PROTOCOL TITLE:

The Effect of High Intensity Walking on Frailty
NCT#: 03654807

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1.0 Purpose of the study:

To test the effect of walking intensity on both frailty category (i.e., frail, prefrail, and nonfrail) and frailty score as a continuous outcome on the SHARE-FI (frailty instrument). *Hypothesis:* The HIW group will have: *(1A)* a greater percentage of participants who improve one frailty category and *(1B)* larger SHARE-FI continuous score changes at 4 months in comparison to the CSW group.

To test the effect of walking intensity on mobility, physical function, balance, and total PA. *Hypothesis:* HIW participants will have: *(2A)* improved mobility as measured by gait speed, Timed Up and Go, and 6-Minute Walk Test, *(2B)* improved physical function on the Short Physical Performance Battery, *(2C)* improved balance as measured by the Berg Balance Scale and Falls Efficacy Scale and *(2D)* greater total PA measured during a 1-week ambulatory monitoring period at 4 months in comparison to the HIW group.

2.0 Background / Literature Review / Rationale for the study:

Frailty is a geriatric syndrome defined by the presence of 3 of the 5 following criteria: weight loss, fatigue, weakness, slow walking speed, and low physical activity. Frailty impacts up to 60% of older adults with a greater prevalence in women and those with increased age, lower educational attainment, and low socioeconomic status. Frailty is a risk factor for dementia and leads to adverse health outcomes that increase the risk for nursing home placement. **The optimal intervention to improve the frailty syndrome remains unknown and is critical to promote healthy aging and reduce the burden of frailty-related impairments.**

Physical activity (PA) has multi-system health benefits and is the most recommended frailty management intervention. However, PA guidelines for frailty, **specifically relative to intensity**, remain unclear. Studies using low to moderate intensity walking (50-70% of heart rate maximum (HR_{max})) have reported improvements in physical functioning, but minimal improvements in the overall frailty diagnosis. In contrast, animal models show high intensity activity **reverses frailty** in mice. We conducted a pilot study of high intensity walking (HIW) within a retirement community that showed: 1) **improvement of one full category (i.e., pre-frail to non-frail)** following the intervention **in 100% of participants** and 2) **no adverse events**. Participants had clinically and statistically significant improvements in mobility, balance, and gait speed that were substantially greater than reported from prior studies of lower-intensity walking interventions. **Thus, high intensity walking has the potential to be a potent therapeutic intervention for reducing or reversing frailty.**

Frail older adults have a 59% higher prevalence of falls compared to non-frail older adults. To date, PA strategies to reduce fall risk in frail adults have focused on balance training or multi-component interventions, but the impact on balance

remains inconclusive. Some studies show increased fall risk among frail groups in response to intervention while others find reduced fall risk. **In our pilot study, participants had an average 5.6-point Berg Balance Scale improvement indicating HIW may provide robust balance improvements.**

Restricted mobility and low PA participation are further frailty-related impairments. Frail older adults average 3 minutes per week in moderate-vigorous physical activity, 85% of waking hours are spent in sedentary behavior (i.e. sitting), and average daily walking is less than 2,000 steps per day. Given the established association between low PA and all-cause mortality, poor health outcomes, and high healthcare utilization, increasing PA is a public health priority. One facilitator of PA participation is capability, the skill required to participate in a given task. **Therefore, identifying an intervention such as HIW that improves the capability to participate in habitual PA is critical to reduce the burden of frailty-related impairments.**

To address these issues, we propose a cluster randomized controlled trial to evaluate the impact of HIW on frailty in older adults. We will randomize 500 participants from 10 retirement communities (50 per site) to a 1:1 supervised, 4-month overground HIW (70-80% HRmax) or self-selected, casual speed walking intervention (CSW). The CSW intervention is based upon the NIA Go4Life recommendations. The 4-month intervention will consist of two phases: (1) a 1-month *ramp-up* phase in which HIW participants will gradually increase intensity levels to reach 70-80% HRmax and (2) a 3-month *intervention* phase whereby HIW participants will walk at 70-80% of HRmax. CSW participants will walk at the self-selected, casual speed for all 4 months. Primary and secondary outcomes will be measured at baseline and 4 months. Our **overall hypothesis** is that HIW will reduce or reverse frailty in comparison to CSW at 4 months, as well as improve overall mobility, balance, physical functioning, and daily PA. We propose two aims:

3.0 Inclusion and Exclusion Criteria:

Inclusion criteria:

- > 60 years of age with pre-frailty or frailty as determined on the SHARE-FI.
- Able to ambulate at least 10 feet with moderate assistance (<50% physical assistance) or less. Participants will be able to use their assistive device (e.g. cane or walker) during sessions.
- Resident of one of the 16 enrolled retirement community locations (see Letters of Support). Individuals must be > 60 years of age to move into the retirement communities by virtue of the individual community policies.
- Provision of informed consent and clearance for participation as determined by the EASY: Exercise and Screening for You.[58]

Exclusion criteria:

- Uncontrolled cardiovascular, metabolic, renal, or respiratory disease that limits exercise participation (e.g., previous heart attack within 3 months of enrollment or uncontrolleddiabetes)
- Resting blood pressure > 180/110mmHg.[59]

We will not exclude participants on the basis of Mini-Mental State Examination (MMSE) scores as long as all other inclusion criteria are met. **This is a community-based clinical trial involving older adult retirement community residents.** The retirement communities enrolled in this study provide meal services to residents and assistance is available for tasks such as bathing, medication management, and housekeeping. To make our findings generalizable and scalable among retirement communities, we aim to enroll pre-frail and frail older adults with a full range of cognitive functioning as long as all other inclusion criteria is met. **Research estimates 20-33% of retirement community dwelling older adults > 71 years of age have cognitive impairment.** Our letters of support indicate that 10-60% of residents in our enrolled retirement communities have cognitive impairment. We will use the MMSE as a guide for obtaining LAR consent. For anyone scoring < 24, we will use semi-structured questions to determine if a participant needs LAR or is able to consent themselves to participate in the research study. Should someone score < 24 on the MMSE, we will have the participant read entire informed consent form (read it with them or to them). Then with the informed consent form in front of them, the research staff will assess decisional capacity using the semi-structured questions. If the participant is able to answer all questions appropriately, we will determine the participant to possess sufficient cognition to consent. If participant is still unable to demonstrate adequate capacity, then the participant cannot participate in the study until LAR consent is obtained. If research staff notices any changes in cognition in participants during the course of the study, we will re-evaluate capacity to consent and will seek LAR input if needed. The Northwestern Institutional Review Board (IRB) has previously approved this protocol and determined physician approval is not needed for participation given that participants are screened using the EASY and that sessions are individually supervised with a research staff member monitoring vital signs. We will not exclude participants should they be hospitalized or ill. We will make every effort to reschedule a missed session during the week of the missed session. In the event that a session cannot be rescheduled, we will make up missed sessions during weeks 17-18.

4.0 Sample Size:

We will study 16 retirement community sites with 50 participants per site for a total of 500 participants. In our previous work with a similar population of older adults, overall attrition was 17% at 3 months. We now assume 20% attrition since this study will follow participants out to 4 months. Power calculations conservatively assume 20% attrition at both the site and participant level; with 20% attrition at the site level (one site per arm dropout or loss of 40 participants) and 20% participant attrition at remaining sites (16 participants per site), we will

have at least 128 participants for whom we will have complete baseline and follow-up data required to compute outcomes on frailty and physical functioning measures at four months. We will report sex differences should they be observed.

5.0 Research Locations:

This study will be conducted through Northwestern University Department of Physical Therapy and Human Movement Sciences. Intervention sessions will

occur at one of the 16 enrolled retirement communities in the Chicagoland area. Study participants will include older adults with pre-frailty or frailty. All participants will be recruited from one of the 16 enrolled retirement communities with which we have established collaborative relationship.

6.0 Multiple sites:

All 16 sites are committed to the proposal (**see letters of support**) with sufficient number of residents for recruitment. If we are unable to recruit enough participants at each site, we will work with site staff to address alternative recruitment strategies.

7.0 Reliance Agreements/Single IRB:

N/A

8.0 Procedures Involved:

This study will be conducted through Northwestern University Department of Physical Therapy and Human Movement Sciences. Intervention sessions will occur at one of the 16 enrolled retirement communities in the Chicagoland area. Study participants will include older adults with pre-frailty or frailty. All participants will be recruited from one of the 16 enrolled retirement communities with which we have established collaborative relationship. The population studied is from the Chicagoland area, and the data management and protection are described below. We will place recruitment flyers in all resident mailboxes as well as make presentations about the study at resident monthly town-hall meetings. Residents will receive a recruitment folder that'll include a flyer, welcome letter, permission to contact, and an FAQ sheet when they move in or during recruitment. Participants will undergo an initial screening by the research coordinator to determine the presence of frailty using the Groningen Frailty Index (GFI). The purpose of the initial screening is to avoid an unnecessary visit to complete the entire baseline assessment if the interested person is non-frail. After informed consent is obtained, screening procedures will include the EASY: exercise and screening for you and medical screening question. Participants will be enrolled who meet inclusion criteria and meet no exclusion criteria. We will screen as many participants as necessary to recruit a sample size of 500 participants (50 per site) for the study. Recruitment procedures are detailed below. Retirement communities will be randomized into one of two arms: 1) high intensity walking or 2) casual speed walking. These intervention approaches are based on our extensive experience with walking interventions for pre-frail and frail older adults.

Participants may be withdrawn from the study for any of the above criteria and will be referred to the most appropriate medical professional. Serious adverse events (SAEs) will be handled with the standard of Good Clinical Practice Guidelines including informing the PI and IRB within 24 hours of the event,

following up and reporting on the event until resolved, and subsequently reported to the Data Safety Monitor.

Screening
Initial screening of each participant will be held in their own apartment within their retirement community or over the telephone. The research coordinator will initially screen participants to determine frailty. The research coordinator will administer the Groningen Frailty Index (GFI) Persons scoring 4 or more points on the GFI will then be oriented to the study, sign informed consent, and make an in-home appointment with the masked evaluator (Dr. Healey) to complete baseline measurements. Once determined to be pre-frail or frail and meeting all other inclusion criteria, an appointment will be made with Dr. Healey (masked evaluator) to administer the EASY: exercise and screening for you and SHARE-FI screening and completion of all other study measures. Baseline measurements will confirm the presence of pre-frailty or frailty and will rule out any medical conditions that preclude participation in walking. If a participant is determined to be pre-frail or frail on the SHARE-FI[64] and meets all other inclusion criteria, we will proceed with enrollment in the study.

Sources of Materials
The following data will be collected on the participants involved in this research study at the beginning and end of the study: Geriatric Depression Scale, Mini-Mental State Examination, SHARE-FI frailty score, gait speed, 6 Minute Walk Test, Short Physical Performance Battery, Berg Balance, Falls Efficacy Scale, Behavioral Regulation in Exercise Questionnaire (BREQ-2) and Explicit Attitudes (affective and instrumental) toward physical activity to measure attitude towards walking, and physical activity measured with an ActivPal. The Research Assistants (RAs) will administer Explicit Attitudes after sessions 12, 24, 36, and 48. The ActivPal accelerometer will be worn at week 1, 8, and end of the study to collect data on physical activity. The ActivPal will also be worn at every session to collect total step counts and data on physical activity. Participants will be will be introduced to the ActivPal at the beginning of the study as a lightweight accelerometer positioned on the thigh that will not be affected by walker or cane use. We will explain to participants the use of the ActivPal is to measure the duration and frequencies of physical activity such as walking, standing and total step counts. We will also capture demographic information such as age, sex, race, and education. All data files will be de-identified and kept in locked files in the study research team office. Only the study biostatistician and research coordinator will have access to individually identifiable private information about human subjects. All electronic data files housed on the secure network at Northwestern University and will be password protected. Only investigators and key research personnel will have access to paper and electronic files.

All participants will receive 48 walking sessions over the course of the 4- month intervention within hallways and stairwells of their retirement community. All communities have the space to run these sessions safely (**see letters of support**). **Our approach of providing intervention sessions within the retirement community instead of a laboratory setting is a strength of the proposed**

protocol, allowing us to recruit and enroll the most frail participants for whom community accessibility is limited. All enrolled participants will receive 3 sessions each week. This 4-month intervention will consist of two phases: (1) a 1-month *ramp-up* phase whereby HIW participants will gradually increase intensity levels to reach 70-80% HRmax and (2) a 3-month *intervention* phase whereby HIW sessions will walk at 70-80% of HRmax. Each walking session lasts approximately 45 minutes of which 15 minutes will be allocated to warm-up

and cool-down and 30 minutes to walking. Participants will be able to take rest breaks as necessary and rest breaks do not count towards the 30 minutes of total walking per session. During all training sessions, RAs will measure blood pressure and assess heart rate using Polar A370 continuous heart rate monitors to ensure each participant is walking within the individually calculated heart rate intensity range given the treatment arm assignment to ensure intervention fidelity. We will also use the Rating of Perceived Exertion (RPE) Scale to record self-reported exertion during walking in both treatment arms.

9.0 Incomplete Disclosure or Deception:

N/A

10.0 Recruitment Methods:

Participants will be recruited from the 16 retirement community sites enrolled in this study (see letters of support). All sites are independent living with the exception of 2 assisted living sites (Gidwitz Place and St Pauls House). We will recruit residents through in-person meetings and flyers. Sites in this study have been purposefully selected throughout the Chicagoland area to reflect a range of racial/ethnic backgrounds to maximize generalizability of findings.

We will place recruitment flyers in all resident mailboxes as well as make presentations about the study at resident monthly town-hall meetings. Residents will receive a recruitment folder that'll include a flyer, welcome letter, permission to contact, FAQ sheet when they move in or during recruitment. After informed consent is obtained, screening procedures will include the EASY: exercise and screening for you and medical screening question. Participants will be enrolled who meet inclusion criteria and meet no exclusion criteria. We will screen as many participants as necessary to recruit a sample size of 500 participants (50 per site) for the study.

Participants will be recruited with the combined efforts of the study staff. Dr. Danilovich will be responsible for the main recruitment efforts and will work closely with the assisted living sites and the study coordinator to ensure success. Interested participants will complete SHARE-FI screening to determine eligibility. If eligible (pre-frail or frail), participants will provide informed consent and proceed with all baseline testing. All study documents will be available in English. Interested participants will complete SHARE-FI screening to determine eligibility.

11.0 Consent Process:

If eligible (pre-frail or frail), participants will provide informed consent and proceed with all baseline testing. Participants will be asked to sign and date the written informed consent (if capable) and will be informed about the research to the extent compatible with their understanding. All study documents will be available in English. The consent form and study recruitment materials will

explain all procedures, risks, and benefits of the study. These materials will also state that participants have the right to withdraw from the study at any time without giving any reason and without any penalty. Participants will need to communicate their intention to leave the study to any research staff personnel and this confidentiality will not be breached.

We will use the MMSE as a guide for obtaining LAR consent. If LAR consent is needed, we will ask the participant or the retirement community for the LAR information. We will then contact the LAR and consent over the phone and attempt to reach 5 times before moving on to next participant. We will explain the study to the participant to the best of our ability and inform them that their LAR provided consent for them to participate.

Risk to participants is further mitigated as all walking sessions are individually supervised. The Northwestern Institutional Review Board (IRB) has previously approved this protocol and determined physician approval is not needed for participation given that participants are screened using the EASY and that sessions are individually supervised with a research staff member monitoring vital signs.

12.0 Financial Compensation:

We anticipate no psychological, financial, or legal risks to participants in our study. As described, if participants were to receive an injury during the course of the study, the individual would be responsible for their own medical care. Receive cash compensation of $10 for primary and secondary outcomes measured at baseline and 4 months for a total of $20.

13.0 Audio/Video Recording

We will video record selected walking sessions only for those participants who consent to recording. These recording will only be used in dissemination activities (i.e. conference presentations) to demonstrate the walking intervention to other researchers. We will attempt to limit identification by recording profile. Video recordings will be stored securely in Northwestern Box.

14.0 Potential Benefits to Participants:

Randomized trials of walking training interventions have shown significant improvements in functioning and balance as a result of training. There is potential for participants in the proposed study to experience the same benefits. These outcomes have implications far outweighing the minimal risks such as muscle soreness that are associated with participation.

15.0 Risks to Participants:

We anticipate no psychological, financial, or legal risks to participants in our study. No questionnaires related to psychological status will be used. Participants will be advised to speak with the PI for any issues concerning dissatisfaction with the study. We have piloted our walking intervention with other pre-frail and frail older adults and found no adverse events. Participants may experience muscle soreness due to walking training that will attenuate as expected following a bout of activity. Research assistants will encourage anyone feeling pain to modify the walking activity. Given that this population has multiple chronic conditions, participants will have walking tasks modified as appropriate for their given health conditions and individual limitations. Research assistants will be trained to recognize clinical signs and are able to monitor vital signs. Stethoscopes, blood pressure cuffs, and heart rate monitors will be available at all times. Should participants face any complications, medical staff can be notified. As described in our IRB protocol and consent form, if participants were to receive an injury during the course of the study, the individual would be responsible for their own medical care.

The risks of walking sessions will be minimized by adhering to the following strategies:

(i) Personnel training: All research staff will be thoroughly trained in the intervention procedures under the direction of a board-certified geriatricphysical therapist. All research assistants will be CPR trained. All research assistants will be instructed in how to implement a special medical call at each community in this study.

(i) Participant screening: All potential participants will complete a medical screening with a board-certified geriatric physical therapist to ensure safety to begin a walking intervention. Serious adverse events are not expected, but all such events will be reported according to the Northwestern IRB policies.

The consent form and study recruitment materials will explain all procedures, risks, and benefits of the study. These materials will also state that participants have the right to withdraw from the study at any time without giving any reason and without any penalty. Participants will need to communicate their intention to leave the study to any research staff personnel and this confidentiality will not be breached.

16.0 Provisions to Protect the Privacy and Confidentiality of Participants and the Research Data:

All data files will be de-identified and kept in locked files in the study research team office. Only the study biostatistician and research coordinator will have access to individually identifiable private information about human subjects. All electronic data files housed on the secure network at Northwestern University and will be password protected. Only investigators and key research personnel will have access to paper and electronic files.

17.0 Data Monitoring Plan to Ensure the Safety of Participants:

N/A

18.0 Data, and if applicable, Specimen Banking:

All study data will be imported and entered into RedCap using forms and tables. All client data will be de-identified and tracked using a unique identifier. All electronic data will be stored on a dedicated hard drive and password protected. The hard drive is secured in a locked office accessible only to study staff. The password will be changed quarterly and known only by staff directly involved in the study. Hard copy documents will be kept in a locked file cabinet in the study office. All study staff are experts in the maintenance of security and confidentiality of research data. Study staff will review and approve study protocols prior to initiation of enrollment. Dr. Huisingh-Scheetz, the data safety monitor, will have access to de-identified data to review SAEs and AEs quarterly and will be altered to any interim concerns.

Dr. Megan Huisingh-Scheetz from the University of Chicago will oversee safety monitoring. Dr. Huisingh-Scheetz is a geriatrician with expertise in frailty. She is the founding director of the University of Chicago Successful Aging and Frailty Evaluation Clinic in which she evaluates and manages medical care for older adults with frailty. She will provide a mechanism to assure monitoring the overall conduct of the study (including issues with safety, ethics, patient recruitment and accrual, retention, adequacy of the study design to achieve the specific aims) and provide to the study team for the possible protocol amendments, and input from this study on future studies.

19.0 Data Sharing:

All data files will be de-identified and kept in locked files in the study research team office. Only the study biostatistician and research coordinator will have access to individually identifiable private information about human subjects. All electronic data files housed on the secure network at Northwestern University and will be password protected. Only investigators and key research personnel will have access to paper and electronic files.

20.0 Qualifications to Conduct Research and Resources Available:

The study PI is a board-certified geriatric physical therapist with expertise in physical activity and exercise interventions for frail older adults. She will collaborate with Drs. Corcos, Ciolino, and Conroy and have primary responsibility for all aspects of the study including recruitment, screening of subjects, monitoring adherence, fidelity of protocols, training research staff, data

collection, analysis, and dissemination. She will train and oversee all research assistants.

We have a variety of resources available to our study.

- The PI is 30% effort to conduct this study and will devote the necessary effort to the successful conduct of this research project.
- Weekly meetings will be held with the research assistants to ensure treatment fidelity and address problems with the protocol that may arise.