Study Protocol and Statistical Analysis Plan

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Title: A Personalized Behavioral Intervention for Older Adults with Musculoskeletal Pain and Sleep Complaints

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1. Abstract

It is well recognized that physical activity/exercise is an effective intervention to improve sleep, reduce pain and improve function in a variety of pain conditions. Traditional interventions to increase physical activity are challenging in older adults due to extensive staffing requirements and low adherence. We plan to conduct a pilot trial in a cohort of older adults (without dementia) with both chronic musculoskeletal pain and nocturnal sleep complaints to test the effectiveness of a 12-week personalized behavioral intervention (compared to a control group) embedded within a smartwatch application in older adults. 20 cognitively intact elders will be enrolled and randomly allocated to intervention or control group. Participants in the intervention arm will receive a 2-hour in person education session, and personalized, circadian-based activity guidelines, with real time physical activity self-monitoring, interactive prompts, biweekly phone consultation with the research team, and financial incentives for achieving weekly physical activity goal. The control group will receive general education on physical activity in older adults and continue their routine daily activity for 12 weeks.

2. Objectives

This study aims to examine 1) the feasibility and acceptability of a personalized behavioral intervention implementing mobile health technology for promoting pain, sleep, and mood in older adults with chronic pain and sleep complaints. 2) The preliminary efficacy of the study on pain and sleep outcomes

3. Background

Chronic musculoskeletal pain is prevalent in later life and has a significant impact on older adults' physical and psychological well-being, including falls, fatigue, depression, and level of functioning. Poor sleep quality/disturbed sleep is a common coexisting condition in older adults with chronic musculoskeletal pain. Epidemiological studies have revealed that 67%-88% of people with chronic pain reported poor sleep. In addition, early research suggests a bidirectional relationship between sleep disturbances and pain and the association may be mediated by negative mood. Poorly managed chronic pain and sleep, particularly in the older adults, may result in multiple adverse health outcomes, including depression, social isolation, decreased mobility, cognitive impairment and increased healthcare utilization and cost. There is a discrepancy between the high prevalence of pain /disturbed sleep in the older adult population and the limited attention paid to these conditions in both research literature and clinical care.

Sedentary lifestyle, which is reported by 90% of older Americans, is an important risk factor for both chronic musculoskeletal pain and sleep disturbances. Older adults with a higher incidence of chronic pain are generally less physically active than others. Although, it is well recognized that physical activity/exercise is an effective intervention to improve sleep and reduce pain and improve function in a variety of pain conditions, traditional interventions to increase physical activity are challenging due to extensive staffing requirements and low adherence. Electronic activity monitors, such as wrist-worn accelerometers, can track heart rate, activity, and sleep to allow individuals to work towards their personal activity and sleep goals. These appealing features make these devices ideal for interventions that aim to change behaviors and improve health outcomes. However, the efficacy of using electronic activity monitors to promote physical activity and health in older adults has not been well examined. In addition, individually tailored physical activity interventions that account for an individual's preference and functional limitation have been proven to improve adherence and study outcomes.

Our proposed theory-derived intervention is guided by theoretical constructs from the self-efficacy theory. Self-efficacy, one's confidence in the ability to perform particular behaviors, influences the performance of those behaviors, which in turn impacts health outcomes. Enactive mastery experiences, verbal persuasion, vicarious experiences, and physiological/ emotional status are the four principle sources of self-efficacy beliefs. Evidence illustrates that physical activity interventions designed based on self-efficacy concepts

effectively promote physical activity in older adults. The personalized behavioral intervention, which includes physical activity training, exercise prescription, goal setting, phone coaching, consultation, and feedback, real-time physical activity self-monitoring, interactive prompts and feedback with smartwatch, and weekly financial incentives will provide older adults with a stronger sense of self-efficacy. This will engage them in physical activity.

4. Study Procedures

Overview of study design: This is a two-group randomized controlled trial to test the effectiveness of a 12-week personalized behavioral intervention implementing smartwatch technology in promoting physical activity, pain, and sleep in older adults in comparison with a control group. We aim to enroll 20 eligible participants in one years and complete the study in 18 months. Length of a subject's participation time in study will be 16-18 weeks in total, which includes 2-3 week of screening and pre-intervention data collection, 12-week intervention/control period, and 2-3 week post-intervention data collection. It is an unblinded trial. Due to the nature of the intervention (ongoing communication between research team and participants), it is impossible to blind the group assignment from the participants and the research team.

Recruitment: The sample will be recruited from multiple sources including community recruitment and sleep and geriatric primary care clinics affiliated with the Johns Hopkins University Health System. We will build upon successful recruitment strategies of the Johns Hopkins Center for Injury Research and Policy as well as the Center for Innovative Care in Aging which involves developing targeted study flyers, sending mailings by agencies and medical practices serving older adults, and working with community based advisory groups. The study flyers will be posted near the front desk and examine rooms of clinics, and the activity rooms in senior community centers; In addition, the study team will do presentations at the community center to inform residents of the research opportunity. Interested older adults will contact the research team or leave their contact information (name and phone number) and give oral permissions that the research team can reach them by phone or onsite. We will also recruit onsite at the sleep and geriatric clinics. Interested older adults may be contacted on site or through phone call by the research team. During initial contact with the older adults, the research assistant will describe the study, address any questions or concerns the participant may have. If interested, the research team will pre-screen to determine eligibility (age, pain, and poor sleep, and mobility). If the participant gives oral consent for participation, the research team will schedule a meeting with the potential participant to complete the informed consent. In addition, older adults who have participated in prior studies and expressed interest in being contacted for future research, will also be invited to participate.

Consent: During the **consent process**, a research personnel will meet with the potential participant at the research team office, clinic office or the elder's apartment per the elder's preference, provide verbal and written description of the study in detail, allow the potential participant as much time as needed to read and ask questions, and then complete the informed consent.

Screening (30minutes): After informed consent, the research team will assess (maximum of 30 minutes) the participants' eligibility for intact Cognition using the Montreal Cognitive Assessment (MOCA) and poor sleep quality by asking "do you have problems with your sleep? Do you feel refreshed after sleep?", and pain by asking "Are you currently troubled by physical pain, either all the time or on and off? Has this pain persisted for at least 3 months?", and readiness for performing regular exercise using the physical activity readiness questionnaire (PAR-Q). Participants who passed the PAR-Q are eligible for participation. For those who failed to pass the PAR-Q, medical clearance along with information about specific exercise limitations needs to be obtained from their primary care providers in order to participate. People who fail to pass the screening will drop the study after the screening process.

Randomization: Eligible participants will be randomly allocated to either intervention or control group (1:1) using blocked randomization with a block size of 4. A computer-based assignment scheme will be used to determine the participant's group assignment.

Intervention description: Based on the self-efficacy theory, participants in the intervention arm will receive personalized, circadian-based activity guidelines, 2 or 3 1-hour in person education session, real time physical activity self-monitoring, interactive prompts, biweekly phone consultation with the research team, and financial incentives for achieving weekly physical activity goal.
The personalized circadian-based activity guideline will be developed based on the individual's typical daily circadian profile, functional status, and preference for exercise. We will advise participants to take afternoon naps (<90 minutes) and avoid napping after 4pm and before 8pm. The research team will work with a certified exercise trainer to develop the personalized physical activity plan for each subject. An afternoon nap of the optimal duration will be advised as healthy napping. All participants will be instructed to nap during this timeframe and to avoid any naps at other times of the day, especially in early evening. The individual's typical circadian profile will be calculated from the two-week baseline Actigraph data.
The participant will receive a 30-minute instruction session from the research team session to provide instructions of how to follow the personalized activity guidance and use the study devices. A smartwatch (Fitbit Versa) and a paired smartphone (if the participant does not have a smart phone) will be distributed to participants.
In person training: Participants will receive a 2 or 3 1-hour in person education sessions with the exercise trainer which includes a 20-minute general education on exercise in older adults and a 40-minute education on personalized exercise and participating the study intervention. Session 1 will be within one week after the baseline; Session 2 will be scheduled 2-3 weeks after session 2. All participants in the intervention group will have session 1 and session 2. If the trainer feels the participant need another session to perform the exercise independently, session 3 will then be scheduled as needed. To facilitate the participant's exercise at home, we will provide a set of dumbbell and resistance band for them to use during the study. The education session will be designed using materials from the Go4Life program from the National Institute on Aging (https://go4life.nia.nig.gov). The participant will receive a copy of Go4Life program book and can find instructions for all selected exercise in the program book.
Self-monitoring: Subjects will self-monitor their level of physical activity (steps & minutes of moderate activity) using the smartwatch. The Google calendar and Fitbit apps will send messages and alerts to the subject's smartwatch that encourage them to achieve their daily goals. For example, a participant may typically be inactive for a long period (e.g., >90 minutes) at 10AM. In this case, the research assistant will program the smartwatch to pro-actively chime or vibrate at 10AM each day with a reminder message through Google Calendar. Similarly, if the smartwatch detects a long sedentary period, the Fitbit app will automatically send an alert via the smartwatch to motivate the subject to increase their physical activity. The smartwatch will be removed every 3-4 days for charging. If a participant has low activity for 3 consecutive days, the research assistant will call the participant to either encourage them to adhere to the plan or provide a modified plan after consulting the exercise trainer.
Phone consultation: Subjects will have biweekly phone consultation with the research team members to receive guidance and adjustment on activity plans. Recognizing that changing behavior is a process, the personalized activity plan will be less intense at the beginning and adjusted every two weeks based on participant's data during the previous two weeks.

Description of control condition: The control group will receive general education on physical activity for older adults and continue their daily activity and healthcare routine. They will also receive a Go4Life program book from the National Institute on Aging.

Data collection includes pre-intervention (baseline, 2weeks) and post-intervention (2weeks). The data collection will take place in a private room at the School of Nursing, a clinic office or the participant's apartment per the participant's preference.

Baseline data collection: After randomization, the research team will distribute an Actigraph to each eligible participant and instruct them to wear it on his/her non-dominant wrist day and night for 14 consecutive days. At the same time, the participants will be instructed to fill out a two-week sleep diary during the days they wear the Actigraph. Pre-intervention (baseline) data collection will take about 45-60 minutes. A research team member will interview eligible participants (up to 30 minutes) for age, race, education, height, weight, life style (tobacco & alcohol use), depression, pain, fatigue, self-reported physical activity, Activity of daily living, self-reported sleep quality, pain, medication use (antidepressant, benzodiazepine, pain and sleep medication), and medical conditions. The research assistant with Phlebotomy training will collect blood sample (5-10ml) from participants.

Post-intervention data collection: After the intervention or control period, a research team member will mail an Actigraph and a two-week sleep diary to the participant's home and contact the participants by phone to provide instructions. The participant will wear the Actigraph and fill out the sleep diary for 2 weeks. A research team member will schedule a meeting with the participant after the Actigraph session to collect post-intervention data. At the meeting, the participants will provide blood sample and be assessed for pain, depression, level of physical activity, and other measures that were collected at screening and pre-intervention following the same procedures. In addition, the participant will be interviewed individually for his/her perspective and experience of the intervention at the meeting for post- intervention data collection. The conversations will be audio recorded and field notes will be taken by a research team member during the interview. We estimate each interview will last no more than 30 minutes. The participant will be asked to answer open-ended questions about the participant's experience of working with smartwatch and the intervention. The voice recordings will be sent to the Production Transcripts for transcription (https://www.productiontranscripts.com/). Production Transcripts is a full-service transcription company that specializes in medical and academic research and has a BAA with Johns Hopkins.

Data management: We will use the REDCap data entry and management system. Data from screening, baseline, intervention sessions, and post-intervention data collection will be entered into forms that the data manager will check for completeness and appropriateness. The data manager will send reports of missing or inappropriate entries to the PI every week for clarification and resolution. **Data that cannot be stored on the REDCap will be stored at either a locked cabinet at the research coordinator (MoCA cognitive screening) / assistants' offices at the JHU School of Nursing or at a folder as electronic files on the JHU box (actigraph data and cognitive assessment, and fitabase data) that could only be accessed by the study team.**

Measurement

Sleep Measures: We will use the Actiwatch to objectively assess nocturnal sleep in terms of total nocturnal sleep time, sleep latency, and wake after sleep onset (WASO); the smartwatch cannot be used to measure sleep due to its need for overnight charging. The Pittsburgh Sleep Quality Index, Epiworth Sleepiness Scale andInsomnia severity index will be used for subject screening and assessing sleep quality subjectively. A two-week sleep diary will be used to confirm Actiwatch-based nocturnal sleep. It will provide information on nap frequency and duration, as well as nocturnal sleep duration. Total nocturnal sleep time is the primary sleep measure, and all others are considered secondary.

Pain Measures: Presence of pain will be determined by affirmative answers to both of the following questions: (1) "Are you currently troubled by physical pain, either all the time or on and off?" and (2) "Has this pain persisted for at least 3 months?"[13]. Older adults answering yes to both questions will then be asked to specify the duration of pain and the pain sites. Pain intensity, severity, and interference with daily life will be measured by two instruments: (1) The brief pain inventory (locations and severity of pain) and (2) PROMIS pain measures (pain intensity, interference, and behaviors). Pain Self-Efficacy will be measured by the Chronic Pain Self-Efficacy Scale.

Fatigue will be assessed by the FACIT Fatigue Scale.

PROMIS measures will be used to assess multiple study outcomes. NINR Common data element of sleep, fatigue, anxiety, depression and cognition If a participant is significantly depressed (rating "Always" in all the 6 items that assess depressive symptoms) and not receiving any treatment for depression during assessments, we would share the information with the participant's primary care provider and refer the participant for treatment with his/her primary care provider.

Functional Status: We will use the Katz Index of Independence in Activities of Daily Living (ADL) and The Lawton Instrumental Activities of Daily Living (IADL) Scale to measure older adult's functional status.

Balance and gait speed will be measured using the Short physical performance battery (SPPB)

Other information includes age, race, body mass index, education, life style (tobacco and alcohol use, BMI), depression (GDS), pain, fatigue, medication use (antidepressant, benzodiazepine, pain and sleep medication), and number of medical conditions. Information will be collected via questionnaires.

The study will not interfere with the participants' routine care. Participants in both groups will receive their routine care. The participants at both groups have the freedom to withdraw anytime from the study. The research team will remove the participants from the study if the research team cannot get contact with the participants for a month or the participant miss two appointments with the research team for no reason.

5. Inclusion/Exclusion Criteria

Key inclusion criteria include 60-85 years, intact cognition [Montreal Cognitive Assessment (MoCA)>23], poor quality of sleep (Insomnia Sleep Index>7), self-reported presence of pain, capacity for mild to moderate physical activity.
Participants will **be excluded** if they 1) have serious underlying illness (such as malignant neoplasms, infection, unexplained fever, weight loss, or recent trauma) causing their pain, 2) are non-ambulatory or have severely impaired mobility, 3) have visual or hearing impairment that interfered with assessments, and 4) have an acute or a terminal illness, 5) have neuropathic pain.

6. Drugs/ Substances/ Devices

N/A

7. Statistical analysis plan (SAP)

7.1. Sample characteristics: We will compare the values of demographic and baseline clinical variables between the two study arms using t-tests or Mann-Whitney U-tests for continuous variables and chi-squared or Fisher's exact tests for categorical measures. This analysis will both describe the overall study sample and confirm that randomization resulted in the expected balance between covariates of interest;
7.2 Descriptive analysis will be used to describe the feasibility data;
7.3 Preliminary efficacy: Repeated Measures ANOVA will be performed to examine if the proposed intervention increases the participants' proposed outcomes compared to the control arm. Analyses will examine the interaction (Time × Group) to access whether there are differences in changes in outcome variables between the two arms. The initial effect size of the intervention will be determined based on results of pain outcomes.

8. Risks

Minimal risks to study participants are expected. There is minimal risk associated with physical activity. We will explain associated risk to the participants. In very rare occasions, the subject may fall or get

injured during physical activities. These adverse events should be minimized by using personalized physical activity plans, which will be developed/designed by the exercise trainer to be most suitable for the subject based on the subject's personal features. Some environmental factors (e.g. weather) may impact on the participant's safety when they perform physical activity outside. We will advise participants of this safety information during the exercise intervention. For example, we will advise them to perform indoor physical activities in the following weather conditions: temperature lower than 32°F or higher than 90°F, rainy, snowy or heavy windy weather. We will also advise them to hydrate during performing physical activity and hot weather. The activity intervention will be based on an existing NIH-funded activity protocol for older adults. Finally, the study participant's primary care provider will be contacted to confirm that the study participant can safely engage in the activity regimen.

Subjects may experience psychological reactions to completing the questionnaire data and cognitive tests. Since the questions are benign, the risk is minimal.

The risk of breaching study participant confidentiality will be minimized by identifying all participants by code numbers and securing all data collected in locked files in the PI's office and screening information to locked file cabinets with limited staff access. Pre-coded data collection instruments are prepared for use with study participants at each testing occasion. Identification numbers to assure subject confidentiality will be used. Only one master log of subject name, address and telephone number and study identification assignment will be maintained in a password protected computer program. Access to these computer files will be password protected, recordings will not contain respondent name or other personal identifying information.

Financial risks to the participants: There are no anticipated financial risks to the participants.

Plan for Data and Safety Monitoring: Aligned with NIH/NINR guidelines, the proposed study is a single site, small scale clinical trial which involves minimal risk to participants. To ensure the safety of participant and integrity of the data, a data and safety monitoring plan (DSMP) is proposed as follows.

The PI will be primarily responsible for the study data and safety monitoring on a continuing basis. The PI is responsible for monitoring the progress of study, including recruitment, retention, study intervention adherence, completeness and quality of data collected, participant safety, and data confidentiality of study participants. The PI will be responsible for submitting annual study progress reports and adverse event reports to the program officer of NINR and University IRB. **The research team members** including the research coordinator, research assistants, and exercise intervention consults are responsible for reporting any adverse events immediately to the PI and informing the PI with any participant's safety concerns. The research team members are responsible for attending and participating in weekly or monthly team meetings. All research personnel will complete the Collaborative IRB Training Initiative (CITI) Basic Human Subjects Protection course and be certified prior to joining the research team.

The PI will 1) meet with research coordinator and research assistants <u>weekly</u> to discuss the progress of study recruitment, retention, intervention adherence, completeness and quality of data collected, participant safety, and any issues or concerns with data integrity and participant's safety raised during the past week. The PI will review the study progress, safety, and confidentiality of each study participant. 2) Monitor the study by requiring the research team to keep notes from all meetings and review meeting notes from the last meeting to ensure that prior alerts are resolved appropriately. 3) Meet with the research coordinator and research assistants <u>immediately</u> to review severity and cause of any discovered adverse or unanticipated event and to determine next steps.

Independent Safety Monitor: The independent safety monitor will be a Geriatrician (MD) or an Adult-Gerontology Geriatric Nurse Practitioner (AGNP) at the Johns Hopkins Healthcare System, who is independent of the study. The independent safety monitor will be available in real time to provide recommendations on appropriate actions regarding adverse events and other safety issues. The independent safety monitor will be contacted by the PI or the research staff after an adverse event is discovered and advise the research team on appropriate actions to the adverse event. In addition, to ensure the participants' safety, the PI will meet with the independent safety monitor every three months to review and follow-up the adverse events and discuss possible safety issues related to the study.

9. Benefits

There are several potential benefits for the subjects from the proposed study that outweigh the minimal risks involved. Subjects may gain knowledge on the health benefits of physical activity from the study; subjects will be aware of their level of physical activity, quality and quantity of sleep and will receive recommendations based on published guidelines. As a result of the study, subjects in the intervention group may have increased physical activity, improved quality and quantity of sleep, reduced pain, and may also benefit from other health aspects, such as reduced blood pressure and better lipid profiles etc. More importantly, the intervention may change their physical activity behaviors in the long run, which will sustain the health benefits from the intervention and facilitate an active and healthy aging process in the elderly population.

10. Payment and Remuneration

As data collection is anticipated to require significant commitment and effort on the part of subjects, remuneration will be provided. Because of the inconvenience and potential burden of data collection, we chose a model of payment where the amount serves as an incentive rather than a reward. The advantage would be more rapid recruitment and avoidance of subject financial sacrifice. Further, completion bonuses encourage subject retention. Using this model, participants will be paid in gift cards. Subjects will receive a $50 gift card after post-intervention data collection. For the intervention group, we will have $5 financial incentives for successful completion (4days/week) of the weekly exercise goal (up to $60 for the 12-week intervention). This is a strategy for intervention adherence. In addition, participants in the intervention group who successfully complete the study will keep the Fitbit in order to maintain the physical activity behavioral change. This amount of subject compensation is not anticipated to be undue inducement, considering the effort and commitment required of the subjects.