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The impact of a resistance training intervention on blood pressure control in older adults with Sarcopenia: The INERTIA Study

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LIST OF ABBREVIATIONS

ACCC	Academic Computing and Communications Center
ACSM	American College of Sports Medicine
AE	Adverse Event
AED	Automated External Defibrillator
AHA	American Heart Association
ALM	Appendicular lean mass
AO-C	Assessment-only control
ALM	Appendicular lean mass
ANOVA	Analysis of variance
BMI	Body mass index
BP	Blood pressure
CEAB	Community Engagement Advisory Board
CCTS	Center for Clinical and Translational Sciences
CHAMPS	Community Health Activity Model Program for Seniors
Co-I	Co-Investigator
COPD	Chronic Obstructive Pulmonary Disease
CV	Cardiovascular
CVD	Cardiovascular Disease
DSMP	Data and Safety Monitoring Plan
DXA	Dual Energy X-ray absorptiometry
EWGSOP	European Working Group on Sarcopenia in Older People
GEE	Generalized estimated equations
GLM	growth linear modeling
HDL	High density lipoprotein
HOMA-IR	Homeostatic model assessment for Insulin Resistance
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
IL-6	Interleukin -6
ICOMPASS	<u>I</u> maging bone and body COM position <u>A</u> cross the heath <u>S</u> pan
INERTIA	<u>I</u> nterventional <u>E</u> xercises for <u>R</u> esistance <u>T</u> raining <u>I</u> n older/sarcopenic <u>A</u> ddults
IPL	Integrative Physiology Laboratory
IRB	Institutional Review Board
LST	Lean soft tissue
lb	pound
MCSA	Muscle cross sectional area
MoCA	Montreal Cognitive Assessment
NIA	National Institutes on Aging
NINR	National Institute of Nursing Research
NIH	National Institutes of Health
NHLBI	National Heart, Lung, and Blood Institute
PA	Physical Activity
PI	Principal Investigator
PPM	Physical Performance Measure
PRT	Progressive Resistance Training
RA	Research Assistant

RAND SF-36	RAND short form health survey-36
REDCap	Research Electronic Data Capture
RM	Repetition maximum
SMC	Safety monitoring committee
SAE	Serious adverse events
UIHHSS	University of Illinois Hospital and Health Science System
WHISH	Women's Health Initiative Strong and Healthy

1.0 Project Summary/Abstract

The overall goal of Dr. Deepika Laddu's pilot study (entitled the INERTIA Study) will be to evaluate the feasibility of recruitment, retention, and implementation of an evidence-based exercise intervention in older adults with sarcopenia.

The objective of this randomized control study (entitled, the 'INERTIA Study') is to determine the response and feasibility of patient tailored pilot PRT intervention trial aimed at improving muscle strength and function and reducing blood pressure (BP) in probable sarcopenic adults aged ≥ 60 years. We propose a 12 week evidence-based progressive resistance training (PRT) intervention, adapted from the American Heart Association, that gradually increases training load, frequency and volume from moderate- to- high intensity, in sarcopenic adults to elicit both gains in muscle strength and function as well as reductions in blood pressure. Additionally, we will also conduct focus groups to obtain feedback on factors that affect a person's willingness to exercise, and assess the satisfaction, acceptability of the intervention. We hope the exercise program will be beneficial in strengthening muscles, and reducing blood pressure as well as other heart disease risk factors (high cholesterol levels, blood sugar, and heart rate, HR, inflammation).

This randomized control intervention pilot study will provide new evidence of the unexplored relationship between muscle strength and high BP in sarcopenia, and experimentally test the effects of an evidence-based progressive resistance training intervention on BP, while also examining reversibility to identify muscle strength as a non-pharmacological target for BP control in older sarcopenic adults. Knowledge gained from this study will serve as the basis a definitively powered R01-funded clinical trial that will evaluate the effectiveness of a PRT versus aerobic intervention on BP, and further explore muscle strength as a novel intervention target for BP control in sarcopenic adults.

2.0 Background/Scientific Rationale

Sarcopenia is associated with a progressive loss of muscle mass (1-2% per year), muscle strength (12-15% per year) and physical function after the fifth decade of life, and decreases more rapidly in the sixth decade of life, particularly after age 65¹. With sarcopenia, there is an increased risk of having clinically low muscle strength²⁻⁵, which may have negative effects on blood pressure (BP) in this population. High BP, which is a serious public health problem that disproportionately affects older adults aged ≥ 60 years (prevalence $\sim 65\%$)⁶, compared to the general populations ($\sim 30\%$)⁶, has been evidenced in various international cohorts of sarcopenic adults⁷⁻¹². Likewise, older adults with chronically high BP are more likely to suffer from muscular strength (and function) deconditioning¹³, and a growing body of prospective evidence suggests that low MusS may be a risk factor for high BP in older adults¹⁴⁻¹⁸. Notwithstanding, sarcopenia and high BP are both worsened by the effects of physical inactivity, presenting a positive-feedback loop that results in greater impairments in muscle quality (strength and function), elevated BP, and further decreases in physical activity². Current prevention and treatment of high BP in sarcopenia, by non-pharmacological approaches remain limited and are far from optimal. Emerging evidence from randomized control trials demonstrate progressive resistance training (PRT) can effectively improve muscle strength in sarcopenic adult^{15, 19-21}, whereas different lines of research have demonstrated the effect of PRT on lowering BP in otherwise healthy older adults^{13, 22-27} (i.e., free of cardiovascular disease), with the greatest improvements found in those with elevated BP or hypertension. Physiological mechanisms suggest that PRT may specifically improve endothelium dependent vasodilation to flow in the microcirculation leading to improved muscle perfusion, and reductions in arterial BP. PRT interventions therefore show promise given the evidence for their physiological benefits that would plausibly improve sarcopenia, and potentially provide protective benefits on BP. Yet there is a paucity of empirical evidence that has tested the effect of PRT on BP in a high-risk sarcopenic population. The proposed study will address this gap by engaging older adults, aged ≥ 60 years with probable sarcopenia in an evidenced-based PRT intervention, with a second aim that will explore the reversibility resulting from the PRT intervention, in order to establish muscle strength as a BP target in this sarcopenic population.

This randomized control intervention pilot study will provide new evidence of the unexplored relationship between muscle strength and high BP in sarcopenia, and experimentally test the effects of an evidence-based progressive resistance training intervention on BP, while also examining reversibility to identify muscle strength as a non-pharmacological target for BP control in older adults with probable sarcopenia. Knowledge gained from this study will serve as the basis a definitively powered R01-funded clinical trial that will evaluate the effectiveness of a PRT versus aerobic intervention on BP, and further explore muscle strength as a novel intervention target for BP control in sarcopenic adults.

3.0 Objectives/Aims

The Specific Aims are as follows:

Aim 1. To address limited evidence on treatment of older adults with sarcopenia by pilot testing a 12-week PRT randomized-control intervention (the 'INERTIA Study') on BP in sarcopenic older adults. I will

- 1.1 Experimentally assess the preliminary efficacy and feasibility (recruitment, retention, acceptability) of PRT on changes in MusS, and other core physical performance measures,

and BP levels at 12 weeks among participants randomized to the PRT intervention (N=60) versus assessment-control (AO-C, n=30) group.

1.2 Evaluate whether MusS mediates the effect of PRT on BP at 12 weeks in intervention participants.

1.3 Test whether improvements in MusS and BP are sustained one year following PRT.

Aim 2: To initiate investigations of potential microvascular mechanisms (e.g., endothelial function) that link muscle (perfusion, strength, function) to improved BP status (microvascular function) in a sub-sample (n=15) of intervention and AO-Cs, at baseline and at 12 weeks following PRT. To investigate microvascular function, a subcutaneous gluteal fat biopsy will be conducted at the UIC Clinical Research Center (CRC).

My central hypothesis is that PRT will reduce BP levels in sarcopenic adults.

Improvements in BP may additionally be mediated by improvements in MusS, as well as physical performance measures (i.e. gait speed, chair stands, balance tests), and microvascular vasodilator function.

The primary data collected in this study will be used to explore other, secondary research questions that are related the primary research study. While these questions are usually thought of after the research study has started (and thus, considered secondary data analysis), the following questions have been developed a-priori. *No new data will be collected to answer the following secondary questions and all secondary data analyses are related to the primary research grant objective.

- 1) To evaluate the individual associations between blood markers and blood pressure in sarcopenic adults and effects from progressive resistance training (as noted in the analysis plan and section 12.0).
- 2) To examine the progressive resistance training effects on muscle strength and each physical performance measure and their mediating effect on BP change (as noted in the analysis plan and Section 12.0).
- 3) Evaluate the risk of falling in older adults with sarcopenia (and subsequently, effects of resistance training on fall risk in adults with sarcopenia).—data from DXA scans, and responses from questionnaires (noted in the Approach and methods section of the grant)
- 4) To explore how frailty and blood pressure and related (frailty phenotype based on Fried's frailty phenotype²⁸ physical performance measures [grip strength, slow gait speed], weight or BMI self-reported responses from medical history and CHAMPS questionnaire]

4.0 Eligibility

4.1. Inclusion Criteria:

- Adults (men and women) aged 60 years and older (any racial/ethnic background)
- Sedentary or low active adults
- Free of significant medical or inflammatory conditions (see exclusion criteria for details)

4.2. Exclusion Criteria:

- Subjects with self-report of inability to walk at least ¼ mile or walk 400 meters in <15 minutes without sitting
- Subjects who self-reported having a history of a CVD event or physician diagnosed CVD (heart attack, heart failure, peripheral vascular disease, coronary revascularization, or angina that required overnight hospitalization)

- Subjects who have a baseline history of mental illness, or cognitive impairment (e.g., dementia, Alzheimer's)
- Subjects who have any serious medical condition that prevents adhering to the PRT protocol or exercising safely (such as an orthopedic pathology or deformity, constant use of- or dependence on a cane/wheelchair, scooter)
- Subjects with chronic inflammatory disease, such as, but not limited to **active** cancer (i.e., recent physician diagnosis, currently receiving treatment, or in remission for less than 5 years).
- Subjects with a chronic autoimmune diseases such as, but not limited to: lupus, multiple sclerosis, advanced/severe rheumatoid arthritis **that would preclude exercising safely**
- Lidocaine allergy
- Participants from the same household as those already enrolled in the study
- Unreliability as a study subject, in the opinion of the Investigator
- Baseline Montreal Cognitive Assessment score of <22 (adjusted by adding 2 points for education 4-9, 1 point for education 10-12 years)
- Current participation in another exercise study
- Currently abusing alcohol or illicit drugs
- Subjects who have a history of abuse of alcohol or drugs
- Subjects who plan to move in the next 6 months or take an extended vacation

4.3 Justification for inclusion of any special or vulnerable populations:

1. Mental illness or Baseline Montreal Cognitive Assessment score of <22 which is an evaluation for the presence of mild cognitive dysfunction. Patients with mental illness or mild cognitive dysfunction may have difficulty adhering the program instruction and performing the exercises safely.
2. Subjects younger than 60 years will not be included sarcopenia typically manifests after age 60 years in both men and women of most race and ethnicity groups. However, in certain high-risk groups, high blood pressure is observed as early as age 60 years. Hence, ages younger than 60 will likely be too early to detect significant loss of muscle mass and strength and high blood pressure.

5.0 Subject Enrollment

Recruitment Plan

We expect to screen at least 150 community-dwelling older adults aged ≥ 60 years will be screened from the greater Chicago area, to determine the number of adults needed to enroll 100 participants with sarcopenia into the INERTIA Study. The UIC campus sits in the near west side of Chicago. Older adults (men and women) aged ≥ 60 years will be recruited from the greater Chicago area by advertisements in the UIC online classifieds, and advertisements, social media sites (e.g., Facebook), flyers posted (with permission) in nearby community churches, senior/community centers, libraries, barber shops/salons, and grocery or convenience stores, and cultural centers. Flyers or electronic announcements may additionally be sent to UIC/UIH listservs and the CCTS Community Engagement Advisory Board (CEAB) resources and community partners (i.e., Chicago parks district, community/senior centers). Potential participants may also be identified via the ResearchMatch.org database, an NIH sponsored initiative to improve clinical trial recruitment that is also supported by the UIC CCTS, the "Be The New Normal™ (TNN) " Research registry, an online registry developed as a partnership between UIC and other major universities and clinical and hospital organizations within the

State of Illinois and the Chicago Department of Public Health as a method to improve health research accessibility to all individuals/populations, as well as through the UIHealthRegistry, an online research registry platform recently developed by the UIC CCTS in collaboration with numerous academic and research institutions within Illinois to increase recruitment of potential participants residing in the state of Illinois. We will also recruit with clinician assistance during routine patient visits (UIC PT Family Practice Clinic [Dr. Keil] and University of Illinois Hospital and Health Science System (UIHHSS) including Division of Internal Medicine and Geriatrics Outpatient Clinics [Dr. Kaur]), which includes visits being conducted in person and via telehealth methods. Specifically in scenarios where patients are pre-identified (via routine clinician review of patient charts) or in the case of telehealth visits, clinicians at these approved clinics will pre-identify potential participants who may be eligible for the INERTIA study and provide their contact information (phone number, email) to INERTIA study RAs. Only clinicians will be pre-identifying potential participants, not any of the RAs or lab staff. INERTIA study RAs may use this contact information to recruit over the phone using the already approved phone/email scripts.

Additional methods of recruitment will include use of advertisements, electronic announcements and flyers posted on the UIC campus and clinics (e.g. UIC PT Family Practice Clinic [Dr. Keil] and UIHHSS including Division of Internal Medicine and Geriatrics Outpatient Clinics [Dr. Kaur]).

In addition, the following recruitment method will be utilized to identify potential participants. Potential participants may be recruited via patient letters. The CCTS Biomedical Informatics Core (CCTS - CRDW/UIC CIRCLE) will access medical records to identify eligible patients from the Division of Internal Medicine and Geriatrics Outpatient Clinics. The IRB approved letter to the potential participant will be sent to them to initiate contact if interested, with an option to opt out. The pre-existing approved screening script will be utilized when they call.

To ensure we meet this target number, recruitment will be rolling over years 1-4 (with annual IRB approval, see timeline table in Protocol).

Contact through UIC Campus and Clinics and Community

Potential subjects who are directly recruited from the Faculty Practice or UIHHSS clinics and provide verbal consent may be screened for initial eligibility (via eligibility screener) in a secure and private room at UIHHSS clinic, Faculty Practice or Integrative Physiology laboratory (depending on where they were recruited from) for their convenience. If found eligible, and if time permits, we will ask all potential participants will undergo up to two additional screening procedures (see below).

Contact through community partners, self-referral or via patient letter

Subjects may also be pre-screened by phone.

Alternatively, participants who initiate contact may be initially screened over telephone (see eligibility script). These participants will have the option of receiving an electronic copy of the consent form to review prior to coming into the laboratory to complete the three screening procedures and baseline assessments.

Preliminary Screening

Participants who are eligible (via the eligibility screener), and express interest will undergo two additional screening procedures (depending on whether they meet each screening criteria): 1) Montreal Cognitive Assessment (MoCA) questionnaire, and those with a score of <22 (will be excluded). Adults who pass the MoCA will be scheduled to come to the ICOMPASS Laboratory

located at 1919 West Taylor Street where written and informed consent will occur, prior to the second and third screening. Screening 2 (grip strength) will be used as the definitive measure for eligibility. Specifically, grip strength which will be measured on all interested participants, and those with normal grip strength will be *excluded*. Adults who meet the cutoff for low grip strength will be eligible for the study and will proceed to baseline testing (visit 1).

- For participants who are screened in person (i.e., through clinics), and if time permits, screening 1 and 2 may take place in the same private room and would take about 30min to complete.
- For participants who are screened over the phone, they will complete both screening 1 and 2 procedures during their visit 1 (screening/baseline visit) at the ICOMPASS laboratory.

Initially eligible subjects who are scheduled to come to Dr. Laddu's Laboratory (ICOMPASS, Rm 422) laboratory for screening and baseline testing (visit 1) will also be asked to bring a list of their prescribed medications (or the actual bottles or a picture of bottles) which will be logged on the medical history form.

Additional baseline testing will occur during visit 2. On baseline visit 2, participants will be instructed to come to the CRC for blood specimen collection (and optional biopsy if consent is provided for this procedure). Everyone will be instructed to take all prescribed medications as normal and to continue to drink plenty of water prior to this visit.

Optional testing: The consent form will include additional language asking potential subjects to volunteer for an optional subcutaneous gluteal fat tissue biopsy to evaluate the microvascular system and test endothelial function. These details will be explained thoroughly during the consent process. For those who agree and consent to this optional procedure, an additional 60 minutes will be added to baseline (visit 1) and the post-intervention visit 29. We hope to collect fat tissue from at least 15 subjects, ideally 10 intervention and 5 controls.

All RAs carrying out recruitment will follow a detailed informed consent process that will include a careful review study requirements, explanation of the study protocol including the randomized assignment to the intervention or treatment, details and expectations of the treatment, and will stress importance to completing baseline, and all follow-up assessment visits regardless of whether treatment adherence is less than optimal. This level of detail will not only assure participants fully understand the demands of the study but will also help to optimize retention by screening those who not willing or motivated to adhere to the study. RAs will reach out to non-compliant participants and engage in strategies to re-engage participants into the study.

*From study enrollment to the last day of the exercise intervention: Eligibility will be initially determined over phone (or in person) by the eligibility screening sheet. Eligibility will be confirmed upon completion of the two-step screening process, first by the MoCA and second by the grip strength test. Eligibility will be confirmed upon completion of a medical and exercise history questionnaire. On subsequent visits, subjects will be asked to report any changes in their health status and changes will be noted on a "Health Tracking and Monitoring" form (see Appendix). During the exercise training, research staff will be supervising and closely be observing if any developments or changes with regards to the other eligibility criteria will be noticed and responded. Any observations of change in health status will be documented on the "health status monitoring form". Though monitoring for eligibility status will not continue after the

intervention, subjects will be asked to report any changes in their health at the 1-year follow-up visit.

6.0 Study Design and Procedures

A brief summary of the research design for each Aim is described as follows:

Aim 1 Intervention Model: The intent of this aim is to assess the response and feasibility of the PRT pilot intervention trial aimed at improving muscle strength and function and reducing blood pressure and hypertension risk in sarcopenic older adults. The goals of this pilot intervention are: 1) To test run the intervention for 12 weeks 2) to assess race/ethnic behavioral response differences to the PRT intervention and 3) inform further refinement of study methods including: a) type of resistance training activities; b) intervention session structure (i.e., combined men and women, frequency and duration); c) data collection procedures and measures.

Before starting the exercise portion of the study, all participants (controls and intervention) will report to UIC's Integrative Physiology Lab to receive an exercise familiarization session which will include instruction on proper technique and to practice the dynamic strength testing protocols. (1 hour). Both controls and intervention participants will receive this to make a proper within and between group comparison on upper and lower body muscle strength, the primary exposure variable of interest.

This familiarization session will include muscle strength and endurance testing, in which participants will be asked to do knee (leg) extension, leg press, chest press, seated row or latissimus pull-down, shoulder press, and leg curl and squat one-repetition maximum (1 RM) assessments, using established methods²⁶. The 1 RM represents the maximum weight that can be used to complete a given exercise and approximate the appropriate limb-specific weight loads for resistance training. Attempts of 1 RM with progressively increasing load will be performed with each attempt separated by 90- to 120-s rest intervals. 1 RM is defined as the highest load lifted through a full range of motion before two failed attempts at a given load.

After the 1 RM is determined and baseline data is collected, participants will start the 12-wk intervention and full training protocol.

Aim 1: Intervention Study Design: 60 Sarcopenic participants will be involved in the resistance training exercise intervention. The PRT intervention will be performed at UIC's IPL, ideally in pairs to promote social support. Prior to starting the intervention, intervention participants may request to have another familiarization session; however this is optional and not required as part of the study program.

The PRT protocol will follow the American Heart Association recommendations²⁶ and will include nine total upper-extremity and lower-extremity exercises (seated leg press, chest press, shoulder press, pull down (upper back), triceps extension, knee extension, knee flexion, bicep curl, calf-raises) using resistance training equipment. We will measure blood pressure and heart rate before, one time during, and immediately after the exercise session, and we will ask participants about their relative perceived level of exertion using the Borg scale protocol²⁹ to help guide the trainer on whether modifications to the exercise protocol are needed during a particular session.

Focus Group Framework and Procedures (Qualitative Analysis). The 60 PRT participants (including those who did not complete the intervention) will partake in focus groups (60 min sessions) after the PRT intervention. Using the “grounded theory” approach,³⁰ focus groups will be conducted in men and women separately, to address preferences and barriers, enablers and provide feedback on modifying the intervention. Focus groups will include no more than nine participants per group. If redundancy is not noted, additional participants will be included until saturation is reached, per Strauss and Corbin and Glaser and Strauss recommendations³⁰. Dr. Laddu will moderate focus groups using an interview guide, with semi-structured, open-ended questions and probes, that are pre-tested for clarity, comprehension, and sensitivity and will provide sufficient flexibility to pursue unanticipated facets of topics that emerge in discussions³¹ (**Appendix: Protocols**). Informed by the WHISH trial and CEAB collaborators, common barriers to PA engagement among older adults are a lack of motivation and exercise knowledge, and concern that nagging musculoskeletal conditions may worsen with PA³²⁻³⁴. This feedback will help refine the research design, and future intervention content tailored to older adults with sarcopenia (or similar debilitation). ****(Please see Appendix for Focus Group Protocol and Script)*

Aim 2: Microvascular mechanisms in a subset of subjects: Briefly, to understand physiologically, the effects of the exercise intervention on BP, we propose to measure the microvascular system pre- and post PRT in a subset of this sample ($n_{\text{total}}=15$), using flow-induced dilation (FID) methods learned by Dr. Phillips^{35, 36}. Before and immediately after PRT intervention completion, we will ask 10 intervention and 5 AO-C subjects ($n_{\text{total}}=15$) to volunteer to have endothelial function assessed using microvascular flow-induced vasodilation (FID), as previously described^{35, 36}. This will involve tissue extraction from subcutaneous fat (fat that lies beneath the skin), dissection of resistance arterioles, followed by flow-induced vasodilation (FID), to promote vasodilation and examine endothelial function under varying experimentally-induced pressures.

• **Recruitment**

We expect to screen at least 150 community-dwelling older adults aged ≥ 60 years will be screened from the greater Chicago area, to determine the number of adults needed to enroll 100 participants with sarcopenia. The UIC campus sits in the near west side of Chicago. The total population in this community is 46,419 giving us a strong local pool of possible subjects to recruit. Older adults (men and women) aged ≥ 60 years will be recruited from the greater Chicago area by advertisements in the UIC online classifieds, and advertisements, social media sites (e.g., Facebook), advertisements posted (with permission) in nearby community churches, libraries, barber shops/salons, and grocery or convenience stores and cultural centers. We will also recruit via advertisements, electronic announcements sent to UIC/UIH listservs and flyers posted on the UIC campus and flyers or electronic announcements may additionally be sent to the CCTS Community Engagement Advisory Board (CEAB) resources and community partners (i.e., Chicago parks district, community/senior centers). Finally, potential participants may also be identified via the ResearchMatch.org database, an NIH sponsored initiative to improve clinical trial recruitment that is also supported by the UIC CCTS, the “Be The New Normal™ (TNN) “ Research registry, an online registry supported by the CCTS and developed as a partnership between UIC and other major universities and clinical and hospital and public health organizations within the State of Illinois as a method to improve health research accessibility to all individuals/populations, and the UIHealthRegistry, an online research registry platform recently developed by the UIC CCTS in collaboration with numerous academic and research

institutions within Illinois to increase recruitment of potential participants residing in the state of Illinois.

Potential participants may additionally be recruited through clinics during routine patient visits (e.g. UIC PT Family Practice Clinic and University of Illinois Hospital and Health Science System (UIHHSS) including Division of Internal Medicine and Geriatrics). In these settings, potential participants may be identified by clinicians during routine visits to physical therapy (Co-I, Dr. Aaron Keil, PT- Director of the Faculty Practice) or by their physicians in Internal Medicine or Geriatrics (Co-I; Dr. Tanjiv Kaur, MD, UIHHSS Geriatrics; see Appendix P). Specifically if recruitment takes place during patient in-clinic visits, Drs. Keil or Kaur's involvement in recruitment will be to notify Dr. Laddu or her research team about whether and when any patients aged 60 years or older who meet general eligibility criteria (i.e., no physician diagnosed heart disease, able to walk unassisted, orthopedic disability, etc) are scheduled to be seen in the clinic during the day, or on the following day. Detailed eligibility will be carried out by our research staff. No names or personal identification will be given out. Drs. Keil or Kaur or her team of physicians will simply communicate to Dr. Laddu and research staff that X number of patients (potential participants) who may meet the study criteria will be seen on (date). During a subject's routine visit, Dr. Keil or Dr. Kaur (or her nursing staff who is seeing the patient) will notify Dr. Laddu or her research assistant when they may approach the potential participant about the study (i.e., while the subject is waiting in the private patient room before being seen or after they have been seen by the clinician).

Further, we will also recruit with clinician assistance at these approved sites (Dr. Keil, Dr. Kaur), conducted via telehealth methods (routine patient visits) and by pre-identifying patients through routine patient chart review. In these scenarios, clinicians at these approved clinics will pre-identify potential participants who may be eligible for the INERTIA study and provide their contact information (phone number, email) to INERTIA study RAs. Only clinicians will be pre-identifying potential participants, not any of the RAs or lab staff. INERTIA study RAs may use this contact information to recruit over the phone using the already approved phone/email scripts.

To further optimize recruitment, Drs. Keil and Kaur may also notify other clinicians or medical staff within their respective departments (with IRB approval) who may also contact Dr. Laddu's research staff regarding potential participants who are being seen on the current or following day.

Additionally, at clinics, potential participants may be recruited via patient letters.

To account for generalizability, recruitment will be staggered over years 1-4 (with annual IRB approval, see timeline table in Protocol).

The consent form will include additional language asking potential subjects to volunteer for an optional fat tissue biopsy to evaluate the microvascular system and test endothelial function. These details will be explained thoroughly during the consent process. We hope to collect fat tissue from at least 15 subjects, ideally 10 intervention and 5 controls.

- ***Screening for eligibility:***

The initial contact with a potential participant may occur during their routine clinic visit with a physician or healthcare provider or may occur after the potential participant initiates contact to inquire about the study.

Subjects expressing interest will initiate contact by phone, where eligibility pre-screening will take place (over phone; see telephone script).

Alternatively, potential subjects who are directly recruited from the Faculty Practice or UIHHSS clinics may be screened for initial eligibility (via eligibility screener) in a secure and private room at UIHHSS clinic, Faculty Practice or Integrative Physiology laboratory (depending on where they were recruited from) for their convenience.

Baseline testing may occur over two days. Initially eligible subjects will be invited to Dr. Laddu's ICOMPASS laboratory located at Rm 422 laboratory located at 1919 West Taylor Street, where further preliminary screening, written informed consent, eligibility confirmation and baseline testing will take place (visit 1). Participants will also be asked to bring a list of their prescribed medications (or the actual bottles or a picture of bottles) which will be logged on the medical history form. On baseline visit 2, participants will be instructed to come to the CRC for blood specimen collection (and optional biopsy if consent is provided for this procedure). Everyone will be instructed to take all prescribed medications as normal and to continue to drink plenty of water.

Enrollment (overview)

All RAs carrying out recruitment will follow a detailed informed consent process that will include a careful review study requirements, explanation of the study protocol including the randomized assignment to the intervention or treatment, details and expectations of the treatment, and will stress importance to completing baseline, and all follow-up assessment visits regardless of whether treatment adherence is less than optimal. This level of detail will not only assure participants fully understand the demands of the study but will also help to optimize retention by screening those who not willing or motivated to adhere to the study. RAs will reach out to non-compliant participants and engage in strategies to re-engage participants into the study.

After informed consent is obtained participants will undergo additional screening and procedures that will inform on study group allocation

• Screening/baseline (overview)

Two screening procedures will follow depending on whether criteria is met³⁷⁻³⁹ (**Figure**): The Montreal Cognitive Assessment (Screening 1) and after written informed consent is obtained, the grip strength test (Screening 2) will be carried out to determine probable sarcopenia following to recommended guidelines³⁷⁻³⁹.

1. Prior to sarcopenia screening, the Montreal Cognitive Assessment score (MoCA) will administered in potential subjects to screen for low cognitive function. The MoCA will assess whether mild cognitive dysfunction is detected. Those with a score of <22 (adjusted by adding 2 points for education 4-9, 1 point for education 10-12 years) will be excluded. Adults who pass the MoCA will be asked to provide written informed consent (30 min). Following, screening 2 (grip strength) will be used as the definitive measure for eligibility

2. Screening 2: Grip strength (<5 minutes)—Definitive measure to determine eligibility

Voluntary maximum strength (kg) of **dominant hand** (unless contra-indicated) will be measured using a hydraulic hand grip dynamometer (Jamar dynamometer). Participants will be instructed to squeeze the handle of the dynamometer as hard as they can and hold for 5 seconds during two trials (15 seconds of recovery in between), and the average or higher score will be used in these analyses. **Clinically meaningful weakness (and thus probable sarcopenia) will to determine study eligibility is defined as a grip strength <30kg in men and <20kg in women.**

- Further, adults with low sex-specific grip strength suggesting clinical weakness will proceed to the additional tests to indicate sarcopenia status (via DXA), in which those with low appendicular muscle mass relative to body habitus will be considered to be clinically sarcopenia. Severity of sarcopenia (via the five time sit to stand test) will further indicate severity of sarcopenia; i.e., those with slow five time sit to stand test (>15 seconds or failure to complete) in at least one of the two trials will be considered to have “severe” sarcopenia.
- However, the 5TSTS and the DXA scan will not be used to determine eligibility.
- Probable Sarcopenic adults will be then be asked to complete baseline data collection, and after, will be then be randomized in this randomized-control study.
 - If potential participants are recruited in person from clinical areas, Screening 1 may take place in a private room and take about 15-20 min to complete. Screening 2 may also occur in the private room after informed consent is provided (30 minutes total to complete two screening steps)
 - Potential participants who are recruited over the phone must undergo both screening procedures in the ICOMPASS laboratory during the visit 1.

At the end of the study, we will destroy the key that links the name and any health information collected with the blood and fat tissue information and participant (i.e., all information will be de-identified). The following health information will be banked with the blood and fat tissue samples: randomization arm, age, race/ethnicity, diagnosis of sarcopenia, grip and muscle strength measures, physical performance results (gait speed, chair stand, balance test, timed up and go), sex/gender, test results (including cholesterol, insulin, glucose, IL-6), microvascular testing results, weight, height, and body mass index. For each clinic visit, participants will receive a reminder phone call, or text, prior to the study visit (see reminder visit script).

During the surveillance period (12-weeks to one-year follow up) follow-up calls (up to 12 calls total) will be made by research staff once a month to intervention and control participants to check in on their well-being. Intervention participants may additionally be asked to report on whether exercise behaviors are being maintained, the duration and frequency, and any barriers experienced to maintaining training. Responses will be recorded in their file and in REDCap. Participants who completed the 12 week clinic visit will also be invited to the IPL (research gym) once a month during the surveillance period to conduct resistance training exercises on their

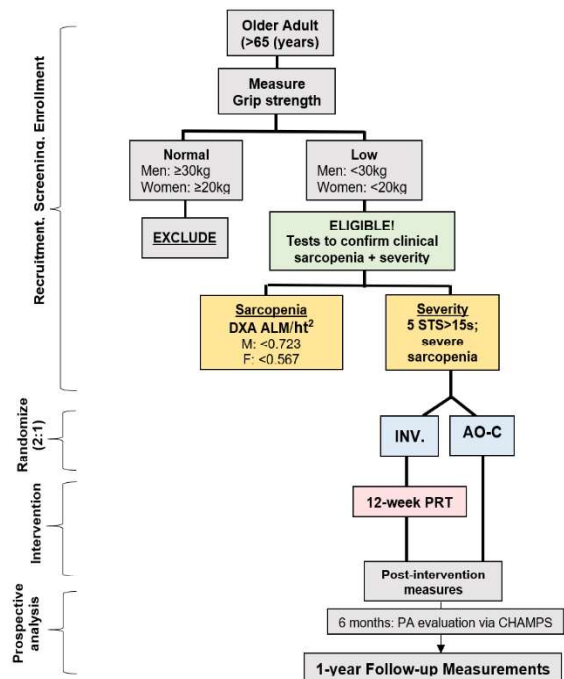


Figure. Modified algorithm for sarcopenia classification and study events
INV. intervention. AO-C. assessment-control

own, (**up to 12 optional visits total**), with monitoring and assistance by a trainer as needed. It will be stressed to participants that exercise visits after completing the 12 week intervention period are optional and not required. Importantly, no formal prescription or instructions will be provided. Additional details are described in Item G of the procedures.

Thus:

- Intervention participants will be asked to come for a total of 30 visits over 1 year (including screening and baseline (visit 1); baseline visit 2; 12 weeks of exercise intervention (plus one mid-intervention visit; total 25 visits); 1 mid-intervention visit, 1 postintervention, and a 1-year follow-up visit).
 - If intervention participants who completed the 12 week clinic visit opts in to the optional exercise sessions during the surveillance period, they may engage in up to 42 visits over the 1 year.
- Sarcopenic controls will only be asked to complete up to 4 visits (baseline visit 1, baseline visit 2, post intervention, 1 year follow up).
 - If control participant completed the 12-week clinic visit and chooses to engage in the 12 optional exercise sessions, then they may attend up to 16 visits during the 1 year study timeline.

A detailed outline of the study procedures (Figure below)

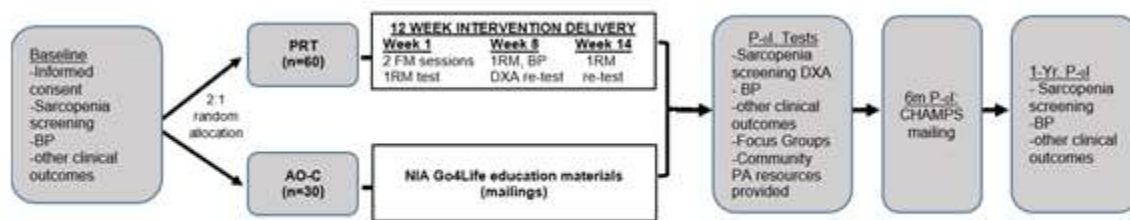


Figure Study visit activities and outcomes collected for AD-C and intervention participants; P_{int}, post-intervention

During visit 1, participants will be asked to bring a list of their prescribed medications (or the actual bottles or a picture of bottles) which will be logged on the medical history form. During baseline visit 2, confirmed and consented eligible subjects will be scheduled to come to CRC for blood specimen collection, for screening and baseline testing (visit 1). **Everyone will be instructed to take all prescribed medications as normal and to continue to drink plenty of water.**

In the case that a participant is not able to complete baseline (V1 or V2), post-intervention (V29) or 1-year follow-up (V30) testing in a single visit (respectively), they will be asked to return to the ICOMPASS laboratory or IPL to complete the remaining assessments within 7-14 days of the prior visit. To manage time, questionnaires pertaining to physical functioning (SF-36), physical activity (CHAMPS), or mood/depression (CES-D) may be sent home with the participant at their request, in which case research staff will schedule a phone meeting to collect responses over phone, or will request the participant return in person questionnaires within 7 to 14 days of the previous visit. See below for additional details.

A. Screening and Baseline Data Collection Week 1 (visit 1, 3 hour visit total)

Screening (if these procedures were not already performed) ~30 minutes: Three screening procedures will follow depending on whether criteria is met: The Montreal Cognitive Assessment (1) and following written informed consent, grip strength (2) to determine probable sarcopenia and eligibility into the study. Each are described below:

1a. Additional screening to evaluate low cognitive function via the Montreal Cognitive Assessment (MoCA, Screening 1). The MoCA will assess whether mild cognitive dysfunction is detected. Those with a score of <22 (adjusted by adding 2 points for education 4-9, 1 point for education 10-12 years) will be excluded. Adults to pass the MoCA test will be asked to provide written informed consent before proceeding to screening 2 and 3 .

1b. Screening for clinical weakness by grip strength (2 min)- Definitive measure to determine eligibility: grip strength (Screening 2) Voluntary maximum strength (kg) of dominant hand will be measured using a hydraulic hand grip dynamometer (Jamar dynamometer). Participants will be instructed to squeeze the handle of the dynamometer as hard as they can during two trials, and the average higher score will be used in these analyses. Clinically meaningful weakness will determine study eligibility is defined as a grip strength <30kg in men and <20kg in women. Grip strength will not only be treated as the eligibility screening criteria, but also as the potential mediator. Adults who meet the cutoff for low sex-specific grip strength suggesting clinical weakness will be eligible for the study (consent + grip strength~30 min)

Following informed consent and enrollment, **90 enrolled sarcopenic participants will be randomized to PRT using 2:1 allocation procedure (computerized random numbers).** Randomization scheme table will be generated using permuted block method with stratification on baseline BMI and gender, and the procedure will be done using REDCap (Research Electronic Data Capture) system, which ensures allocation concealment. This will be conducted by a staff member having no knowledge of the participants' baseline profile. BP will specifically be evaluated in 60 intervention participants and compared to 30 assessment-only control (AO-C) participants.

Control participants will receive education material (or emailed via REDCap if requested) NIH/National Institutes on Aging (NIA) Go4Life® educational materials every 3 weeks . Materials include non-specific at-home exercises focused on endurance, balance, strengthening, and flexibility with minimal equipment and items commonly found at home (chair, tennis ball, soup cans). A total of 4 mailings will be sent to controls during the 12 week exercise intervention. With each exercise mailing, we will include an exercise log that asks participants to document the type and duration of exercise performed each day, along with any comments they wish to share. Control participants will be asked to complete an exercise log for every day exercise is performed (regardless of whether it is from the exercise materials received or other exercise, or no exercises performed), and return to the ICOMPASS laboratory 3 weeks after receipt.

Intervention participants will feed into the 12-week PRT program. Intervention participants will report to UIC's Integrative Physiology Laboratory located at 1640 West Roosevelt for the exercise intervention. During this time and throughout the intervention study period, ongoing efforts to maintain engagement and optimize retention of control participants.

The following procedures will be collected in **all** eligible (sarcopenic) adults:

1. **Secondary confirmation of Sarcopenia status by Dual Energy X-ray Absorptiometry (DXA): (20min).** The DXA scan will occur after written informed consent has been obtained.

As part of the most recent 2019 European Working Group on Sarcopenia in Older People (EWGSOP), muscle quantity assessment of sarcopenia serves a secondary confirmation of sarcopenia diagnosis, following poor grip strength and five time sit to stand test performance.³⁷⁻³⁹ . However this DXA scan will not be used to determine eligibility.

Appendicular lean mass (ALM, sum of lean soft tissue of the extremities, minus bone mineral content) will be measured from total body scans on all participants using the Horizon A Platform (Hologic Inc., Bedford, MA, USA) with Apex software version 5.5 and standard positioning techniques. The total test takes 20 minutes, including changing into clinic gowns. Total scan acquisition times takes approximately 3-7 minutes, with a weight limit of 227 kg (500lb).

Whole body and regional body fat compartments, lean soft tissue (LST), fat-free mass (sum of LST and bone mineral mass), and bone mineral mass will also be obtained from whole body DXA scans.

During a DXA scan, low-radiation x-rays of 2 different photon energy levels pass through the body and are identified by a photon detector that measures the amount of energy absorbed (attenuation) by soft tissue and bone at each pixel. Soft tissue is further subdivided into fat and LST based on the empiric attenuation of both pure fat and bone-free soft tissue. The attenuation of these two x-ray energy beams can be quantified as a function of the elemental composition of tissue and is illustrated as a relative attenuation number (R-value), fat mass having a lower R-value (reflecting lower density), lean (muscle) mass having a higher R-value, and hence, higher density, and bone having the highest R-value (density). DXA measures of total body fat mass and fat free mass are validated⁴⁰ and generally correlate highly with criterion methods⁴¹⁻⁴³. The Hologic body composition methods were calibrated in a large (n = 1,555 participants) multi-center study using deuterium dilution, hydrostatic weighing and 4-compartment models⁴⁴.

Sarcopenia confirmation will be determined immediately after scanning, using the operational EWGSOP criteria, defined as clinically low ALM/ht²<0.723 (men) and <0.567 (women)³⁷. Participants will be instructed to avoid alcohol and caffeine before the exam. Machine QC and calibration is conducted daily using Hologic's automatic internal reference system.

As part of this study, we will provide participants with a copy of the DXA scans to keep for their own records. However, we will not provide any medical advice concerning the results of the scan. If we learn anything that is considered to be clinically relevant and thus important to their health or treatment (e.g., low bone mineral density), we will share this finding with the participant in person, however, we will not provide any advice, nor will we share results with their physician regarding this finding. We will instruct participants to meet with experts should the chose to learn more about these study results.

The amount of radiation exposure by DXA is considered small and safe for repeated measures. The radiation exposure from this research is about 60 microsievert (units of radiation). The amount of radiation is approximately equal to 6 days of radiation exposure from natural sources like the sun, ground and water (approximately 0.05 microSieverts (units of radiation) - 45 microSieverts). This research gives you about the same amount of radiation as you would get from living in a high altitude city such as Denver for 4 days, or taking 1 airplane flight from New York to Los Angeles. This amount of radiation involves minimal risk and is necessary to obtain the research information.

2. Anthropometric and vitals data collection: (30 min)

- a. Weight
- b. Height
- c. Body mass index (BMI)- computed using weight and height
- c. Waist circumference
- d. Blood pressure and heart rate

3. Questionnaires (30min)—See Appendix for forms

- a. Medical History (includes including lifestyle and diet habits and medication information)
- b. CHAMPS Physical Activity Questionnaire
- c. Self-reported physical functioning (RAND SF-36)
- d. Center for Epidemiologic Studies Depression Scale (CES-D)

4. Physical Performance testing (30 min)

- a. 4 or 6-meter gait speed
- b. grip strength
- c. 4-stage balance
- d. Timed up and go test (assessment of mobility)
- e. 5-time Sit to stand (5STS) test ***used to assess sarcopenia severity**
 - The chair stand test measures the amount of time needed for a participant to rise five times from a seated position without using his or her arms. Participants will be instructed to perform the five time sit to stand test as fast as they can during two trials.
 - Subjects must rise fully and backs should not touch the backs of the chair (this is ok, but not recommended) and sit back down completely.
 - inability to complete five repetitions without assistance or use of upper extremity support indicates failure of the test
 - >15 seconds to complete 5 chair stands indicates severe sarcopenia and warrants intervention^{38, 39}
 - Participants who meet the criteria for slow chair stand performance in either trial 1 or trial 2 also indicates probable severe sarcopenia.

5. Muscle Strength and Endurance testing; Familiarization #1 (1 hour)

Both controls and intervention participants will receive this to make a proper with-in and between group comparison on upper and lower body muscle strength, the primary exposure variable of interest. For those in the intervention group, it will also serve as a method to familiarize participants with equipment they will use during the 12 week exercise period.

- a. All 90 participants will report to UIC's Integrative Physiology Lab for an exercise familiarization session to receive instruction on proper technique and to practice the dynamic strength protocols to perform the muscle strength and endurance testing.
- b. Dynamic Strength testing- participants will be asked to do knee (leg) extension, leg press, chest press, seated row or latissimus pull-down, shoulder press, and leg curl and squat one-repetition maximum (1 RM) assessments. The 1 RM represents the maximum weight that can be used to complete a given exercise, and approximate the appropriate limb-specific weight loads for resistance training. Attempts of 1 RM with progressively increasing load will be performed with each attempt separated by 90- to 120-s rest intervals. 1 RM is defined as the highest load lifted through a full range of motion before two failed attempts at a given load

To be conducted at the CRC

B1. Week 2, Baseline Visit 2: Blood collection and Familiarization Session, Optional Fat Biopsy Aim 2: (total participant time, 1 hour; 1.5 hour total if volunteer for optional fat tissue biopsy for microvascular testing):

If Participants do not opt to complete blood tests during week 1/visit 2, they will be asked to come to the CRC to complete the blood (and) fat biopsy test. **Everyone will be instructed to take all prescribed medications as normal and to continue to drink plenty of water.**

This visit will be scheduled as soon as Visit 1 is completed, no later than within 7-14 days from Visit 1.

1. Blood draw of 30 ml, or about 2 tablespoons per person of blood (12 hours) to characterize biochemical profile including:

- a. Total Cholesterol
- b. High Density Lipoprotein (HDL)
- c. Low-density lipoprotein
- d. insulin and glucose level (used to calculate HOMA-IR)
- e. Interleukin-6 (IL-6)

Optional Microvascular testing: Subcutaneous gluteal fat biopsy(Aim 2) (60 min)

a. Biopsy procedure performed at the CRC: Subcutaneous fat biopsies have been use by us and others to investigate microvascular function in humans. **Biopsy procedure:** Subcutaneous fat biopsies have been used by my con-investigator, Dr. Philips and others to investigate microvascular function in humans and the procedure is associated with minimal discomfort. Biopsy procedures will be performed by a trained physician or advanced practice nurse using sterile technique. A small fat biopsy will be obtained just underneath the skin (subcutaneous). After the skin is locally anesthetized with a small amount of lidocaine (1% buffered solution), an incision (0.5-1 cm) will be made to expose the subcutaneous fat that extrudes through the incision site. Approximately 1-2 ml of fat tissue will be removed by sharp dissection and the incision will be closed with Steristrips and covered with a waterproof clear bandage. If sufficient fat tissue cannot be obtained from sharp dissection, the subject may also undergo a syringe aspiration of fat tissue from the same site. Since fat tissue is relatively avascular and will be obtained under direct inspection, there is minimal risk of excessive bleeding or other complications. Individuals will be instructed to keep the area dry for 24-48 hours after which the bandage can be removed. The Steristrips will remain in place until they spontaneously fall off in approximately 4-5 days.

Microvascular Function in Dr. Phillips laboratory (AHS 124): SF will be immediately isolated from the gluteal biopsy, followed by dissection of resistance arterioles, ~100 μ m diameter (~4), and prepared for flow induced vasodilation (FID). Two to three microvessels will be dissected from extracted fat tissue and transferred to a videomicroscopic apparatus for continuous measurement of vascular diameter during application of pharmacological and physiological stimuli (i.e., single vessels will be maintained in an organ perfusion chamber at an intraluminal pressure of 20 mmHg for 30 min for testing under various controlled pressures to examine the function of the brachial artery in pumping blood). Single vessels will be maintained in an organ

perfusion chamber at an intraluminal pressure of 20 mmHg for 30 min, after which pressure will increase slowly to 100 mmHg and maintained for 30 min. Vessels will be precontracted 30–50% with endothelin-1 (ET-1; 100–200 pM). After an equilibrium period, changes in the vessel diameter will be determined to step increases in intraluminal flow (from 0 to 50 µl/min; induced by a pressure gradient). Experiments will be performed in the absence and presence of the eNOS inhibitor L-NAME (10⁻⁴ M) or polyethyleneglycol catalase (PEG-CAT; 500 U/ml) to block NO production and reactive oxygen species (ROS) during FID. In the case of impaired vasodilation superoxide and hydrogen peroxide generation in microvessels will be prevented with MnTBAP and catalase, respectively. In separate experiments these inhibitors will be applied to the microvessels for 30 minutes prior to administration of flow or agonist induced dilation. In these studies, microvessels will be incubated with the fluorescence indicators dichlorofluorescein and dihydroethidium for H₂O₂ and superoxide, respectively. ROS measurements will be obtained prior to and during the application of an agonist or flow through the vessel. Some arteries will not be placed into an apparatus, but rather will be prepared for evaluation of arterial wall concentrations of endothelial nitric oxide synthase and free radical production (hydrogen peroxide and peroxynitrate) (via Western blot techniques).

2. All intervention participants will have the option to return to UIC's Integrative Physiology Lab to receive an additional exercise familiarization session to receive instruction on proper technique and to practice the dynamic strength testing protocols. All control participants will have the option to return to the IPL or the ICOMPASS laboratory (depending on availability) to receive instruction on the educational exercises that will be provided in mailings over the 12-week exercise period. For both participants, the familiarization/education component is optional and not necessary to continue with the program.

After eligibility is confirmed and baseline data is collected, intervention participants will start the 12-wk intervention and full training protocol.

C. 12-week Resistance Training Intervention Protocol + 1 week of mid-intervention assessments Total 13 weeks: Visit 3-27, Week 3-16.

- 60 sarcopenic adults will participate in the supervised 12-week PRT intervention. The proposed 12-week study is consistent with American Heart Association (AHA) and the American College of Sports Medicine (ACSM) recommendations for PRT²⁶ and similar resistance programs^{45, 46}
- Exercise training protocol at UIC's Integrative Physiology Lab (IPL) at 1640 West Roosevelt; (1 hour, 30 min including warm up each session)
- Each participant will be asked to attend 2 visits per week.
 - 2 non-consecutive days a week participation: **36 hours total**

Each session will begin with a 10-minute warm-up of low-intensity aerobic exercise (treadmill walking) and flexibility exercises targeting the major muscle groups. Additionally, we will measure blood pressure and heart rate before, one time during, and immediately after the exercise session (see below for contraindications).

The PRT intervention will be performed at the IPL, ideally in pairs to promote social support and to maximize pragmatic and feasibility of design. The PRT protocol will include eight to nine total upper-extremity and lower-extremity exercises (squats, seated leg press, seated row or latissimus

pull-down, chest press, knee/leg extension, leg curls, shoulder press, triceps flexion /bicep curl, calf-raises, supine glute bridges) using resistance training equipment. Participants will start the 12-week full training protocol with 1 to 2 sets/exercise, resistance at 40-50% of their 1-RM (established during the strength/familiarization session), 10-15 repetitions (reps) per set for 2 non-consecutive days for the first week. On week 2, subjects will perform 3 sets of 8-12 repetitions with a moderate-intensity training load of 60-65% 1-RM. By week 3, participants will perform 3 sets of 8-12 repetitions with a moderate-to-vigorous intensity training load of 70-75% 1-RM. By week 4, participants will perform 3 sets of 8 to 12 repetitions with a moderate-intensity load of 80% 1-RM. Once overload is reached (that is, the “upper limit” of the prescribed repetition range), gradual increases in reps (i.e., 12-15 reps), then the training load weight may increase by 5% (~5% increase in weight; e.g., 2 to 5 lb increase in weight for arm exercises, 5 to 10 lb increase in leg exercises). Finally, once overload of the prescribed loaded weight is achieved, then increasing the number of sets per exercise, and decreasing the rest period between sets or exercises will follow.. Resistance will be incremented only when a subject completes 12 reps for at least two of the three total sets at a given resistance. In addition to measuring performance, we will also ask participants about their relative perceived level of exertion using the Borg scale protocol²⁹, which is scaled from 1-10, with 1 rated as “really easy,” and 10 rated as “maximal, just like my hardest race”.

1-RM testing will be repeated at week 6 of the intervention (week 8 of study), post-intervention and at 1-year to evaluate improvements and maintenance in muscle strength and function. BP, DXA will re-assessed at week 8 to capture timing of BP change, relative to changes in muscle mass and strength.

All tests will be performed under standardized conditions in a stable laboratory environment and monitored by a qualified exercise physiologist and/or research staff. Each session will end with a 5-minute cool-down of stretching, and flexibility exercises. Participants will be asked to fill out a brief exercise acceptability questionnaire at the end of each session. Pre and post workout snacks and water will be provided throughout the 12-week intervention.

Special considerations/contraindications: Having too high of uncontrolled blood pressure (i.e. no medication) prior to exercise is considered a contraindication to exercise as per ACSM and AHA guidelines. The following considerations should be evaluated to determine if a person is eligible to participate in a planned exercise session visit.

- If initial or 2nd BP is too high SBP \geq 200 mmHg **OR** a DBP \geq 110 mmHg, then have the participant rest for 6-10 min and recheck.
 - If the BP remains too high then they cannot exercise. In this case, we will provide the participant with water and ask them to remain seated for 5-10 minutes before escorting them to their vehicle or mode of transportation to ensure safety of the participant.
 - Participants will be encouraged to consult with the physician to discuss to blood pressure reading. However, since is study is for research purposes only, none of our research staff will be contacting participant’s physician. Follow up will the participant’s responsibility.
 - Participants with a BP \geq 200 will sit out from the exercise session without being completely excluded from the study. If a participant

consistently has high BP \geq 200 at 3 visits (i.e. 3 readings measured during 3 separate visits), the PI has liberty to exclude them from the study

- If an unexpected event were to occur (i.e., fainting, loss of consciousness), we will immediately call 911 and/or 5-5555 for Campus/ Police Emergency, as well as alert the IPL manager.
 - If BP comes down but remains high after the warm up, have the participant do the warm up and then recheck.
 - If BP comes down but remains high after the warm up (i.e., SBP <200 mmHg OR a DBP <110 mmHg), have the participant do the warm up and then recheck.
 - If after warmup and rechecking and BP remains high but within the range that permits exercise safely, allow the participant to do one set of exercises and then recheck BP. Continuously monitor patients for signs and symptoms that would warrant immediate medical attention (see next bullet point)
 - In patients with a BP that remains elevated (and despite meeting BP standards that would permit exercise safely), RAs should check for additional symptoms that would qualify for urgent medical attention. In patients who experience fainting or loss of consciousness or who exhibit symptoms such as shortness of breath chest pain, change of vision, difficulty speaking, urgent 911 calls to request immediate medical assistance should be placed by the RA

Mid-intervention (week 8): Re-assessment ~2 hours max

- Reassessment of the following measures will be conducted after 6 weeks of the exercise intervention has been completed (and at the last training session of exercise intervention) to capture timing of BP change relative to changes in muscle (mass, strength, mass) and performance.
- DXA scan
- 1-RM test – (Section B1 above; also to be re-assessed on the last day of the 12 week exercise program)
- BP
- Physical performance including grip strength and the five time sit to stand test

D. Post-Intervention Assessments (Visit 28, week 17) and 1 year follow-up visit (~visit 30 week 69): (3 hours for Post-intervention visit; 4 hours if volunteer for optional fat tissue biopsy for microvascular testing; 3 hours for 1 year follow-up visit): All participants (intervention and Controls) will report back to Dr. Laddu's ICOMPASS laboratory for testing. We will also ask participants to bring a list of their prescribed medications (or the actual bottles or a picture of bottles) which will be logged on the medical history form.

Participants will repeat baseline testing:

1. DXA scan of muscle mass (quantity); secondary sarcopenia measure
2. Anthropometric and vitals data collection:
 - a. Weight
 - b. Height

- c. BMI
 - c. Waist circumference
 - d. Blood pressure and heart rate
3. Questionnaires (30min)—See Appendix for forms
 - a. Medical History (includes including lifestyle and diet habits and medication information)
 - b. CHAMPS Physical Activity Questionnaire; *** the CHAMPS questionnaire will also be reassessed at 6 months post intervention.
 - c. Self-reported physical functioning (RAND SF-36)
 - d. Center for Epidemiologic Studies Depression Scale (CES-D)
 4. Physical Performance testing (30 min)
 - a. 4 or 6-meter gait speed
 - b. grip strength
 - c. five time sit to stand (chair stands)
 - d. 4-stage balance
 - e. Timed up and go test (assessment of mobility)

5. Repeat Muscle strength/endurance testing: (~45 min-1 hour total):

*Participants in the intervention may perform this on the last day of their intervention visit.

To be conducted at the CRC

Here, we describe it as part of the post-intervention visit and **not** a separate visit

6. Blood draw of 30 ml, or about 2 tablespoons per person of blood (12 hours), to characterize biochemical profile including:
 - a. Total Cholesterol
 - b. High Density Lipoprotein (HDL)
 - c. Low-density lipoprotein
 - d. insulin and glucose level (used to calculate HOMA-IR)
 - e. Interleukin-6 (IL-6)

6. Optional Microvascular testing -(Aim 2) (60 min)

Repeat subcutaneous gluteal fat biopsy procedure performed at the CRC (no repeat at 1 year visit)

E. Post Intervention Focus groups (week 18, visit 29; 1 hour max) The 60 PRT participants (including those who did not complete the intervention) will partake in focus groups (60 min sessions) after the PRT intervention. Focus groups will include no more than nine participants per group. The goals of the focus groups include: identify potential barriers to PA related to their sarcopenia, potential motivators, and provide feedback on recommendations regarding culturally-sensitive methods to recruit and engage in exercise. Participants will also be asked to provide suggestions on the recruitment materials, as well as content, structure, and approach of the resistance training intervention, as well as common barriers to PA engagement among older adults are a lack of motivation and exercise knowledge, and concern that nagging musculoskeletal conditions may worsen with PA³²⁻³⁴. This feedback will help refine the research

design, and future intervention content tailored to older adults with sarcopenia (or similar debilitation).

F. 6 month PA activity questionnaire reassessment via mailing (~week 38) ~10minute (NOT A CLINIC VISIT)

The CHAMPS physical activity questionnaire will be emailed via REDCap or postal mailed with pre-stamped return envelope to all participants.

G. Surveillance period follow up calls and Optional Exercise Session visits for all participants: Once per month (12 optional visits total) ~60minutes

During the surveillance period (12-weeks to one-year follow up) follow-up calls (up to 12 calls total) will be made by research staff once a month to intervention and control participants to check in on their well-being. Intervention participants may additionally be asked to report on whether exercise behaviors are being maintained, the duration and frequency, and any barriers experienced to maintaining training. Responses will be recorded in their file and in REDCap.

Further, all participants (intervention and control) who have completed the 12-week clinic visit will be offered the option to attend the IPL research gym to perform resistance training exercises on their own, one time per month during the surveillance period (**up to 12 optional visits total**). The purpose of these optional exercise sessions are consistent with constructs of the Social Cognitive Theory⁴⁷ and Transtheoretical Change model⁴⁸ for behavior change, to promote adoption of the tailored PRT program, optimize behavioral maintenance, and maximize the likelihood of achieving improvements in blood pressure outcome and muscle strength gains. Consistently, in intervention participants, the optional sessions will assist in reinforcing strength training behaviors and supporting maintenance of learned behaviors following the 12-week intervention, and among control participants, will encourage and promote resistance training exercise behaviors. All sessions will be monitored by the trainer, and assistance will be provided as needed. However, no formal exercise prescription or structured one-on-one training instruction will be provided. Blood pressure and grip strength measurements will be taken prior to exercise to monitor potential changes in strength. Additionally blood pressure will be assessed after exercise completion. Other precautionary steps to ensure participant safety including evaluation of contraindications to exercise will be followed during the optional training sessions, as described above and in Section 7.0 (Risk and precautions).

Throughout the entire study:

Various retention activities will be followed to maintain contact, and optimize retention and engagement with both intervention and controls participants, such as: Raffles for low-priced gift items (e.g., coffee mug, water bottle, resistance band, Walgreens gift card), Birthday Cards, Cards for national holidays; Cards for monthly awareness and events (e.g., Feb- national heart month, October- National Diabetes month); Monthly newsletters (examples): Feature on research team members; Healthy heart diets and recipes; Fun facts; Activities taking place in Chicago, and Bingo activity days.

Retention activity content will be carefully designed to ensure that materials do not contain information related to the intervention or study outcomes.

• **Specimen collections:**

Adipose tissue biopsies: these samples will be stored in HEPES buffering solution or saline and transported from the CRC to the Phillips Lab in the College of Applied Health Sciences.

After vessels have been extracted from the samples, they will be discarded in a biohazard waste container. They will be labeled solely with the subject's study ID number. Only study staff will have access to these samples.

- **Blood and Tissue storage**

At the time of consent, we will provide participants the option to bank blood and fat tissue for any future research studies. We will explain to each participant that all study data and blood and tissue collections will be immediately coded with the key locked in the PI's office (AHS 443), and only accessible to the PI. At the end of the study, we will destroy the key that links the name and any health information collected with the blood information and participant (i.e., all information will be de-identified). The following health information will be banked with the blood:

randomization arm, age, race/ethnicity, diagnosis of sarcopenia, grip and muscle strength measures, physical performance results (gait speed, chair stand, balance test, timed up and go), sex/gender, blood test results (including cholesterol, insulin, glucose, IL-6), microvascular testing results, weight, height, and body mass index.

Blood and Tissue coded samples will be stored in a secure freezer in Dr. Phillip's laboratory (AHS 124), with access limited to Dr. Laddu and approved study personnel.

Compensation

In year 1 We will pay \$25 (1st testing visit) to the 90 individuals that will be screened and complete baseline blood measurements (**\$2250 total**). The form of payment will be a **\$25 cash or check or a VISA gift card and provided upon completion of the visit 1 tests**.

In year 2, we will reimburse the 60 intervention participants \$125 if they complete the 12 week exercise intervention (**\$7,500 total**). If a participant drops out in the middle of the intervention, they will be compensated depending on how much of the 12-week intervention they completed (i.e., 4 weeks or less - \$50, at least 6 weeks- \$75, 7 to <12 weeks- \$100), see table below. We anticipate the total **\$7,500** subject reimbursement to be distributed as follows: Year 2: \$2,000; Year 3: \$4000; Year 4: \$1,500

In the beginning of Year 3, the 60 intervention and 30 control participants will receive \$25 (**total \$2,250**) for completion of post-intervention follow up visit tests.

At year 4, the 60 intervention and 30 control participants will receive \$50 (**total \$4,500 total**) for completion of the 1-year follow up visit tests.

In addition, we may reimburse for transportation to/from the University via bus/train/PACE (\$3) for exercise training sessions and for other visits during the 18 weeks of the study, at 1-year follow up visits for all participants who attend the requested study visits during the study period.

Subjects will receive \$25 by cash/check upon completion of the visit 1 and visit 2 tests. If subjects are participating in the exercise intervention, subjects will receive a cash/check for the number of sessions completed (i.e. first 4 exercise sessions completed, subjects will receive \$20, completion of 8 sessions, they will receive an additional \$20; completion of 12 sessions, they will receive an additional \$20. The summation of the compensation from session completed at the end of 12 weeks totals \$125

If subjects do not finish the study, they will be compensated for the visits they do complete. Details of pro-rated compensation is described below (Table 1).

Visit	Compensation Amount	Payment type
Education and exercise Group – total \$100 if all three visits are completed		
Baseline testing (Clinic visit 1 and visit 2)	\$25 will be received	Cash, check or GC
Post-intervention testing (Clinic visit 28)	\$25 will be received	Cash, check or GC
1-year testing (Clinic visit 30)	\$50 will be received	Cash, check or GC
Exercise participants only (may receive up to an additional \$20 if all sessions completed)		
Completion of 4 sessions	\$20 will be received	Cash, check or GC
Completion at 8 sessions	Additional \$20 will be received	Cash, check or GC
Completion at 12 sessions	Additional \$20 will be received	Cash, check or GC
Completion of 16 sessions	Additional \$20 will be received	Cash, check or GC
Completion of 24 sessions	Additional \$45 will be received	Cash, check or GC

Example: if 8 sessions total are completed, the participant will be awarded \$40; if 16 sessions total are completed, the participant will be awarded \$80.

*** **Optional fat biopsy:** Participants who opt in for the optional fat biopsy procedure may receive compensation (\$10 per biopsy pre-intervention and \$10 post intervention by cash/check upon completion of the procedure at each time point

Lottery/raffles to boost retention

Regardless of randomized group, each participant will have equal chance of earning tickets for the raffle

Intervention group: To motivate participants to maintain attendance and adherence in training, a bingo card will be given. After each session, the participant will have the chances to roll the dice and the corresponding square on the bingo card will be stamped. When one stamped line is completed on the bingo card, the participant will earn one raffle ticket. The more lines completed, the more raffle tickets a participant earns. A new bingo card will be distributed every 6 weeks, there is a possibility of getting 12 stamps total. To make a line, you need 4 stamps so a participant can only win a maximum of three raffle tickets per bingo card. **(6 tickets max possible over the 12 week period).**

The raffle tickets will be entered in the raffle box. One raffle ticket will be drawn every month over the 3 months [12 week] for a prize (water bottle, t-shirt, coffee mug; resistance band, Walgreens gift card, etc.). **Total prizes draw for intervention group = 3 prizes**

Control Participants

To motivate participants to maintain interest in the program, we will use different retention methods. One such method is allotting them **two raffle tickets** every time they mail back a completed exercise log (3 returned mailings over 12 weeks, **6 tickets max possible**).

The raffle tickets will be entered in the raffle box. One raffle ticket will be drawn every month (over the 3 months [12 week] period for a prize (water bottle, t-shirt, coffee mug, resistance band, Walgreens gift card, etc etc.). **Total prizes draw for control group = 3 prizes**

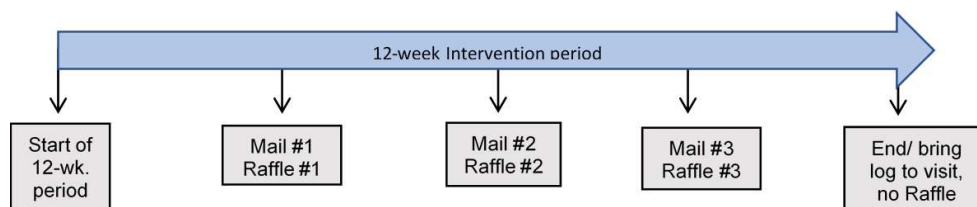
	1	2	3	4	5
1	WEIGHT	HEALTH HISTORY	MDL	GRIP STRENGTH	2 STAGE BALANCE
2	4M GAIT SPEED	DXA SCAN	WAIST	FASTING GLUCOSE	COGNITION
3	TUG	CHAIR RISE	FREE SPACE	MUSCLE	PHYSICAL ACTIVITY
4	CHOLESTEROL	FASTING INSULIN	BLOOD DRAW	LIFESTYLE	LDL
5	BLOOD PRESSURE	BMI	EXERCISE	MOBILITY	HEIGHT

Odds of winning:

Assuming all participants use all opportunities to win tickets, we will have 90 participants X 6 total prizes for entire study= 540 tickets total over the whole time of the study. Because this study involves rolling recruitment, the odds of winning a raffle is difficult to calculate as this will depend on how many participants we have enrolled at that time and how many participants earn a ticket (i.e., complete the required tasks).

7.0 Expected Risks/Benefits

Benefit



We cannot promise any benefits to any subjects from taking part in this research. The study exercise

program may work better than standard care (education) for those with sarcopenia condition, but we cannot promise this will happen.

Risks:

1. Risks associated with drawing blood include: temporary discomfort from the needle stick, bruising, excessive bleeding, and rarely, infection. The phlebotomist will minimize these risks by using sterile technique and applying sustained pressure to the site.

2. There is minimal risk and a small amount of radiation associated with a DXA scan. The amount of radiation exposure by DXA is considered small and safe for repeated measures. The radiation exposure from this research is about 60 microsievert (6 millirem), total, for 2 scans).

This research gives the same amount of radiation as you would get from living in a high-altitude city such as Denver for 4 days, or taking 1 airplane flights from New York to Los Angeles. The radiation dose we have discussed is what the participant will receive from this study only. Importantly, this exposure will not add to the risk of the research.

*No review by the UIC Environmental Health and Safety Office is needed since the estimated equivalent doses per person (and total) are below 100 mrem per year, a limit set by the Nuclear Regulatory Commission for "general" public

3. Functional performance measures; There is minimal risk of falling and possible injury while performing the functional tests. Additionally, subject may feel uncomfortable or embarrassed or have difficulty in their ability to complete functional tests as instructed.

- To minimize the possibility of such occurrences, all functional performance tests will be carried out by a trained Research Assistant (or Dr. Laddu) who will monitor the subject during the performance of these tests, and assist when needed. Subjects will be encouraged to perform all tests to the best of their abilities and at ease, and to inform the Research Assistant or Dr. Laddu if they are unable to do so.

4. Exercise and muscle strength assessments and endurance tests are each associated with fatigue and muscle soreness, exhaustion, and possible injury. Additionally, there is also minimal risk of elevated blood pressure associated with very high intensity (80%-100% 1RM) resistance training. The AHA advises sedentary individuals should not initiate vigorous or high intensity resistance training without exposure to moderate intensity training first.

- To minimize the possibility of such occurrences, the exercise program will be of moderate-intensity and individually tailored and designed in such a way that encourages participants to begin slowly and progress gradually as recommended by published guidelines (ACSM, AHA).
- Analogous to aerobic exercise, the rare incidences of exercise-related sudden cardiac death and acute myocardial infarction (heart attack) are associated with high-intensity exercise and are more frequent among sedentary individuals.
- Risk prevention measures during the exercise protocol will include: implementation of a warm-up, a cool-down, and flexibility exercises during each session, proper rest periods between exercise sessions. For the leg strength assessments and endurance tests, we will follow ACSM guidelines in which a practice session (warm up) will be included at lower intensity, and the trained research assistant will continue to observe of ease or difficulty a participant experiences lifting the load for the required assessment and intervene if necessary to prevent injury. For all procedures, there will be continued monitoring and supervision of each participant's training program by qualified study staff in the Integrative Physiology Laboratory and the Department of Physical Therapy with training in cardiac life support. Control participants will be told (and reminded in each mailing) to only exercise within their means and to stop if they feel pain, fatigue or exhaustion.
- Moreover, because the contraindication for exercise in an older population with BP is having a resting SBP ≥ 200 mmHg or DBP ≥ 110 mmHg (ACSM guidelines), thus anyone in the intervention group with a BP above this cut point will not be permitted to performing the exercise protocol during the given session. To prevent risk of an adverse event, we will monitor BP during each session and determine safety to exercise based on BP by taking a resting BP reading prior to starting each exercise session.

5. Questionnaires: subject may feel uncomfortable providing any personal information.

- Subject will be advised to skip any questions they do not wish to answer.

6. Focus group questions: Subject may feel uncomfortable, shy, or nervous speaking in front of participants.

- We will aim to minimize this risk by creating a warm and friendly environment during focus group sessions, and remind participants that there are no wrong or right answers, and that all responses will be anonymous as we will not write down any names that will link a person to a response

7. There is a possible risk of confidentiality loss with research data.

- Coding and locking of data will minimize the risk of confidentiality loss. Blood samples will be coded and stored in a locked freezer in the Co-I's laboratory (Phillips, AHS building, Rm 124). All other data collected during visits (DXA scans, focus group transcriptions, anthropometrics) linking study and health information will also be coded and stored in the PI's laboratory. Only the PI (Laddu) will have access to the key to the code that links coded data with the identity of the participant (which will be password protected) and this key will be stored in the PI's locked office (Rm 443).

8. Tissue biopsy (Aim 2; optional): The biopsies involve a procedure of minimal risk. The risks include bleeding at the site, infection, discomfort at the site, and fainting. The injection of local anesthetic is somewhat uncomfortable and could cause bleeding. Preliminary studies indicate these wounds heal quickly, usually within 3-5 days. There is minimal risk of infection at the biopsy site. It is possible that temporary soreness, bruising, or bleeding could occur at the incision site. During or after the procedure, the subject may experience pain, and a small scar may develop where the incisions was made. An allergic reaction may develop if the subject is allergic or sensitive to the skin cleanser or local anesthetic, which could range from minor itching and a rash to severe respiratory arrest and death. This is a possibility with all medications and we will include subjects to receive biopsies only if they are without a history of an allergic reaction and do not have a known history of being allergic to lidocaine.

- A skilled nurse who is trained in collecting tissue biopsies will minimize these risks. All procedures will be conducted by using sterile technique. A local anesthetic will be used to minimize pain. Prior to starting the tissue removal, the nurse will ask the subject if they are allergic to lidocaine and note accordingly. The second biopsy site (placed 12 weeks after the initial visit) will not be made if there is evidence of dehiscence or infection. Additionally, temporary soreness, bruising, or bleeding at the incision site will be minimized with an ice pack administered 10-20 minutes following the biopsy.
- Subjects will be monitored closely to assess impairment of wound healing in person (intervention subjects) or asked to call the study team if impairment in wound healing is suspected at 3-5 days.
- The risk of allergic reaction will be further minimized as dose used will be below the toxic threshold.

8.0 Data Collection and Management Procedures

All data collected for Aims 1 and 2 will be performed by trained Research Assistant/staff, supervised by Dr. Laddu, or personally conducted by Dr. Laddu.

- Consent: UIC ICOMPASS Laboratory: 1919 W. Taylor Street (AHS) Rm: 422
- Baseline data collection: UIC ICOMPASS Laboratory UIC Clinical Research Center, 912 S. Wood Street, Room 200 or UIC Integrative Physiology Laboratory

- Baseline blood sample collection: UIC Clinical Research Center, 912 S. Wood Street, Room 200
- Baseline Subcutaneous fat biopsy (Aim 2): UIC Clinical Research Center, 912 S. Wood Street, Room 200
- Baseline Microvascular Testing (Aim 2): Dr. Phillips' Laboratory, AHS 124
- Resistance training and mid-intervention reassessment: UIC ICOMPASS Laboratory and UIC Integrative Physiology Laboratory
- Post Intervention data collection: UIC ICOMPASS Laboratory, UIC Clinical Research Center or UIC Integrative Physiology Laboratory
- Post-intervention blood sample collection: UIC Clinical Research Center, 912 S. Wood Street, Room 200
- Post-intervention Subcutaneous fat biopsy (Aim 2): UIC Clinical Research Center, 912 S. Wood Street, Room 200
- Post-intervention Microvascular Testing (Aim 2): Dr. Phillips' Laboratory, AHS 124
- Post intervention focus groups: ICOMPASS Laboratory or conference room in Applied Health Sciences, 1919 W. Taylor Street Blood and tissue sample storage: Dr. Phillips laboratory in a secure freezer: UIC Applied Health Sciences (AHS), Rm 124
- Optional Resistance training exercise sessions during surveillance period (12 total): UIC Integrative Physiology Laboratory

We understand the importance of protecting the confidentiality of information from our research subjects. The following paragraphs provide information about the applications/systems that will be used to collect and manage human subjects' data.

Recruitment methods specifically using CCTS - CRDW/UIC CIRCLE

Data will be collected with the assistance of CCTS using the CRDW/UIC CIRCLE as data source. REDCAP will be used to extract data that will later be transferred to excel spreadsheet that will be kept by the PI in a password protected computer, locked in the PI's office. Subjects will be identified using MRN initially but at the completion of the study, the data will be de-identified and participants will only be identified with an assigned study number. A link will be created which will only be known to the PI. The coded data set without direct identifiers will be kept on a password protected Excel database on the PI's locked desktop computer, in the PI's locked office. Only the PI and Co-investigators will have access to the coded data set.

The raw data will be collected as hard copies (reporting of assessment results, questionnaires) and then transferred into electronic form in the REDCap (database), primarily. Additional storage of coded data may be backed up onto UIC BOX, through a secure server (AHS). Where practical, study data will be directly entered into the REDCap database by research staff. Additionally, REDCap allows for questionnaires to be sent to subjects (and received) securely through email. Potential subjects will be informed that questionnaires or other mailings may be received through email. Study data will be managed on-site by Dr. Laddu at UIC using REDCap and may be additionally back up using UIC BOX. All project staff will be trained in the use of REDCap for entry of study data. Appropriate logic and limits checking (including cross-form validity checks) will be implemented in REDCap to facilitate accurate and consistent data entry. Alternatively, information can be captured on paper and entered into the system from the forms. For data integrity, we will carry out double entry of all data items, a feature that is supported by REDCap, and all double-keyed data will be verified for accuracy. To address data security issues, servers are encrypted and the web-based application to interface with the server is SSL encrypted, and staff may access the server through SSL encrypted log-in to remotely monitor

and analyze data. Routinely throughout the study the REDCap database will be downloaded into a secure virtual computing environment (virtual servers and virtual workstations (i.e., UIC BOX); secured behind software and hardware firewalls) available through the College of Applied Health Sciences. Study information within the virtual environment will be available for subject tracking activities such as production of results, tracking of recruitment and enrollment data and other feasibility outcome measures. As part of the data quality assurance process, Dr. Laddu (PI) will generate a final report at the end of the data collection for review by the research team, and to ensure regular quality control and data cleaning/ error reports. Reports will include: number of persons recruited, eligibility and excluded, length of visits, reasons for declining to participate, and high-level summary of variables (e.g., missingness, min, max and standard deviations; and questionable values) measured at each study visit. These reports will be reviewed with Co-Is and research team members. Errors will remain on reports until they are resolved. No interim looks are anticipated but quality control and data entry errors and omissions will be continuously monitored and reported to staff for remediation. All data will be incrementally backed up each day, and each week a full backup will be performed. Data will be viewed as coded using an assigned subject ID number. Only the PI (Laddu) will have access to the key to the code that links coded data with the identity of the participant (which will be password protected) and this key will be stored in the PI's locked office (Rm 443).

All data collection and experimentation will take place at private UIC facilities, so there is minimal risk of participants being recognized as research subjects.

At the end of the study, we will destroy the key that links the name and any health information collected with the blood information and participant (i.e., all information will be de-identified). For those who agree to the optional blood and tissue banking, the following health information will be banked with the blood: randomization arm, age, race/ethnicity, diagnosis of sarcopenia, grip and muscle strength measures, physical performance results (gait speed, chair stand, balance test, timed up and go), sex/gender, blood test results (including cholesterol, insulin, glucose, IL-6), microvascular testing results, weight, height, and body mass index.

9.0 Data Analysis

Statistical data analysis will be conducted using SPSS (v.11) or SAS (v. 9.4) statistical analysis software. Dr. Michael Berbaum (see Appendix P) will assist in data analysis.

10.0 Quality Control and Quality Assurance

Deepika Laddu, as the PI, will monitor the data and safety of the study including data collection, drop-outs because she is directly involved in recruitment, obtaining informed consent, data collection, data management and confidentiality. She will review the process monthly to ensure data collection, recording, and storage is occurring properly, and the research protocol is being followed.

Separation of Clinical and Research Responsibilities

The entire study staff will have received training in working with human subjects. In the consenting process, we will communicate to all potential subjections that the PI, Co-I's and all research staff are interested in both their clinical welfare and in the conduct of this study. Further, all participants are made to understand both verbally and in writing that before entering this study or at any time during the research, they may ask for a second opinion about care from a clinician who is not associated with this project. Their participation in this research study is voluntary and they do not have to participate. The decision to not participate will not affect their ability to participant in other research projects or receive clinical care now or in the future.

Should the subject choose to withdraw, the health information already collected will continue to be used for research, however, no further health information will be collected. All health information and collected data will be stored coded on paper and in the database in REDCap and may additionally be backed up using UIC Box. Only the PI and Co-Is will have access to the key to the code that links coded data with the identity of the subject (which will be password protected).

11.0 Data and Safety Monitoring

DATA SAFETY, MONITORING, AND MANAGEMENT PLAN

The research project is two-arm randomized controlled trial that includes a single site. The University of Illinois at Chicago (UIC) Institutional Review Board (IRB) will review and approve the research protocols and procedures before the research is conducted and an IRB-approved data and safety monitoring plan will be documented.

Although the intervention is low risk, we will use a safety monitoring committee (SMC) to ensure the safety of participants and integrity of the study protocols and data following the Policy of the National Institute of Nursing Research (NINR) for Data and Safety Monitoring of Extramural Clinical Trials (NINR, 2014). Members of the SMC will review the procedures for the protection of human subjects at the outset of the project. The essential elements of the data safety monitoring plan (DSM) plan are detailed below.

Explicit written procedures will be established for monitoring the safety of study participants. Key elements include: 1) specific attention to patient safety as a component of the intervention, 2) periodic review of collected data to search for specific study related participant problems, 3) an adverse event reporting process, 4) phone contact numbers so that study staff may be alerted to specific problems or adverse events, and 5) periodic assessment of study results to evaluate whether the study should be continued. The essential elements of the data safety monitoring plan are detailed below.

a. Monitoring entity and responsibilities

Data safety monitoring will be ongoing. A Safety Monitoring committee (SMC) with at least two members who are independent of the study protocol will be formally established within 3 months of the initiation of the study to meet and review data and adverse events. The following members of the research team will serve on the committee and participate in the SMC meetings: Deepika Laddu (PI); Jun Ma (Co-Mentor); Shane Phillips (Co-Mentor); and Mike Berbaum (Co-Mentor). Additional members may be selected who hold a senior Faculty (Associate Professor or Professor level position, who are not part of the investigative team, and have expertise in a variety of disciplines including physical or occupational therapy, kinesiology (exercise science), geriatric

medicine, cardiology, bio-behavioral medicine, biostatistics, clinical trial designs, and bioethics of research conduct. Dr. Laddu will be responsible for overall monitoring of the study and for submitting necessary reports to NINR. Dr. Phillips and Dr. Ma will be involved with recruitment, intervention delivery, and monitoring of the assessment-control group. Drs. Phillips and Ma will be involved with delivery and fidelity of the resistance training intervention, as well as the assessment of blood pressure, and sarcopenia measurements. Dr. Ma and Dr. Berbaum will aid in assessment of feasibility, and specifically with the analysis of focus group transcripts. Drs. Ma and Phillips will be involved in monitoring of recruitment and retention procedures to ensure compliance with IRB requirements. Dr. Berbaum will be involved in monitoring of health-related data collected, data integrity, management, and ensure the protection and confidentiality of participants' data.

The SMC will provide the cognizant IRB(s), and the sponsor with objective, scientific monitoring of the conduct of the study from the standpoint of ensuring 1) the protection of human subjects and 2) the integrity of the trial. It will do so by regularly monitoring quality of data, as well as reviewing and assessing the performance of the study's operations, and will report any unexpected adverse events (AEs) and serious adverse events (SAEs) or unanticipated problems to the IRB and NINR. The SMC will discuss and provide objective recommendations, as appropriate, with respect to:

- reports related to study operations and the quality of the data
- possible modifications in the study protocol concerning recruitment, participant retention, data quality, or trial operations more generally.
- Any unexpected breach of confidentiality despite all efforts to maintain protected health information to the IRB, and to co-mentors of the study
- ascertainment and any actions to be taken in response to AEs and SAEs reported during the study

b. Procedures for monitoring study safety, minimizing research associated risk, and protecting the confidentiality of participant data

Schedule. The SMC will meet twice during year 2 (when the intervention starts) to initially review the research protocol and initial progress, including the randomization process and group comparability on the balancing variables. During year 2-3, they will meet to review intervention adherence, intermediate outcome data, and indicators of data quality, participant safety, unanticipated problems or adverse events, and new information relevant to the risk and benefits of the intervention, and during year 4 and 5, to review end of study outcome data, data quality and integrity of the study protocols.

Auditing selected cases for compliance with IRB requirements, conformance with informed consent requirements. First, research team members (PI, Research Assistant/Project Manager, Graduate students) will meet weekly with the PI and review all aspects of the study, including preparation of consenting and NIA Go4Life education materials, exercise equipment and IPL environment (where the intervention will take place), recruitment, data collection, data entry procedures and data quality assurance, reports related to study operations and the quality of the data; protocol adherence. Questions or concerns will be addressed. Second, data will be monitored weekly by Dr. Laddu, as well as with her mentoring and SMC members, Drs. Ma, Phillips, and Berbaum for the first 3 months (estimated time to *initiate* baseline data collection), and for the entire 12-week (3 month) intervention of data collection. Considerations of participant

early termination because of unlikely but potential intervention treatment safety concerns or inadequate performance, and possible modifications in the study protocol concerning recruitment, participant retention, data quality, or general trial operations will also be discussed and addressed accordingly. Monthly reviews will be scheduled thereafter to ensure the accuracy and completeness. Two cases will be selected and reviewed for compliance at each weekly/monthly meeting.

Minimizing research-associated risk. Participants reporting low scores on measures for general cognitive function (MoCA) or report a baseline history of mental illness (i.e., depression), or cognitive impairment (e.g., dementia), or a chronic autoimmune illness (i.e., lupus), orthopedic or rheumatological diseases that precludes exercising safely will be excluded from the study. Given the characteristics of a sarcopenic older adult population recruited, the intervention delivery will be supervised and the protocol for the intervention will be tailored to the participant's initial (baseline) one-repetition maximum test, which indicates the heaviest weight that can be lifted with *maximum* effort in a single *repetition*. Participants' activity prescription will include gradual increases in the following metrics based on individual progress a) number of reps; b) weight load; c) and intensity. The one-repetition maximum test will be re-evaluated during the 8 week time point of the intervention (or sooner if necessary) and at 12-weeks when the intervention program is completed.

Further, perceived general health, depression, and physical functioning level as noted on baseline questionnaires and the SF-36 form and perceived exertion during each exercise session and resting BP measured prior to starting the exercise session will provide indication to the research staff to adjust the PRT prescription prior to initiating the program, and take all the necessary steps to ensure the patient's safety while enrolled in the study. Dr. Laddu will assist with follow-up with the trainers who are supervising the PRT program regarding participant progress, self-reported pain or soreness that may occur from the PRT intervention. She will also periodically follow-up with participants (intervention and controls) who have reported low perceived general health or low physical function scores at baseline, and address questions or concerns regarding the study protocol and procedures.

Adherence to the safety protocols will be reviewed at weekly team meetings with the PI and again at monthly meetings. In addition, Dr. Laddu, will provide continuous, close monitoring of protocol adherence and referral of patients if needed.

Protecting the confidentiality of participant data. All patient data collected in this study are confidential and therefore, we will use anonymously-coded identifiers for each subject. The master patient index file will be stored on a password-protected, HIPAA-compliant server located in UIC Academic Computing and Communications Center's (ACCC)'s Secure Research Environment. Only the PI and members of the research team will have access to identifiable health information. Paper copies of signed informed consent forms will be maintained in locked filing cabinets in Dr. Laddu's a locked office at UIC accessible only to her team members.

We will use the Research Electronic Data Capture (REDCap) for randomization, data management and entry. REDCap is a secure web application for building and maintaining online surveys and databases. This application allows users to create a database for data entry, a built-in project calendar, export data to data analysis packages, build custom queries and reports, and

easily manage contact lists of respondents. It also has advanced features which include auto validation, file uploading, and calculated fields and branching logic within electronic forms.

The data collected will be entered by trained research assistants or graduate students and supervised by Drs. Laddu, or Co-I's (Ma, Phillips, Berbaum). All data entry will be verified by a second research assistant or graduate student to ensure accuracy. For data integrity, we will carry out double entry of all data items, a feature that is supported by REDCap, and all double-keyed data will be verified for accuracy by another member of the team. The computers that will be used for data collection will be password-protected, encrypted, and maintained in secure, locked offices. No identifiable data will be transmitted electronically. Drs. Laddu, Phillips, Ma, and Berbaum will have access to monitor the data weekly from their office computers or smart phones that are compliant with UIC's ACCC Secure Research Environment. The final database for analysis will be created by Dr. Laddu in collaboration with Drs. Berbaum from REDCap into a format appropriate for analysis using SPSS or SAS.

c. Procedures for identifying, reviewing, and reporting adverse events and unanticipated problems to the IRB and NINR.

Dr. Laddu will be responsible for reporting adverse events and unanticipated problems as required by the UIC IRB and NINIR. Members of the research team will be trained as to what situations constitute adverse events (AEs), serious events (SEs) and unanticipated problems. (see below).

Protocol for unlikely or unanticipated AEs, SEs or unanticipated problems:

Few intervention-related adverse events are anticipated in this study. As with any physical activity or exercise, there is minimal risk for poor outcomes related to increasing physical activity especially among those who may have been sedentary/inactive prior to study enrollment. All participants will be monitored closely during and immediately following the exercise test. Dr. Laddu will comply promptly with reporting any adverse event or any symptoms of undue distress (ex. Marked chest pain, disorientation) and abnormal signs (ex. Abnormal heart rate or Blood pressure beyond what is expected from participating in resistance training). When in doubt as to the appearance or behavior of the participant while exercising or the blood pressure responses, we will terminate the test, assist the subject to a chair or plinth and assess the clinical situation.

In the case of an emergent situation (e.g., heart attack, suspected stroke), research and IPL staff (Neil McMillan, IPL manager; ph: (312) 996-9594) will be advised to immediately follow the IPL emergency protocol and call 9-11 from cell-phones or 5-5555 for Campus/ Police Emergency.

Adverse Event Reporting: The PI will keep a running record of each event on the IPL Incident Report form. Per IPL protocols, all emergencies that occur in the IPL (both major and minor) will be documented by completing an Incident Report form, which are found in a plastic sleeve near the AED. Laboratory director or manager (Neil McMillan; ph: (312) 996-9594, or Tracy Baynard) will be notified as soon as possible. Completed forms will be handed directly to the director or manager or placed in their mailbox in AHSB.

The UIC IRB will be notified in writing of adverse events within 72 hours of identification of events using the "Prompt reporting to the IRB form", as well as to the NINR and other members of the SMC (Drs. Ma, Phillips, Berbaum). All adverse events will be reviewed within one week of

identifying them by the PI and at investigator team meetings. The SMC will review all adverse events at the annual meetings.

12.0 Statistical Considerations

i. **Planned statistical analysis:** Baseline characteristics across the intervention and AO-C participants will be presented (e.g., means, medians, proportions, missingness), and Analysis of variance (ANOVA) and chi-squared tests for continuous and categorical variables will be used to test statistically significant differences in participant characteristics between intervention and AO-C groups. We will control for significantly different and clinically meaningful descriptive variables in the mixed effect model described below. The covariates' multicollinearity and model goodness of fit or likelihood ratio test will be considered when needed to select covariates.

Multiple linear mixed effects model, Generalized linear model (GLM), or Generalized estimated equations (GEE) will be used to examine the PRT intervention effect on the change in systolic and diastolic BP (systolic or diastolic; ΔBP), modeled as continuous over time, adjusting for covariates and confounders that may affect the outcome (BP): $\Delta BP = \beta_0 + \beta_1 * Time + \beta_2 * Group + \beta_3 * Group * Time + U_0 + U_1 * Time + other\ covariates + \epsilon$, where group represents intervention or AO-C group, and U_0 represents a random intercept (i.e., subject baseline effect) and U_1 for random trend. Potential covariates include age, race/ethnicity, education, BMI, waist circumference, smoking status, employment status, alcohol intake, living alone, SF-36 score, CHAMPS score, cholesterol-lowering medication and history of COPD, diabetes, arthritis, or falls in the past 12 months. Analyses for 2.2-2.3 will also be adjusted for baseline BP, muscle strength and PPM values. Separate models will be conducted, substituting BP for 2017 AHA/ACC BP categories⁴⁹, or secondary outcomes (lipid profile, glucose, HOMA-IR, HDL-C, IL-6). Exploratory analyses will examine PRT effects on muscle strength and each PPM and their mediating effect on BP change. Despite limitations in power, additional post-hoc subgroup analyses will be conducted in sarcopenic and Control participants to better understand the characteristics of each population. The PI will perform these analyses under Dr. Berbaum's supervision (see letter of support), who has extensive experience utilizing these methods. All analyses will be performed using SPSS (v.11) or SAS (v. 9.4). A two-tailed p-value<0.05 will define statistical significance.

ii. **Focus Group Analysis.** Responses from focus groups will be transcribed verbatim and saved as text files and entered into ATLAS.ti (SCOLARI, 2003) for data analysis. "Classical content analyses," frameworks will be used to analyze data. Evaluation of unexpected themes and recurring themes particularly focused on health concerns, injuries, or barriers and enablers that may be used to ensure adherence, acceptability and tolerance to the intervention will be identified. The list of themes will serve as data for intervention refinement in future R01 applications.

iii. **Rationale for selection of subject:** Adults with probable sarcopenia aged 60 years and older will be recruited for the pilot study. Data resulting from this pilot study will be used to refine the content, intervention design and test the feasibility for future, larger scaled PRT intervention.

Power: The given sample size N=60 for PRT and 30 for control group with estimated 15% drop-out rate will ensure power 80% with the significance level 0.05 to detect about the medium effect size, $d=0.6$ which corresponds to the mean BP (SBP or DBP) change difference 1.3 with standard deviation (SD) for both groups 2.0. A change difference of 1mmHg is evidenced to substantially prevent time-to first events of heart failure, coronary heart disease and stroke in older multi-racial populations⁵⁰. The total sample size 100 (86 after 15% drop-out) also may detect a difference in

linear regression slopes 0.59 between the two groups with the SD of an outcome 2. All power calculation were based on the two-sided test with significance level 0.05.

Aim 2: Flow induced vasodilation (FID) dose-response comparisons will be analyzed using a two-way repeated measures ANOVA, with vessel diameter as the primary covariate, followed by pairwise comparisons using a Bonferroni adjustment [pressure gradient x treatment (baseline, L-NAME, and PEG-CAT)].

13.0 Regulatory Requirements

13.1 Informed Consent

- Subjects expressing interest in participating in the study will initiate contact by phone with research personnel. Oral consent will be obtained so that eligibility screening can be conducted. An alteration of consent and a waiver of documentation of consent will be obtained for the eligibility screening, the MoCA screener and grip strength assessment.
- Subjects who are eligible and agree to participate will be invited to come to the UIC ICOMPASS laboratory (Rm 422) to obtain additional testing. Written informed consent will be obtained prior to screening and baseline testing.
- The PI will keep the original signed consent form, and the subject will receive a copy.
- After the subject is recruited by phone and learned about the study, there will be ample time for the subject to think about being involved in the study. Additionally, upon signing the consent form, they have the option of starting the exercise intervention during years 1-3.5 of the grant.
- PI, Co-Investigators, and Key Research Personnel will obtain consent. Beside the PI and co-investigators, study staff thoroughly trained by the PI in the consenting process, and who have complete their CITI and HIPPA training may also obtain consent from participants.
- Recruitment via Subjects will be identified using MRN initially but at the completion of the study, the data will be de-identified and participants will only be identified with an assigned study number. A link will be created which will only be known to the PI, and coded data with without direct identifiers will be kept on a password protected Excel database on the PI's locked desktop computer, in the PI's locked office.
- All consent documents will be stored in Dr. Deepika Laddu's locked office in a locked filing cabinet.
- The process of recruitment, enrollment and obtaining written informed consent will be in English and Spanish. Lay language will be used to describe technical and medical terms

13.2 Subject Confidentiality

- Coding and locking of data will minimize the risk of confidentiality loss. Blood and fat tissue samples will be coded and stored in a locked freezer in the Co-I's laboratory (Phillips, AHS building, Rm 124), DXA scans and focus group and anthropometric (visit

1) data collection and other paper and/or electronic data associated with the samples will also be coded and stored in the PI's locked office (AHS 443). The AHS network, which is a secure network server will be used to store data. All research personnel will have access to the coded data and samples. Only the PI (Laddu) will have access to the key to the code that links the code to the subject. The key to the code and the stored, coded data samples will be stored separately. The key to the code will be stored in locked file cabinets in the PI's office (AHS, Rm 443). Access to the key, and computerized data will be password protected, with only access limited to the PI.

- Plans for destruction/removal of identifiers will occur at the end of the study
- Personal or private identifiable data WILL NOT be stored on portable devices. There will be no sharing of research data with any research investigators (UIC or non-UIC) OTHER THAN those listed on Appendix P.

13.3 Unanticipated Problems

Written communication via the Prompt Report Form from the PI to the IRB will be conducted immediately upon knowledge of any unanticipated problems.

14.0 References

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