**Protocol**

**Study Title:** Mobile Technology and Data Analytics to Identify Real-time Predictors of Caregiver Well-Being

**NCT #:** NCT04556591

**IRB Approval Date:** April 22, 2021

**Protocol Version Date:** March 23, 2021

# Mobile Technology and Data Analytics to Identify Real-Time Predictors of Caregiver Well-Being

**Protocol Number: HUM000184455**

**National Clinical Trial (NCT) Identified Number: NCT04556591**

**Principal Investigators: Noelle E. Carlozzi, Ph.D.; Sung Choi, M.D., M.S., Srijan Sen, M.D., Ph.D.; and Zhenke Wu, Ph.D.**

**Sponsor: University of Michigan**

**Grant Title: Mobile Technology and Data Analytics to Identify Real-Time Predictors of Caregiver Well-Being**

**Funded by: Michigan Institute for Clinical & Health Research (MICHR) in partnership with University of Michigan Institute for Healthcare Policy & Innovation (IHPI)**

**Version Number: v. 5.0**

**23 March 2021**

## Protocol Amendment History:

| Version | Date | Description of Change | Brief Rationale |
|---|---|---|---|
| 2.0 | 12/3/2020 | Updated version date and number and table of content page numbers | Administrative update |
| 2.0 | 12/3/2020 | Added clinicaltrials.gov number to cover page (NCT04556591) | Added CT.gov posting number since it has been assigned |
| 2.0 | 12/3/2020 | In section 8.1.5.3, noted that the monthly surveys could also be given via interview format (in addition to the CareQOL app) | Provides flexibility with administration, especially with feasibility questionnaire which is the primary outcome measure |
| 3.0 | 1/21/2021 | Updated version date and number and table of content page numbers | Administrative update |
| 3.0 | 1/21/2021 | Updated sample size from "60" to "60 – 90" for the overall study sample, from "20" to "20-30" for each participant population, and from "10" to "10-15" for each arm within each participant population. Changes were made in sections 1.1 and 4.1. | We are over-recruiting to account for missing data |
| 3.0 | 1/21/2021 | Removed the criteria that the spinal cord injury needed occur when the person with SCI was at least 16 years old. Change was made in section 5.1. | The age at which the spinal cord injury was obtained is not important scientifically as long as the person with the SCI is currently an adult (at least 18). |
| 4.0 | 2/3/2021 | Updated version date and number and table of content pages numbers. | Administrative update. |
| 4.0 | 2/3/2021 | In section 5.1, the inclusion criteria were clarified to indicate that medical documentation was required for each condition. | Clarified that medical documentation is needed as an inclusion criteria. |
| 5.0 | 3/23/2021 | Updated version date and number and table of content page numbers | Administrative update |
| 5.0 | 3/23/2021 | Updated SOA (section 1.3) to include optional semi-structured interview for active group only | Added an optional semi-structured interview for intervention group to learn more about participant experiences and perceptions of the intervention messages |
| 5.0 | 3/23/2021 | Updated section 8.1.6 to include a description of the optional semi-structured interview | Added optional semi-structured interview (see above) |
| 5.0 | 3/23/2021 | Updated section 10.1.1.2 to describe consent procedure for optional semi-structured interview | Added optional semi-structured interview (see above) |

| | | | |
|---|---|---|---|
| 5.0 | 3/23/2021 | Updated section 10.1.2 to provide information on confidentiality and privacy related to optional semi-structured interview | Added optional semi-structured interview (see above) |
| | | | |

**CONFIDENTIALITY STATEMENT**

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigators or other participating study leadership and as consistent with the terms of award.

# Table of Contents

## STATEMENT OF COMPLIANCE

This trial will be carried out in accordance with the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812) and research best practices. The PIs and all study team members who are responsible for the conduct, management, or oversight of NIH-funded clinical trials will complete Human Subjects Protection and best practices training.

The protocol, informed consent document, and all participant materials will be submitted to IRBMED, for review and approval. Approval of both the protocol and the consent documents will be obtained before any participant is consented. Any amendment to the protocol will be submitted for review and approval by IRBMED before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

## INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and research best practices.

Principal Investigators:

Signed: _____ Date: _____

Name: Noelle E. Carlozzi, Ph.D.

Title: Associate Professor

Affiliation: Department of Physical Medicine & Rehabilitation, University of Michigan

Address: 2800 Plymouth Rd., NCRC Bldg. 14, Ann Arbor, MI 48109-2800

Telephone: 734-763-8917

Email: carlozzi@med.umich.edu

Signed: _____ Date: _____

Name: Sung Choi, M.D., M.S.

Title: Edith S. Briskin and Shirley K. Schlafer Foundation Research Professor of Pediatrics and Associate Professor

Affiliation: Department of Pediatrics and Communicable Diseases, University of Michigan

Address: D4118 MPB, Ann Arbor, MI 48109-5718

Telephone: 734-615-5707

Email: sungchoi@med.umich.edu

Signed: _____ Date: _____

Name: Srijan Sen, M.D., Ph.D.

Title: Frances and Kenneth Eisenberg Professor of Depression and Neurosciences and Associate Professor

Affiliation: Department of Psychiatry

Address: 1066 MBNI, Ann Arbor, MI 48109

Telephone: 734-936-1031

Email: srijan@med.umich.edu

Principal Investigator:

Signed: _____ Date: _____

Name: Zhenke Wu, Ph.D.

Title: Assistant Professor

Affiliation: Department of Biostatistics, School of Public Health

Address: 1415 Washington Heights, Ann Arbor, MI 48109-2029

Telephone: 734-764-3771

Email: zhenkewu@med.umich.edu

# 1 PROTOCOL SUMMARY

## 1.1 SYNOPSIS

**Title:** Mobile Technology and Data Analytics to Identify Real-Time Predictors of Caregiver Well-Being

**Study Description:** Care partners (i.e., informal family caregivers) of individuals with health problems are faced with considerable physical and emotional stress, often with substantial negative impact on the health related quality of life (HRQOL) of both the care partner and care-recipient. Care partners may be suddenly thrust into this full-time role and are often unprepared. As responsibilities accumulate, they face emergent health risks, including anxiety, fatigue, isolation, sleep problems, and decreased physical activity. Indeed, there is growing recognition that these psychological, social, and physical risks inadvertently affect patient health and well-being (i.e., outcomes). Thus, it is imperative to develop novel interventions to support caregivers to ensure better patient outcomes.

Despite the growing awareness about the importance of caregiving with the aging U.S. population and evolving health-care system, very little action has been taken to understand and improve conditions for caregivers. Thus, family caregiving (i.e., care partners) is an urgent public health issue. With high risk for developing depression, insomnia, and stress-related disorders, care partners are an ideal population to target for early detection and intervention strategies to treat compromised well-being. While psychoeducation, skills training, or therapeutic counseling interventions can be effective for care partners, these interventions require intensive time and face-to-face commitment (with trained personnel), which can be prohibitive for an individual that is already overwhelmed by existing caregiving responsibilities and unable to make time for self-care.

In this study, we will examine the acceptability and feasibility of a data collection protocol that involves the delivery of a personalized self-management intervention to promote care partner self-care. This just-in-time adaptive intervention (JITAI) is an emerging intervention that incorporates passive mobile sensor data feedback (sleep and activity [step] data from a Fitbit ®), and real-time self-reporting of HRQOL via study specific app called CareQOL to provide personalized feedback via app alert. The proposed trial will examine the acceptability and feasibility of the JITAI in three distinct groups of care partners: 1) care partners for persons with a chronic condition that was caused by a traumatic event (i.e., spinal cord injury [SCI]); 2) care partners for persons with a progressive, fatal neurodegenerative disease (i.e., Huntington disease [HD]); and 3) care partners for persons with an episodic cancer condition that requires intense, prolonged inpatient and outpatient treatment (persons with hematopoietic cell transplantation [HCT]).

Participants in this study will be randomized either to a control group, where they will wear the Fitbit® and provide daily reports of HRQOL over a three-month (90 day) period (without the personalized feedback), or the JITAI group, where they will wear the Fitbit®, provide daily reports of HRQOL and receive personalized pushes for 3 months. 60-90 participants will be enrolled (n=20-30 care partners of persons with SCI; n=20-30 care partners of persons with HD; and n=20-30 care partners of persons with HCT). Half of the care partners of each condition will be randomized into the JITAI group and half of the care partners of each condition will be randomized in the control group.

We hypothesize that this intensive data collection protocol will be both feasible and acceptable for care partners, and that the intervention will have a positive impact on care partner mood (strain, depression and anxiety).

**Objective:**
**Primary Objective:** To establish feasibility and acceptability of our intensive data collection protocol.

**Endpoints:**

**Primary Endpoints:** Feasibility and Acceptability as measured by the responses on the individual items on the Feasibility Questionnaire (items are scaled from 1 to 5 to indicate level of agreement, where "1" indicates "strong disagreement" and "5" indicates "strong agreement").

**Secondary Endpoints:** 1) Attrition as measured by the percent of participants completing the study; and 2) Adherence as measured by the percentage of missing data over the course of the study.

**Study Population:** 20-30 care partners of person with SCI, 20-30 care partners of persons with HD and 20-30 care partners of persons with HCT will participate in this study. Participant recruitment and enrollment will take place at the University of Michigan. Care partners must be at least 18 years old, be able to read and understand English and be caring for an adult (age 18 or above) with a medically documented diagnosis of SCI, HD or HCT. They must be willing to use their personal mobile device (e.g., smartphone, tablet) for this study, be willing to download the study app (CareQOL) and Fitbit® app and be willing to complete all study assessments.

**Phase or Stage:** Not applicable; behavioral intervention.

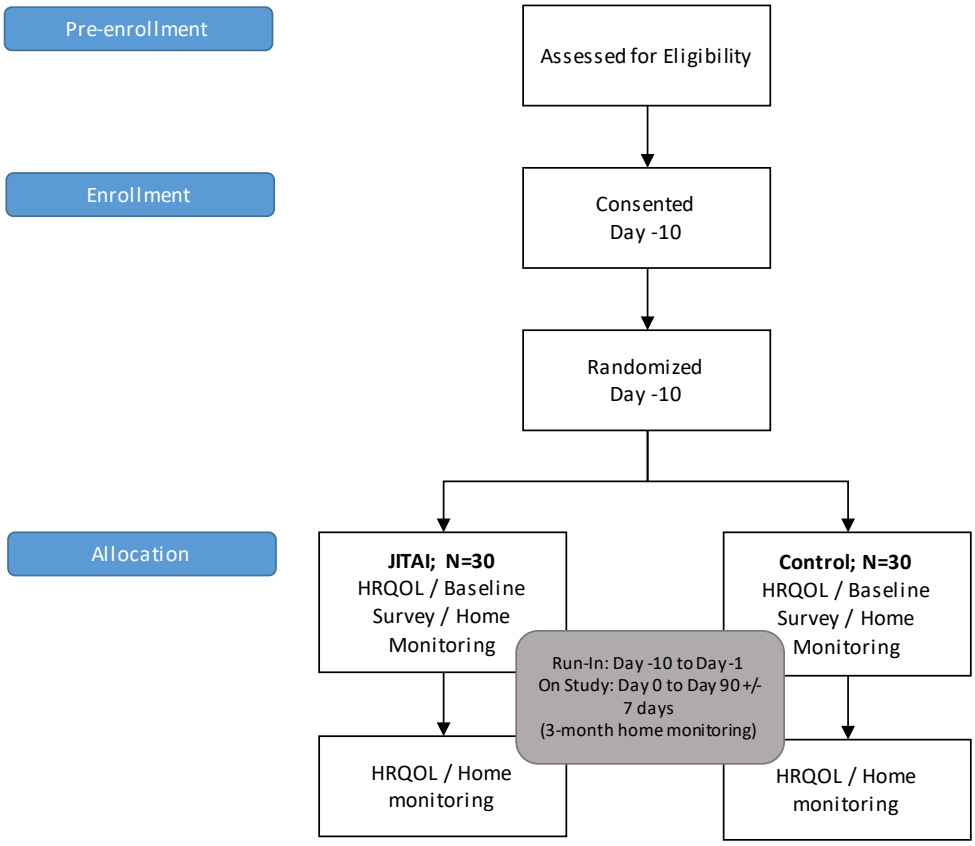
**Description of Sites Enrolling Participants:** There is one data collection site for this study: The University of Michigan in Ann Arbor, MI (n=20-30 care partners of person with SCI, n=20-30 care partners of persons with HD and n=20-30 care partners of persons with HCT).

**Description of Study Intervention:** Just-in-time adaptive intervention (JITAI) is a mobile health behavior-change approach that operationalizes the selection and delivery of personalized mobile device intervention strategies based on real-time data collection. In this study, a study-specific app (CareQOL app) will integrate sensor data from a Fitbit® (on physical activity and sleep) with real-time self-report ratings of HRQOL (caregiver strain, depression, anxiety) to inform the JITAI. The JITAI will deliver personalized messages via the app ~50% the days during the intervention period.

**Study Duration:** Data collection is expected to take 3 months.

**Participant Duration:** The participant duration in the study is ~100 days.

## 1.2 SCHEMA


Pre-enrollment
Assessed for Eligibility
Enrollment
Consented
Day -10
Randomized
Day -10
Allocation
JITAI; N=30
HRQOL / Baseline Survey / Home Monitoring
Control; N=30
HRQOL / Baseline Survey / Home Monitoring
Run-In: Day -10 to Day -1
On Study: Day 0 to Day 90 +/- 7 days
(3-month home monitoring)
HRQOL / Home monitoring
HRQOL / Home monitoring

## 1.3 SCHEDULE OF ACTIVITIES

| | Pre-enrollment | Enrollment Day -10 | ~ 3 months[1] | | | |
|---|---|---|---|---|---|---|
| | | | Run-in[2] Days -10 to -1 | End of months 1-2 assessments 30, 60 (+/- 7 days) | | End of 3 month assessment[3] 90 (+/- 7 days) |
| SCI/HD/HCT Documentation | X | | | | | |
| Caregiver Eligibility | X | X | | | | |
| Informed Consent | | X | | | | |
| Demographics/Baseline Survey | | X | | | | |
| Caregiver Appraisal Scale | | X | | | | X |
| UHDRS Independence Scale | | X | | | | |
| SRS | | X | | | | |
| Medical Record Confirmation CRF | | X | | | | |
| HRQOL Measures | | X | | X | X | X |
| Fitbit® & CareQOL app Instructions | | X | | | | |
| Randomization | | X | | | | |
| JITIA[4,5] or Control Home Monitoring[5] | | | ← | — | — | → |
| Daily EMA[6] | | | ← | — | — | → |
| Feasibility/acceptability questionnaire | | | | | | X |
| Medications/Therapies/Med History/COVID | | X | | | | X |
| Adverse Events Reporting | | | | | | X |
| OPTIONAL: Semi-structured interview[4,7] | | | | | | X |

1 – Individual participant duration may vary depending on when they complete their HRQOL assessments; 2 – Approximately 10 days in duration, to include time for shipping and at least 3-4 days of data collection; 3 – Primary outcome assessment time point; 4 – Active intervention, includes personalized push notifications; 5 – Includes daily wearing the Fitbit® for sleep and physical activity monitoring for both groups; 6 – for both active and control groups; 7- Optional semi-structured interview for active group only; separate consent required

# 2 INTRODUCTION

## 2.1 STUDY RATIONALE

**SIGNIFICANCE**

Illness impacts the entire family, and the complete picture of human disease is a collage of the experiences of both the affected patient and family care partner(s).[1] While significant scientific discoveries and advances in human health are prolonging life for individuals who previously may not have survived a serious illness or injury, the complexities of more advanced disease management and multifaceted care needs are also growing substantially. As a society, responsibility for addressing these needs has always been placed on family care partners, who face an enormous and growing burden providing care to a loved one while trying to maintain their own health and well-being (e.g., HRQOL).[2]

While interventions exist to help improve these care partners' HRQOL, they are typically time-intensive and expensive, and have limited success at improving HRQOL in these individuals. Despite clear advantages in terms of convenience, reach and scalability with using mobile technologies (including JITAIs) to support healthy behavior change, their clinical utility in care partners remains untested. Furthermore, while much research on care partners has focused on a one-size-fits all approach to assessment and treatment, there is a growing body of evidence to suggest that while there are many commonalities in the caregiver experience, there are aspects of care that are inherently unique to different caregiver groups.[3-5] In order to better understand these commonalities and differences among different populations, this proposal includes *three distinct caregiving populations* designed to represent three different patient populations: 1) caring for a person with a chronic condition that was caused by a traumatic event (i.e., TBI); 2) caring for a person with a progressive, fatal neurodegenerative disease (i.e., HD); and 3) caring for a person with an episodic cancer condition that requires intense, prolonged inpatient and outpatient treatment (persons with hematopoietic cell transplantation [HCT]). These diverse caregiver groups not only allow for important between-population comparisons that can be used to inform future trial designs and maximize their impact; they also maximize the generalizability to other caregiving populations.

Specifically, this study is designed to establish the acceptability and feasibility of an intensive data collection protocol that involves passive mobile sensor data (using a Fitbit Charge®) and real-time patient-reported outcome (PRO) reports of symptoms and functioning (collected daily) in these three diverse caregiving populations.

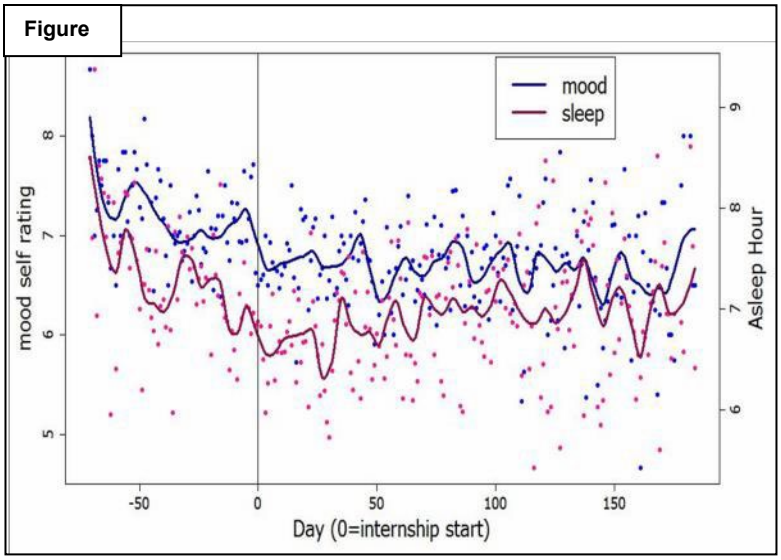
## 2.2 BACKGROUND

**Preliminary Studies.**

*The proposed JITAI study methodology is modeled after and informed by the current findings from the Intern Health Study (R01MH101459; PI Srijan Sen).* In an early phase of the Intern Health Study, physical activity and sleep were assessed using Fitbit® Trackers, and daily ratings of mood were completed via text for N=38 medical interns. In this study, 92% of participants provided sleep, activity, and mood data on at least 80% of days. Data showed an expected strong association between sleep and mood, but found that sleep predicted mood the following day substantially more strongly than mood predicted subsequent sleep (Sleep→Mood b=0.12; p<0.001; Mood→Sleep b=0.05; p=0.04; **Figure**). They also found that, on a given night, the farther an individual's sleep midpoint was from their pre-internship baseline midpoint, the lower their mood (p<0.001).[6] In a more recent study phase (a randomized

controlled trial comparing a *JITAI* with usual care; n=2053), findings indicated that receptivity to mobile health interventions was moderated by participants' current state related to the target of the intervention. For instance, interventions around increasing sleep duration were most effective when participants had low sleep the night before, adding further conceptual backing for the JITAI approach. In addition, the JITAI intervention demonstrated significant improvements in depression.

**Figure**




## 2.3 RISK/BENEFIT ASSESSMENT

### 2.3.1 KNOWN POTENTIAL RISKS

The risks associated with the proposed study are minor and infrequent and include risks to: i) confidentiality; ii) frustration, stress and/or anxiety; iii) and skin irritation:

i. Confidentiality. Confidentiality is a concern in this study. Every possible effort will be made to keep the research information in the strictest confidence, but we cannot absolutely guarantee that accidental disclosure will not happen. We remind participants that the responsibility of confidentiality rests with everyone: they should think carefully before discussing their role in this study with anyone since the effects of disclosure are unknown. Additionally, during the 3-month home monitoring period, participants may receive alerts when the participant is not in a private area. Participants will be informed that it is up to them where they complete the daily assessments, and if it is inconvenient/uncomfortable for them to complete the assessments when prompted they can wait and do it when it is more convenient/private or skip that assessment.

   To reduce the risk to confidentiality, no personal identifying information will appear on or with the participant data, where possible. Each participant will be assigned a participant ID by the study team to maintain confidentiality. The participant's self-report data and CRF data will be identified with the participant ID. Additionally, an access code will be assigned

to each participant which they will use to enroll in the CareQOL app. Participants will register their study Fitbit® on the Fitbit® app using a username and email address of their choice. The study team will help the participant configure the Fitbit® app for minimal sharing; however, participants may opt to change those settings on their own (without study team knowledge). The data collected on the Fitbit® will be linked to the CareQOL app by user authentication token, which is comprised of a random series of characters that is used to securely query for user activity data; no identifying information (including email address or Fitbit® user ID) is saved in the CareQOL app.

The study team will keep a master list of participant names and matching participant IDs. This master list will not be shared outside of the study team, and will be kept by site personnel in a password-protected file on a secure server or in a secure environment (e.g., locked cabinet, restricted access). No one other than the study team will have access to their master list. Informed consents will be stored in a study-specific database which contains only the informed consents and the informed consents will only be available to the study team members. The electronic data collection and storage systems used (e.g., CareQOL app, REDCap, Qualtrics, Fitbit®) are secure, web-based systems, with access to the study data limited to authorized individuals.

Lastly, the identities of all participants will be held in strict confidence to the extent provided by law. If findings from the study are published and/or presented at a professional meeting, no participant will be identified by name.

ii. Fatigue, Frustration, Stress and/or Anxiety. It is possible that participants may experience fatigue, frustration or feel inconvenienced when completing the self-report surveys, when receiving the personalized interventions from the CareQOL app or from wearing the Fitbit®. Participants may also feel fatigue, stress and/or anxiety related to completing the study activities. Participants will be instructed that they can skip any questions that make them feel uncomfortable, and if they receive an app alert when it isn't convenient for them, they can wait and open the app when it is more convenient.

iii. Skin Irritation. Some participants may get skin irritation from wearing the Fitbit®. Participants will be instructed to remove the device if this occurs and to contact the study team. Their band may be swapped out for a different type of wristband if they experience irritation. We offer a wide variety of wristbands to help make the Fitbit® as comfortable as possible.

To minimize the potential for risks, participants will be briefed in detail as to what they will experience throughout the study. All participants are informed that they may terminate participation from the study at any time without penalty.

### 2.3.2 KNOWN POTENTIAL BENEFITS

The proposed study aims to investigate the feasibility and acceptability of an intensive data collection protocol that involves the administration of the JITAI intervention in care partners of persons with

significant health conditions. While there may not be any direct benefits to participants, it is possible that participants may find that the JITAI improves their mood, stress levels, and/or overall quality of life. Additionally, some participants may also have a positive benefit from wearing the Fitbit®, as it may make them more aware of their activity levels and sleep. Overall, we expect that the findings from this study will help researchers further develop a personalized, easy to deploy, clinical intervention for care partners of persons with significant health conditions.

### 2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

As described above, there are minimal risks for the study participants and several potential benefits. Thus, the risk/benefit ratio is highly favorable.

# 3 OBJECTIVES AND ENDPOINTS

| Objectives | Endpoints |
|---|---|
| Primary | |
| To establish feasibility and acceptability of our intensive data collection protocol. | Primary Endpoint: Feasibility and Acceptability as measured by the responses on the individual items on the feasibility and acceptability questionnaire |
| | Secondary Endpoint: Attrition as measured by the percent of participants completing the study |
| | Secondary Endpoint: Adherence as measured by the percentage of missing data over the course of the study |
| Exploratory | |
| Examine the impact that the JITAI has on improving self-reported mental health (caregiver strain, depression and anxiety) in care partners. | Change from baseline in self-reported strain as measured by Care-QOL Strain at the end of the 3-month 90 day) intervention period |
| | Change from baseline in self-reported depression as measured by PROMIS Depression at the end of the 3-month (90 day) intervention period |
| | Change from baseline in self-reported anxiety as measured by PROMIS Anxiety at the end of the 3-month (90 day) intervention period |

# 4 STUDY DESIGN

## 4.1 OVERALL DESIGN

**Study Design:** This behavioral trial will use a two-arm randomized controlled design. Each of the 60-90 care partner participants will be randomized to an active "JITAI" arm (n=10-15 care partners of SCI, n=10-15 care partners of HD, n=10-15 care partners of HCT) or to a control arm (n=10-15 care partners of SCI, n=10-15 care partners of HD, n=10-15 care partners of HCT). The random allocation of participants to the treatment arm or control arm establishes the basis for testing the statistical significance or difference between the groups.

**Randomization:** Blocked randomization will be used to limit bias and achieve an equal distribution of participants to the control and treatment arms. A randomization list will be generated for each condition (SCI, HD, HCT) and the study statistician will oversee randomization. The participant will be randomized once he/she is deemed eligible and has provided informed consent (i.e. at enrollment prior to baseline data collection). The study coordinator/research assistant who consented the participant will use the appropriate condition's randomization list to assign the participant to the correct study arm.

**Duration of Study Participation:** Study participation for both arms of the study (control and JITAI) involves a baseline assessment, followed by an approximate 10-day run-in period then a 3-month (90 day) home monitoring period (in which the intervention will be administered to the JITAI group). Thus, the total duration of the study is ~100 days.

**Study Sites**: This is a single-site study at the University of Michigan.

**Study Intervention:** The just in time adaptive intervention (JITAI) uses sensor data derived from the Fitbit® (e.g., accelerometer-based estimates of physical activity and sleep) and real-time self-report ratings (assessed once daily) of HRQOL (caregiver strain, depression, anxiety) to deliver personalized "pushes" to participants via a study specific app (CareQOL app). The personalized pushes will be delivered on ~50% of the days over the 3-month intervention period.

### 4.2 END-OF-STUDY DEFINITION

The end of the study is defined as the completion of the 3-month home monitoring period, specifically the end of month questionnaires (occurring at 90 days +/- 7 days).

## 5 STUDY POPULATION

### 5.1 INCLUSION CRITERIA

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

1. Provide informed consent
2. Be at least 18 years of age
3. Be able to read and understand English
4. Provide emotional, physical, and/or financial support/assistance to the individual with SCI/HD/HCT, indicating a response ≥1 to the following question: "On a scale of 0-10, where 0 is

"no assistance" and 10 is "assistance with all activities", how much assistance does the person you care for require from you to complete activities of daily living due to problems resulting from his/her SCI/HD/HCT? Activities could consist of personal hygiene, dressing and undressing, housework, taking medications, managing money, running errands, shopping for groceries or clothing, transportation, meal preparation and cleanup, remembering things, etc."

5. Have access to necessary resources for participating in a technology-based intervention (smartphone/tablet and internet access) and be willing to use their personal equipment/internet for this study, including downloading the study app and the Fitbit® app on their mobile device
6. Is able and willing to complete all study assessments for the duration of their study participation (approximately 100 days)
7. **Care partners of persons with HD:** Be caring for an adult (18 years or older) with a clinical diagnosis of HD. Medical documentation of the HD is required.
8. **Care partners of persons with SCI:** Be caring for an adult (18 years or older) that is ≥1 post-injury and sustained a medically documented SCI. Medical documentation of the SCI is required.
9. **Care partners of persons with HCT:** Be caring for an adult (18 years or older) who is receiving, has received or is scheduled to receive HCT. Medical documentation of the HCT is required.

## 5.2 EXCLUSION CRITERIA

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

1. Is a professional, paid caregiver (e.g., home health aide)
2. Anything that would preclude safe or meaningful participation in the study

## 5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- Wear a Fitbit® 24 hours/day, except when charging during the 10-day run-in period and 3-month (90 day) home monitoring period.
- Install the CareQOL app and Fitbit® app on their personal mobile device, and keep these apps installed for the duration of the study (~100 days).

## 5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Screen failures are unlikely in this study because eligibility assessment occurs pre-informed consent. However, if during the 10-day run-in period before the 3-month home monitoring period starts the study team is made aware of something that would change their eligibility, the participant will be noted as a screen failure.

## 5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment: All recruitment activities will take place at University of Michigan (U-M). Recruitment and retention methods used in this study will be approved by the IRBMED and are detailed in the IRBMED submission. Potential participants will be recruited directly or through the person they are caring for.

*SCI Recruitment:* The study team will primarily recruit through clinical databases (e.g., Data Direct and EMERSE) and participant registries, including the CODA registry and Spinal Cord Injury Model Systems registry. Participants may also be recruited through outreach to SCI community groups and organizations.

*HD Recruitment:* The study team will primarily recruit through clinical databases (e.g., Data Direct and EMERSE) and participant registries, including the CODA registry and the Enroll-HD study, where participants opt to be contacted about participating in future research studies (both the CODA registry and Enroll-HD have individuals with HD and their care partners). Participants may also be recruited through outreach to HD community groups and organizations.

*HCT Recruitment:* The study team will recruit participants using several methods. Participants will be recruited through the U-M Blood and Marrow Transplantation Program (BMT); weekly meetings are held where patients are considered for clinical trials/research studies. Clinical databases (e.g., Data Direct and EMERSE) will be used for recruitment. The Long-Term Follow-Up Biorepository will also be used for recruitment. Lastly, participants may be recruited from the Outpatient BMT clinic and through outreach to BMT health care providers and community engagement partners.

Individuals who are interested in participating will be encouraged to ask questions about the study and their participation, and if they opt to enroll, they will provide informed consent prior to completing any study assessments.

In order to ensure that recruitment targets are being met, teleconference calls with the study recruitment teams by the project manager will be conducted to review progress, discuss problems, and guide additional recruitment efforts to meet stratification goals.

Retention: Given the intensive nature of this study, we expect that participants will miss some daily assessments and have times when they do not wear the Fitbit®; our retention plan is focused on minimizing these missed assessments and engaging participants throughout the study.

Retention will be facilitated by several strategies:

- App development will consider factors known to increase participant engagement including strategies to target engagement and minimize fatigue (easy to navigate platform, app tailoring based on Fitbit® sensor feedback, etc.).[7] The app will also include a study team dashboard that we will use to monitor participant engagement.
- User guides and contact information for the study team (phone and email) will be supplied to participants and they will be encouraged to contact the study team with any questions or concerns.

- When enrolling participants, we will offer participants a choice of wristbands; they can select the wristband that is most comfortable and visually appealing to them. If they are not happy with their selection, we will provide an alternate wristband.
- Study staff will maintain regular contact with the study participants. All study participants will be contacted at least once during the study run-in period, at least once during the first week of the 3-month home monitoring period and at least once each month during the remaining months of the 3-month home monitoring period.
- Participants who do not complete any study assessments (e.g., uploading Fitbit® data or answering EMAs) for several days will receive a reminder from the study team.
- In case of lost equipment/equipment failure during the run-in and home monitoring periods, we will send replacements as supplies allow.

Participant Incentives: We will compensate participants for their time and inconvenience, as follows:

  - Baseline assessment: Participants will receive $20 for completing this assessment ($20 total possible).
  - Monthly HRQOL surveys during the home monitoring period: Participants will complete end of month surveys during the home monitoring period. Participants will receive $10 for completing each end of month survey for months 1-3 ($30 total possible).
  - Daily EMA assessments and Fitbit® data during the 3-month home monitoring period: Participants will receive $1 per day for each day that they have EMA and/or Fitbit® data during the three-month (90 day) home monitoring period ($90 total possible).
  - Participants who complete the study will be allowed to keep the Fitbit® that they use in the study.
- Compensation will occur monthly to encourage prompt responding.
- We may send out nominal value items (e.g., notepads, pens) throughout the duration of study participation to encourage engagement.

# 6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

## 6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

All participants will receive a Fitbit ® for the collection of sleep and activity (steps) data, and will download the Fitbit® app and study app, CareQOL, on their personal mobile device (iOS or Android). The CareQOL app will deliver ecological momentary assessments (EMAs) once per day, compile and display data (including that collected on the Fitbit®), and deliver study notifications, including messages for the participant to complete the daily EMA and other study surveys as well as delivering the personalized study intervention prompts to the intervention group (Just-in-time adaptive intervention [JITAI] group).

All study participants will complete 3 EMA questions daily on the CareQOL app. Each participant will be prompted by a push notification in a five-hour window (based on participant preference) from the app to answer the questions. The EMA questions are comprised of: 1 question on caregiver strain (taken from the CareQOL Caregiver Strain item bank), 1 question on anxiety (taken from the PROMIS Anxiety

item bank) and 1 question on depression (taken from the PROMIS Depression item bank). Questions are on a five-point scale, with higher scores indicating more of the named construct.

In addition to the collection of the EMA data, the app complies and displays a graphical summary of historical data for caregiver stress (strain), worry (anxiety), sadness (depression), steps (collected by the Fitbit®) and hours of sleep (collected by the Fitbit®) on a participant dashboard. Participants can view this information for the past week, past month or past year. This is available to all participants as a pull – that is, it is available at all times but is accessed only if the user chooses to access it.

In this study, half of the participants will be randomized to receive the intervention (JITAI; described below); the remaining participants will be in the control group, who will not receive the JITAI but will complete the activities already described in this section. Participants who are randomized to receive the JITAI will have a 50/50 chance of receiving the intervention each day.

The JITAI aims to promote behavioral change through motivational messages that are delivered through the CareQOL app as push notifications. These notifications provide a trigger for participants to initiate or continue behavior change and/or monitor behaviors (through engagement with the with the app). The push notifications are low burden: participants can personalize the administration time (in a 5-hour window) and notifications can be viewed quickly on their phone's lock screen. Participants can also choose not to engage with the notification at the time it is sent if it is inconvenient – they can return to it later if needed.

The JITAI push notifications are aimed at promoting healthy behaviors (physical activity and good sleep hygiene) and improving mood (anxiety, depression, caregiver strain). If receiving a notification, the message will be randomly drawn from this pool of messages. Some messages will use participants' data directly in the messages (e.g., You walked an average of 8,120 steps this week), and most of messages will be personalized based on data (e.g., someone with low steps will get a different message than someone with medium steps than someone with high steps; high-medium-low). Messages are comprised of one or more of the following different types: 1) Data feedback; 2) Facts; 3) Tips; and 4) Support. Randomization of the days the participants receive messages and the message the participant receives from the pool will be done through the CareQOL app.

The study intervention period is 90 days (3 months); in addition, there is an ~10-day run-in period where participants will install/adjust/troubleshoot the study technology and the app will gather baseline data to use to tailor messages once the intervention period begins.

## 6.2 FIDELITY

For this study, the intervention will be administered via the CareQOL app. The study team will conduct training during the baseline visit with each participant which will include:

- Helping the participant download and register for the CareQOL and Fitbit® apps on their personal device
- Helping the participant set any relevant app settings (e.g., make sure alerts are turned on/off, privacy settings, etc.)
- Demonstrating the CareQOL app features to the participant (e.g., participant dashboard, etc.)

- Ensuring that the participant understands the importance of entering the daily ratings and wearing the Fitbit®
- Explaining the relationship between the daily ratings and Fitbit® data and the intervention prompts (JITAI group only)
- Demonstrating how to sync the Fitbit® (including using the Fitbit® app) and how to enter the daily ratings in the CareQOL app

During the 10-day run-in period between the baseline visit and the start of the intervention, study team members will assist participants to make sure that participants can:

- Successfully wear and sync the Fitbit®
- Successfully respond to the EMA prompts

Participants who are unable to successfully complete the run-in period will be terminated from the study and noted as a screen failure.

Training and training materials will be provided to all study team members. New study members will undergo training before the study is started. Training will be documented in the electronic regulatory binder.

Participant adherence to the protocol will be assessed throughout the study. Study staff will have access to the CareQOL app dashboard which can be used to monitor participant engagement and adherence with the app. Specifically, study staff will monitor:

- Adherence to EMA entry
- Adherence to Fitbit® use/syncing
- Adherence to completing the end of month surveys (~30, 60, 90 day)

Adherence will be calculated as a percentage for each of these areas for all participants who are not withdrawn or lost to follow-up.

### 6.3 CONCOMITANT THERAPY

There are no concomitant treatment or management strategy restrictions for this study. Information about current treatments (medications and non-medications) will be collected at baseline. Changes in treatments will be captured at the end of month 3 (~90 days) during the home monitoring period.

## 7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

### 7.1 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

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

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

- Lost-to-follow up; unable to contact participant (see **Section 7.2, Lost to Follow-Up**)
- Any event or medical condition/situation that occurs that would indicate that continued collection of follow-up study data would not be in the best interest of the participant or might require treatment that would confound the interpretation of the study
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- The participant is non-compliant with the study protocol

The reason for participant discontinuation or withdrawal from the study will be recorded. Participants who provide informed consent and are randomized but do not complete the 10-day run-in period will be replaced. Participants who withdraw or are discontinued before the end of the 3-month (~90 day) home monitoring period will be replaced.

### 7.2 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if: 1) he or she does not complete the end of month survey at the end of the 3-month (~90 day) home monitoring period ***and*** 2) study staff are unable to contact the participant after a minimum of 3 attempts.

The following actions must be taken if a participant fails to complete the end of the month survey at the end of the 3-month (~90 day) intervention period:

- The site will attempt to contact the participant and counsel the participant on the importance of completing the survey and ascertain if the participant wishes to and/or should continue in the study.
- The site will make every effort to regain contact with the participant (where possible, 3 telephone calls/emails/texts and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods) before a participant is deemed lost to follow-up. These contact attempts will be documented in the participant's study file.
- Participants that continue to be unreachable will be considered to have withdrawn from the study (with a primary reason recorded as lost to follow-up).

## 8 STUDY ASSESSMENTS AND PROCEDURES

### 8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Participants will complete a baseline assessment, and daily and monthly assessments during a 3-month (~90 day) home monitoring period. Study data will be collected via self-report into web or app-based surveys and a consumer wearable (Fitbit®).

Eligibility and baseline procedures and assessments can be conducted virtually via teleconference/webinar. Daily, monthly and follow-up assessments will be conducted virtually through

the CareQOL app.

### 8.1.1 CONDITION (SCI, HD, HCT) DOCUMENTATION

We will verify and document status of their condition (SCI, HD, HCT). Data must be obtained from official medical documentation (e.g. medical records).

### 8.1.2 CARE PARTNER ELIGIBILITY

Confirmation of care partner eligibility according to criteria listed in Section 5, above, will be documented on the Eligibility CRF. It will occur prior to informed consent being obtained and before any study procedures associated with baseline assessment. Eligible individuals will then participate in the consent process, followed by randomization and baseline data collection.

### 8.1.3 DEMOGRAPHICS & CHARACTERIZATION

All participants will complete a series of surveys designed to characterize the sample with respect to demographics, caregiving experiences, and usual coping or management strategies.

- Participant Demographics. A study-designed form will be used to capture demographic data including age, gender, race, ethnicity, education, marital status, work status, COVID history/status, care partner data, care recipient data, etc. Administration time for this assessment is ~5-10 minutes.
- Medical History, Medications, Treatments, COVID Questionnaire. Study designed forms will be used to capture medical history and current treatments/management strategies (medication and non-medication – e.g., exercise, mindfulness) and COVID history. Administration time for this assessment is 10 minutes.
- Caregiver Appraisal Scale (CAS). The CAS assesses positive and negative aspects of the caregiving role. Four separate subdomain scores (perceived burden, caregiver relationship satisfaction, caregiving ideology, and caregiving mastery) can be calculated; higher scores indicating better functioning. Administration time for this 47-item measure is ~5-10 minutes.
- United Huntington Disease Rating Scale (UHDRS) Independence Scale. The UHDRS Independence Scale is a single rating that the caregiver provides about the current level of the person that they care for's independence. Higher ratings indicate higher level of independence. Administration time is less than 1 minute.
- Supervision Rating Scale (SRS). This is a single rating that the caregiver provides about the overall amount of "supervision" that the person they care for receives. Ratings range from 1-13; higher ratings indicate greater levels of required supervision. Administration time is ~2 minutes.
- Care Recipient Medical Record Information. Study staff will complete a CRF with information about the person with SCI, HD or HCT for whom the care partner is providing care (e.g., date of diagnosis, details of diagnosis, disease stage/severity, etc.). This data will be entered into the study database by study staff.

### 8.1.4 FITBIT® AND CAREQOL APP

Participants will be taught how to install both the Fitbit® and CareQOL apps onto their personal mobile devices. Participants will also to be taught how to create and login to the necessary accounts. See section 6.2 for details regarding participant education.

- The study team will provide an access code for login to the CareQOL app.

- Participants will use a user id and personal email address of their choosing for their Fitbit® account.
- Data collected from the Fitbit® will be securely transmitted to the CareQOL app by user authentication token, which is comprised of a random series of characters that is used to securely query for user activity data.
- Participants will view their Fitbit® sleep and step-count data through the CareQOL app, though there are not restrictions on them also viewing the information in the Fitbit® app.

#### 8.1.4.1 FITBIT®

All participants will don a wrist-worn Fitbit® with heart rate recording capabilities for the duration of the 10-day run-in period and 3-month (90 day) home monitoring period to monitor activity and sleep. While we intend to use the Fitbit Inspire HR®, we reserve the option to adopt a comparable device in the event of supply limitations or changes to the product line as long as there is minimal impact on the intervention delivery or primary outcome data integrity.

- Participants may use a personal Fitbit® if it has comparable features.
- Participants are expected to wear the Fitbit® continuously except for when charging and uploading data.
- Participants are expected to sync the Fitbit® daily.

#### 8.1.4.2 CAREQOL APP

The study app (CareQOL) is the participant-facing platform for all daily, monthly and follow-up assessments, for viewing sleep and step count data from the Fitbit®, and for intervention delivery. The daily and monthly assessments, the link with the Fitbit®, and intervention delivery will cease after the home monitoring period has elapsed.

#### 8.1.4.3 RUN-IN HOME MONITORING PERIOD

A 10-day run-in period will follow the baseline assessment. This period is to allow shipping time of the Fitbit® and provide the participant time to familiarize themselves with the study technology (Fitbit®, CareQOL app) and procedures. This period will also allow the study team to troubleshoot any potential barriers or issues that arise before the official start of the 3-month (90 day) home monitoring period. It also allows for data collection that can be used to inform the intervention messages once the home monitoring period begins.

### 8.1.5 HRQOL ASSSESSMENT

Participants will complete a battery of HRQOL surveys; some will be administered daily and be used to drive the intervention, and others will be administered at baseline, monthly and during follow-up. The individual survey administration schedule is shown in the Table, and descriptions are provided below.

**Table: HRQOL Assessment Schedule**

| | Baseline | Daily* | 1m-2m (30, 60d) | 3m (90d) |
|---|---|---|---|---|
| Caregiver Strain SF | X | | X | X |
| Caregiver-Specific Anxiety SF | X | | X | X |
| Sleep-Related Impairment SF | X | | X | X |
| Fatigue SF | X | | X | X |
| Anxiety SF | X | | X | X |
| Depression SF | X | | X | X |
| Anger SF | X | | X | X |
| Self-Efficacy SF | X | | X | X |
| Positive Affect & Well-Being SF | X | | X | X |
| Perceived Stress | X | | X | X |
| Ability to Participate in Social Roles & Activities SF | X | | X | X |
| Global Health | X | | X | X |
| COVID HRQOL | X | | X | X |
| Single-item Caregiver Strain | | X | | |
| Single-item Anxiety | | X | | |
| Single-item Depression | | X | | |
| MedHistory/Medications/Treatment/COVID | X | | | X |
| Adverse Event Status | | | | X |
| Feasibility & Acceptability | | | | X |

- TBI-CareQOL Caregiver Strain Short Form (SF). TBI-CareQOL Caregiver Strain assesses perceived feelings of feeling overwhelmed, stressed and "beat-down" related to the care partner role. This measure is scored on a *T* metric (M = 50; SD = 10). Higher scores indicate more strain. The administration time for this measure is ~1 minute.
- TBI-CareQOL Caregiver-Specific Anxiety SF. TBI-CareQOL Caregiver-Specific Anxiety assesses perceived feelings of worry and anxiety specific to the safety, health, and future well-being of the person with TBI. This measure is scored on a *T* metric (M = 50; SD = 10). Higher scores indicate more anxiety. The administration time for this measure is ~1 minute.
- PROMIS Sleep-Related Impairment SF. PROMIS Sleep-Related Impairment evaluates the effect of poor sleep on daytime functioning. This measure is scored on a *T* metric (M = 50; SD = 10). Higher scores indicate more sleep-related impairment. Administration time for this measure is ~1 minute.
- PROMIS Fatigue SF. PROMIS Fatigue evaluates self-reported symptoms of fatigue, ranging from mild subjective feelings of tiredness to overwhelming exhaustion that may decrease one's ability to perform activities of daily living. This measure is scored on a *T* metric (M =

50; SD = 10). Higher scores indicate more fatigue. Administration time for this measure is ~1 minute.

- PROMIS Anxiety SF. PROMIS Anxiety assesses self-reported feelings of fear, anxiety and hyperarousal. This measure is scored on a *T* metric (M = 50; SD = 10). Higher scores indicate more anxiety. Administration time for this measure is ~1 minute.
- PROMIS Depression SF. PROMIS Depression assesses self-reported feelings of sadness and worthlessness. This measure is scored on a *T* metric (M = 50; SD = 10). Higher scores indicate more depression. Administration time for this measure is ~1 minute.
- PROMIS Anger SF. PROMIS Anger assesses self-reported feelings of irritability and frustration. This measure is scored on a *T* metric (M = 50; SD = 10). Higher scores indicate more anger. Administration time for this measure is ~1 minute.
- NIH Toolbox Self-Efficacy. NIH Toolbox Self-Efficacy assesses self-reported confidence in the ability to successfully perform specific tasks or behaviors related to one's overall functioning. This measure is scored on a *T* metric (M = 50; SD = 10). Higher scores indicate more self-efficacy. Administration time for this measure is ~1 minute.
- Neuro-QoL Positive Affect & Well-Being SF. Neuro-QoL Positive Affect and Well-Being assesses parts of an individual's life that are related to overall life meaning and purpose, well-being and satisfaction. This measure is scored on a *T* metric (M = 50; SD = 10). Higher scores indicate greater satisfaction. Administration time is ~1 minute.
- NIH Toolbox Perceived Stress SF. NIH Toolbox Perceived Stress is a self-report measure designed to assess an individual's feelings about the nature of events and individual coping resources. This measure is scored on a *T* metric (M = 50; SD = 10). Higher scores indicate more perceived stress. Administration time is ~1 minute.
- PROMIS Ability to Participate in Social Roles and Activities SF. PROMIS Ability to Participate in Social Roles and Activities assesses involvement in one's ability to participate in usual social roles and activities. This measure is scored on a *T* metric (M = 50; SD = 10). Higher scores indicate more ability to participate. Administration time is ~1 minute.
- PROMIS Global Health v1.2. This 10-item patient-reported outcome measure assesses overall physical, mental, and social health. This measure is scored on a *T* metric (M = 50; SD = 10); separate scores are generated for physical and mental health. Higher scores indicate better health. The administration time for this measure is ~3 minutes.
- COVID HRQOL. This 1-item patient-reported outcome measure asks how concerned the participant is about COVID-19 from 0 – 10. The administration time for this measure is less than 1 minute.

#### 8.1.5.1 BASELINE ASSESSMENTS

Participants will be prompted by the CareQOL after registration to complete the baseline HRQOL assessments. Administration time is 10-15 minutes.

#### 8.1.5.2 DAILY ASSESSMENTS

Participants will be prompted by the CareQOL app to complete a brief 3-item assessment once per day during the run-in and three-month (90 day) home monitoring periods. These questions will be answered directly on the app and involve <1 minute administration time in total. The daily assessments will include:

- TBI-CareQOL Caregiver Strain – single item assessment to evaluate self-reported caregiver strain. The individual items that are administered each day will vary.
- PROMIS Anxiety – single item assessment to evaluate self-reported anxiety. The individual items that are administered each day will vary.
- PROMIS Depression – single item assessment to evaluate self-reported depression. The individual items that are administered each day will vary.

**8.1.5.3 MONTHLY ASSESSMENTS**

Participants will be prompted by the CareQOL app to complete a series of self-report surveys at the end of each month (day 30, 60, 90) during the 3-month (90 day) home monitoring period. They will also complete a post-intervention/app feasibility survey and retake the CAS (described above) at the end of month 3 (day 90). These surveys will be answered directly on the CareQOL app and/or by interview, and should take ~10-20 minutes to complete.

- Feasibility & Acceptability Questionnaire: At the 3-month (90 day) assessment only, participants will complete a Study Feasibility survey to assess the experience of the participant with the study methodology and technology, including the CareQOL app, Fitbit®, and the JITAI. Items are scaled from 1 to 5 to indicate level of agreement, where "1" indicates "strong disagreement" and "5" indicates "strong agreement." Administration time is 5 minutes.

Additionally, participants will update their medical history, medications, therapies, and COVID history and be queried about AEs at the end of month 3 (day 90).

- Medical History, Medications, Treatments, COVID Questionnaire. Participants will update their medical history and current treatments/management strategies (medication and non-medication – e.g., exercise, mindfulness) and COVID history. Administration time for this assessment is 10 minutes.
- Adverse Events. Participants will be asked about any changes in mental or physical health. Administration time is 5 minutes.

**8.1.6 SEMI-STRUCTURED INTERVIEW (OPTIONAL: JITAI Group Only)**

Participants who have been randomized to the intervention group (JITAI) may be invited to complete an **optional**, in-depth semi-structured interview that will assess participant experiences and perceptions of the intervention messages that they received from the CareQOL app. The interview will be conducted via Zoom, audio-recorded and last for 45-60 minutes. Participants will be asked about their general experiences with the intervention messages they received while using the CareQOL app. Additionally, they will be shown specific messages from the CareQOL app and will be asked to provide their thoughts about these specific messages and their experiences with them. The interview will be completed after the 90-day study intervention period is completed (no more messages are being sent).

Participants who opt to complete this optional interview will be required to provide separate informed consent for this portion of the study, and participants will receive $20 for completing the interview. The audio-recording of the interview will be transcribed and analyzed using qualitative analysis software (e.g., NVivo).

## 8.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

### 8.2.1 DEFINITION OF ADVERSE EVENTS

The U-M IRBMED definition of an adverse event will be used for this study. The definition can be found at https://az.research.umich.edu/medschool/glossary and is below:

An adverse event (AE) is any experience or abnormal finding that has taken place during the course of a research project and was harmful to the subject participating in the research, or increased the risks of harm from the research, or had an unfavorable impact on the risk/benefit ratio. The event may or may not be caused by an intervention. Adverse events also include psychological, social, emotional or financial harms.

### 8.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS

The U-M IRBMED definition of a serious adverse event (SAE) will be used for this study. The definition can be found at https://az.research.umich.edu/medschool/glossary and is below:

A serious adverse event (SAE) is any adverse experience occurring at any dose or level of participation that results in any of the following outcomes:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

### 8.2.3 CLASSIFICATION OF AN ADVERSE EVENT

#### 8.2.3.1 SEVERITY OF EVENT

All AEs will be assessed by a principal investigator(s), and/or if necessary, a study co-investigator.

The following guidelines will be used to describe severity.

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

#### 8.2.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately-trained investigator based on temporal relationship and his/her clinical judgment. All AEs will be categorized according to the likelihood that they are related or not related to the study intervention.

- **Related (Possible, Probable, Definite)**
  - The event is a known or suspected effect of the intervention or research procedures (e.g., listed in the protocol documents including, consent, publications, etc.)
  - There is at least a reasonable temporal relationship between the intervention or procedure and the event onset
  - The event abates when the intervention is discontinued
  - The event reappears upon a re-challenge with the intervention
  - The event includes data that was collected solely for research purposes
  - The event included disturbing or upsetting questions asked solely for research purposes

- **Not Related (Unlikely, Not Related)**
  - The event is NOT a known or suspected effect of the study intervention or procedures
  - The event is readily explained by characteristics of the study population
  - There is no temporal relationship between the intervention and event onset
  - An alternate etiology has been established

#### 8.2.3.3 EXPECTEDNESS

An investigator with appropriate expertise will be responsible for determining whether an adverse event (AE) is expected or unexpected. An event that is expected has been addressed or described in one or more of the following: Informed consent document for this study, IRB application for this study, grant application or study agreement, protocol or procedures for this study, published literature, other documentation, or characteristics of a study population. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information described.

### 8.2.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of the study team via spontaneous report or formal assessment during month 3 of the 3-month home monitoring period, where participants will be asked to describe any physical or mental health worries/concerns since they began participating in the study. Regardless of the reporting mechanism, the study team will probe any concerns to get additional information and determine if it is an adverse event. Details will be documented in the participant study record.

Any side effects that are determined to be adverse events related to study participation will be documented on the study adverse event form in the study REDCap database and followed until resolution.

### 8.2.5 ADVERSE EVENT REPORTING

For this study, only related adverse events will be reported. Adverse events will be reported to U-M IRBMED using the standard IRBMED reporting schedule: (https://az.research.umich.edu/medschool/guidance/adverse-event-reporting). The U-M IRBMED reporting schedule is dependent on the severity of the event, and whether such adverse events were expected. Any serious adverse events will be reported to U-M IRBMED as soon as possible but not later than 7 days of learning of the event. Non-threatening potentially serious adverse events that are causally related to the research will be reported within 14 days of learning of the event to the U-M IRBMED.

Staff will report study-related adverse events using the adverse event form in the REDCap study database promptly. In the case of a serious adverse event, the project PI and project manager should be notified by email or phone as soon as possible. Adverse events will be discussed at investigator and project staff meetings.

# 9 STATISTICAL CONSIDERATIONS

## 9.1 STATISTICAL HYPOTHESES

Primary Endpoint:

1) We hypothesize that this intensive data collection protocol will be both feasible and acceptable for care partners (regardless of group assignment)
    a. Feasibility and Acceptability as measured by ≥80% of participants indicating that care partners either 'Agree' or 'Totally Agree' that the different study elements are feasible and acceptable

Secondary Endpoints:

2) We hypothesize that this intensive data collection protocol will be both feasible and acceptable for care partners (regardless of group assignment)
    a. Attrition as measured by the percent of participants completing the study (i.e., we expect ≥80% of participants to complete the study)
    b. Percent missing data of total expected data for each person and on average will also be calculated to characterize the feasibility of this data collection method (i.e., we expect ≤60% missing data for the daily assessment questions and ≥80% completion rates for the three monthly surveys)

Exploratory Endpoints:

1) We hypothesize decreases from baseline to 3-months in caregiver strain among participants in the JITAI group.

2) We hypothesize decreases from baseline to 3-months in depression among participants in the JITAI group.

3) We hypothesize decreases from baseline to 3-months in anxiety among participants in the JITAI group.

## 9.2 SAMPLE SIZE DETERMINATION

The main purpose of the current trial is to establish the feasibility and acceptability of an intensive data collection protocol in order to inform the a larger, later-stage effectiveness study on the JITAI in care partners of persons with chronic medical conditions. Thus, the current study is designed to provide a point of estimate for the effect of the JITAI for this future large-scale trial. Given that there are no formal power analysis calculations for this type of analysis, we have based the proposed sample size on our previous experience conducting these types of trials. Specifically, we believe that ~50 participants will provide sufficient numbers and diagnostic diversity to evaluate feasibility and acceptability of new mobile health apps. Thus, or sample size of N=60 caregivers (30 per arm and 20 per care partner group), exceeds this estimate and should provide a reasonable range of scores on the HRQOL outcome measures to guide later phase trial work.

## 9.3 POPULATIONS FOR ANALYSES

The primary endpoint will examine survey responses on the feasibility and acceptability questionnaire that is designed to evaluate our intensive data collection protocol in the full sample (i.e., N=60 care partners). Secondary endpoints will include attrition and adherence estimates (again across the full sample). Exploratory analyses will be conducted to identify trends for an improvement in HRQOL scores (i.e., strain, depression, and anxiety) for care partners that are randomized to the intervention group. These analyses will also look for a trend for an improvement in the remaining HRQOL scores for care partners that are randomized to the intervention group, and will compare the JITAI group with the control group on all of the different HRQOL measures. Exploratory analyses may also compare important subgroups (e.g., caregiver groups that differ by diagnosis [SCI, HD or HCT], relationship type [parent vs. spousal caregivers], caregiver groups that differ by sex [male vs. female caregivers], caregiver groups that differ according to the functional status of the person with TBI (e.g., complicated mild vs. moderate vs. severe TBI or perceived functional status based on Mayo Portland Adaptability Index scores). Exploratory analyses will be an intention-to-treat approach where the participant will contribute data to the arm he/she was randomized to regardless of the amount of data contributed (i.e. the duration of participation).

## 9.4 STATISTICAL ANALYSES

### 9.4.1 GENERAL APPROACH

Continuous measures will be described using means and standard deviations (or medians and ranges if non-normality is detected), while categorical measures will be summarized with frequencies and percentages.

For inferential tests, a two group t-test will be used to look for trends in the data.

Analyses for primary and secondary endpoints are described individually, below.

The distribution of the data will be examined to ensure that parametric testing is appropriate. In cases where data distributions are not normal, nonparametric tests will be used to analyze the data.

### 9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Primary Endpoint:

- Feasibility & Acceptability Questionnaire: At the 3-month (90 day) assessment only, participants will complete a Study Feasibility survey to assess the experience of the participant with the study methodology and technology, including the CareQOL app, Fitbit®, and the JITAI. Items are scaled from 1 to 5 to indicate level of agreement, where "1" indicates "strong disagreement" and "5" indicates "strong agreement." Administration time is 5 minutes.

Frequency counts for each of the Feasibility and Acceptability items. Descriptive statistics will also be calculated.

### 9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary Endpoints:

- Attrition (% of participants completing the final assessment—the assessment that is given at the end of month 3)
- Adherence (% missing data of total expected data for each person)

Attrition will be reported as the number of participants that complete the final assessment out of the total of number of study participants that completed the baseline assessment. In addition, the total number of days that participants completed EMA assessments, the monthly surveys, and the number of participants that complete the study will be calculated. Descriptive statistics will be calculated for missing data across the study period and by moment/day.

### 9.4.4 BASELINE DESCRIPTIVE STATISTICS

Care partners in each study group (JITAI and control) will be compared descriptively according to Consolidated Standards of Reporting Trials Guidelines.[8]

T tests/ANOVA will be used to examine group differences for continuous variables (e.g., age, HRQOL outcomes). Chi-squared/Fisher exact tests will be used to examine group differences for categorical variables (e.g., caregiver type [SCI, HD, HCT], sex, ethnicity, race, education, marital status, relationship to care recipient).

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

### 10.1.1 INFORMED CONSENT PROCESS

#### 10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

The participant will be provided with a PDF of their certified consent form approved by the U-M IRBMED describing in detail the study intervention, study procedures, and risks. Informed consent will be obtained prior to the participant completing any study-related assessments. An example can be found in the U-M IRBMED application for this study.

#### 10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

All consent procedures will be approved by the U-M IRBMED. Informed consent will be conducted virtually (e.g., Zoom, Bluejeans, telephone, etc.). Consent will be documented using the REDCap consent platform; participants will indicate their consent by entering their name and the date into the REDCap consent document. All individuals who are interested in participating in the study will be encouraged to ask questions about the study and their participation, and will be given as much time as needed to make a decision about participating. Participants will receive a pdf copy of their 'signed' consent.

Participants completing the optional semi-structured interview portion of the study (see section 8.1.6) will consent for this portion of the study using a separate consent form, following the same procedures above.

A waiver of informed consent and HIPAA waiver is requested for eligibility screening for this study and for collection of medical record data for the individual that the participant (care partner) is caring for. The medical record data is needed to accurately capture date of diagnosis, details of diagnosis, disease stage/severity, etc.

### 10.1.2 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff and the funder. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team.

All research activities will be conducted in as private a setting as possible. The study participant's contact information will be securely stored for internal use during the study. Study staff will keep a master list of their participant names and matching participant IDs. This master list will not be shared outside of the study team, and will be kept by study personnel in a password-protected file on a secure server or in a secure environment (e.g., locked cabinet, restricted access). No one other than the study

team will have access to their master list. Informed consents will be stored in a study-specific database which contains only the informed consents. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the U-M IRBMED and Institutional policies.

No personal identifying information will appear on or with the participant data, where possible. Each participant will be assigned a participant ID by the study team to maintain confidentiality. The primary unique identifier is the study-assigned participant ID. The participant's self-report data and CRF data will be identified with the participant ID. Additionally, an access code will be assigned to each participant which they will use to enroll in the CareQOL app. Participants will register their study Fitbit® on the Fitbit® app using a username and email address of their choice. The data collected on the Fitbit® will be linked to the CareQOL app by user authentication token, which is comprised of a random series of characters that is used to securely query for user activity data; no identifying information (including email address or Fitbit® user ID) is saved in the CareQOL app.

For participants completing the optional semi-structured interview portion of the study (see section 8.1.6), no personal identifiers will be kept with the transcription of the interview. Only audio will be recorded during the interview (no video), and the participant will be instructed and reminded (if needed) to avoid using names, other identifiers, etc. during the interview. Audio-recordings and transcripts will be stored securely (e.g., password protected server, study-specific M-Box).

The study data entry and study management systems (e.g., CareQOL app, REDCap, Qualtrics, M-Box, Fitbit®, etc.) used in the study are secured and password protected. At the end of the study, all study databases will be de-identified and archived securely at the University of Michigan.

Measures Taken to Ensure Confidentiality of Data Shared
The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant).

### 10.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

Data Retention
Research data and information will be retained for both study record-keeping purposes and for future research use. Any materials with identifiers (e.g., informed consents) will be stored in locked filing cabinet or on a secure server separate from coded study information.

Data from participants who withdraw from the study will be retained in the study database.

Study Record Keeping
During the study, we will maintain identifiable data to facilitate day-to-day study operations such as follow-up contact, distribution of study incentives, etc. These records may be destroyed after 7 years per U-M record keeping guidelines (*https://az.research.umich.edu/medschool/guidance/record-keeping-guidelines*).

Data for Future Research Use

We will archive de-identified data for future research use. These data may be used for additional analyses related to the main study, new analyses, and in grant proposals for new research.

- The data will be stored on Michigan Medicine servers in a HIPAA-compliant electronic data capture system and/or statistical datasets that are stripped of identifiers.
- Access to the data will be at the discretion of the PIs.
- Any data shared with collaborators and other researchers will be transferred using secure methods (e.g. MiShare, encryption, etc.)

### 10.1.4 SAFETY OVERSIGHT

The study investigators will be responsible for monitoring the data quality and safety for this study. No human subject activities will occur until U-M IRBMED approval is received.

Dr. Carlozzi (administrative PI) will supervise the conduct of the study team and ensure that all relevant U-M IRBMED policies and procedures are following by the study team. These include: (1) All participants will provide informed consent before participating; (2) All participants will be notified of their right to withdraw or refuse to answer questions; (4) Identifying information, where possible, will be kept separate from the coded participant data; (5) All identifying information will be keep securely at all times (e.g., password protected, limited access, secure environment; (6) Participants will be informed in the consent form on how to contact the study team and IRBMED with any questions and/or concerns; and (7) Adverse events, unanticipated problems and ORIOS are reported to the U-M IRBMED per the study reporting plan.

### 10.1.5 QUALITY ASSURANCE AND QUALITY CONTROL

QA and QC practices will be the responsibility of all team members. Training and regular meetings will be conducted to monitor and facilitate quality data collection.

**Training:**
All study staff will be trained on the project protocol, project data collection systems and other study-related topics prior to beginning data collection. Additionally, the project manager, in cooperation with the study PIs, will develop a manual of procedures, case report forms and other related study materials. The manual of procedures will provide step-by-step instructions on the conduct of the trial, including how to use and troubleshoot the data collection platforms. The manual of procedures and other study documents will be reviewed in detail with the study coordinators as part of the training, and all materials will be available on the study-specific shared MBox site for access at any time. Study staff will be encouraged to use the step-by-step instructions when conducting participant visits to ensure that they are adhering to the study protocol. Ongoing training will occur via regular conference. Additionally, any staff who join the team after the project starts will be required to complete the standardized training prior to enrolling participants. Training will be documented in the electronic regulatory binder.

**Meetings:**

- **Study Kickoff/Training** – A study kickoff and training meeting will be held prior to the start of project recruitment.

- **Investigator Meetings** – Meetings with the study investigators will be held monthly to discuss study activities, progress and troubleshoot any issues. Other project staff will attend as needed.
- **Project Staff Meetings** – The Project Manager will hold monthly meetings with the project staff after recruitment begins. These meetings will be focused on tracking recruitment efforts, data collection (including data management and clearing of queries), and discussion of protocol deviations, unanticipated problems or adverse events. Investigators may attend as needed.

## 10.1.6 DATA HANDLING AND RECORD KEEPING

### 10.1.6.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

This project uses multiple electronic data capture and management platforms (e.g., REDCap, CareQOL, Qualtrics, Fitbit®, U-M server, Google Cloud, AWS Cloud). All platforms are designed for human subjects research and comply with federal and local data and information security practices.

Data collection is the responsibility of the study coordinators/research staff under the direction of the Project Manager and Dr. Carlozzi (HD and SCI)/Dr. Choi (HCT). All data are entered or captured on the platforms by study staff or directly by participants (e.g. sleep/activity data, daily EMAs etc.). Any study documents completed on paper will be completed legibly and in ink.

The Project Manager and Dr. Carlozzi will directly oversee the QA/QC activities using standard operating procedures, checklists, and built-in and study-specific data validation rules to uphold data integrity. Routine data backups will be part of this process.

The Project Manager, in cooperation with other study team members, will be responsible for setting up, monitoring and maintaining the data collection systems, and the initial implementation checks of data quality. Initially, data from the mobile app will be reviewed following the run-in period from the first 5 participants to ensure that daily data is being appropriately collected. We will continue to monitor the same 5 participants throughout the completion of the study. We will evaluate procedures to ensure that data transfers at all points are accurate. Review of the data quality will be conducted by the study statistician and PI. Irregularities or problems detected will be discussed with the study team and addressed. Following any needed adjustments or corrections to study procedures, subsequent data quality as described above will be monitored for the next 5 participants and then by random inspection of the data independently by the statistician and PI. Quarterly audits will confirm proper data transfers and downloads, and include checks for missing and/or out-of-range data, logic errors, etc. Quality control and reliability of the data will be discussed at regular team meetings.

### 10.1.6.2 STUDY RECORDS RETENTION

Study records will be retained according to University of Michigan guidance for research records retention involving health-related data (https://az.research.umich.edu/medschool/guidance/record-keeping-guidelines).

## 10.1.7 OTHER REPORTABLE INCIDENTS & OCCURRENCES (ORIOS)

We will follow the U-M IRBMED guidance for reporting Unanticipated Problems (https://az.research.umich.edu/medschool/guidance/unanticipated-problems-involving-risks-subjects-or-others) and ORIOs (https://az.research.umich.edu/medschool/guidance/other-reportable-information-or-occurrence-orio), with some exceptions for protocol deviations, shown below.

**Unanticipated Problems:**

An Unanticipated Problem Involving Risks to Subjects or Others (UaP) is an actual incident, experience or outcome that warrants consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare or rights of subjects or others. The following criteria must be met:

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

Unanticipated problems will be reported by a study investigator to the U-M IRBMED per their standard reporting timeline. See: https://az.research.umich.edu/medschool/guidance/unanticipated-problems-involving-risks-subjects-or-others

Study staff will report study-related unanticipated problems using the unanticipated problem form in the REDCap study database. Unanticipated problems will be discussed at investigator and project staff meetings.

**Protocol Deviations:**

This protocol uses the U-M IRBMED definition of a protocol deviation (https://az.research.umich.edu/medschool/glossary/deviation) which defines a protocol deviation as "an incident involving non-compliance with the protocol, but one that does not have a significant effect on the subject's rights, safety or welfare, and/or on the integrity of the data. Deviations may result from the action of the participant, researcher or staff."

We will follow the U-M IRBMED reporting guidance for protocol deviations found here https://az.research.umich.edu/medschool/guidance/other-reportable-information-or-occurrence-orio.

Reportable protocol deviations will be reported and tracked in the study REDCap database and will be discussed at investigator and project staff meetings.

The following events will not be reported as protocol deviations:

- A protocol deviation will not be reported for participants who skip/do not complete study survey questions or entire surveys (like end of month assessments or post-intervention surveys).

Participants can decline to answer any survey question for any reason. We expect in an intensive, long duration protocol like this that participants may miss some assessments.

- A protocol deviation will not be reported for out-of-window assessments. Use of this data will be assessed by the study investigators for each study analysis; some analyses may need tighter compliance to the assessment window while others will not.
- A protocol deviation will not be reported for participants who miss/do not complete the EMA assessments or do not wear/miss uploading Fitbit® data during the home-monitoring period. For example, we expect that there may be instances where participants are unable to complete the EMA assessments (for example, they are somewhere where it is inconvenient for them to answer) or forget to put on or sync the Fitbit®.
- A protocol deviation will not be reported for participants who decline the participant payment. It has been our experience that some research participants do not wish to receive payment for their participation in research studies.

Reportable protocol deviations will be reviewed at the project staff and investigator meetings.

### 10.1.8 PUBLICATION AND DATA SHARING POLICY

The Principal Investigators will make unique research resources readily available for research purposes to individuals within the scientific community after publication. U-M has previously used a variety of means as appropriate and expeditious to share data resulting from sponsored projects with research colleagues, such as depositing data into secure web-accessible data warehouses or arranging distribution of data, and protocols to other researchers using established mechanisms and repositories.

U-M will assure the timely release and sharing of data no later than the acceptance for publication of the main findings from the final dataset and will protect the rights and privacy of human subjects who participate in research by redacting all identifiers, and adopting other strategies to minimize risks of unauthorized disclosure of personal identifiers in accordance with authorization and consent documents. U-M agrees that data sharing is essential for expedited translation of research results into knowledge, products, and procedures to improve human health. To enable efficient data sharing, the U-M Project Manager will coordinate requests for data and maintain documentation for requests and distributions. The University has an established Institutional Data Use Agreement that can easily be adapted and deployed.

This study will also comply with the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov.

REFERENCES

1. Rothing M, Malterud K, Frich JC. Caregiver roles in families affected by Huntington's disease: a qualitative interview study. *Scand J Caring Sci.* 2013.

2. Verhaeghe S, Defloor T, Grypdonck M. Stress and coping among families of patients with traumatic brain injury: a review of the literature. *J Clin Nurs.* 2005;14(8):1004-1012.

3. Caregiving. FCANCo. *https://www.caregiver.org/caregiver-statistics-demographics*. Accessed January 3, 2019.

4. Reinhard SC, B. G, N.H. P, A. B. Supporting family caregivers in providing care. In: Hughes RG, ed. *Agency for Healthcare Research and Quality: An Evidence-Based Handbook for Nurses.* Rockville (MD): Agency for Healthcare Research and Quality (US); 2008.

5. Talley RC, Crews JE. Framing the public health of caregiving. *Am J Public Health.* 2007;97(2):224-228.

6. Kalmbach DA, Fang Y, Arbedt JT, et al. Effects of Sleep, Physical Activity, and Shift Work on Daily Mood: a Prospective Mobile Monitoring Study of Medical Interns. *J Gen Intern Med.* 2018;33(6):914-920.

7. Nahum-Shani I, Smith SN, Spring BJ, et al. Just-in-Time Adaptive Interventions (JITAIs) in Mobile Health: Key Components and Design Principles for Ongoing Health Behavior Support. *Ann Behav Med.* 2018;52(6):446-462.

8. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. *J Pharmacol Pharmacother.* 2010;1(2):100-107.