Increasing Adherence to Pulmonary Rehabilitation after COPD related Hospitalizations

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General Study Information

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Study Title: Increasing Adherence to Pulmonary Rehabilitation after COPD related Hospitalizations

Protocol version number <u>and date</u>: Version 4, March 3, 2020

Research Question and Aims

Hypothesis: Pulmonary Rehabilitation (PR) is a critical part of chronic obstructive pulmonary disease (COPD) treatment, reducing breathlessness, increasing health-related quality of life (QOL), and decreasing healthcare utilization. However, only a small portion of patients with COPD complete PR, mostly due to access issues or frailty. In this application we propose to test the effectiveness of a home-based PR program developed in our previous NIH awards that aims to improve program adherence, QOL, daily physical activity, and healthcare utilization.

Aims, purpose, or objectives: Aim 1: To refine the current program of home PR (crafted through NIH grant R44HL11416/IRB 14-009016 for out patients) via a pilot test of subjects with COPD after a disease-related hospitalization and further refinement based on a qualitative feedback of patient caregivers and coaches by (a) completing a pilot study of 10-15 subjects and refining the home-based PR program developed in our previous applications to be used in subject with COPD after a hospitalization; and (b) analyzing the experience of subjects, caregivers, and coaches through a formal qualitative study and refining the intervention in year 1. The refined home-based PR program will be tested in a well-powered phase 2 randomized, clinical trial of 150 patients that will be started in the R61 period and finalized in the R33 period.
Aim 2: To start a phase 2 randomized, clinical trial (recruit 30/150) testing the feasibility and study accrual of a refined home-based PR delivered after a COPD related hospitalization compared to a control group of patients referred to conventional PR (center-based) in year 2.

Background: Despite proven benefits, the proportion of people with COPD who receive Pulmonary Rehabilitation (PR) is very small. The current model of a center-based PR program fails to address the needs of many patients with COPD. The most common patient barrier to attendance is travel to center-based programs, particularly for frail patients with more severe COPD who need transportation assistance. Home-based, unsupervised PR has been proposed as an alternative model to hospital-based programs and has been found to be safe and effective. In particular PR post-hospitalization has been reported as the most effective intervention to prevent a hospital readmission; however, the reality is that many times this is not a feasible intervention as only 4% of eligible individuals are able to adhere to PR after a hospital admission (for multiple reasons).While COPD is responsible for nearly 700,000 hospitalizations annually, many of these hospitalizations, which account for a large proportion of the annual direct medical costs of COPD, are potentially preventable readmissions.
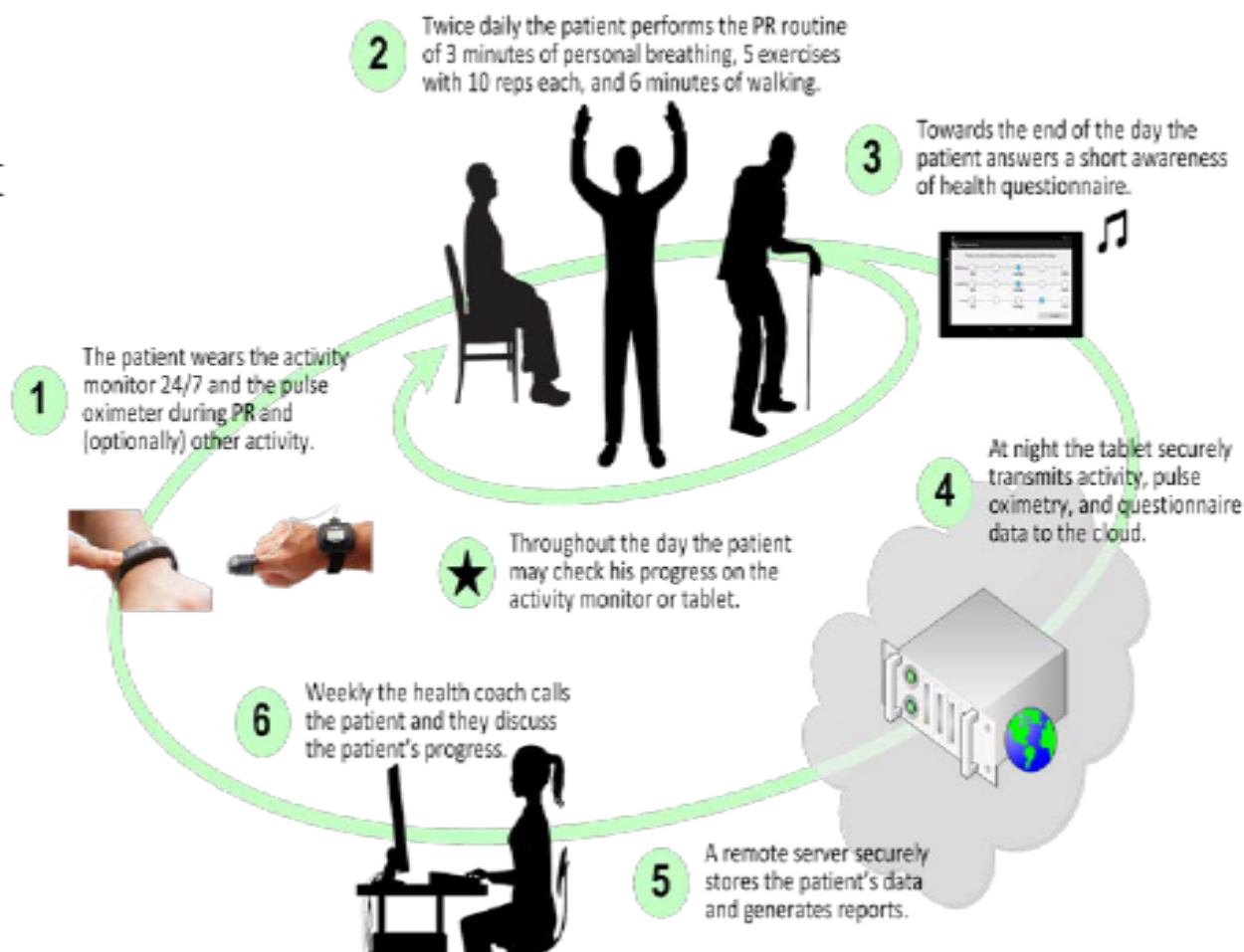
Study Design and Methods

Methods:

Figure 1

Phase 1 (R61): A cohort of 10-15 patients will be recruited after a COPD-related hospitalization (COPD exacerbation or pneumonia) to use the home PR program system plus telephonic coaching for twelve weeks, and provide feedback through a qualitative study to refine the PR program system to be acceptable for the post-hospitalization period. Patients will be recruited until themes saturation (no more new feedback from patients).

We will use a natural language processing program to query the electronic medical records of Mayo Clinic Rochester to identify all patients presenting with COPD-related illness. In addition we will screen the patients admitted to the Chest Service (Domitilla 6B) of Saint Mary's Hospital. The study coordinator will receive the list of participants (with research authorization already processed through the natural language program) and will meet the patient in the hospital before they are discharged.

During the consent process, the patient will have the opportunity to try the proposed home-based PR system in the hospital room, aiding in their confidence in their ability to use the system and the ease of the exercises. The study team will provide a step by step demonstration of the exercises (following the exercises on the computer tablet). The participant will be asked to rate their confidence to use the technology presented and their confidence (self-efficacy) to perform the home rehabilitation routine on a scale from 0 (no confidence) to 10

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(great confidence). A rating of five or greater will be deemed an acceptable confidence level to participate in the study.

Each participant will be asked to define a particular place and time they can perform the home-based PR. The physical and mental environment is critical for the successful adoption of new behavior (PR). Participants will learn about the weekly calls with the coach to discuss their rehabilitation and monitored measures (steps, level of shortness of breath, well-being, and fatigue). They will then go over the daily answers to well-being questions (mood, breathlessness, and energy, as tested in the pilot study and shown in Fig.2; see participant software application section below). After performing the PR routine (to ensure safety and understanding) and reviewing the use of the monitors, a plan for a PR coach call, a week to 10 days after discharge. The participant will use the criterion activity monitor (Actigraph, Fig. 3) that will determine the baseline physical activity during the first week immediately after discharge to define a baseline physical activity. The coordinator will discuss the in-home activities with the participant to identify possible exercise-related fall hazards in the home environment.

Figure 2   Figure 3   Figure 4

Participants are expected to engage in the home-based PR at least six days a week. The Garmin Vívofit™ activity monitor (Fig. 4) is to be worn at all times (battery lasts one year) to capture daily steps and the metabolic equivalent of tasks (METs) per day. The PR routine begins with a slow breathing awareness exercise, "pursed lips breathing," followed by upper-extremity exercises (Fig. 2), then two walks (in the home or outside) for 6 minutes, and finishing with another slow and mindful pursed-lips breathing exercise. The exercise protocol lasts about 20 minutes, which is the amount of *daily dedicated exercise* time associated with a risk reduction in hospitalization and improved QOL22,23 and is recommended by current PR guidelines.13 The proposed protocol is also currently being used by the PI of this proposal in a prospective COPD trial (R01 CA163293) in addition to the work cited in the preliminary data (R44 HL114162). The PR coach will contact by phone or mail the primary care, or referring, provider before initiating the PR program to introduce the provider to the study, as well as to coordinate and develop a strategy in case of a COPD exacerbation (a common cause of PR abandonment).

The proposed home-based PR system (Fig.1) consists of three commercial devices and two software applications. The devices are a Garmin Vívofit™ (AM), a Nonin 3150 WristOx2® Pulse Oximeter (PO), and a 7"

Android™ tablet with 3G/4G cellular service (Verizon). The AM and PO wirelessly communicate with the tablet

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via Bluetooth. During the upper extremity exercise routine and walks, the PO measures the participants' heart rate (HR) and oxygen saturation (SpO2). Near the end of the day, the tablets periodically sound a musical alarm and display a short health status questionnaire (Fig. 2) asking participants to rate their well-being,24 ease of breathing, and energy level. At night, the tablets securely transmit the device data and well-being questionnaire answers to a remote Web server, which securely stores the data and generates reports. Health coaches call the participants weekly to discuss their progress in PR and SM (see below).

Participant software application (tablet): When the participant turns on the Android™ tablet, the application logs in, and the participant accesses to the main screen (Fig. 5). To initiate one of these activities, the user selects the corresponding action from the "To-Do" column. Selecting "Exercise" from the "To-Do" column initiates a video guiding the user through the PR exercises (Fig. 6). Similarly, selecting "Walk" from the "To-Do" column starts a 6-minute countdown once the application detects that the participant has initiated walking. Before displaying the exercise and walking videos the application verifies that the participant is wearing the AM and PO to assure measure and compliance (during exercise an increase in heart rate is expected). When the participant finishes the selected activity, it appears in the "Done" column. The application provides instructions before and between each activity. Patients are asked to follow the videos in all PR sessions to maintain a minimal and equal "dose" of PR for all participants. The oximeter data during exercise is used as a measure of adherence and exercise time.
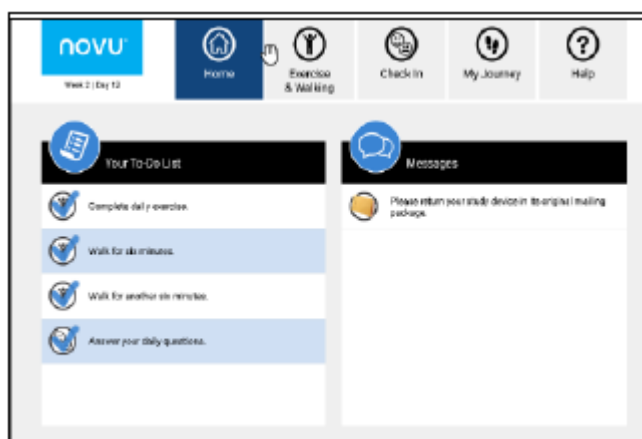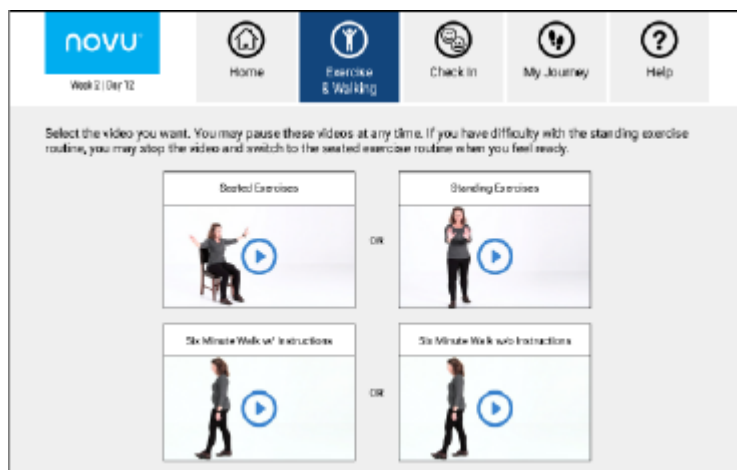

Figure 5

Figure 6

The "my journey" screen (Fig.7) plots historical data, allowing participants to see trends as in the pilot study.

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Figure 7

From this screen, users can view daily steps, average heart rate, SpO2, and questionnaire answers. The user also can select the historical window (e.g., last week, last month, last quarter).

Coaching PR Calls (weeks 1-12) content for PR
feedback plus SM: After the hospital and consenting visit, coaching calls will occur weekly for twelve weeks following this protocol: (1) Listen to the participant's journey. (2) Provide feedback of the PR process at home based on the feedback from the coach application. Sessions will generate dialogue by listening to "change participant's comments on anticipated activities. (3) If problems arise, resist the urge to attempt to solve the participant's problems and barriers. (4) Listen carefully and kindly (ambivalence from the participant in changing their behavior). (5) Discuss how behaviors connect to the participant's values and strengths. (6) Collaborate in setting goal(s) for the following week. A goal can be anything the patient wants to discuss even beyond PR (like smoking cessation, vaccinations, weight loss, etc.) (7) Discuss the process of action planning: elicit the participant's preferences. (8) Elicit the participant's choice; do not assign goals, and use the participant's language to describe the goal. (9) Assess confidence for goal completion, reaffirm commitment to the action plan, and express optimism. (10) Thank the participant and plan the next call.
(11) All calls will be recorded to ensure **fidelity** and **compliance** with the protocol and MI principles (10% of all calls will be reviewed).
Health Coach Software Application: The health coach software application provides three types of reports. The overview report (Fig. 8) allows health coaches to succinctly ascertain the status of their participants and flag anyone who may be experiencing problems. The health coach may select a participant from the overview to display the trend report (Fig. 9). The trend report allows the health coach to review the participant's progress between weekly health coaching sessions. Finally, the health coach may select a day from the trend report to display a detailed report (figure 10).
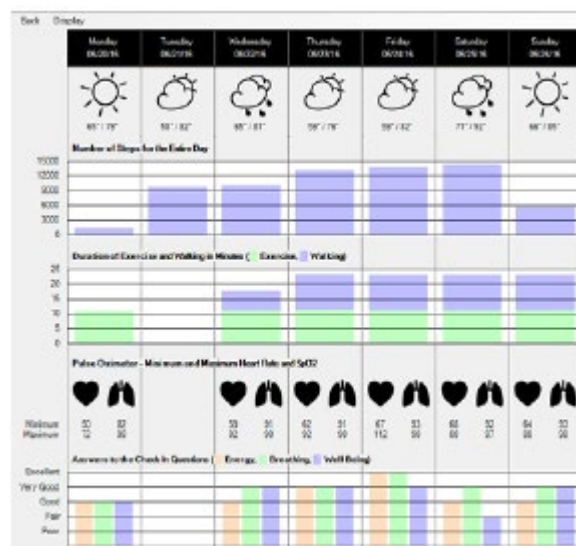
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Figure 8

Figure 9

Figure 10

While participant monitoring does not occur in real time, any significant physiologic abnormaility measured during rehabilitation and transmitted to the server (02 saturation less than 80% or heart reate grater than 140 or less than 40 beats per minute) prompts a message to the coach to call the particpant to investigate the event. The PI also is alerted within 24 hours by tet message if a physiologic abnormality is measured to ensure the appropratie response. In R44HL114162-03 Home-Based Health Management of COPD Patients, the remote rehabilitation and health coaching system has been pilot tested together and found feasible, actionable,and acceptable. After the pilot is completed, a qualitatitve study will be done to identify areas of deficits to be changed and then adapted for the the second phase of the study, a randomized control trial.

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Phase 2 (R61): Mayo Clinic Rochester and Jacksonville Fl will participate in this Phase. Phase 2 will take part in year 2 of the study. After the study has been refined in Phase 1, thirty (30) participants (of the planned 150 subjects) will be recruited and randomized to one of two to the home-based PR or referred to conventional PR (standard of care).   After the 30 subjects are enrolled, the study staff will review the feasibility, informing the team about accrual and outcome completion rate (questionnaires and activity monitors).   This will allow the study team to forcast a complete and informative study for the R33.

The particpants randomized to control/conventional care will be offered mileage reimbursement to and from a pulmonary rehab center. The miliage rate used will be the current IRS standard rate (57.5 cents per mile in 2020). The study will pay mileage up to a total of $500. Study staff will use MapQuest to determine the miles from participants residence to the rehab center. The participants will be asked to sign an Authorization to Release Protected Health Information-Research in order to obtain Pulmonary Rehabiliation Records. Mileage will be paid monthly when possible, or when in reciept of the medical records confirming attendence.

Phase 3 (R33): Mayo Clinic Rochester and Jacksonville Fl will participate in this Phase.   After review of the first 30 participants, the remaining 120 patients with a COPD-related hospitalization (exacerbation or pneumonia) will be randomzied at hospital discharge to the home-based PR or usual care (referral to conventional center-based PR). Inclusion, exclusion criteria and recruitment will be identical to the Phase 1 and 2 of the study. Randomization will be completed online through a centralized program Research Electronic Data Capture (REDCap).

The participants randomized to home-based PR will follow the same procedures in the R61 phase, plus any changes suggested by the qualitative study. Any changes will involve a protocol modification and submitted to the IRB for review.

Questionnaires and Activity Monitor: All participants will be asked to complete questionnaires and wear a small activity monitor (Actigraph) at Baseline and Months 3,6 and 12.   The participants will be supplied with postage paid envelopes to return the questionnaires and activity monitor.

Questionnaires: Questionnaires include the Medical Research Council (MRC), Chronic Respiratory Questionnaire (CRQ), EureoQol-5D (EQ5D), Patient Health Questionnaire- 9 question (PHQ9), General Anxiety Disorder – 2 question (GAD2), Interpersonal Support Evaluation List (ISEL), Self-Management Ability Scale (SMAS30), Linear Analog Scale Assessment (LASA) , Meaning in Life Questionnaire (MIL) and the Working Alliance Inventory (WAI). All questionnaires with the exception of the WAI will be administered at baseline and 3, 6 and 12 Month. The WAI questionnaire will be administered when the participant has completed the Health Coaching Period. For participants randomized to the Intervention arm, the WAI will be administered at 3 months. Participants randomized to the Control/Wait arm will receive the WAI at 6 months. The Charlson Cormobidity Index (CCI) will be included in the baseline questionnaire packet. The CCI will assist in summarizing the enrolled subjects in statistical models.

The PHQ9 will be reviewed by study staff within 24 hours of receiving the questionnaire in the mail. The study staff will score the PHQ9 and a total score >14 (15 and above) and Item 9 is a zero will prompt a review of medical records for current mental health treatment (in consultation or pharmaceutically) of depression. If the patient is not being treated for mental health issues a licensed health care provider will contact the patient and offer a referral or other treatment suggestions.   If anything other than "not at all" on Item 9 "Thoughts that you

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would be better off dead or of hurting yourself in some way? The participant will be called by a licensed health care provider.

Health Care Utilization: The Study Coordinator will contact all participants at Months 3,6 and 12 via telephone to determine health care utilization, the participants will be asked how many times they have gone to the doctor/Emergency Room/Hospital for breathing problems. In addition, the particpants will be asked if they have taken antibiotics or prednisone for breathing related illnesses since the last time the Study Coordinator called them.

Conventional PR group: Referral to Conventional PR (retention strategies)
We plan to optimize the possibility of patients referred to conventional PR to attend by generating a dialogue about the importance of PR, facilitating the referral and then follow up with a call. This optimization initiative includes targeting the most prevalent problems that explain the current poor utilization of the traditional hospital-based PR after a hospitalization: (1) lack of a referral or strong recommendation from a physician (we plan to do a dedicated referral to the [patient indicating the nearest PR program and contact information including the proper referral order), and (2) inadequate follow-up or facilitation of enrollment after referral (we will communicate with the individuals two weeks after discharge to encourage PR program adherence). Finally, we acknowledge that many patients/caregivers will clearly express being unable to attend conventional PR and realize then that the control arm receive no active intervention. The latter is a significant problem in behavioral interventions that cannot be blinded. *To palliate that problem* and given that the project targets daily physical activity, we will provide every individual in the conventional PR group a Garmin Vivofit (Fig. 3), an activity monitor that has a large display and is easy to use so that they can monitor steps every day. We have ample experience on the use of this monitor in current pour proposal. This is the same monitor that individuals in the Home PR receive for daily use. The study does not cover standard of care treatment. **Home PR group: Proceedings will be as in the pilot study plus refinement (see R61, Phase 1 and 2).**

Recording of calls and qualitative interviews: All health coaching calls and the qualitative interviews will be recorded. The health coaching calls are recorded and the voice file saved on a secure research drive that only study team has access too. The files are saved under the participants subject number and the week of the call. The calls are randomily selected to be reviewed by the PI Dr. Benzo and the Fidelity Officer, Dr. Matt Clark. Dr.'s Benzo and Clark will score the health coach using the MITI worksheet (attached, Appendix 1). The voicefiles will be deleted off of the research drive at the end of the study.

Resources:
The Mindful Breathing Lab has a dedicated staff assigned to the PI, Dr. Benzo. The Mindful Breathing Lab has space located on the 8th floor of Stabile and an exam room on Gonda 18 South. Mayo Clinic Rochester will be part of all phases of the study.
Margaret Johnson is Co-Investigator located in Jacksonville, FL. Margaret Johnson is a Pulmonologist and has vast experience treating COPD patients. Dr. Johnson has a study coordinator dedicated to her COPD studies. Mayo Clinic Florida will take part in Phase 2 and Phase 3.

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual:
Study 1 (R61): 15 participants
Study 2 (R33): 150 participants

Subject population (children, adults, groups): Men and Woman 40 years of age or older, who have been hospitalized with a COPD related illness.

Inclusion Criteria
- COPD related hospitalization and eligible for PR
- Age 40+
- Confidence (score > 5 in a self-efficacy question (1-10 scale): how confident you feel to use this system on a daily basis)

Exclusion Criteria
- Inability to walk (orthopedic-neurologic problems or confined to bed)

Research Activity

Check all that apply and complete the appropriate sections as instructed.

1. ☐ **Drug & Device**: Drugs for which an investigational new drug application is not required. Device for which (i) an investigational device exemption application is not required; or the medical device is cleared/approved for marketing and being used in accordance with its cleared/approved labeling. (Specify in the Methods section)

2. ☐ **Blood**: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture.

3. ☐ **Biological specimens other than blood**: Prospective collection of human biological specimens by noninvasive means that may include: urine, sweat, saliva, buccal scraping, oral/anal/vaginal swab, sputum, hair and nail clippings, etc.

4. ☒ **Tests & Procedures:** Collection of data through noninvasive tests and procedures routinely employed in clinical practice that may include: MRI, surface EEG, echo, ultrasound, moderate exercise, muscular strength & flexibility testing, biometrics, cognition testing, eye exam, etc. (Specify in the Methods section)

5. ☒ **Data** (medical record, images, or specimens): Research involving use of existing and/or prospectively collected data.

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6. ☒ **Digital Record**: Collection of electronic data from voice, video, digital, or image recording. (Specify in the Methods section)

7. ☒ **Survey, Interview, Focus Group:** Research on individual or group characteristics or behavior, survey, interview, oral history, focus group, program evaluation, etc. (Specify in the Methods section)

Review of medical records, images, specimens – Category 5

For review of existing data: provide a date range or an end date for when the data was generated. The end date can be the date this application was submitted to the IRB. Example: *01/01/1999 to 12/31/2015* or all records through *mm/dd/yyyy*.

Date Range:

Check all that apply (data includes medical records, images, specimens).

☐ (5a) Only data that exists before the IRB submission date will be collected.

☒ (5b) The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.
Examples
- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ (5c) The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol.*

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ (5d) This study will obtain data generated from other sources. Examples may include receiving data from participating sites or an external collaborator, accessing an external database or registry, etc. Explain the source and how the data will be used in the Methods section.

☒ (6) Video audio recording: *Describe the plan to maintain subject privacy and data confidentiality, transcription, store or destroy, etc.*

Health Coaching calls are recorded for fidelity analysis. Calls will be randomly selected and reviewed by the PI, Dr. Roberto Benzo and Motivational Interviewing expert, Dr. Matt Clark. The calls are reviewed to ensure that the health coach is adhering to the principles of Motivational Interviewing and the protocol. Feedback will be provided to the coach. The recorded files are stored on a secure research drive within the Mayo firewall and only accessible by the study staff. At the completion of the study and the final analysis, the files will be deleted.

HIPAA Identifiers and Protected Health Information (PHI)

Protected health information is medical data that can be linked to the subject directly or through a combination of indirect identifiers.

Recording identifiers (including a code) during the conduct of the study allows you to return to the medical record or data source to delete duplicate subjects, check a missing or questionable entry, add new data points, etc. De-identified data is medical information that has been stripped of <u>all</u> HIPAA identifiers so that it cannot be linked back to the subject. De-identified data is **rarely** used in the conduct of a research study involving a chart review.

Review the list of subject identifiers below and, if applicable, check the box next to each HIPAA identifier being recorded at the time of data collection or abstraction. Identifiers apply to any subject enrolled in the study including Mayo Clinic staff, patients and their relatives and household members.

Internal refers to the subject's identifier that will be recorded at Mayo Clinic by the study staff.
External refers to the subject's identifier that will be shared outside of Mayo Clinic.

Check all that apply:	INTERNAL	EXTERNAL
Name	x	
Mayo Clinic medical record or patient registration number, lab accession, specimen or radiologic image number	x	
Subject ID, subject code or any other person-specific unique identifying number, characteristic or code that can link the subject to their medical data	x	
Dates: All elements of dates [month, day, and year] directly related to an individual, their birth date, date of death, date of diagnosis, etc. **Note:** Recording a year only is not a unique identifier.	x	
Social Security number		
Medical device identifiers and serial numbers		
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images	x	
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address		
Street address, city, county, precinct, zip code, and their equivalent geocodes	x	
Phone or fax numbers	x	
Account, member, certificate or professional license numbers, health beneficiary numbers		

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Vehicle identifiers and serial numbers, including license plate numbers		
Check 'None' when none of the identifiers listed above will be recorded, maintained, or shared during the conduct of this study. (exempt category 4)	☐ None	☐ None

Data Analysis

Power analyses may not be appropriate if this is a feasibility or pilot study, but end-point analysis plans are always appropriate even if only exploratory. Provide all information requested below, or provide justification if not including all of the information.

Power Statement: The primary endpoint of this study will be the rate of adherence compared between the two groups. Secondary endpoints include rates of COPD related hospitalization or death, activity levels as measured by the average number of steps per day, and the CRQ scales of dyspnea, fatigue, emotional function, physical, mastery, and the total score. Differences between groups will be compared with Fisher's exact tests for proportions and ttests for continuous endpoints. These analyses will be supplemented with logistic regression models and linear models to compare groups after adjusting for confounding factors.

Data Analysis Plan: One hundred and forty-four patients will be entered on this study (72 per arm). After adjusting for multiple comparisons, this sample size will provide at least 80% power to detect a difference in the rates of adherence of 6% in the control group to 50% in the intervention group. This sample size will also provide at least 80% power for detecting a 50% reduction in hospitalization/death rates (from 50% in the control group at 6 months to 25% in the intervention group at 6 months), a difference of 1000 steps at 3 months (assuming a standard deviation [SD] of 2,000 steps), and a 0.5 difference in CRQ summary scores at 3 months (assuming an SD of 1.0). The sample size will be increased to 150 (75 per arm) to account for a 5% drop out rate.

Statistical Analysis and Power
The primary endpoint of this study will be the rate of adherence compared between the two groups. Secondary endpoints include rates of COPD related hospitalization or death, activity levels as measured by the average number of steps per day, and the CRQ scales of dyspnea, fatigue, emotional function, physical, mastery, and the total score. Differences between groups will be compared with Fisher's exact tests for proportions and ttests for continuous endpoints. These analyses will be supplemented with logistic regression models and linear models to compare groups after adjusting for confounding factors.
One hundred and forty-four patients will be entered on this study (72 per arm). After adjusting for multiple comparisons, this sample size will provide at least 80% power to detect a difference in the rates of adherence of 26% in the control group to 50% in the intervention group. This sample size will also provide at least 80% power for detecting a 50% reduction in hospitalization/death rates (from 50% in the control group at 6

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months to 25% in the intervention group at 6 months), a difference of 1000 steps at 3 months (assuming a standard deviation [SD] of 2,000 steps), and a 0.5 difference in CRQ summary scores at 3 months (assuming an SD of 1.0). The sample size will be increased to 150 (75 per arm) to account for a 5% drop out rate.

Outcomes for the Phase 2 Randomized study

Aim 3a: Adherence will be our primary outcome

Overview: The reported adherence for PR after a hospitalization is 4% and in the best case scenario (free PR and free transportation like in the UK) is 10%. From our preliminary data, now in press (Respiratory Care), we found an adherence of >80% to the proposed system in outpatients with COPD. We hypothesize the adherence to a complete home-based PR program by post-hospitalized patients will be around 50%, and the adherence to the conventional hospital-based PR program to be 25% (due to our strong efforts to encourage people attend) will consider a complete PR when 75% of the expected PR visits are completed. We will compute the degree of completion of conventional PR from our electronic health record (EHR). The home-based PR compliance will be assessed by the entries of the PR coach in REDCap.

Aim 3b: CRQ Physical and Emotional Summary scores post PR

To determine the effect size of the home-based PR system with health coaching on physical and emotional QOL, we will analyze the CRQ physical and emotional summary scores. The CRQ Physical Summary score includes dyspnea (symptom #1 in COPD) and fatigue (symptom #2 in COPD) domains; the CRQ Emotion Summary score, includes the emotion (independent factor for admissions and poor quality of life) and mastery (self-management) domains of the CRQ.25 The CRQ is a 20-question inventory assessing the areas of dyspnea, fatigue, emotion, and feelings of mastery. The fatigue, emotion, and mastery subscales ask patients to rate how often in the last two weeks they have been afflicted with a particular feeling or experience on a scale of 1 to 7, with higher ratings indicating less symptom impairment. The CRQ has shown to be valid and has high internal consistency reliability.25 Test-retest reliability is adequate in all subscales, but is particularly high in the subscales of fatigue (r=0.90), emotion (r=0.93), and mastery (r=0.91).25 The minimal clinically important difference for this instrument of 0.5 points is universally recognized.13 The CRQ will be measured at baseline, and 3, and 6 months post-hospital discharge.

Aim 3 c: Daily Physical activity post PR

Physical activity is the strongest predictor of survival in COPD and is independently related to hospitalization.26,27 Physical activity will be measured by the ActiGraph™ wGT3X-BT activity monitor (**Fig. 8**), which has been validated and used to assess physical activity in COPD populations.27-29 The ActiGraph activity monitor has tri-axial accelerometers and will be worn on the wrist for seven days at baseline and at 3, and 6 months post-hospital discharge at the pre-specified time points (Figure 17) and will measure steps and minutes spent in sedentary, light, and moderate activity.30,31 **The main daily physical activity outcome is the number of daily steps (most common, generalizable and simple)**. Secondary, but important, measures to be analyzed are activity counts, minutes per day spent in daily physical activities of at least moderate intensity, and sedentary time (<2METs metabolic equivalents).32We will also measure sleep time and sleep efficiency with this monitor.

Aim 3d: COPD-related hospital readmission (COPD exacerbation or pneumonia as discharge diagnosis) at one month, three months and six months. They will be assessed by the EHR and also by Care Utilization Calls (a safety measure in case individuals are rehospitalized outside the Mayo system). The calls will occur every three months (to avoid recall bias), will use a scripted protocol as in a previous application, and will be conducted by a coordinator blinded to the intervention. Emergency Department (ED) visits and hospitalizations (all cause) will also be recorded.

Aim 4: CE analysis EuroQol Five Dimensions questionnaire

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The EuroQol Five Dimensions questionnaire (EQ-5D) is a standardized instrument for measuring generic health status. The health status measured with EQ-5D is used for estimating preference weight for that health status, then, by combining the weight with time, a quality-adjusted life year (QALY) can be computed. QALYs gained its used as an outcome in the cost-utility analysis, which is a type of economic evaluation that compares the benefit and cost of healthcare programs or interventions. EQ-5D is one of the most commonly used generic health status measurements, and its good validity and reliability have been reported in various health conditions. It will be the tool to be used in the proposed cost-effectiveness analysis (CEA).

Secondary Outcomes

Self-Efficacy: The Mastery domain of the CRQ will be used to assess self-efficacy. The CRQ questions assessing self-efficacy are "In the last two weeks, how much of the time did you feel very confident and sure that you could deal with your illness?" and "How often during the last two weeks did you feel you had complete control of your breathing problems?

Baseline Demographics and comorbidities: Baseline demographics to be collected include age, mMRC, FEV1, highest grade completed in school, marital status, gender, structural and functional social support,33 race, steroid (prednisone) use in the three months before the study, comorbid conditions (Charlson Comorbidity Index), smoking status, and previous hospitalizations and ED visits.

Analyses

There are three *distinct* quantitative study hypotheses (inform different aspects of the process).

Hypothesis 3a (Aim 3a) states that adherence will be higher in subject referred to home PR, will be tested with Fisher's exact test supplemented with logistic regression adjusting for dyspnea MRC, age, social support, comorbidities, and FEV1. Exploratory analyses will be performed to examine how the number of rehab sessions impacts hospitalization/ED rates, CRQ dyspnea score, CRQ emotional score, and number of daily steps.

Hypothesis 3b (Aim 3b): participants on home-based PR will have higher physical (dyspnea fatigue) and, higher emotional CRQ summary scores at month three than participants who were referred to conventional PR. Tested with t-tests supplemented with linear regression models adjusting for baseline scores and dyspnea MRC, age, social support, comorbidities and FEV1.

Hypothesis 3 c (aim 3c): participants on home-based PR will have more daily PA than participants referred to conventional PR at month three. This will be measured by daily steps and minutes spent in sedentary, light, and moderate activity measured by the ActiGraph.30,31 This study has two activity monitors, the ActiGraph, a gold standard activity monitor used for outcome measures (7-day wearing) at baseline, 3, and 6 months; and the Garmin Vivofit PR activity monitor, which will be used daily, but will NOT be used as an outcome measure, rather for PR and health coaching and participant awareness of physical activity (participant will keep this activity monitor). Tested with Wilcoxon tests supplemented with linear regression models adjusting for baseline values and dyspnea MRC, age, social support, comorbidities and FEV1.

Hypothesis 3d (Aim 3d): individuals in the home-based PR program will have lower readmissions and ER visits compared to individual referred to conventional PR. Tested with Fisher's exact test supplemented with logistic regression models adjusted for hospitalizations in the previous year, age, dyspnea, and comorbidities.

For the continuous study outcomes, changes from baseline to three months will be compared between the study arms using two-sample, two-sided t-tests with 5% type I error rates. Changes in QOL, number of steps, and length of stay will be compared between the two treatment sequences using two-sample two-sided t-tests. No adjustments will be made for multiple testing. Means, SDs, medians, ranges, and frequency distributions will be reported and plotted over time by study arm. Linear models will be used to assess the impact of treatment arm on three-month outcomes after adjusting for the corresponding baseline measure and other variables related to the outcome (age, degree of breathlessness at baseline using the mMRC dyspnea, and

FEV1). Repeated measures mixed models will be used to estimate the intervention effect over the 6 months of the study (this will measure trajectory and maintenance of benefits / behavior change). Intent-to-treat analyses will also be performed to determine the sensitivity of the results to dropouts and missing values. In the intent to-treat analyses, if a month three measure is missing for any reason, it will be described as not changing from baseline. Healthcare utilization (number of ED visits, hospitalizations, and length of stay) between baseline and three months will be treated (analyzed) as both binary (for incidence rates) and continuous (for the number of events). The binary endpoints will all be compared between groups using Fisher's exact test. Logistic regression models will also be fit to look for differences in these outcomes by arm after adjusting for age, mMRC, FEV1, baseline levels of anxiety, depression, and fear, and baseline healthcare utilization, (before starting the study) particularly hospitalizations in the previous year.

Descriptive summaries of the changes between baseline, three, six, and nine months will be used to assess the effect of the home based intervention on the control arm and the residual beneficial effect on the intervention arm. These results will be only descriptive and exploratory. No formal hypothesis testing will be done. All data will be stored in REDCap and analyzed using SAS (Cary, NC).

*Per-Protocol Analysis (Dose Response):*We will conduct an exploratory analysis to assess the effect of dose of PR sessions on study outcomes. This analysis will control for potential confounders of dose.

Assessment of Bias: Potential bias due to loss to follow-up will be assessed using a time to event analysis for the association of patient characteristics with time to dropout; results will be reported and used to evaluate the robustness of the study findings. We will also conduct sensitivity analyses in which missing data for dropouts are imputed under plausible missing-not-at-random assumptions.

Missing data: A common affliction with randomized clinical trial field experiments is noncompliance with both treatment and missing study participation data. To estimate the overall treatment effect for the entire sample, an "intention to treat" analysis will be conducted, using our above likelihood-based analysis method for repeated measures, including data on all subjects who were randomized to the study group. This allows us to use all available data, rather than delete participants with missing values from the analysis of treatment effects.[34]

Aim 4: **Cost-Effectiveness Analysis**

This aims to estimate the value of implementing Home PR compared to subjects referred to conventional PR. The CEA, will estimate the ratio of the average change of cost per patient divided by the average change in QALYs per patient for health coaching compared to delivering standard care. QALYs will be based on the EQ-5D-3L[35] using a preference-based value set derived from a sample of the US population. QALYs will be calculated by multiplying the utilities by a number of time participants spent in a particular health state. Transitions between health states will be linearly interpolated. The perspective for the CEA is that of the healthcare provider.

For both arms, all resource utilization at the health centers for the one-year period following index hospitalization discharge will be collected. Estimated costs will be standardized using a bottom-up approach. Professional services defined by Current Procedure Terminology code will be valued using national reimbursement amounts from the Medicare fee schedules. Billed charges for hospital services will be valued using department specific cost-to-charge ratios based on the hospital's annual Medicare cost report. All costs will be inflated to a common year using the Gross Domestic Product implicit price deflators.

Multivariate regression models will be employed to control for differences between study groups. Due to the highly skewed nature of healthcare costs, a generalized linear model incorporating a gamma distribution and log-link function will be used. The cost-effectiveness of the home PR intervention will be determined using the threshold of $50,000/QALY. The 95% CI of the cost-effectiveness ratio will be calculated using nonparametric bootstrapping.

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Healthcare utilization occurring at facilities outside of our network will not be captured. Sensitivity analysis of the cost-effectiveness will be performed based on residency status (local, regional, and distant).

Limitations: We acknowledge that comparing to completed regular PR would be ideal, however, given that the completion rate post-hospitalization is so low, accruing for such a study would be unrealistic. We strongly believe that the proposed design truly represents "a real world" study and the result from it would be applicable to the practicing clinicians and regulatory agencies and payers to further support alternative ways of PR (if our hypothesis is confirmed: increased adherence, decreased readmission and patients' critical outcomes like daily physical activity and quality of living).We will put a dedicated effort to motivate individual to attend conventional PR if they are randomized to arm.

We will not know if the improvement in adherence is because of the home-based PR or health coaching. However, given that, only 4% complete conventional PR after a hospitalization, a meaningful improvement in adherence would not require much effort from the patients the home-based PR program.

R61 milestones (two years)
Year 1
1. Finalization of the protocol and the informed consent document
2. Development of the manual of operations and case report forms
3. Establishment of a Data and Safety Monitoring Board
4. Institutional Review Board approval of the trial
5. Pilot cohort of 10-15 patients to refine the intervention already developed for outpatients
6. Qualitative study and application of the necessary changes to the proposed Home PR

Year 2

Begin enrollment into the clinical trial to allow for an evaluation by the end of the R61 phase of early enrollment and the probability of completing the trial on time and budget. Target for year two will be to recruit 30 of 150 subjects planned for the whole study.

R33 milestones

Meeting the projected recruitment for all study participants, including women and minorities (50 subjects per year).
1. Year 3 – 80/151 subjects recruited,
2. Year 4 – 130/151 subject recruited;
3. Year 5 – 151 of 151 subjects recruited, Database lock and analysis, Submission of the primary manuscript(s) to peer-reviewed scientific journal(s) and dissemination of results including the submission of study results to ClinicalTrials.gov within 12 months of the primary completion date.
4. **All years milestones** – Report of monitoring protocol implementation and collection of data related to primary and secondary endpoints and adverse events.

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