E2902-P

Enhancing Functional Capacity in Older Adults with Short Session High Intensity Interval Training

NCT03750006

January 25, 2022

Complete Research Protocol

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PROTOCOL TITLE:

Include the full protocol title.

Response: Enhancing functional capacity in older adults with short session high intensity interval training

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VERSION:

Include the version date or number.

Response: Version 12.0 1/24/2022

GRANT APPLICABILITY:

Indicate whether this protocol is funded by a grant (e.g. NIH, foundation grant). For a grant with multiple aims, indicate which aims are covered by this research proposal.

NOTE: This question does not apply to studies funded by a sponsor contract.

Include a copy of the grant proposal with your submission.

Response: This work is funded by a CTSI pilot project grant (Grant is pending) and a SUNY Seed Center-Scale Planning Grant

RESEARCH REPOSITORY:

Indicate where the research files will be kept, including when the study has been closed. The repository should include, at minimum, copies of IRB correspondence (approval, determination letters) as well as signed consent documents. This documentation should be maintained for 3 years after the study has been closed.

Response:

Location: Clinical and translation research building room 8030A

Address: 875 Ellicott Street, Buffalo NY 14203

Department: Medicine

1.0 Objectives

1.1 Describe the purpose, specific aims, or objectives of this research.

Response: The purpose of this proposed work is to assess the feasibility of recruiting and administering a short session high intensity interval training regimen to older adults (60-90 years of age), as well as performing routine physical performance and quality of life assessments, and obtain blood samples for analysis of inflammatory biomarkers, testosterone, and serum microRNA.

After 20-months of COVID-19 restrictions, we will contact previously enrolled participants and ask them to return for 1 follow-up visit in order to investigate changes in physical fitness, muscle strength, physical activity, functional capacity, and microRNA profiles among participants who completed our short-session high intensity interval training program, 16-months previously. This will be conducted to explore possible de-training-associated loss of fitness, function, and quality of life among participants who previously completed a 12-week HIIT intervention.

1.2 State the hypotheses to be tested, if applicable.

NOTE: A hypothesis is a specific, testable prediction about what you expect to happen in your study that corresponds with your above listed objectives.

Response: We hypothesize that we will demonstrate adequate recruitment rates and low attrition rates such that we can justify future studies designed to demonstrate the benefits of HIIT in older populations.

We also hypothesize that participants who complete 12-weeks of HIIT and then become sedentary over the following 16-months will demonstrate reduced fitness, function, and quality of life, along with alterations in key underlying biological processes.

2.0 Scientific Endpoints

2.1 Describe the scientific endpoint(s), the main result or occurrence under study.

NOTE: Scientific endpoints are outcomes defined before the study begins to determine whether the objectives of the study have been met and to draw conclusions from the data. Include primary and secondary endpoints. Some example endpoints are: reduction of symptoms, improvement in quality of life, or survival. Your response should ***not*** *be a date.*

Response: This is a longitudinal study to assess changes in function and physiological parameters following a 3-month exercise intervention.

The Primary Aim is to assess recruitment and attrition rates as benchmarks to gauge the feasibility of administering High Intensity Interval Training in older individuals.

Our secondary aim is to assess the feasibility of assessing maximal respiration (VO2max), quadriceps strength, frailty status, functional capacity (Short physical performance battery), quality of life status, attrition rates, serum inflammatory biomarkers, testosterone, miRNA, and change in skeletal muscle regional blood flow and oxygen saturation in response to HIIT training.

3.0 *In addition, we will explore how fitness, function, and quality of life change 16-months after completion of a 12-week HIIT program among adults 60 – 90 years old.*

4.0 Background

4.1 Provide the scientific or scholarly background, rationale, and significance of the research based on the existing literature and how it will contribute to existing knowledge. Describe any gaps in current knowledge. Include relevant preliminary findings or prior research by the investigator.

Response: Frailty is characterized by reduced physiological function that increases vulnerability to greater dependency and/or death [1], as well as a greater allocation of resources to achieve requisite care [2]. Fried et al. defined frailty as including three or more of the following: diminished gait speed, reduced grip strength, unintentional weight loss, low activity, and fatigability [1]. Pre-frail individuals exhibit 1 or 2 of the characteristics. Exercise is beneficial for frailty [3-5], yet only 12% of individuals over the age of 65 participate in exercise activities such as strength training [6]. Lack of time, length of exercise sessions, and injury concerns are cited as the most common barriers to participation [7-9]. High intensity interval training (HIIT), with short sessions and less time commitment, is emerging as an alternative to standard exercise. Even with lower time investment, HIIT has often been shown to be equivalent or better than MICT for improving fitness, including increasing VO2max, heart function, aerobic fitness, and perceptions of health-related quality of life [10-13]. However, these studies did not examine frail or older adults.

HIIT has been safely administered to vulnerable populations in numerous reports. Fiatarone et al. [14] pioneered the use of a progressive resistance HIIT as an intervention for the very old in a study involving frail nonagenarians (age 90 ± 1) and found excellent tolerance while improving strength and gait speed over 10 weeks. Furthermore, an uphill treadmill walking HIIT regimen, featuring 4 x 4

minute intervals at 85 95% HRmax with a total time of 25 minutes, has been shown to be safe and effective in 70-year-old men [15], as was a 12 x 1 minute walking intervals with a total time of 23 minutes in 75-85 year old women [16]. HIIT has also been successfully implemented in patients with significant co-morbidities, including congestive heart failure [17], coronary artery disease [18], and chronic obstructive pulmonary disease [19]. Additionally, a systematic review including 4,846 patients with coronary heart disease across 175,820 training hours found the risk of cardiovascular events related to HIIT to be low [20]. However, the exciting aspect of HIIT is the low time commitment; in particular short session HIIT regimens (≤ 10 minutes total and only ≤ 4 minutes at high intensity) have demonstrated physiological benefits that were comparable to longer MICT regimens [21-24]. To our knowledge short session HIIT has not been attempted in individuals older than 65 years of age. However, our recently published pre-clinical study [25] demonstrates that a 3-times-a-week program of 4 x 1 minute intense intervals for a total of 10 minutes markedly improved muscle mass and quality, physical performance, and reduced frailty in old mice. To our knowledge there are no studies that investigate the therapeutic potential of short-session high intensity interval training in individuals >65 years of age.

4.2 Include complete citations or references.

Response:

1. Fried, L.P., C.M. Tangen, J. Walston, et al., Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci, 2001. 56(3): p. M146-56.
2. Lutomski, J.E., M.A. Baars, H. Boter, et al., [Frailty, disability and multi-morbidity: the relationship with quality of life and healthcare costs in elderly people]. Ned Tijdschr Geneeskd, 2014. 158: p. A7297.
3. de Vries, N.M., C.D. van Ravensberg, J.S. Hobbelen, et al., Effects of physical exercise therapy on mobility, physical functioning, physical activity and quality of life in community-dwelling older adults with impaired mobility, physical disability and/or multi-morbidity: a meta-analysis. Ageing Res Rev, 2012. 11(1): p. 136-49.
4. Vina, J., A. Salvador-Pascual, F.J. Tarazona-Santabalbina, et al., Exercise training as a drug to treat age associated frailty. Free Radic Biol Med, 2016. 98: p. 159-64.
5. Marzetti, E., R. Calvani, M. Tosato, et al., Physical activity and exercise as countermeasures to physical frailty and sarcopenia. Aging Clin Exp Res, 2017.
6. Centers for Disease, C. and Prevention, Strength training among adults aged >/=65 years--United States, 2001. MMWR Morb Mortal Wkly Rep, 2004. 53(2): p. 25-8.
7. Allen, J. and V. Morelli, Aging and exercise. Clin Geriatr Med, 2011. 27(4): p. 661-71.
8. Schutzer, K.A. and B.S. Graves, Barriers and motivations to exercise in older adults. Prev Med, 2004. 39(5): p. 1056-61.
9. Justine, M., A. Azizan, V. Hassan, et al., Barriers to participation in physical activity and exercise among middle-aged and elderly individuals. Singapore Med J, 2013. 54(10): p. 581-6.
10. Angadi, S.S., F. Mookadam, C.D. Lee, et al., High-intensity interval training vs. moderate-intensity continuous exercise training in heart failure with preserved ejection fraction: a pilot study. J Appl Physiol (1985), 2015. 119(6): p. 753-8.

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12. Hwang, C.L., J.K. Yoo, H.K. Kim, et al., Novel all-extremity high-intensity interval training improves aerobic fitness, cardiac function and insulin resistance in healthy older adults. Exp Gerontol, 2016. 82: p. 112-9.
13. Knowles, A.M., P. Herbert, C. Easton, et al., Impact of low-volume, high-intensity interval training on maximal aerobic capacity, health-related quality of life and motivation to exercise in ageing men. Age (Dordr), 2015. 37(2): p. 25.
14. Fiatarone, M.A., E.C. Marks, N.D. Ryan, et al., High-intensity strength training in nonagenarians. Effects on skeletal muscle. JAMA, 1990. 263(22): p. 3029-34.
15. Askim, T., A.E. Dahl, I.L. Aamot, et al., High-intensity aerobic interval training for patients 3-9 months after stroke: a feasibility study. Physiother Res Int, 2014. 19(3): p. 129-39.
16. Thomas, E.E., G. De Vito, and A. Macaluso, Speed training with body weight unloading improves walking energy cost and maximal speed in 75- to 85-year-old healthy women. J Appl Physiol (1985), 2007. 103(5): p. 1598-603.
17. Ellingsen, O., M. Halle, V. Conraads, et al., High-Intensity Interval Training in Patients With Heart Failure With Reduced Ejection Fraction. Circulation, 2017. 135(9): p. 839-849.
18. Villelabeitia-Jaureguizar, K., D. Vicente-Campos, A.B. Senen, et al., Effects of high-intensity interval versus continuous exercise training on post-exercise heart rate recovery in coronary heart-disease patients. Int J Cardiol, 2017.
19. Bjorgen, S., J. Hoff, V.S. Husby, et al., Aerobic high intensity one and two legs interval cycling in chronic obstructive pulmonary disease: the sum of the parts is greater than the whole. Eur J Appl Physiol, 2009. 106(4): p. 501-7.
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23. Gillen, J.B., B.J. Martin, M.J. MacInnis, et al., Twelve Weeks of Sprint Interval Training Improves Indices of Cardiometabolic Health Similar to Traditional Endurance Training despite a Five-Fold Lower Exercise Volume and Time Commitment. PLoS One, 2016. 11(4): p. e0154075.
24. Ruffino, J.S., P. Songsorn, M. Haggett, et al., A comparison of the health benefits of reduced-exertion high-intensity interval training (REHIT) and moderate-intensity walking in type 2 diabetes patients. Appl Physiol Nutr Metab, 2017. 42(2): p. 202-208.
25. Seldeen, K.L., G. Lasky, M.M. Leiker, et al., High Intensity Interval Training (HIIT) improves physical performance and frailty in aged mice. J Gerontol A Biol Sci Med Sci, 2017.

5.0 Study Design

5.1 Describe and explain the study design (e.g. case-control, cross-sectional, ethnographic, experimental, interventional, longitudinal, observational).

Response: The study is an interventional study that examines physical performance, functional capacity, quality of life, and physiologic parameters before and after a 3-month short session high intensity interval training regimen. The exercise regimen will be tailored to the individual based upon watts generated at VO2max determined during maximal respiratory analysis. The regimen will be a total of 11.5 minutes that includes: a 30 second warm-up at a watts value that corresponds to 25% of VO2max, and then 3 minutes continued warm-up at the watts value at 50% VO2max, then 3 intervals of 1-minute at the watts value at 80% VO2max then 1-minute active recovery at the watts value at 50% VO2max, and then ending with 1-minute at at the watts value at 80% VO2max and one final minute at 10 watts for cool down.

Parameters include:

Frailty using the Fried physical frailty scale [1],that includes grip strength, gait speed (15-foot test), body weight change, and survey questions for endurance and activity levels.

Functional capacity using the SPPB that includes a chair rise test, balance and coordination testing, and a gait speed test. We will also conduct surveys to assess activities of daily living (ADLs) and the quality of life, enjoyment, and satisfaction questionnaire – short form (Q-LES-Q-SF) during consultation to assess general well being and perceived quality of life. We will also conduct the physical activity enjoyment scale (PACES) survey [43] to determine the participant's perceived enjoyment of the exercise protocol.

Serum inflammatory profile: While frailty is correlated with high levels of the pro-inflammatory serum markers C reactive protein and interleukin-6, regular exercise can attenuate inflammation [47]. Of particular interest, HIIT reduced pro-inflammatory IL-6 expression in obese subjects. Given the significance of inflammation in both frailty and exercise, we will examine the baseline and endpoint serum inflammatory profiles for changes in C reactive protein, interleukin-6, and the anti-inflammatory interleukin-10 using multiplex ELISA analysis (Millipore).

Testosterone: Testosterone is an important hormone that regulates muscle mass and strength and declines during aging. To investigate how testosterone levels affect HIIT exercise and change during exercise we will measure free and total testosterone in serum samples using LC-Mass spectroscopy (Quest diagnostic services).

Next-GEN miRNA-SEQ: We will isolate RNA and perform RNA-SEQ analysis on baseline and endpoint serum samples to determine the quality (miRNA purification, total sequence reads, and unique miRNAs identified) and whether we can identify differentially expressed miRNAs. As depicted in the preliminary results, we will also perform principal component analyses on the complete miRNA profiles. This project will lay the foundation for prognostic methodology that optimizes the exercise prescription providing the framework for tailoring exercise programs to enhance the benefits of training. In addition, we expect to identify miRNA

species that with future studies may provide potential pathways for the development of interventions to maintain muscle mass and physical performance, reduce frailty, and ultimately improve quality of life.

Skeletal muscle hemodynamic response: Continuous functional near infrared spectroscopy (fNIRS) will be utilized to assess changes in regional blood flow and oxygen saturation within the exercising quadriceps muscle of each research subject. Tissue oxygen saturation is highly correlated to cardiorespiratory fitness and is used to measure physiological adaptation to exercise training. Use of this non-invasive measurement technique will allow us to better quantify how subjects respond to high intensity interval training.

In addition, we are seeking to conduct an analysis to examine physical performance, functional capacity, free-living physical activity, quality of life, and key underlying biological factors including microRNA profiles and cellular energetics 16-months after completing our high intensity interval training program.

Parameters being assessed in this analysis are:

Frailty using the Fried physical frailty scale [1], that includes grip strength, gait speed (15-foot test), body weight change, and survey questions for endurance and activity levels.

Functional capacity using the SPPB that includes a chair rise test, balance and coordination testing, and a gait speed test. We will also conduct surveys to assess activities of daily living (ADLs) and the quality of life, enjoyment, and satisfaction questionnaire – short form (Q-LES-Q-SF) during consultation to assess general well-being and perceived quality of life. We will also conduct the physical activity enjoyment scale (PACES) survey [43] to determine the participant's perceived enjoyment of the exercise protocol. Additionally, free-living physical activity will be assessed using a Fitbit activity monitor over the course of 7 days. Sleep quality will be determined using the Pittsburgh Sleep Quality Index (PSQI).

Next-GEN miRNA-SEQ: We will isolate RNA and perform RNA-SEQ analysis to determine the quality (miRNA purification, total sequence reads, and unique miRNAs identified) and whether we can identify differentially expressed miRNAs. As depicted in the preliminary results, we will also perform principal component analyses on the complete miRNA profiles. We expect to identify miRNA species that with future studies may provide potential pathways to better understand how de-training / de-conditioning impact function and quality of life.

Metabolomics

Recovery Measures: A graded cycle exercise test will be administered to assess changes in pulse rate and skeletal muscle hemodynamic response to an acute exercise challenge. A ramped protocol will be utilized beginning with 1-minute of cycling with resistance increasing incrementally with each minute of exercise. The test will be terminated by the participant

based upon dyspnea or lower-limb fatigue. Each test will begin and end with a 10-minute rest phase for baseline measurement purposes. Serum collection will take place before and immediately after each graded exercise test.

Skeletal muscle hemodynamic response: Continuous functional near infrared spectroscopy (fNIRS) will be utilized to assess changes in regional blood flow and oxygen saturation within the exercising quadriceps muscle of each research subject. Tissue oxygen saturation is highly correlated to cardiorespiratory fitness and is used to measure physiological adaptation to exercise training. Use of this non-invasive measurement technique will allow us to better quantify how subjects respond to high intensity interval training.

Global Cognition: Cognition will be assess using the Cognivue Clarity, an FDA-cleared technology that facilitates a 10-minute self-administered computerized assessment of 6 cognitive domains: visuospatial, executive function/attention, naming/language, memory, delayed recall and abstraction. Cognivue Clarity also measures two speed performance parameters: reaction time and speed processing.

6.0 Local Number of Subjects

6.1 Indicate the total number of subjects that will be enrolled or records that will be reviewed locally.

Response: *The initial plan to enroll 45 participants was disrupted due to the onset of the pandemic at which time patient recruitment/enrollment had ended. At this time no further recruitment of new participants will occur and we will only be completing the 27 subjects with their final visit. We will update the protocol and ICF to reflect this information.*

6.2 If applicable, indicate how many subjects you expect to screen to reach your target sample (i.e. your screen failure rate).

Response: We expect our screening success rate will be 20%, thus we will need to screen approximately 50 participants to reach our enrollment goals.

6.3 Justify the feasibility of recruiting the proposed number of eligible subjects within the anticipated recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?

Response: Data from the VA Western New York primary care facility indicates there were nearly 7,000 unique patient visits last year of individuals within our desired age range. From this pool we would need to recruit roughly 2 individuals

per month during the study period. Although we anticipate we will be successful in accomplishing this recruitment rate, the goal of this proposal is to determine the feasibility of doing so.

7.0 Inclusion and Exclusion Criteria

*7.1 Describe the criteria that define who will be **included** in your final study sample.*

NOTE: This may be done in bullet point fashion.

Response:

Inclusion criteria includes:

- Ages 60-90
- Male or Female
- Any race
- Medical clearance for exercise
- Able to evaluate, understand, and sign informed consent documents
- Able to provide small blood samples (5 ml one tube)

*7.2 Describe the criteria that define who will be **excluded** from your final study sample.*

NOTE: This may be done in bullet point fashion.

Response:
Exclusion criteria include:

- Severe co-morbidity (e.g. – CHF (≥ class III), COPD (GOLD stage IV), CKD (> stage 3))
- VAMC SLUMS score ≤ 20 (Mental status test)
- Physical impairment that prevents use of a recumbent exercise bike

7.3 Indicate specifically whether you will include any of the following special populations in your study using the checkboxes below.

NOTE: Members of special populations may not be targeted for enrollment in your study unless you indicate this in your inclusion criteria.

Response: NONE

☐ Adults unable to consent

☐ Individuals who are not yet adults (infants, children, teenagers)

☐ Pregnant women

☐ Prisoners

7.4 Indicate whether you will include non-English speaking individuals in your study. ***Provide justification if you will exclude non-English speaking individuals.***

In order to meet one of the primary ethical principles of equitable selection of subjects, non-English speaking individuals may ***not*** *be routinely excluded from research as a matter of convenience.*

In cases where the research is of therapeutic intent or is designed to investigate areas that would necessarily require certain populations who may not speak English, the researcher is required to make efforts to recruit and include non-English speaking individuals. However, there are studies in which it would be reasonable to limit subjects to those who speak English. Some examples include pilot studies, small unfunded studies with validated instruments not available in other languages, studies with numerous questionnaires, and some non-therapeutic studies which offer no direct benefit.

Response: As this is a pilot study we will seek only English-speaking individuals at this stage.

8.0 Vulnerable Populations

If the research involves special populations that are considered vulnerable, ***describe the safeguards included to protect their rights and welfare.***

NOTE: You should refer to the appropriate checklists, referenced below, to ensure you have provided adequate detail regarding safeguards and protections. You do not, however, need to provide these checklists to the IRB.

8.1 For research that involves ***pregnant women,*** *safeguards include:*
NOTE CHECKLIST: Pregnant Women (HRP-412)

Response: **N/A**: This research does not involve pregnant women.

8.2 For research that involves ***neonates of uncertain viability or non-viable neonates,*** *safeguards include:*
NOTE CHECKLISTS: Non-Viable Neonates (HRP-413), or Neonates of Uncertain Viability (HRP-414)

Response: **N/A:** This research does not involve non-viable neonates or neonates of uncertain viability.

8.3 For research that involves ***prisoners****, safeguards include:*
NOTE CHECKLIST: Prisoners (HRP-415)

Response: **N/A:** This research does not involve prisoners.

8.4 For research that involves ***persons who have not attained the legal age for consent to treatments or procedures involved in the research ("children")****, safeguards include:*
NOTE CHECKLIST: Children (HRP-416)

Response: **N/A:** This research does not involve persons who have not attained the legal age for consent to treatments or procedures ("children").

8.5 For research that involves ***cognitively impaired adults****, safeguards include:*

NOTE CHECKLIST: Cognitively Impaired Adults (HRP-417)

Response: **N/A:** This research does not involve cognitively impaired adults.

8.6 Consider if other specifically targeted populations such as students, employees of a specific firm, or educationally or economically disadvantaged persons are vulnerable. ***Provide information regarding their safeguards and protections, including safeguards to eliminate coercion or undue influence.***

Response: The possibility exists that economically disadvantaged individuals may be included in our study, although this group is not specifically targeted. Participants will be receiving remuneration for their effort, however, the amount chosen (~$400) is fair based on the length of the study and that travel to the VAMC during the 3-4-month period is required.

For the post-HIIT examination, participants will be provided with a Fitbit activity monitor and $250 dollars for their participation.

9.0 Eligibility Screening

9.1 Describe ***screening procedures*** *for determining subjects' eligibility. Screening refers to determining if prospective participants meet inclusion and exclusion criteria.*

Include all relevant screening documents with your submission (e.g. screening protocol, script, questionnaire).

Response: Please refer to our attached scripts and questionnaires for detailed information. Briefly, providers at the VA Western New York (VAWNY) primary care clinics will inform their patients about the study, if the patients express interest, they will be given contact information for the research team so that the patient can contact them directly if they wish to participate. Once the patient is in touch with a member of the research team, they will follow the approved pre-screening script to see if the patient meets initial eligibility criteria.

If the patient agrees to participate, and meets the pre-screening eligibility criteria over the phone, they will be invited to the VA medical center (VAMC) pulmonary rehabilitation clinic for a secondary screen to confirm the participant fulfills the inclusion/exclusion criteria, including a demonstration that they are capable of utilizing recumbent exercise bikes.

VAWNY providers will be informed about the inclusion and exclusion criteria. Special population such as minors, pregnant women, prisoners, cognitively impaired patients will not be included. The inclusion and exclusion criteria will be discussed with the providers who will use their best judgment to decide if a patient they see in their clinic is eligible to participate or not.

10.0 Recruitment Methods

☐ **N/A:** This is a records review only, and subjects will not be recruited. NOTE: If you select this option, please make sure that all records review procedures and inclusion/exclusion screening are adequately described in other sections.

10.1 Describe when, where, and how potential subjects will be recruited.

NOTE: Recruitment refers to how you are identifying potential participants and introducing them to the study. Include specific methods you will use (e.g. searching charts for specific ICD code numbers, Research Participant Groups, posted advertisements, etc.).

Response: Candidates may be identified by pre-screening of primary care clinic patient lists in CPRS. If potential participants are identified, an IRB approved letter will be mailed to them containing some information about the study and the contact information for them to reach the research study team. If the research team does not hear from the patients in 2 weeks, they may give them a follow-up phone call to determine whether the patients are interested.

If potential participants are identified by their own VAWNY primary care physicians during their routine visit, they will be told about the study in brief (Please see our screening scripts attached file.) and if interested, they will be given contact information for the research team.

An additional method of recruitment would be to have a table set up in the lobby or outside the cafeteria where potential participants may receive additional information about the study. This may be done on an intermittent basis. VA Public Affairs has been consulted and this method of recruitment is permitted if IRB approved.

An IRB approved recruitment poster advertising the study will also be displayed around the VA medical center.

10.2 Describe how you will protect the privacy interests of prospective subjects during the recruitment process.

NOTE: Privacy refers to an individual's right to control access to him or herself.

Response: The referring physician will not provide any protected health information (PHI) to the study team, all PHI will be obtained only after the informed consent is signed.

During the screening phone call, a verbal consent to ask PHI (only those listed in the screening script and questionnaire file) will be requested. No PHI questions will be asked if consent was not given, and no PHI other than those listed in the screening script and questionnaire file will be asked if the verbal consent is given.

Study procedures are performed in private exam areas. Study procedures are performed only by study staff. Study documents are maintained in a locked staff office that is only accessed by designated personnel

10.3 Identify any materials that will be used to recruit subjects.

NOTE: Examples include scripts for telephone calls, in person announcements / presentations, email invitations.

For advertisements, include the final copy of printed advertisements with your submission. When advertisements are taped for broadcast, attach the final audio/video tape. NOTE: You may submit the wording of the advertisement prior to taping to ensure there will be no IRB-required revisions, provided the IRB also reviews and approves the final version.

Response: Candidates will be referred by their own VAWNY primary care physicians, please refer to screening script and questionnaire. Poster and recruitment letter materials will also be used.

11.0 Procedures Involved

*11.1 Provide a description of **all research procedures or activities** being performed and when they are performed once a subject is screened and determined to be eligible. Provide as much detail as possible.*

NOTE: This should serve as a blueprint for your study and include enough detail so that another investigator could pick up your protocol and replicate the research. For studies that have multiple or complex visits or procedures, consider the addition of a schedule of events table in in your response.

Response: Our study involves several procedures, surveys, and questionnaires that will be administered during baseline and end point assessments. These include the following:

Frailty Assessment: Frailty is determined based upon assessment of grip strength (using a Jamar hand grip dynamometer, Average of the best 3 of 5 attempts from the dominant hand), gait speed (Time to walk 15 feet), body weight change (participant questioned if they have experienced unexpected weight loss of 10% or greater over the past year), and surveys to assess endurance and activity levels (Survey instruments attached).

Short physical performance battery (SPPB): The SPPB is an assessment of functional capacity based upon gait speed (using data from frailty), chair rise test (participant is instructed to rise from a seated position as many times as possible within 30 seconds), and balance and coordination (participant is asked to stand, stand with one foot in front of another, and stand with feet in an offset position).

Functional capacity and quality of life surveys: To assess functional capacity we will also administer an activities of daily living survey (ADLs – survey instrument attached), the quality of life, enjoyment, and satisfaction survey (Q-LES-Q-SF, instrument attached), and the physical activity enjoyment scale (PACES, instrument attached) to assess perceived enjoyment of the exercise protocol.

Mental status: To assess mental status we will administer the VA-ST. Louis university Mental Status (SLUMS) examination (instrument attached)

Physiologic status: We will assess several indicators of physiologic health including body weight, pulse rate and blood pressure (before and after exercise sessions), quadriceps strength and biceps strength (microFET2 digital handheld dynamometer – device is placed on the lower leg of participant as the individual is asked to lift leg – or the wrist as the individual is asked to lift their forearm), and maximal oxygen uptake (VO2max). The VO2max test is a symptom limited maximal incremental cardiopulmonary exercise test on an electronically braked cycle ergometer. After one minute of unloaded cycling, workload is increased by a fixed amount each minute (ramp protocol) until the subject has to stop due to dyspnea or leg fatigue.

Regional Tissue Oxygen Saturation: fNIRS will be used to measure blood flow to each subject's exercising quadriceps muscle. The fNIRS device will be strapped atop the right quadriceps muscle using a neoprene sleeve prior to the VO2max test and will remain in place through cessation of exercise and recovery. The fNIRS device communicates wirelessly via Bluetooth to a laptop computer for data acquisition. The fNIRS device is both small (~5 cm x ~7 cm x ~2.5 cm) and non-invasive.

Exercise protocol: The high intensity interval training (HIIT) regimen will be a 11.5 minute program featuring a 30-second warm up (at 25% of the watts at VO2max), an additional 3-min warm up (50% VO2max), followed by 3 intervals of 1 min high intensity (80% VO2max), then 1 min recovery (50% VO2max), one additional 1-min interval at high-intensity (80% HRmax), and then a final minute at cool down (10 watts). The programs will be given 3 days a week for 12 weeks total, with intensity increase the greater of 5% or 5 watts for each speed every 2 weeks. The participant may be asked to do an additional 1-2 sessions at the completion of 36 sessions if their last session happens to fall on a Monday or Wednesday. Additionally, a Borg scale (essentially a 1-10 scale) will be used to determine breathlessness, fatigue, and overall difficulty of the HIIT regimen and the intensities will be decreased 5 watts if individuals score an 8 or higher in any of these categories and increased the greater of 5 watts or 5% if individuals score 3 or less in all categories. The HIIT regimen will be performed on a Matrix R3x recumbent exercise bikes.

Serum collection: We will collect 10 ml of serum for assessment of inflammatory biomarkers (IL-6, IL-10, and C-reactive Protein), free and total testosterone, and to isolate microRNA for miRNA-SEQ analysis.

<u>For the post-HIIT follow-up analysis, the following procedures will be conducted</u>.

Frailty Assessment: Frailty is determined based upon assessment of grip strength (using a Jamar hand grip dynamometer, Average of the best 3 of 5 attempts from the dominant hand), gait speed (Time to walk 15 feet), body weight change (participant questioned if they have experienced unexpected weight loss of 10% or greater over the past year), and surveys to assess endurance and activity levels (Survey instruments attached).

Short physical performance battery (SPPB): The SPPB is an assessment of functional capacity based upon gait speed (using data from frailty), chair rise test (participant is instructed to rise from a seated position as many times as possible within 30 seconds), and balance and coordination (participant is asked to stand, stand with one foot in front of another, and stand with feet in an offset position).

Physiologic status: We will assess several indicators of physiologic health including body weight, pulse rate and blood pressure, quadriceps strength and biceps strength (microFET2 digital handheld dynamometer – device is placed on the lower leg of participant as the individual is asked to lift leg – or the wrist as the individual is asked to lift their forearm).. A graded cycle exercise test will be administered to assess key changes in pulse rate, regional tissue oxygenation, and cellular energetics in response to an acute exercise stimulus. . For the test, after a 10-minute rest phaseafter one minute of unloaded cycling will commence. Workload will then increase by a fixed amount each minute (ramp protocol) until the subject has to stop due to dyspnea or leg fatigue. A 10-minute post-exercise rest phase will then follow. Serum collection will take place immediately before and after each exercise test.

Regional Tissue Oxygen Saturation: fNIRS will be used to measure blood flow to each subject's exercising quadriceps muscle during the maximal exercise test. The fNIRS device will be strapped atop the right quadriceps muscle using a neoprene sleeve prior to the VO2max test and will remain in place through cessation of exercise and recovery. The fNIRS device communicates wirelessly via Bluetooth to a laptop computer for data acquisition. The fNIRS device is both small (~5 cm x ~7 cm x ~2.5 cm) and non-invasive.

Functional capacity and quality of life surveys: To assess functional capacity we will also administer an activities of daily living survey (ADLs - survey instrument attached), the quality of life, enjoyment, and satisfaction survey (Q-LES-Q-SF, instrument attached), and the physical activity enjoyment scale (PACES, instrument attached) to assess perceived enjoyment of the exercise protocol. In addition, the Pittsburgh Sleep Quality Index (PSQI – instrument attached) will be administered. For a duration of 7-days, leisure-time physical activity will be measured using Fitbit activity monitors.

Mental status: To assess mental status we will administer the VA-ST. Louis university Mental Status (SLUMS) examination (instrument attached) as well as the Cognivue Clarity.

Serum Collection: When participants return for the post-HIIT visit, we will also collect 80 mL as a follow-up to the previous analysis as well as to be used in blood cell metabolism experiments.

11.2 Describe what data will be collected.

NOTE: For studies with multiple data collection points or long-term follow up, consider the addition of a schedule or table in your response.

Response:
Participants' basic demographics (age, gender, race)

Past medical history as it pertains to inclusion/exclusion criteria (co-morbidity status)

Frailty status and parameter scores (Gait speed, weight change, grip strength, activity and endurance)

Short physical performance battery status and parameter scores (Gait speed, chair rise test, balance testing)

Mental status score (VA SLUMS instrument and Cognivue Carity

Activities of daily living score (ADLs instrument)

Quality of life score (Q-LES-Q-SF instrument)

Physical activity enjoyment score (PACES instrument)

Sleep Quality (PSQI Instrument)

Leisure-time physical activity (Fitbit activity monitor)

Heart rate max score (VO2max test)

Quadriceps strength (MicroFET2 device)

Body weight, pulse rate, and blood pressure (scales and blood pressure analyzers)

Regional skeletal muscle blood flow and oxygen saturation (Functional near infrared spectroscopy)

11.3 List any instruments or measurement tools used to collect data (e.g. questionnaire, interview guide, validated instrument, data collection form).

Include copies of these documents with your submission.

Response:

Frailty assessment form

Short physical performance battery form

VA-ST. Louis university Mental Status (SLUMS)

Activities of daily living survey (ADLs)

Quality of life, enjoyment, and satisfaction survey (Q-LES-Q-SF)

Physical activity enjoyment scale (PACES)

Pittsburgh Sleep Quality Index (PSQI)

11.4 Describe any source records that will be used to collect data about subjects (e.g. school records, electronic medical records).

Response: None.

*11.5 Indicate whether or not **individual** subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings will be shared with subjects or others (e.g., the subject's primary care physician) and if so, describe how these will be shared.*

Response: Individual results will not be shared with participants or others.

*11.6 Indicate whether or not **study** results will be shared with subjects or others, and if so, describe how these will be shared.*

Response: De-identified study results will be submitted in aggregate for scientific conferences and medical journals consideration for publication.

12.0 Study Timelines

12.1 Describe the anticipated duration needed to enroll all study subjects.

Response: 18 months from the start date of funding (October 1st, 2018)

The post-training assessment will be completed by September 28th, 2021.

12.2 Describe the duration of an individual subject's participation in the study. Include length of study visits, and overall study follow-up time.

Response: Once enrolled in the study the participant will be administer baseline assessment protocols that combined will take approximately 2 hours. The individual will then perform 12 sessions (3 per week – Monday, Wednesday, and Friday) of HIIT exercise. The exercise protocol plus body weight and blood pressure measurements will take no more than 20 minutes. A final assessment will also take approximately 2 hours. Participants in the post-HIIT examination will be required to participate for one additional visit.

12.3 Describe the estimated duration for the investigators to complete this study (i.e. all data is collected and all analyses have been completed).

Response: Two years from the enrollment of the last participant. Post-HIIT assessment will require three months to complete.

13.0 Setting

13.1 Describe all facilities/sites where you will be conducting research procedures. Include a description of the security and privacy of the facilities (e.g. locked facility, limited access, privacy barriers). Facility,

department, and type of room are relevant. Do not abbreviate facility names.

NOTE: Examples of acceptable response may be: "A classroom setting in the Department of Psychology equipped with a computer with relevant survey administration software," "The angiogram suite at Buffalo General Medical Center, a fully accredited tertiary care institution within New York State with badge access," or, "Community Center meeting hall."

Response:

- Subject interaction inclusive of obtaining consent, blood draw, functional capacity assessments, surveys, will take place in room 827B in the VA medical center and nearby hallways (for gait speed test)
- Exercise sessions will take place in room 823-B2 in the VA-medical center.
- Isolation of serum miRNA and analysis of serum inflammatory biomarkers will be performed in Dr. Troen's laboratory in building 20 of the VA.
- Measurements of testosterone will be performed as a service by Quest Diagnostics.
- Sequenced miRNA data will be generated by the NYS Center of Excellence in Bioinformatics and Life Sciences.

13.2 For research conducted outside of UB and its affiliates, describe:

- *Site-specific regulations or customs affecting the research*
- *Local scientific and ethical review structure*

NOTE: This question is referring to UB affiliated research taking place outside UB, i.e. research conducted in the community, school-based research, international research, etc. It is not referring to multi-site research. UB affiliated institutions include Kaleida Health, ECMC, and Roswell Park Cancer Institute.

Response: **N/A:** This study is not conducted outside of UB or its affiliates.

14.0 Community-Based Participatory Research

14.1 Describe involvement of the community in the design and conduct of the research.

NOTE: Community-Based Participatory Research (CBPR) is a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. CBPR begins with a research topic of importance to the community, has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities.

Response: **N/A:** This study does not utilize CBPR.

14.2 Describe the composition and involvement of a community advisory board.

Response: **N/A:** This study does not have a community advisory board.

15.0 Resources and Qualifications

*15.1 Describe the qualifications (e.g., education, training, experience, expertise, or certifications) of the Principal Investigator **and** staff to perform the research. When applicable describe their knowledge of the local study sites, culture, and society. Provide enough information to convince the IRB that you have qualified staff for the proposed research.*

NOTE: If you specify a person by name, a change to that person will require prior approval by the IRB. If you specify a person by role (e.g., coordinator, research assistant, co-investigator, or pharmacist), a change to that person will not usually require prior approval by the IRB, provided that the person meets the qualifications described to fulfill their roles.

Response: All local research staff has completed CITI training. All research staff has extensive experience conducting clinical trials.

The physicians conducting the research specialize in exercise rehabilitation programs and have conducted similar clinical trials.

Describe other resources available to conduct the research.

15.2 Describe the time and effort that the Principal Investigator and research staff will devote to conducting and completing the research.

NOTE: Examples include the percentage of Full Time Equivalents (FTE), hours per week. The question will elicit whether there are appropriate resources to conduct the research.

Response:

25% of PI effort

10% of each co-investigators' effort

10 hours weekly for each of the research assistants

15.3 Describe the availability of medical or psychological resources that subjects might need as a result of anticipated consequences of the human research, if applicable.

NOTE: One example includes: on-call availability of a counselor or psychologist for a study that screens subjects for depression.

Response: Procedures will be performed at the Buffalo VA medical center (VAMC). Additionally, the laboratory is equipped with oxygen and one automatic electronic defibrillator. During the maximal exercise tests, a physician will be present. In case of an emergency, procedures are in place to expedite medical care. All staff will be CPR and first aid certified.

15.4 Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

Response: All study staff are trained on the study protocol by first reviewing the protocol itself in detail. The PI conducts a training session to ensure that the research team understands the protocol and each individual's responsibility. A major focus of training will be to ensure that confidentiality measures are in place and will be followed.

16.0 Other Approvals

16.1 Describe any approvals that will be obtained prior to commencing the research (e.g., school, external site, funding agency, laboratory, radiation safety, or biosafety).

Response: IRB approval must be obtained before study initiation, no other approvals are required

17.0 Provisions to Protect the Privacy Interests of Subjects

17.1 Describe how you will protect subjects' privacy interests during the course of this research.

NOTE: Privacy refers to an individual's right to control access to him or herself. Privacy applies to the person. Confidentiality refers to how data collected about individuals for the research will be protected by the researcher from release. Confidentiality applies to the data.

Examples of appropriate responses include: "participant only meets with a study coordinator in a classroom setting where no one can overhear", or "the participant is reminded that they are free to refuse to answer any questions that they do not feel comfortable answering."

Response: Study procedures are performed in private exam areas. Study procedures are performed only by study staff. The participants will be reminded that they are free to refuse to answer any questions that they do not feel comfortable answering

17.2 Indicate how the research team is permitted to access any sources of information about the subjects.

NOTE: Examples of appropriate responses include: school permission for review of records, consent of the subject, HIPAA waiver. This question ***does apply*** *to records reviews.*

Response: Existing records will be reviewed after obtaining informed consent from the selected participants.

18.0 Data Management and Analysis

18.1 Describe the data analysis plan, including any statistical procedures. This section applies to both quantitative and qualitative analysis.

Response: The project serves as a pilot to demonstrate our ability to administer high intensity interval training in older individuals and provide preliminary data to aid power calculations in future studies. With this in mind we will compare baseline and endpoint parameters using a paired student's T-test for the following parameters: SPPB scores, ADLs, Q-LES-Q-SF, quadriceps strength, and VO_2MAX, and in our ELISA analysis of the inflammatory biomarkers and LC-MS measurement of serum free and total testosterone. For microRNA analysis we will examine differentially expressed miRNA using statistical analysis that includes adjustment for false positives.

18.2 If applicable, provide a power analysis.

NOTE: This may not apply to certain types of studies, including chart/records reviews, survey studies, or observational studies. This question is asked to elicit whether the investigator has an adequate sample size to achieve the study objectives and justify a conclusion.

Response: This is a pilot feasibility study. No power calculation is deemed necessary.

18.3 Describe any procedures that will be used for quality control of collected data.

Response: Data is subjected to quality review by research staff at time of data entry. The data is cleaned up using a logic check system to ensure accuracy. Data that does not pass logic check criteria are queried for clarification.

19.0 Confidentiality

A. Confidentiality of Study Data

*Describe the local procedures for maintenance of confidentiality of **study data and any records that will be reviewed for data collection**.*

*19.1 A. Where and how will all data and records be stored? Include information about: password protection, encryption, physical controls, authorization of access, and separation of identifiers and data, as applicable. Include physical (e.g. paper) **and** electronic files.*

Response: Data in this study refers to clinical data (via patient surveys, questionnaires, and assessments), lab generated research data such as ELISA analysis of inflammatory biomarkers, serum free and total testosterone levels, and sequenced data of miRNA from serum.

A unique subject number will be assigned to each subject at inclusion, immediately after informed consent has been obtained. This number will serve as the subject's identifier in the trial as well as in the storage database. Only the PI or designated research personnel will be able to link the subject's data to the identified subject via an identification list that will be stored on a secured research SharePoint that is accessible only to designated and approved research personnel.

Obtained health data, documents, and research generated data will be stored in a passkey protected cabinet in the Co-PI's laboratory located at CTRC 8031, the laboratory requires ID and clearance. The data will not contain any identifiers. The PI will store that file in the passkey protected cabinet.

Clinical and research data collected will be stored digitally on PI and Co-PI's computers. To ensure security of data, using the assigned letter code as the new identifier, no medical record or any identifier will be placed in that file. Additionally, all computers are located in locked rooms and are password protected.

The Center for Excellence in bioinformatics and laboratory sciences will receive de-identified samples for sequencing. Only the PI will be able to identify samples and will work closely with biostatisticians to ensure anonymity of samples is maintained during the statistical analyses.

19.2 A. How long will the data be stored?

Response: Indefinitely

19.3 A. Who will have access to the data?

Response: The PI, Co-PI and delegated research staff (research assistants listed in this protocol) will have access to data as necessary for data entry, data clarification and analysis. De-identified specimens will be processed by lab staff (listed in this protocol)

The consent will include language asking participants if they are ok with the research data being used for other relevant research beyond the scope of this study. In addition, the consent document will request permission to contact participants for additional follow-up analyses if deemed appropriate.

19.4 A. Who is responsible for receipt or transmission of the data?

Response: The Principal Investigator and delegated research staff will be responsible for the transmission of the data.

19.5 A. How will the data be transported?

Response: Data generated in the PI's lab will be entered in the data file. These data are de-identified and transferred to co-investigators for further analysis as needed.

Physical data will be transported from the site of generation at the VAMC to storage sites at the CTRC by the PI and other members of the study team.

De-identified miRNA sequence data will be accessed remotely using the core facility system with a provided log in and password info.

B. Confidentiality of Study Specimens

*Describe the local procedures for maintenance of confidentiality of **study specimens**.*

☐ **N/A:** No specimens will be collected or analyzed in this research. *(Skip to Section 19.0)*

19.6 B. Where and how will all specimens be stored? Include information about: physical controls, authorization of access, and labeling of specimens, as applicable.

Response: All samples will be labeled using the same code mentioned above to de-identify the samples.

All samples will be stored in -80C freezer in the Research Core lab, Room 105, in the Research Building 20 of the VA Hospital. The lab is secure and cannot be accessed without ID badge and the proper authorization.

19.7 B. How long will the specimens be stored?

Response: Indefinitely

19.8 B. Who will have access to the specimens?

Response: The specimens will be accessed by the lab staff member listed in this IRB.

In future, these de-identified samples could be made available to other researchers and partners (new projects utilizing these samples and associated data will go through IRB approval)

19.9 B. Who is responsible for receipt or transmission of the specimens?

Response: The PI's lab staff listed in this IRB will be responsible for receiving, handling, storage and further distribution of samples.

19.10 B. How will the specimens be transported?

Response: De-identified specimens will be transferred from the point of collection to the PI's research lab in building 20 of the VA Western New York. Additionally, processed miRNA samples will be transported to the New York State Center of Excellence Bioinformatics & Life Sciences.

20.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

NOTE: Minimal risk studies may be required to monitor subject safety if the research procedures include procedures that present unique risks to subjects that require monitoring. Some examples include: exercising to exertion, or instruments that elicit

suicidality or substance abuse behavior. In such cases, N/A is not an acceptable response.

20.1 Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

Response: During baseline, endpoint, and follow-up assessments a physician will be present to identify acute markers that would indicate a risk to safety. During the exercise phase of our experiment, we will evaluate heart rate and blood pressure data to ensure both are within acceptable limits. Additionally, participant self reported concerns will be addressed as soon as possible.

20.2 Describe what data are reviewed, including safety data, untoward events, and efficacy data.

Response: To assess safety we will examine blood pressure and heart rate in addition to participant self reports of health status.

20.3 Describe any safety endpoints.

Response:

- Significant drop in systolic blood pressure (20 mmHg) or a failure of systolic blood pressure to increase with increasing intensity
- Excessive rise in blood pressure (systolic > 220 mmHg or diastolic > 105 mmHg)
- Drop in diastolic blood pressure ≥ 15 mmHg
- Failure of heart rate to increase with increasing intensity
- Participant self reports of
    - *Injury*
    - lightheadedness, confusion, ataxia, dizziness, nausea
    - Severe subject fatigue

20.4 Describe how the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).

Response: Body weight and heart rate will be collected during participant visits, including participant self reports.

20.5 Describe the frequency of safety data collection.

Response: Safety data will be collected during baseline and endpoint assessments and at each of the thrice weekly exercise sessions.

20.6 Describe who will review the safety data.

Response: Safety data will be reviewed by the research team (Drs. Troen, Mador, Seldeen, and Ray).

20.7 Describe the frequency or periodicity of review of cumulative safety data.

Response: Cumulative safety data will be reviewed weekly, unless notification of a significant event needing immediate attention.

20.8 Describe the statistical tests for analyzing the safety data to determine whether harm is occurring.

Response: Risk of harm will be determined by safety data reaching or surpassing specific thresholds.

20.9 Describe any conditions that trigger an immediate suspension of the research.

Response: Suspension of the research for specific participants will be considered if safety parameters reach or surpass specific thresholds.

21.0 Withdrawal of Subjects

☐ **N/A:** This study is not enrolling subjects. This section does not apply.

*21.1 Describe **anticipated** circumstances under which subjects may be withdrawn from the research without their consent.*

Response: Participants may be withdrawn if during safety evaluation they reach or surpass our specific thresholds for safety. Additionally, participants may be removed if they develop an injury that prevents further participation.

21.2 Describe any procedures for orderly termination.

NOTE: Examples may include return of study drug, exit interview with clinician. Include whether additional follow up is recommended for safety reasons for physical or emotional health.

Response: The clinical data and blood samples will be removed as per patient request.

21.3 Describe procedures that will be followed when subjects withdraw from the research, including retention of already collected data, and partial withdrawal from procedures with continued data collection, as applicable.

Response: In the event that the samples degrade, and the subject is not included in the study, the collected samples will be destroyed as per EHS guidelines for managing biohazardous waste.

If the subject wishes to withdraw from the study, the subject's sample will be destroyed. No further data will be collected from this subject.

22.0 Risks to Subjects

22.1 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related to their participation in the research. Consider physical, psychological, social, legal, and economic risks. Include a description of the probability, magnitude, duration, and reversibility of the risks.

NOTE: Breach of confidentiality is always a risk for identifiable subject data.

Response: The methodology is relatively low risk to participants, with the highest risk methods being blood draw, a maximal respiration test, and 36 exercise sessions (plus 1-2 optional sessions) over a 12 week period. Additionally, participants will be asked to travel to the Buffalo VAMC for assessments and exercise sessions, which thus includes the risk of transit. The overall probability of adverse events is low and in all but the most rare events, harm will be reversible.

22.2 Describe procedures performed to lessen the probability or magnitude of risks, including procedures being performed to monitor subjects for safety.

Response: We will perform safety monitoring of participants as necessary to minimize risk of harm.

*22.3 If applicable, indicate **which procedures** may have risks to the subjects that are currently unforeseeable.*

Response: Exercise testing and training carries inherent risks that may vary from participant to participant.

22.4 If applicable, indicate which research procedures may have risks to an embryo or fetus should the subject be or become pregnant.

Response: Not applicable.

22.5 If applicable, describe risks to others who are not subjects.

Response: Not applicable.

23.0 Potential Benefits to Subjects

23.1 Describe the potential benefits that individual subjects may experience by taking part in the research. Include the probability, magnitude, and duration of the potential benefits. Indicate if there is no direct benefit.

*NOTE: Compensation **cannot** be stated as a benefit.*

Response: This research has the potential to improve functional capacity and quality of life in study participants. This study also introduces participants to a maintainable exercise strategy for older individuals, who previously may not have considered exercise to be a viable option to maintain functional capacity.

24.0 Compensation for Research-Related Injury

☐ **N/A:** The research procedures for this study do not present risk of research related injury (e.g. survey studies, records review studies). This section does not apply.

*24.1 **If the research procedures carry a risk of research related injury,** describe the available compensation to subjects in the event that such injury should occur.*

Response: There is no compensation for research related injury.

24.2 Provide a copy of contract language, if any, relevant to compensation for research related injury.

NOTE: If the contract is not yet approved at the time of this submission, submit the current version here. If the contract is later approved with ***different language regarding research related injury****, you must modify your response here and submit an amendment to the IRB for review and approval.*

Response:

25.0 Economic Burden to Subjects

25.1 Describe any costs that subjects may be responsible for because of participation in the research.

NOTE: Some examples include transportation or parking.

Response: Participants will be responsible for travel arrangements to the Buffalo VAMC training facility.

26.0 Compensation for Participation

25.1 Describe the amount and timing of any compensation to subjects, including monetary, course credit, or gift card compensation.

Response: Participants will receive remuneration in the form of a check of $100 for completion of baseline assessments and $300 for completion of endpoint assessments. This compensation is for time spent, travel expenses and participation in the study.

For participants allowing follow-up examination after the training program, we will provide a Fitbit activity monitor as well as a check for $2500 for time spent, travel costs, and participation.

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

☐ **N/A:** There is no compensation for participation. This section does not apply.

27.0 Consent Process

27.1 Indicate whether you will be obtaining consent.

NOTE: This does not refer to consent documentation, but rather whether you will be obtaining permission from subjects to participate in a research study. Consent documentation is addressed in Section 27.0.

☒ ***Yes*** *(If yes, Provide responses to each question in this Section)*
No *(If no, Skip to Section 27.0)*

27.2 Describe where the consent process will take place. Include steps to maximize subjects' privacy.

Response: Informed consent will be obtained at the Buffalo VAMC Pulmonary Cardiac Rehabilitation facility. The process itself will occur in a private exam room at this location.

27.3 Describe how you will ensure that subjects are provided with a sufficient period of time to consider taking part in the research study.

NOTE: It is always a requirement that a prospective subject is given sufficient time to have their questions answered and consider their participation. See "SOP: Informed Consent Process for Research (HRP-090)" Sections 5.5 and 5.6.

Response: Subjects may take as much time as they wish to consider participation. Subjects will be informed about the study by their primary care physician, then within few days will receive a call from the study personal, followed by a study visit. This will ensure that there is ample of time to think and decide about participation

27.4 Describe any process to ensure ongoing consent, defined as a subject's willingness to continue participation for the duration of the research study.

Response: It is regularly reinforced with subjects that they are participating in a research study and that participation is voluntary and that they may ask questions at any time.

27.5 Indicate whether you will be following "SOP: Informed Consent Process for Research (HRP-090)." If not, or if there are any exceptions or additional details to what is covered in the SOP, describe:

- *The role of the individuals listed in the application who are involved in the consent process*
- *The time that will be devoted to the consent discussion*
- *Steps that will be taken to minimize the possibility of coercion or undue influence*
- *Steps that will be taken to ensure the subjects' understanding*

Response: We have reviewed and will be following "SOP: Informed Consent Process for Research (HRP-090)."

Non-English Speaking Subjects

N/A: This study will not enroll Non-English speaking subjects.
(Skip to Section 26.8)

27.6 Indicate which language(s) other than English are likely to be spoken/understood by your prospective study population or their legally authorized representatives.

NOTE: The response to this Section should correspond with your response to Section 6.4 of this protocol.

Response: Not Applicable

27.7 If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.

NOTE: Guidance is provided on "SOP: Informed Consent Process for Research (HRP-090)."

Response:

Cognitively Impaired Adults

☒ **N/A**: This study will not enroll cognitively impaired adults.
(Skip to Section 26.9)

27.8 Describe the process to determine whether an individual is capable of consent.

Response: Not Applicable

Adults Unable to Consent

☒ **N/A**: This study will not enroll adults unable to consent.
(*Skip to Section 26.13)*

When a person is not capable of consent due to cognitive impairment, a legally authorized representative should be used to provide consent (Sections 26.9 and 26.10) ***and, where possible, assent of the individual should also be solicited*** *(Sections 26.11 and 26.12).*

27.9 Describe how you will identify a Legally Authorized Representative (LAR). Indicate that you have reviewed the "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" for research in New York State.

NOTE: Examples of acceptable response includes: verifying the electronic medical record to determine if an LAR is recorded.

Response: Not applicable – our target demographic is 60-85 year old adults.

27.10 ***For research conducted outside of New York State****, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the*

research. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "legally authorized representative" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

Response: All work will be conducted within the state of New York.

*27.11 Describe the process for **assent of the adults**:*

- *Indicate whether assent will be obtained from all, some, or none of the subjects. If some, indicate which adults will be required to assent and which will not.*

Response: All participants will have to give informed consent personally, and will have to have the capacity to participate in a study and give consent

- *If assent will not be obtained from some or all subjects, provide an explanation of why not.*

Response: Not applicable.

*27.12 Describe whether **assent of the adult** subjects will be documented and the process to document assent.*

NOTE: The IRB allows the person obtaining assent to document assent on the consent document using the "Template Consent Document (HRP-502)" Signature Block for Assent of Adults who are Legally Unable to Consent.

Response: Not applicable.

Subjects who are not yet Adults (Infants, Children, and Teenagers)

☒ **N/A**: This study will not enroll subjects who are not yet adults. *(Skip to Section 27.0)*

*27.13 Describe the criteria that will be used to determine **whether a prospective subject has not attained the legal age for consent to treatments or procedures involved in the research** under the applicable law of the jurisdiction in which the research will be conducted **(e.g., individuals under the age of 18 years)**. For research conducted in NYS, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children."*

NOTE: Examples of acceptable responses include: verification via electronic medical record, driver's license or state-issued ID, screening questionnaire.

Response: Not applicable

*27.14**For research conducted outside of New York State**, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review*

your protocol along the definition of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

Response: Not applicable

27.15 Describe whether parental permission will be obtained from:

Response:

☐ One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.

☐ Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

☐ Parent permission will not be obtained. A waiver of parent permission is being requested.

NOTE: The requirement for parent permission is a protocol-specific determination made by the IRB based on the risk level of the research. For guidance, review the "CHECKLIST: Children (HRP-416)."

*27.16 Describe whether permission will be obtained from individuals **other than parents**, and if so, who will be allowed to provide permission. Describe your procedure for determining an individual's authority to consent to the child's general medical care.*

Response: Not applicable

*27.17 Indicate whether assent will be obtained from all, some, or none of the **children**. If assent will be obtained from some children, indicate which children will be required to assent.*

Response: Not applicable

27.18 When assent of children is obtained, describe how it will be documented.

Response: Not applicable

28.0 Waiver or Alteration of Consent Process

Consent will not be obtained, required information will not be disclosed, or the research involves deception.

☒ **N/A:** A waiver or alteration of consent is not being requested.

28.1 If the research involves a waiver or alteration of the consent process, please review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" to ensure that you have provided sufficient information for the IRB to make the determination that a waiver or alteration can be granted.

NOTE: For records review studies, the first set of criteria on the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" applies.

Response:

28.2 If the research involves a waiver of the consent process for planned emergency research, please review the "CHECKLIST: Waiver of Consent for Emergency Research (HRP-419)" to ensure you have provided sufficient information for the IRB to make these determinations. Provide any additional information necessary here:

Response:

29.0 Process to Document Consent

☐ **N/A:** A Waiver of Consent is being requested.
(Skip to Section 29.0)

29.1 Indicate whether you will be following "SOP: Written Documentation of Consent (HRP-091)." If not or if there are any exceptions, describe whether and how consent of the subject will be obtained including whether or not it will be documented in writing.

NOTE: If your research presents no more than minimal risk of harm to subjects and involves no procedures for which written documentation of consent is normally required outside of the research context, the IRB will generally waive the requirement to obtain written documentation of consent. This is sometimes referred to as 'verbal consent.' Review "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" to ensure that you have provided sufficient information.

If you will document consent in writing, attach a consent document with your submission. You may use "TEMPLATE CONSENT DOCUMENT (HRP-502)". If you will obtain consent, but not document consent in writing, attach the script of the information to be provided orally or in writing (i.e. consent script or Information Sheet).

Response:

☒ We will be following "SOP: Written Documentation of Consent" (HRP-091).

30.0 Multi-Site Research (Multisite/Multicenter Only)

☒ **N/A:** This study is not an investigator-initiated multi-site study. This section does not apply.

*30.1 If this is a multi-site study **where you are the lead investigator**, describe the processes to ensure communication among sites, such as:*

- *All sites have the most current version of the IRB documents, including the protocol, consent document, and HIPAA authorization.*

- *All required approvals have been obtained at each site (including approval by the site's IRB of record).*
- *All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.*
- *All engaged participating sites will safeguard data as required by local information security policies.*
- *All local site investigators conduct the study appropriately.*
- *All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.*

Response: Not applicable.

30.2 Describe the method for communicating to engaged participating sites:

- *Problems*
- *Interim results*
- *Study closure*

Response: Not applicable.

30.3 Indicate the total number of subjects that will be enrolled or records that will be reviewed across all sites.

Response: Not applicable.

30.4 If this is a multicenter study for which UB will serve as the IRB of record, and subjects will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) describe those methods.

Response: Not applicable.

31.0 Banking Data or Specimens for Future Use

☒ **N/A:** This study is not banking data or specimens for future use or research outside the scope of the present protocol. This section does not apply.

*31.1 If data or specimens will be banked (stored) for **future use, that is, use or research outside of the scope of the present protocol**, describe where the data/specimens will be stored, how long they will be stored, how the data/specimens will be accessed, and who will have access to the data/specimens.*

NOTE: Your response here must be consistent with your response at the "What happens if I say yes, I want to be in this research?" Section of the Template Consent Document (HRP-502).

Response: The intent is to build a central data repository housing de-identified data which can then leveraged by other researchers and partners towards the single goal of better understanding the disease and thereby developing more efficient clinical tools to help with diagnosis and treatment options

Where data/specimens will be stored, how long they will be stored, how they will be accessed, and who will have access to them: all exactly as detailed in section 18.0

31.2 List the data to be stored or associated with each specimen.

Response: De-identified samples will be stored in the Research Core lab, The PI will keep the link file (the file that will identify the source of the samples as mentioned above

31.3 Describe the procedures to release banked data or specimens for future uses, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

Response: The Research staff listed in this protocol will have access to the data to perform future studies. Any request from a researcher not listed in this protocol should be first approved by IRB without the need to re-consent the participants, this will be clearly mentioned in the consent form.

32.0 Drugs or Devices

☒ **N/A:** This study does not involve drugs or devices. This section does not apply.

32.1 If the research involves drugs or devices, list and describe all drugs and devices used in the research, the purpose of their use, and their regulatory approval status.

Response: Not applicable.

32.2 Describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.

Response: Not applicable.

If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:

32.3 Identify the holder of the IND/IDE/Abbreviated IDE.

Response: Not applicable.

32.4 Explain procedures followed to comply with FDA sponsor requirements for the following:

	Applicable to:		
FDA Regulation	***IND Studies***	***IDE studies***	***Abbreviated IDE studies***
21 CFR 11	***X***	***X***	
21 CFR 54	***X***	***X***	
21 CFR 210	***X***		
21 CFR 211	***X***		
21 CFR 312	***X***		
21 CFR 812		***X***	***X***
21 CFR 820		***X***	

Response: Not applicable.

33.0 Humanitarian Use Devices

☒ **N/A:** This study does not involve humanitarian use devices. This does not apply.

33.1 For Humanitarian Use Device (HUD) uses provide a description of the device, a summary of how you propose to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures.

Response: Not applicable.

33.2 For HUD uses provide a description of how the patient will be informed of the potential risks and benefits of the HUD and any procedures associated with its use.

Response: Not applicable.