Gerofit Exercise Intervention for Older Adults with Sickle Cell Disease

Document Date: 08/20/2024

NCT05714098

Principal Investigator:	Charity Oyedeji, MD Assistant Professor of Medicine Duke University School of Medicine [redacted]
Co-Investigator:	John Joseph Strouse, MD, PhD Director of the Adult Sickle Cell Program Associate Professor of Medicine and Pediatrics Duke University School of Medicine [redacted]
Funding Sponsor:	REACH Equity Career Development Award National Institute on Minority Health and Health Disparities under award number U54MD012530 National Heart, Lung, Blood Institute K01Mentored Career Development Award to Promote Diversity Grant #: 1K01HL166369-01

Protocol Summary

Title	Gerofit Exercise Intervention for Older Adults with Sickle Cell Disease
Short Title	SICKLE-FIT Study
Brief Summary	We will adapt and pilot the tele-Gerofit personalized exercise intervention for older adults with sickle cell disease. We will enroll up to 50 older adults (age ≥ 40) with sickle cell disease from the Duke University Adult Sickle Cell Center. Sickle Cell Disease Functional Assessments will be performed at steady state at baseline and every 3 months to track progress. We will use an ACTIGRAPH activity monitor for one week to assess physical activity after each visit. We will collect blood and urine at study entry and at each study visit for future analysis of biomarkers. All participants will be interviewed to identify barriers and facilitators to exercise and how to better optimize the exercise intervention
Objectives	1) to adapt and pilot a personalized exercise training program to improve physical health and quality of life for adults with SCD, and 2) to evaluate participants' motivation for continuing exercise long-term.
Endpoint	After study exit assessment is completed
Study Duration	*5 years*
Participant Duration	*Each virtual session will be up to 90 minutes 3 days a week for up to 12 weeks. The sessions include up to 60 minutes of exercise and 15-30 minutes for safety/health check-ins before and after the work out. Each functional assessment in clinic will be 1 hour. Each cohort will be followed up to 5 years*
Population	Adults age ≥ 40 years at Duke University Adult Sickle Cell Center

Index

V. Protecting Data

A. Data and Safety Monitoring Plan

I. Background

Median life expectancy for individuals with sickle cell disease (SCD) increased from 14 years in 1973 to 61 years in recent cohorts from academic centers. Despite this increase, older adults with SCD experience progressive functional impairment with complications seen frequently in geriatric populations such as impaired mobility, depression, and decreased cardiovascular reserve. This population has experienced a lifetime of sickling and microvascular occlusion that affects every organ of the body. Compared to younger adults with SCD, they are more likely to have chronic complications, such as avascular necrosis of the joints requiring joint replacement, pulmonary hypertension, and heart failure. There is a critical need for interventions to maintain mobility, cardiovascular health, and independence in older adults with SCD.

To address this need, we adapted and piloted a geriatric functional assessment battery, the Sickle Cell Disease Functional Assessment (SCD-FA), to detect functional impairments early since there are no validated assessment tools and interventions for functional impairment in older adults with SCD. The SCD-FA is a multidimensional battery of geriatric measures to assess physical function, psychological state, cognition, comorbid medical conditions, social support, nutritional status, and medications. In our pilot study of the SCD-FA, both younger adults (age 18-49) and older adults (age ≥ 50) demonstrated functional impairment in physical performance for multiple measures similar to individuals 20-30 years older than their chronological age. The results of the SCD-FA pilot study identified an urgent need to develop interventions to maintain and improve function in adults with SCD. Therefore, in this study, we will pilot an exercise intervention for older adults with SCD adapted from Gerofit, a supervised personalized exercise and health promotion program. Our collaborators developed Gerofit for older adults with chronic disease and/or impaired mobility in the Veteran Affairs Medical Center. Gerofit has been shown to improve function, well-being, quality of life and survival in older adults with longstanding chronic conditions.[1] Our proposed exercise training intervention will focus on adults (age ≥ 40 years) with SCD given the accelerated functional aging we identified in the pilot study and the impact of Gerofit in reversing functional decline.[2,3]

Gerofit

Gerofit is a supervised exercise and health promotion program for older veterans developed at the Durham Veterans Affairs (VA) Medical Center in 1986. It has been incredibly successful in improving physical function in older adults.[1] Gerofit enrolls veterans aged ≥ 65 years with chronic disease and/or impaired mobility who are at risk of premature functional decline. Gerofit exercises are customized to each person's heath status and underlying functional deficits. An exercise expert works with each person to develop an exercise regimen that includes moderate intensity aerobic and strength training and group exercises to improve balance and mobility. Session are 60 minutes and occur 3 days a week. Functional assessments are conducted at baseline, 3, 6, and 12 months and annually thereafter. Gerofit has also been effective in improving outcomes beyond physical function, such as quality of life, mental health, social connectedness, and survival.[1,3-5] Even individuals with cardiovascular and musculoskeletal disease experience the same benefits as those without these co-morbidities.[6] Gerofit has exceptional representation of African Americans as 59% of participants in the Durham VA Gerofit Program are African American.[7] Gerofit has been successfully expanded to 29 VA Medical

Centers across the United States. The Gerofit facility-based assessment and exercise procedures have been adapted to a video telehealth format to allow older adults in rural areas to participate with in-person participants.[8] During the COVID-19 pandemic, Gerofit successfully transitioned to a group-based telehealth-supported exercise intervention tailored for individual functional status.[9]

Tele-Gerofit has demonstrated safety and improvements in physical performance in older adults. A study in Greater Los Angeles VA showed improvements in endurance (measured by 2-minute step test) after 3 months of tele-Gerofit (P = .049).[8] Tele-Gerofit is currently available in over 30 VA clinical sites across the country and continue to accrue evidence of the effectiveness of tele-Gerofit.[9] (manuscript in press entitled "Physical Function Effects of Live Video Group Exercise Interventions for Older Adults: A Systematic Review and Veteran's Gerofit Group Case Study" in Telemedicine and e-Health). Performing Gerofit physical performance tests virtually demonstrated reliability (ICC of 0.98) for the 2 min step test, 30s chair stand, and 30s arm curl test.[8]

Self-Determination Theory and adherence to long-term exercise

The Self-Determination Theory is a common framework used to evaluate motives for long-term exercise and physical activity.[10] The Self-Determination Theory states that motivation can be divided into intrinsic and extrinsic motives. Intrinsic motives refer to engaging in an activity for its inherent enjoyment, challenge, and satisfaction. Extrinsic motives refer to engaging in activity due to external pressures or rewards. A systematic review examining the relationship between exercise and self-determination theory-based constructs showed that intrinsic motivations were more predictive of long-term exercise adherence.[10] Long-term adherence to Gerofit was evaluated in 97 veterans. They found that compared to short term adherers (less than 2 years), long-term adherers (greater than 2 years) had a lower body mass index (BMI) and no difference in physical function and comorbid conditions. The ability to overcome environmental barriers (i.e. bad weather or difficulty getting to the location) and social barriers (i.e. having to exercise alone or instructor not offering encouragement) were associated with long-term adherence.[11] Gerofit is structured to overcome environmental and social barriers, which is part of its success among adults with long standing chronic conditions.

Exercise in adults with sickle cell disease

There is limited data on exercise in older adults with SCD. A study on exercise capacity using maximal exercise treadmill testing in adults with Hb SS/Sβ0 (mean age 42 +/- 7.5 years) showed that older age, higher BMI, female sex, and lower hemoglobin were associated with lower fitness.[12] Pain and hospitalizations were not associated with exercise capacity.[12] We chose to use Gerofit for our pilot exercise intervention in older adults with SCD because it is effective, well-established, readily scalable, has a video telehealth option, and exercise prescriptions are carefully tailored to individual patient's impairments. Gerofit's tailored approach is ideal for individuals with SCD who experience musculoskeletal and cardiopulmonary complications similar to older veterans. Gerofit has not been used outside of the VA setting; however, it is logical to assume that if it is effective in improving function in disabled older adults, then it can be effective in improving function in older adults with SCD, as these clinical populations share similar characteristics. An additional benefit of Gerofit is it includes moderate intensity exercise, which has been shown to be beneficial and safe in individuals with SCD.[13,14]

Objectives

The purpose of this study is to 1) to adapt and pilot a personalized exercise training program to improve physical health and quality of life for adults with SCD, and 2) to evaluate participants' motivation for continuing exercise long-term.

II. Study Design

A. Study Design and Population

We will evaluate the feasibility and acceptability of an exercise intervention in a single-center prospective cohort of up to 50 older adults with SCD (age ≥ 40 years) divided into cohorts of 5-8 participants. We will enroll participants with a variety of SCD genotypes, complications, and treatments representative of our clinic population in the Duke Comprehensive Adult Sickle Cell Center.

Cohort 1: The initial cohort will be up to 5 participants integrated into the Durham VA tele-Gerofit program along with our exercise instructor for 3 days a week for up to 8 weeks in order for our study team to become more familiar with delivering the Gerofit intervention with support of Durham VA Gerofit team. Participants will participate by video via zoom.

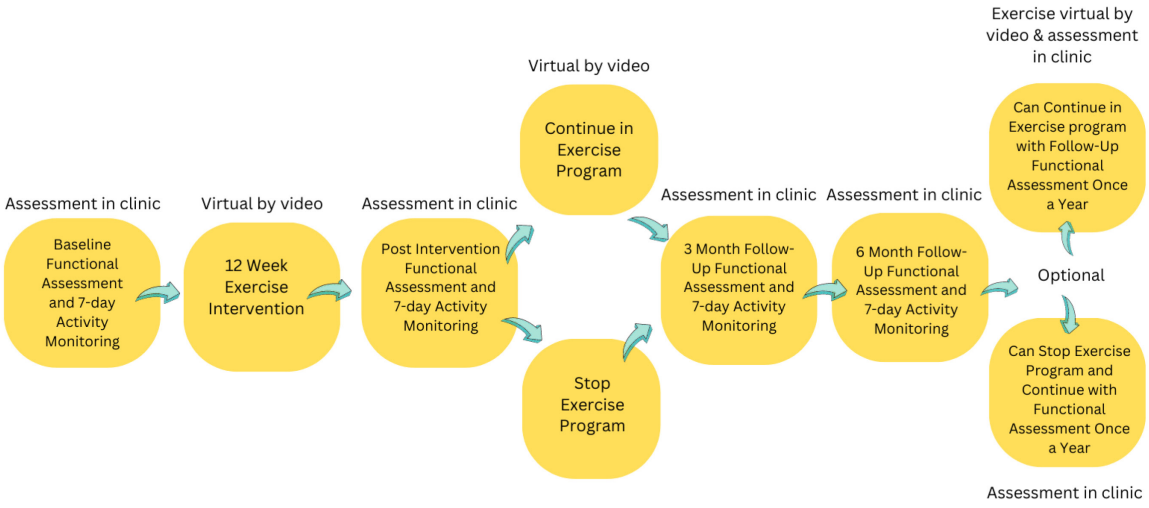
Cohorts 2-4: Subsequent cohorts will consist of 5-8 participants and will include only our study participants with SCD and study team. These cohorts will participate in the exercise program for up to 12 weeks for 3 days a week virtually using zoom or in-person.

Participants will have the option to continue exercising in the SickleFit program after completing the up to 8–12-week feasibility evaluation. Participants will be allowed to continue their extended participation for up to 10 years. This will be at the discretion of the study team based on participants with no significant safety concerns present and if the participant continues to benefit from the exercise program. There will be no cost for participants to continue exercising in the SickleFit program.

We will administer a functional assessment in-person before and after the virtual exercise program, 3 months after the exercise program, 6 months after the exercise program and then annually for up to 10 years as part of their usual annual Sickle Cell Disease Functional Assessment (SCD-FA).

After the up to 8-12 week feasibility evaluation and the post-exercise, 3-month, and 6-month assessments, we will continue to track adverse outcomes during each exercise session and we will perform a functional assessment annually for all participants (whether or not they choose to continue exercising in the SickleFit group). We will include these results in the data analysis.

We will analyze data on adverse outcomes and functional assessment of participants in 2 groups: those that continue to exercise and those that choose to stop exercising after the feasibility evaluation period. We will track these 2 groups in REDCap.



Communication

We will communicate with participants via their preferred method, which may be by email, phone or text message. We will also respond to any messages participants send using responses in the following categories:

- Scheduling questions for functional assessments and exercise sessions
- General study-related questions
- Evidence-based advice on exercises in the SickleFit Program
- Advice on managing soreness and pain based on the participant's established safety/care plan

Participants will be informed that email and text message are not a secure form of communication.

Participants will be sent a survey link via email from a secure database called REDCap to complete your study-related surveys.

Exercise Sessions Video Recording

Participants may be video recorded during the online exercise sessions to allow the study team to improve the SickleFit exercise program. the video recording may take place while the group of participants are exercising in-person or while exercising online via Zoom. The recordings will be used for educational purposes. Based on participant feedback, video-recordings will be made available to participants so they may exercise at their leisure outside of the scheduled exercise sessions. We will get participants feedback on the usefulness of the available recorded videos.

The study team will also review the recorded exercise sessions to improve the program. Recordings of the exercise sessions will be made available to participants via email from a secure database called REDCap.

If participants agree to be recorded during the exercise sessions, they will be asked to sign a Video Release HIPAA Form and will be provided a copy of the signed form. They will have the option to not be recorded (by clicking "hide video" in their video box on zoom during recorded sessions).

B. <u>Data Extraction at Enrollment</u>

We will use a structured data extraction form in REDCap to collect information from electronic medical record and participants including:

1. Socio-demographic data
2. Complications from sickle cell disease
3. Non-SCD comorbidities
4. Steady state laboratory values
5. Healthcare utilization (emergency department visits, sickle cell day hospital visits, and hospitalizations)

C. Gerofit

Each participant will receive a written exercise prescription that is customized to their health status as identified by the physical performance test in the SCD-FA. Our exercise instructor is trained in common complications of SCD and has interned in the Durham VA tele-Gerofit program to obtain sufficient expertise to lead the classes. Prior to starting each virtual exercise session, the exercise instructor will check in with participants to assess if complications, such as vaso-occlusive episodes, have occurred to determine if they are safe to exercise that day. Each session will be a total of 90 minutes occurring 3 days a week and includes ~15-30 min of safety/health check-ins, cardio exercise, strength training, balance training, and warm-up and cool-down exercises which include stretching and mindfulness breathing. Participants will progressively work up to this duration over the course of the program, consistent with American College of Sports Medicine guidelines for exercise prescription and progression.

Intensity of exercises will be determined by participants providing a rating of perceived exertion (RPE) on a scale of 0 (easy) to 10 (very hard) throughout the session. Initial exercise sessions will start at low-intensity and will gradually increase the duration and intensity to allow each person to reach recommended exercise levels at their own pace. The instructor will be familiar with the results of each participant's functional assessment and will recommend modifications. Options for performing exercise from sitting or standing will be included at each session and delivered in real time which allows for personalization of the exercise routines.

Equipment Participants will need a non-rolling chair, so we will provide a stable folding chair without arms. We will provide resistance bands (3 levels) and additional equipment for strength and balance training. We will provide tablet computers and Wi-Fi for participants who do not have internet access or a computer/tablet with a camera, microphone, and speakers.

The Gerofit intervention has training focused on meeting the physical activity guidelines and incorporating cardiovascular, strength, and balance training. Sessions will also include a mindfulness component, warm up, cool-down, and safety checks. General guidelines include having the participants move at a manageable pace throughout the exercise session and offering varying levels of difficulty for each of the exercises. Exercises may vary between sessions, but each session will have the following components:

Warm Up

1. Basic concept: prepare the body for an increased cardiovascular workload
2. General Guidelines:
    a. Targeting legs before arms
    b. Focus on large muscle groups
3. Example exercises include:
    a. Walking/marching in place
    b. Teaching or mimicking exercises from the cardio sections
    c. Stepping patterns

Cardiovascular Training

1. Basic concept: to optimize cardiovascular physical fitness
2. General Guidelines:
    a. Menu of exercises will target all muscle groups
    b. Aerobic training may be broken into smaller segments
    c. Target goal of 4-6 on RPE scale
    d. Use of interval training may be incorporated to achieve desired effort level
3. Examples exercises include:
    a. Marching variations
    b. Side stepping
    c. Jumping jack variations
    d. Mountain climbers
    e. Circuit training

Strength Training

1. Basic Concept: to optimize strength and power across the body
2. General Guidelines:
    a. Menu of exercises will target all muscle groups
    b. Target goal of 7-8 on RPE scale
    c. Use of resistance bands/weights will be incorporated to achieve desired effort level
3. Examples exercises include:
    a. Sit to stand or squat variations
    b. Hip flexion-abduction-extension variations
    c. Plank variations
    d. Triceps extension

Balance Training

1. Basic Concept: to optimize balance and prevent falls
2. General Guidelines:
    a. Menu of exercises will target various levels

b. Target goal to challenge current balance level
3. Examples exercises include:
    a. Tai Chi
    b. Standing exercises with varying base of support

Cool-Down/Flexibility/Mindfulness

1. Basic Concept: Allow the cardiovascular system to safely return to resting level, to focus in on being present in the moment and to maintain appropriate muscle length in muscles that contribute to posture and mobility
2. General Guidelines:
    a. Flexibility exercises will be completed bilaterally
    b. Target goal to hold positions for 30-60 seconds
    a. Focus on breathing and control of breath
2. Examples exercises include:
    a. Yoga
    b. Guided Imagery
    c. Meditation

Safety & RPE Checks

1. Basic concept: to ensure location of participants, safety throughout the sessions, and assessment of effort levels during the session
2. General Guidelines:
    a. Participants will report to staff when not at their primary home location during exercise classes
    b. Participants will respond to instructors throughout the session as appropriate regarding their health during the session
    c. Participants will rate their perceived effort on the session with guidance from staff

D. Protocol for Sickle Cell Disease Functional Assessment (SCD-FA)

In each cohort we will perform a total of 4 functional assessments at 3-month intervals with 7 days of activity monitoring using an accelerometer after each assessment to evaluate baseline function and change in physical function in response to the exercise intervention. This includes assessments at baseline, after the 12-week exercise intervention, 3 months after, 6 months after and annually up to 10 years.

Functional assessments will be performed using the SCD-FA. The measures included in the SCD-FA have been validated in the geriatric assessment for oncology and we are currently evaluating validity and reliability of the measures in adults with SCD.[15] In the SCD-FA we included physical performance measures and the PROMIS® 10-iitem Physical Function measure because they are sensitive to change in response to interventions that target physical function in individuals with various chronic conditions.[16,17] All functional assessments will be at steady state defined as at least 30 days from the last hospitalization and at least 2 weeks from the last ED or Sickle Cell Day Hospital visit. At each follow-up visit we will ask each participant “Compared to your last visit, how would you rate your physical health now: ‘much better’, ‘somewhat better’, ‘about the same’, ‘somewhat worse’, ‘much worse’?”.[18] We will account for major health events (such as hospitalizations or new SCD complications such as strokes) that have occurred since their last study visit. Participants will be able to

complete survey portions at home. Physical performance assessments will be administered in the Duke Adult Sickle Cell Center.

1. *Length of time expected for SCD-FA:* 1 hour

2. *Domains and Measures of SCD-FA*
    a. Functional Status:
        - Activities of Daily Living (ADL) (subscale of Older Americans Resources and Services (OARS)) which is a subscale of the Medical Outcome Study: 3-point likert scale measuring independence
        - Number of falls in last 6 months: self-reported number of falls
        - Medical Outcome Study (MOS) social functioning: four-item subscales that measures the extent an individual's physical issues interferes with social activities
        - Patient-Reported Outcomes Measurement Information System PROMIS® 10-iitem Physical Function Comorbid medical conditions (10 items)
        - SQUASH (*Short QUestionnaire to ASsess Health enhancing physical activity*) Physical Activity Questionnaire
    b. Psychological State:
        - Patient Health Questionnaire – 9 (PHQ-9)
        - Generalized Anxiety Disorder 7 (GAD-7)
    c. Social support (20 items)
        - MOS social support survey – subject's perceived availability of social support
    d. Nutritional status (2 items)
        - Body Mass Index
        - Unintentional weight loss in last 6 months
    e. Cognition
        - Mini-Cog
    f. Medications (1 item) # of medications

3. *Physical Assessment:*
    a. *Usual Gait Speed:* Subject will be observed and timed walking back and forth on a 15 ft course at usual walking pace
    b. *Timed Up and Go-* performance test of physical mobility. This will measure the number of seconds it takes to stand up from a standard chair (46cm), walk a distance of 10 ft (3 meters), turn back to the chair, and sit down again
    c. *6-minute walk:* We will use the 6-minute walk test to measure aerobic endurance. The subject will walk as fast and as safely as possible for 6 minutes with prompts given every minute. Distance traveled in 6 minutes will be recorded with a measuring wheel by examiner walking behind the subject. Heart rate and oxygen saturation will be measured using a pulse oximeter after the 6-minute walk (immediately after finishing and 1 and 2 minutes later)
    d. *Seated Grip strength:* This will measure upper body strength. Jamar hydraulic hand dynamometer (Jamar Technologies) will be used to measure grip strength in triplicate for both hands while subject remains seated.

e. *30 second Chair stand test:* This will measure lower body strength. The subject will sit in a folding chair without arms with chair pressed against the wall to prevent slipping. The subject will stand up and sit back down with arms across their chest as many times as possible in 30 seconds.
f. *Functional Movement Screen (FMS):* Include deep squat and mobility test of upper and lower extremities.
g. *Core Strength Test:* Plank to test core strength

E. Optimization of the Intervention

We will optimize the intervention after each cohort in an iterative, feedback-driven process. Exercise sessions will be video recorded. The principal investigator will debrief weekly with the exercise expert and quarterly with Gerofit experts to determine if changes are needed to improve the program. We will ask participants to provide brief written reflections on how the exercise program is going for them. We will conduct focus groups and/or individual interviews with participants during and/or after each 12-week program to determine barriers to performing Gerofit workouts, acceptability of the virtual option, willingness to participate again, and to provide feedback on how to improve the exercise intervention. Interviews will be in person, by zoom, or by phone, will be recorded and transcribed verbatim. Based on feedback from participants and our exercise expert, we will adapt the program to develop an acceptable and safe personalized exercise intervention for older adults with SCD to be studied in a larger-scale clinical trial.

F. <u>Activity Monitoring</u>

We will measure physical activity at home (average steps per day, time spent being sedentary, and time spent doing moderate-vigorous physical activity) using an Actigraph wGT3X-BX or GT9X Link accelerometer device worn on the non-dominant wrist.[2,19] The Actigraph unit is an activity monitor designed for research that includes a 3-axis accelerometer, digital filtering, and integrated wear time and ambient light sensors, to measure physical activity (Table 3).

We will measure activity for each subject for one week after each study visit. For steady state activity monitoring, subjects must be greater than 30 days after their last hospitalization and greater than 2 weeks after their last emergency department or Day Hospital visit. We will be using the ActiLife program to upload the activity monitoring information. This will be done on a computer in the Division of Hematology Research Offices and de-identified activity data on each subject will be uploaded to a file in Duke Box.

TABLE 3: Actigraph Objective Measures

Measure	**Description**
Steps	Average steps in 24 hours
Energy Expenditure (kcals)	Physical activity energy expenditure
Activity Bouts (minutes)	Average active time in 24 hours
Sedentary Bouts (minutes)	Average sedentary time in 24 hours

G. <u>Biospecimen Collection</u>

We will collect blood and urine at the baseline and each functional assessment study visit to assess how biomarkers of physical functional impairment and frailty (such as IL-6, TNF-alpha, VCAM-1) change in response to exercise. Study personnel will separate serum and plasma within 1 hour and freeze specimens at 80° C in a freezer located in the Division of Hematology. Biospecimens will be stored with the plan for batch processing for future research related to sickle and aging.

Samples will be identified by a study ID number. The study ID will be linked to patient's age, gender, and ethnic background. Samples will be discarded if patients request for the ssmples to be destroyed. Samples will be kept for at least 10 years. After that time, the study team will determine if samples should be de-identified or discarded by methods in accordance with laboratory or institution procedures.

Experienced personnel will perform specimen collection, including phlebotomy, with subjects sitting to reduce the risk of syncope or falls.
Biospecimens will be collected at steady state. Participants must be greater than 30 days after their last hospitalization and greater than 2 weeks after from their last emergency department or Day Hospital visit.

There will be no use of device or point of care diagnostic device.

H. Determining Motives for Exercising Long-term

We will use Motives for Physical Activity Measure–Revised (MPAM-R) survey to determine motivations for continuing exercise and activity long term. The MPAM-R was developed based on the Self-Determination Theory and has been validated across several cultures for its ability to measure motives for physical activity.[20] There are 30 items in the MPAM-R divided into five factors: (1) Fitness; (2) Appearance; (3) Competence/Challenge; (4) Social; and (5) Enjoyment. We will track exercise frequency at each study visit and determine which motivators are the strongest for maintaining exercise and physical activity long term.
The MPAM-R survey will be administered in up to 50 participants prior to the exercise intervention, immediately after the 12-week exercise intervention, and at the 6-month post-intervention follow up visit.

I. Recruitments and Retention Strategies

We will recruit participants from Duke South Clinics, Community events, or over the phone. The PI, Dr. Charity Oyedeji and research specialists will introduce the study to potential participants at Duke South Clinics, Community events, or over the phone. Before approaching participants, we will review the electronic medical record to ensure they meet study inclusion/exclusion criteria and confirm this with the patient's sickle cell provider. To ensure recruitment is equitable and the relevant demographic groups have access to study participation, we will contact patients from various locations (urban and rural) who are seen in the Duke Sickle Cell Center. Since the exercise intervention is mostly virtual, this allows for a variety of patients to participate.
We will maintain contact with the research subjects at scheduled clinic visits, by Mychart, or by phone and by checking the Duke Maestro medical record and Care Everywhere once a week for each subject.
We may use Twillio to send SMS text messages to deliver study related information. Participants' phone number will be entered into REDCap for this purpose. There is a

chance Twillio may see and use their phone number. Also, as SMS text messages are not secure, there is a possibility mobile carriers or others may have access to the SMS text messages exchanged with the study team. In addition, there is also a chance that identifiable information may be seen by others outside of the research team. There is a potential risk to confidentiality through use of Twillio and by sending and receiving SMS text messages.

We will identify hospitalizations, ED visits, and Day Hospital visits by weekly medical record review of each subject, asking the Duke Adult Sickle Cell Center APPs to contact Dr. Oyedeji or Dr. Strouse if subjects are hospitalized, and ask participants to contact us if they are hospitalized. We will provide a study information card with emergency contact numbers to all study participants

III Human Subjects Review Specific Information

A. **Subject Population**

We enroll up to 50 older adults (age ≥ 40 years) with sickle cell disease (Hemoglobin SS, SC, S-beta+, S-beta0 or S-other) at Duke University Sickle Cell Center over the course of the study.

Inclusion and Exclusion Criteria

Inclusion Criteria:

1) Have a diagnosis of SCD (any genotype) confirmed by hemoglobin electrophoresis, high performance liquid chromatography, or genotyping
2) Understand and speak fluent English.

Exclusion Criteria

1) Diagnosed with moderate or severe cognitive impairment based on ICD-10 codes or report from their outpatient provider
2) Unable to self-consent
3) Wheelchair-bound
4) Successfully treated with hematopoietic stem cell transplantation for SCD
5) Have moderate to severe uncorrected visual or auditory impairment
6) Oxygen-dependent
7) Pregnant
8) Have severe avascular necrosis requiring an assist device
9) Unstable cardiac disease.[1]

B. **Confidentiality Measures**

1. Informed Consent Process **-** Subjects will be approached by one of the study team members at Duke South Clinics, during community outreach events , or while hospitalized at Duke University Hospital. The consent process will take place in person at the time of enrollment in a private room in Duke South Clinics or Hanes House. Our established patients may also be contacted by phone call and asked if they would like to participate. PI Charity Oyedeji, MD, co-investigator, John Strouse, MD, PhD, and our research specialists will consent the eligible people with SCD. We will inform the potential subjects about the study, indicate that participation is voluntary and he/she/they has the right to stop at any time. The rationale for the study and study procedures

will be described in detail. Risks and benefits are enumerated in the informed consent form and described orally during the consent process.

2. To minimize risk to privacy and confidentiality of data we will use unique study specific ID for participants and enter data in REDCap database hosted at Duke University School of Medicine on a secure system with regular back-ups.

3. Data will be presented in a blinded manner in data safety reports.

C. **Risks**

Potential Risks (physical, psychological, financial, legal, other)

1. Gerofit Exercise Intervention:

Participants may experience vaso-occlusive pain event (VOE) or injury during or with in 48 hours of exercising due to overexertion or dehydration. We will provide participants with education and materials on how to minimize risk of adverse events.

The risk of physical injury and pain crisis events are further defined below:

- **Minor adverse events** are defined as having a VOE or injury that can be successfully managed at home. Participant will return to exercise when they feel able to tolerate exercising.
- **Major adverse events** are defined as a VOE that cannot be managed at home and require participants to be evaluated in the Duke Sickle Cell Day Hospital, ED or hospitalization. Participants will be able to return to exercise a week after resolution of a major adverse event.
- **Major life-threatening events** are defined as acute life-threating complications such as acute chest syndrome, multi-system organ failure, or stroke. If participants have a major life-threatening event, they will be removed from the exercise intervention. If a participant has a non-SCD-related hospital admission, the research team will evaluate these on a case-by-case basis.

2. *Sickle Cell Disease Functional Assessment:* Physical injury/fall or sickle cell crisis may occur during the geriatric assessment or within 24 hours of the assessment

3. *Activity Monitoring:* There are no known risk associated with activity monitoring. Subjects will be wearing the activity monitor for 1 week at enrollment and after each study visit for 1 week. The activity monitor is not designed to be an intervention, but it is meant for monitoring of activity. Subjects will be encouraged to continue normal activity.

4. *Specimen Collection:* Specimens will be collected during routine lab collection times at clinic visit and occasionally as an extra collection. The risks of venous blood sampling include transient pain, bruising, and a very small risk of syncope, infection, excessive bleeding or clotting. Experienced personnel will collect all blood samples to minimize these risks.

5. *Potential loss of confidentiality*: There is a small risk of loss of confidentiality that could lead to emotional distress or impact a subject's ability to obtain health, life, or disability insurance.

D. Consent Statements

Subjects will have the opportunity to review the consent form and ask questions in a confidential area in clinic. We will review the content of the consent form with them and answer any questions about the study or consent form. We will then ask the potential participant to provide written consent by signing the consent form. The subject will receive a copy of the consent form. They will also have the option for electronic consent. For eConsenting, participants will be notified by email. RedCap will be used to capture eConsent signature. All electronic communications (emails) and distribution of consent documents will be done using secure/encrypted means. A sample email letter has been included in the IRB application.

E. Subject Compensation

Subjects will be reimbursed up to $40 per functional assessment for the expenses related to their participation including transportation and other associated costs. They will also receive parking passes and compensation for the number of miles you travel to come to in-person study visits, based on the standard mileage rate, up to $100 per study visit. Compensation will be provided at completion of each study visit. Participants will receive an electronic tablet and exercise equipment to participate in the virtual exercise intervention (which they will keep at completion of the study). Participants will also receive an additional $25 in compensation for participation in the focus group. Participants will have the option to receive Clincards (prepaid debit card) for compensation. Total monetary compensation will be up to $185 + mileage compensation (varies) per participant.

IV. Statistical Data Analysis

Analysis of Exercise Intervention Feasibility and Exploratory Endpoints

We will use descriptive statistics to assess the outcomes for the exercise pilot intervention. Our primary outcome will be defined as proportion of participants completing at least 50% of the sessions in the up to 12 week feasibility period with a goal of >80%. The secondary outcomes are adverse events and acceptability. We defined these as: 1) number of moderate or severe adverse events within 48 hours after each exercise session and 2) proportion of participants reporting the intervention as acceptable.

We will analyze data on adverse outcomes and functional assessment of participants in 2 groups: those that continue to exercise and those that choose to stop exercising after the initial up to 6-12 week feasibility period. We will track these 2 groups in REDCap.

Exploratory outcomes of this study include changes in physical performance, including Usual Gait Speed (mobility and overall health), Timed Up and Go (balance), 6MWT (aerobic endurance), grip strength (upper body strength), 30-second chair stand (lower body strength), and quality of movement measured by functional movement screen. Given the nature of feasibility studies without control groups and the small sample size rather than relying on statistical tests, we will be looking for patterns of change across variables that are consistent with benefits of Gerofit/SickleFit for older adults with SCD.

Exploratory analysis beyond the feasibility period will focus on assessing rate of change in function longitudinally in individual exercising in the SickleFit Program compared to participants who stop exercising in the program.

Analysis of Focus Groups and Interviews

Focus group and individual interviews will be analyzed using conventional content analysis since there is limited data on exercise in older adults with SCD.[21] Consistent with methods of qualitative content analysis, the interview transcripts will be analyzed in 3 phases: preparation, organizing, and reporting.[22] After editing transcripts for accuracy, we will read through each transcript to get a sense of what participants are saying in response to each question. In the organization phase we will take an inductive approach to analysis (meaning not based on prior theory). We will code the transcript using sentences as our unit of analysis and will use Nvivo 12 to manage the analysis. With support from a research assistant trained in qualitative research, we will independently code the focus group transcripts for key topics surrounding acceptability, preferences, facilitators, and barriers performing the exercise intervention. During coding, the principal investigator and research assistant will discuss and compare codes and coding discrepancies until consensus is reached. We will create and revise a codebook, which will have all codes, categories, sub-themes, themes, and quotation exemplars. We will keep an audit trail of our process to ensure dependability and confirmability are upheld throughout the analysis process.[22] During the reporting phase we will described our participant selection process and analytic process in detail and include quotes from a variety of participants to support each theme.[22]

Analysis of Motives for Physical Activity Measure–Revised (MPAM-R) survey

We will perform descriptive statistics to determine the most common motivators for exercise and physical activity for all participants. We will also perform a subgroup analysis by gender. We will determine which motivators were most common in 1) participants who had the best adherence to the exercise intervention (top 50th percentile for attendance) and 2) participants who report the highest weekly physical activity (top 50th percentile for activity). Characteristics between the most adherent and least adherent participants will be compared using t-tests for continuous variables and chi-square tests for categorical variables. Depending on whether scores are normally distributed, we will use paired t-test (parametric) or Wilcoxon signed range test (nonparametric) to determine if motives for exercise significantly change over time from baseline to immediately after the 12-week exercise intervention is completed and 6 months after the exercise intervention is completed.

Interim Analysis

We will evaluate the feasibility of the intervention after each cohort. This may lead to modification of the procedures if there is excessive burden to subjects or we identify adverse events associated with procedures.

V. Data Safety Monitoring Plan:

The PI will be informed of serious adverse events as soon as they occur and will notify the Duke IRB and NIH of unexpected adverse effects and those related to study procedures within 24 hours of notification.

We will write safety reports after each cohort completes the exercise program. We will include a detailed analysis of study progress, recruitment and completed visits, data and safety issues, related and unrelated adverse events, and completion of study forms.

Data in safety reports will be presented in a blinded manner.

- For **minor adverse events** (defined as having a vaso-occlusive pain event (VOE) or injury that can be successfully managed at home), participant will return to exercise when they feel able to tolerate exercising.
- For **major adverse events** (defined as a VOE that cannot be managed at home), participants will be instructed come to the sickle cell center for evaluation and treatment in the Duke Sickle Cell Day Hospital or ED depending in the severity of the VOE and time of day. Participants may require hospitalization for VOEs. Participants will be able to return to exercise a week after resolution of a major adverse event.
- For **major life-threatening events**, (defined as acute life-threating complications such as acute chest syndrome, multi-system organ failure, or stroke), participants will be removed from the exercise intervention. If a participant has a non-SCD-related hospital admission, the research team will evaluate these on a case-by-case basis.

SAFETY FEATURES FOR EXERCISE INTERVENTION

To maximize safety and minimize risk of fall/injury during or within 24 hours of each exercise session, we will:

- Every session we will have a health and safety check in before and after the work out
- Evert session we will 1) inquire about health concerns, 2) monitor all participants in the zoom gallery view in real time, 3) instruct participants with balance issues to hold on to a non-rolling chair, and 4) warm-up and cool-down/stretch
- During exercise, participants will report their RPE and will be given guidance on how to safely adjust the intensity as needed. Of note, the exercise instructors provide counseling in real time that addresses issues such as what to expect relative to soreness versus pain; they are continually reminded that if anyone has pain they should immediately inform the staff so that adaptations can be made as needed.
- We will inform participants to expect mild soreness during the first 1-2 weeks of exercising. We will scale back the exercises if soreness persists beyond the first 2 weeks. If their pain is similar to their usual pain crises, then we will ask the participant to hold off on exercising until they feel ready.
- The amount (duration, intensity) of exercise is unique to each individual. Participants will start the program by doing 10-15 minutes of low- to moderate-intensity exercise and will gradually increase over the course of the intervention as determined by their tolerance level (RPE, muscle soreness outside of class) and improved capacity (aerobic endurance, strength, balance). This is consistent with American College of Sports Medicine guidelines for older adults with chronic conditions.
- Research staff will have emergency contact information for each participant.
- If major or life-threatening adverse events (AEs) occur during or within 24-hours of exercise activities, participants will know to immediately call research staff in the Duke Sickle Cell Clinic or page Dr. Oyedeji or Dr. Strouse if it is after hours.

Safety Features for SCD-FA:

Participants will be given frequent breaks during the assessment. We will allow the participants to remain seated when a particular portion of the exam does not require standing. Water will be provided in the exam room during the assessment and the subject will be encouraged to remain hydrated 24 hours after the exam. Providing water to subjects will help avoid dehydration. This, in turn, will help to minimize the risk of

triggering a sickle cell crisis. These measures have all been used extensively in geriatric patients and have demonstrated excellent safety. The most difficult and longest part of the physical assessment is the 6-minute walk test (6MWT) and this has commonly been done in patients with sickle cell disease with severe complications specifically pulmonary HTN. Machado et al. (Blood July 2011) used a 6MWT to assess response to sildenafil and some subjects in that assessment were even O2 dependent. Also De Castro et al. (Blood 2008) noted no adverse effects in 6MWT in patients with sickle cell disease. These measures have been used successfully in frail elderly with excellent safety and some measures (6MWT) in adults with sickle cell disease and severe co-morbidities. To mitigate risk of injury during assessments:

- Participants will take rest and schedule breaks as needed.
- The physical assessments will not be performed back-to-back. There will be rest periods in between each physical function test and the SCD-FA questionnaires portions will be interspersed in between the physical function testing. Questionnaires also will be able to be completed at home.
- Subjects will remain seated during portions of the test that do not require standing
- The assessment will be in a well-lit area in Duke South clinic with limited foot traffic and no barriers or obstacles.

VI. Patient Advisory Board

We will include adults with sickle cell disease as patient advisors. Their role will include providing insight on study design, study implementation, suggestions on optimization of the exercise intervention and functional assessment, outcome measures, and future directions. They will be compensated at least $25/hour for this role.

References

1. Morey MC, Lee CC, Castle S, et al. Should Structured Exercise Be Promoted As a Model of Care? Dissemination of the Department of Veterans Affairs Gerofit Program. *J Am Geriatr Soc*. 2018;66(5):1009-1016. doi:10.1111/jgs.15276
2. Oyedeji CI, Hall K, Luciano A, Morey MC, Strouse JJ. The Sickle Cell Disease Functional Assessment (SCD-FA) tool: a feasibility pilot study. *Pilot Feasibility Stud*. Mar 4 2022;8(1):53. doi:10.1186/s40814-022-01005-3
3. Morey MC, Pieper CF, Crowley GM, Sullivan RJ, Puglisi CM. Exercise adherence and 10-year mortality in chronically ill older adults. *J Am Geriatr Soc*. Dec 2002;50(12):1929-33. doi:10.1046/j.1532-5415.2002.50602.x
4. Morey MC, Cowper PA, Feussner JR, et al. Evaluation of a supervised exercise program in a geriatric population. *J Am Geriatr Soc*. Apr 1989;37(4):348-54. doi:10.1111/j.1532-5415.1989.tb05503.x
5. Wilkins SS, Melrose RJ, Hall KS, et al. PTSD Improvement Associated with Social Connectedness in Gerofit Veterans Exercise Program. *J Am Geriatr Soc*. Apr 2021;69(4):1045-1050. doi:10.1111/jgs.16973
6. Morey MC, Pieper CF, Sullivan Jr. RJ, Crowley GM, Cowper PA, Robbins MS. Five-Year Performance Trends for Older Exercisers: A Hierarchical Model of Endurance, Strength, and Flexibility. *J Am Geriatr Soc*. 1996;44(10):1226-1231. doi:https://doi.org/10.1111/j.1532-5415.1996.tb01374.x
7. Addison O, Serra MC, Katzel L, et al. Mobility Improvements are Found in Older Veterans After 6-Months of Gerofit Regardless of BMI Classification. *J Aging Phys Act*. Dec 1 2019;27(4):848-854. doi:10.1123/japa.2018-0317

8. Briggs BC, Jain C, Morey MC, et al. Providing Rural Veterans With Access to Exercise Through Gerofit. *Fed Pract*. 2018;35(11):16-23.
9. Jennings SC, Manning KM, Bettger JP, et al. Rapid Transition to Telehealth Group Exercise and Functional Assessments in Response to COVID-19. *Gerontol Geriatr Med*. Jan-Dec 2020;6:2333721420980313. doi:10.1177/2333721420980313
10. Teixeira PJ, Carraça EV, Markland D, Silva MN, Ryan RM. Exercise, physical activity, and self-determination theory: A systematic review. *International Journal of Behavioral Nutrition and Physical Activity*. 2012/06/22 2012;9(1):78. doi:10.1186/1479-5868-9-78
11. Brown CS, Sloane R, Morey MC. Developing Predictors of Long-Term Adherence to Exercise Among Older Veterans and Spouses. *J Appl Gerontol*. Oct 2020;39(10):1159-1162. doi:10.1177/0733464819874954
12. Badawy SM, Payne AB, Rodeghier MJ, Liem RI. Exercise capacity and clinical outcomes in adults followed in the Cooperative Study of Sickle Cell Disease (CSSCD). *Eur J Haematol*. Oct 2018;101(4):532-541. doi:10.1111/ejh.13140
13. Gellen B, Messonnier LA, Galactéros F, et al. Moderate-intensity endurance-exercise training in patients with sickle-cell disease without severe chronic complications (EXDRE): an open-label randomised controlled trial. *Lancet Haematol*. Nov 2018;5(11):e554-e562. doi:10.1016/s2352-3026(18)30163-7
14. Merlet AN, Messonnier LA, Coudy-Gandilhon C, et al. Beneficial effects of endurance exercise training on skeletal muscle microvasculature in sickle cell disease patients. *Blood*. 2019;134(25):2233-2241. doi:10.1182/blood.2019001055
15. Hurria A, Akiba C, Kim J, et al. Reliability, Validity, and Feasibility of a Computer-Based Geriatric Assessment for Older Adults With Cancer. *J Oncol Pract*. 2016;12(12):e1025-e1034. doi:10.1200/jop.2016.013136
16. Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. *J Am Geriatr Soc*. May 2006;54(5):743-9. doi:10.1111/j.1532-5415.2006.00701.x
17. Schalet BD, Hays RD, Jensen SE, Beaumont JL, Fries JF, Cella D. Validity of PROMIS physical function measured in diverse clinical samples. *J Clin Epidemiol*. May 2016;73:112-8. doi:10.1016/j.jclinepi.2015.08.039
18. Garratt AM, Ruta DA, Abdalla MI, Russell IT. SF 36 health survey questionnaire: II. Responsiveness to changes in health status in four common clinical conditions. *Quality in health care : QHC*. 1994;3(4):186-192. doi:10.1136/qshc.3.4.186
19. Oyedeji CI, Hall K, Luciano A, Morey MC, Strouse JJ. Geriatric assessment for older adults with sickle cell disease: protocol for a prospective cohort pilot study. *Pilot Feasibility Stud*. 2020;6:131. doi:10.1186/s40814-020-00673-3
20. Albuquerque MR, Lopes MC, de Paula JJ, Faria LO, Pereira ET, da Costa VT. Cross-Cultural Adaptation and Validation of the MPAM-R to Brazilian Portuguese and Proposal of a New Method to Calculate Factor Scores. *Front Psychol*. 2017;8:261. doi:10.3389/fpsyg.2017.00261
21. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. *Qual Health Res*. Nov 2005;15(9):1277-88. doi:10.1177/1049732305276687
22. Elo S, Kyngäs H. The qualitative content analysis process. *J Adv Nurs*. 2008;62(1):107-115. doi:https://doi.org/10.1111/j.1365-2648.2007.04569.x