Title: Predictors of Recovery and the App-Facilitated Tele-Rehabilitation (AFTER) Program for COVID Survivors

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Project Title: Predictors of Recovery and the App-Facilitated Tele-Rehabilitation (AFTER) Program for COVID Survivors
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I. Hypotheses and Specific Aims:

Nine months ago, SARS-CoV-2 was first identified as the cause of the severe disease, COVID-19. Older adults and adults with comorbidities or disability are at highest risk for morbidity and mortality from COVID-19, with adults aged 65 and older accounting for 25% of cases but 80% of deaths. However, many healthy middle-aged adults without underlying risk factors also experience severe disease, likely driven by a profound and exaggerated inflammatory response. Those who develop severe COVID-19 with acute respiratory distress syndrome (ARDS) often require prolonged mechanical ventilation with prone positioning to maintain adequate oxygenation. In contrast to most other hospitalized patients, patients with COVID-19 have limited contact with hospital personnel (including rehabilitation providers) due to infectivity and shortages of adequate personal protective equipment. These critically ill patients experience more severe disease, are exposed to even more sedation and neuromyotoxic agents, which, in turn, are associated with poor long-term outcomes. Even patients with less severe COVID-19 who do not require lengthy hospitalization often experience prolonged fatigue, myalgias, and activity-limiting dyspnea. Although the long-term consequences of COVID-19 are not yet known, we hypothesize that the combination of immobility, limited in-hospital interventions, and heightened inflammation will have detrimental effects on physical function lasting well beyond that seen with other critical illness. The functional consequences of this disease will be further exacerbated by more limited opportunities for post-hospitalization rehabilitation with 'stay-at-home' restrictions and the stress and uncertainty of a more extended global pandemic.

Our overarching hypothesis is that both healthy middle-aged and older adults with multimorbidity who experience the 'accelerated aging' effects of profound inflammation associated with COVID-19 will experience significant ongoing physical and neuropsychological impairment (Aim 1 of parent grant, approved through COMIRB 20-0703 and COMIRB 20-0690). Novel, scalable interventions that can overcome many of the barriers imposed by COVID-19 are urgently needed to reverse physical and neuropsychological impairments and prevent the long-term functional consequences (Aim 2 of parent grant, described in this protocol). We will investigate this hypothesis through the following aim**:**

Aim: Investigate the feasibility and initial efficacy of a multicomponent tele-rehabilitation program during COVID-19 recovery.

Hypothesis A: Tele-rehabilitation is safe and feasible. We anticipate that no injuries will occur, ≤20% of telehealth sessions will experience technical difficulties, ≥50% of participants will adhere to the exercise program, and ≥50% of participants will use the Platform between face-to-face online sessions.

Hypothesis B: Participation in tele-rehabilitation improves physical function (measured by 30 Second Chair Stand Test) compared with controls.

This study will contribute immediately to our knowledge of the course of recovery for survivors of COVID-19 and will advance the feasibility of tele-rehabilitation as a more generally useful intervention in patients lacking access (distance, availability, mobility) to standard rehabilitative services. Overall, development of effective tele-rehabilitation programs as alternatives to delivering rehabilitation to populations lacking access could transform the way in which we deliver acute rehabilitation and post-hospital care for all patients.

II. Background and Significance:

Significance of the proposed research centers on: 1) the recent COVID-19 pandemic that has unknown impacts on long-term health among patients who survive the disease; and 2) the need to deliver care to patients who are recovering from COVID-19 while concurrently in quarantine or with limited in-person care availability.

COVID-19 is a Pandemic with Unknown Long-Term Impacts on Health

The novel coronavirus SARS-CoV-2 was first identified as causing severe infection (COVID-19) in December 2019. COVID-19 appears to be associated with greater mortality, thromboembolic disease, and acute respiratory distress syndrome (ARDS) compared with usual seasonal viruses.[1] Older adults and adults with comorbidities or disabilities are among those at highest risk for morbidity and mortality,[2] although healthy younger adults with a profound, exaggerated inflammatory response are also experiencing severe disease. Based in part on the post-hospitalization CT scan findings of COVID-19,[3] experts suspect that a significant portion of patients will experience post-COVID decline in lung function and longer-term physical function impairments.[4,5] Further, some patients with COVID-19 require admission to the intensive care unit (ICU) and/or mechanical ventilation, both of which have negative impact on health outcomes. Health outcomes following COVID-19 related hospitalization and the long-term impact of this infection on return to function is unknown.

Need to Identify Predictors of Physical and Neuropsychological Recovery After COVID-19

Beyond lung function impairments, up to half of all survivors experience profound reductions in physical, cognitive, and psychologic function post-critical illness.[6] This Post-Intensive Care Syndrome (PICS) impacts and is associated with marked reductions in health-related quality of life, inability to return to work, increased healthcare utilization, and premature death.[7] The prevalence of PICS is higher with increasing age, and older adults with critical illness experience worse long-term outcomes than their younger counterparts.[8,9] Early ICU rehabilitation and implementation of the standard critical care "ABCDEF bundle" to reduce sedation, limit immobility, and promote early ventilator liberation are key to preventing PICS. ***Notably, these interventions are not feasible in the setting of COVID-19***.[7,8] A shortage of personal protective equipment, isolation precautions, and limited personnel make the delivery of routine hospital rehabilitation nearly impossible. Additionally, the severity of disease and the need for interventions known to increase the risk of PICS, including neuromuscular blockade and excessive sedation, place COVID-19 patients at particularly high risk of developing poor post-hospitalization outcomes.[9] Thus, in addition to the expected high hospital morbidity, post-hospital recovery will be prolonged, leading to significant reductions in quality of life, mobility, and ability to return to work or prior activities.

Patients hospitalized with less severe COVID-19 are also expected to have major mobility limitations following COVID-19. Interventions to promote early mobility in hospitalized patients are key for preventing the loss of functional independence experienced by many older adults.[10]

Infection control measures for COVID-19 keep patients restricted to their room with little opportunity for walking. For infection control purposes, even in-room chairs have been removed from dedicated COVID-19 units, resulting in prolonged bedrest. The commonly experienced symptoms of dyspnea, profound fatigue, confusion, dizziness, and myalgias[11-13] further limit in-hospital mobility and are expected to contribute to significant functional impairment following hospitalization.

In addition to physical impairments, the fear and uncertainty associated with COVID-19, restriction on hospital visitors, and need for post-hospitalization physical distancing or quarantine are expected to contribute to longer-term social isolation, stress, and anxiety.[14,15] Patients are at high risk for delirium because of direct central nervous system invasion of SARS-CoV-2, high levels of inflammatory markers, prolonged ventilation time, and use of sedation.[16] Additionally, measures to limit hospital-related delirium, including avoidance of urinary catheter placement, presence of family members to help orient patients, and bedside sitters for safety are severely limited or not possible. These factors will exacerbate the neuropsychological effects of critical illness and prolonged hospitalization, placing patients at increased risk for adverse neuropsychological outcomes. Indeed, survivors of other novel respiratory viruses experienced lower quality of life than survivors with less severe illness[11,17,18] or than the general population 6 months following hospitalization.[12]

Need to Deliver Care to Patients Recovering from COVID-19 with Physical Distancing or in Quarantine

The unprecedented factors associated with care delivery in patients with COVID-19 require novel approaches for rehabilitation. Virtual services may be a viable alternative for rehabilitation delivery. Tele-rehabilitation in the outpatient setting allows patients to access rehabilitative services in their preferred environment, potentially improving adherence and tolerability of long-term therapy. However, at the time of grant submission, there were no published studies using tele-rehabilitation services following a critical care hospital admission and only one registered trial (NCT03926533) developing multi-disciplinary telehealth strategies in addition to in-person care following a diagnosis of PICS related to septic shock and ARDS. Accessing in-person services immediately following COVID-19, however, will not be possible for many discharged patients due to personal quarantine requirements or other household contacts with COVID-19. Even following the quarantine period, in-person rehabilitation may not be feasible due to limitations imposed by physical distancing regulations, closure of outpatient facilities, limited personnel, ongoing mobility limitations, need for institutionalized care, or fear of triggering memories associated with hospitalization that exacerbate psychological distress. **Tele-rehabilitation has not been as widely implemented as telemedicine because of the need for hands-on interventions** and concerns regarding safety during activities.[15] Therefore, developing the means to provide tele-rehabilitation in this population will not only help prepare for anticipated future pandemics including a likely second wave of COVID-19, but also facilitate future applications to other populations (e.g., rural, mobility-restricted, low resource settings). This study proposes to develop these means through innovative applications of existing tele-rehabilitation technology.

III. **Preliminary Studies/Progress Report:**

Preliminary Data

As of May 11, 2020, when the NIH proposal was submitted, 19,879 persons in Colorado had been diagnosed with COVID-19, with the majority (>70%) of those cases occurring in the Denver Metropolitan Area. Over 3600 persons had been hospitalized (50% ≥ 60 years) and 987 had died (91% ≥60 years) as per data from the Colorado Department of Public Health. As the

largest academic and tertiary care hospital in the Denver Metropolitan Area, the University of Colorado Hospital (UCH) has cared for a large proportion of these patients.

Investigative Team Experience

Our research team includes cross-disciplinary expertise in Infectious Diseases, Geriatrics, Critical Care Medicine, Physical Therapy and Rehabilitation, and Statistics, and leverages both rich previous collaborative experiences and innovative new collaborations to enable success. Co-PI Erlandson is a clinical researcher and physician in infectious diseases with additional training in gerontology who has experience in implementing exercise interventions in vulnerable older adults with HIV (R01AG066562, K23AG050260), in implementing electronic consultations (U01HL142103) and validating electronic disability assessments (R21 AG062380) for older adults, and in longitudinal physical function assessments related to statin therapy (R01AG054366). PI Stevens-Lapsley has more than 20 years of clinical research experience in working with medically complex patients and interdisciplinary teams in implementing rehabilitation programs (NIH R01 NR016209, VA RR&D I21 RX002054, VA RR&D I01 RX001978, NIH R01 HD065900, NIH R03 AR054538, NIH K23 AG029978, and NIH R01 AG056585). Dr. Stevens-Lapsley also has prior experience in implementing the tele-rehabilitation platform in collaboration with Dr. Flynn (NIA R44 AG055341; see Letter of Support). Dr. Erlandson and Dr. Stevens-Lapsley have also interacted through the Division of Geriatrics IMAGE team. Dr. Jolley focuses on the role of muscle injury/repair on long-term recovery after critical illness, explores biomarkers of muscle injury and regeneration in critically ill patients (K23AA026315), and directs the ICU Recovery clinic at UCH. Additional expertise is provided by Dr. Nordon-Craft who has overseen multicomponent rehabilitation programs in hospitalized patients receiving intensive care as well as post-hospitalization (home health) in collaboration with Dr. Jolley. Dr. MaWhinney (Delson) has collaborated with Dr. Erlandson for more than 10 years and has extensive experience in the design and monitoring of clinical trials.

IV. Research Methods

Justification for changes:

Given the rapidly developing nature of the COVID pandemic and the short timeline for submitting the initial NIH grant proposal, we have subsequently made some changes to the design of the study that will improve the quality and rigor of the science and allow for more robust comparisons. The NIH allows for changes in design that improve the quality and rigor of the science. Notably, we have added a control group (n=15) that will receive a tablet with standard guidelines for exercise following COVID-19 infection and hospitalization, the Platform (for testing only) and a Fitbit activity monitor, but not any formal tele-rehabilitation. To collect safety data and encourage retention, a research assistant will contact control participants 1x/week over the course of the intervention (12 weeks). The intervention group (n=30) will receive care as described herein. Therefore, the total projected sample size for this study will be 45 participants. Including a formal control group in addition to the intervention group will allow for more robust evaluation of the value of tele-rehabilitation sessions combined with biobehavioral interventions. We will still be able to compare both the intervention and control groups described to a no-treatment sample that is followed as part of COMIRB 20-0703. We therefore believe the proposed changes are justified to improve the quality of the science and the comparisons/conclusions we will be able to make from these data.

Research Design and Methods

For this rehabilitation pilot, individuals from a separate hospital follow-up study (COMIRB 20-0703) who are 35 years of age and older and speak English will be randomly approached regarding potential participation. Participants will also be recruited through treatment relationships with Dr. Jolley, Dr. Erlandson, and Dr. Pisney (Co-Investigators). Participants will also be recruited via HIPAA A and COMIRB approved flyers in Colorado. Individuals who consent to participate will be randomly allocated to the intervention or control group in a 2:1 ratio; randomization will be stratified based on age (<55 and ≥55), length of mechanical ventilation (<5 days, ≥ 5 days), and gender. The **A**pp-**F**acilitated **Te**le-**R**ehabilitation (AFTER) program involves tele-rehabilitation delivered in individual formats with biobehavioral interventions to augment adherence and recovery. Outcome assessors will be blinded to group allocation within the AFTER program.

A. Outcome Measure(s):

Data Collection and Outcomes.

Outcomes, unless specified otherwise, will be collected at baseline, week 6 (primary endpoint), week 12, and week 26. Baseline testing will occur following the pre-session to set up the Platform and prior to the Physical Therapy Evaluation (session 1). The primary functional outcome for Hypothesis B (30" chair stand test) will be collected through the Platform (more details below). Each test session will include the standardized procedures described in the next sections. Importantly, all test sessions will occur in the participant's home and when possible, be facilitated via the Platform and verified concurrently by a trained outcomes assessor who oversees the testing remotely.

Feasibility (Hypothesis A) will be measured by program adherence, defined as the number of sessions attended divided by the total number of prescribed sessions (n=12). Individuals will be considered adherent if they attend at least 75% (9 visits) of the total sessions. Secondary adherence will be measured by the number of days the HEP is completed divided by the total number of prescribed sessions (n=60 [5x/12 weeks]), with adherence defined by completion of ≥ 75% (45 sessions) of prescribed sessions. System Usability Scale (SUS) will be collected at program end only. The SUS is a 10-item survey that uses a 5-point Likert scale (Strongly disagree (1) to Strongly agree (5)). Scores range from 0 to 100 and higher scores indicate better usability. It is a valid scale and is frequently used by the Platform to assess its usability. Safety will also be measured as a marker of feasibility. Safety events will be categorized and counted; safety events will be collected during each session and through the diary feature on the Platform. Additionally, falls will be graded using the Falls-Grading Scale.[83] The scale ranges from 1 to 4; a grade of 1 is defined as a near fall, grade 2 is a fall that does not receive medical attention, grade 3 is a fall that requires medical attention but no hospital admission, and grade 4 is a fall resulting in hospital admission. All the aforementioned outcomes will be collected in the intervention group, and only safety will be collected in the control group.

Initial efficacy for change in physical function will be measured by the 30" Chair Stand Test (Hypothesis B primary outcome). The 30" Chair Stand Test requires only a standard height chair (approximately 45cm) and can be visualized on video. The test requires the participant to stand up and sit down as many times as possible in 30 seconds. To facilitate accuracy of the test over video, the participant will be instructed to count out loud during the test each time he/she stands. Further, the test will also be facilitated by the Platform. The 30" Chair Stand Test is responsive to change. Initial efficacy for behavior change will be assessed by Average Daily Step Count, PROMIS Short Form (SF) v1.0 General Self-Efficacy 4a, and PROMIS Short Form (SF) v1.0 Self- Efficacy for Managing Chronic Conditions. Average Daily Step Count (per week)

will be collected via Fitbit. The PROMIS SF v1.0 General Self-Efficacy 4a was developed from the NIH self-efficacy scale, and the short form consists of 4 items rated on a 5-point Likert scale [I am not at all confident (1) to I am very confident (5)].[84] The PROMIS SF v1.0 Self-Efficacy for Managing Chronic Conditions will also be collected since items on this scale are more specific to managing symptoms during various tasks. The short form is an 8-item scale rated on a 5-point Likert scale which is identical to the General Self-Efficacy scale. It has been validated in individuals with chronic neurological and general medical conditions.[85] For both PROMIS measures, a higher score is indicative of higher levels of self-efficacy. Additional outcomes for Hypothesis B include 4-stage balance test, Timed Up-and-Go test, MRC dyspnea, and activities-specific balance confidence (ABC) scale to identify and monitor fall risk. The PROMIS Scale v1.2 Global Health will be used to measure quality of life; a higher score is indicative of better quality of life. The 3-Item Loneliness scale will be used to assess loneliness. The Patient Health Questionnaire 8 (PHQ8) will be used to measure depression; a higher score indicates increased severity of depressive symptoms. All the aforementioned outcomes will be collected in both groups.

The following is specific to data collected through the Platform:
In addition to the data regarding comorbidities and hospitalization which is collected through medical record review as part of COMIRB 20-0690 and 20-0703, data will be collected through the Platform. The Platform can track usage data, results from tests and measures, and health information. Usage data will be used to monitor and describe adherence to prescribed activities (e.g., Home exercise program, learning modules). It will also be used to collect the following outcomes: 30" Chair Stand Test, Timed Up-and-Go test, 4-stage balance test, system usability scale, activities-specific balance confidence (ABC) scale, and the PROMIS Scale v1.2 Global Health. While participants will be encouraged to use the Platform for this data collection since it is part of our feasibility outcome, alternatives will be provided for the main testing points (baseline, week 6, week 12and week 26) to achieve complete data collection. Through the health diary feature, participants will be encouraged to log data pertaining to but not limited to medical history (medications, comorbidities), smoking status, demographics (age, gender, height, weight), and health events (e.g., hospitalization, injury, fall). This data entry is optional and completed via self-report. Any data entered into the Platform will be accessible by the research team. The participant's name is NEVER associated with the Platform in any way, and once a participant is enrolled, he/she will be assigned a login/password such as "Telerehab_P01" to indicate telerehabilitation study and participant 01; the initial account password is randomly generated through Blue Marble's webapp.

B. Description of Population to be Enrolled:

Potential participants will be recruited ideally during the first 2 to 6 weeks following hospital discharge to home, though if recruitment targets are slow, enrollment will be allowed up to 12 weeks post-discharge to home.

Inclusion Criteria:

1. Confirmed COVID-19, per diagnostic criteria (PCR testing)
2. Hospitalized for at least 24 hours
3. 35 years of age or older
4. Able to provide informed consent
5. Internet capability to access the platform
6. Community-dwelling prior to hospitalization

Exclusion Criteria:

1. Unstable medical comorbidities that would preclude participation in exercise
2. Receipt of >1 session of outpatient physical therapy
3. Known pregnancy, as the impact on physical function, pulmonary function, and other outcomes will vary well beyond any expected effects of COVID 19
4. Not anticipating concurrent additional physical therapy services during study period (12 weeks)

Participants will be consented either face to face or via remote e-consent. Participants who consent remotely will be provided an e-consent via REDCap. The e-consent will be available to the participant prior to the consent discussion. A qualified study team member will Zoom phone/video call the potential participant. The potential participant will verify their identity. The study team member will explain the consent process and that the participant can navigate forward and backward through the consent form pages and that they may return to the form later if they want time to think about their participation. The study team member will read the consent form with the participant and will answer all questions that the participant has. The participant and the study team member will both sign and date the consent form and the participant will be able to download or email themselves a copy of the signed form.

C. Study Design and Research Methods

Participants will be recruited from COMIRB 20-0703 and via HIPAA A throughout Colorado.

Procedures will include
Virtual assessments include:
1) *30" Chair Stand Test (Primary Outcome)*. The 30" Chair Stand Test requires only a standard height chair (approximately 45cm) and can be visualized on video. The test requires the participant to stand up and sit down as many times as possible in 30 seconds. To facilitate accuracy of the test over video, the participant will be instructed to count out loud during the test each time he/she stands. Further, the test will also be facilitated by the Platform. The 30" Chair Stand Test is responsive to change.

2) Timed Up-and-Go (TUG) Test: The TUG test measures the time it takes for a person to rise from a chair, walk 3 meters, turn around, walk back to the chair, and sit down. Patients are asked to walk as quickly but as safely as they can.

3) 4-stage balance test: The 4-stage balance test measures static balance in 4 different positions (narrow base of support, semi-tandem, tandem, and single-leg). The test is facilitated by the Platform; it requires participants to hold each position for up to 10 seconds. If a participant is unable to hold a position for 10 seconds, the next hardest position is not performed (e.g. if participant unable to hold semi-tandem for 10 seconds, then the test stops, and tandem and single-leg stance are not assessed). The 4-stage balance test is indicative of fall risk.

4) *MRC Dyspnea*. Interviewer-administered or self-report assessment of the perception of difficulty breathing during five different tasks. Participants respond either yes or no to each task.

5) *Montreal Cognitive Assessment (MoCA)-BLIND*. The MoCA-BLIND is an adapted version of the original MoCA, a rapid screening instrument for mild cognitive dysfunction. The MoCA-BLIND assesses different cognitive domains: attention, concentration, memory, language, conceptual thinking, calculations, and orientation. The MoCA-BLIND has removed assessments

requiring vision, thus can be completed using telehealth or telephone assessments. It will be collected only at baseline.

Participants will complete online questionnaires including: 1) Assessment of *pre-hospitalization and post-hospitalization frailty*. Participants will estimate function using the Clinical Frail Scale, an easy to interpret estimate of function than has been validated in several populations. The participant will select perceived level of function prior to and following admission ranging from very active to bedridden/terminal. Additional questionnaires are described above for Hypotheses A and B and will be collected either through the Platform or online via REDCap survey.

Characteristics of patients and of the hospitalization are collected from the medical record in all hospitalized COVID-19 patients (COMIRB protocol 20-0690), including duration of hospitalization, need for and duration of mechanical ventilation, comorbidities, medications, demographics, and zip code among others. Post-hospitalization data is also collected, including readmission, need for/duration of supplemental oxygen, receipt of rehabilitation care, imaging, and laboratory results. Electronic medical records for participants not hospitalized in the UCH system will be requested using a HIPAA A form.

The AFTER Program Procedures (Intervention Group).

Participants will begin the AFTER program following enrollment into the study and randomization to the intervention group. The program was developed around key elements of rehabilitation that patients and providers have identified as important aspects: 1) ability to communicate with healthcare providers, 2) ability to monitor response to exercise and progress, and 3) individualized care that changes based on a person's response.[81] The rehabilitation program follows current recommended guidelines and includes therapeutic exercises, functional activities, balance training, and aerobic conditioning.[26] The program will consist of 12 individual sessions. There will be 3 sessions during the first week, 2 sessions per week during weeks 2-4, 1 session per week during weeks 5-6, and 1 booster session during week 9 or 10. Therapists will be instructed on the standardized protocols for individual sessions. During weeks 7-12, in addition to the booster session, if adherence to the HEP drops below 75% as measured through the Platform, the therapist will follow up with the participant.

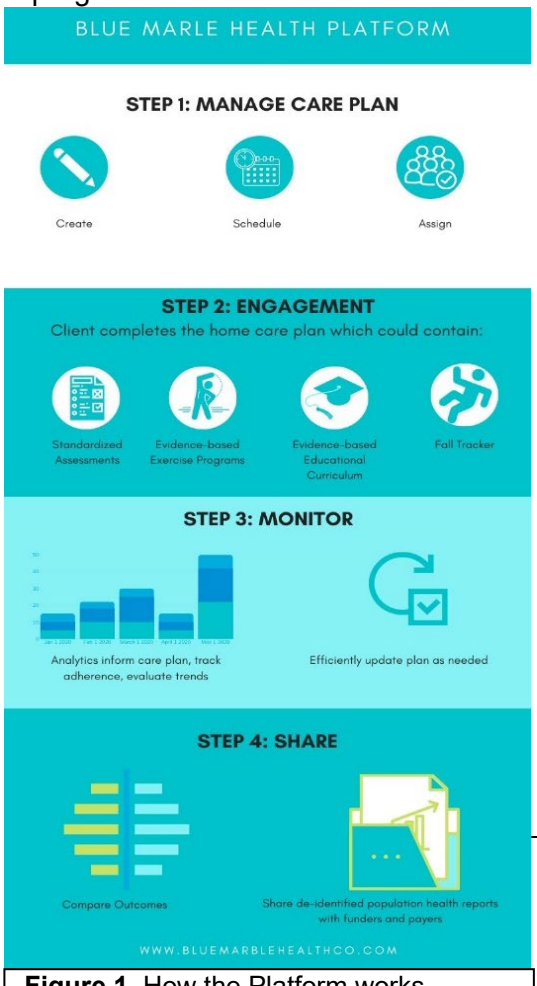

Figure 1. How the Platform works.

Platform.

The Platform is a combination downloadable app (patient-side) and web-app (administrative-side) software tool that contains digital translations of standardized, evidence-based tests, exercises, and educational modules for a variety of conditions (Figures 1&2). The Platform will be used to facilitate multicomponent tele-rehabilitation. Participants will use the app to test and track their physical function, perform avatar-guided exercises, and obtain educational content. The ability to track their activity

minutes, repetitions, changes in resistance difficulty, and session participation will provide necessary feedback for the biobehavioral strategies. The educational content is based on current clinical practice guidelines and recommendations from the National Institute of Health (NIH). Core educational modules will be assigned on topics including the following: management of anxiety and depression, breathing techniques, and healthy eating.

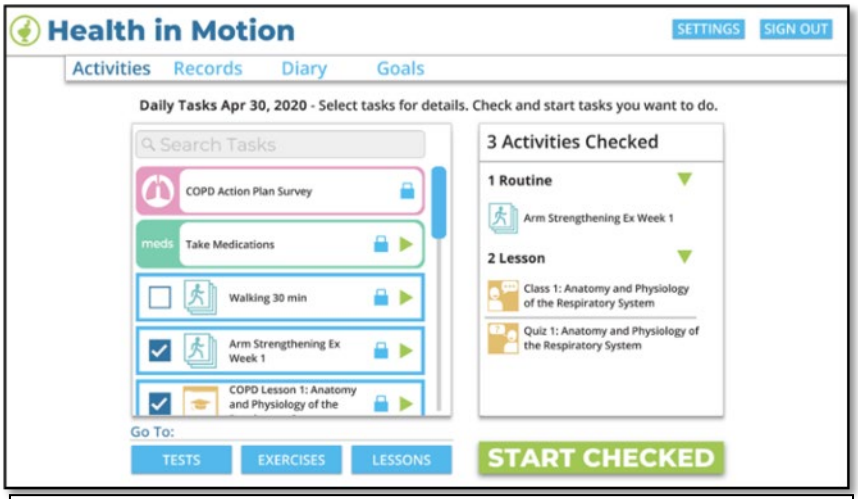

Figure 2. Activities Dashboard.

Figure 3. Example of avatar-led exercise

Therapists can assign personalized avatar-led home exercise programs (Figure 3) to the participant allowing for individual-level modifications to the rehabilitation program. The participant logs into the app, and data is sent instantaneously to the supervising researcher to inform care plans.

The app also has many built-in safety features including 0-10 Rate of Perceived Exertion (RPE) scales for exertion and dyspnea (Figure 4). The Platform is an extensive data collection tool and will allow for detailed tracking of recovery from COVID-19. The Platform is affordable, accessible, scalable, and sustainable. The Platform has completed five validation and efficacy studies and has two ongoing clinical trials funded by NIH (R44AG055341, R44HL137502) with another pilot study (R44DC016245) starting soon. The investigative team has experience working with this tele-rehabilitation technology (NIH R44AG055341) (COMIRB 18-2532).

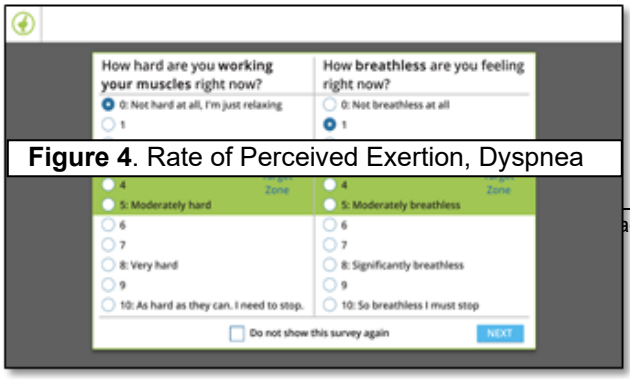

Figure 4. Rate of Perceived Exertion, Dyspnea

<u>Multicomponent Tele-Rehabilitation.</u>

Individual sessions will consist primarily of biobehavioral interventions in addition to assessment and progression of the participant's Home Exercise Program. The first individual session will consist of a standard physical therapy evaluation, which requires approximately 60 minutes. Goals of the evaluation are to establish the participant's baseline physical function and identify impairments, activity limitations, and participation restrictions to inform the individual's personalized plan of care. The participant will also be oriented to the overall structure of the tele-rehabilitation program and the Platform. Remaining individual sessions will primarily focus on biobehavioral interventions (30-45 minutes) and assessment and progression of the Home Exercise Program (15-20 minutes).

Biobehavioral Intervention.

The biobehavioral interventions will be integrated into the tele-rehabilitation program and augmented by the Platform. There will be 10-12 individual biobehavioral intervention sessions of approximately 30-45 minutes/session. The therapist will provide an overview and will develop an action plan with the patient that addresses the seven components of the behavior interventions (Table 2). The biobehavioral interventions will focus on increasing physical activity through various means. For example, the Fitbit will track daily steps to provide participants feedback about daily walking activity; these data will be used to set goals. Additional forms of feedback are provided by the Platform and include percentage completion of assigned exercises; these data can also be used to set goals. Goals will be set and tracked using the Platform Goal feature. Another focus of the biobehavioral intervention is to provide participants with the knowledge and tools to progress their exercise plans; emphasis will be placed on encouraging participants to dose resistance exercises to their 8-repetition maximum (8-RM). Achievement of 8-RM dosing means the participant would be unable to complete a 9th repetition during one set. This principle has been shown to be effective for improving strength and physical function and has been implemented by the research team safely in a medically complex population (Cite-Allison's SNF paper).

Table 2. Components of the Biobehavioral Intervention

Intervention	Progression from Therapist Coaching to Participant Self-Management	
Education	Therapist delivers education topic* (e.g., Self-Monitoring, Problems Solving, Identifying Barrier/Facilitators, Action Plans).	Participant reports most important information learned.
Self-Monitoring	Therapist guides participant in tracking daily activity minutes & session participation since last visit.	Participant tracks weekly activity minutes and session participation.
Tailored Feedback	Therapist leads collaborative review of activity and participation data for action plan goal setting.	Participant leads review of activity and participation data and other physical activity goals.
Barrier/Facilitator Identification	Therapist guides participant to identify barriers/facilitators of goal attainment.	Participant self-identifies barriers and facilitators for goal attainment.
Promotion of Problem Solving	Collaborative generation of solutions to overcome barriers to goal attainment.	Participant generates solutions to identified barriers to goal attainment.
Action Planning	Collaborative activity goal generation. Therapist guides, using 5-10% increase from daily activity minutes from previous week target.	Participant-led weekly goal generation. Therapist ensures independence in action planning.
Encouragement	Therapist reviews plan for the next week, while encouraging participant on successes attained toward improved physical health.	Participant leads the review of the plan for upcoming week.

* Each week will have a specific "take-home" message linking physical activity and movement behavior to health. Messages will be brief and based on research evidence.

Home Exercise Program (HEP).

The HEP will include therapeutic exercises, functional activities, balance training, aerobic conditioning, and breathing practice. Specific exercises will be selected based on results from the physical therapy evaluation, and subsequent adjustments will be made based on patient preference and priorities which will be enhanced in the biobehavioral interventions. In preparation for weeks 7-12, participants will be educated on how and when to progress strengthening and aerobic exercises, and they will take a more active role in determining their own progression. Participants will collaborate with the therapist to develop a robust program. The therapist will remotely monitor as described above, and participants will be responsible for progressing their exercises.

Participants will be screened for safety and high fall risk upon entry into the program, but the **design of the intervention is to target even the most medically deconditioned participants and tailor the program to address any safety concerns** (e.g., sitting exercises with progression to standing as able). Prior to starting the 6-week program, enrolled participants will receive step-by-step instructions to trial the Platform; a research assistant will help the participant troubleshoot technical issues. The treating therapist will modify the set-up as needed during session 1 and throughout the program. The therapist will monitor and assess the patient, progress the rehabilitation program, and track adherence through the Platform and videoconferencing. Validated physical function measures and surveys will also be collected through the Platform at testing timepoints (baseline, week 6, week 12, and week -26), and may be collected up to every 2 weeks during both phases of the program.

Some telerehabilitation sessions will be audio and/or video recorded to verify interventionist fidelity. Participants will be given the option to allow or to disallow any recordings.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

Exercise:
We recognize there may be an increased risk for falls with greater exposure to physical activity and reduced functional capacity due to recent hospitalization. However, the increase in balance, confidence, and mobility gained through this rehabilitation program may also decrease fall risk over the long term.

Confidentiality and privacy:
The use of questionnaires and collection of personal medical information poses a risk to confidentiality and privacy (see Protection Against Risk below). Additionally, subjects may experience distress when answering questions related to their recent hospitalization.

Adequacy of Protection Against Risks

Protection Against Risk:
The inclusion/exclusion criteria are designed to assure that the sample is as representative as possible of the population of patients who are hospitalized for COVID-19 and allows the participants most likely to benefit from the rehabilitation intervention while excluding women who are known to be pregnant and who would therefore have expected variability beyond that of other patients.

Rehabilitation and Exercise:
Intervention will be carefully monitored and progressed on an individual basis by a licensed physical therapist. Education on muscle soreness, shortness of breath, and fall risk reduction

will occur before any intervention is initiated. Education will also include signs of distress that should be communicated to the study team (e.g., dizziness, light headedness, symptoms of myocardial infarction). Participants who are identified to be at risk for falls will initially perform exercises seated or while holding onto a sturdy surface. When training is performed in standing or walking (e.g., conditions with a potential risk for falling), safeguards will be taken to ensure a sturdy surface is nearby for steadying should a loss of balance occur. For the purpose of safety monitoring, we will consider any fall, defined as "inadvertently coming to rest on the ground, floor or other lower level, excluding intentional change in position," (World Health Organization) as unrelated, possibly, probably, or definitely related to study procedures. Baseline fall risk will be evaluated using the Platform (ABC scale questionnaire and the 4 Stage Balance Test) to inform each individual rehabilitation plan. Exercise will then be tailored to address any safety concerns (e.g., sitting exercises with progression to standing as able, additional balance-focused exercises). Occurrence, circumstances around, and injury associated with any fall will be recorded via the Platform's health diary feature and a red flag notice will display on the dashboard if a fall is recorded. The treating physical therapist will also ask about falls and other adverse events (AEs) at each session for the intervention group, and a research assistant will ask about falls and other AEs during each weekly follow-up for the control group. Due to remote nature of the AFTER program, we will institute emergency procedures to respond to any AE that occurs during individual sessions. The physical location of participants will be verified prior to each individual session in the event that emergency response is necessary (call to 911). Any reported falls occurring outside of individual sessions will be discussed at the subsequent individual session or within 24 hours if medical care is required. Fall occurrences (injurious and non-injurious) and other AEs will be reported directly to the PI. Other exercise side-effects, such as muscle pain, fatigue, shortness of breath, and minor strains during therapy will be documented and monitored by Dr. Stevens-Lapsley and Dr. Erlandson in consultation with Dr. Jolley. Based on the existing literature and our own clinical experience with tele-rehabilitation (VA RR&D I01RX002417), we anticipate the frequency of these side-effects to be extremely low.[95]

Confidentiality, privacy, protection of data:
Risks will be minimized by not including personal identifying information on the forms, when possible, and by conducting interviews, functional assessments, and collection of personal information in a secure telehealth platform. All data will be collected using unique patient identification codes. All evaluation forms, reports, and other records will be identified by a coded number to maintain participant confidentiality. All records will be stored in a locked file cabinet. Study data will be collected and managed using REDCap (Research Electronic Data Capture). Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the IRB or NIH. Finally, subjects will be monitored for evidence of distress associated with study completion. Any subjects who express a desire for additional support will be referred to mental health services by Dr. Jolley via established clinical referral pathways.

E. Potential Scientific Problems:

Potential Recruitment Difficulties: Due to uncertainty surrounding the COVID-19 pandemic, there may be difficulty recruiting 45 participants for the study. For September 22-23, 2020, the current census of COVID-19 positive patients in UCHealth hospital was 23 of which 2 were new admits in the past 24 hours. In the same time period, there were a total of 27 admitted patients (1 new in past 24 hours) who tested positive for COVID-19 in hospitals affiliated with the University of Colorado.

Missing Data: All participants with outcome measurements will be included in analysis. The importance of reassessment for data collection will be stressed during enrollment and consent and repeated during study participation. Participants will be contacted repeatedly if they miss reassessment time points, and all efforts will be made to collect data.

Technical Issues: Technical issues are a concern for telerehabilitation and telehealth programs. As such, we have a detailed approach to address any technical issues which may arise.

1. Participants may call the Research PT (or designee) anytime, during regular business hours, with issues or concerns.
2. If a technical issue should arise that the Research PT cannot address, they will contact Blue Marble's Research Associate, Charlotte Kurchian, to discuss.
3. If needed, Charlotte will speak directly with the participant to solve the issue.
4. Although unlikely, Blue Marble's programmer may need to participate on the call to resolve the issue. The programmer has human subjects training.
5. The Research PT (or designee) will keep track of any and all technical issues as this is a feasibility outcome of the study.

F. Data Analysis Plan:

Sample Size: We estimate the proportion of participants at any session with technical difficulties (anticipate ≤20%), use the platform between sessions (anticipate ≥50%), and adhere to the intervention (anticipate ≥50%). Assuming these rates, a sample size of 30 and a two-sided 95% CI, provides a margin of error of 15% for technical difficulties and 18%, for platform use and adherence. We use preliminary 5-time chair rise data to estimate our effect size (SD=8.7) in our outcome and assume adjustment variables, including baseline measures, will explain at least 50% of the total variance (R2). Using linear regression, we anticipate the width of our 95% confidence interval for the group coefficient to be +-0.90*1 SD at week 6. We anticipate additional precision by using all longitudinal outcome data. We will also provide descriptive statistics for the change from baseline over time, for each group.

We hypothesize (B) tele-rehabilitation is associated with improved physical function in participants previously admitted to the hospital, as measured by change in the 30" Chair Stand Test at 12 weeks. Randomization will be stratified by age (<55, ≥55), sex, and length of mechanical ventilation (< 5 days, ≥ 5 days). Hypothesis A: Descriptive statistics will assess feasibility (i.e., adherence, SUS score, and safety). Hypothesis B will be analyzed with group assignment (AFTER program versus control) as the primary explanatory variable; secondary analyses will be made to COMIRB 20-0703 cohort. Analyses will utilize R (https://www.R-project.org), SAS (Cary, NC), and GraphPad Prism (San Diego, CA). Code will be portable and reproducible with documenting libraries and raw data location, as well as code documenting cleaning.

G. Summarize Knowledge to be Gained:

The proposed study will 1) address a great and urgent need to identify predictors of multisystem recovery and long-term health in survivors of COVID-19 and 2) evaluate rehabilitative care to these individuals even, and especially, when they face post-hospitalization barriers to in-person care.

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