Our team has had remarkable success with this approach, exceeding study goals for adherence and retention in several federally-funded trials of physical movement-based interventions in adults with chronic disease, e.g., cancer.

Healthy Living Control Group (Arm 2)

Those participants randomized to the control arm will come to a centralized meeting location or receive an invitation for an online meeting to participate in organized health workshops. Each session will last 60 minutes and match the number of visits to the rehab centers for the PAI in a 1:1 fashion with 2 sessions offered per month on Reynolda Campus and remaining sessions over the telephone over the 6 months. (Table 4). Make up sessions either in person or over the telephone will be offered for those participants who have to miss a group session. It is the objective of this HLI intervention to match participant contact with the PAI.

Session Content: Introduction and Review past material (10 mins); Interactive Healthy Living Presentation (30 mins); Short instructor-led program of upper body stretching exercises (10 mins); Wrap-Up & discussion of next Workshop (10 mins). The topic list is shown Table 5. The purpose of the "Healthy Living" study arm is to control for attention from study staff and social interaction in the intervention group. The design of the control group was informed by the following principles; 1) to positively impact recruitment, participant interest in participation, and on-going adherence to the healthy living arm of study; 2) to have a comparison group that does not directly influence the primary outcome; and 3) to provide a program that would offer benefit to the study participant. There is no evidence to suggest that health education alone will impact physical activity participation or exercise capacity. In addition, the decision to use a once

per week schedule was based on careful review of science, adherence, and expense considerations and the request to match the number of interventions in the HLI group with the once per week minimum cardiac rehabilitation center visits received by the PAI participants. Note that participants will receive referrals to exercise facilities at study completion (Table 4).

The Healthy Living presentations will be interactive and will provide useful information on such topics as proper nutrition, management of stress, and sleep practices (Table 5). Experts (we have used from prior studies across a broad range of relevant topics will be brought in to give guest lectures over the course of the 6 months. Participants will be asked to complete homework assignments, review past topics, and engage in small group discussions as a means to increase active involvement in this study arm. The final component of the workshop, the upper body stretching component, was chosen to be part of the control arm to enhance adherence to this arm of the study. Specifically, this "placebo exercise" activity will serve to increase the benefit perceived by the participants of the workshops without directly affecting the study outcomes.

Table 4. Multi-level Participant Contact from Both Study Arms

Study Arms	LEVEL I Initial 2 Visits with Study staff	LEVEL II Participant bi- weekly phone calls	LEVEL III 1-2/week Cardiac rehab center intervention	LEVEL IV Home- based Activity
PAI	X	X	X	X
HLI	X	X	X	X*

* *Weekly discussion with study staff to match home- based activity intervention*

Table 5: Topics for the HLI intervention

Health Benefits of Recreation, Laughing, and close relationships
Music for the Soul
Mental Health Overview regarding Depression: Causes & Treatments
Calming the Body & Mind
Relationships and Friendships
Financial Q&A
Organization 101 for life!!
Brain Health
The Sun and your Skin during cancer treatment
Staying Healthy and Functional as we Age
Fighting cancer with your fork!
Massage for Tired Muscles
Food Safety: A Review for the Holidays
Coping with Stress
Living Healthy
Vitamin D: Maximizing Strength With Age
XX cancer survivor - His Personal History
Sleep Apnea
Pet Therapy
Are you concerned about your blood pressure?
How to Research Any Health Topic for Yourself
Ways to Relieve Stress
Managing Pain
Adaptive Gardening
Caring for your legs to keep moving
CSI Behind The Scenes
Radiation (the ins and outs)
Keeping your Balance to Prevent Falls
Hands on Class: Planting Basil to Grow at Home

All individuals in the HLI will participate in qualitative assessments using our QPRO program as described in the Resources Section of the document.

5.0 Outcome Measures

5.1 Primary Outcome

5.1.1 The primary outcome will be feasibility. The data gathered will be used to inform the development of a larger future study. Feasibility

in this study will be defined as follows: the proportion of patients who agree to participate in the intervention. Among patients who agree to participate the proportion that are able to complete the intervention and document barriers to participation.

5.1.2 For all patients – both in the active and control groups, we will determine the proportion who are able to have the baseline and follow-up assessments of measures of interest (cardiovascular imaging, exercise measures (peak VO_2 and 6 min walk distance).

5.2 Secondary Outcomes

5.2.1 In the 21 patients, the following outcomes will be assessed at the first visit and then 3 and 6 months after initiating Anth-bC or other potentially cardiotoxic cancer therapies; to assess the ability to ascertain: peak exercise cardiac output, calculated A-V O_2 difference and VO_2, and pre- exercise measures of LV & cognitive function, HRQOL, six-minute walk distance (6minWD) and fatigue

Detailed descriptions of these outcomes are below.

Measurements and quality control

MRI Variables. We will measure LV volumes (including LV stroke volume and heart rate to determine exercise associated cardiac output), EF because a) these values deteriorate shortly after cancer treatment,[19] b) influence exercise capacity,[16,38,39] and c) are used clinically to guide medical therapy to reduce CV events.[16,32,40,41] MRI has been selected as the primary assessment of cardiac and vascular function because of a) its reliability (>98% acquired valuable subjects within the Jackson Heart Study),[42] b) its reproducibility (>98% for repeated measures in pilot data from cancer participants),[22] c) its accuracy (ability to detect informative changes indicative of prognosis regarding both the cardiac and vascular systems), d) its translational capability (existing large NHLBI efforts to assess CV disease from which cross-sectional comparisons with the data set can be made),[43-45] and e) the low variance and inter-observer variability for technologists to acquire reliable data relative to other imaging modalities such as transthoracic echocardiography, which is highly technologist dependent and exhibits high variance.

Our images will be acquired and analyzed according to previously published techniques (for which Dr. Hundley has extensive experience)[32,46,47] using techniques from other NIH funded initiatives. Briefly, the individual will be

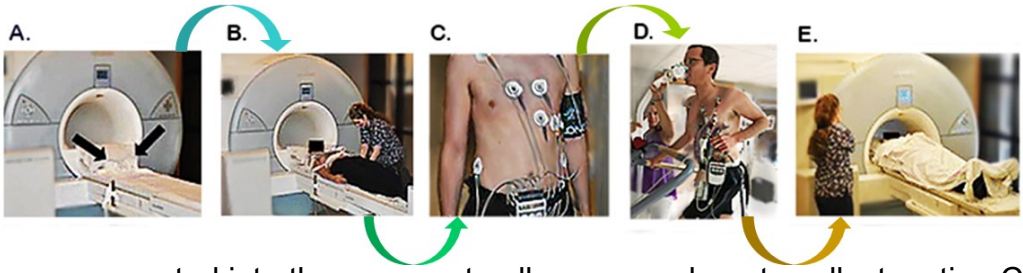


Figure 7: Upright Treadmill Exercise CMR-CPET Stress Test Protocol. (a) CMR scanner with shoulder harnesses (*black arrows*) to aid with correct patient/participant positioning (b) obtaining rest cine imaging; (c) placement of electrode patches and blood pressure cuff for patient monitoring; (d) treadmill exercise stressing with expired gases, and (e) repositioning the patient/participant into the scanner for post-stress cine images.

escorted into the scanner to allow researchers to collect resting CMR images (Figure 7). Upon completion, the participant then will perform a CPET, according to the Bruce or Modified Bruce protocol. When the individual indicated they were at their maximal capacity the test will be terminated and the subject will be immediately escorted quickly back into the scanner to collect immediate post exercise CMR measures. *In our pilot data and in our publications, all post-exercise CMR data are initiated 20 seconds after exercise completes and acquisitions are completed within 50 seconds of leaving the treadmill.* After the post exercise CMR is completed, the individual will be monitored to ensure that HR falls to <100 bpm during which recovery LV wall motion assessments will be made. All images will be acquired using the Siemens 1.5 Tesla Avanto scanner located in the Cardiovascular Imaging Center (Reynolds Tower, Wake Forest Health Sciences, Winston-Salem, North Carolina).

The CMR protocol is performed according to prior techniques[48-50] & includes a series of white blood steady-state free precession cine images acquired in the short-axis plane to cover the entire left ventricle (LV) using a 5 to 10 second real-time, cardiac-gated, free breathing acquisitions with the following parameters: 6-10 slices of 8 mm thickness and 2 mm gap spanning the entire LV, a 128x72 matrix, a 340 x 255 mm field of view, 72 views per segment with view sharing, and echo spacing of 2.1 ms, resulting in a temporal resolution of 46 ms and voxel size of 2.6 x 2.6 x 8 mm. From these images, LV end-diastolic (LVEDV) and end-systolic (LVESV) volumes will be determined for calculation of the LV ejection fraction and stroke volume. Identical sets of volumetric images were acquired pre-exercise and post-exercise (<30 sec from maximal exercise stress test).

All images will be processed offline by an image analyst blinded to study group using Medis software (Leiden, Netherlands). For each slice of the cine stack obtained, pre- and post-exercise, the endocardial border of the myocardium will be contoured to determine the area of the LV blood pool at both end-systole

and end-diastole. Using Simpson's rule, the areas will then be summed together and multiplied by the slice volume plus slice gap to determine LVEDV and LVESV.[51] Ventricular volumes and cardiac output will be indexed to the subject's body surface area and expressed as mL/m^2 or $L/min/m^2$. Brachial artery blood pressure (BP) and heart rate (HR) will be recorded during volumetric image acquisition. Cardiac output will be calculated from the LV stroke volume multiplied by the HR during CMR acquisition. For quality control, A complete double reading on 15% of the CMR cases will be performed for quality control purposes. The reader variability results will be reported at 3-month intervals or if a change in personnel could affect image analysis and interpretation. Any scans with irregularities will be subjected to expert review. Like other studies conducted over the past 7 years, these images will also be used for data interpretation and for education purposes.

Maximal (peak VO_2) and (6-minute walk) exercise capacity outcomes. In this study, measures of both maximal (peak $V0_2$)[22,33,34,52-56] and sub-maximal (6-minute walk) exercise capacity will be obtained. Peak $V0_2$ is selected as the primary outcome measure because it is the most reproducible measures of exercise capacity and integrates the physiologic response to exercise. [22,33,34,52-56]. It provides an objective threshold of disability and a metric that forecasts adverse cardiac prognosis as well as a parameter that can be utilized to modify medical regimens to reduce the likelihood of morbidity and mortality. [22,33,34,52-56] It is feasible in large multi-center studies, it is reproducible and standardized. It is semi-automated and is relatively inexpensive to perform. Our team of investigators has extensive experience with using peak $V0_2$ as a primary measure. [22,33,34,53,54] Amongst 3 studies for which our team serves as the core lab, the reproducibility and variance of the measure in elderly individuals (>65 years old) or those with evidence of congestive HF ranges from 7% to 12% in repeated measures. [22,33,34,52-56] We will also perform a 6-minute walk, widely used in trials of physical function interventions, measurement that is relatively easy to administer and quite feasible and provides a very accurate assessment of sub-maximal exercise capacity. Similar to peak $V0_2$, the 6-minute walk is an independent predictor of CV mortality. Its acquisition will allow cross comparisons of data from this cohort with other large NHLBI sponsored multi-center initiatives. Our investigative team has utilized the 6-minute walk as an outcome measure in studies of exercise interventions in individuals treated for cancer.[57,58]

The 6-minute walk will be administered by trained study personnel using a long, enclosed corridor with a cone placed at each end of the course. Participants will be allowed to use any mobility aids they traditionally use. Participants will be instructed to walk from end to end at their own pace while attempting to cover as much ground as possible in the six minutes.

Cardiopulmonary Exercise Test as part of the MRI acquisition

After obtaining resting CMR images, the participant will perform a CPET on the treadmill following the Bruce or Modified Bruce protocol, based on current fitness level (Figure 7). Speed and grade of the treadmill will be increased gradually every three minutes until the participant reaches volitional fatigue. Throughout the CPET, ECG, rate of perceived exertion (RPE) and BP will be monitored regularly, and expired air will be collected continuously through a one-way breathing mask to determine VO_2 peak and other cardiopulmonary measures.

The metabolic system used to collect the expired gases will be calibrated, according to the manufactures specifications, before each test. During the CPET, a 12-lead ECG will be continuously monitored and printed at the end of each 3-minute stage. Any arrhythmias or ST-segment changes that occurred will be documented. Blood pressure and RPE will be taken during the last minute of each stage and recorded. Oxygen uptake and respiratory equivalence ratio (RER) will be monitored continuously throughout exercise. The goal for each subject will be to exceed an RER of 1.05 indicating maximal effort. Throughout the CPET, the staff will maintain constant communication with the participant to determine when the participant is at their final 30 seconds of exercise. At this point, the staff will complete a peak exercise 12-lead ECG, disconnect the electrodes, and transfer the participant to the CMR scanner. The test will be discontinued if the participant has complaints of angina or ST-segment depression >1.5 mV, or if the staff decides to terminate the test in accordance with established test termination criteria.[53-55]

Following the CPET a report is generated including a time-down report (30 second averaged) of VO_2 (ml/kg/min), VO_2 (L/min), VCO_2, METS, RER, VE, RR, FEO_2, $FECO_2$ and a plot for ventilatory threshold (VAT) determination. Heart rate will be determined from the ECG tracings.

Fatigue and health-related quality of life questionnaires. The Functional Assessment of Cancer Therapy–Fatigue scale (FACT-fatigue) will be used to assess fatigue.[59] The FACT-fatigue scale is 13-item scale that has been widely used in many studies to assess cancer related fatigue. The 42-item Functional Assessment of Cancer Treatment-Lymphoma (FACT-Lym) and the 37-item FACT-B questionnaires will be used to assess disease-specific HRQOL. The FACT-Lym and FACT-B measures are composed of the FACT-General which assesses four primary HRQOL domains: physical well-being (PWB), social well-being (SWB), and emotional well-being (EWB); and an additional sub-scale that measures patient concerns related to lymphoma or breast cancer (e.g., pain, fever, swelling, fatigue, and loss of appetite). The MOS 36-item Short Form Health Survey (SF-36) will also be used as a general measure of health status. The SF-36 is perhaps the most widely used measure of health status and includes domains of vitality and physical function. A 6-item measure

of self-efficacy for exercise will be used to assess confidence in walking at a moderately fast pace for increments of 10 to 60 minutes.

Cognitive function. Based on studies of chemotherapy and cognition, cardio-function and cognition and statin therapy and cognition, we propose a battery of validated neurocognitive measures (Hopkins Verbal Learning Test-Revised, Digit Span-Backward, Controlled Oral Word Association and Trail Making Test). These tests will evaluate verbal memory, attention/concentration, working memory, language, psychomotor speed, processing speed, and executive functions, according to standardized procedures utilized currently in multiple studies by Stephen Rapp, PhD, including one with Dr. Hundley (RO1HL118740). Additionally, key patient reported outcomes (cognitive symptoms, fatigue, mood, pain, social and physical functioning and sleep) will be assessed. Following standardized procedures used in other studies by this research team, staff will be trained in the administration of all questionnaires. Each questionnaire will be self-administered and then reviewed by a study interviewer for completeness before being uploaded into the Oncore database. A study team member will be trained to administer and scoring of all cognitive tests following standardized procedures used in other studies of cognition and cancer conducted by members of this research team.

Participants will be given the option to complete these questionnaires electronically at their convenience prior to their research visits using a link to the secure web application REDCap.

Alternatively, if in person testing is either restricted or participants prefer, we would like to be able to carry out a limited battery of physical tests that can be safely completed in the home. In addition to the self-reported data that will be collected via REDCap (as per protocol) we are planning to send a sanitized container with the following contents (see Appendix P):

1. Detailed instruction packet for completing the test battery, including:
    a. Balance test
    b. Grip strength test
    c. 6-minute walk test
    d. Chair stand test
2. A smartphone that is not connected to the internet or cellular service, but which contains software for administering a balance assessment.
3. A grip strength dynamometer for measuring upper body strength
4. The previously approved Actigraph device for assessing physical activity patterns over a 7-10-day period.

5. A 15-meter length of rope to mark out the course for a 6-minute walk test and 4-meter walk test.
6. A return shipping label to use to return the exercise kit to the research team after completion of home based testing

Once participants have received the box containing the equipment for completing a short battery of tests designed to measure some of the outcomes in the original procedures, we will identify a time for them to complete the tests. During the initial exercise testing and program initiation (home or supervised) we will teach participants how to use rating of perceived exertion (RPE) and how it relates to intensity (heart rate response, dyspnea). Given the focus on home-based programming, we also emphasize the importance of monitoring their daily symptoms and response to previous exercise sessions. Any concerns can be communicated to the intervention staff prior to starting exercise. Additionally, the study team has access to and will regularly monitor the heart rate and sleep data of participants in order to track their status continuously. To begin the testing session, we will contact the patients via video conferencing software and go over the instructions for completing the tests. For the balance test, the chair stand test and the walking tests, the study participant, the spouse/partner, and the study team will confirm that all tests can be completed in a safe area that is free of obstructions and that the ground is even/level. This will be done to minimize the possibility of injury. The first goal is to familiarize the participants with the smartphone, so they can operate the app for testing balance, and access and use the video camera for recording the tests. At this time, we will ask the participants spouse/partner to also familiarize themselves with the toolkit as they will be asked to take a series of short videos as the participant completes the tests. For security purposes this device is not connected to the internet so there is a reduced chance the material will be compromised. Instead, videos taken will be downloaded from the device once it is received by the PI.

We will then proceed to guide the participant through the instructions, clarifying any queries they may have. We will require the participant to identify a safe, flat space in their home where they can complete the balance test. As the balance test completes the participant is given immediate feedback based on their results as to their fall risk. The study assessors will verify the participant can safely perform the rest of the tests. This first test (a validated tool to assess fall risk in elderly MS patients) will help us to determine whether our participants are safe to complete tests in their home.

We will then ask the participant to identify a standard dining-room type chair (approx. 17-19" seat height), from which they can perform the chair stand tests. Via video conference the study assessors will verify the participant can safely stand from seated. We will then ask the participant to set up the 15 meters course in a passage way in their home (if available) or on a flat surface on or near their property (e.g. drive way). Once the set-up is complete we will let the participant and spouse/partner complete the tests. We will be available to consult during this time, but to minimize distraction will not interfere.

The chair stands (time taken to stand 5 times from seated and amount of chair stands completed in 30 seconds) will be filmed in order to determine accurately the parameters of the test.

Next the 4m walk will be performed by walking the first 4 meters of the 15m course at a usual pace. This test will be repeated (and filmed 3 times).

The participant will now be encouraged to take a short break.
Finally, the 6-minute walk test will be completed (and filmed) with the participant walking as many laps of the 15- meter course as they can in 6 minutes. Using the video, we will use pre-marked guides to determine accurately the number of laps and distance covered during the test. During this test the participant will also wear a pulse oximeter to track pulse and oxygen saturation.

While the tests are encouraged, safety is of paramount importance and should the participant feel they wish to stop the test at any time they may do so.

There is a slight burden of using the technology to complete these tests, though all our participants are required to have a smart phone in order to sync their tracking devices regularly and we do not expect the level of expertise needed here is more than already required. Included in the instructions are links to short video clips demonstrating the procedures for clarity.

The participants may contact us at any time throughout the procedures.

Once testing is complete will ask the participants to send back the locked container using a pre-addressed shipping label. This can be picked up by the shipper if the participant does not feel safe. Finally, upon receipt of the materials all equipment will be sanitized with medical grade cleaners.

Blood testing. With each study visit, serum hemoglobin/hematocrit will be obtained to assess for the presence of anemia, and serum chemistries will be obtained to assess serum creatinine to identify renal dysfunction. Additionally, at baseline,3 & 6 months, blood will be obtained for long-term storage of serum and plasma for future studies. Planned studies include assessments of markers of inflammation and CV injury.

Database management
All data management activities will be accomplished through a secure web-based Oncore application managed and administered by the CCCWFUHS (see

Resources – Dr. D'Agostino, Jr.). This system allows flexibility in processing data management tasks, including the ability to register participants and verify eligibility criteria before randomization, provide the randomization assignment, and allow real-time monitoring and reporting of accrual, retention, and intervention adherence.

6.0 Analytic Plan

We will enroll 21 patients with 14 in the PAI and 7 in HLI. The goal of this study is to determine feasibility and preliminary efficacy data. We now describe these measurements.

Feasibility:
We will determine the proportion of patients who agree to participate in the intervention. Next, among patients who agree to participate we will determine what proportion are able to complete the intervention and document barriers to participation. For all patients – both in the active and control groups, we will determine the proportion who are able to have the baseline and follow-up assessments of measures of interest (cardiovascular imaging, exercise measures (peak VO_2 and 6 min walk distance).

In addition, for the patients receiving the active intervention we will assess the change in outcomes of interest to determine preliminary efficacy estimates. The control patients will also provide some preliminary efficacy assessments.

With 21 patients we can estimate a 95% exact confidence interval (using the Clopper-Pearson method) for the proportion of patients who have measurements taken with a width of 0.578 (i.e., from 0.211 to 0.789 if the observed proportion is 0.5 – most conservative assumption).

For estimating the outcomes of interest, a 95% confidence interval will extend +/- 0.769 standard deviation if there are 8 patients in the active group, +/- 0.635 if the sample size is 12 and +/- 0.554 SDs if the sample size is 15.

A number of assessments will be made on the patients enrolled. These include measures of peak exercise cardiac output, calculated A-V O_2 difference and VO_2, and pre- exercise measures of LV & cognitive function, HRQOL, six-minute walk distance (6minWD) and fatigue. For each of these measures we will calculate descriptive statistics in order to get some preliminary data concerning the mean values and variability of these measures. We will also obtain mean and variability values of the MRI cardiac function and HRQOL data from the 47 lymphoma patients in the parent study that did not undergo the two arms of the intervention as noted in this pilot addendum. This information will be helpful for designing a future clinical trial.

Accrual:
It is anticipated that at least 1 patient a month will be accrued so that the total time of enrollment should be no more than 1.5 year.

Study Length:
Two years

7.0 Data Management

Informed consent document	WISER/OnCore/PIC/Hundley Research Server/Research Chart
Protocol registration form	ORIS/Hundley Research Server/Research Chart
Quality of Life Questionnaires	REDCap
MRI and CPET data	Hundley Research Server
Self-Efficacy for Walking	REDCap
FACT-Lym	REDCap
Neuro-Cognitive Measures	REDCap

8.0 Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed (state the anticipated time the data will be destroyed, e.g. three years after closure of the study, and the method of destruction), consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

9.0 Data Safety and Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

10.0 Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

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Appendix A – Protocol Registration Form

DEMOGRAPHICS

Patient: Last Name: _____ First Name: _____

MRN: ___ ___ ___ ___ ___ ___ ___ ___ DOB (mm/dd/yy): ___ ___ / ___ ___ / ___ ___

ZIPCODE: ___ ___ ___ ___ ___

SEX: ☐ Male ☐ Female Ethnicity (choose one): ☐ Hispanic ☐Non-Hispanic

Race (choose all that apply): ☐ WHITE ☐BLACK ☐ ASIAN ☐ PACIFIC ISLANDER ☐ NATIVE AMERICAN

Height: ___ ___.___ inches Weight: ___ ___ ___.___lbs.(actual)

Surface Area: ___ ___.___m^2

Primary Diagnosis: _____

Date of Diagnosis: ___ ___ /___ ___/___ ___

Performance Status: ___ ___ ___ ☐ ECOG ☐ Karnofsky

PROTOCOL INFORMATION

Date of Registration: ___ ___ / ___ ___ / ___ ___

MD Name (last) : _____

Date protocol treatment started: ___ ___ / ___ ___ / ___ ___

Informed written consent: ☐ YES ☐ NO
(consent must be signed prior to registration)

Date Consent Signed: ___ ___ / ___ ___ / ___ ___

PID # (to be assigned by ORIS): ___ ___ ___ ___ ___ ___ ___ ___

Protocol Registrar can be contact by calling 336-713-6767 between 8:30 AM and 4:00 PM, Monday – Friday.

Completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at 336-7136772 or registra@wakehealth.edu.

Appendix B – Subject Eligibility Checklist

IRB Protocol No.	**CCCWFU Protocol No.**
Study Title: Improving Exercise Capacity with a Tailored Physical Activity Intervention in Lymphoma and Breast Cancer Patients Undergoing Treatment – An addendum to NIH R01CA167821 "Early Imaging Detection of CV Injury after Cancer"	
Principal Investigator: Dr. W. Gregory Hundley	

Inclusion Criteria (as outlined in study protocol)	**Criteria is met**	**Criteria is NOT met**	**Source Used to Confirm * (Please document dates and lab results)**
Male or Female	☐	☐	WakeOne
Aged 18-85 years	☐	☐	WakeOne
Stage I-IV Lymphoma (Hodgkin or non-Hodgkin) or stage I-IV breast cancer	☐	☐	WakeOne
Expect to receive an anthracycline based chemotherapeutic regimen or other potentially cardiotoxic cancer therapies	☐	☐	WakeOne
Capacity to walk at least 2 city blocks on a flat surface	☐	☐	WakeOne
Expected survival beyond 6 months	☐	☐	WakeOne
Exclusion Criteria (as outlined in study protocol)	**Criteria NOT present**	**Criteria is present**	**Source Used to Confirm * (Please document dates and lab results)**
Contraindication for MRI	☐	☐	WakeOne
Contraindications for exercise training or testing	☐	☐	WakeOne
Inability to exercise on treadmill or stationary cycle	☐	☐	WakeOne
Claustrophobia	☐	☐	WakeOne
Unstable angina	☐	☐	WakeOne
Pregnant	☐	☐	WakeOne
Inability to provide informed consent	☐	☐	WakeOne

This subject is ☐ eligible / ☐ ineligible for participation in this study.
ORIS Assigned PID: ___ ___ ___ ___ ___ ___ ___ ___

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Signature of research professional confirming eligibility:_____
Date: ___ ___ / ___ ___ / ___ ___
Signature of Principal Investigator confirming eligibility:_____
Date: ___ ___ / ___ ___ / ___ ___
* Examples of source documents include clinic note, pathology report, laboratory results, etc. When listing the source, specifically state which document in the medical record was used to assess eligibility. Also include the date on the document. Example: “Pathology report, 01/01/14” or “Clinic note, 01/01/14”

APPENDIX C: MRI-CPET Protocol and Encounter Form

CPET Stress Cardiovascular MRI Procedure Guidelines

Non-Contrast Exam

Abbreviations:

BH: Breath hold

CMRI: Cardiovascular magnetic resonance imaging

CPET: Cardio-Pulmonary Exercise Test

ECG: Electrocardiography

GRE: Gradient recalled echo

LAO: Left anterior oblique

IR: Inversion recovery

NBH: Non breath hold

PSIR: Phase sensitive inversion recovery

SSFP: Steady state free precession

TSE: Turbo spin echo

VLA: Ventricular long axis

Study image and completion form transfer note to MRI Technologist:

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Immediately upon completion of the study, technologists should submit images to the MRI Reading Center at Wake Forest via the CTP node on the scanner. From that PC, participants' images will be automatically encrypted and transmitted to the MRI core lab for further analysis. The encryption schema used is https, the standard for secure website transactions, used by banks and e-commerce worldwide. Additionally, technologists should burn a CD to give to the Study Coordinator for secured storage. Data should also be stored on the local PACS system. MRI technologists should fill-out the MRI completion form and give to the Study Coordinator for transmission to the MRI Reading Center.

***Please place the following information in the Patient Registration Window <u>before the exam begins</u>:**

- Place with the study ID number (PID) in the MRN Field.
- Place the acrostic in the Patient Name Field.
- These should be given to you by the Study Coordinator.

<u>General Overview</u>

This is a cardiovascular MR exam that acquires baseline imaging (pre-exercise stress test) with a peak CPET test performed in the MRI facility. Patients are escorted from the CPET test to the MRI table with auto-scanning enabled for MRI measures of post-exercise stress test beginning <20 seconds after peak exercise. Recovery LV cines are acquired after the heart rate has normalized to ensure no wall motion abnormalities were induced with stress testing.

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MRI Protocol – List of Sequences

BASELINE (Pre-Exercise)
Localizers
3 PLANE LOC BH
2CH LOC FB
SAX LOC FB
4CH LOC FB
LAO SCOUT FB
ABD LOC
Body Composition
T1 AX ABDOMEN FAT (L2-L4)
Axial Phase Contrast
BASELINE AX Aorta Arch 2D PHASE CONTRAST
BASELINE AX Aorta Bifur 2D PHASE CONTRAST
Fast Cines
BASELINE_SAX_CINE_RT (GATED) (Slices to cover the entire LV)
***POST CPET EXERCISE ***
Fast Cines
EXERCISE_SAX_CINE_RT (GATED) (Slices to cover the entire LV)
Axial Phase Contrast
exercise AX Aorta Arch 2D PHASE CONTRAST
exercise AX Aorta Bifur 2D PHASE CONTRAST
RECOVERY
Fast Cines
RECOVERY_SAX_RT (GATED) (Slices to cover the entire LV)

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Participant Preparation

1. Complete the MRI safety screening form required at your institution. All participants must be screened for MRI safety/compatibility.

2. Request participant use the rest room before the study.

3. Breath-holding is done at resting lung volume for the entire protocol.

    a. Test breath-holding. **The participant is required to be able to hold their breath for 15 seconds at resting lung volume twice in order to participate in the protocol.**

    b. Inform and train participant on breath-holding, example: "Breath in … Let your air out until you are comfortable, and stop breathing."

4. Make sure that the connectors for cardiac coils and ECG are in place.

5. Remember to place nonferromagnetic brachial blood pressure cuff on participant's arm prior to beginning the MRI scans. This is needed to record blood pressures during certain sequences as marked on the encounter form.

    Thoroughly clean the ECG contact area with alcohol swabs. With participant supine on the table, attach ECG electrodes to his/her chest according to your MRI manufacturer suggestions.

Image Acquisition

MRI encounter form
Complete the MRI encounter form during each scan and complete the notes regarding sedation/completion of study. ***The encounter form is included in the last page of this appendix.***

It is recommended that this form is completed in real-time during the study to ensure no sequences are skipped and the blood pressures and heart rates are recorded as necessary.

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Series Name: **_3_PLANE_SCOUT**

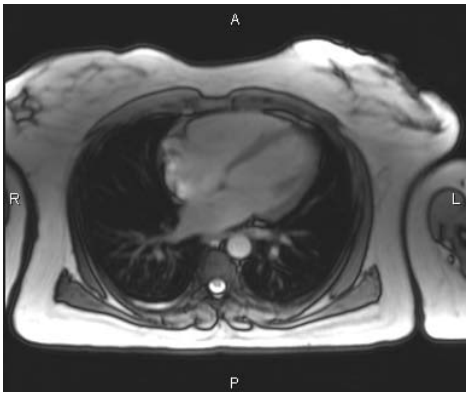
Series Description: 3 Plane Localizer

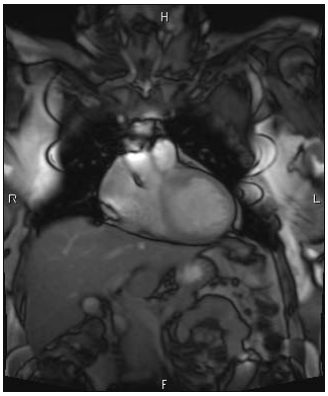
Notes: Steady-state free precession scout images

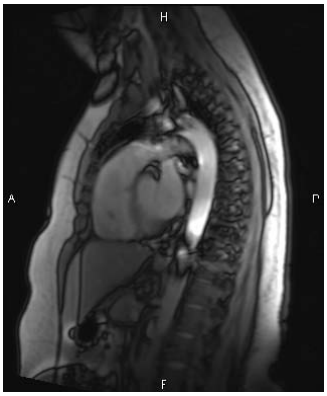
Series Prescription Details

	Series Rx Notes
Prescribe series from:	Localize the heart at the isocenter.
Orientation:	three orthogonal planes (axial, coronal and sagittal)
Number of Slices	At least three slices per plane (at least 9 image
Breath-holding:	Yes, resting lung volume

Sample Images







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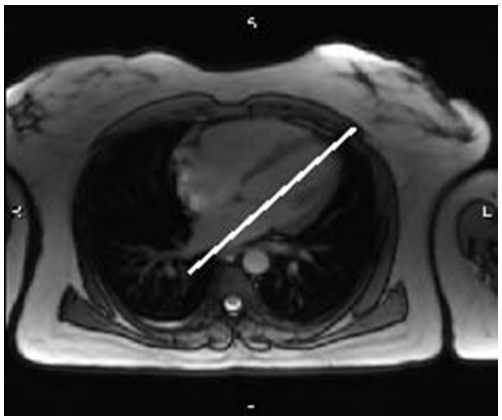
Series Name: **2CH LOC FB**

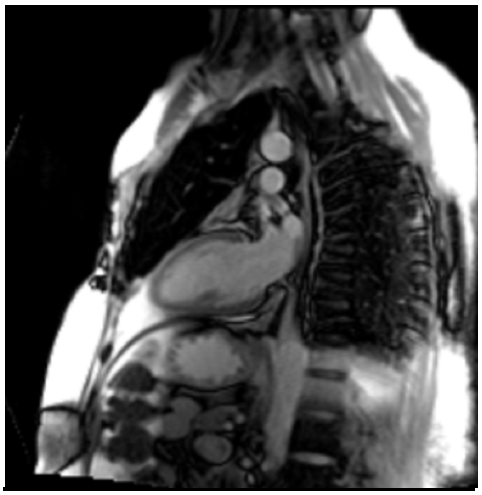
Series Description: White-blood 2 Chamber localizer; Pseudovertical long-axis localizer

Notes: This is a bright-blood steady-state free precession, one slice (non-cine) image.

Series Prescription Details

	Series Rx Notes	***Sample Series Rx***
Prescribe series from:	Plan this on the axial scout view (_3_PLANE_SCOUT) with the largest volume of heart, from the base (middle of the mitral valve) to apex of the LV, on the axial scouts.	
Orientation:	Oblique	
Number of Slices	1	
Breath-holding:	No	

Sample Image



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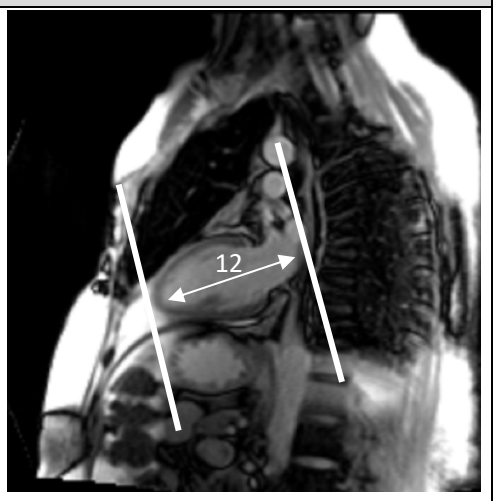
Series Name: **SAX LOC FB**

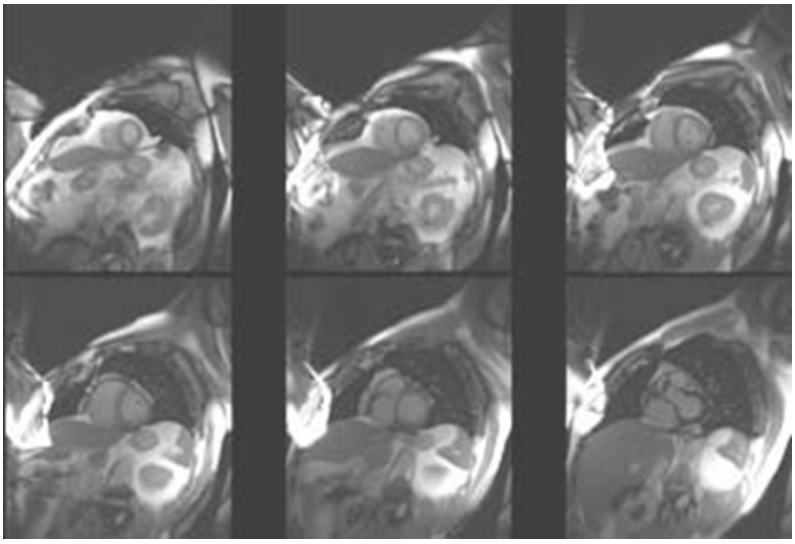
Series Description: White-blood short-axis localizers

Notes: These are a bright-blood steady-state free precession, non-cine images covering the whole heart from great arteries to the apex. Data acquisition at the **diastolic phase**.

Series Prescription Details

	Series Rx Notes	*Sample Series Rx*
Prescribe series from:	2CH_LOC cross-referenced with 4CH_LOC	
Orientation:	Oblique	
Number of Slices	12	
Breath-holding:	No	

Sample Images

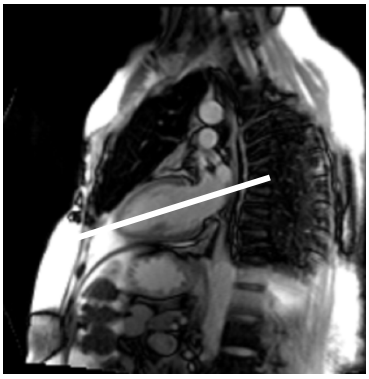


Series Name: **4CH LOC FB**

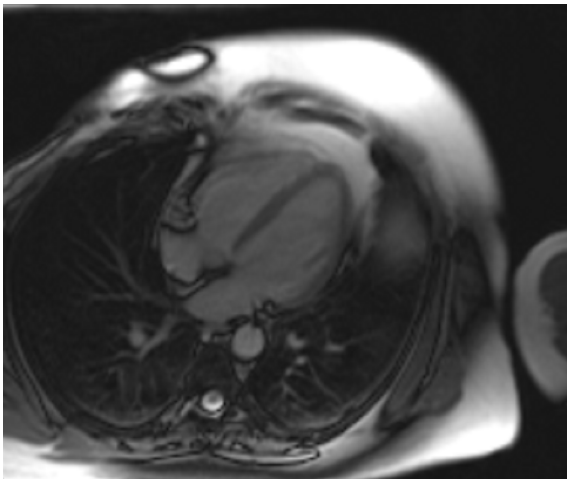
Series Description: White-blood 4 Chamber localizer; horizontal long-axis localizer

Notes: This is a bright-blood steady-state free precession, one slice (non-cine) image.

Series Prescription Details

	Series Rx Notes	***Sample Series Rx***
Prescribe series from:	Plan this on the axial scout view (_3_PLANE_SCOUT) with the largest volume of heart, from the base (middle of the mitral valve) to apex of the LV, on the axial scouts. Cross-reference with 2CH Scout	
Orientation:	Oblique	
Number of Slices	1	
Breath-holding:	No	

Sample Image



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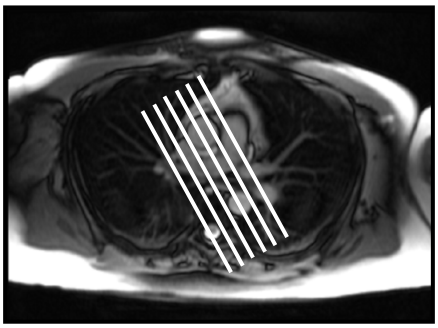
Series Name: **LAO_SCOUT_FB**

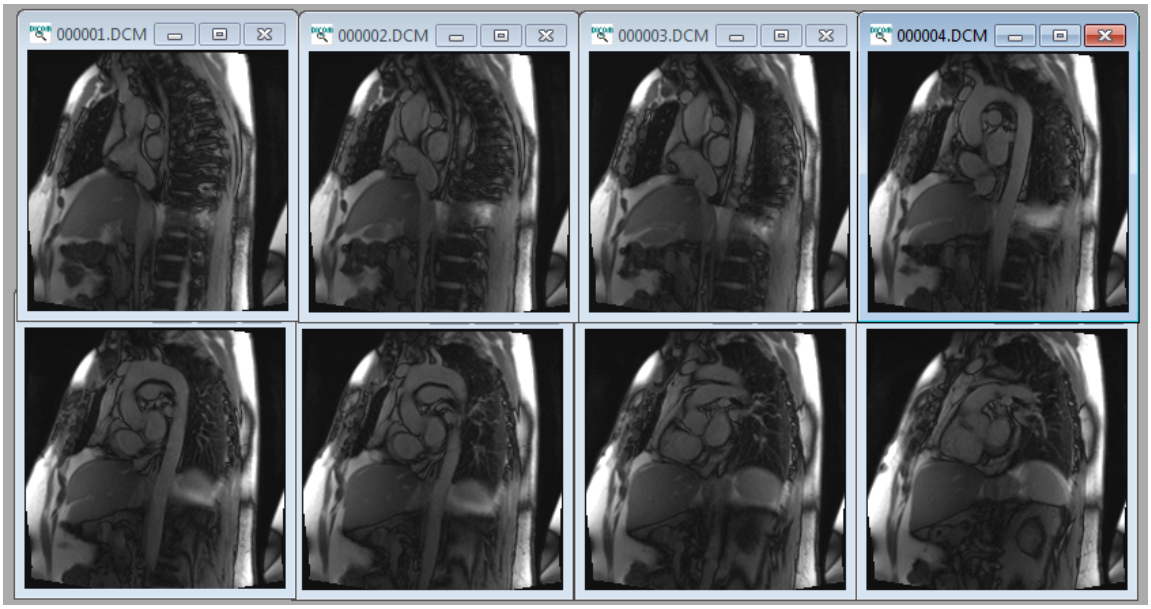
Series Description: Aorta candy cane localizer, free-breathing

Notes: This localizer is a left anterior oblique in the candy cane plane of the thoracic aorta. This multi-slice localizer will be used for planning the aorta phase contrast images.

Series Prescription Details

	Series Rx Notes	***Sample Series Rx***
Prescribe series from:	_3_PLANE_SCOUT axial image with ascending and descending aorta	
Orientation:	Left anterior oblique; plane center slice through ascending and descending aorta	
Number of Slices	6-8	
Breath-holding:	No	

Sample Image(s)



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Series Name: **ABD_LOC**

Series Description: Abdominal Localizer

Notes: Perform multi-plane abdominal localizer (coronal and sagittal); Siemens sequence name = tfi2d1_84. A coronal plane that appreciates the aorta bifurcation will be used in planning future series. A sagittal plan that appreciates L2-L4 will be used in planning future series.

Series Prescription Details

	Series Rx Notes
Prescribe series from:	_3_PLANE_SCOUT
Orientation:	Coronal and Sagittal
Number of Slices	3-5 sagittal slices; 8-10 coronal slices
Breath-holding:	Yes

Image Parameters

Image Parameter	**Value**
Slice Thickness	5mm
Slice Gap	5 mm
TR	260
TE	1.08
Number of Phase Encodings	143
Percent Sampling	75 %
Percent Phase FOV	100%
Pixel Bandwidth	1132
Matrix	192 x 144
Flip Angle	65 degrees

Sample Images:

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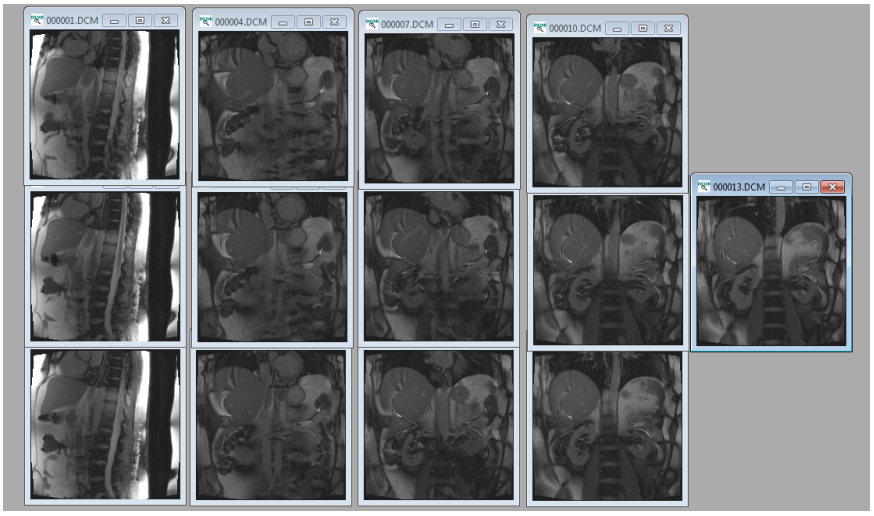

000001.DCM
000004.DCM
000007.DCM
000010.DCM
000013.DCM

Series Name: **T1_AX_ABDOMEN_FAT**

Series Description: T1 weighted turbo spin-echo sequence acquired with 3 evenly spaced axial slices with 1st and 3rd centered at L2 and L4.

Notes: To assess visceral fat, a series of images will be acquired to assess visceral fat volume. Open up FOV to encompass all of the abdomen.

Series Prescription Details

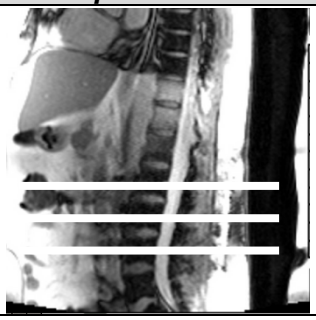
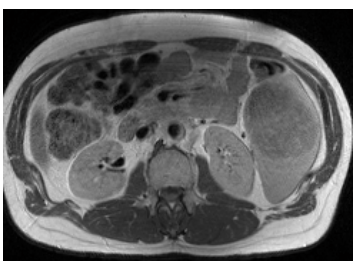
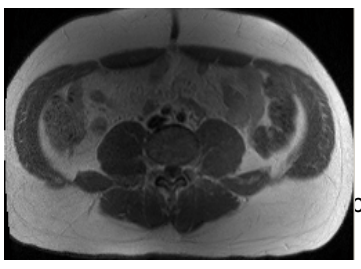
	Series Rx Notes	***Sample Series Rx***
Prescribe series from:	Sagittal plane on **ABD_LOC**	
Orientation:	Axial	
Number of Slices	3 - evenly spaced axial slices with 1st and 3rd centered at L2 and L4.	
Breath-holding:	Yes	

Image Parameters

Image Parameter	**Value**
FOV	Open to encompass all of the abdomen
Slice thickness (mm)	5mm
Slice gap (mm)	Variable – change distance factor as necessary
TR	800 ms
TE	36 ms
Flip angle (degrees)	180
Matrix	256 * 256
Acceleration factor	2
Bandwidth	305 Hz/Px
Turbo factor	11
Echo trains per slice	13
Gating	ECG triggering

Sample Image(s)





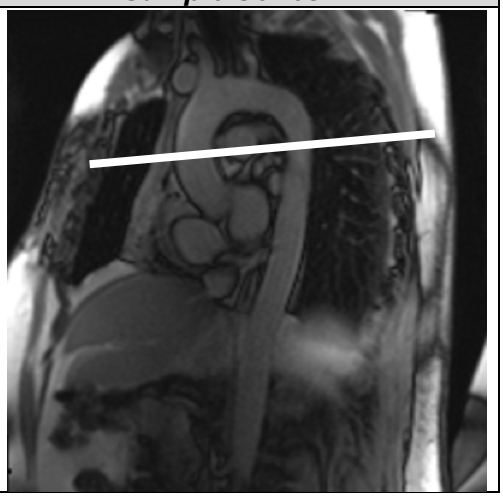
Series Name: **AX Aorta Arch 2D PHASE CONTRAST**

AX Aorta Bifur 2D PHASE CONTRAST

Series Description: ***Free breathing***, 2D Phase Contrast images of the aorta in 2 planes: the ascending-descending aorta at the level of the arch and at the level of 2 cm above the bifurcation.

Notes: Phase-contrast gradient-echo images will be acquired in axial planes for determination of aortic stiffness. Measures of distensibility and pulse wave velocity will be performed on the phase-contrast images. ***Roughly 30 phases should be acquired.*** This is performed at baseline and again post-exercise (following LV Cine stack).

Series Prescription Details - AX Aorta Arch 2D PHASE CONTRAST

	Series Rx Notes	***Sample Series Rx***
Prescribe series from:	Prescribe off of the **LAO_SCOUT_FB** images and select the slice with the best view of the aorta candy cane. Prescribe an oblique plane running perpendicular through the ascending and descending aorta as shown on the right.	
Orientation:	Axial; oblique	
Number of Slices	1	
Breath-holding:	No	

Series Prescription Details - AX Aorta Bifur 2D PHASE CONTRAST

	Series Rx Notes	***Sample Series Rx***
Prescribe series from:	Prescribe off of the **ABD_LOC** images and select the slice with the best view of the aortIc bifurcation. Prescribe a plane running perpendicular through the aorta at the level 2 cm	

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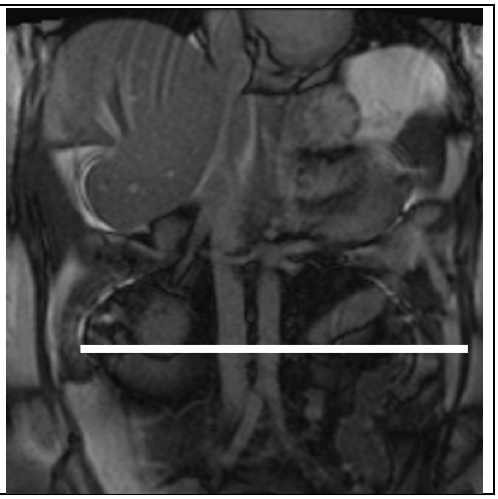
	superior to the bifurcation as shown on the right.	
Orientation:	Axial	
Number of Slices	1	
Breath-holding:	No	

Ph Con Image Parameters

Image Parameter	Siemens	GE	Philips
Coil	Body Matrix	Gore Full	Cardiac
Plane	Oblique	Oblique	Axial
Field of View	360	360	360
Repetition Time (TR; ms)	12.0	12.0	12.0
Echo Time (TE; ms)	3.14	Min	2.8
Flip Angle (degrees)	15	30	12
Averages	1		1
BW	389	31.25	477.8
NEX		1.00	1
Gated	Cardiac	Cardiac (auto # phases, TrigWin 10)	Retrospective
Sequence type	Phase-contrast GRE	Phase-contrast GRE	2D FFE
Axial Velocity encoding direction	Through-plane	Through-plane	Through-plane
Parasagital Velocity encoding direction	Head-Foot or Superior-Inferior	Head-Foot or Superior-Inferior	Head-Foot or Superior-Inferior
Slice Thickness	6 mm	6	6
Distance Factor	20% (1.2m)		
Segments	6		
Matrix	128 x 128	128 x 128	128x128
Phase FOV	100%	1.00	100%

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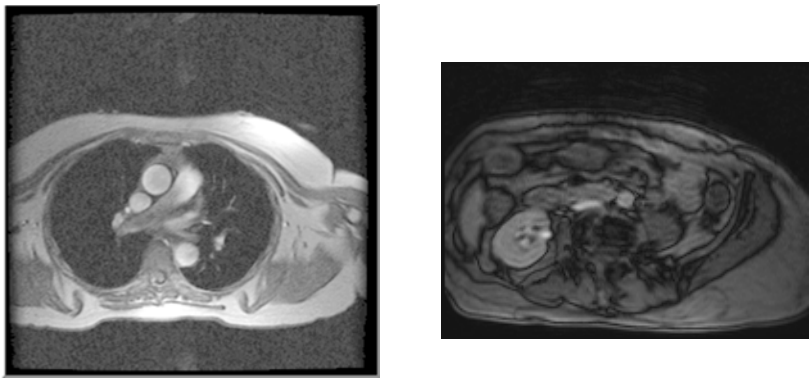
Phase encode direction	A-P	A-P	A-P
Phases	20	20	20
PSD		Vasc PC (Fast 2D Phase Contrast	
Options		Gat, Seq, Fast	
Flow Comp		Off	Yes
Gap		0	0
VPS		2 (adjust per patient's heart rate for ~30 phases)	
Frequency		S/I	
Grad Mode		Whole	Default
VENC	Start with 200, may increase if aliasing	200	200
Vascular Screen		Venc: 200, Collapse: off, Recon: Ph Diff, Flow Analysis: on, Flow Dir: Slice, Additional Images: Obl S/I	
User CV Screen		All set to zero	Turn off Complex Difference

Ph Con Sample Image(s)

Resulting magnitude (top row) and velocity maps (bottom row) images



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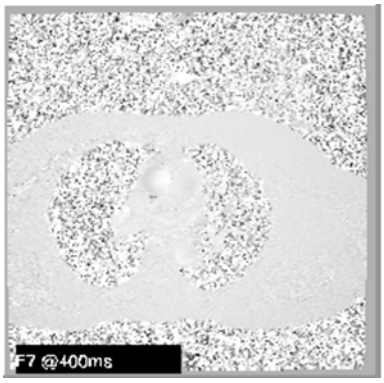

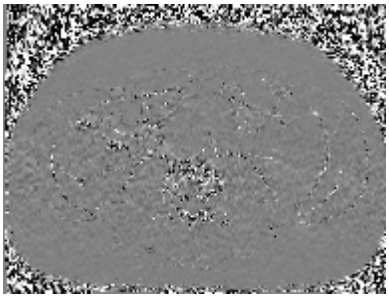

Series Name: **SAX_CINE_RT (GATED) – Performed at baseline, post exercise, and recovery**

Series Description: Fast short axis cine stack encompassing LV with ECG gating

Notes: **** Record BP and HR during acquisition ****

This is real-time, cardiac triggered, free-breathing cine stack acquired in the SAX plane with minimum of 20 phases, covering the whole heart from the atria to apex. Temporal resolution should be <40 ms. Cine short axis images should be obtained at baseline, immediately following exercise, and when heart rate recovers to <100 bpm.

Parallel imaging (e.g. ASSET, SENSE, or GRAPPA) with an acceleration factor of 2 to reduce acquisition time (optional). Flip angle should be set at the largest possible (usually 45-70º). The last apical slice should locate within the myocardium such that the slices could cover left atrium as much as possible.

Series Prescription Details

	Series Rx Notes	***Sample Series Rx***
Prescribe series from:	4 Ch Loc and SAX Loc.	
Orientation:	SAX Oblique	

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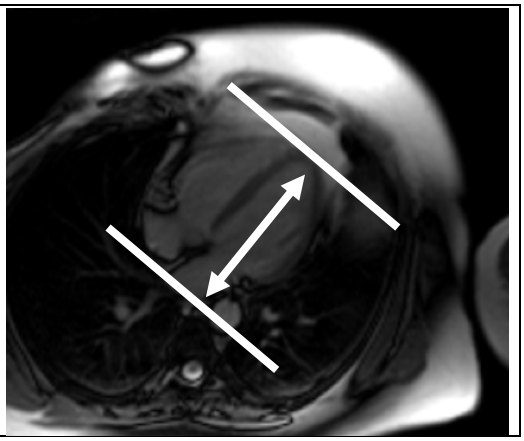
Number of Slices	As needed to cover apex to atria with slice thickness = 8 mm and slice gap = 2mm.	
Breath-holding:	No	

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CPET Stress MRI Encounter Form

Date of scan: _____ Tech: _____ Time: _____ Visit #: _____ Height:_____inches Weight:_____lb	Participant Name/MRN and Study ID / Label Here	
BASELINE	**Series#**	**Record INVIVO BP/HR(MRITech)**	**INVIVO STRIP HR (Nurse)**
Localizers		BP:____/____ HR: _____	HR: _____
3 PLANE LOC BH			
2CH LOC FB			
SAX LOC FB			
4CH LOC FB			
LAO SCOUT FB			
ABD LOC			
Body Composition			
T1 AX ABDOMEN FAT (L2-L4)			
Axial Phase Contrast			
BASELINE AX Aorta Arch 2D PHASE CONTRAST		BP:____/____ HR: _____	
BASELINE AX Aorta Bifur 2D PHASE CONTRAST			
Fast Cines			
BASELINE_SAX_CINE_RT (GATED) (Slices to cover the entire LV)		BP:____/____ HR: _____	*HR: _____
***POST CPET EXERCISE ***			
Fast Cines (Run INVIVO STRIP when Participant is positioned on MRI table)			*HR: _____
EXERCISE_SAX_CINE_RT (GATED) (Slices to cover the entire LV)		BP:____/____ HR: _____	*HR: _____
Axial Phase Contrast			
Exercise AX Aorta Arch 2D PHASE CONTRAST		BP:____/____ HR: _____	
Exercise AX Aorta Bifur 2D PHASE CONTRAST			
RECOVERY			
Fast Cines			
RECOVERY_SAX_RT (GATED) (Slices to cover the entire LV)		BP:____/____ HR: _____	*HR: _____

WFSM PROTOCOL NON-CONTRASTTRANSFER images to the STYX and WEBPAX

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Appendix D – FACT-Fatigue Questionnaire

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
cfquAn2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4

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An16	I have to limit my social activity because I am tired	0	1	2	3	4

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Appendix E – FACT-Lym

Have you ever been diagnosed with Lymphoma? Yes / No
If the participant responds "No," continue to the next questionnaire.

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	<u>PHYSICAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section*					
GS7	I am satisfied with my sex life	0	1	2	3	4

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Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4

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GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	<u>ADDITIONAL CONCERNS</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, orgroin)	0	1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LYM1	I am bothered by itching	0	1	2	3	4
LYM2	I have trouble sleeping at night	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
Ga1	I have a loss of appetite	0	1	2	3	4
HI8	I have trouble concentrating	0	1	2	3	4

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N3	I worry about getting infections	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU4	Because of my illness, I have difficulty planning for the future	0	1	2	3	4

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Appendix F - Self Efficacy for Walking

Please indicate below how confident you are that you can successfully carry out each of the activities listed below.

I BELIEVE THAT I CAN WALK:

1. For **10 minutes at a moderately fast pace** without stopping

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

NOT AT ALL CONFIDENT — MODERATELY CONFIDENT — HIGHLY CONFIDENT

2. For **20 minutes at a moderately fast pace** without stopping

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

NOT AT ALL CONFIDENT — MODERATELY CONFIDENT — HIGHLY CONFIDENT

3. For **30 minutes at a moderately fast pace** without stopping

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

NOT AT ALL CONFIDENT — MODERATELY CONFIDENT — HIGHLY CONFIDENT

4. For **40 minutes at a moderately fast pace** without stopping

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

NOT AT ALL CONFIDENT — MODERATELY CONFIDENT — HIGHLY CONFIDENT

5. For **50 minutes at a moderately fast pace** without stopping

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

NOT AT ALL CONFIDENT — MODERATELY CONFIDENT — HIGHLY CONFIDENT

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6. For **60 minutes at a moderately fast pace** without stopping

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
NOT AT ALL CONFIDENT				MODERATELY CONFIDENT						HIGHLY CONFIDENT

RESTORE FORM 16

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Appendix G – SF-36 (RAND)

Choose one option for each questionnaire item.

1. In general, would you say your health is:

- 1 - Excellent
- 2 - Very good
- 3 - Good
- 4 - Fair
- 5 - Poor

2. **Compared to one year ago**, how would you rate your health in general **now**?

- 1 - Much better now than one year ago
- 2 - Somewhat better now than one year ago
- 3 - About the same
- 4 - Somewhat worse now than one year ago
- 5 - Much worse now than one year ago

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The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3**. Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	○ 1	○ 2	○ 3
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○ 1	○ 2	○ 3
5. Lifting or carrying groceries	○ 1	○ 2	○ 3
6. Climbing **several** flights of stairs	○ 1	○ 2	○ 3
7. Climbing **one** flight of stairs	○ 1	○ 2	○ 3
8. Bending, kneeling, or stooping	○ 1	○ 2	○ 3
9. Walking **more than a mile**	○ 1	○ 2	○ 3
10. Walking **several blocks**	○ 1	○ 2	○ 3
11. Walking **one block**	○ 1	○ 2	○ 3
12. Bathing or dressing yourself	○ 1	○ 2	○ 3

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	Yes	No
13. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
14. **Accomplished less** than you would like	○ 1	○ 2
15. Were limited in the **kind** of work or other activities	○ 1	○ 2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	○ 1	○ 2

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During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	1	2
18. **Accomplished less** than you would like	1	2
19. Didn't do work or other activities as **carefully** as usual	1	2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- 1 - Not at all
- 2 - Slightly
- 3 - Moderately
- 4 - Quite a bit
- 5 - Extremely

21. How much **bodily** pain have you had during the **past 4 weeks**?

- 1 - None
- 2 - Very mild
- 3 - Mild
- 4 - Moderate
- 5 - Severe
- 6 - Very severe

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22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

- 1 - Not at all
- 2 - A little bit
- 3 - Moderately
- 4 - Quite a bit
- 5 - Extremely

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

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32. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

- 1 - All of the time
- 2 - Most of the time
- 3 - Some of the time
- 4 - A little of the time
- 5 - None of the time

How TRUE or FALSE is **each** of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5

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Appendix H – Godin Leisure-time Exercise Questionnaire

1. During a typical 7-Day period (a week), how many times on the average do you do the following kinds of exercise for more than 15 minutes during your free time (write on each line the appropriate number):

Times Per Week

a) Strenuous Exercise
(*HEART BEATS RAPIDLY*) _____

(e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)

b) Moderate Exercise _____
(*NOT EXHAUSTING*)

(e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)

c) Mild Exercise _____
(*MINIMAL EFFORT*)

(e.g., yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking

2. During a typical 7-Day period (a week), in your leisure time, how often do you engage in any regular activity long enough to work up a sweat (heart beats rapidly)?

1. Often _____ 2. Sometimes _____ 3. Rarely/Never _____

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Appendix I: Quality of Life Questionnaires

This page is not to be given to the patient.

General Instructions:

Examiner: Now I have several questionnaires I would like you to complete on your own. Each has instructions that are easy. I cannot interpret the items for you but I can read them to you if you cannot read them yourself. There is no time limit with these so take your time and read each item carefully.

Let's start (Give pages 25 – 30 to the patient for completion on their own).

Do not interpret questions or words. If a patient asks for clarification remind them that you cannot assist and they are to do the best they can. Questionnaires included in this booklet are:

PROMIS Applied Cognition – General Concerns – Short Form 4a (4 items)

PROMIS Applied Cognition – Abilities – Short Form 4a (4 items)

PROMIS Fatigue – Short Form 4a (4 items)

PROMIS Mood – Emotional Distress - Anger – Short Form 5a (5 items)
Emotional Distress - Anxiety – Short Form 4a (4 items)
Emotional Distress - Depression – Short Form 4a (4 items)

PROMIS Pain Intensity - Short Form 3a (3 items)

PROMIS Pain Interference - Short Form 4a (4 items)

PROMIS Sleep Disturbance - Short Form 4a (4 items)

PROMIS Physical Function - Short Form 4a (4 items)

PROMIS Ability to Participate in Social Roles and Activities - Short Form 4a (4 items)

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PROMIS Applied Cognition – General Concerns – Short Form 4a (4 items)

Please respond to each item by marking one box per row.

	In the past 7 days…	Never	Rarely (Once)	Sometimes (Two or three times)	Often (About once a day)	Very often (Several times a day)
PC2	My thinking has been slow	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PC35	It has seemed like my brain was not working as well as usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PC36	I have had to work harder than usual to keep track of what I was doing	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PC42	I have had trouble shifting back and forth between different activities that require thinking	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

PROMIS Applied Cognition – Abilities – Short Form 4a (4 items)

Please respond to each item by marking one box per row.

	In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
PC43_2	My mind has been as sharp as usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PC44_2	My memory has been as good as usual...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PC45_2	My thinking has been as fast as usual.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PC47_2	I have been able to keep track of what I am doing, even if I am interrupted.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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PROMIS Fatigue – Short Form 4a (4 items)

Please respond to each question or statement by marking one box per row.

	During the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
1	I feel fatigued	☐	☐	☐	☐	☐
2	I have trouble starting things because I am tired	☐	☐	☐	☐	☐
	In the past 7 days…					
3	How run-down did you feel on average?	☐	☐	☐	☐	☐
4	How fatigued were you on average?	☐	☐	☐	☐	☐

PROMIS Mood – Emotional Distress - Anger – Short Form 5a (5 items)

Please respond to each item by marking one box per row.

	In the past 7 days...	Never	Rarely	Sometimes	Often	Always
EDANG03	I was irritated more than people knew	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANG09	I felt angry	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANG15	I felt like I was ready to explode	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANG30	I was grouchy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANG35	I felt annoyed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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Emotional Distress - Anxiety – Short Form 4a (4 items)

Please respond to each question or statement by marking one box per row.

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
1	I felt fearful.....	☐	☐	☐	☐	☐
2	I found it hard to focus on anything other than my anxiety	☐	☐	☐	☐	☐
3	My worries overwhelmed me.....	☐	☐	☐	☐	☐
4	I felt uneasy	☐	☐	☐	☐	☐

Emotional Distress - Depression – Short Form 4a (4 items)

Please respond to each question or statement by marking one box per row.

In the past 7 days...

		Never	Rarely	Sometimes	Often	Always
1	I felt worthless.....	☐	☐	☐	☐	☐
2	I felt helpless	☐	☐	☐	☐	☐
3	I felt depressed	☐	☐	☐	☐	☐
4	I felt hopeless	☐	☐	☐	☐	☐

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PROMIS Pain Intensity - Short Form 3a (3 items)

Please respond to each item by marking one box per row.

	In the past 7 days…	Had no pain	Mild	Moderate	Severe	Very severe
PAINQU6	How intense was your pain at its worst?....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAINQU8	How intense was your average pain?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
		No pain	**Mild**	**Moderate**	**Severe**	**Very severe**
PAINQU21	What is your level of pain right now?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

PROMIS Pain Interference - Short Form 4a (4 items)

Please respond to each question or statement by marking one box per row.

In the past 7 days…

		Not at all	A little bit	Somewhat	Quite a bit	Very much
1	How much did pain interfere with your day to day activities?.....	☐	☐	☐	☐	☐
2	How much did pain interfere with work around the home?.....	☐	☐	☐	☐	☐
3	How much did pain interfere with your ability to participate in social activities?	☐	☐	☐	☐	☐
4	How much did pain interfere with your household chores?.....	☐	☐	☐	☐	☐

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PROMIS Physical Function - Short Form 4a (4 items)

Please respond to each question or statement by marking one box per row.

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
1	Are you able to do chores such as vacuuming or yard work?	☐	☐	☐	☐	☐
2	Are you able to go up and down stairs at a normal pace?	☐	☐	☐	☐	☐
3	Are you able to go for a walk of at least 15 minutes?	☐	☐	☐	☐	☐
4	Are you able to run errands and shop?	☐	☐	☐	☐	☐

PROMIS Sleep Disturbance - Short Form 4a (4 items)

Please respond to each question or statement by marking one box per row.

In the past 7 days…

		Very poor	Poor	Fair	Good	Very good
1	My sleep quality was	☐	☐	☐	☐	☐

In the past 7 days…

		Not at all	A little bit	Somewhat	Quite a bit	Very much
2	My sleep was refreshing.	☐	☐	☐	☐	☐
3	I had a problem with my sleep	☐	☐	☐	☐	☐
4	I had difficulty falling asleep	☐	☐	☐	☐	☐

PROMIS Ability to Participate in Social Roles and Activities - Short Form 4a (4 items)

Please respond to each item by marking one box per row.

		Never	Rarely	Sometimes	Usually	Always
SRPPER11_CaPS	I have trouble doing all of my regular leisure activities with others	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER18_CaPS	I have trouble doing all of the family activities that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER23_CaPS	I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER46_CaPS	I have trouble doing all of the activities with friends that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

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Appendix J: NEUROCOGNITIVE FUNCTION TESTING BOOKLET

Preparing for Testing:

- Test in a comfortable and quiet place. Distractions will affect patient's performance
- Arrange your materials so the patient cannot see this document. A tilted clipboard works well.
- Patient should be seated comfortably and directly in front of you.
- Have all the equipment ready before you begin.

Creating Rapport:

- Use a friendly manner of speech.
- You may encourage patients by saying simple phrases **("You are doing fine")** but be careful not to signal correct or incorrect responses to test items. If a patient asks you if a response is correct say, **"I cannot give you feedback, so just do the best you can,"**
- If the patient needs a break be sure it is not done during the HVLT-R Immediate Recall, Trail Making Test, or between words in the Controlled Oral Word Association Test. It is always better to suggest they use the bathroom before testing begins.
- Should a patient appear distressed or nervous about their performance offer only a general encouragement such as, **"You are doing fine"** and remind them not to worry about mistakes.

General Guidelines:

- Speak clearly and slowly. Enunciate. You are not allowed to repeat instructions for most tests so you must get it right the first time. Take your time to explain the tests.
- Read exactly what is written in this document. Do not invent instructions or modify them. Read what is there.
- Never make a statement like, **"Oh, this one is hard"** as it could affect performance.
- Familiarize yourself with the procedure before testing. If you are rusty, pre-read this form and remove the rust. It will help to read the instructions out loud to yourself or someone else before you administer the battery.

Introducing the test battery:

Examiner: "Thank you for agreeing to participate in this study……Other patients could benefit from your efforts…….If you are ready, let's get started…….I am going to have you do a series of tasks that challenge your memory and other thinking abilities. You will not get every item correct, so don't worry about it. Just relax and do the best you can on each and every one. I will instruct you before each task so you will know what to do. Some of the tasks will be timed so you will have to do them as quickly as you can. I will alert you about the timed tasks. Shall we get started now?"

Administer the tests in the following order to every patient

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1. HOPKINS VERBAL LEARNING TEST - REVISED (HVLT-R)

This test has three parts and two alternate forms:

Part A - Free Recall: Complete the three learning trials first

Part A – Free Recall: Trial 1

Examiner*: "I am going to read a list of words to you. Listen carefully, because when I am through, I'd like you to tell me as many of the words as you can remember. You can tell them to me in any order. Are you ready?"*

- Read the words at the rate of one word every 2 seconds.

***Examiner: "OK. Now tell me as many of those words as you can remember*."**

- Check off the words the patient recalls on the form.
- If a word is said that is not in the list (*referred to as an, "intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
- If not, move on to trial 2. Later, you can record the number of words that were correctly repeated on the summary form.

Part A – Free Recall: Trial 2

Examiner*: "Now we are going to try it again. I am going to read the same list of words to you. Listen carefully, and tell me as many of the words as you can remember, in any order, including the words you told me the first time."*

- Read the words at the rate of one word every 2 seconds.
- Check off the words the patient recalls on the form.
- If a word is said that is not in the list (an *"intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
- If not, move on to trial 3. Later, you can record the number of words that were correctly repeated on the summary form.

Part A – Free Recall: Trial 3

Examiner*: "I am going to read the list one more time. As before, I'd like you to tell me as many of the words as you can remember, in any order, including all the words you've already told me."*

- Read the words at the rate of one word every 2 seconds.
- Check off the words the patient recalls on the form.

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- If a word is said that is not in the list (an *"intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
- Do *not* tell the respondent that recall of the words will be tested later.

HOPKINS VERBAL LEARNING TEST
FREE RECALL (TRIALS 1-3)

	PART A – FREE RECALL:	For each trial, mark the box next to each word The patient accurately recalls for each trial.		
		Trial 1	**Trial 2**	**Trial 3**
	LION	☐	☐	☐
	EMERALD	☐	☐	☐
	HORSE	☐	☐	☐
	TENT	☐	☐	☐
	SAPPHIRE	☐	☐	☐
	HOTEL	☐	☐	☐
	CAVE	☐	☐	☐
	OPAL	☐	☐	☐
	TIGER	☐	☐	☐
	PEARL	☐	☐	☐
	COW	☐	☐	☐
	HUT	☐	☐	☐

__ Month	Site:	Date:	Patient Initials:	Patient ID:	CRA:

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2. <u>TRAIL MAKING TEST – Parts A & B [Timed Test]</u>

<u>Part A – Sample</u>*:* **The Sample for Part A must be completed/attempted by each patient at every assessment. Place the Sample A worksheet flat on the table, directly in front of the patient *(the bottom of the worksheet should be approximately six inches from the edge of the table).* Give the patient a <u>black pen</u> and say:**

Examiner*: "On this page* (point) *are some numbers. Begin at number 1* (point to 1) *and draw a line from 1 to 2* (point to 2), *2 to 3* (point to 3)*, 3 to 4* (point to 4), *and so on, in order, until you reach the end* (point to the circle marked END). *Draw the lines as fast as you can. Ready, begin."*

If the patient completes Sample A correctly, and in a manner demonstrating that s/he understands what to do, proceed immediately to Test A. If the patient makes a mistake on Sample A, point out the error and explain it.
The following explanations of mistakes serve as illustrations:

- ***"This is where you start (point to number 1)"***
- ***"You skipped this circle (point to the circle omitted)"***
- ***"You should go from number 1 to 2, 2 to 3, and so on, until you reach the circle marked END"***

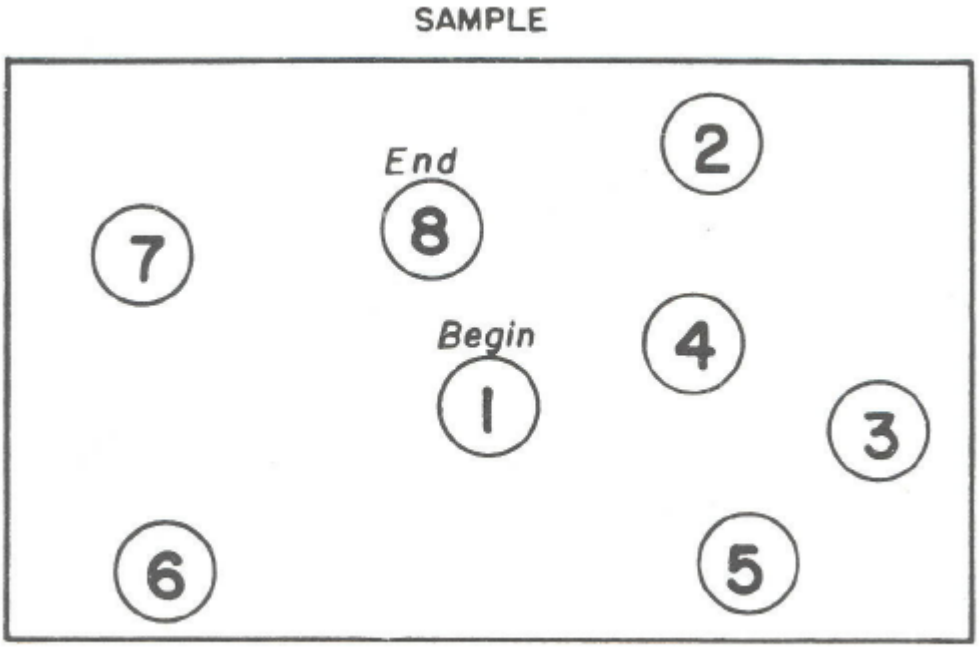
If it is clear that the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient still cannot complete Sample A, take his/her hand and guide him/her through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on the copy. Then say:

Examiner*: "Remember, begin at number 1 (*point to 1*) and draw a line from 1 to 2 (*point to 2*), 2 to 3 (*point to 3*), 3 to 4 (*point to 4*) and so on, in order, until you reach the circle marked END (*point*). Do not skip around, but go from one number to the next in proper order. Remember to work as fast as you can. Ready, begin."*

If the patient does not succeed, or it becomes evident that s/he cannot do the task, DISCONTINUE testing <u>and</u> indicate the corresponding reason on the Trail Making Data Sheet. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Part A.

.

Trailmaking - Part A Sample



__ Month	Site:	Date:	Patient Initials:	Patient ID:	CRA:

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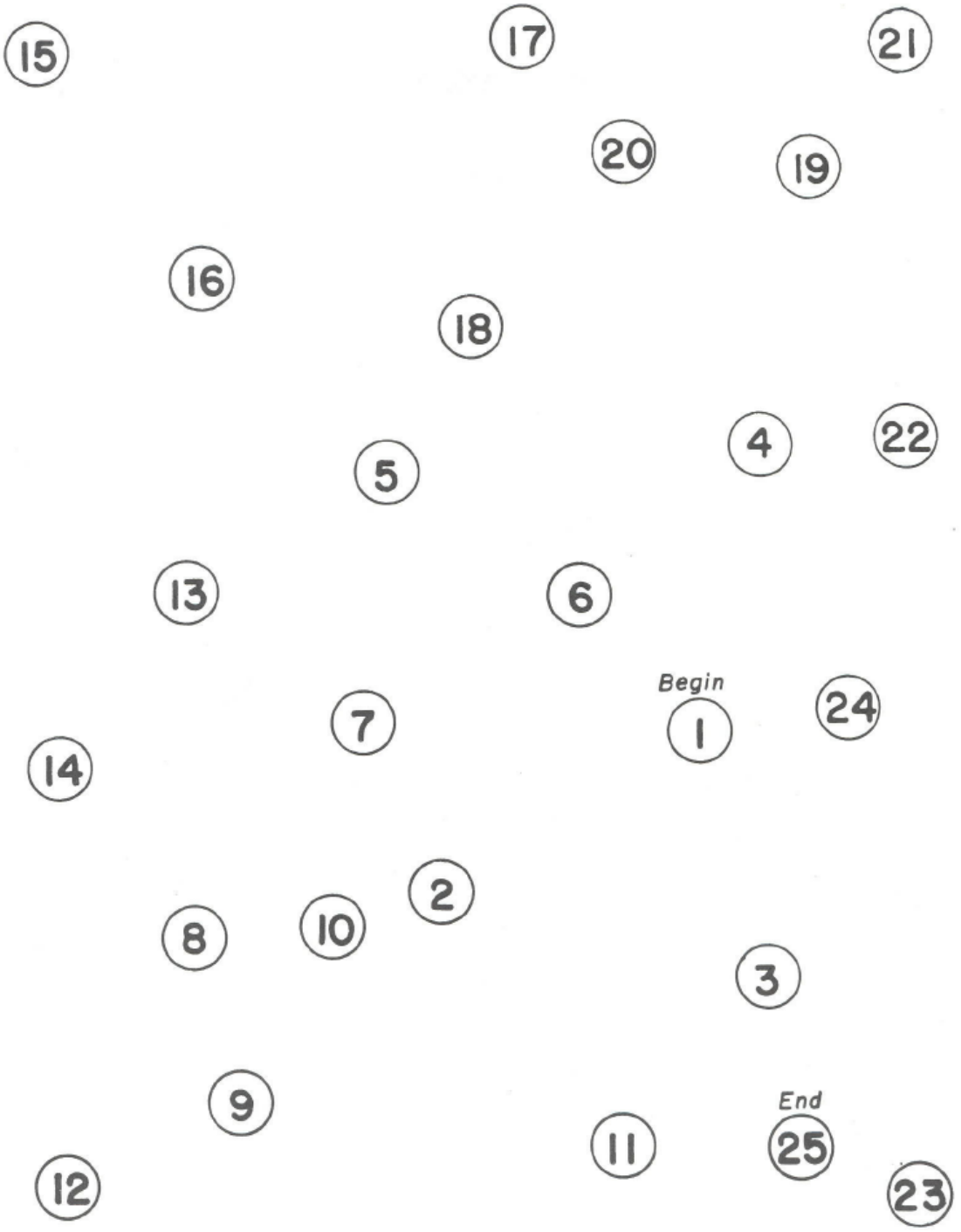
Trailmaking - Part A – Test:

After the patient has completed Sample A, place the Part A test worksheet directly in front of the patient and say:

Examiner*: "Good! Let's try the next one. On this page are numbers from 1 to 25. Do this the same way. Begin at number 1 (*point*) and draw a line from 1 to 2 (*point to 2*), 2 to 3 (*point to 3*), 3 to 4 (*point to 4*) and so on, in order, until you reach the circle marked END (*point*). Do not skip around, but go from one number to the next in proper order. Remember to work as fast as you can. Ready, begin."*

- Start timing as soon as the instruction is given to "begin"
- Watch closely in order to catch any errors as soon as they are made. If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred
- The patient must complete the test in 5 minutes or less
- DO NOT STOP TIMING UNTIL HE/SHE REACHES THE CIRCLE MARKED "END"
- If the patient does not complete the test within 5 minutes terminate the testing. The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Collect the worksheet and complete the Trail Making Data Sheet indicating the reason the test was terminated and the number of last correct circle reached on the test.
- If the patient successfully completes the test collect the worksheet and record the time to completion on the Trail Making Data Sheet in minutes and seconds. Then say, ***"That's fine. Now we'll try another one."***

.



__ Month	Site:	Date:	Patient Initials:	Patient ID:	CRA:

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Trailmaking - Part B – Sample: The Sample for Part B must be completed/attempted by each patient at every assessment. Place the Sample B worksheet flat on the table, directly in front of the patient (the bottom of the worksheet should be approximately six inches from the edge of the table) and say:

Examiner*: "On this page (***point***) are some numbers and letters. Begin at number 1 (***point to 1***) and draw a line from 1 to A (***point***), A to 2 (***point to 2***), 2 to B (***point to B***), B to 3 (***point to 3***), 3 to C (***point to C***) and so on, in order, until you reach the end (***point to the circle marked END***). Remember, first you have a number (***point to 1***), then a letter (***point to A***), then a number (***point to 2***), then a letter (point to B), and so on. Draw the lines as fast as you can. Ready, begin."*

If the patient completes Sample B correctly, and in a manner demonstrating that s/he understands what to do, proceed immediately to Part B. If the patient makes a mistake on Sample B, point out the error and explain it.

The following explanations of mistakes serve as illustrations:

- *"You started with the wrong circle. This is where you start (point to number 1)"*
- *"You skipped this circle (point to the circle omitted)"*
- *"You should go from number 1 (***point***) to A (***point***), A to 2 (***point to 2***), 2 to B (***point to B***), B to 3 (***point to 3***) and so on, until you reach the circle marked END (***point***)"*

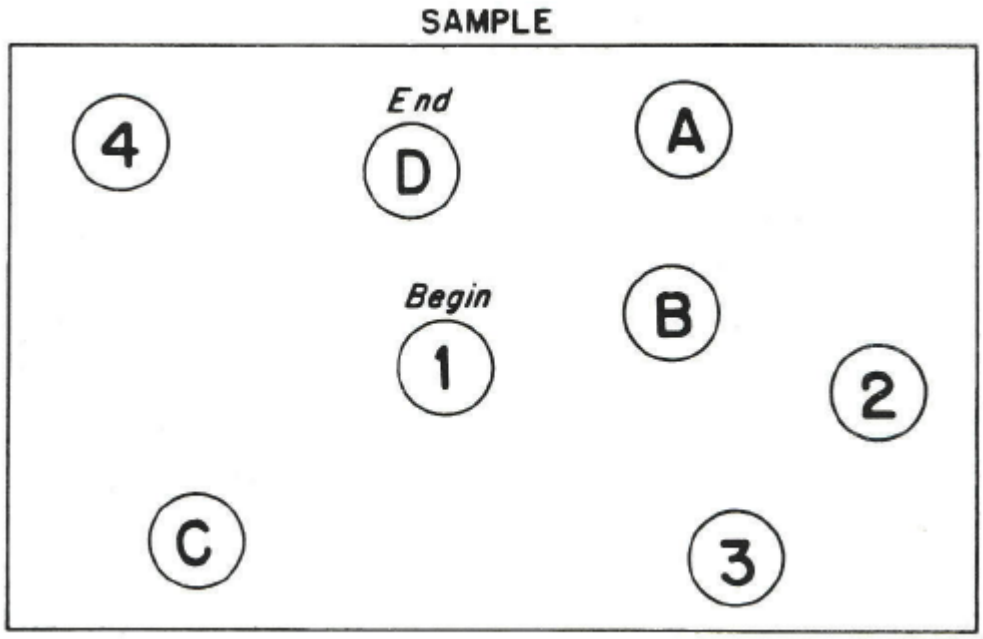
If it is clear the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient still cannot complete Sample B, take their hand and guide them through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on the copy. Then say:

Examiner*: "Now you try it. Remember, begin at number 1 (***point to 1***) and draw a line from 1 to A (***point to A***), A to 2 (***point to 2***), 2 to B (***point to B***), B to 3 (***point to 3***) and so on, in order, until you reach the circle marked END (***point***). Ready, begin."*

If the patient does not succeed or it becomes evident that s/he cannot do the task, DISCONTINUE testing and indicate the corresponding reason on the Trail Making Data Sheet. If the patient completes Sample B correctly and appears to understand what to do, proceed immediately to Part B.

.

Trailmaking - Part B Sample



__ Month Visit	Site:	Date:	Patient Initials:	Patient ID:	CRA:

Trailmaking – Part B - Test:

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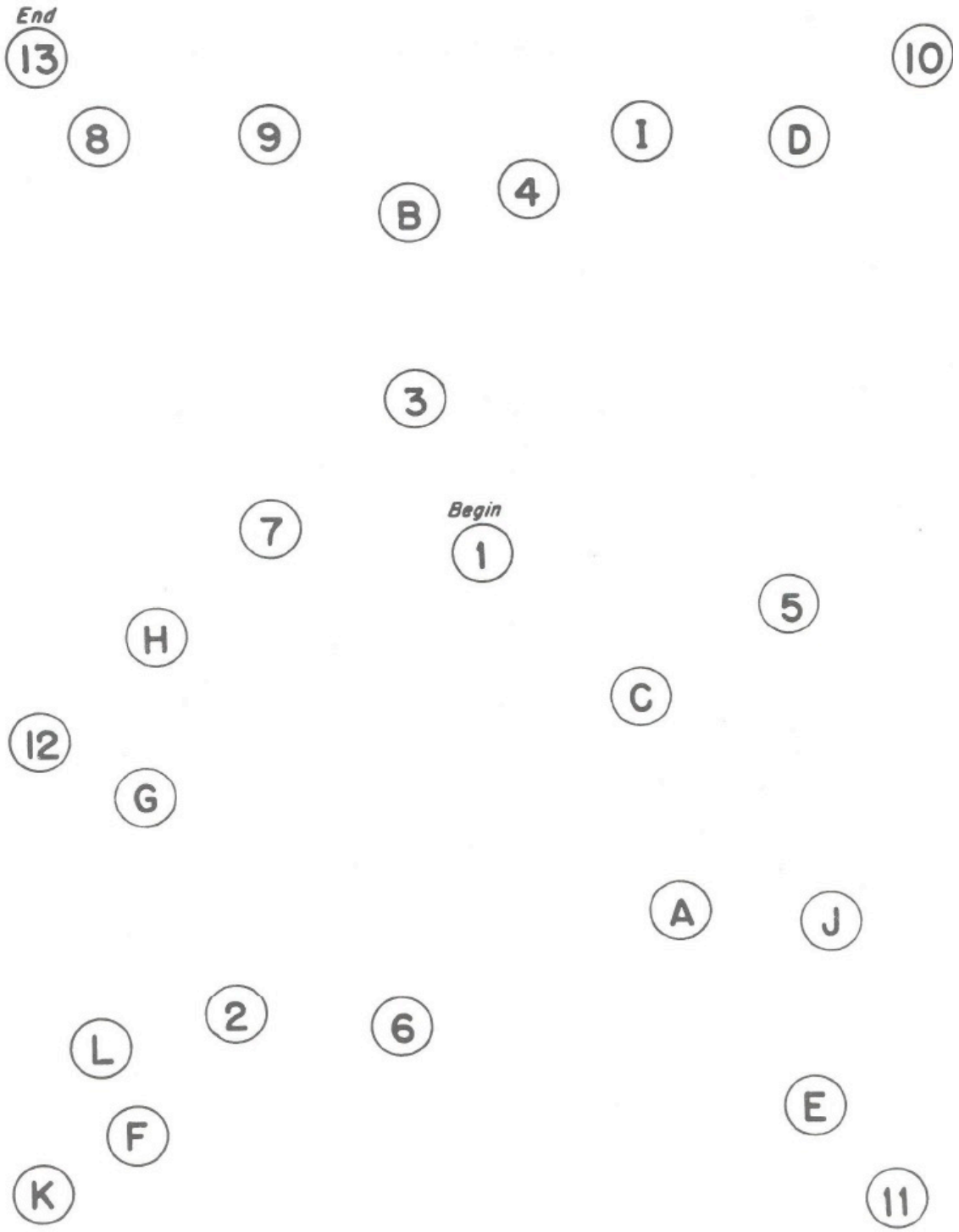
After the patient has completed Sample B, place the Part B Worksheet directly in front of the patient and say:

Examiner*: "Good! Let's try the next one. On this page are both numbers and letters. Do this the same way. Begin at number 1 (*point*) and draw a line from 1 to A (*point to A*), A to 2 (*point to 2*), 2 to B (*point to B*), B to 3 (*point to 3*), 3 to C (*point to C*) and so on, in order, until you reach the circle marked END (*point*). Remember, first you have a number (*point to 1*), then a letter (*point to A*), then a number (*point to 2*), then a letter (*point to B*), and so on. Do not skip around, but go from one circle to the next in the proper order. Draw the lines as fast as you can. Ready, begin."*

- Start timing as soon as the instruction is given to "begin"
- Watch closely in order to catch any errors as soon as they are made. If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred. **"You were correct up to here** (point to last correct circle)**. Start here and continue as quickly as you can."**
- The patient must complete the test in 5 minutes or less. (Do not tell patient).
- DO NOT STOP TIMING UNTIL HE/SHE REACHES THE CIRCLE MARKED "END"
- Collect the worksheet and record the time to completion on the Trail Making Data Sheet in minutes and seconds
- If the patient does not complete the test within 5 minutes terminate the testing. (Say: **"That's fine. We will need to move on to the next task")** The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Collect the worksheet and complete the Trail Making Data Sheet indicating the reason the test was terminated and the last correct number or letter reached on the test.

.



__ Month	Site:	Date:	Patient Initials:	Patient ID:	CRA:

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TRAIL MAKING TEST DATA SHEET (PART A & B)

Maximum time allotted for each part is 5 minutes (300 seconds)

PART A

Total time: _____ minutes _____ seconds

Highest circle connected: _____

Number of errors: _____

PART B

Total time: _____ minutes _____ seconds

Highest circle connected: _____

Number of errors: _____

.

4. CONTROLLED ORAL WORD ASSOCIATION TEST (COWA) [Timed Test]

This test has three parts (letters).

Examiner*: "I am going to say a letter of the alphabet, and I want you to say as quickly as you can all of the words that you can think of that begin with that letter. You may say any words at all, except proper names such as the names of people or places. So you would not say 'Rochester' or 'Robert'. Also, do not use the same word again with a different ending, such as 'Eat,' and 'Eating.'*

"For example, if I say 'S,' you could say 'son', 'sit,' 'shoe,' or 'slow.' Can you think of other words beginning with the letter 's'?"

- Wait for the patient to give a word. If it is a correct response, say ***"good"***, and ask for another word beginning with the letter "s". If a second appropriate word is given, proceed to the test itself.
- If the patient gives an inappropriate word on either occasion, correct the patient, and repeat the instructions. If the patient then succeeds, proceed to the test.
- If the patient fails to respond, repeat the instruction. If it becomes clear that the patient does not understand the instructions or cannot associate, stop the procedure, and indicate the reason(s) on the scoring sheet.
- If the patient has succeeded in giving two appropriate words beginning with the demonstration letter, say:

Examiner*: "That is fine. Now I am going to give you another letter and again you say all of the words beginning with that letter that you can think of. Remember, no names of people or places, just ordinary words. Also, if you should draw a blank, I want you to keep on trying until the time limit is up and I say STOP."*

"You will have a minute for each letter. The first letter is '___'" (see scoring sheet).

Allow exactly one minute for each letter

- If the patient discontinues before the end of the time period, encourage him/her to try to think of more words.
- If he/she is silent for 15 seconds, repeat the basic instruction and the letter (e.g., **"Tell me all the words you can think of that begin with a "c"**).
- No extension on the time limit is made in the event that instructions are repeated.
- Continue the evaluation with the remaining two letters, allowing one minute for each.

.

Examiner*: Remember, no names of people or places, just ordinary words. Also, if you should draw a blank, I want you to keep on trying until the time limit is up and I say STOP. You will have a minute for each letter. "The next letter is '___'"* (see scoring sheet).

Recording and Scoring:

- The record sheet provides lines on which the patient's responses can be entered *(e.g., write in the word that is said by the patient)*. If his/her speed of word production is too fast to permit verbatim recording, a "+" should be entered to indicate a correct response and try to write an abbreviated version. When time permits complete the abbreviation.
- Incorrect responses either should not be recorded or, if recorded, should be struck through with a line.
- If the patient provides more responses than there are lines on the record sheet, write in the margins.
- Count all the correct responses. The number of correct words should be indicated below each column on the recording sheet and on the summary data form that is sent to the CCCWFU.

Comments on scoring:

- Note: It can be helpful for the first several patients and for patients known to be fast with their word production to tape record the session for transcription at a later time.
- The instructions include a specific prohibition against giving proper names or different forms of the same word. Therefore, inflections of the same word *(e.g., eat-eating; mouse-mice; loose-loosely; ran-run-runs)* are not considered correct responses.
- Patients often give both a verb and a word derived from the verb or adjective *(e.g., fun-funny; sad-sadness)*. These are not considered correct responses. On the other hand, if the word refers to a specific object *(e.g., foot-footstool; hang-hanger),* it would be counted as a correct answer.
- Many words have two or more meanings *(e.g., foot; can; catch; hand)*. A repetition of the word is acceptable IF the patient definitely indicates the alternative meaning to you.
- Slang terms are OK if they are in general use.
- Foreign words *(for example, pasta; passé; lasagna)* can be counted as correct if they can be considered part of that relevant language, the criterion being their listing in a standard dictionary of that language. All incorrect and repeated responses MUST be crossed out with one single line, initialed and dated. Additionally, all duplicate entries that have been verified to have different meanings must be marked "ok", initialed and dated. Refer to the descriptions above for guidelines for acceptability. Add the total number of correct responses in each column and input the totals where indicated on the COWA worksheet.
- If the test is discontinued or omitted, please mark this on the bottom of the test form and indicate the reason.

.

CONTROLLED ORAL WORD ASSOCIATION TEST (COWA)

"C"	**"F"**	**"L"**
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

"C" Total: _____ "F" total: _____ "L" Total: _____

__ Month	Site:	Date:	Patient Initials:	Patient ID:	CRA:

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4. DIGIT SPAN 4. Digit Span Test

Digits Backward

- Administer the digit spans in order
- Do not repeat a span once read.
- Administer both spans of the same length regardless of how the participant performs.
- Say the digits at a rate of 1 digit about every 1 sec.
- Use a monotonic voice; without inflections at the end

Examiner: "Now I am going to say some numbers, but this time when I stop I want you say them backwards. For example, if I say 7-1-9, what would you say?"

- If the participant responds correctly (9-1-7), say, **That's right,"** and proceed to Item 1.
- If the participant fails the example, say: "**No, you would say 9-1-7. I said 7-1-9, so to say it backwards you would say 9-1-7. Now try these numbers. Remember, you are to say them backwards 3-4-8."**
- Whether the participant succeeds or fails with the second example (3-4-8), proceed to Item 1. Give no help on this second example or any of the items that follow.
- Discontinue after failure on **both trials of any item.**

Scoring: Each span is scored '0' or '1'. Give 1 point if the participant passes the trial; and no points if the participant fails the trial. Only discontinue test when participant has failed both trials of the same span length (e.g., 5a. and 5b.).

DIGIT SPAN TEST--- BACKWARD

Item	Digit span	Score (0 or 1)
1a.	2 – 4	
1b.	5 – 7	
2a.	6 – 2 – 9	
2b.	4 – 1 – 5	
3a.	3 – 2 – 7 – 9	
3b.	4 – 9 – 6 – 8	
4a.	1 – 5 – 2 – 8 – 6	
4b.	6 – 1 – 8 – 4 – 3	
5a.	5 – 3 – 9 – 4 – 1 – 8	
5b.	7 – 2 – 4 – 8 – 5 – 6	
6a.	8 – 1 – 2 – 9 – 3 – 6 – 5	
6b.	4 – 7 – 3 – 9 – 1 – 2 – 8	
7a.	9 – 4 – 3 – 7 – 6 – 2 – 5 – 8	
7b.	7 – 2 – 8 – 1 – 9 – 6 – 5 – 3	

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5. HOPKINS VERBAL LEARNING TEST - REVISED (HVLT- R)

Part B – Delayed Recall

- ***DO NOT READ THE WORD LIST AGAIN*.**

- HVLT-R 'Part B – Delayed Recall' should be administered approximately 20 minutes after Part A of the HVLT-R.

Examiner: "*Do you remember that list of words you tried to learn before? Tell me as many of those words as you can remember."*

- Check the box on the corresponding line of the HVLT-R worksheet for each word the patient accurately recalls.
- If a word is said that is not in the list (*referred to as an, "intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.

.

HOPKINS VERBAL LEARNING TEST (F1)--PART B

DELAYED RECALL

DO NOT READ WORD LIST

Check words correctly recalled

	Delayed Recall
LION	☐
EMERALD	☐
HORSE	☐
TENT	☐
SAPPHIRE	☐
HOTEL	☐
CAVE	☐
OPAL	☐
TIGER	☐
PEARL	☐
COW	☐
HUT	☐

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Part C – HVLT-R Delayed Recognition

Examiner*: "Now I'm going to read a longer list of words to you. Some of them are words from the original list, and some are not. After I read each word, I'd like you to say "Yes" if it was on the original list or "No" if it was not. Was [word] on the list?"*

- Read the words from the top of the columns down.
- Check either the "**Y"** (Yes) or "**N"** (No) box next to each word to indicate the patient's response.
- Guessing is allowed.
- If the test is discontinued or omitted, please mark this on the bottom of the test form and indicate the reason.

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HOPKINS VERBAL LEARNING TEST (F1)--PART C

DELAYED RECOGNITION

Check either "Y" or "N" for each word

	Y	N		Y	N
HORSE	☐	☐	**balloon**	☐	☐
house*	☐	☐	**boat**	☐	☐
HUT	☐	☐	**dog***	☐	☐
TENT	☐	☐	**HOTEL**	☐	☐
ruby*	☐	☐	**coffee**	☐	☐
OPAL	☐	☐	**scarf**	☐	☐
EMERALD	☐	☐	**apartment***	☐	☐
Mountain	☐	☐	**COW**	☐	☐
CAVE	☐	☐	**LION**	☐	☐
TIGER	☐	☐	**PEARL**	☐	☐
SAPPHIRE	☐	☐	**penny**	☐	☐
cat*	☐	☐	**diamond***	☐	☐

_ Month	Site:	Date:	Patient Initials:	Patient ID:	CRA:

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DATA SUMMARY SHEET

1. HVLT-R – Immediate Recall

(TO BE SCORED AT COORDINATING CTR)

2. Trail Making Test

Part A

Time: _____ min. ____ sec

Highest circle connected: _____

Errors: _____

Part B

Time: ____ min ____sec

Highest circle connected: _____

Errors: _____

3. Controlled Oral Word Association Test

Letter 1 Word Total _____

Letter 2 Word Total _____

Letter 3 Word Total _____

4. Digit Span

(TO BE SCORED AT COORDINATING CTR)

5. HVLT-R Delayed & Recognition

(TO BE SCORED AT COORDINATING CTR)

__ Month	Site:	Date:	Patient Initials:	Patient ID:	CRA:

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Appendix K

: Body Composition assessments

Directions for Measuring Waist Circumference

- Patient should be instructed to not hold their breath.
- The measuring tape should be secure but not tight.
- The area being measured can be found by placing the hands on the waist and moving them downward until the top curve of the hip bone can be felt.
- Place the tape measure around the top of the hip curve and wrap around at the level of the belly button. (This may not be the same level as the top of the pants.)

Record this measurement in inches below:

_____ inches

- Record height and weight: _____height (inches) _____weight (kg)

Peripheral Edema Evaluation

Does the patient have peripheral edema? Yes / No

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Appendix L: Physical Activity Program Evaluation

Please circle the number below that best describes your feeling about each statement.

PART I.

1. **I liked the physical activity program overall.**

0	1	2	3	4
Not At All	A Little Bit	Somewhat	Quite A Bit	Very Much

2. **The physical activity program was helpful to me.**

0	1	2	3	4
Not At All	A Little Bit	Somewhat	Quite A Bit	Very Much

3. **I plan to continue to practice physical activity.**

0	1	2	3	4
Not At All	A Little Bit	Somewhat	Quite A Bit	Very Much

4. **I plan to start or continue to practice another type of physical activity.**

0	1	2	3	4
Not At All	A Little Bit	Somewhat	Quite A Bit	Very Much

5. **The physical activity program had an impact on my physical function.**

0	1	2	3	4
Not At All	A Little Bit	Somewhat	Quite A Bit	Very Much

6. **The physical activity program had an impact on my mental health.**

0	1	2	3	4
Not At All	A Little Bit	Somewhat	Quite A Bit	Very Much

7. **The interventionist made physical activity enjoyable.**

0	1	2	3	4
Not At All	A Little Bit	Somewhat	Quite A Bit	Very Much

.

PART II.

1. **What did you like best about participating in this study and the physical activity program?**

_____

_____

_____

2. **What did you like least about participating in this study and the physical activity program?**

_____

_____

_____

3. **What did you learn from participating in the physical activity program?**

_____

_____

_____

4. **What other suggestions would you make to improve this program?**

_____

_____

_____

5. **Please share any other thoughts and comments about your participation in the physical activity program. (Feel free to use additional space below or on the back of this page if you would like.)**

_____

_____

_____

6. **May we contact you about participating in future studies?**

Yes If yes, E-mail _____

No Phone _____

.

Appendix M: Health Education Program Evaluation

Please circle the number below that best describes your feeling about each statement.

PART I.

8. I liked the educational program overall.

0	1	2	3	4
Not At All	A Little Bit	Somewhat	Quite A Bit	Very Much

9. The educational program was helpful to me.

0	1	2	3	4
Not At All	A Little Bit	Somewhat	Quite A Bit	Very Much

10. I plan to continue to practice what I learned.

0	1	2	3	4
Not At All	A Little Bit	Somewhat	Quite A Bit	Very Much

11. The educational program was a valuable use of my time.

0	1	2	3	4
Not At All	A Little Bit	Somewhat	Quite A Bit	Very Much

12. The interventionist made learning about health enjoyable.

0	1	2	3	4
Not At All	A Little Bit	Somewhat	Quite A Bit	Very Much

.

PART II.

1. **What did you like best about participating in this study and the health education program?**

_____

_____

_____

2. **What did you like least about participating in this study and the health education program?**

_____

_____

_____

3. **What did you learn from participating in the education program?**

_____

_____

_____

4. **What other suggestions would you make to improve this program?**

_____

_____

_____

5. **Please share any other thoughts and comments about your participation in the health education program. (Feel free to use additional space below or on the back of this page if you would like.)**

_____

_____

_____

6. **May we contact you about participating in future studies?**

Yes If yes, E-mail _____

No Phone _____

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APPENDIX N: THE Q-PRO SHARED RESOURCE FOR QUALITATIVE RESEARCH SUPPORT SERVICES

QPRO offers the following services:

- Community-based study recruitment and engagement
- Qualitative research methodological expertise and infrastructure
- Patient-reported outcomes measurement consultation

We will utilize the Q-PRO Shared Resource to provide methodological expertise for qualitative research. This expertise applies to all areas of qualitative inquiry including the design and selection of methods, selection and recruitment of study sample, data collection, management of textual data, and data analysis. Additionally, Q-PRO offers assistance with proposal writing as it pertains to qualitative methodology, progress report and presentation development, manuscript development, and team- specific training and mentoring in collecting and analyzing qualitative data. Q-PRO also provides support facilitating the dissemination of research findings to the community.

Personnel

The Q-PRO Developing Shared Resource is co-directed by two faculty members and staffed by a Senior Research Associate and a full-time Program Manager. Q-PRO co-directors engage other qualified faculty on a per-project basis when external expertise is needed. The co- directors were chosen to lead this developing shared resource based on complementary areas

Q-PRO Developing Shared Resource services are provided through the CCCWFUHS and are housed in the Department of Social Sciences and Health Policy. For this study, the QPRO resources will be available to Dr. Lucas for evaluating participant feedback to identify issues with the exercise mediated physical activity intervention.

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Appendix O – FACT-B questionnaire

Have you ever been diagnosed with breast Cancer? Yes / No
If the participant responds "No," continue to the next questionnaire.

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	<u>PHYSICAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	<u>SOCIAL/FAMILY WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4

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GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section*	☐				
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	<u>EMOTIONAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

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	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

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Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
B1	I have been short of breath	0	1	2	3	4
B2	I am self-conscious about the way I dress	0	1	2	3	4
B3	One or both of my arms are swollen or tender	0	1	2	3	4
B4	I feel sexually attractive	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
B6	I worry that other members of my family might someday get the same illness I have	0	1	2	3	4
B7	I worry about the effect of stress on my illness	0	1	2	3	4
B8	I am bothered by a change in weight	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4

Appendix P – PALS Home-Based Testing Kit

PALS Home-Based Testing Kit

This document contains both instructions for the participant who will perform the tests, and for the testing assistant who will use the camera app on the Samsung Android device to film each of the tests for scoring purposes.

Participant Instructions

To begin with, please check the package you received to make sure it contains the following items.

Package Contents

1. Instruction booklet (can also be emailed beforehand).
2. 1 x Android device.
3. 1 x Camry Grip strength dynamometer.
4. 1 x 15m length rope (marked in 1m increments).
5. 2 x weighted markers for securing ends of 15m rope.

Other Equipment Needed

6. A flat area of the home without obstructions to complete balance tests. The back of a chair, a table, or a shelf at about hip height is recommended if you need to catch your balance.
7. A flat area for set-up and completion of the 4-meter and 6-minute walk test (15-20 meters/ 50-70 feet).
8. Standard dining room-type chair for chair stand test (17-19" in height).
9. Your own smartphone device with the following app installed 6WT (IOS) or (Android).

Important Notes:

10. ***Before you begin, please be aware that participant safety is more important than any test outcome. Please let the research team know about any conditions including fatigue and concerns related to balance that may make the completion of some of the following exercise tests unsafe.***

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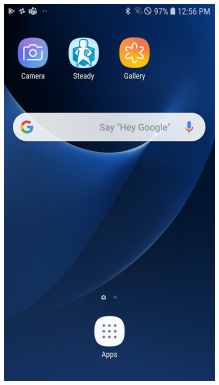
11. ***Please have the person who is helping you to conduct these tests, become familiar with the Android device. Specifically, they will need to be able to operate the camera/video app found on the home screen.***
12. ***We would like you to complete all the tests in one attempt. The total time taken to complete the full battery of tests should be between 40-60 minutes.***
13. ***One of the walking tests will be completed at a usual walking pace (4m walk), while the other is done as fast as you can without running (6MWT).***
14. ***Please complete the following tests in the stated order. It is important to be adequately recovered for the start of each test.***

Test Order

1. **Balance tests - Steady App** (If your balance test results show you have a low risk for a fall [≤40/100], you may continue to the rest of the tests.)
2. **4-meter walk test.**
3. **Chair stand test.** (You may rest after this test, until such time as you feel you have regained your breath and can talk normally.)
4. **Grip strength test.**
5. **6-minute walk test.**

Balance Test - Steady App Instructions



The Steady App is designed to evaluate your balance and determine your fall risk before continuing with the rest of the physical tests. The App can be found on the Home screen of the Samsung device you received in your package.

Find a firm, safe, flat area to complete the balance tests. A room with a table or shelf at about hip height can be used for support should you feel it may be necessary to catch your balance. You may also stand behind the chair you will use for some of the remaining tests. Do not do this test on a soft surface like grass, or a thick carpet.

1. Open the Steady App 

2. When prompted, insert your test subject number (if not sure ask the research team)

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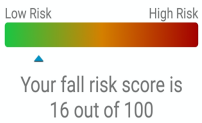
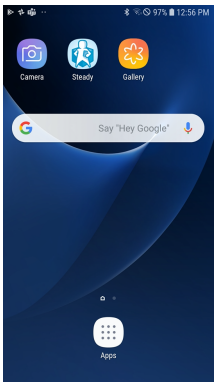
3. Follow the audio instructions on the device as it talks you through 4 separate balance tests, each taking approximately 30 seconds to complete.
4. When the tests have finished, you will be provided with a fall risk score.



If your score is ≤40, you may continue with the rest of the tests.

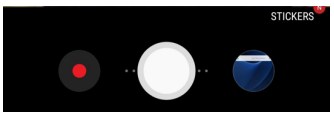
General Testing Assistant Instructions



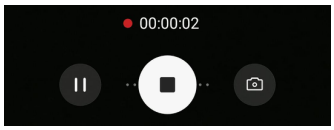
Once the participant has completed the balance tests using the Steady app, if low risk for a fall, they will then perform the remaining physical tests. The Camera app, located on the home screen of the Samsung Android device will be used to film the participant completing each test.

The position you will stand in is slightly different for filming each test so check the specific instructions for each test section before you start.

With the Camera app open, you will see a smaller red dot to the left of the large white dot in a bar across the bottom of the screen. This is how you will start the video.



1. To film the participant performing each test, make sure both you and they are ready to begin.
2. Hold the phone in the vertical position. Make sure you can clearly see the participant in the frame of the camera before starting the test.
3. Start with your finger on the red dot and release the button as you start to count down "3, 2, 1, **GO**". You will begin each test that you film with the same instructions for consistency. *Note: Do not press the button as you say **GO** as there will be a slight delay at the start of the video and it is important to capture the beginning of the test.*



4. To end the test, press the white dot (*with a smaller black square)* in the middle of the bar across the bottom of the screen.
5. Before you perform any of the tests, practice filming a few short clips.

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Set up for the 4-meter walk, chair stand, grip strength, and 6-minute walk tests

First, find a level unobstructed area to complete the 6-minute walk test. This can be a driveway, the edge of the road/street outside your home (if not too busy), an open parking area (ideally towards the perimeter, where it is not too busy). The space chosen should be safe and firm. Do not complete this test on a soft, uneven surface like a lawn or a busy sidewalk where you will be interrupted.


1. Hook the loops at the ends of the 15m rope onto the weighted markers in the test kit.
2. Place the weighted anchors (marked with orange crosses) in a straight line until the slack is removed from the rope. Be careful to not overstretch the rope.
3. Place a chair perpendicular (at a right angle) to the marker at the end of the walking course (close to position **A)**. Make sure the chair does not obstruct the walking course. You will use this same chair for the sit-to stand tests (chair stands) and to provide you with somewhere to sit should you become fatigued or should you need a break during the walking test.
4. You will also perform the grip strength tests while seated in this chair.

4-meter Walk Test

The test will require you to walk at a usual pace for a distance of 4 meters. You will complete 2 sets (repeats) of this test.

Testing Assistant Position and Instructions

As the person filming the test you will want to stand in line with the end marker the participant will walk towards. This will be opposite position **A.** From this vantage point, you will follow the participant until they walk past the marker at the end of the rope.

To film the test:

5. Open the camera app on the Samsung device.
6. Make sure the participant is fully viewable in the frame of the screen.
7. Ask the participant to slowly walk towards the marker at the end of the rope and make sure you can follow them through the 4m course.

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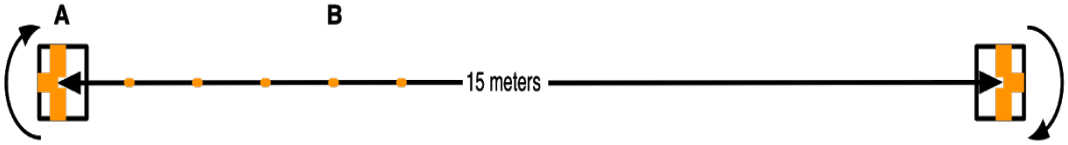
8. When you are ready, have the participant start with their toes just behind the 4th mark (position **B**) from the end of the rope.
9. Remind the participant to walk at a normal/usual pace and to not stop or slow down before reaching the end of the rope.
10. Place your finger on the red dot and release as you start to say “3, 2, 1, **GO**”.
11. Repeat the test.
12. Open the gallery app on the phone and make sure both tests are filmed.

Participant Instructions

Start with the toes of your feet placed at position **B,** in line with the 4th mark from the end of the rope (4 meters) facing the marker at position **A.**



When both the participant and the person who is videoing the test are ready, have the person filming, start the test with “3, 2, 1, **GO**.” On **GO** walk towards and past position **A**, in line with the marker at the end of the rope. Walk at a normal pace and do not stop or slow down before reaching the end of the rope. Return to the starting position (Position **B**) and repeat the test for a second time.

Chair Stand Test

The goal of this test is to complete as many chair stands as possible in 30 seconds, but be sure to stand up completely and return to a seated position with a straight spine each time. See images below for the start and stop positions of each chair stand.


Start


Stop

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Testing Assistant Position and Instructions.

As the person filming the test you will want to stand perpendicular to the participant so you have the same view as in the picture above**.** From this vantage point, you will film the participant for approximately 35 seconds (this allows for the capture of the exact position of the participant at 30 seconds after the test starts).

To film the test:

1. Open the camera app on the Samsung device.
2. Make sure the participant is fully viewable in the frame of the screen.
3. Ask the participant to slowly stand up from seated and make sure they have correct form.
4. When you are ready, have the participant start with their arms crossed and hands placed on their shoulders.
5. Remind the participant to stand upright completely before returning to the seated position.
6. Place your finger on the red dot and release as you start to say "3, 2, 1, **GO**".
7. After 35 seconds press the white dot and say **"STOP"** loudly to end the test.
8. Open the gallery app on the phone and make sure the test was filmed.

Participant Instructions

1. Start seated toward the front edge of the chair with your feet shoulder-width and positioned behind your knees, and arms folded across your chest (see start stop positions in picture above).
2. You may complete one practice trial, and ask for any corrective feedback as necessary.
3. When both the participant and the person who is videoing the test are ready, have the person filming, start the test with "3, 2, 1, **GO**." After they say '**GO**,' you will stand all the way up, and return to the original seated position.
4. Repeat the stands as many times as you can until you hear the assistant say **STOP!**
5. You may stop the test early if you become very tired or short of breath during the repeated chair stands.
6. End your test by returning to the seated position.

Grip Strength Test

The goal of this test is to measure your upper body strength.

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Testing Assistant Instructions

It is not necessary to film or photograph this test.

Participant Instructions

1. To begin with, turn on the device.
2. Find the user-number you have been designated by pressing the up or down arrows and press start. (check with research team contact if you are unsure of your number).
3. Start in the seated position, with your feet hip-width apart, ankles vertically below your knees (see picture at right).
4. Sit upright with the shoulders vertically over your hips. The elbow should be tucked in at the side, falling on a line approximately halfway between your shoulder and your hips.
5. Bend the elbow to 90 degrees so your forearm is parallel to the tops of the thighs.
6. Hold the grip dynamometer in your dominant hand, so that your thumb is pointing directly up towards the sky. The screen of the device should be facing away from the palm of your hand.
7. When you are ready, squeeze the grip handles as tightly as you can, maintaining the position you started in. Repeat 3 times, recording the value for each test.
8. You may rest for up to 1 minute between each of the 3 attempts.
9. Switch to the other arm and repeat 3 times.

6-minute walk test

The goal of this test is to walk as fast, but safely, as you can without running for a period of 6 minutes.

Testing Assistant Position and Instructions

As the person filming the test you will want to stand in line with the midpoint of the rope about 6-8 feet back from the rope. From this vantage point, you can follow the participant as they walk alongside the rope and around the markers at each end**.**

To film the test:

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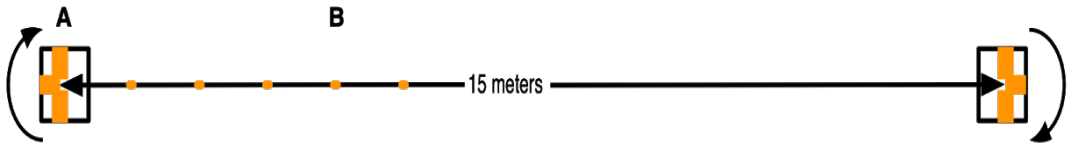
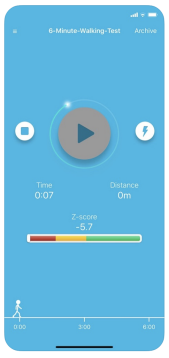
1. Open the camera app on the Samsung device.
2. Have the participant start with their toes in line with a marker at the end of the rope (position **A**) facing the other end of the rope.
3. Make sure the participant is fully viewable in the frame of the screen.
4. Practice starting the test with “3, 2, 1, **GO”**, filming as the participant slowly walks one length of the course.
5. Open the gallery app and make sure you are capturing the video accurately as they move around the course.
6. Open the Camera app and remind the participant to walk as fast a pace as possible without running and to not stop or slow down before you ask them to **STOP**.
7. Place your finger on the red dot and release as you start to say “3, 2, 1, **GO**”.
8. You may tell the participant each minute that has passed.
9. Film the test for 6 minutes and a few seconds (approximately 5 seconds), waiting for the participant to complete the length of the course they are on before telling them to stop.
10. Open the gallery app on the phone and make sure the test was filmed.

Participant Instructions

1. Start with your feet placed at position **A** on the diagram facing the opposite marker.



2. Find the 6WT App on your own device and open it to the screenshot to the right.
3. When the participant and person who is videoing the test are ready, have the person filming start the test with “3, 2, 1, **GO**.” On **GO** start the test on your own device (press the play icon) and place it into your pocket. It will automatically stop when the test is over.
4. Walk as fast but as safely as possible towards and around the marker at the end of the rope.
5. Continue walking until the person filming the test says **STOP**.



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You have completed you tests, well done. If you are tired or unsteady on your feet take a few moments to rest. If you are thirsty make sure to hydrate following your tests.