Strong Evidence: Randomized Digitally Delivered Fall-Prevention Exercise Trial in Older Adults

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STRONG EVIDENCE

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Strong Evidence

Study Description: We have successfully completed a pilot project focused on feasibility and user acceptability of a digitally delivered program for fall prevention in older adults. It was well received among our population of lower and moderate risk individuals. We propose to extend this research by repeating the training program with the inclusion of a wait list control group.

Group A (immediate intervention) will start their initial 12 week exercise program (**Intensive Exercise)** within 4 weeks of baseline (BL) measurement (as a cohort). This will be followed by an optional additional 12 week exercise program (**Maintenance Exercise 2)** that participants who complete at least 10 of the Exercise 1 classes will be invited to join. This will be followed by a 12 week wash out period. Measurements will occur each 12 weeks (BL, 12 wk post randomization, 24 wk post randomization, 36 wk post randomization)

Group B (waitlist control) will start with a 12 week life as normal period that is concurrent with Group A's intensive Exercise. They will start Intensive Exercise when Group A is doing Maintenance exercise. They will be invited to Maintenance Exercise while Group A is doing washout. They will not have a washout period. Measurements will occur at the same period(s) as Group A (i.e. all participants measured during the same time period).

The intervention will be identical to what was offered in the past, and measurements will be very similar (removing those that did not show change with intervention or were deemed too difficult for participants).

Objectives:

Primary Objectives:

1) Reduce fall risk in both moderate and low risk populations using a digitally delivered exercise intervention.
2) Compare intervention data with a wait list control to determine intervention effectiveness
3) Measure peripheral blood mononuclear cells (PBMCs) based autophagy flux in older adults and relate these values to established measures of body composition and physical function, including fitness, balance, gait speed, posture, strength.

Secondary Objectives:

1) Determine the associations between changes in measures of body composition and physical function and changes in autophagy flux. functional maeasues

2) Determine the associations/reliability of zoom based measurements of common physiological field tests delivered via zoom to those delivered in person.
3) To evaluate an ongoing, pooled cohort of the *Strong Foundations* digitally-delivered program extended beyond the initial 12 week onboarding, with reduced individualized coaching for an additional 12 week, weekly program, and to assess programmatic feasibility, acceptability, and changes in measures of physical function.

Endpoints:

Primary Endpoint:

1) Balance and fall risk: This will be measured in-person using a variety of commonly deployed assessments of balance and physical function.
2) Posture: This will be measured in-person using both prone and standing measures of posture
3) Body composition utilizing Bioelectrical Impedience
4) Strength: Measured by grip strength and 30 second chair stand for upper and lower body respectively.
5) Cellular Autophagy measured in PBMC

Secondary Endpoints:

1) Usability/Acceptability of exercise classes delivered via a digital format will be assessed using a questionnaire that uses the System Usability Scale (SUS).
2) Attendance at exercise sessions.

Study Population:

Older adults with low to moderate risk of falling.
We will extend our earlier research using a digitally delivered fall-prevention exercise program (IRB 202026 and 806696) by engaging 1) two cohorts of up to 15 individuals each at low to moderate risk of falls and 2) two additional cohorts, of up to 15 individuals who will serve as a wait list control and will start their intervention 12 weeks after the initial groups.

Phase:

1/2

Description of Sites/Facilities Enrolling Participants:

The Exercise and Physical Activity Resource Center (EPARC) is a fully operating exercise physiology laboratory within the Herbert Wertheim School of Public Health.

Description of Study Intervention:

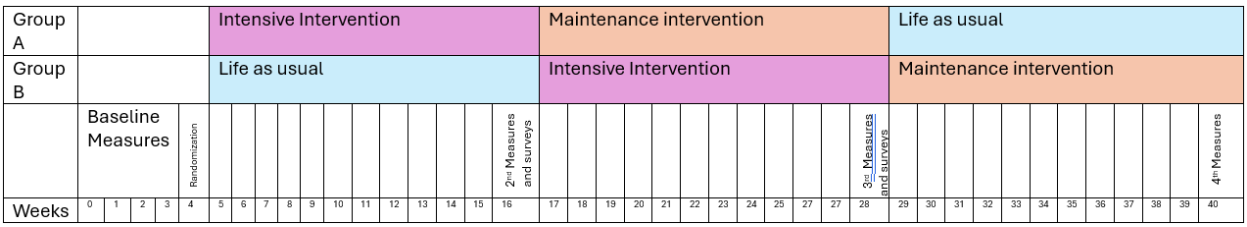
Our fall- risk reduction program, *Strong Foundations,* was designed to be delivered digitally, and while there are many such programs currently available on the Internet, especially in the time of COVID-19, the novel feature of this program is the delivery of *semi-individualized* instruction in *real* time within a small group setting.
The program was designed with physician input and by exercise physiologists and a Doctor of Physical Therapy candidate, all with extensive training in both group and individualized exercise for geriatric populations.

Strong Foundations is a 12 week iterative curricular program with three core components: *postural alignment and control, balance and mobility,* and *muscular strength and power.* All the exercises offered over the course of the intervention are appropriate for the target population and are standardized so all participants receive the same basic instruction, but level of difficulty is scaled to participant experience, capability, and musculoskeletal limitations.

Study Duration: 1 year

Participant Duration: 36-40 weeks deponding upon when basline measurement is completed

1.2 SCHEMA –FIGURE 1



1.3 SCHEDULE OF ACTIVITIES (SOA)

NOTE: All of these measures will be done at all (n=4) timepoints.

The prescreening questionnaire (by phone or in person) and consent process are not documented here but will occur prior to the completion of assessment and/or intervention.

Measurements are listed in more detail below.
Measurements listed as “lab-based” will be completed in person at baseline, 12 weeks post randomization, 24 weeks post randomization, and 36 weeks post randomization.

Lab based assessments will precede zoom based assessments by 1-3 days. We will have a two week buffer period around the measurement times (16, 28, 40 weeks) shown below to accommodate participant scheduling needs.

All baseline measures will be completed no more than 4 weeks before randomization.

Table 1: Assessments/Measures Collected:

Timepoints: Baseline, 12, 24 and 36 weeks post randomization.

Measures	Domain and Participant Position	Description	Lab-based	Zoom-based
Short Physical Performance Battery (SPPB)	Strength / Balance; Standing	4-part validated scale for fall risk	Yes	No
Timed Up and Go (TUG)	Fall Risk; Standing	Standardized assessment of functional mobility	*Yes*	Yes
Better Balance Testing	Balance; Standing	Measure of proprioceptive and vestibular function utilizing computerized dynamic posturography	Yes	No
25 foot walk	Fall Risk; Standing	Standardized assessment of gait speed and variability associated with fall risk	Yes	No
2.5 minute walk test	Endurance, strength	Standardized 2.5 minute timed distance walk with indirect calorimetry measurements	Yes	No
Grip Strength	Strength; Standing	Standardized assessment of grip strength, which has good correlation with strength across all muscle groups	Yes	No

30 Second Chair Stands	Strength; Standing	Common field measure of muscular strength and endurance of the legs	Yes	Yes
Occipital to Wall Distance	Posture; standing	Measurement of kyphotic curvature of the spine.	Yes	No
Block Measurement	Posture; Supine	Measurement of kyphotic curvature of the spine.	Yes	No
Kyphometer and Flexiruler measurements	Posture; standing	Measurement of kyphotic curvature of the spine.	Yes	No
Multiple measures of height	Posture; standing	Measurement of height while standing normally vs. standing 'as tall as possible'. Indicative of non-specific postural deficiencies.	Yes	No
Bio-Electrical Impedience Scale	Body Composition	Non-Invasive measure of body fat, muscle, and bone	Yes	No
(Optional) Blood Draw	Autophagy	See description below. 9 mL of fasting blood	Yes	No

		drawn via venipuncture.		

Additional Activities after the intense and maintenance intervention periods

Following the end of both the intense and maintenance intervention periods, participants will be asked to complete the survey titled "Strong Evidence_SUS and follow up questions" via redcap. In the event that participants are unable or unwilling to complete the survey via email they will be mailed (and asked to return) a paper copy with a preaddressed stamped envelope. We envision that this survey will be sent within 3 days of completing the intervention.

Additional Collection of Falls Information

Finally, follow-up falls information will be gathered for up to 12 months after completion of the intervention. Participants will be contacted at the beginning of each calendar month to inquire if they have had any falls in the previous month, and if yes, were there any injuries. These communications will occur by email if participants are able, and if not, by pre-stamped postcard or phone calls.

2 INTRODUCTION

2.1 STUDY RATIONALE

Falls represent a significant cause of preventable injury, contributing to premature mortality and morbidity. Fall related injuries are the major cause of accidental death and disability among older adults. Approximately one-quarter of community-residing men and women ≥65 years of age, and almost half of those over age 80, fall annually[1]. Alarmingly, the rate of fall-related mortality has increased over 30% just between 2007 and 2016.[2] In San Diego County, falls remain the second most common cause of accidental deaths, with the age adjusted rate of mortality, emergency room discharge, and inpatient admission per 100,000 at 9.18, 1,939, and 336, respectively, in 2017. Moreover, these numbers have all increased or remained steady from the preceding 5 years[3].

COVID-19 has confounded social isolation in older adults, especially those in congregate settings. Appropriate technology/technologic driven approaches has promise (but limitations) to mitigate some aspects of loneliness/isolation in this population.[16] Digitally delivered programs are an opportunity that help balance risks and benefits during times of social distancing, improve dissemination, and possibly improve objective measures of function.[17] Therefore, approaches to improve access to fall-risk reduction exercise, including balance and strength training opportunities is imperatively important, and growing data suggests digitally formatted delivery may be feasible[18].

Additionally, aging is accompanied by progressive loss of physiological reserve, leading to frailty, functional decline, and increased risk of falls, the leading cause of injury and loss of independence in older adults. At the cellular level, aging is marked by accumulation of damaged proteins and organelles, reflecting a decline in homeostatic mechanisms such as autophagy, a conservation oriented recycling pathway. Autophagy is essential for maintaining proteostasis and cellular quality control. Evidence from model organisms, such as mice, *Drosophila* and *C. elegans*, and post-mortem human tissues indicates that autophagy declines with age, and interventions that restore it improve healthspan and lifespan[79]. Despite its central role in aging biology, the relevance of autophagy to human health and resilience has been difficult to establish, largely because of the absence of reliable biomarkers. Recently, assays of autophagy flux in peripheral blood mononuclear cells (PBMCs) have been developed, enabling minimally invasive, reproducible measurement of this process in human cohorts. While these methods provide an

unprecedented window into peripheral autophagy dynamics, it remains unclear to what extent PBMC flux reflects organismal fitness, systemic resilience, or autophagy status in other tissues, particularly in humans. This interventional study provides an excellent opportunity to gather low-risk/high-yield data regarding links between PBMC-based assays of autophagy with functional outcomes in older adults. Establishing PBMC autophagy flux as a biomarker of resilience in this context would address a major translational gap, bridging basic mechanisms of aging biology with functional outcomes of intervention and help guide strategies to maintain health and independence in older adults.

Data from Strong Foundations 2.0 (IRB # 806696) was very promising. However, it was determined that possible conclusions would be strengthened by inclusion of a control group. Given the challenge of having individuals come for 4 measurment visits without a desirable intervention we felt that a wait list control was best.

As such individuals will be randomized by cohort into either

- Group A: who will start their 12 week exercise program with the intensive Intervention within 4 weeks of baseline measurement. For those who qualify (see below) this will be followed by a 12 week maintenance program. This group will finish the program with 12 weeks life as usual.
- Broup B: who willl have a 12 week lead in period of life as usual. They will then begin their 12 week intensive intervention. Those who qualify, this will be followed by a 12 week maintenance program.

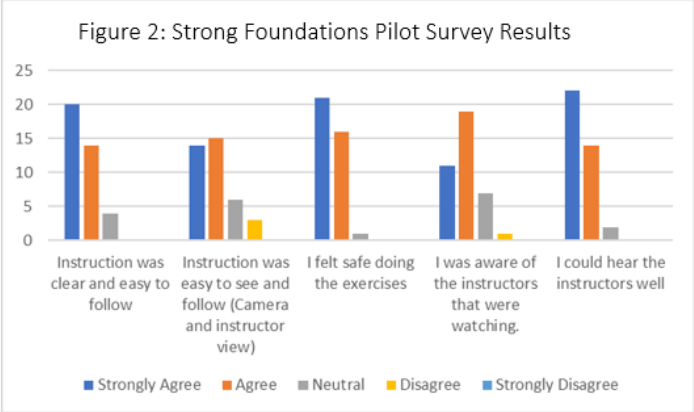
2.2 BACKGROUND

While fall risk is multifactorial, identification of risk factors and referral to/participation in appropriate fall-risk reduction programs are established as an effective, evidenced-based approach to reduce fall-risk[4]. Specifically, targeted strength and balance exercise have consistently been shown to improve fall risk, and accordingly, the Centers for Disease Control and Prevention (CDC) has outlined an evidenced-based *clinical* approach to identify those at risk for falls to help assess known risk factors and to refer for community-based fall-prevention programs[5,6]. This toolkit, however, has been slow to penetrate in routine clinical practice, as barriers reported by physicians to implementing comprehensive falls-prevention screening are time constraints, poor reimbursement for falls screening, and that existing toolkit utilization does not easily fit into a Medicare wellness visit[7]. Because of this, only approximately one-third of older adults report being asked about fall-risk, and similarly only around a third of those who fall report discussing this with their healthcare provider.[8,9] Compounding this, COVID-19 has created uncertainty in accessing community resources, increased sedentary behavior, isolation and subsequent fall risk[10]. This is especially disconcerting as a single fall predicts recurrent falls: between 10% and 44% of elderly patients with a history of falls will sustain additional falls.[11–15]

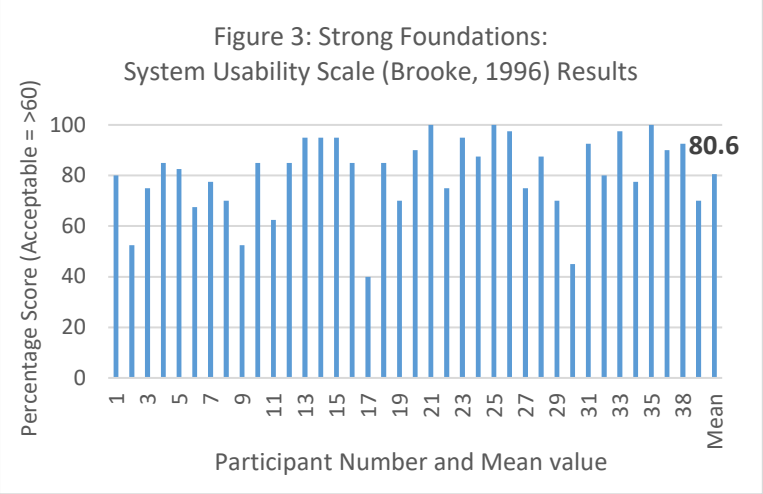
COVID-19 has confounded social isolation in older adults, especially those in congregate settings. Appropriate technology/technologic driven approaches has promise (but limitations) to mitigate some aspects of loneliness/isolation in this population.[16] Digitally delivered programs are an opportunity that help balance risks and benefits during times of social distancing, improve dissemination, and possibly improve objective measures of function.[17] Therefore, approaches to improve access to fall-risk

reduction exercise, including balance and strength training opportunities is imperatively important, and growing data suggests digitally formatted delivery may be feasible[18].

This project also offers the potential to expand our knowledge regarding successful aging using the basic sciences. Specifically, autophagy is the process by which the body packages and recycles damaged proteins and organelles making it essential for maintaining proteostasis and cellular quality control. Autophagy is a dynamic, multi-step process, and static measurements (e.g., LC3 protein levels) are insufficient to distinguish increased flux from impaired degradation. Recently, assays of autophagy flux in peripheral blood mononuclear cells (PBMCs) have been developed, enabling minimally invasive, reproducible measurement of this process in human cohorts, but there has currently been limited application to human models. Thus, this project creates a unique opportunity to begin linking autophagy biology with functional outcomes in older adults. Even more meaningfully, autophagy flux in PBMCs has not yet been assessed after any form of exercise, despite its known impact of functional outcomes and resilience. Establishing PBMC autophagy flux as a biomarker of resilience in this context would address a major translational gap, bridging basic mechanisms of aging biology with functional outcomes of intervention and help guide strategies to maintain health and independence in older adults.



Fall Prevention Program: Our fall- risk reduction program, *Strong Foundations,* was designed to be delivered digitally, and while there are many such programs currently available on the internet, especially in the time of COVID-19, the novel feature of this program is the delivery of *semi-individualized* instruction in *real* time within a small group setting. This is accomplished largely by use of the 'breakout room' feature on the Zoom platform, where 2-3 trained intern instructors correct form while the lead instructor teaches the larger group. The program was designed with physician input and by exercise physiologists and a Doctor of Physical Therapy candidate, all with extensive training in both group and individualized exercise for geriatric populations. *Strong Foundations* is a 12 week iterative curricular program with three core components: *postural alignment and control, balance and mobility,* and *muscular strength and power.* All the exercises offered over the course of the intervention are appropriate for the target population and are standardized so all participants receive the same basic instruction, but level of difficulty is scaled to participant experience, capability, and musculoskeletal limitations.



While many exercise interventions for fall prevention have been validated in different populations, our program is designed with the community in mind and with a novel platform to improve dissemination/availability across many populations.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The potential risks associated with study participation are deemed by the research team to be no greater than minimal. Risks will be mitigated as part of this study by only inviting participants not at elevated risk based on clinically available screening for falls. Because activities aim to address balance, strength, and posture, many of these activities potentially predispose individuals to injury or fall potential; therefore, we have included many mechanisms to safeguard against injury throughout this pilot as described below. See below in section 8.3.3.2 for additional details regarding risk assessment/mitigation.

Potential risks include:

1. Adverse effect of an injury during objective, lab collected or digitally collected measures of fall risk. We will have supervision throughout all lab measures, and EPARC has an excellent precedent of being able to conduct these measures in high(er) risk individuals without injury. For digitally collected measures, as described above, we have identified only measures which are relatively safe to do by video, and will be directly supervised throughout the collection process, including safeguarding for the individual to be able to necessary measures before starting (eg. if there is a perceived lack of space, the instructor will assure the area is cleared of clutter before starting).
2. Adverse effect of a potential fall during a group exercise class. Participants will be invited only if clinically assessed as not elevated risk. Class sizes will be kept to 10-15, which is thought to be appropriately sized for monitoring both the in-person and by electronic interface.
3. The participant may experience a musculoskeletal injury, or muscle fatigue and soreness due to the assessments of strength or from the exercises performed in the class.
4. There is a small risk of cardiovascular event during in-lab testing, although the assessments are at an intensity of sufficiently low level that this is very unlikely.
5. There is a small risk of cardiovascular event during at home training, although, because the focus of the training is not on cardiovascular development, the intensity will be kept very low, so the likelihood of cardiovascular injury is very low.

6. Body composition measured by BIA passes a weak electrical current through the body which could interfere with and cause the malfunction of electrical medical implants. To ensure that we do not assess people who could be harmed we have included individuals with electrical medical implants in our exclusion criteria.
7. The specific risk associated with the autophagy assays to be employed in this study is based on the drawing of blood. As with all blood draws, participants may experience temporary pain, bruising, bleeding and a small risk of infection or fainting or dizziness during the collection process. Only trained staff will be responsible for the collection of blood samples.
8. Data compromise risk: clinical data without identifiers will be collected as part of this study. We will be video recording the instructor during classes. This will ensure that participant's images are not included but if they speak during the exercise session their voices will be captured.

   A. While personal information will not be shared, it will occasionally be possible for participants to view each other during the exercise sessions. This risk is no larger than if participants were completing group exercise in person at an exercise training facility.

   B. Exercise sessions will be recorded to provide in-home practice opportunities to participants between classes. The "spotlight" feature will be used to ensure that only the demonstrating instructor is seen during the class period. However, if participants speak during the recorded portion of the session their voice will be captured.

   Additional data protections are detailed in Section 10 of this protocol.

2.3.2 KNOWN POTENTIAL BENEFITS

For the individual participant, potential benefits include increased awareness of fall risk. Further, individuals enrolled in exercise training may enhance their cardiovascular fitness, strengthen their muscles, improve balance and posture and/or reduce their fall risk.

Benefits to the academic community include understanding the barriers and limitations, and benefits of digitally delivered exercise vs in person fall-prevention program, and the reception of these programs in a community setting. Additionally, establishing the utility of PBMC autophagy flux as a biomarker of resilience and functional capability in an older adult population will address a major translational gap, bridging basic mechanisms of aging biology with functional outcomes of intervention and help guide strategies to maintain health and independence in older adults.

While there are no known direct benefits to society, integrating *Strong Foundations* program and evaluating which modality is most effective and useful will be important to numerous stakeholders—namely residence facilities and other similar community-based organizations. As falls are increasing, and COVID-19 has presented increased uncertainty, there remains great importance to better understand mechanisms to provide scalable services to those with risk factors safely in a feasible, appropriate, participant-focused manner

In addition, this program serves to potentially indirectly benefit society by introducing a larger awareness of falls prevention.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The risks described above are inherent to an exercise program delivered via digital means. The main risks (falling, musculoskeletal injury) have been minimized with the design of the program and will continue to be minimized by using appropriately trained and certified staff members.

Risks will be managed as follows (in order of risks presented above):

1) All electronic data and statistical analysis will be performed on a secured password protected computer with only study-identified potential users.
2) Surveys will be kept either in electronic form as part of participants' electronic medical record, or will be performed by phone or mail and stored/collected in a locked facility, recorded as above, and discarded/shredded as PHI is discarded in customary/usual practice.
    a. Participants will be allowed to skip any questions that they are uncomfortable answering.
3) Assessments will be conducted by specially trained individuals and overseen by a licensed clinical exercise physiologist. Our research unit has established standard operating procedures for these assessments and have successfully gathered data from thousands of participants without significant injury.
4) Zoom based exercise classes will be monitored by certified and experienced personal trainers or senior research staff with extensive experience in exercise prescription and group-exercise instruction among geriatric populations. These individuals are specifically trained to identify fatigue and instability likely to contribute to a fall. Further, all classes will include cueing to utilize balance assistance (chair and/or wall) during exercise to minimize fall risk.
5) Classes are designed to be progressive and participants will carefully monitored by licensed personal trainers to ensure that proper form and progressions are followed to minimize risk of musculoskeletal injury or soreness.
6) Participants will be excluded if they have a non-removable implanted electrical device (pacemaker, cochlear implant, etc.)
7) Only trained phlebotomists will draw blood.
8) To prevent the loss of confidentiality, we will use our best efforts to keep participant information secure. Participants will be assigned an identification number, which will be used for data analysis purposes. The Project Manager will have a link between the subject number and the subject's name. This information will be locked in a filing cabinet in the Project Manager's office. All data that are securely downloaded during data collection procedures will be de-identified and stored on secure, password-protected servers.

A. We will utilize the "spotlight" option in zoom to ensure that the participant's view is of the demonstrating instructor.

B. We will preview all recording prior to sharing to ensure that no participant images are captured (videos will be edited to remove participants in the event that they are inadvertently recorded).

We do not believe that the risks outweigh the potential benefit to individual participants in terms of reduced fall risk and do believe that the potential benefits of "in-person" digital design outweigh the (minimal) risks that this modality imposes.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To measure and compare objective measures of physical function related to fall- and fracture-risk in older adults at low to moderate risk of falls between the intervention and wait list control.	**Balance/Fall Risk:** This will be measured in-person using a variety of commonly deployed assessments of balance and physical function. These include the Short Physical Performance Battery (SPPB), Better Balance Test, the Timed up-and-Go (TUG), and measures of gait speed during a 25 foot walk completed both as fast as possible, and at normal walking speed. **Muscular Strength:** Strength will be measured both in person and digitally using commonly deployed field measures (30 second chair stands). We will also be completing additional in-lab only measures of strength via grip strength **Spinal Posture:** Good posture is important to reducing the risk of vertebral fractures and has been identified as a potential locus of intervention for fracture prevention[33]. We propose to measure posture using a variety of measures that can be easily integrated into clinical practice (occipital to wall distance and standing height), as well as those that require a higher level of expertise (standing measures of postural tilt, and standing and lying measures of kyphosis.) Body Composition: This will be measured using a completely non-invasive tool called BioElectrical Impedience Analsysis (BIA) which provides well validated data regarding the absolute amount of	All of the balance/muscular strength/postural measures chosen are commonly used to assess fall risk, muscular strength, and postural control and were specifically chosen as being appropriate for this population. Measures of body composition will provide data regarding frailty and relative risk for negative health outcomes. Follow up questionnaires will allow us to determine if individuals who have participated in this program fall less and/or have less injurious falls than an age-matched epidemiologically drawn sample (i.e. prevalence rates reported for national samples).

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	an individual's fat, muscle, and bone. Ongoing questionnaires about falls for up to 1 year following the intervention.	
Identify and quantify associations between cellular autophaghy and outcomes related to body composition and functional capabilities	All of the above and **(optional)** blood draw	Establishing PBMC autophagy flux as a biomarker of resilience in this context would address a major translational gap, bridging basic mechanisms of aging biology with functional outcomes.
Secondary		
To compare objective measures of fall-risk, including balance, and muscular strength, assessed digitally vs. in-person.	Test/retest from an in-lab to a digital (zoom) environment for a limited number of the physical assessments to determine the validity and repeatability of these assessments in a zoom based environment.	These were chosen based on being appropriate to being safely assessed in a zoom based testing environment/
To determine feasibility and participant acceptance of deploying this digitally-delivered program.	System Usability Scale[22] (SUS). The SUS is a nonpriority validated questionnaire designed to understand the ease of use of new systems or programs using a 5 element Likert scale. This questionnaire includes the 10 questions typically included in a SUS, 8 questions designed to assess the patient experience in the program and 2 questions assessing falls in the recent past.	The SUS is a commonly used assessment tool to determine the ease of using new systems or programs and is commonly used to assess digital programs/tools.
Tertiary/Exploratory		
To evaluate an ongoing, pooled cohort of the Strong Foundations digitally-delivered program extended beyond the initial 12 week onboarding, with reduced individualized coaching for an additional 12 week, weekly program, and to assess	Attendance	This is, we believe, the best determination of the likelihood for ongoing engagement and exercise intervention compliance.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
programmatic feasibility, acceptability, and changes in measures of physical function.		

4 STUDY DESIGN

4.1 OVERALL DESIGN

We hypothesize that using a novel exercise program that is delivered digitally with real time instruction and direct coaching we will be able to reduce objective measures of fall risk, will improve muscular strength, and will improve posture.

This trial is between phase 1 and 2 and will be a randomized intervention with a wait list control group. We do not believe that there will be substantial bias as part of this trial, and will ensure that measurement staff are blinded to the randomization group of all participants. We will also ensure that all measurement staff are specifically trained in the assessments they are completing.

This is a single site study conducted by the Exercise and Physical Activity Resource Center (EPARC) and is entitled **Strong Evidence**.
We will be extending our earlier research using a digitally delivered fall-prevention exercise program (IRB 202026 and 806696). Data from Strong Foundations 2.0 (IRB # 806696) was very promising. However, it was determined that possible conclusions would be strengthened by inclusion of a control group. Given the challenge of having individuals come for 3 to 4 measurement visits without a desirable intervention we felt that a wait list control was best.
With this in mind, we will be engaging 1) two cohorts of up to 15 individuals each at low to moderate risk of falls and 2) two additional cohorts, of up to 15 individuals each at low to moderate risk of falls who will serve as a wait list control and will start the intensive intervention 12 weeks after their matched/randomized group .

As such individuals will be randomized by cohort into either

- Group A: who will start their 12-week exercise program with the Intensive Intervention within 4 weeks of baseline measurement. For those who qualify (see below) this will be followed by a 12-week maintenance program. This group will finish the program with 12 weeks life as usual.
- Broup B: who willl have a 12 week lead in period of life as usual. They will then begin their 12-week intensive intervention. Those who qualify, this will be followed by a 12-week maintenance program.

For all cohorts enrolled, we aim to gather up to 4 lab-based measurement visits to assess physical function:
(1) at baseline,
(2) following the initial 12 weeks during which Group A will have received the intense intervention and Group B will have continued life as usual (e.g., 12 weeks post randomization),
(3) after an additional 12 weeks (e.g. 24 weeks post randomization) after the completion of the intense intervention for Group B and the end of the maintenance intervention for Group A, and
(4) a final time 12 weeks later (e.g. 36 weeks post randomization) when Group A has had a 12 week life as usual “washout” period and Group B has completed the maintenance intervention.

This is summarized in our schema section, and the specifics of what is performed via Zoom or in-lab are outlined in Table 1.

Briefly, all participants will have some measures collected both in person (at EPARC) and by Zoom. Specifically, the TUG and 30-second chair rise will be gathered digially within three days of the in-person measurements. These assessments are believed to be appropriate and safe for participant's to be able to complete at home. They are being gathered in support of answering the questions of the secondary aims (i.e. to test digital vs. in-person measurement for accuracy and precision). With this in mind, lab-based collection will also occur.

In the lab, additional measures as outlined in Table 1 and below will be collected to perform deep phenotyping of balance, strength and posture, and (**optionally)** markers of autophagy gathered via traditional venipuncture blood draw. These will include (in addition to the two measures listed above): block measurements of kyphosis, measurements of kyphosis (kyphomemeter and flexiruler), occipital to wall distance, multiple measures of height, grip strength, a 2.5 minute walk test, a 25 foot walk test, the SBBP, and Better Balance testing.

Completion of all measures will be encouraged, however, participants may opt to not perform one or more based on their discretion. In particularly, it will be made clear to participants during the initial gathering of informed consent that **the blood draw is completely optional** and not providing blood will not preclude participants from engaging in the rest of the study. In addition, the team may determine a participant unsafe or inappropriate for some measures. Please see Sections 6.4 and 7. for how this will be noted.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Falls represent a significant cause of preventable injury, contributing to premature mortality and morbidity. Fall related injuries are the major cause of accidental death and disability among older adults. Approximately one-quarter of community-residing men and women $\geq$65 years of age, and almost half of those over age 80, fall annually[1]. Alarmingly, the rate of fall-related mortality has increased over 30% just between 2007 and 2016.[2] In San Diego County, falls remain the second most common cause of accidental deaths, with the age adjusted rate of mortality, emergency room discharge, and inpatient admission per 100,000 at 9.18, 1,939, and 336, respectively, in 2017. Moreover, these numbers have all increased or remained steady from the preceding 5 years[3].

While fall risk is multifactorial, identification of risk factors and referral to/participation in appropriate fall-risk reduction programs are established as an effective, evidenced-based approach to reduce fall-risk[4]. Specifically, targeted strength and balance exercise have consistently been shown to improve fall risk, and accordingly, the Centers for Disease Control and Prevention (CDC) has outlined an evidenced-based *clinical* approach to identify those at risk for falls to help assess known risk factors and to refer for community-based fall-prevention programs[5,6]. This toolkit, however, has been slow to penetrate in routine clinical practice, as barriers reported by physicians to implementing comprehensive falls-prevention screening are time constraints, poor reimbursement for falls screening, and that existing toolkit utilization does not easily fit into a Medicare wellness visit[7]. Because of this, only approximately one-third of older adults report being asked about fall-risk, and similarly only around a third of those who fall report discussing this with their healthcare provider.[8,9] Compounding this, COVID-19 has

created uncertainty in accessing community resources, increased sedentary behavior, isolation and subsequent fall risk[10]. This is especially disconcerting as a single fall predicts recurrent falls: between 10% and 44% of elderly patients with a history of falls will sustain additional falls.[11–15]

COVID-19 has confounded social isolation in older adults, especially those in congregate settings. Appropriate technology/technologic driven approaches has promise (but limitations) to mitigate some aspects of loneliness/isolation in this population.[16] Digitally delivered programs are an opportunity that help balance risks and benefits during times of social distancing, improve dissemination, and possibly improve objective measures of function.[17] Therefore, approaches to improve access to fall-risk reduction exercise, including balance and strength training opportunities is imperatively important, and growing data suggests digitally formatted delivery may be feasible[18].

Autophagy is a conserved, multi-step pathway that maintains proteostasis and organelle integrity by degrading and recycling cytoplasmic components. It is dynamically regulated by stressors such as nutrient deprivation and exercise, and its dysregulation has been implicated in aging and numerous age-related diseases (REF). Yet, its role in human aging remains unclear. Progress has been limited by methodological barriers: most approaches provide static snapshots that cannot distinguish between active flux and impaired degradation, leaving a fundamental gap in our ability to study autophagy dynamics in humans1.

We recently optimized an ex vivo PBMC autophagy flux assay using chloroquine-mediated lysosomal inhibition2. Applying this assay to participants from the San Diego Nathan Shock Center Healthy Aging Cohort (SHOCK), we found that PBMC autophagy flux does not decline uniformly with age. Rather, flux becomes more heterogeneous across individuals, and may even trend upward with advancing age. In older adults, higher flux correlated with reduced VO_2max, suggesting that elevated peripheral autophagy flux may reflect physiological stress or diminished resilience rather than improved function. To extend these observations, we examined older adults enrolled in the Strong Foundations 2.0 and 2.5 (STRONG) digital fall-prevention programs. At baseline, STRONG participants had higher PBMC autophagy flux than the SHOCK cohort; after 12 weeks of balance- and strength-focused training, flux decreased to SHOCK baseline levels and coincided with improvements in mobility and function. Although limited by small sample size and short follow-up, these preliminary data raise the novel possibility that PBMC autophagy flux is a modifiable biomarker of intervention response in humans.

Fall Prevention Program: As noted above (Background, see Figures 2 and 3), our fall- risk reduction program, *Strong Foundations* was designed to be delivered digitally, and while there are many such programs currently available on the internet, especially in the time of COVID-19, the novel feature of this program is the delivery of *semi-individualized* instruction in *real* time within a small group setting. This is accomplished largely by use of the 'breakout room' feature on the Zoom platform, where 2-3 trained intern instructors correct form while the lead instructor teaches the larger group. The program was designed with physician input and by exercise physiologists and a Doctor of Physical Therapy candidate, all with extensive training in both group and individualized exercise for geriatric populations. *Strong Foundations* is a 12 week iterative curricular program with three core components: *postural alignment and control, balance and mobility,* and *muscular strength and power.* All the exercises

offered over the course of the intervention are appropriate for the target population and are standardized so all participants receive the same basic instruction, but level of difficulty is scaled to participant experience, capability, and musculoskeletal limitations.

While many exercise interventions for fall prevention have been validated in different populations, our program is designed with the community in mind and with a novel platform to improve dissemination/availability across many populations. Our program content is drawn from several rigorously tested fall/fracture prevention exercise programs,[4,19–21] which we have tested in a pilot trial described below:

4.3 JUSTIFICATION FOR DOSE

This is a relatively standard dose for an exercise intervention in this population.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including responding to follow up queries regarding falls for up to 1 year following the final measurement visit.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Screening and Enrollment:

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Has the capacity to provide informed consent
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Age 60 or older, ambulatory, including with the use of a cane or walker, and able to read and speak English.
4. Completion of the STEADI *Stay Independent Risk for Falling Questionnaire* (uploaded as Supporting materials),
    a. A score of 7 or greater will make a participant ineligible for this study (see below).
5. Access to internet/computer and Zoom-interface / broadband with a device with a minimum screen size of 7 inches (i.e. tablet or larger).

Older adults will be recruited in blocks of up to 30 (minimum 24) to form cohorts of 12-15 that will be randomized to either Group A or Group B as described in the randomization section. These individuals will be contacted via outreach to the UCSD Bone Health Interest Group, via communication with volunteers associated with the UCSD Bone Densitometry Training Program who have expressed an interest in being part of reseach studies, via the list of previous participants and patients who have

indicated that they are willing to be contacted regarding research opportunities maintained by EPARC, and via referral from the UCSD Osteoporosis Clinic and associated physicians, and from the Internal Medicine practice Fall Prevention Shared Medical Appointment.In all cases, individuals will be provided information via flyers. This will be distributed via email for those on interest lists, and with physical flyers for those associated with programs that conduct in-person meetings (i.e. Bone Health Interest Group, physicians, etc.). Only participants who initiate further contact by reaching out via phone or email will be screened/recruited.

All participants who express interest will be contacted by study personnel to be screened for eligibility by phone or in person (if applicable); those who meet the eligibility requirements will be invited to participate.

Potential participants will be scheduled to attend the first study visit and will be emailed a copy of the informed consent document to review. Informed consent will be conducted either in-person at Visit 1 or remotely face-to-face using a UC Health-encrypted Zoom appointment one to six days prior to Visit 1. Selection of digital vs in-person consent will be based on the logistics and participant preference (asked during initial phone discussion for eligibility). If a participant does not feel comfortable consenting remotely/digitally, they will be met at the initial visit to review consent in person. During the informed consent process, regardless of if it is completed remotely or in person, trained EPARC staff will review the study's purpose and procedures, answer any questions, confirm the study inclusion and exclusion criteria. Regardless of the manner in which consent was presented, written consent will be gathered at the first visit. In the event that participants received digital/zoom based familiarization with the consent document they will be asked if they have any questions and additional discussion, review, and answers will be available as needed.

5.2 EXCLUSION CRITERIA

Additional screening criteria:

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Individuals who are wheel-chair bound
2. Score 7 or more on the STEADI Risk for Falling questionnaire.
3. Individuals who have non removable (i.e. implanted) electrically driven medical implants (pacemakers, cochlear implants, etc)

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to

meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

We do not expect to have a substantial number of screen failures, as the inclusion criteria are straight forward and do not require confirmatory testing.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Fall Prevention Program: Our fall- risk reduction program, *Strong Foundations* was designed to be delivered digitally, and while there are many such programs currently available on the internet, especially in the time of COVID-19, the novel feature of this program is the delivery of *semi-individualized* instruction in *real* time within a small group setting. This is accomplished largely by use of the 'breakout room' feature on the Zoom platform, where 2-3 trained intern instructors correct form while the lead instructor teaches the larger group. The program was designed with physician input and by exercise physiologists and a Doctor of Physical Therapy candidate, all with extensive training in both group and individualized exercise for geriatric populations.

Strong Foundations is a **12 week iterative curricular program** with three core components: *postural alignment and control, balance and mobility,* and *muscular strength and power.* All the exercises offered over the course of the intervention are appropriate for the target population and are standardized so all participants receive the same basic instruction, but level of difficulty is scaled to participant experience, capability, and musculoskeletal limitations.

For this project we will be delivering the well-received Strong Foundations program—denoted here as **intensive intervention--**and following with a maintenance intervention of **an additional 12 classes** for individuals who attend at least 10 classes during the intensive period. Thus, all participants will be be able to attend 12 classes, and some will be able to attend a total of 24.

All classes will be delivered remotely. The substantive difference between the intensive (initial 12 weeks) and maintenance (following 12 weeks) interventions is that the maintenance intervention will have less personalized guidance and feedback.

6.1.2 DOSING AND ADMINISTRATION

There are a total of 12 classes in the intensive intervention that all participants will be eligible to receive.
There are a total of 12 classes in the maintenance intervention that only participants who complete at least 10 classes in the intensive intervention will be invited to receive.
Thus, a participant could receive a maximum of 24 classes.

Class times will be determined during the recruitment phase based upon the availability of instructors and preferred times of participants.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Not applicable

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Not applicable

6.2.3 PRODUCT STORAGE AND STABILITY

Not applicable

6.2.4 PREPARATION

Not applicable

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

We will be using a random generator to provide a binary choice (1=Group A, 2=Group B) in blocks of 30. We will be recruiting and consenting up to 30 people within 4 weeks, and at the end of that period revealing the group allocation. Participants will be provided the group allocation based on the order in which they are consented (i.e. first person consented receives first randomization slot). In the event that less than 30 people are consented in the requisite four weeks, or some participants choose not to continue following consent, we will allow unequal class/group sizes.
All measurement staff will be blinded to randomization group at all measurement timepoints.
Not applicable

6.4 STUDY INTERVENTION COMPLIANCE

Attendance will be taken at each class; additionally, those unable or unwilling to complete some measures (physical, internet-based, lab, or questionnaire) will be noted in data collection without identifiers.

6.5 CONCOMITANT THERAPY

Not applicable

6.5.1 RESCUE MEDICINE

Not applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Rudeness or disruptive behavior during instruction
- Inability or unwillingness to follow exercise recommendations regarding safety
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to attend a minimum of 6 of the Strong Evidence classes

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from The Strong Foundations 2.0 intervention does not mean discontinuation from the study, and remaining study assessment procedures should be completed as indicated by the study protocol.
If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include all scheduled follow up measures.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

The reason for participant discontinuation or withdrawal from the study will be recorded. Research participants who sign the informed consent form but did not attend at least one class may be replaced.

Research participants who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for more than one follow up (i.e. non baseline) scheduled visits, or is unable to be contacted by the study site staff.

The following actions will be taken if a participant fails to attend a scheduled laboratory visit or misses an exercise class without making contact prior to the date of instruction.

- The site will attempt to contact the participant and reschedule the missed visit for up to 3 weeks following the expected visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Effort to regain contact with the participant will be made using 3+ telephone calls and/or email communications. These contact attempts will be documented in the participant's study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

UCSD research staff will be gathering and holding all data for this program. All objective measures collected at EPARC will have the order of deployment randomly determined, (re)clustered by every 5 participants to account for the possible contribution of fatigue during these assessments. We anticipate the time-burden for participants in lab will last approximately 60 minutes to complete all measures (but are budgeting up to 90 minutes in the informed consent in case some individuals require additional rest time between measurements). We anticipate the digital measures as outlined below to take no more than 15 minutes and anticipate both surveys to last approximately 20 minutes. Measures below will be collected throughout the study as outlined above in our Schema.

Primary Outcomes:

1. **Balance/Fall Risk:** This will be measured in-person using a variety of commonly deployed assessments of balance and physical function. These include the Short Physical Performance Battery (SPPB), Better Balance Test, the Timed up-and-Go (TUG), and measures of gait speed during a 25 foot walk completed both as fast as possible, and at normal walking speed. Balance tasks are expected to take a total of 20 to 25 minutes.
   a) **Short Physical Performance Battery (SPPB):** The SPPB measures gait speed, leg strength (via chair stand time) and the three stage balance assessment recommended by the CDC for assessing fall risk. This composite measure includes evaluating side-by-side, semi-tandem, and tandem position, time to walk 4 meters , and time to rise from a chair and return seated five times[23].

b) **Better Balance Testing** (Balance Tracking Systems, Inc).: Better Balance testing is a standardized approach to understanding balance based on measured sway via force transducer plates which participants stand upon with their feet hip distance apart and their eyes closed. [24,25]. Specifically trained research assistants will maintain "spotting position" to ensure safety.

c) **Timed Up-and-Go:** The TUG is an easy to administer office-based assessment in which a person rises from a seated position without using their arms, walks three meters (approximately 10 feet), turns around, returns to the chair, and sits down while being timed. The TUG has been found to be reliable with good inter-rater and intra-rater reproducibility, and is a good predictor of frailty.[26] While there is some disagreement regarding its role in falls-prediction,[27–29] the CDC suggests a cutoff time of 12 seconds to discriminate fall risk.[26] This will be performed twice and the better of the two scores recorded.

d) **The 25 Foot Walk Test** is a quantitative mobility and leg function performance test in which the participant is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 feet. We will ask the participant to complete the assessment 3 times. Twice walking at a normal speed, and once walking as quickly as possible while still remaining safe. The time is calculated from the initiation of the instruction to start and ends when the patient has reached the 25-foot mark. Patients may use assistive devices when doing this task.

e) **2.5 Minute Walk:** The 2.5 minute walk test is an abbreviated test compared with the 6-minute walk, where a participant has indirect calorimetry measured as they walk comfortably around a prespecified track for 2.5 minutes; distance is measured along with measures of cardiorespiratory fitness[30].

2) **Muscular Strength:** Strength will be measured both in person and digitally using commonly deployed field measures (30 second chair stands). We will also be completing additional in-lab only measures of strength via grip strength. Strength testing is expected to take 10 minutes or less.

a) **30-Second Chair Stand:** The 30-Second Chair Stand is intended to evaluate lower body and hip flexor strength and short endurance. This assessment is easy and quick to administer, and has been shown to predict falls[31] with cut-offs that are age and gender adjusted.[32] Individuals are instructed to sit in in an arm-less chair of approximately 17" seat-height, cross their arms across the chest, keep their feet flat on the floor and back straight, and sequentially rise and sit as many times as possible within a 30-second time frame.

b) **Grip Strength:** Hand grip strength will be measured in both hands using an adjustable grip strength dynamometer that quantifies force in kilograms (BL5001 Hydraulic Hand Dynamometer). The grip bar of the instrument will be adjusted so the second joint of the fingers first snugly under the handle and the hand position will be recorded (1-5). The dynamometer will be set to zero and the participant will be given a chance to familiarize themselves with the measurement by giving a submaximal effort on both hands to feel how the instrument will react. For the assessment, the participant will stand and hold the dynamometer in their hand with their arm down at their side. The participant will be instructed to take a deep breath in, and squeeze as hard as possible as they exhale. The measurement will be repeated twice on each hand, alternating between each side, and the highest score for each hand will be recorded to the nearest kilogram.

3) **Spinal Posture:** Good posture is important to reducing the risk of vertebral fractures and has been identified as a potential locus of intervention for fracture prevention[33]. We propose to measure posture using a variety of measures that can be easily integrated into clinical practice (occipital to wall distance and standing height), as well as those that require a higher level of

expertise (standing measures of postural tilt, and standing and lying measures of kyphosis.) Postural measures are expected to take between 15 and 20 minutes.

a) **Height** will be measured with participants instructed to stand normally, and then also to stand as tall as they can with a full breath of air to assess differences in height based upon postural changes reflective of activation of core muscles.
b) **Occipital to Wall Distance (OWD)** will be measured with participants standing with their feet together and their heels and buttocks touching the wall while they look forward (or as close to the wall as possible. The distance from the wall to their occiput (back of the head) will be measured to the nearest 0.1 cm. Measurements will be taken twice, with a third measurement gathered in the event that there is greater than 0.3 cm difference between the first two measures. An average of the closest two measurements will be used for analysis. Pictures will be captured via Zoom to collect this measure.
c) **Kyphosis** will be measured using three standard procedures: 1) *Blocks method*: Participant will have 1.7cm blocks placed in sequence beneath the head while in a supine position.
    a. Blocks will continue to be added under the participants' head until their neck is observed to be in a neutral position. The number of blocks needed to obtain a neutral position will be recorded.
    b. *Debrunner kyphometer*: Participants will be required to expose their back and have a device (similar to a protractor) placed against the C2 and T12 vertebra and the angle will be recorded by a trained technician and
    c. *Flexiruler:* A flexible ruler will be molded to the mid-line of the participants back, with one end on the spine at the C7 vertebra. The molded flexiruler will be traced onto a piece of paper and a straight line between the ends of the spinal curve. Distances will then be used to calculate the index of kyphosis measurement using a well validated formula[34].
d) **Body Composition** will be measured by bioelectrical impedance analysis (BIA) using a Tanita DC-430U Dual Frequency Total Body Composition Analyzer (device manual included as attachment). This machine looks like a doctor's scale, but it also measures body composition using a weak constant current source with a high frequency current (6.25kHz, 50kHz, 90μA), which is not a significant amount of energy. The 4 electrodes are positioned so that electric current is supplied from the electrodes on the tips of the toes of both feet, and voltage is measured on the heel of both feet.
e) **Autophagy Flux** will be measured in freshly isolated human peripheral blood mononuclear cells (PBMCs). A trained phlebotomist will draw 9 mL (of fasting blood into Vacuette lithium heparin tubes using standard venipuncture. Freshly-drawn whole blood will be treated with the late-stage autophagy inhibitor chloroquine, after which peripheral blood mononuclear cells (PBMCs) will be isolated, lysed, and analyzed by Western blot. PBMC isolation, lysing, and analysis will occur either at UCSD facilities located at the Stein Institute of Aging or the Sanford Burnham Prebys laboratory.

Secondary Outcomes:

1) **Usability/Acceptability of exercise classes delivered via a digital format** will be assessed using a questionnaire that uses the System Usability Scale[22] (SUS). The SUS is a nonpriority validated

questionnaire designed to understand the ease of use of new systems or programs using a 5 element Likert scale. This questionnaire includes the 10 questions typically included in a SUS, 8 questions designed to assess the patient experience in the program and 2 questions assessing falls in the recent past. In general, scores >60 on the SUS are considered to have appropriate acceptability of a program/platform. As noted in Figure 2 above, in our initial *Strong Foundations* pilot program, approximately 90% of the respondents found the program acceptable.

2) **Attendance:** Attendance at exercise sessions will be recorded at each class and reported by cohort and by group. For the extension/pooled cohort program as described above, attendance will be monitored/recorded and compared with paired attendance rates for the same participant as part of the initial 12 week program.

For demographic purposes we will also assess the following:

Participants will be asked to complete the following self-report questionnaires regarding their medical history, current mood/emotional state, and fall-history.

a) Demographics and Medical History: This questionnaire provides an overview of an individual's education and demographic background, personal medical history, family medical history, drug/alcohol use, current and recent medications, allergies, social history, diet, and mental health.
b) Questionnaires - PROMIS-29 V.2.0 and an additional survey about experience: We will use the Health-related PROMIS scales to evaluate for social isolation, depression, emotional stress, and global perceived health,[35] as well as created questionnaires to inquire about challenges accessing the program.
c) Follow-up falls information – this will be conducted after completion of the intervention, by email if participants are able, and if not, by pre-stamped postcard or phone calls, monthly, for 12 months to follow-up and inquire a participant has had any falls.

Questionnaires*:* All questionnaires will be made available for participants to fill out either electronically or by paper, and include Medical History form for all participants, the Staying Independent Brochure at enrollment, and if enrolled, the PROMIS-29, follow-up falls questions, and SUS at program completion and at the completion of the longitudinal program. An additional questionnaire will inquire about experiences/barriers for digital grouping/participant. Thus, participants may have up to 4 surveys once enrolled, after the small cohort completion, and at the completion of this study if continued onto the pooled longitudinal cohort.

Follow-up of Outcomes: Although the study duration and the sample size do not allow for adequate evaluation of falls, it is still important to assess falls to determine trends indicative of intervention effects. Thus, falls will be collected by self-report as noted above, monthly for 12 months after participation in the class. Methods of outreach may include, telephone interview, email, or pre-stamped post-cards demarcating a fall.

Specific information collected as part of this project will include:

1. Data outlined above Cohort grouping
2. Number in cohort

3. Baseline and Change scores in objectively collected functional measures
4. Baseline and Change scores in objectively measured autophagy flux
5. Score from the System Usability Scale Questionnaire
6. Satisfaction/efficacy Questionnaire (PROMIS-29)
7. Follow-up contact about falls and if behavioral change has been sustained

8.2 SAFETY AND OTHER ASSESSMENTS

While a computer/ Zoom interface is required to participate, demographics showcase at least 70% of the larger population have access to a smartphone; thus, we do not feel having this requirement impedes a significant number of potentially interested individuals. We will track the number of individuals who are unable to enroll because of technological barriers/access to the requisite technology to determine if this affects their ability to participate.

Lab based measures will be directly observed by staff trained both in the methods for data collection (respectively listed above) and on providing input for individuals to modify or stop should they be in a situation predisposing to injury. Zoom based data collection will be directly observed by the research assistant, and in the unlikely event of an injury, we will collect a contact number and inform individuals if they're unable to verify they are ok or respond that they are ok, we will call 9-1-1 on their behalf. We will have and confirm their location addresses before all Zoom based sessions. Throughout the intervention, similar protocols will occur such that individual communication (if appropriate by Breakout room, or phone, or 9-1-1) be made to assure the safety of participants.

Blood draws will be conducted by licensed phlebotomists with experience drawing blood from older adults.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

The FDA definition of an Adverse event is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

All Adverse events (AE) based on the definition of 21 CFR 31232 (a) will be captured by study staff and reported to IRB and/or participant physician's as needed.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of

the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

SAE in the context of this intervention may include sudden death, cardiac death/cardiac event during exertion, and fall from intervention culminating with hospitalization, incapacity, or death.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

The following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".]

In the context of this intervention, either remotely or in the lab, musculoskeletal injury or a fall may occur which would be unexpected and an adverse event. In the event of this culminating with injury requiring emergency room visit, but not inpatient hospitalization, or injury sufficient for withdrawal from the study, we will consider these AE and report accordingly.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All AEs will be reviewed by the study PI and the following determination of their relationship to the study will be determined. These will be reported to the IRB and other regulatory bodies following the timelines described below.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

The potential risks associated with study participation are deemed by the research team to be no greater than minimal. Risks will be mitigated as part of this pilot by only inviting participants not at elevated risk based on clinically available screening for falls. Because activities aim to address balance, strength, and posture, many of these activities potentially predispose individuals to injury or fall potential; therefore, we have included many mechanisms to safeguard against injury throughout this pilot as described below.

Potential expected risks include:

1. Adverse effect of potential injury or fall during objective balance measurement, which are performed as part of routine clinical procedures and directly supervised by clinical staff at the time of potential enrollment;
2. Adverse effect of an injury during objective, lab collected or digitally collected measures of fall risk. We will have supervision throughout all lab measures, and EPARC has an excellent precedent of being able to conduct these measures in high(er) risk individuals without injury. For digitally collected measures, as described above, we have identified only measures which are relatively safe to do by video, and will be directly supervised throughout the collection process, including safeguarding for the individual to be able to necessary measures before starting (e.g. if there is a perceived lack of space, the instructor will assure the area is cleared of clutter before starting).
3. Adverse effect of a potential fall during a group exercise class, or any activity related to this study where there is synchronous digital connection (e.g. home-based measurement of balance/strength). At intake, all information for contacting participants in the event of a disconnection, fall, or other observed event whereby the participant is unable to safely continue in the class without notifying the study team.
    a. Information collected will include: a preferred/available phone number; a point-of-contact/next of kin preferred contact; their planned location of performing the Zoom-based intervention, including barriers to entry if applicable (e.g. in a condominium with several doors, presence of pets, etc.).
    b. Participants will be instructed that while they are participating and have their camera on, should they need to leave/depart for any reason, they must notify the instructor(s) within 5 minutes of departure. If this is not received and an injury is suspected, 9-1-1 will be called if the study team is unable to contact the participant by active means including phone, collected at enrollment. If injury is not suspected, the point of contact/next of kin will be contacted if the participant is unable to be contacted. Participants will be invited only if clinically assessed as not elevated risk. Class sizes during the intensive intervention period of instruction will be kept to 10-15, which is thought to be appropriately sized for monitoring both the in-person and by electronic interface.
    c. Classes during the maintanance intervention will focus only on exercises that have been thoroughly taught during the initial 12 intensive intervention period. While these classes will be less personalized, they will still have some direct instruction and exercises will be familiar and safe for participants.
        i. Only participants who attended at least 80% of the initial 12 week instruction period (i.e. 10+ classes) will be allowed to participate in the extended instruction.
4. The participant may experience a musculoskeletal injury, or muscle fatigue and soreness due to the assessments of strength or from the exercises performed in the class.
5. Data compromise risk: clinical data without identifiers will be collected as part of this study. We will be video recording the instructor during classes. This will ensure that participant's images are not included but if they speak during the exercise session their voices will be captured.

   A. While personal information will not be shared, it will occasionally be possible for participants to view each other during the exercise sessions. This risk is no larger than if participants were completing group exercise in person at an exercise training facility.

B. Exercise sessions will be recorded to provide in-home practice opportunities to participants between classes. The "spotlight" feature will be used to ensure that only the demonstrating instructor is seen during the class period. However, if participants speak during the recorded portion of the session their voice will be captured.

There are no other known risks associated with this study.

8.3.3.3 EXPECTEDNESS

Ryan Moran, MD, MPH (PI) will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention and study procedures.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

At the beginning of exercise classes, participants will be informally queried regarding how they are feeling (unsolicited query). In the event that a participant shares a potential AE a staff member will take them to a "breakout room" to get further information including event description, self-reported severity and time of onset. These data will be shared with the study PI who will make an additional assessment of severity, and likely relationship to study measures or intervention. Follow up will continue until resolution/stabilization of the event has occurred with ongoing documentation.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study coordinator, Dr. David Wing, or the study PI, Dr. Ryan Moran will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

SAE and AE will be reported to the PI, Ryan Moran by exercise instructors and/or clinical staff, immediately for considered SAE, and within 1 week for AE; these will be investigated within 1 week of occurrence.

8.3.5 ADVERSE EVENT REPORTING

We have no sponsors. The PI, or study team under the direction of the PI will report all AE's to the IRB and other UCSD regulatory bodies using timelines described above.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

There is no study sponsor. All AE's and other unexpected events will be reported to the IRB and UCSD regulatory bodies in a timely fashion in line with that described above.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Not applicable. We will not be informing participants of AE or SAE not related to themselves. We do not anticipate there being any new risks beyond those described above and relayed to participants during the consent process.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable given inclusion criteria.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).]

We believe that this is not applicable because this is a digitally delivered intervention using exercises and instruction that are well established for in-person participation.
In the event that there are unanticipated problems that meet the definition above we will notify all participants and the IRB, and get updated consent that includes awareness of the new problems.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) in a timely fashion using the following timing guidelines.

- UPs that are serious adverse events (SAEs) will be reported to the IRB three (3) days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and either at the time of continuing review in the event of very minor UP, or within 14 days for UPs which may have involve increased risk across the study population.
- All UPs will be reported to the Office for Human Research Protections (OHRP) following the same timelines described above.

The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not applicable beyond informing the individual who has been affected. We will maintain ongoing contact in this event until the problem is fully resolved.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

In this extension of our earlier work, we hypothesize that this digitally delivered program will result in improved performance in our primary (physical) outcomes, and high acceptability in our secondary outcomes. Further, we hypothesize that there will be significant differences following exercise between the intervention group and the wait list control group at the 12 weeks post randomization timepoint, but that there will not be significant differences between the two groups after both have gone through the exercise intervention. For all analyses, the sample will be characterized using descriptive statistics determined for the entire sample and stratified fall risk, as well as attendance/participation in the exercise classes. Analyses will be carried out according to the intention-to-treat rule (based on appropriate denominator) consistent with standard practice in most clinical trials. Outcomes will include usability, and objective markers of physical function related to fall risk.

- Primary Efficacy Endpoint(s): 1) Objective changes in markers of fall risk from Strong Foundations

Descriptive statistics and paired Repeated Measures ANOVA's will be used to compare changes for measures outlined above across groups over time. Significant demographic, medical and social characteristics (via self-report) will be tested for additions to our model.

Logistic regression modeling will be used to characterize changes in objective markers of fall risk, controlling for socio-demographic, and comorbid conditions (via the self-report record). Measurement of programmatic feasibility, per the SUS, will also be calculated and controlled for sociodemographic data, as collected, objective markers of risk (and risk-improvement based on intervention), attendance, and comorbid conditions. Follow-up assessment (monthly, up to 12 additional months) will allow for determining if interventions changed behavioral aspects associated with falls and falls-based outcomes.

- Primary Efficacy Endpoint(s): 2) Baseline associations between autophagy flux and objective markers of body composition and physical function

Descriptive statistics and Pearson's correlation coefficients will be calculated to identify significant associatinos beteen authophagy flux and metrics of body composition and functio.
Logistic regression modeling will be used to identify predictors of autophoghy flux while controlling for socio-demographic, and comorbid conditions (via the self-report record).

- Primary Efficacy Endpoint(s): 3) Changes in autophaghy flux from the *Strong Foundations* intervention and associations between change in autophagy flux and objective markers of body composition and physical function.

Descriptive statistics and paired Repeated Measures ANOVA's will be used to compare changes across groups over time.

Logistic regression modeling will be used to characterize changes in autophagy flux and identify predictors of that change while controlling for socio-demographic, and comorbid conditions (via the self-report record). Secondary Efficacy Endpoint(s): Compare lab vs digital measures of fall-risk; to showcase the feasibility of longitudinal Strong Foundations.

- Secondary Efficacy Endpoint(s): Compare lab vs digital measures of fall-risk; to showcase the feasibility of longitudinal Strong Foundations.

Descriptive statistics and Repeated Measures ANOVA's will be used to compare digital / in person collected measures of fall risk across groups over time. Additional analysis will explore the feasibility of attenuating programmatic improved fall risk in a larger group, with the hypothesis that there will be no change in objective markers at the completion of the 12 week program.

- Exploratory Endpoint: Further, a final survey will measure SUS scores as well as subjective markers of programmatic success. We will also collect digital measures of balance/fall risk as outlined above and explore how measures of feasibility (attendance, SUS scores) correlate with changes in these measures through this study.

9.2 SAMPLE SIZE DETERMINATION

This pilot is designed to showcase usability, feasibility and objective measures in outcomes, and compare measures collected digitally to best-practice lab based measures. Given the pilot nature of these data, they will be used to fuel further research which will be appropriately powered based upon the magnitude of change observed here.

9.3 POPULATIONS FOR ANALYSES

We will utilize a modified intention to treat analysis including all individuals who consent and attend at least one of the visits, and follow up lab visits; we are unable to do otherwise given without the participant showing up, we are unable to calculate changes for our primary outcome. However, these will be noted in our measures of feasibility including attendance.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

For primary and secondary outcomes, descriptive statistics will include:
Percentages, means with standard deviations, median, ranges. Paired T tests and Chi squares will be utilized to showcase changes between individuals and groups, and to differentiate statistical differences ($P<.05$).

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Repeated measures mixed analysis will be conducted to assess pre/post changes across the different cohorts (i.e. different level of risk and different SES status).
Missing data will be excluded from all analysis.
Outliers will be reviewed and if appropriate will be excluded from analysis.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Paired sample t-tests will be used to determine if there is a difference in the assessment of interest based upon in-lab vs. digital data collection.

9.4.4 SAFETY ANALYSES

Not applicable. We do not have any safety endpoints.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Intervention groups will be compared on baseline characteristics, including demographics and laboratory measurements, using descriptive statistics.

9.4.6 PLANNED INTERIM ANALYSES

Data analysis will be done based upon all cohorts completing their initial 12 week intervention.
A second set of data analysis will be done when all individuals have completed the follow up "maintenance" 12 week extended instruction period.

9.4.7 SUB-GROUP ANALYSES

We will analyze sub-groups based on SES (CC Cohort vs. SD Cohort) and fall risk categories (low vs moderate risk) as well as total group.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual data will be maintained based upon participant ID for each measure at each timepoint.

9.4.9 EXPLORATORY ANALYSES

Not applicable

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, and regulatory authorities by the Principal Investigator (PI).

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the PI and IRB.

10.1.2 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and other regulatory agencies for the University or State of California may inspect

all documents and records required to be maintained by the investigator, including but not limited to, medical and assessment. The clinical study site will permit access to such records.

The study participant's identifiable information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, and institutional policies. Identifiable information will be destroyed after the required retention period

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Exercise and Physical Activity Resource Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number.

10.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the Exercise and Physical Activity Resource Center.

Blood Specimens: Blood Specimens will not be stored for future research and will only be tested for the Autophagy flux and destroyed after results are confirmed.

10.1.4 KEY ROLES AND STUDY GOVERNANCE

Ryan Moran, MD, MPH (PI): Dr. Moran is an early-career investigator and Associate Clinical Professor in the Department of Family Medicine and the Department of Medicine. Dr. Moran is a member of the Center for Wireless and Population Health Systems, and is the Medical Director for EPARC, and a core member of the DXA Training School, all based in the Qualcomm Institute. He sees primary care patients at La Jolla Internal Medicine at UCSD. He serves as the PI for the ongoing pilot that has developed the Strong Foundations curricula.

Address: 9500 Gilman Drive, La Jolla, 92093 Mail Code 0811
Phone: 858-534-9315
Email: rjmoran@health.ucsd.edu

10.1.5 SAFETY OVERSIGHT

The PI will ensure that all study staff have appropriate certification and training to safely provide the measurement and intervention for this study.

10.1.6 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed periodically by the PI and the study coordinator and CO-I Dr. David Wing.
- On site review of gathered data and intervention fidelity will occur at least 1x per month.
- Independent audits will not be conducted by individuals outside the study unless there are concerns from the IRB or other regulatory bodies.

10.1.7 DATA HANDLING AND RECORD KEEPING

10.1.7.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. We expect the majority of our data to be entered directly into redcap at the time of measurement. Redcap captures data regarding who entered the data and any changes that occur after initial data entry.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.

Identifiable Information: All identifiable information such as (name, contact information, MRN# will be protected in a HIPAA compliant manner as per UCSD policies. Some identifiable information, notably name, phone number, and email will be stored in the HIPAA compliant secured REDCaP database. However, these data will be stripped for data analysis and coding. Further, only staff members with direct contact with participants (instructors and recruiters) will be given access to this portion of the database.

Clinical data (including adverse events (AEs), and assessment data will be entered into redcap, a 21 CFR Part 11-compliant data capture system provided by the University of California San Diego. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.7.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last exercise session. These documents will be retained for a longer period if required by local regulations. After the retention period is met all identifiable information will be destroyed.

10.1.8 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, or International Conference on Harmonisation Good Clinical Practice (ICH GCP). The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

The study PI and coordinator to use continuous vigilance to identify and report deviations within seven (7) working days of identification of the protocol deviation, or within seven (7) working days of the scheduled protocol-required activity. All deviations will be addressed in study source documents. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable

10.3 ABBREVIATIONS

AE	Adverse Event
ANOVA	Analysis of variance
BIA	Bioelectrical Impedience Analyses
CFR	Code of Federal Regulations
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
eCRF	Electronic Case Report Forms
EPARC	Exercise and Physical Activity Resource Center
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
PBMC	Peripheral Blood Mononuclear Cells
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	San Diego
SF	Strong Foundations
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
SPPB	Short Physical Performance Battery
SUS	System Usability Scale
TUG	Timed Up and Go
UCSD	University of California San Diego
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

11 REFERENCES

Include a list of relevant literature and citations for all publications referenced in the text of the protocol. Use a consistent, standard, modern format, which might be dependent upon the required format for the anticipated journal for publication (e.g., N Engl J Med, JAMA, etc.). The preferred format is International Committee of Medical Journal Editors (ICMJE). Include citations to product information such as manufacturer's IB, package insert, and device labeling.

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