**Study Protocol**

## 1. Project Title:

Home-based digital exercise training program to improve physical function of older sepsis survivors - HEAL Sepsis Trial

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## 3. Abstract:

Sepsis, an exaggerated response to infection, affects all ages, but it is more prevalent in older adults. Older sepsis survivors are commonly discharged to long-term acute care facilities, where they often die within 1 year. We believe that those who return home from the hospital lose the momentum of physical function improvement after early in-hospital rehabilitation and often face exacerbation of comorbidities and decline in physical function. Based on our longitudinal observational data, older sepsis survivors have poorer health status and physical function lasting at least 1 year after sepsis than younger sepsis survivors; and in contrast with younger survivors, older patients do not regain their function. Our aging research suggests that physical activity interventions prevent mobility disability in rather healthy older adults, but older sepsis survivors will be profoundly frailer, more sedentary, lower-functioning, and will unlikely be capable of traveling to participate in supervised exercise training programs in our research facilities. Currently, we are unaware of any home-based therapeutic approaches to improve the physical function of older sepsis survivors. Current mobile health applications can deliver structured home-based exercise programs to reach daily activity goals. For example, the Blue Marble Health Platform (BMHP) - Health in Motion app developed and validated with the support of NIH contains over 100 avatar-guided strengthening, balance, and aerobic exercises, along with 23 standardized assessments and a personal health diary. This digital and remotely delivered exercise training program might be promising for sepsis survivors with poor health status, who are unlikely to be able to travel to participate in exercise interventions. Our proposed study will test the safety, feasibility, and efficacy of a novel 12-week physical activity intervention to improve physical function in older sepsis survivors utilizing an app-based digital exercise training platform. We propose to randomize 40 sepsis survivors (aged $\geq$55 years) with an SPPB score $\leq$ 10 within 3 days of their discharge to home from the hospital into the intervention or a standard care control group. We will recruit at \ UF Health Gainesville site. We will also recruit via the use of advertisements (e.g. flyers). \Both groups will receive a tablet with the BMHP - Health in Motion app, which contains all of the physical function assessments, and a health diary. The intervention group will also receive personalized avatar-guided exercises as well as phone call or text message reminders to exercise for 30min each day, 5 days/week. The control group participants will record their daily activities using the BMHP - Health in Motion health diary. A research coordinator will call all participants weekly to ask questions about their health status and remind them to charge the tablets. At baseline and 12-week follow-up, participants will use the app to complete the app-guided physical function assessments. This project will be the first to test the safety, feasibility, and efficacy of a digital physical activity intervention in this high-risk population of older sepsis survivors. The results will provide important information

regarding the feasibility, tolerability, and efficacy of this novel approach to enhance these patients' physical function.

## 4. Background:

Sepsis, an exaggerated response to infection, affects all ages [1]. However, older adults ≥65 years are affected more commonly [2]. Despite improvements in survival, many sepsis survivors become chronically critically ill with chronic low-grade multiple-organ failure and inflammation [3, 4]. Older sepsis survivors are more likely to be discharged from the hospital to long-term acute care (LTACs) or skilled nursing facilities (SNFs) where some require re-hospitalization or die within 1 year [3]. Those who return home often face exacerbation of comorbidities and physical function decline due to the lack of continuous physical function-enhancing interventions such as physical therapy (PT) or occupational therapy (OT) [1]. Post-sepsis persistent chronic inflammation appears to perpetuate physical function decline in older adults by sustained muscle wasting leading to difficulties in daily activities [1, 4-6].

Our Sepsis and Critical Illness Research Center (SCIRC) in partnership with our Institute on Aging (IoA) have successfully followed and assessed changes in physical function in 320 sepsis survivors over the course of 1 year. We learned that older (≥ 65 years) sepsis survivors remain poorly functioning as demonstrated by Short Physical Performance Battery (SPPB) score (score <9 poses risk of disability) 3.5±1.28 at 3 months and 4.9±1.1 at 1-year post-discharge. These scores suggest that older sepsis survivors are unlikely to complete traditional exercise training programs, which we have previously shown effective in improving function and reducing risk of mobility disability in moderately functioning older adults [7]. While early hospital PT/OT aims to improve physical function, patients often do not have access to structured interventions once discharged to home. Thus, sedentary, home-bound sepsis survivors appear to be at high risk for stagnating physical function, despite initial improvements in physical function gained during early rehabilitation. There is a need for post-discharge exercise interventions customized to older sepsis survivors aimed at improving and sustaining their physical function at home. Aside from traditional home-based PT/OT available to few, a feasible home-based approach to improve the physical function of older sepsis survivors does not exist.

Current mobile health applications can deliver structured home-based exercise programs to reach daily activity goals. For example, the Blue Marble Health Platform (BMHP) - Health in Motion app, developed and validated [8-12] with the support of NIH NHLBI/NIA/NIDCD, contains over 100 avatar-guided strengthening, balance, and aerobic exercises, along with 23 standardized assessments and a personal health diary. We plan to use the BMHP - Health in Motion app to deliver personalized, progressive, avatar-guided home exercise programs to older sepsis survivors for 12 weeks. We will use the BMHP - Health in Motion app to track progress over time by remotely monitoring participants' progress and advancing the exercise programs as appropriate. We will use the platform to capture all of the self-performed outcomes, including physical function measures, entirely via the mobile application. We believe that this unique approach may be the key to keep improving physical function in older sepsis survivors with poor health status, low physical function and distant living locations who are unlikely to participate in institution-based exercise intervention programs. Our central hypothesis, therefore, is that a 12-week digital, home-based, remotely-monitored intervention that guides physical activity will be feasible and efficacious in improving physical function in older sepsis survivors.

## 5. Specific Aims:

Our proposed study will test the feasibility and efficacy of a novel 12-week physical activity intervention to improve physical function in older sepsis survivors utilizing an app-based digital exercise training platform. We propose to enroll 40 sepsis survivors (aged ≥55 years) with an SPPB score ≤ 10 within 3 days of their discharge to home from the hospital. The eligible patients will be randomized into 2 groups. Both groups will receive tablets with the BMHP - Health in Motion app, which contains all of the physical function assessments, and a health diary. The intervention group will also receive personalized avatar-guided body-weight, strengthening, balance, stretching and walking exercises as well as phone call or text message reminders to exercise each day (5 days/week). For the control (standard care group),

participants will record their daily activities using the BMHP - Health in Motion health diary. A research coordinator will call all participants weekly to ask questions about their health status and remind them to charge the tablets. At baseline and 12-week follow-up, participants will use the app to complete the physical function assessments (balance, strength, and walking speed).

**Aim 1:** Test the feasibility of recruitment at the Gainesville site and via the use advertisements/medical provider referrals, of acceptability and safety of the intervention. We hypothesize that the intervention in older sepsis survivors will be safe, and feasible, 75% of the participants will adhere to more than 50% of their exercise prescription, and our retention rate will be at least 70%.

**Aim 2:** Determine the efficacy of the intervention on physical function and activity levels. We hypothesize that the intervention will be efficacious to improve physical function.

## 6. Research Plan:

**Table 1. Inclusion and exclusion criteria.**

**Inclusion Criteria**

- Able to perform lower and upper-body movements
- Sepsis survivor
- Age 55 years and older
- SPPB ≤ 10
- Being discharged to home from the hospital after surviving sepsis
- Willingness to be randomized to either treatment or control group
- Willingness to use the devices and technology in the study
- Willingness to participate in all study procedures

**Exclusion criteria**

- Failure to provide informed consent
- Pregnant
- Discharge to a long-term facility
- Involvement in a structured rehabilitation program
- Inability to perform lower or upper-body exercises (e.g. being in wheelchair)
- Severe cardiac disease, including NYHA Class III or IV congestive heart failure, clinically significant aortic stenosis, history of cardiac arrest, use of a cardiac defibrillator, or uncontrolled angina
- Diagnosed significant cognitive impairment, including known dementia diagnosis
- Organ transplant recipient on immunosuppressive agents
- HIV/AIDS with CD4 count < 200
- Severe immunocompromised state (e.g. subject has neutropenia receiving cytotoxic chemotherapy with absolute neutrophil count < 500/ul or expected to decline to < 500/uL within the next 3 days)
- Progressive, degenerative neurologic disease, e.g., Parkinson's Disease, multiple sclerosis
- Severe pulmonary disease, requiring either steroid pills or injections or the use of supplemental oxygen
- Simultaneous participation in another intervention trial
- No internet access in primary place of living

We propose to conduct a randomized, controlled pilot trial to test if a remotely delivered exercise intervention is safe, feasible, and efficacious to improve physical function in older sepsis survivors. Following study entry, participants (N = 40) will be randomly assigned to either exercise or standard care for 12 weeks. During the second in-person home/hospital visit, all participants will receive tablets with the BMHP - Health in Motion application on it and will be provided instructions (online and on paper) on how to use the tablets, the exercise application, and health diaries. The participants will be provided with tablets compatible with the exercise application that are Wi-Fi enabled. Participants in the exercise group will train 5 times a week on the self-reported exertion level ~3-4.

**6.1 Participants:** Eligible participants will be sepsis survivors (males and females) ≥ 55 years of age with an SPPB score **≤** 10 who are discharged to a home from the hospital.

**Table 2.** Data collection summary.

| **Study phase** | **Hospital/ Home*** | **Hospital/ Home*** | **Home-based Assessments** | | |
|---|---|---|---|---|---|
| Time-point description | Screening visit* *(V1)* | Check-in Visit* *(V2)* | Baseline visit *(V3)* | Follow-up Visit *(V4)* | 12-week Follow-up visit *(V5)* |
| Week (W) number | -8-0 W | -2-0 W | 0 W | 1-12 W | 12 W *(V5 – 3 days to + 7 days)* |
| Method of the visits | In-person | In-person | Zoom call | Weekly call | Zoom call |
| Consent, review of inclusion/exclusion criteria | **X*** | | | | |
| Demographic and contact information | **X*** | | | | |
| Medical history review | **X*** | | | | |
| Medication inventory | **X*** | | **X** | | **X** |
| Release of medical records authorizations form | **X*** | | | | |
| Depression questionnaire using CES-D questionnaire | **X*** | | | | |
| Montreal Cognitive Assessment questionnaire – MOCA/BLIND | | | **X** | | **X** |
| Quality of life questionnaire – EQ-5D-5L version | | | **X** | | **X** |
| Short Physical Performance Battery test | **X*** | | | | |
| Pregnancy test | | **X** | | **X**** | |
| Randomization | | **X** | | | |
| Distribute TheraBand | | **X** | | | |
| Distribute/collect tablets and pre-addressed return package | | **X** | | | **X** |
| Update of medical history | | | **X** | | **X** |
| BMHP - Health in Motion app-guided physical function assessment | | | **X** | | **X** |
| Collection of adverse experiences | **X*** | | **X** | **X** | **X** |

| | | | | | |
|---|---|---|---|---|---|
| ECOG/WHO/Zubrod Scale | **X** | | **X** | | **X** |

****** The Screening Visit (V1) and the Check-in Visit (V2) may be scheduled on the same day for those patients recruited post-hospital discharge.*

******* We will send urine pregnancy tests every month for participants to complete at home. Pregnancy status will also be reassessed during the weekly calls.*

6.2 Recruitment:

Identifying sepsis patients by the clinical team: Screening for sepsis is carried out using UF Health's sepsis alert system, which quantifies derangements in vital signs, white blood cell count, and mental status. After a putative diagnosis of sepsis, the patient is transferred to the Intensive Care Unit (ICU) and sepsis treatment bundles are initiated. If a patient is believed to have an infection and they are located in, or transferred to the ICU, they are entered into the sepsis management protocol as standard of care which implements a variety of standard operating procedures (SOPs) of clinical ICU care. All critically ill patients with sepsis will be managed via their evidence-based management protocol that emphasize early antibiotic administration, fluid resuscitation and hemodynamic monitoring and support, consistent with current Surviving Sepsis Campaign guidelines. Patients who screen positive for sepsis and are being treated by the standard-of-care sepsis protocol are candidates for this study. Sepsis will be defined using the new Sepsis-3 criteria. Members of the study will assist in screening the UF Health inpatient population to identify sepsis patients not captured by the sepsis alert system. The clinical team will then be asked to confirm the patients meet the sepsis-3 criteria.

Recruitment of sepsis survivors to our study:

We will recruit participants from UF Health Gainesville site. The investigator, designated study coordinators, and clinical care staff members will identify and recruit subjects from the inpatient population at UF Health. In particular, the co-investigator Dr. Philip Efron or his clinical staff members who directly care for sepsis patients will inquire potential participants about their willingness to be approached about our study. If potential participants would like to learn more about the study, the clinical staff members will contact our study coordinators to approach the potential participants in-person and introduce the study. This coordinator will approach the patients before discharge within 8 weeks of their baseline visit and consent the appropriate candidates. The coordinator will assess for the main inclusion/exclusion criteria, and will monitor the clinical trajectory daily and look out for notes on patient discharge to home via the electronic medical record.

Patients may also be identified and recruited for the study via advertisement. The study flyers will be shared with medical providers. The general population will self-identify by responding to recruitment materials. Individuals who come into contact with the study flyers may reach out to the study team to express interest in participating in the clinical trial.

Patients may come into contact with the flyers via a referral from their medical providers. Although medical providers who receive the flyer will not actively recruit participants, they may refer patients to the study by sharing the IRB-approved flyer with them if they express interest. These medical providers will not disclose any patient contact information to the study team. If potential participants express interest in the study, they may receive the flyer from their medical provider. To be screened for study participation, they will need to contact the study team within 3 days of discharge home from the hospital using the contact information provided on the study flyer. The study team will communicate with these patients to schedule their first visit (V1 +/- V2). Patients will be screened during this visit.

Consent will be sought by research staff, all of whom are familiar with institutional logistics and infrastructure, sample acquisition and preparation, and are experienced in the nuances of enrollment and informed consent for this challenging patient population.

6.3 Screening, Study Entry and Randomization:

The study team will help the UF Health clinical staff by pre-screening the UF Health inpatient population for patients seeming eligible for the study. The UF Health clinical staff members will be asked to review those patients identified as potentially eligible for study eligibility and are asked to approach those patients and see if they are interested in hearing about the study. If they are agreeable, the UF Health clinical members will let the study team members know that the patient is interested and the study team will proceed with introducing the study to the patient. The study procedures following their introduction to the study are detailed below. No patients will be approached by the study team before they are approached by a member of their clinical staff and confirmation of their interest is received by a member of the study team.

For UF Health inpatients identified by the UF Health clinical staff members, potential study subjects may also be identified by these medical providers who will inform the research study team about sepsis patients who are 55 and older that meet the main criteria. The study coordinator will be looking out for the potential participants' discharge, consent and screen them at the hospital for the inclusion/exclusion criteria. We will review the participants' medical history. We will also assess physical function in-person by SPPB, which comprises a 4-meter walk, repeated chair stands, and three increasingly difficult standing balance tests. We will also screen for depression using a CES-D questionnaire and participants' cognitive status at the in-person hospital screening visit. If participants score ≥ 16 on the CES-D questionnaire, we will notify their clinical care team to provide them appropriate resources and course of treatment. They will be encouraged to consult with their primary care physician about the results. If eligible, we will randomize participants to either an intervention or a standard care control group at the second in-person visit (V2).

For those patients recruited via the flyer after discharge, the patient will be scheduled for a screening visit with a study coordinator. During this visit, the patient will be screening for inclusion/exclusion criteria, and consented if interested and eligible for participation. We will review the participants' medical history. We will also assess physical function in-person by SPPB, which comprises a 4-meter walk, repeated chair stands, and three increasingly difficult standing balance tests. We will also screen for depression using a CES-D questionnaire and participants' cognitive status at this visit. If participants score ≥ 16 on the CES-D questionnaire, we will notify their clinical care team to provide them appropriate resources and course of treatment. They will be encouraged to consult with their primary care physician about the results. If eligible, we will randomize participants to either an intervention or a standard care control group at the second in-person visit (V2).

We understand that participants who are discharged to home may be overwhelmed with all the health circumstances and new information about the study. We will schedule a second in-person home/hospital visit (V2) with each participant to explain all aspects of the study again and make sure that all study devices are functional. Visit 2 may be paired with Visit 1 if the patient was recruited post-discharge, or, if they choose to combine the visits due to other preferences/constraints. During this visit, we will also equip the eligible participants with the TheraBand, and tablets that will connect to a home or personal internet network via Wi-Fi and an activated exercise app for the intervention group (**Table 2**) or the app with a deactivated training feature for the control group. The tablet will also have the applications to synchronize the Zoom application to connect with our staff during the assessment visits. Participants will receive in-person training and paper instruction on how to use and navigate the Zoom call, tablet, and the Blue Marble Health Platform (BMHP) - Health in Motion app. Additionally, female participants who are 55 to 62 years old with undetermined childbearing status on their medical record will need to complete a urine pregnancy test. We will also send them urine pregnancy tests every month to complete at home. We will reassess their childbearing status during the weekly calls. If they reported that they could potentially be pregnant, we will send them the urine pregnancy test via mail promptly to confirm their pregnancy status.

6.4 Baseline Assessment:

On the day before starting the 12-week intervention/standard care period, we will activate the health diary and the physical function assessment (baseline and 12-week follow-up: Timed Up and Go, 30 Second Sit to Stand, 4 Stage Balance Test) for both groups. The physical function test will be supervised by a blinded research coordinator via a Zoom call to ensure the participant's safety and appropriate execution of the test

**Table 1.** A comparison between the SPPB (Screening Visit) and the BMHP - Health in Motion app guided self-assessments (Baseline and 12-week Follow-up Visits).

| **SPPB** | **BMHP App-guided assessment** |
|---|---|
| ***Balance Test*** | ***4 Stage Balance Test*** |
| Side by Side Stand | Side by Side Stand - Stage 1 |
| Semi-Tandem Stand | Semi-Tandem Stand - Stage 2 |
| Tandem Stand | Tandem Stand - Stage 3 |
| | Standing on One Leg – Stage 4 |
| ***Gait Speed*** | ***Gait Speed*** |
| First Gait Speed Test (4 m walk) | Timed Up and Go - 3 m walk (out and back) |
| ***Lower-Limb Strength*** | ***Lower-Limb Strength*** |
| 5x Sit to Stand Test | 30 Second Sit to Stand Test (Stand as many times as you can in 30s) |

6.4. Online home-based exercise training intervention.

The intervention will be delivered entirely digitally by the BMHP (Digital Assessments, Interventions, Monitoring, and Analytics platform) - Health in Motion app. A research coordinator will be present via Zoom call during the baseline and 12-week follow-up assessments. The BMHP – Health in Motion technical staff will be available to solve application glitches remotely. The participants will receive daily reminders (5 days/week) for the first two weeks on their phones via text message or phone call to perform training sessions. After the first two weeks, participants will receive a weekly reminder call. The training app with an avatar demonstrating and guiding the exercise will register the progress and the intensity will be adjusted according to the progress based on the self-reported exertion score [16] inserted during each session into the app. A request to assess exertion level will pop up in the application at the beginning, middle, and end of each session. Each session should be perceived at exertion level ~3-4 (0-10 with 0 being "not hard at all" and 10 being "so hard, I need to stop"), and the exercise routine will be manually adjusted by the study staff so that the repetition number and intensity maintain continuous progress during the intervention [17] **(Figure 5b).** Each session will take 30 minutes including a 5 min warm-up, 20 min of aerobic and resistance/bodyweight exercises, and 5 min of cool down. The progression of resistance exercises will include the addition of TheraBand's, an increase in the number of repetitions/workloads, or a reduction of support such as a countertop for balance. Participants will be reminded during weekly phone calls to charge the devices overnight every 4 weeks.

6.7 Adherence to interventions.

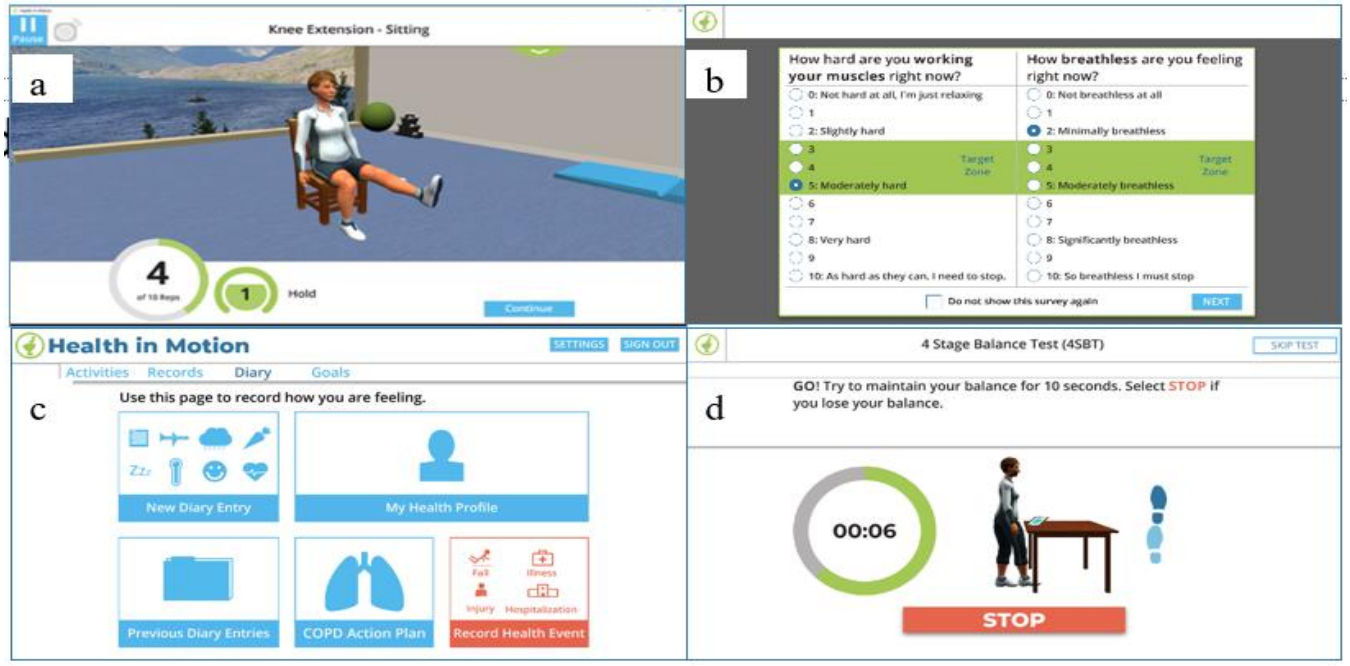


**Figure 5**. (a) Screenshot of an in-app avatar guided exercise, b) self-reported exertion & breathlessness measures, c) Health Diary Menu, d) sample guided test screen (4SBT).

To enhance adherence to the study interventions (compliance), we will utilize empirically-supported techniques which we have successfully utilized in prior studies. Our first step will be to fully inform participants of study requirements before randomization and enroll only those persons who are willing to complete all study procedures. Undoubtedly, however, issues arise after randomization with the potential to limit compliance. Common causes of poor compliance include vacations, spouse care, fatigue, and fluctuations in motivation, perceived lack of benefit, physical discomfort, and adverse health experiences. During weekly phone calls, a coordinator who is not involved in baseline and follow-up testing will emphasize the importance of adherence to the exercise intervention. If at least 2 sessions are missed in a particular week, a coordinator will ask for the reasons and emphasize the importance of adherence. This approach assumes that the process of changing behavior is a collaborative effort between the participant and the research staff and that behavior change can be readily undertaken during the regular weekly contacts that the intervention staff will initiate throughout the intervention. Our team has successfully applied this type of problem-solving approach in promoting adherence to behavioral interventions in prior studies. For this study, we will be tracking the number of days the participant exercised in a given time period on the Health in Motion app.

6.8 12-week Follow-up Visit

In addition to baseline visits, assessment visits will be conducted at 12 weeks follow-up visit (**Table 2**). After completing the intervention/control period, the participants will perform the same evaluations as during the baseline visit (Timed Up and Go Test, 30 Second Sit to Stand Test, 4 Stage Balance Test). At the end of the 12-week follow-up visit, participants will be offered to keep the Theraband to continue physical activity. At the second in-person visit (V2), participants will be provided with pre-addressed, padded and insured boxes to be used for mailing the tablets back to us. We will arrange additional home visits in case of arising issues that cannot be solved by phone/Zoom such as difficulties navigating the tablet and/or software.

6.9. Outcome Measures.

**Physical activity**
The participants will perform a physical function test, with elements similar to SPPB, guided by the BMHP - Health in Motion app with a blinded coordinator present via a Zoom call. (Timed Up and Go Test, 30 Second Sit to Stand Test, 4 Stage Balance Test)

**Questionnaires.**
We will administer questionnaires to assess the participant's mental state including depression – CES-D at the in-person hospital screening visit. We will evaluate the participant's cognitive function (Montreal Cognitive Assessment, telephone/zoom MoCA-BLIND), and quality of Life by EQ-5D at baseline and follow-up via a zoom call.

- Depression - CES-D - is a 20-item measure assessing symptoms of depression with items phrased as self-statements (e.g., "I felt hopeful about the future"). Respondents rate how frequently each item applied to them over the course of the past week. Ratings were based on a 4-point Likert scale ranging from 0 (rarely or none of the time [less than 1 day]) to 3 (most or all of the time [5–7 days]). This questionnaire will be conducted at screening visit.

- Montreal cognitive assessment: The MoCA is a widely used screening assessment for detecting cognitive impairment. The MoCA assesses the domains of short-term memory recall, visuospatial abilities, executive functions, attention, concentration, working memory, language, and orientation to time and place. MoCA will be conducted at baseline and 12-week follow up visit. Telephone MoCA-BLIND – this abbreviate telephone version will have no visual elements, scored out of 12 [18].

- Quality of Life by EQ-5D: The telephone/zoom version of quality of life by EQ-5D-5L comprises five questions on mobility, self-care, pain, usual activities, and psychological status with three possible answers for each item (1=no problem, 2=moderate problem, 3=severe problem. A summary index with a maximum score of 1 can be derived from these five dimensions by conversion with a table of scores. The maximum score of 1 indicates the best health state, by contrast with the scores of individual questions, where higher scores indicate more severe or frequent problems. This questionnaire will be conducted at baseline and 12-week follow up visit.

- The ECOG/WHO/Zubrod Scale. A 5-point scale that measures the performance status of a patient's ambulatory nature: 0) Asymptomatic (fully active), 1) Symptomatic but completely ambulatory (restricted in physically strenuous activity), 2) Symptomatic, <50% in bed during the day (ambulatory and capable of all selfcare but unable to perform any work activities), 3) Symptomatic, >50% in bed, but not bedbound (capable of only limited self-care), 4) Bedbound (completely disabled, incapable of any self-care), and 5) Death. This will be administered to the subject at the Hospital (V1), baseline visit (V3) and the 12 week follow-up visit (V5). We would like to ask some questions about the patients' pre-hospitalization status, based on the ECOG/Zubrod questionnaire, in order to compare it with their condition at discharge and during the final visit.

6.10 Sample size justification.

This pilot study will help generate precise estimates of effect variance in physical function in the population in which a subsequent larger-scale study will be conducted. Published recommendations for the design of pilot studies indicate that a sample of 15 participants per randomized arm is typically sufficient to estimate a parameter for a future trial [27-29]. Based on our observational cohort, the mean change in SPPB between 3 and 6 months among the survivors 65 years and older (n=118) was 0.4±0.81. We expect similar results in our control group. Considering this is a frailer population than normal older adults, which may involve a higher drop-out rate, the enrollment sample of 20 participants in the intervention group (allowing for at least 14 evaluable participants in each group after the expected 30% loss due to attrition) is to provide sufficient data to indicate the feasibility of a larger study and to provide descriptive estimates of effects, but is not intended to be powered for detection of significant changes in control/standard care group). Additionally, it will provide data for nominal estimation (using a 95% confidence interval) of the mean changes in physical function as the key outcome of this pilot study.

6.11 Safety monitoring plan.

To maximize participant safety, we will implement a number of safety procedures. First, we will follow a standardized screening protocol. Accordingly, all potential participants will undergo screening for cardiovascular and other major diseases using a medical history questionnaire. Each participant will be instructed to report the occurrence of an adverse event at weekly phone calls and scheduled data collection times by phone/zoom and via the in-app health diary. During weekly phone calls, participants will have a chance to report any concerns and events. Participants will also have access to study personnel at any times to report serious adverse events or concerns about the safety of participating in the study. In particular, the principal investigator and the main study coordinator will provide their cell phone numbers for urgent matters. In consultation with study physicians (Drs. Philip Efron and Faheem Guirgis), a participant will be advised to seek medical attention or a telemedicine visit with our study physician. We also created a Data and Safety Monitoring Plan, approved by the NIH personnel, that included a local safety officer (UF Health Geriatrician: Dr. Brianna Wynne) who will independently assess the reported adverse events bi-annually. If necessary, Release of Medical Records Authorizations signed by the study participants at the second in-person home/hospital visit will be used to obtain medical records to collect details and outcomes of SAEs for safety and reporting purposes.

Procedures to minimize exercise discomfort include warm-up and cool-down activities. The participants will also be progressively introduced to the intervention exercises, such that they begin with light intensity and gradually increase throughout the study. Participants will also be instructed during the second in-person home/hospital visit to move slowly when rising from a seated or lying position to reduce the risk of experiencing orthostatic hypotension. At the second in-person home/hospital visit, participants will be instructed to stop an exercise session when feeling sudden pain, tightness or pressure in the chest, significant shortness of breath, feeling faint, lightheaded or dizzy, or significant other medical problems. They will need to report it in the Record Health Event feature on the app and on the phone during a weekly phone call (the interventionist will ask whether there were any events that made them stop an exercise session during the past week).

Written informed consent will be obtained after explanation to subjects of all procedures and time commitments. The study interviewer will explain to prospective participants the purpose, methods and extent of the study. Potential participants will be asked to read the informed consent form and to ask questions. The form will be written in simple, easy-to-understand language. Staff members will also review all key aspects of the study verbally.

Confidentiality: Data will be used only in aggregate and no identifying characteristics of individuals will be published or presented. Confidentiality of data will be maintained by using research identification numbers that uniquely identify each individual. Data will be used only in aggregate and no identifying characteristics of individuals will be published or presented. Safeguards will be established to ensure the security and privacy of participants' study records. The information collected from participants in this study has a low potential for abuse, because the data do not address sensitive issues. Nevertheless,

appropriate measures will be taken to prevent unauthorized use of study information. The research records will be kept in a locked room at the Department of Aging and Geriatric Research. The files matching participants' names and demographic information with research ID numbers will be kept in a separate room and will be stored in a locked file that uses a different key from that of all other files. Only study personnel will have access to these files, and they will be asked to sign a document that they agree to maintain the confidentiality of the information.

After the study is completed, local data will be stored with other completed research studies in a secured storage vault. In compliance with the Health Insurance Portability and Accountability Act (HIPAA) and the Standards for Privacy of Individually Identifiable Health Information of the Department of Health and Human Services, we will access personal health information and medical records only after receiving signed informed consent, as described above. Finally, the study protocol will be registered at www.ClinicalTrials.gov before study enrollment begins.

## 7. Possible Discomforts and Risks:

### General Approach

Contact numbers for emergency services will be provided to participants, and community EMS services will be activated if needed.

Participants will be instructed to talk with the investigators about any discomforts that occur during the study. If a participant reports an injury, chest pain, leg swelling, excessive shortness of breath, palpitations, or dizziness, he/she will be referred to medical attention (his/her doctor, or Emergency Department).

All research staff complete protection of human research subjects training required by the University of Florida Institutional Review Board (IRB) and National Institutes of Health (NIH). This training includes education about the importance of maintaining confidentiality of personal health information.

**Specific Potential Risks.** Potential risks for this study are related to the following: (1) Remotely delivered exercise intervention, (2) short physical performance test, (3) online supervision physical function test include Timed Up and Go Test, 30 Second Sit to Stand Test, 4 Stage Balance Test, (4) potential loss of confidentiality related to study questionnaires, (5) cognitive test (6) potential loss of confidentiality using the Health in Motion app and tablet, (7) pregnancy test.

**The potential risks and protection against these risks for each study specific risk are described below.**

Risk associated with exercise intervention

The primary risk associated with moderate-intensity exercise training is skeletal muscle soreness. There are also other risks that relate to falls and fractures, exacerbation of arthritis and other joint conditions, post-exercise hypotension, and cardiovascular events. There is a risk that a participant may trip, stumble, or fall during the exercise sessions and experience shortness of breath, dizziness, palpitations, chest pain or discomfort, heartburn, light headedness, or feeling about to faint.

To minimize this risk, the exercise levels will be tailored to individual capabilities to gradually improve physical function without over-straining. The BMHP - Health in Motion app guides the participants through the exercise and encourages them to perform the exercise in a safe environment. The app also demonstrates how to do the exercise safely and encourages participants to stand near by sturdy furniture or countertop in case of losing balance. Participants are informed to stop the exercise immediately if they

experience chest pain, intolerable dyspnea, leg cramps, staggering, diaphoresis, or pale or ashen appearance during the exercise intervention. Additionally, the app has an exercise symptom rating scale that includes breathlessness, pain/exertion/dizziness that can be added to participants' exercise routine before/at midpoint/ and after they complete the exercise. Also, if the participants exist the exercise routine before it is completed, the app will ask them why they did that and has them fill out the exercise symptom scale again.

The study team will enable the Record Health Event feature of the BMHP - Health in Motion app to monitor participants' safety. This feature enables participants to record if they have a fall, illness, or injury. It will ask for the date/time of the fall or illness; if participants went to the hospital, cause of the fall, and a text box to describe the event in detail (**Figure 6**).

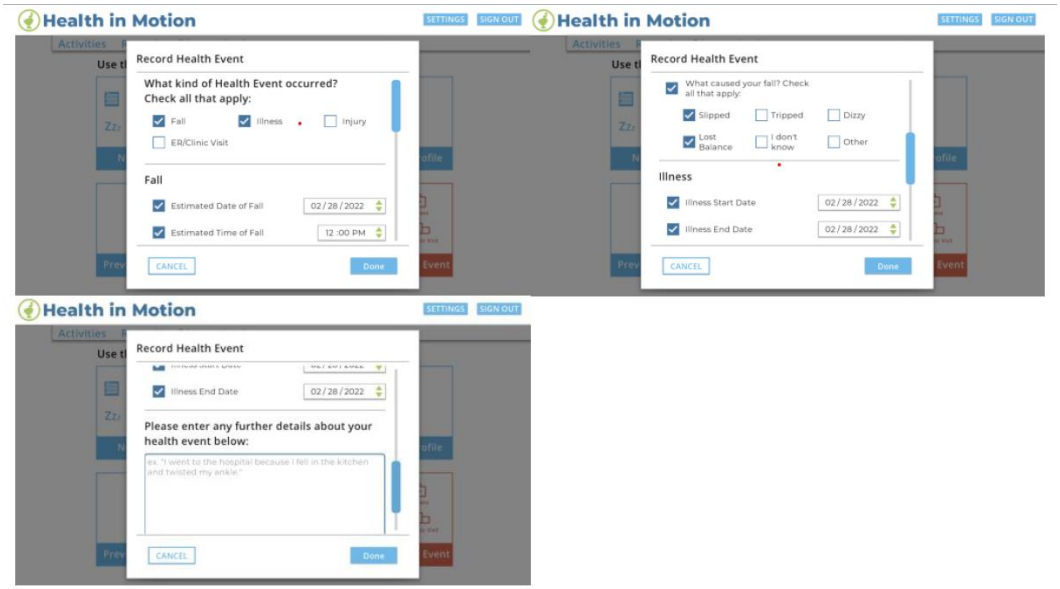


**Figure 6. Screenshot of the Record Health Event feature of the BMHP - Health in Motion app.**

Study coordinator will see the reports and follow up with participants to ensure participant's' safety. We will provide participant with the NAME/ADDRESS/and EMERGENCY CONTACT in case they fall while performing the exercise. They will also be advised to call 911 in case of injury during exercise sessions. Research staffs will call participants weekly to monitor their health status and collect adverse events.

Risk associated with short physical performance test

The SPPB may be associated with the risk of falling or development of chest discomfort due to coronary ischemia or dyspnea due to heart failure or lung disease. Rarely, falling during the SPPB test may result in a fracture. Research staff members who collect data will be trained on proper administration of the SPPB prior to administering the SPPB test to a participant.

To minimize these risks, research staff are trained in the conduct of all physical performance tests and certified by Dr. Mankowski or his designee before they work with study participants. Study staff are instructed to advise the participants not to perform these tests if they feel that testing is unsafe for an individual participant or if the participant is concerned about safety. If safety concerns are identified by either the study staff or the participant during the testing procedures, testing is halted and the participant is not allowed to complete the test. In either case, the participant is assessed to determine the need for medical intervention and the cause for concern is evaluated. All study staff are trained in activating the emergency response system at The University of Florida facility.

Risk associated with the supervised online physical function test include Timed Up and Go Test, 30 Second Sit to Stand Test, 4 Stage Balance Test

All of these tests may put a participant at risk of falling. Participants are encouraged to perform all tests safely, with the assistance of another person, using an assistive device, or using a sturdy support surface. If the participant is unable to complete the tests, they may be excluded from the study. For each follow-up test, the BMHP - Health in Motion app guides the participant through the test and encourages them to perform the test in a safe environment.
To mitigate falls, the BMHP - Health in Motion app describes and demonstrates each physical assessment (TUG, 30STST, 4SBT, OLST). The app also demonstrates how to do the test safely with the assistance of another person, sturdy furniture, and a chair placed behind them just in case they lose their balance. Should a participant feel that they are unsafe to perform the test, they may skip the test and document their reason for skipping using the BMHP - Health in Motion Health Diary feature. For the baseline test, if a person demonstrates higher risk of falls from the questionnaires, a study staff member or in-home support person will guard the participant to ensure they are safe to perform the test. The study staff will educate the participant on ways to perform the follow-up tests independently safely in their home. Fall Risk due to the tests: The fall risks associated with tests are minimal. Most of the tests are questionnaires, however a few require the participant to walk 10 feet (TUG), stand on one leg (OLST and 4SBT), standing with one foot in front of the other (4SBT), or stand up from a chair as many times as possible in 30 seconds (30STST). To prevent or reduce the likelihood of falling or losing their balance we will encourage participants to only complete tests they feel safe to complete and to have another person nearby to assist them if they lose their balance. Furthermore, the in-app instructions encourage participants to stand near a sturdy table or countertop and place a chair behind them when performing the balance tests so that if they lose their balance, they can quickly and safely sit down.

During the screening visit, we will provide participant with the NAME/ADDRESS/and EMERGENCY CONTACT should someone fall while performing the test. The study coordinator present on Zoom will call 911 should someone fall and unable to call, otherwise the study coordinator will ask participant to call 911 and we will remain on the Zoom call until the first responders arrive.

Risk associated with questionnaires administration

Participation includes a risk of loss of confidentiality of personal health information. A number of methods are employed to maintain confidentiality of participants. First, questionnaire data are collected in secure spaces where the interview cannot be overheard. Second, only study investigators and key research staff have access to the study database. Third, participants are assigned a unique study identifier. Individual names will ultimately be removed from the study database and only the unique study identifier is used to distinguish participants in the database. Fourth, collected data are maintained in locked computer files and file cabinets to which only study investigators have access. Collected data will be used only for research purposes. Published data will not contain any individual identifiers. Finally, all research staff members have to retake refresher course certification exams.

To minimize this risk, questionnaire data are collected in secure spaces where the interview cannot be overheard. Participants can decline to answer questions that are uncomfortable or concerning. All research staff members complete annual HIPAA for Researchers training as required by UF. Collected data will be maintained in locked computer files and file cabinets to which only study investigators have access. Only study investigators and key research staff (i.e. data manager and study programmers) have access to the study forms or database. Participants will be assigned a unique study identifier; individual names will be removed from the study database and only the unique study identifier used to distinguish participants in the database. Collected data will be used only for research purposes, and publications will not contain any individual identifiers.

Risks associated with Cognitive Tests.

There is a risk that participants will find memory and concentration tests stressful and might feel tired or sad because it may be difficult to remember things that they are asked to remember. Participants may skip any question they do not wish to answer. Research staff will explain what to do and answer questions that participants might have during cognitive testing.

To minimize this risk, questionnaire data are collected in secure spaces where the interview cannot be overheard. Participants can decline to answer questions that are uncomfortable or concerning. All research staff members complete annual HIPAA for Researchers training as required by UF. Collected data will be maintained in locked computer files and file cabinets to which only study investigators have access. Only study investigators and key research staff (i.e. data manager and study programmers) have access to the study forms or database. Participants will be assigned a unique study identifier; individual names will be removed from the study database and only the unique study identifier used to distinguish participants in the database. Collected data will be used only for research purposes, and publications will not contain any individual identifiers.

Risk associated with the potential loss of confidentiality the BMHP - Health in Motion app, Zoom call and tablet.

Participation includes a risk of loss of confidentiality of participants' health and personal information when using the BMHP - Health in Motion app, Zoom call and tablet.

To minimize this risk, participants will be assigned a unique study identifier associated with all of their accounts on the Blue Marble Health Platform - Health in Motion app and Zoom. The tablet that will be given to participants will only have the active BMHP - Health in Motion app and the Zoom app. Participants will be instructed to use the tablet only to complete study-specific tasks. Participants' accounts and collected data will be de-identified and associated only with their study-specific ID number. We will not collect or store any identifiable information about them, such as their name or date of birth, on either the BMHP - Health in Motion app, Zoom account and tablet. The data from these devices will be saved internally on our secure departmental drive. All research staff members complete annual HIPAA for Researchers training as required by UF.

Risk associated with the urine pregnancy test

The pregnancy test may provide a false-positive or false-negative result. To minimize this risk, participants are encouraged to take an additional urine pregnancy test to confirm the result.

## 8. Possible Benefits:

Importantly, the proposed project should have tangible benefits for participants. These benefits include information about their health and assessments of their physical function status. All study participants will be encouraged to communicate the results from the study to their primary care providers. Moreover, participants in exercise groups will receive remotely delivered exercise training at their home. We expect that these benefits will improve quality of life for participants.

## 9. Conflict of Interest:

None

## Literature cited


1. Prescott, H.C. and D.C. Angus, *Enhancing Recovery From Sepsis: A Review.* JAMA, 2018. **319**(1): p. 62-75.
2. Stortz, J.A., et al., *Benchmarking clinical outcomes and the immunocatabolic phenotype of chronic critical illness after sepsis in surgical intensive care unit patients.* J Trauma Acute Care Surg, 2018. **84**(2): p. 342-349.
3. Mira, J.C., et al., *Persistent Inflammation, Immunosuppression and Catabolism Syndrome.* Crit Care Clin, 2017. **33**(2): p. 245-258.
4. Gardner, A.K., et al., *The Development of Chronic Critical Illness Determines Physical Function, Quality of Life, and Long-Term Survival Among Early Survivors of Sepsis in Surgical ICUs.* Crit Care Med, 2019.
5. Hawkins, R.B., et al., *Chronic Critical Illness and the Persistent Inflammation, Immunosuppression, and Catabolism Syndrome.* Front Immunol, 2018. **9**: p. 1511.
6. Dos Santos, C., et al., *Mechanisms of Chronic Muscle Wasting and Dysfunction after an Intensive Care Unit Stay. A Pilot Study.* Am J Respir Crit Care Med, 2016. **194**(7): p. 821-830.
7. Pahor, M., et al., *Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial.* JAMA, 2014. **311**(23): p. 2387-96.
8. Flynn, S.M., et al., *Reliability, Valdity, and Usability of a Digital Educaiton and Self-assessment App for Adults with Knee Osteoarthritis.* Gerontechnology, 2018. **17**(Supplemental): p. 158s.
9. Hall, C.D., et al., *Development of Rock Steady 1.0- a mobile, gamified vestibular rehabilitation therapy app*, in *International Conference for Vestibular Rehabilitation*. 2018.
10. Walker, B.A., et al., *Establishing the Reliability and Validity of Health in Motion Automated Falls Screening Tool.* Advances in Aging Research, 2018. **7**(03): p. 39.
11. Flynn, S.M., et al., *Feasibility, Usability, Efficacy of Health in Motion Otago- a Digital Fall Prevention Program.* Physical Therapy Journal, 2019. **submitted**.
12. SM Flynn, O.V., Hoffmann WN, Grindo T, Limberg T, Niemeier JP, Robinson K, Stearns M, Smith BK *Initial Usability and Validation of Inspiration Point: A Digital Pulmonary Rehabilitation Tool for Use with Self-Management Interventions*. in *American Association of Cardiovascular and Pulmonary Rehabilitation*. 2018.
13. American College of Sports, M., et al., *American College of Sports Medicine position stand. Exercise and physical activity for older adults.* Med Sci Sports Exerc, 2009. **41**(7): p. 1510-30.
14. Pavasini, R., et al., *Short Physical Performance Battery and all-cause mortality: systematic review and meta-analysis.* BMC Med, 2016. **14**(1): p. 215.
15. Fisher, S., et al., *Short Physical Performance Battery in hospitalized older adults.* Aging Clin Exp Res, 2009. **21**(6): p. 445-52.
16. Clegg, A., et al., *The Home-based Older People's Exercise (HOPE) trial: a pilot randomised controlled trial of a home-based exercise intervention for older people with frailty.* Age Ageing, 2014. **43**(5): p. 687-95.
17. Bray, N.W., et al., *Exercise prescription to reverse frailty.* Appl Physiol Nutr Metab, 2016. **41**(10): p. 1112-1116.
18. Pendlebury, S.T., et al., *Telephone assessment of cognition after transient ischemic attack and stroke: modified telephone interview of cognitive status and telephone Montreal Cognitive Assessment versus face-to-face Montreal Cognitive Assessment and neuropsychological battery.* Stroke, 2013. **44**(1): p. 227-9.