Study Title

Feasibility of High Intensity Interval Training for Knee Osteoarthritis

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Feasibility of High Intensity Interval Training for Knee Osteoarthritis

Manual of Operating Procedures (MOOP)

Version 1.1
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CONFIDENTIAL STATEMENT
This document contains confidential information, which should not be copied, referred to, released or published without written approval from Drs. Golightly and Smith-Ryan. Investigators are cautioned that the information in this protocol might be subject to change and revision. Any conclusion regarding efficacy and safety must be considered provisional.

Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

Background

This proposal focuses on the novel use of high-intensity interval training (HIIT) as a method to improve physical function in patients with symptomatic knee osteoarthritis (OA).

Knee OA is one of the top five causes of disability in the United States.[1] The estimated lifetime risk of symptomatic knee OA is nearly 45% by 85 years of age, and this risk grows to 60% among those who are obese.[2] Physical activity reduces pain and increases physical function in people with knee OA and is a mainstay for treatment of OA.[3-7] The Department of Health and Human Services (DHHS) guidelines support ≥150 minutes of moderate-to-vigorous physical activity per week for improved health and weight management,[8, 9] but less than 10% of adults and few people with symptomatic knee OA achieve these recommended levels.[10, 11] Lack of time and motivation are common reasons for not maintaining regular physical activity.[12] Furthermore, many people with OA are unable to complete the DHHS recommended duration of moderate intensity aerobic exercise because of pain levels or functional limitations. Given the current high rates of inactivity in symptomatic knee OA patients, novel approaches are needed to help individuals achieve physical activity levels that will result in reduced disability.

High-intensity interval training (HIIT) is a time-efficient exercise strategy in which short intense exercise periods are interspersed with recovery periods. HIIT requires as little as 10 minutes of exercise per session and results in improved health and physical function, often in as few as 2 weeks.[13] This form of exercise requires less frequent and shorter duration exercise (e.g., 2 times per week for 10 minutes) than either traditional long duration low-moderate intensity exercise or high intensity resistance (strength) training. HIIT is safe in a variety of clinical populations including patients with heart failure,[14] stroke,[15] cancer,[16] and chronic obstructive pulmonary disease, [17] with high tolerability and few adverse events. Importantly, HIIT programs are highly adaptable, accommodating individual limitations to minimize pain and joint impact, and maximize comfort. Recently, the need for more data on higher intensity exercise in OA patients has been highlighted.[18] To date, research examining HIIT among people with OA is sparse, with only 1 previous study showing benefits of a 6-week combined aquatic treadmill walking and balance program on joint pain, balance and function.[19] Longer term data are needed on a HIIT program tailored to a patient's access to and comfort with exercise equipment. Our preliminary evidence[20, 21] suggests that HIIT is a promising approach for maximizing physical activity among people with knee OA because it allows for short exercise bouts with rest periods (which may be more feasible for people with knee OA), yet results in comparable or greater benefits to traditional, continuous moderate intensity exercise.[22, 23] Furthermore, HIIT dramatically improves muscle strength and body composition within three weeks,[24-27] two risk factors for progression of knee OA symptoms.

Study Aims

For this feasibility and proof-of-concept study, we will conduct a HIIT intervention for people with knee OA (40-75 years old) and obtain preliminary data on changes in outcomes during and after HIIT. A protocol previously evaluated by our research group will be implemented under the supervision of trained research personnel 2 times per week for 12 weeks. An acute evaluation (week 6) will occur to better understand the feasibility of the intervention in 30 participants with symptomatic knee OA for the primary outcomes of performance-based physical function and knee OA symptomatic burden (pain), along with secondary outcomes of balance, isometric knee extensor and flexor strength (factors associated with physical function and symptomatic knee OA progression), cardiorespiratory fitness, and body composition.

Aim 1. To examine the feasibility and acceptability of the HIIT program in patients with knee OA symptoms ranging from mild to severe. We will determine adherence to and tolerability of HIIT, acceptability, and recruitment and retention rates of patients through 6- and 12-week assessments.

Aim 2. To determine short-term changes in outcomes among patients with symptomatic knee OA participating in a HIIT intervention. Hypothesis: Patients with knee OA will have clinically important improvements in physical function, knee OA symptomatic burden (pain), balance, isometric knee extensor and flexor strength, cardiorespiratory fitness, and body composition after completing HIIT for 6 weeks and 12 weeks, respectively.

Study Protocol

This project is a single-arm feasibility and proof-of-concept study in which all participants will receive 12 weeks of HIIT. All patients will undergo a series of baseline (week 0), mid- (week 6), and post-intervention (week 12) evaluations, as described below. Baseline values for all measures will be collected within the 10 days prior to initiation of the intervention. Testing will occur at 6 weeks (± 5 days) and 12 weeks (± 5 days). Testing at 6 weeks is included due to the rapid results often reported after as little as 2 weeks of HIIT. This testing point will more fully inform the development of a larger scale trial and the appropriate duration of HIIT for a knee OA population, as well as allow for modification of intensity to maintain sufficient training intensity. All

training will be performed in the Applied Physiology Laboratory or Campus Recreation Center on the UNC campus, with one-on-one supervision from trained research personnel, 2 times per week for 12 weeks. The project timeline is shown below.

Project Timeline (2 years)

	Year							
Activity	***1***				***2***			
Quarter	1	2	3	4	1	2	3	4
Training and IRB approvals								
Informed Consent and Cardiovascular health screening								
Baseline Assessments								
6 week Assessments								
12 week Assessments								
Data Analysis, Abstract & Manuscript Preparation. Development of larger grant								

Tolerability, Feasibility, Compliance and Adherence (Aim 1). We will determine the percent of participants that screen into the study versus those approached and the percent of participants retained at the 6- and 12-week post-tests. Frequency and reasons for initial refusal, ineligibility, and drop out will be collected. Adherence and tolerability will be evaluated based on number of sessions attended/completed, modifications, such as change in mode; number of training days per week; recovery days needed between sessions to complete training, and severity of pain on a scale of 0-10 (no pain-extreme pain) during and after exercise as a measure of tolerability. The physical activity enjoyment scale[28] will be given to assess participant enjoyment of exercise on each training day.

Outcomes (Aim 2). Because HIIT in people with knee OA is novel, a set of functional, symptomatic, and physiological variables will be included as outcomes. These outcomes will allow for the monitoring of initial changes related to the intervention and to identify the most appropriate measures for inclusion in a larger trial.

Physical Function will be measured with performance based tests: 40 m fast-paced walk test, 30-s chair stand test, a stair-climb test, and Timed Up and Go Test. All physical function tests are in accordance with the Osteoarthritis Research Society International recommendations.[29, 30]

Knee OA Symptomatic Burden. Participants will be asked to complete the Knee Injury and Osteoarthritis Outcome Score (KOOS). The KOOS questionnaire was developed to assess the patient's opinion about his or her knee and associated problems. It is widely used for research purposes in clinical trials of knee OA, and its psychometric properties have been confirmed.[31-33] The KOOS is available online for free use. An advantage of the KOOS is that it includes the Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC). The WOMAC, a measure of lower extremity pain (5 items), stiffness (2 items), and function (17 items), will be used to measure overall symptomatic burden of OA.[34] All items are rated on a Likert scale of 0 (no symptoms) to 4 (extreme symptoms). The reliability and validity of the WOMAC total score and subscales have been confirmed,[34] and this scale has been widely used in trials of behavioral interventions for patients with knee OA, confirming its sensitivity to change. The total WOMAC score will be assessed, as well as the pain and function subscales.

Balance will be evaluated with the single leg stance[35] and side-by-side, semi-tandem, and tandem tests.[36]

Muscle Strength. A Humac isokinetic dynamometer will be used to measure isokinetic power and isometric strength of knee flexors and extensors.[37, 38] Measures will be assessed according to manufacturer's instructions, with the primary assessment of power at 60 degrees per second and for strength at 60 degrees of knee flexion. These selections are based on clinical relevance and that persons with OA exhibit high correlations ($r>0.7$) for assessments of power at varying speeds and of isometric strength at varying angles.[39]

Cardiorespiratory fitness, measured by peak oxygen consumption (VO2peak), is the gold standard for identifying fitness level and evaluating cardiovascular effects. This test will be used to establish individual training intensity. All participants will perform a ramp based cycling ergometer test with respiratory gases continuously monitored with open-circuit spirometry using a calibrated metabolic cart (True One 2400®, Parvo-Medics, Inc., Provo, UT). Data will be averaged over 15-second intervals, with the highest 15-second oxygen consumption, minute ventilation and heart rate recorded as the peak oxygen consumption (VO2peak), time to exhaustion, and maximum heart rate, respectively. In accordance with the Exercise and Sport Science Institutional Review Board Standard Operating Procedures (EXSS-IRB SOP), following a 12 lead electrocardiogram (EKG) cleared by a study physician, 3 trained research personnel (for safety purposes per IRB procedures) will perform cardiorespiratory fitness testing.

Body composition will be assessed to evaluate the effects of HIIT on fat mass, lean body mass, and visceral fat. Previous data demonstrated positive effects of HIIT on fat mass, visceral fat, and, more importantly for this OA population, lean mass. Dual energy x-ray absorptiometry (DXA; GE Lunar iDXA, Software version 16, Chicago IL) will be used to determine whole-body fat mass, lean mass, bone mineral density, and segmental (arms, legs) body composition. Each scan will be performed by the same certified DXA technician, and previous data from this lab indicate high test-retest reliability for fat mass (intraclass correlation coefficient [ICC]=0.98, standard error of measurement [SEM]=0.85 kg), and lean mass (ICC=0.99, SEM=1.07 kg). In accordance with the EXSS-IRB SOP, personnel trained with radiation exposure training will complete the DXA scans.

HIIT Intervention: All training will be performed in the Applied Physiology Laboratory or Campus Recreation Center on the UNC campus, with one-on-one supervision from trained research personnel, 2 times per week for 12 weeks.[21] Details are described below and in Figure 3.

- Type: Mode of exercise will vary based on participant limitations and choice, including activities such as walking, biking, elliptical machine, and swimming, with individual mode being consistently maintained whenever possible throughout the duration of the study. Cycling will be suggested as the primary mode, but another mode will be selected if cycling is not feasible. If limitations arise for the participant during familiarization and throughout the study (i.e. discomfort, inability to increase heart rate), training mode will be modified, and noted, to inform feasibility components (Aim 1).

- Intensity: Individualized training intensity for each participant will be established from baseline cardiovascular fitness (VO2peak) testing. Baseline maximal oxygen consumption testing and maximum workload will be used to determine the intensity of each exercise bout (90% of maximum heart rate obtained during testing).

- Session: Each training session will consist of a 3-5 minute warm-up, followed by 10 repetitions of 1-minute bouts at individualized training intensity with 1-minute rest periods. We anticipate that most participants in this study will be able to complete all 10 1-minute bouts during the first session, based on our prior experience of HIIT in people with other diseases who have low levels of physical activity at baseline. Individuals who are

unable to achieve this protocol in initial sessions will be encouraged to complete all 10 bouts for as long as possible each bout. If they cannot finish the entire minute, the 1-minute rest period will begin as soon as they stop, followed by the next bout. Intensity will be re-established and adjusted following the 6-week testing. Sessions will take place twice per week, with at least 24 hours in between training sessions.

Structured Interview. A structured one-on-one interview will occur with participants after completion of the HIIT program. The interview will be used to learn about barriers and concerns they experienced with regard to the current training protocol; preference of exercise mode and instruction; and opinions on what information participants would find helpful to transition to an at-home and or independent program. While we do not intend to formally analyze the interview responses, we do anticipate that they will be useful for refining our intervention program for inclusion and development of a home-based component for future trials.

Study Flow Diagram

Enrollment & Baseline Assessments
(Physical Function, Cardiorespiratory Fitness, Body Composition, Balance, Symptoms, Muscle Strength) (N=30)

1st 6 weeks of HIIT

6-week Assessment
(Physical Function, Cardiorespiratory Fitness, Body Composition, Balance, Symptoms, Muscle Strength)

2nd 6 weeks of HIIT

12-week Assessment
(Physical Function, Cardiorespiratory Fitness, Body Composition, Balance, Symptoms, Muscle Strength)

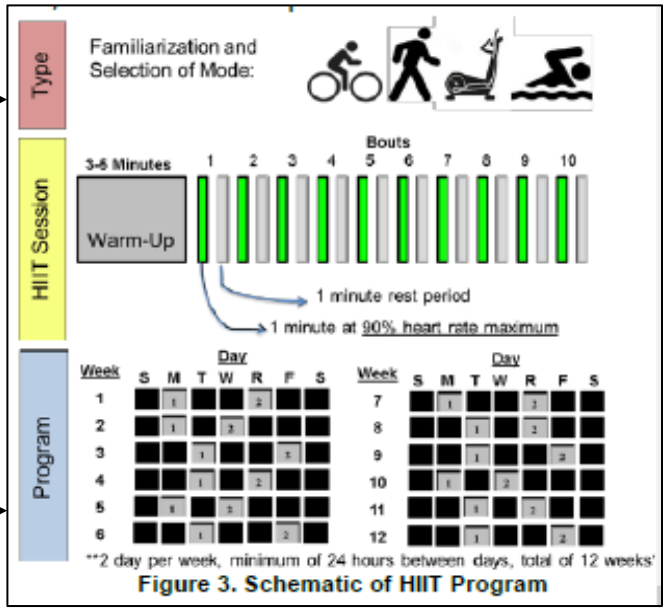


Figure 3. Schematic of HIIT Program

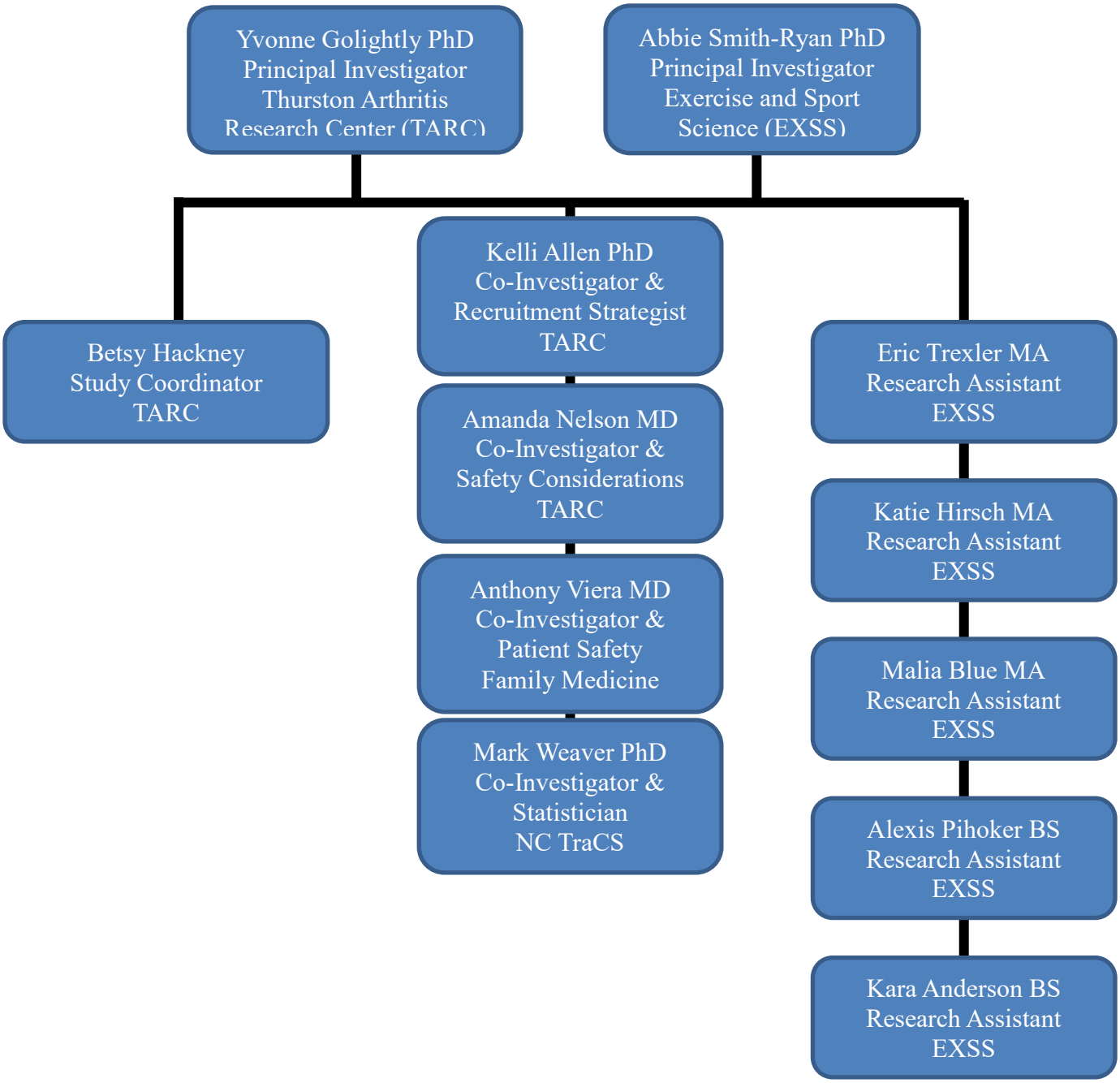
Staff Roster and Responsibilities

Staff Roster, Roles and Contact Information			
Personnel	Role	Email	Phone
Key Personnel			
Yvonne Golightly	Lead Principal Investigator	golight@email.unc.edu	919-966-0566
Abbie Smith-Ryan	Principal Investigator	abbsmith@email.unc.edu	919-962-2574
Kelli Allen	Co-investigator & Recruitment Strategist	kdallen@email.unc.edu	919-966-1739
Amanda Nelson	Co-investigator & Clinical and Safety Considerations	aenelson@med.unc.edu	919-966-4191
Anthony Viera	Co-investigator & patient safety	anthony_viera@med.unc.edu	919-966-0758
Mark Weaver	Statistician	mark_weaver@med.unc.edu	919-843-7680
Betsy Hackney	Study Coordinator	bshackne@email.unc.edu	919-966-0574
Data Collection			
Eric Trexler	Research Assistant	trexlere@live.unc.edu	919-962-2163
Katie Hirsch	Research Assistant	ktrose23@live.unc.edu	919-962-1663
Malia Blue	Research Assistant	mnm3303@email.unc.edu	919-962-1663
Alexis Pihoker	Research Assistant	alexisap@live.unc.edu	
Kara Anderson	Research Assistant	kca11@live.unc.edu	

Responsibilities		
Responsibility	Involved Personnel	Description
Development & Maintenance of all Study Materials	Yvonne Golightly Abbie Smith-Ryan Kelli Allen Amanda Nelson Anthony Viera Mark Weaver	Personnel in this section will create and maintain the documents that comprise the MOOP, as well as all regulatory and source documentation
Reporting & Monitoring of All Adverse Events	Yvonne Golightly Abbie Smith-Ryan Anthony Viera	All adverse events will be reported to the PI. The PI will discuss circumstances of the adverse events with the medical monitor and report all adverse events to the safety officer as outlined in section 3.k. Dr. Viera will also oversee all cardiovascular adverse events that may arise
Recruitment and enrollment	Betsy Hackney Yvonne Golightly Kelli Allen Amanda Nelson	Dr. Golightly and Betsy Hackney will lead recruitment and enrollment efforts for this study and will be in charge of recruiting directly from physicians at UNC Hospital and Department of Family Medicine. Dr. Allen will advise on strategies for recruitment and retention. Dr. Nelson will advise on safety and OA considerations during the study intervention.
Informed Consent & Scheduling	Abbie Smith-Ryan Eric Trexler Katie Hirsch Malia Blue	These personnel will be in charge of consenting each participant, explaining the study to each participant and acquiring written informed consent from each participant.
Screening	Anthony Viera Amanda Nelson Abbie Smith-Ryan Eric Trexler Katie Hirsch Malia Blue	Dr. Viera will review all patient charts, health history, and EKG for clearance for participation. Dr. Nelson will advise on safety and OA considerations during the study intervention. Dr. Abbie Smith-Ryan, along with her team (Eric Trexler, Katie Hirsch, Malia Blue) will oversee screening and enrollment of interested participants including conducting the EKG and reviewing health history.
Collection of Data (Baseline and Follow-up Measures)	Abbie Smith-Ryan Eric Trexler Katie Hirsch Malia Blue Alexis Pihoker Kara Anderson	These personnel will collect all outcome measures at baseline, follow-up one (4 weeks) and follow-up two (8-weeks). Dr. Smith-Ryan directly oversee the collection of data at the UNC laboratory.
Delivery of HIIT Intervention	Abbie Smith-Ryan Eric Trexler Katie Hirsch	Dr. Smith-Ryan will oversee all training and is responsible for training and supervision of graduate students involved in the study. One-on-

	Malia Blue Alexis Pihoker Kara Anderson	one HIIT sessions will be led by Eric Trexler, Katie Hirsch, Malia Blue, Alexis Pihoker, and Kara Anderson.
Study Compliance & Accountability	Yvonne Golightly Abbie Smith-Ryan	Dr. Golightly will guarantee institutional compliance with US laws and DHHS and NIH policies including biosafety, human research, data and facilities. Dr. Smith-Ryan will ensure all research assistants are trained and instructed on the procedures for the study.
Data Entry, Error Identification and Correction, and Data Analysis	Abbie Smith-Ryan Mark Weaver Yvonne Golightly Eric Trexler Katie Hirsch Malia Blue Alexis Pihoker Kara Anderson	All research assistants will assist with data entry. Dr. Smith-Ryan check all entries for potential error and calculate means and standard deviations separately for all outcomes measures. Mark Weaver will perform all statistical analyses.
Creation of Reports- Enrollment, adverse events, participant status	Yvonne Golightly Abbie Smith-Ryan Anthony Viera	These personnel will compile and promptly file reports as needed.
Ensuring Compliance with Human Subjects Regulation	Yvonne Golightly Abbie Smith-Ryan Kelli Allen	Dr. Golightly will guarantee institutional compliance with US laws and DHHS and NIH policies including biosafety, human research, data and facilities.
Submission of Regulatory NIH and IRB Documents	Yvonne Golightly Abbie Smith-Ryan Betsy Hackney	Dr. Golightly, assisted by Betsy Hackney, will assume administrative and scientific roles for this award and will be responsible for all communication with the NIH and IRB. She also will be responsible for the progress reports, noncompeting continuations, and IRB submissions for the project.

Study Personnel Organization



Participant Recruitment and Retention

This study will be conducted in the Applied Physiology Lab within the Department of Exercise and Sport Science and Campus Recreation Center at the University of North Carolina at Chapel Hill. Recruitment will take place at the University of North Carolina Hospital, the Thurston Arthritis Research Center, and the Department of Family Medicine.

Recruitment
All relevant members of the research team will be instructed on the procedures for recruitment of study participants. We will use methods that are currently successful for recruiting individuals with knee OA for exercise interventions at UNC. In the first 9 months of enrollment for a previous study, "Physical Therapy vs. Internet-Based Exercise Training for Patients with Knee Osteoarthritis" (PI Dr. Allen, co-I Dr. Golightly),[40] 218 people with knee OA have been enrolled in the UNC area, surrounding communities, and Smithfield, North Carolina using inclusion/exclusion criteria and methods similar to the current study (total needed 350). In a similar manner to that study, patients will be initially identified from UNC medical records based on ICD-10 codes; individuals who meet initial eligibility criteria based on the medical record will be mailed introductory letters. Additionally, flyers and brochures will be posted at UNC and the surrounding community, and UNC healthcare providers in rheumatology, orthopedics, primary care, and physical therapy will provide brochures to patients. Individuals interested in the study will be screened for eligibility criteria via telephone. Individuals who meet eligibility criteria and are interested in participating will meet a study team member to complete informed consent and inclusion criteria. All potential patients will undergo a 12-lead electrocardiogram and will be cleared to participate following medical history review from Drs. Viera and Nelson. Following clearance, baseline testing will occur.

We will enroll patients who have sought care for knee osteoarthritis from the University of North Carolina at Chapel Hill (UNC), a large not-for-profit healthcare system that provides both primary and specialty care. Over 800,000 people receive outpatient care at UNC clinics annually. Based on the patient populations in our enrollment site and experience from our previous studies, there will be an ample number of patients eligible for the proposed study. Our estimate of potentially eligible patients at UNC is based on the number of outpatients age 55, n=119,517, and the prevalence of symptomatic knee OA in this age group (about 12%). Based on these numbers, we estimate there will be a total of over 14,000 patients with knee OA at UNC. Given this large number, we will be able to focus recruitment on patients who live within reasonable driving distance to study enrollment sites and physical therapy clinics (which still encompasses a range of geographic regions in terms of urban/rural status).

Inclusion of Women and Minorities
The sample in the current study will be comprised of approximately 50% women. The University of North Carolina community is comprised of 58.1% of females as reported by the U.S. News and World Report in 2015. Knee osteoarthritis is highly prevalent among both men and women, and women have a higher risk of knee osteoarthritis than men. Therefore, we do not anticipate problems recruiting women into the proposed study.

All races and sexes will be included in the current study. The racial/ethnic composition of the current study is expected to be representative of the diversity of the United States and greatly reflect the composition of the Chapel Hill, North Carolina area. According to the 2010 Census Bureau, the Chapel Hill, North Carolina area is comprised of 72.76% white, 9.66% African American, 0.31% Native American, 11.86% Asian, 0.02% Pacific Islander, while 2.68% are considered other and 2.70% consider themselves as two or more races. There was

6.36% of the population that was considered Hispanic or Latino. We will recruit minority races/ ethnicities aggressively to ensure the study sample is representative of the general population (See Targeted/ Planned Enrollment Table).

Targeted/Planned Enrollment Table

Targeted/Planned Enrollment: Number of Subjects			
Ethnic Categories	Sex		
	Males	Females	Total
Hispanic or Latino	2	2	4
Not Hispanic or Latino	13	13	26
Ethnic Categories: Total of All Subjects	**15**	**15**	**30**
Racial Categories			
Native American	1	1	2
Asian	1	1	2
Pacific Islander	1	1	2
African American	1	1	2
White	10	10	20
Two or More Races	1	1	2
Racial Categories: Total of All Subjects	**15**	**15**	**30**

Participant Retention Plan

All relevant members of the research team will be responsible for participant retention. The following section details the procedures for participant retention, which will be carried out by the Research Assistant, the Study Coordinator and the Principal Investigator throughout the entire duration of the study.

Role of the Research Assistant, Study Coordinator and the Principal Investigator

The Research Assistant, Study Coordinator and the Principal Investigator will be responsible for ensuring participant recruitment and retention through 1) informing the research team of appropriate recruiting and retention procedures 2) determining the success of current strategies to recruit and retain study participants, and 3) evaluating and improving participant recruitment and retention strategies throughout the duration of the study. The following major principles will be implemented throughout the study in order to maximize participant retention.

Retention: Role of All Study Personnel

All members of the study team will be responsible for ensuring participant retention throughout the duration of the study. Dr. Golightly will manage participant recruitment, with the assistance of Betsy Hackney, and communicate with study physicians about safety considerations during enrollment and the intervention. Kelli Allen, who conducts research in knee OA individuals, will advise on strategies for recruitment and retention.

Monthly meetings of the Research Team will be coordinated by Betsy Hackney. Monthly meetings will ensure that the described aims are completed in a timely fashion and that the overall direction of the project is guided by recent discoveries in each of the aims. Dr. Golightly will lead monthly meetings of the research team and Dr.

Smith-Ryan will be responsible for organizing, scheduling and facilitating the meetings. The meetings will provide an opportunity to discuss recent progress, scientific design, data interpretation and future directions. Inclusion of additional members at the monthly meetings (for advice and scientific expertise) will be agreed upon by both Dr. Golightly and Dr. Smith-Ryan. Drs. Golightly and Smith-Ryan currently have weekly communications, providing a foundation for timely interaction and trouble-shooting of issues that may arise.

Dr. Smith-Ryan will manage the training of the laboratory team with the HIIT protocol and laboratory testing, provide checks to confirm protocol and testing fidelity, and oversee the one-on-one HIIT instruction. Dr. Smith-Ryan will hold bi-monthly meetings with the laboratory team in which scientific and project issues will be discussed. All members of the research team will be made aware that retention efforts begin with participant recruitment, and informed consent is an ongoing process throughout the entire duration of the study. During each meeting all members of the research team will be reminded to address all study participants with congeniality, respectfulness and friendliness during each interaction with a participant or potential participant. Additionally, all members of the research team will be asked to ensure all questions from the study participants and family members of the study participants are completely answered throughout each interaction with study participants.

Three participants per month are expected to be enrolled with at least 80% retention during the study period. As part of Aim 1, adherence to and tolerability of HIIT, acceptability, and recruitment and retention rates of patients through 6- and 12-week assessments will be determined. This will be determined as the percent of participants that screen into the study versus those approached and the percent of participants retained at the 6- and 12-week post-tests. Frequency and reasons for initial refusal, ineligibility, and drop out will be collected. Adherence and tolerability will be evaluated based on number of sessions attended/completed, modifications, such as change in mode; number of training days per week; recovery days needed between sessions to complete training, and severity of pain on a scale of 0-10 (no pain-extreme pain) during and after exercise as a measure of tolerability. If the HIIT intervention is shown to be well-tolerated and promising, results of this preliminary study will lay the foundation for a large randomized controlled trial to establish the efficacy of HIIT as a revolutionary approach for enhancing the rehabilitation and management of knee OA.

Enhancing Participants Understanding of the Study

During the initial meeting with a potential study participant the Research Assistant or Study Coordinator will be responsible for describing all aspects of the study in detail in order to ensure the participant completely understands the scope of the study and what will be required of each participant. The Research Assistant will provide the participant with a copy of the informed consent form, and will talk through each component with the participant. The participant will be able to ask any questions necessary in order to ensure the participant is informed about the purpose of the study and what he/she will be asked to complete. Additionally, study participants will be made aware they have an active role in the research study and are a valuable part of the research team. Throughout the course of the study all participants will have the opportunity to meet directly with the Research Assistant, Study Coordinator or Principal Investigator each week in order to ask any questions the participant may have.

All clinical and functional assessments will be described and demonstrated before the participant is asked to complete them; participants may choose not to engage in a particular assessment if they anticipate it will not be tolerable, and they may ask to stop an assessment at any time.

Determining Participant Satisfaction

As part of Aim 1, the physical activity enjoyment scale[28] will be given on each training day, to assess participant enjoyment of exercise. After completion of the HIIT program, a structured one-on-one interview will occur with participants. The interview will be used to learn about barriers and concerns they experienced with regard to the current training protocol; preference of exercise mode and instruction; and opinions on what information participants would find helpful to transition to an at-home and or independent program. While we do not intend to formally analyze the interview responses, we do anticipate that they will be useful for refining our intervention program for inclusion and development of a home-based component for future trials.

Identifying Potential Problems
The Principal Investigators, with the assistance and advice of Research Assistants and Co-Investigators, will be responsible for monitoring participant recruitment and retention throughout the duration of the research study. The Principal Investigators will assess recruitment rates and retention rates each month and determine any potential problems. The Principal Investigators and Co-Investigators will also determine key retention factors that should be emphasized in order to maximize participant retention throughout the duration of the study. In the event retention issues arise throughout the study the Principal Investigators, with advice from Co-Investigators, will develop new intervention strategies to maximize participant retention and revise the MOOP as necessary. Drs. Golightly and Smith-Ryan currently have weekly communications, providing a foundation for timely interaction and trouble-shooting of issues that may arise. Problems requiring immediate attention of the research lab team will be communicated by Dr. Smith-Ryan.

Monetary Compensation
Participants will be paid to help compensate for their time and travel. Participants will receive a total of $100. Payments will be prorated; $14.00 for pre-testing and post-testing, respectively; a total of $6.00 per week of completed training will also be provided. There will also be free parking provided for testing and training purposes.

Participant Screening and Eligibility Criteria

Participant Screening
Individuals interested in the study will be screened for eligibility criteria via telephone, reducing the chance of participants coming to the lab for lab screening if they would be excluded based upon demographic factors or level of physical function, which have been outlined in the exclusion criteria. Individuals who meet eligibility criteria and are interested in participating will meet a study team member to complete informed consent and inclusion criteria. All potential patients will undergo a 12-lead electrocardiogram and will be cleared to participate following medical history review from Drs. Viera and Nelson. Following clearance, baseline testing will occur.

Thirty patients with symptomatic knee OA will be recruited, which we will define as a diagnosis of knee OA and current knee symptoms in at least one knee. Patients with physician diagnoses of knee OA will be identified from University of North Carolina (UNC) electronic medical records. For current joint symptoms, participants must have a minimum score of 6 out of 20 on the Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC),[34, 41] pain subscale. We will include participants 40-75 years old with body mass index of 18.5-50 kg/m2 because: 1) knee OA onset typically begins after age 40 and is more common with greater obesity, and 2) HIIT is well-tolerated in middle-aged to older adults who are normal weight, overweight, obese,

and morbidly obese. Inclusion of these participants will improve generalizability of study results to real-world patients.

We will aim to ensure that participant selection is equitable and all relevant demographic groups have access to study participation by contacting (via initial letter and telephone call) all participants who meet inclusion / exclusion criteria, regardless of demographic characteristics. We have also aimed to produce recruitment and intervention materials that are appropriate for individuals with low literacy or education levels. We will continue to recruit participants until we reach our sample size goal of N=30.

Interactions with participants during the recruitment process will include both telephone and in-person interaction. When study teams are speaking with participants via telephone (e.g., recruitment/screening call or when participants call to self-refer for the study), this will be done in a private location. In-person baseline visits, which will include giving information about the study so participants can decide whether to participate, will also be conducted in private locations.

The list of potential study participants, based on medical record review, will be transferred into a secure computerized tracking database. Likewise, participant data for all participants enrolled in the study will be entered into a secure computerized enrollment log. These data will be accessible only to study personnel needing access to fulfill their study related duties.

Eligibility Criteria

All participants must meet the following criteria:

- Between the ages of 40 and 75 years old
- Body mass index of 18.5-50 kg/m^2
- Exhibits symptomatic knee OA, defined as a diagnosis of knee OA, as identified from UNC electronic medical records, and current knee symptoms in at least one knee, having a minimum score of 6 out of 20 on the Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC) pain subscale.

Potential participants meeting any of the following criteria (based on the electronic medical record or in laboratory screening) will be excluded if:

- Individuals diagnosed with a cardiovascular condition restricting exercise
- Individuals currently meeting Department of Health and Human Services Guidelines for physical Activity (≥ 150 minutes per week)
- Individuals currently doing HIIT
- Individuals currently participating in physical therapy for knee OA
- Individuals currently participating in another OA intervention study
- Received a corticosteroid or hyaluronic acid intra-articular injection involved in the knee in the previous 3 weeks or scheduled for during the intervention
- Diagnosis of gout in the knee
- Diagnosis of Rheumatoid arthritis
- Diagnosis of Fibromyalgia
- Other systemic rheumatic disease
- Severe dementia or other memory loss

- Active diagnosis of psychosis or uncontrolled substance abuse disorder
- Hospitalization for a stroke, heart attack, or heart failure, or had surgery for blocked arteries in the past 3 months
- Total joint replacement knee surgery, other knee surgery, meniscus tear, or ACL tear in the past 6 months
- On a waiting list for total joint replacement
- Severely impaired hearing or speech
- Pregnant or planning to become pregnant while enrolled in the study
- Inability to speak English
- Serious or terminal illness as indicated by referral to hospice or palliative care
- Nursing home residence
- Inability to ride a stationary bike
- Any other health problems that would prohibit safe participation in the study.

Use and changes of medications for OA will be monitored and recorded during the study but will not be a reason for exclusion. Participants will be withdrawn if they develop any new health problems or other events that would either a) make participation in the study intervention or measures unsafe or b) confound study outcomes. These largely mirror study exclusion criteria and are as follows:

- new diagnosis of rheumatoid arthritis, fibromyalgia, or other systemic rheumatic disease
- new diagnosis of dementia or other memory loss condition with symptoms significant enough to impede ongoing study participant
- new diagnosis of psychosis or current uncontrolled substance abuse disorder
- total joint replacement (knee or hip) surgery, other significant knee or hip surgery, or ACL tear
- serious/terminal illness as indicated by referral to hospice or palliative care
- other health problem that would prohibit participation in the study

Informed Consent and HIPPA

Informed Consent Process

Prior to performing any study related activities, potential participants will provide written informed consent. A qualified professional on the research team will inform each potential participant of the purpose of the project, possible risks, their personal rights, and potential benefits of the study. All possible exclusion criteria will be verified following informed consent, prior to screening. The informed consent form clearly states the rights of a participant, including the telephone number and email address for the Committee on the Rights of Human Subjects of the UNC School of Medicine. This office may be contacted in the event of perceived violation of rights. The informed consent forms are written in large print at a level understandable to the participants. For low-literacy participants, the consent form will be read aloud verbatim. The interviewers are highly experienced and have successfully completed ethics training. Participants will only be included if they have the capacity to give legally effective consent. We will not include participants who lack decision making capacity, so consent from legally authorized representatives will not be required. The original signed consent forms will be kept in a separate folder from the individual study folder. This folder will be stored in a locked file cabinet of the Applied Physiology Laboratory. Participants will be provided with a copy of the consent form for personal reference.

Informed Consent Form

See Appendix A.1 for Approved Consent form

HIPPA Authorization
See Appendix A.2 for HIPAA Authorization Form

The privacy and confidentiality of research participants are to be respected and protected at all times. This research study will comply with the HIPAA Privacy Rule as well as all other state, federal, and institutional regulations intended to protect the rights, safety, and welfare of human participants involved in research studies. We will attempt to minimize the collection, storage, and transmission of information containing participants' personal identifiers, and, whenever identifiers are necessary, protect against unauthorized access or disclosure. In addition, we will employ several rigorous procedures for protecting against risks to participant privacy and confidentiality of data. We will only collect and store information about study participants that is relevant to the research as outlined in the protocol. We will minimize the use of paper documents by entering the majority of study data directly into secure computer databases. All study databases will be password protected and only study team members whose job functions require access to these data will have permissions. Whenever possible, data will not be stored on laptop computers. Individual participant data will not be shared with individuals outside the study team, except as required by law and/or for regulatory purposes.

All study staff must regularly fulfill certification requirements in Human Subjects Protection training. Study personnel are also regularly trained in stringent computer and information security procedures. All electronic study data will be stored electronically on secure UNC servers, accessible only to study personnel.

Research study records will be maintained for no less than 7 years following the completion of the study, after which time personal identifying information will be removed. Research information in a participant's medical record will be kept indefinitely.

Participant Evaluations and Follow-up

Timeline and Visit Schedule
The current study consists of 27 total visits: 3 testing visits and 24 training sessions. All visits will take place at the Applied Physiology Laboratory and/or the Student Recreation Center. The three testing visits will consist of assessments of physical function, cardiorespiratory fitness, body composition, balance, symptoms, and muscular strength. These visits will occur at baseline, 6-weeks, and 12 weeks. The HIIT intervention will occur over the course of 24 separate training sessions, occurring two times per week for two 6-week sessions.

Week	Visit #	Testing	Training	Measures Collected
0	1	X		• *Physical function*: 40 m fast-paced walk test, 30-s chairstand test, a stair-climb test, and Timed Up and Go Test • *Knee OA Symptomatic Burden*: WOMAC • *Balance*: single leg stance and side-by-side, semi-tandem, and tandem tests • *Muscle Strength.* isokinetic dynamometer for power at 60 degrees per second and for strength at 60 degrees of knee flexion. • *Cardiorespiratory fitness:* peak oxygen consumption (VO2peak)

				• *Body composition*: DXA for fat mass, lean body mass, and visceral fat
1-5	2-11		X	• *Heart rate:* chest strap heart rate monitors to identify heart rate and intensity during each training bout • *Ratings of perceived exertion:* Borg perceived exertion scale • *Severity of pain:* visual analog scale of 0-10 (no pain-extreme pain) during and after exercise • *Training bouts completed* • *Mode of exercise* • *Exercise enjoyment*
6	12	X		• *Physical function*: 40 m fast-paced walk test, 30-s chairstand test, a stair-climb test, and Timed Up and Go Test • *Knee OA Symptomatic Burden*: WOMAC • *Balance*: single leg stance and side-by-side, semi-tandem, and tandem tests • *Muscle Strength.* isokinetic dynamometer for power at 60 degrees per second and for strength at 60 degrees of knee flexion. • *Cardiorespiratory fitness:* peak oxygen consumption (VO2peak) • *Body composition*: DXA for fat mass, lean body mass, and visceral fat
7-12	13-26		X	• *Heart rate:* chest strap heart rate monitors to identify heart rate and intensity during each training bout • *Ratings of perceived exertion:* Borg perceived exertion scale • *Severity of pain:* visual analog scale of 0-10 (no pain-extreme pain) during and after exercise • *Training bouts completed* • *Mode of exercise* • *Exercise enjoyment*
13	27	X		• *Physical function* • *Knee OA Symptomatic Burden* • *Balance* • *Muscle Strength* • *Cardiorespiratory fitness* • *Body composition* • *Structured interview*: barriers and concerns experienced with current training protocol; preference of exercise mode and instruction; opinions on what information participants would find helpful to transition to an at-home and or independent program

Concomitant Medications

Use and changes of medications for OA will be monitored and recorded during the study but will not be a reason for exclusion. Subjects will be asked to self-report all medications that they are currently using and/or being prescribed during the 7 days prior to study enrollment at the baseline visit. At subsequent study visits, participants will be asked

to report any changes with their medications (e.g., discontinuation, new medications). Medications will be considered when conducting analyses and interpreting results.

Statistical Considerations

Aim 1 Analyses
Analyses will be primarily descriptive and will include data from all participants during their experience using HIIT. First, the flow of participants through the study (i.e., screened, recruitment, enrollment [along with refusals and ineligibility, with reasons], and follow-up at each time point) will be descriptively summarized using frequencies and proportions. Then, compliance and tolerability of HIIT (i.e., proportion of sessions completed, change in mode, number of training days per week, recovery days between sessions), along with 95% confidence intervals, will be summarized. We will also descriptively summarize pain on a 0-10 scale, during and after exercise, as well as participant enjoyment of exercise by training day, and will use informative graphical approaches where useful.

Aim 2 Analyses
All available data from all enrolled participants, regardless of extent of adherence to HIIT, will be descriptively summarized in tables and graphs. Longitudinal models will be fit for all outcomes (physical function, knee OA symptomatic burden, balance, muscle strength, cardiorespiratory fitness, and body composition) using all available data with linear mixed models. Mixed models allow for inclusion of all observed outcome data for each participant under the assumption that any missing data are missing at random. No missing data will be imputed. Separate models will be fit for each outcome with no adjustments for multiple comparisons since this is an exploratory proof-of-concept study; however, data from all outcomes assessed will be reported regardless of "significance". For each model, fixed effects will include visit, gender, baseline BMI, age, and severity of baseline OA symptoms. Additionally, if at least 10% of participants are not using prescribed pain medications at each time point, we will include dichotomous use of pain medication as a time-dependent fixed effect. Each model will also include random participant effects to account for correlation between repeated outcome measurements. For each outcome, we will use the model to estimate the mean change from baseline to each follow-up visit along with 95% confidence intervals.

Power and Sample Size.
For this study, we chose the 40 m fast-paced walk test as our primary measure of physical function on which to base power calculations based on recent recommendations.[29] We assume that the standard deviation for walk times is 10 seconds, based on results from a study among patients with knee OA;[42] in this study, the estimated standard deviation was 9.2 seconds, and we computed an upper 80% confidence bound of 10 seconds. We further assume that loss at 12 weeks would be at most 10%, and that correlation between repeated outcomes from the same participant would be at least 0.6 (a conservative value). Under these assumptions, enrolling 30 participants would provide at least 80% power to detect a mean 5-second difference between baseline and the 12-week assessment using a two-sided test at the 5% level.

Analyses of Safety Data and OA Medications
Any accumulated data on adverse events, particularly those adjudicated to be at least potentially related to HIIT, will be descriptively reported using frequencies and proportions. Additionally, medications prescribed for the treatment of OA will be descriptively summarized, along with changes in these medications over the course of the study. No inferential statistics will be presented for safety or medication data.

Safety Reporting Overview

Definitions
Adverse events will be determined using the NC TraCS Safety Monitoring Plan guidelines for Minimal Risk Studies. The Grading Scale is as follows:

- **Mild** - Event results in mild or transient discomfort, not requiring intervention or treatment; does not interfere with daily activities (e.g. transient muscle soreness)

- **Moderate** - Event is sufficiently discomforting so as to limit or interfere with daily activities; may require additional interventional treatment (e.g. musculoskeletal injury such as a muscle strain)

- **Severe** - Event results in significant symptoms that prevent normal daily activities; may require invasive intervention

In the event that two adverse events are classified as either moderate or severe the study will be placed on hold in order to reassess the study procedures in order to decrease the risk of another adverse event. Based on previous data, the potential for adverse events are minimal. The potential benefits outweigh potential musculoskeletal and cardiovascular risks.

Monitoring Roles
Dr. Golightly (Lead PI) and Dr. Smith-Ryan (PI) will oversee data collection monitoring and all issues related to participant safety data collection protocols, and participant confidentiality. Dr. Smith-Ryan will oversee the training of lab team members and monitor training sessions. Lab team members who become aware of any adverse event or unanticipated problems related to the study will notify Dr. Smith-Ryan immediately.

Dr. Viera, a physician who specializes in cardiovascular disease will advise on cardiovascular safety and approve participation of each participant. Dr. Amanda Nelson (rheumatologist, epidemiologist), an expert in knee OA management, will advise on clinical and safety considerations relevant to OA.

The Institutional Review Board (IRB) is a committee established by the grantee/sponsoring institution to review and approve research involving human subjects. The IRB ensures human subject research is conducted in accordance with all federal, institutional, and ethical guidelines.

Based on previous experience with HIIT and knee OA patients, it is not anticipated that there will be any serious physical or psychological adverse events associated with this study. However, federal regulations require prompt reporting to the University of North Carolina at Chapel Hill Institutional Review Board (IRB), all injuries, adverse events, or other unanticipated problems involving risks to patients or others that occur in the course of a patient's participation in this research study.

Routine Safety Reports
All adverse events and study-related safety events will be collected by Drs. Golightly and Smith-Ryan and co-investigators (Allen, Nelson, Viera) and will be reported to the Thurston Arthritis Research Center Methodology Core, which works directly with the Regulatory Core of the NC TraCS Institute for monitoring

adverse events of research. The PI's will review aggregated unanticipated problems and adverse events on a monthly basis, or more often if urgent matters arise. This summary will be reported to the IRB as necessary.

Expedited Reports - Serious Adverse Events

We do not expect any serious adverse events to occur based on our previous experience with HIIT and knee OA patients. However, in the event that two adverse events are classified as either moderate or severe, the study will be placed on hold in order to reassess the study procedures in order to decrease the risk of another adverse event.

All interventional studies, independent of phase or type, must report Serious Adverse Events (SAEs). All SAEs, unless otherwise specified in the protocol and approved by the IRB and the National Institute of Child Health and Human Development (NICHD), require expedited reporting by the Principal Investigators (Drs. Golightly and Smith-Ryan). If a potential SAE is reported to any study personnel, the study personnel should make Dr. Smith-Ryan aware of the potential SAE at once. Dr. Smith-Ryan will personally collect information from healthcare professionals involved in the study, the study participant and close relatives (if possible), and other study personnel.

Drs. Golightly and Smith-Ryan will provide written documentation to 1) the Institutional Review Board at the University of North Carolina at Chapel Hill and 2) the Thurston Arthritis Research Center Methodology Core (serving as a data safety monitoring board), within 48 hours of learning about the SAE. A single form (Appendix F) will be completed and sent to both the Safety Officer and the IRB by electronic mail with signatures of the Principal Investigator, Drs. Golightly and Smith-Ryan. The action regarding the treatment of that specific patient taken by Dr. Smith-Ryan and/or lab members will be indicated on the form, as well as actions that are taken for the study in general (No action, modification of HIIT, modification of consent documents to include a description of newly recognized risks, revised protocol to eliminate apparent immediate hazards to subjects, other). The Thurston Arthritis Research Center Methodology Core and IRB will be asked to notify Drs. Golightly and Smith-Ryan if they disagree with the specific actions taken within 72 hours. The immediate reports should be followed by detailed, written reports as soon as possible. Follow up information may be required.

Expedited Reports - Unanticipated Problems

For an event to qualify as an unanticipated problem, all three of the following criteria must be met: 1) unexpected in nature, severity, or frequency, 2) related or possibly related to participation in the research, and 3) a serious adverse event. The Office for Human Research Protections (OHRP), the Department of Health and Human Services (HHS), provides a complete definition and the following guidance for reporting unanticipated problems to the Institutional Review Board(s) (IRBs): *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events*. (http://www.hhs.gov/ohrp/policy/advevntguid.html). OHRP recognizes that it may be difficult to determine whether a particular incident, experience, or outcome is unexpected and whether it is related or possibly related to participation in the research. OHRP notes that an incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of participants or others.

Unanticipated problems must be reported to the IRB within 14 days and the Thurston Arthritis Research Center Methodology Core within 48 hours of the PI's receiving notification of the event. The same reporting process described under SAE reporting will be followed.

On occasion, there may be disagreements between the investigator and the DSMB regarding the assessment and/ or management of an event that qualifies as an unanticipated problem. The following excerpt gives guidance for cases where there is a difference of opinion among the DSMB (referred to as the "monitoring entity" in the excerpt below) and the investigator http://www.hhs.gov/ohrp/policy/advevntguid.html.

> *Note: If the investigator determines that an adverse event is not an unanticipated problem, but the monitoring entity subsequently determines that the adverse event does in fact represent an unanticipated problem (for example, due to an unexpectedly higher frequency of the event), the monitoring entity should report this determination to the investigator, and such reports must be promptly submitted by the investigator to the IRB (45 CFR 46.103(b)(5)).*

Please note: The independent safety officer and the Investigator may have iterative discussions regarding the assessment and may later come to agreement regarding the assessment and/or management of an AE. In cases where the independent safety officer and Investigator come to an agreement after discussions and the event is determined not to be an unanticipated problem, the Investigator is not required to report the event as an unanticipated problem to the IRB. Such discussions should take place promptly so as not to delay appropriate reporting to the IRB.

Examples of corrective actions or substantive changes that might need to be considered in response to an unanticipated problem include:

- changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects;
- modification of inclusion or exclusion criteria to mitigate the newly identified risks;
- implementation of additional procedures for monitoring subjects; suspension of enrollment of new subjects;
- suspension of research procedures in currently enrolled subjects;
- modification of informed consent documents to include a description of newly recognized risks;
- provision of additional information about newly recognized risks to previously enrolled subjects.

Study Compliance

Definitions
Protocol deviation - any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the IRB.

Protocol violation - a deviation from the IRB-approved protocol that may affect the participant's rights, safety, or wellbeing and/or the completeness, accuracy and reliability of the study data.

Procedures

Any protocol deviations or violations will be reported and addressed by Dr. Smith-Ryan, who is overseeing all lab testing and training. As part of Aim 1 of this feasibility and proof-of-concept study, HIIT adherence and tolerability will be evaluated. The proposed protocol also allows for individualization of HIIT (i.e. adjustment of mode and intensity of exercise). Any adjustments in training will be recorded. Adherence and tolerability information from this study will be used to for developing a larger scale trial that includes a home-based component to establish evidence for HIIT as a long-term therapeutic strategy for OA.

In order to minimize the risk of a protocol deviation or protocol violation Dr. Yvonne Golightly, a licensed physical therapist, will track compliance of the study procedures related to informed consent, follow up testing, IRB compliance, and compliance to treatment protocols.

Follow-Up Testing – Each month Dr. Golightly will ensure that follow-up testing of each participant was performed in for each participant.

IRB Compliance - Dr. Golightly will confirm each month that protocol information and consent forms used are approved by the IRB and any changes in the protocol are confirmed with the IRB and have been included in the revised protocol and regulatory documentation.

Biweekly meetings are scheduled with the study team to assist in a rapid implementation for any issues brought up, yet the PIs may take immediate action with the study team to ensure adherence of study protocols if an urgent issue is brought to attention. The PIs will report protocol violations and deviations to the IRB at the University of North Carolina at Chapel Hill within 48 hours of the violation/deviation via the online IRBIS reporting system. Protocol deviations will addressed by modification to the IRB protocol, informed consent form and manual of operating procedures if necessary. All events will be reported at the time of the biannual at submission of the safety report. The study coordinator, Betsy Hackney, will maintain a log of all protocol deviations/violations and will report them to Dr. Golightly each month. These deviations / violations will be discussed with the Methodology Core at the Thurston Arthritis Research Center, who can provide monitoring and guidance regarding safety aspects of OA projects.

In the case of serious violations, a review of the personnel involved will be performed by Drs. Golightly and Smith-Ryan. Depending on the nature of the violation or deviation, study recruitment and treatment may be stopped until the violation/deviation is addressed. Actions may be taken to remove a participant from the data set if the deviation affects the data collected. It is possible that if a violation is deemed egregious study personnel may be dismissed from further involvement in the study in order to ensure future validity of the data collected and safety for study participants.

Bi-annual Reporting
The Principal Investigator will develop reports as indicated in section 3.k.1. All reports will be sent bi-annually to the Safety Officer, NCMRR as soon as available. See section 3.k.1 for full description of bi-annual reporting.

Data Collection and Management

Data to be Collected. Materials for the research purposes of the proposed project will be collected by interview and clinical assessment. Interview data will be collected by experienced and trained interviewers, and clinic visit data will be obtained by experienced and trained examiners.

Data Management. Data will be collected electronically using Research Electronic Data Capture (REDCap). This system is a secure web application for building and managing surveys and other data capture mechanisms for clinical research. The REDCap that will be used for the proposed project is housed at and managed by UNC's North Carolina Translational and Clinical Sciences Institute (NC TraCS; Clinical and Translational Science Award).

Upon enrollment in this study, each participant will be assigned an identification number. All written information collected will be associated with this identification number and stored in a locked file cabinet located in the Applied Physiology Laboratory in Fetzer Hall, UNC-CH. Only the PIs and research assistants will have access to this information. All electronic files will be password protected and stored on an encrypted external USB drive owned by the PI or on the Thurston Arthritis Research Center (TARC) server. Data management will be completed using good clinical practices. Specifically, hard copy data sheets/case report forms will be used to capture initial data. This will then be transferred by a member of the research team to REDCap. Additional metrics will be used to identify potential mis-entries or outliers. Data will be further managed in statistical software, such as SPSS or SAS, by the PIs.

Data Access and Protection. All interview data and results of clinical examinations will be kept private to the extent allowed by law. Records will be marked by identification number, not names. The electronic file that links a participant's name to a study identification number will be kept on a computer that is password protected. Drs. Golightly and Smith-Ryan and designated project staff (study physicians, research assistants involved with recruitment, training, and testing) will be able to link study identification numbers to names. For the proposed project, other members of the study team will not have access to these links or to participants' names.

Confidentiality of data. Extreme care will be taken to ensure that there will be no breach of participant confidentiality. Each subject and their associated information will be identified by a 4-digit alpha-numerical identification code. Subjects will be identified by this code only when labeling any data collection sheets or computer printouts. Only one code list linking the subject identification number and their name and email address will exist and will be viewed by the research team only, and will be stored in a secure filing cabinet in the APL with the consent forms. This list will serve as the only link between a subject's name and ID code and will be destroyed (shredded by the principle investigator immediately after the study has been completed). Email addresses and phone numbers will be obtained solely for the purpose of contacting subjects to schedule testing and data collection times. All data will be stored in electronic format on both the data collection computer and the principle investigator's personal computer. Computer access will be protected via confidential passwords, and backup devices will be stored under lock-and-key in the APL. Only qualified members of the research team will have access to these data. In the event of a confidentiality breach, responsible personnel will be severely reprimanded and potentially dismissed.

Retention of Study Documents

All study related files will be maintained for at least 7 years, as mandated by the Institutional Review Board at the University of North Carolina at Chapel Hill. All study files will remain in a locked file cabinet located within the Applied Physiology Lab, which is secured via swipe card access. Once 7 years' time has passed, all study documents will be shredded.

Administrative Forms

Five administrative forms have been included in order to assist with the management of participant enrollment. Each administrative form is described below and is included.

Telephone Contact Log
The telephone contact log will be used to document all conversations regarding the study and study participants. The contact log will be used any time the Principal Investigators, Study Coordinator or Research Assistant makes a telephone call to either a member of the research team or a study participant in regards to this study. The Principal Investigators, Study Coordinator or Research Assistant will record the date of the phone call, their name, the individual the call is made to, the reason for the call and the length of the conversation.

Screening Log
The screening log will be used to record all participants which are screened for participation into the study. The screening log will be kept up to date at all times throughout the study.

Participant Identification Code List
The participant identification code list will be used to document the participant's name, medical record number, randomization number, and study entry and study exit dates. The participant identification code list will be kept within a filing cabinet located in the Principal Investigators office, which is a secure location and separate from all other study files.

Study Completion and Closeout Procedures

Types of Study Close-out
The two types of closeouts include a scheduled closeout, which occurs upon completion of the trial, and an unscheduled closeout which may occur as a result of failure to obtain continuation funding, negative or positive findings, findings in other studies that impact on the clinical trial, or other unforeseen events. Dr. Golightly is responsible for ensuring the following activities are completed prior to study close-out along with the Participant Close-out Procedures described below.

Participants Notification
Dr. Golightly and Dr. Smith-Ryan will need to approve any public disclosure of data or results. After all data for main outcome measures are calculated and published in peer-reviewed publications, participants will be notified about the main finding of the study with a summary publication shared electronically.

Policies

Privacy and Confidentiality Procedures
Confidentiality of participant data is always a priority, and measures to protect confidentiality are described below. There are no known social or legal risks associated with this project. The privacy and confidentiality of research participants are to be respected and protected at all times. Recruitment calls will be conducted from a private location within UNC study team staff space. Baseline and follow-up assessments will be conducted in private rooms where other personnel cannot hear interviews. Mailings will include only the address of the participant and return address that does not indicate health status, focus of the study or study name.

This research study will comply with the HIPAA Privacy Rule as well as all other state, federal, and institutional regulations intended to protect the rights, safety, and welfare of human participants involved in research studies. We will attempt to minimize the collection, storage, and transmission of information containing participants' personal identifiers, and, whenever identifiers are necessary, protect against unauthorized access or disclosure. In addition, we will employ several rigorous procedures for protecting

against risks to participant privacy and confidentiality of data. We will only collect and store information about study participants that is relevant to the research as outlined in the protocol. All electronic data will be collected and stored on password protected computers. Paper documents will be stored in a locked file cabinet in the lab which is locked and accessible only through key card access. Individual participant data will not be shared with individuals outside the study team, except as required by law and/or for regulatory purposes.

Publication Policy

Results will be shared by all involved professional personnel, and both Dr. Golightly and Dr. Smith-Ryan will need to approve any public disclosure of data or results. All members of the Research Team and the funding source will be acknowledged in public presentations. Authorship on publications will be determined based on the extent of scientific and intellectual input from each of the members of the team. In the event of conflicts regarding publication, outside and impartial advisors will be requested to help with deliberations. Specifically, members of the Executive Committee and the Advisory Board of the Thurston Arthritis Research Center's Multidisciplinary Clinical Research Center can assist with conflict resolution. UNC has policies and formal procedures in place for dealing with scientific and intellectual property disputes.

MOOP Maintenance

Dr. Golightly and Dr. Smith-Ryan will maintain and update the Manual of Operations and Procedures (MOOP) throughout the study. To ensure accuracy and facilitate revisions and/or additions, pages of the MOOP will contain the version date. If any piece of a MOOP is changed the date on the front cover of the MOOP will be adjusted for easy identification. If a new version of the MOOP is created it will be electronically mailed to all participants on the study team. Additionally, the MOOP will be maintained in a three-hole binder and available to all study staff members for review. MOOP maintenance will be on the meeting agenda each month.

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