Brief Title: Depression Prevention in Older Spousally-bereaved Adults

NCT Number: NCT04016896

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Study Protocol and Statistical Analysis Plan

This document contains the following items

1. FINAL PROTOCOL

Overview

This study will enroll 150 older spousally-bereaved adults who are high risk for major depressive disorder (MDD) due to subthreshold symptoms of depression. These subjects will be randomly assigned to digital monitoring of sleep, meals, and physical activity behaviors or enhanced usual care. Subjects will be followed for 12 months after the intervention. We selected a 12-week intervention because this length of time was (a) sufficient to observe change in the proposed mechanism of action (circadian rest activity rhythm); and (b) acceptable to participants in our pilot RCT.

Participants and Study Design

Participants. A total of 150 older adults will be enrolled in the proposed study. We have chosen to target spousally-bereaved adults aged 60 years and older for the following clinical and methodological reasons: (a) adults aged 60 years and older experience bereavement differently than younger age groups because older adults are also experiencing declines in physical, mental, and cognitive health that may inhibit adaptive functioning following bereavement; (b) recently bereaved elders (≤ 12 months post spousal death) are at heightened risk for depression and other mental health problems related to poor self-care; (c) there is an urgency to understand strategies to modify the trajectories of depressive symptoms in bereaved elders already at risk for developing depression (indicated prevention) given the growing population of older adults who become bereaved each year, (d) examining bereaved elders who are at risk for depression is necessary to observe changes in response to the intervention over the short period of time that is

feasible to conduct a RCT. Targeting older adults who are not at risk for depression would increase the likelihood of ceiling effects.

Eligibility Criteria. Inclusion criteria will be (1) aged 60 years and older; (2) spousally bereaved within 12 months post-loss; and (3) at-risk for MDD, based on high-risk markers defined as subthreshold symptoms of depression (Hamilton Depression Rating Scale score ≥ 9),[1] together with absence of current MDD, post-traumatic stress disorder, or persistent complex bereavement disorder Exclusion criteria will be (1) current DSM-5 criteria for syndromal mood, psychosis, or anxiety disorder within the last 12 months; (2) dementia; Modified Mini-Mental State Examination <80;[2] (3) acute suicide risk; based on Herbeck et al. protocol for suicide risk management[3]; and (4) patients taking new psychotropic medications *after* spousal death to stabilize depression including antidepressants and benzodiazepines >4 days/week for more than two months. Individuals who have been on a stable dose for at least 1 month and agree not to change during participation, unless it is medically necessary, will be included.

Recruitment & Screening Strategy. To enroll a total of 150 participants (n=30 in Year 01, n=50 in Years 02-03, n=20 in Year 04), we will take advantage of our network of community partners including: (1) Allegheny Health Network's Healthcare @ Home Hospice Care, (2) primary and specialty medicine at the University of Pittsburgh, (3) faith-based organizations; (4) extensive print and on-air advertising via the UPMC Aging Institute (aging.upmc.com); and (5) University-affiliated research registries (ctsi.pitt.edu). We have successfully recruited participants from each of these partners for the pilot study. We recognize that efforts to recruit adults who are not seeking treatment may be difficult. Recruitment materials will emphasize healthy aging, thereby

encouraging participation by individuals who are interested in health, rather than illness-related research. Once interested participants are identified, they will be scheduled for a clinical assessment during which they will complete a battery of psychosocial questionnaires. Those identified 'at-risk' will be enrolled.

Procedures

Baseline. All participants will receive written *education* about healthy lifestyle choices including pamphlets from the National Sleep Foundation, the US Department of Agriculture's *Choose My Plate*, the NIA's Age Page on *Aging and Alcohol Abuse*, and the NIH's *Getting Fit for Life*. We will help participants to choose a personal *health goal* on which to focus during the study; examples include: (a) engage in 150 minutes of moderate-intensity activity/week; (b) don't skip breakfast; and (c) get 7-8 hours of sleep per night, among others.

Widowed Elders' Lifestyle after Loss (WELL) Intervention Protocol. The WELL intervention is a multicomponent intervention that uses digital monitoring and motivational health coaching to encourage a regular routine of sleep, meals, and physical activity. The combination of self-monitoring, performance feedback, and motivational health coaching will help to ensure the

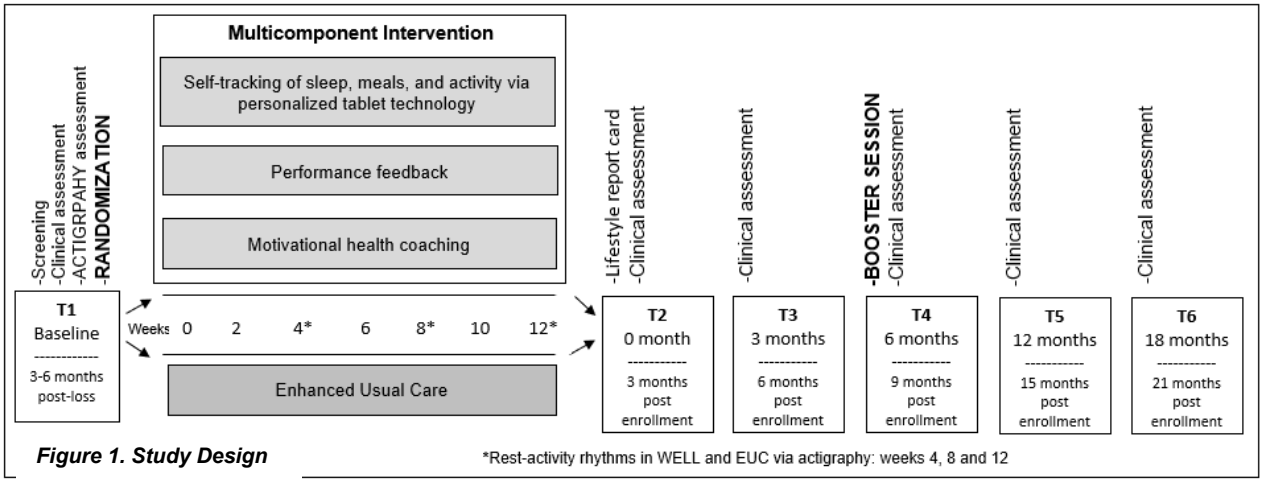
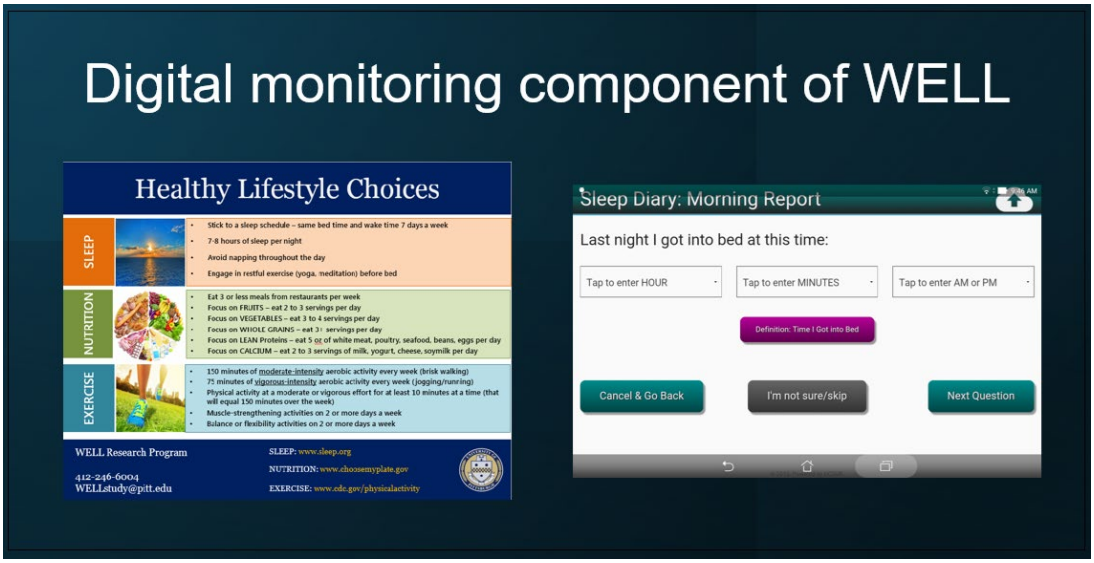


Figure 1. Study Design

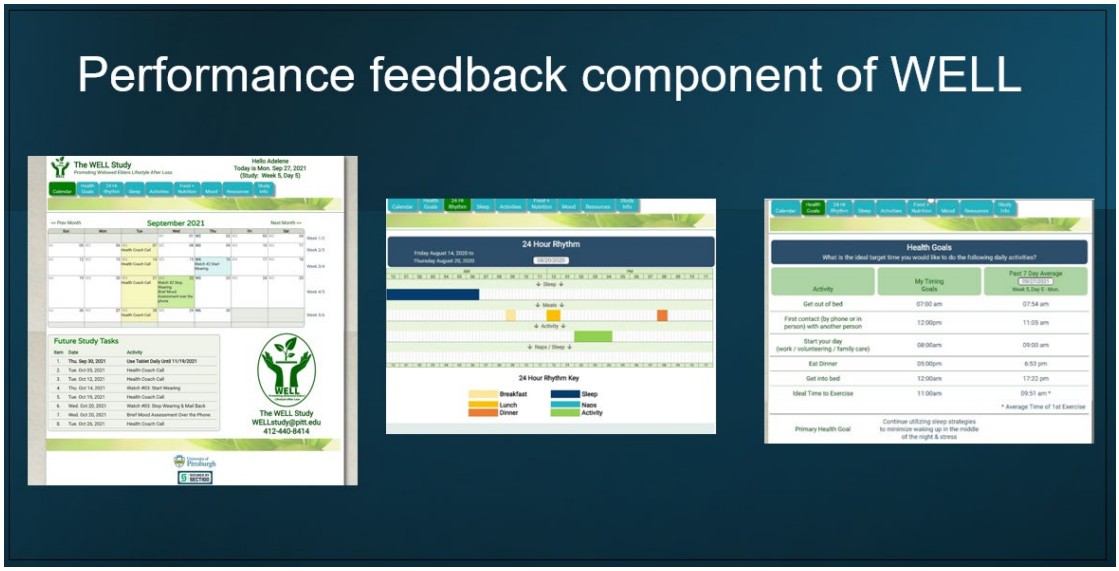
success of study participants. This multicomponent strategy has proven acceptable, with 93% retention in our pilot RCT. **Figure 1** shows the study design.

- *Digital Monitoring Component.* We chose to implement an intervention that we hypothesize might reduce depression symptoms via re-entraining a regular routine: behavioral self-monitoring of sleep, meals, and physical activity. Behavioral self-monitoring interventions teach individuals to become mindful of their behaviors and the conditions in which they occur. By increasing awareness and understanding of one's own behavior, improvements in physical activity, dietary behavior, weight status, and sleep have been observed across diverse populations.[4–6] Monitoring is usually performed over several months, with individuals recording specific behaviors (e.g., minutes exercising, bedtime/wakeup). Participants randomized to WELL will record the timing of sleep, meals, and physical activity twice daily via Qualtrics on their tablet, smartphone, or PC, for 12 weeks. Tablets will be provided to participants who do not own their own device, to improve the sustainability of a technology-based treatment in population subgroups. The digital diaries includes questions to re-entrain a regular routine; including items from the Pittsburgh Sleep



Diary;[7] the (1) *Morning Diary* asks about the previous night's sleep including bedtime (hh:mm); time to fall asleep (minutes); number of nighttime awakenings; mood at bedtime (alert, sleepy, worried, anxious; scale 1-10); quality of sleep (scale 1-10); time of morning awakening (hh:mm), time out of bed to start daily activities (hh:mm); and mood at morning awakening (scale 1-10; very good – very bad); the (2) *Evening Diary* asks about physical activity, diet, and sleep behaviors throughout the day including time daily activities started (hh:mm); time of first contact with another person via phone or in-person (hh:mm); time of breakfast, lunch, and dinner (hh:mm); number of servings of whole grains, fruits, vegetables, calcium-rich foods, proteins, and alcohol); number of meals at a sit-down/take out restaurant; number of naps; time spent in light, moderate, and vigorous activity (min); time spent in sitting, walking, muscle strengthening activities (min); and mood throughout the day (scale 1-10; very bad-very good).

- *Performance Feedback Component.* The WELL intervention includes performance feedback to promote participant engagement and self-knowledge. During the intervention, a web-based "Lifestyle Log" illustrates the timing of and regularity of sleep, meals, and physical over the



last 7 days. User data from the Qualtrics surveys are fed into the Lifestyle Log, creating figures that update in real-time, providing users with up-to-date information about their self-behaviors.

- *Motivational Health Coaching Component.* Improving self-care behavior can be challenging, requiring effort and motivation. Therefore, the effects of self-monitoring to optimize engagement in routine self-care may be enhanced by using motivational interviewing (MI) – a patient-centered approach to strengthen bereaved elders' motivation and commitment to change.[8] MI facilitates healthy lifestyle change by helping patients resolve ambivalence about change in an empathetic and encouraging climate.[9,10] During weekly phone conversations, a "lifestyle coach" will use MI techniques (express empathy through reflective listening, develop discrepancy between current situation and future goals, avoid argument, and support self-efficacy) to help strengthen older adults intrinsic motivation to engage in a regular behavioral routine

2. FIDELITY MONITORING PLAN

Fidelity to digital monitoring was calculated by summing the number of times participants completed the digital diaries: 2 diaries per day for 3 months = 168 possible diaries. Using the gold-standard for coding fidelity of motivational interviewing – the Motivational Interviewing (MI) Treatment Integrity Coding Manual – four components of MI will be coded during each health coaching session: open-ended questions, affirmations, reflective listening, and summarizing statements.[11] All MI sessions were audio recorded and 20% of sessions (from early, middle, and late intervention) were randomly selected for fidelity ratings (by a MI expert) to ensure maintenance of treatment specificity and integrity. The MI expert suggested therapeutic

strategies over the course of contact with participants to ensure fidelity to the desired target – regularity of sleep, meals, and physical activity.

Table 1 shows our fidelity plan for monitoring intervention delivery, receipt, and enactment.[12] Using the gold-standard for coding fidelity of motivational interviewing – the Motivational

Table 1. Fidelity Monitoring Plan

Domain	*Monitoring procedures*
Delivery Is the intervention delivered as intended?	- Monitoring checklists for each session (BL, T2, T3, T4, T5) which provide quantification of adherence to session protocols <u>Interventionists (for MI)</u> - Use of a treatment manual - Certified in the use of MI for behavior change by the Motivational Interviewing Network of Trainers (MINT) - Completion of session-by-session tracking forms - Audiotaped sessions
Receipt Did participants receive intervention as intended?	- Tracking the # of diaries participants enter in the tablet - Tracking the # of times performance feedback was viewed - Checking in during MI sessions to evaluate what works and what is not working - Identification of any participant barriers to participation (e.g., use of a paper diary in lieu of the tablet because of dexterity barriers)
Enactment Did participants enact the behavioral skills imparted?	- Attainment of personal health goal(s) - Follow-up survey of awareness of daily routine - Follow-up survey of continued self-monitoring and progress towards health goal

Interviewing (MI) Treatment Integrity Coding Manual – four components of MI will be coded during each coaching session: open-ended questions, affirmations, reflective listening, and summarizing statements.[11] All coaching sessions will be audiotaped and 20% will be randomly selected for fidelity ratings (by a MI expert, TBH) to ensure maintenance of treatment specificity and integrity. [13] The MI expert will suggest therapeutic strategies over the course of contact with participants to ensure fidelity to the desired target – regularity of sleep, meals, and activity.

3. STATISTICAL DESIGN AND POWER

Descriptive Statistics

Data will be examined descriptively using observed means, standard deviations, and percentiles for continuous variables; and frequencies and proportions for categorical variables. We will

examine continuous variables to determine if distributional assumptions, for e.g., normality and homoscedasticity, are satisfied. Transformations or nonparametric techniques will be applied as needed. Statistical comparisons will be performed to compare the intervention and control arms with respect to demographic characteristics and important health characteristics at baseline. Standard techniques include t-tests for continuous variables and Fisher's exact test and/or Pearson χ^2 procedures for categorical variables. The baseline values of the outcome variables will be analyzed in a similar manner to determine whether any systematic differences between the treatment arms remained after randomization. The proposed study is a randomized clinical trial with repeated measures, with the purpose of (1) assessing change over time for the intervention group relative to the enhanced usual care group and (2) comparing the change between the intervention and enhanced usual care group with regards to the primary outcome (depression symptoms).

Randomization

Groups will be randomized using a 1:1 randomization scheme to minimize threats to internal validity.[14] We will use permutated-block randomization where subjects are allocated randomly within blocks known only to statisticians. Given the possibility of insomnia as an effect modifier we will stratify randomization based on presence of insomnia (Insomnia Severity Index ≥10).[15] We will follow the CONSORT 2010 checklist for randomization. *Sequence generation*: Dr. Krafty will generate the randomization sequence using the R statistical software. *Allocation concealment*: the randomization sequence will remain concealed to research staff. Research staff who are enrolling participants will not know the allocation sequence in advance. *Implementation*: after a participant is determined eligible, research staff will contact Dr. Krafty about treatment

allocation. *Consideration of sex as a biological variable*: groups will be stratified by sex because women are more likely to experience the death of their spouse compared to men (75% of participants in our pilot RCT were women).

Efficacy Analyses

We will employ repeated-measures mixed-effects ANCOVA, which extend the standard repeated measures ANCOVA to allow for missing values, error structures other than compound symmetry, and measurements taken non-equal intervals. The test of efficacy for the intervention will be analyzed under an 'intent-to-treat' criteria.[16] We will control for important baseline variables, including baseline levels of the outcome of interest (HAM-D), and, to extend the 'intent to treat' mechanism, all participants randomized into the study are included in all analyses irrespective of protocol violations arising post randomization. Inclusion of covariates may add precision to the estimates and allow us to assess the generalizability of the effects across the covariates. The list of covariates, (e.g., age, sex, race, medical co-morbidity) will be developed prior to any analysis. Statistical significance will be $\alpha=0.05$ (two-tailed). Controlling for baseline variables will allow us to assess both group differences (main effect of group) and for differential change over time for depression symptoms repeatedly over the course of the study (group X time interaction). If the group X time interaction is significant, we will assess in post hoc tests, where the two groups differ. If no group X time interaction, will test main effects only. In all analyses, the time (in days) since spousal death will be included as a covariate.

Missing Data

Missing values are inevitable in clinical research. Participants may drop out from the intervention for a variety of reasons, including time constraints, competing interests, and personal choice. If, despite our projections, there is substantial missing values, we will incorporate the impact of censoring due to lost to follow-up and dropout into the analysis to assess if possible bias exists. We will use pattern mixture models to evaluate if the missing mechanism has an influence on parameter estimates. We will use standard multiple imputation for conducting inference on full data effects. If our data are not missing at random (MAR)[17] (i.e., pattern of 'missingness' is similar between groups), we will assess the impact of missingness on our estimates and will use pattern mixture models to check that there are no untoward influences of missing values. Pattern mixture models compare the outcomes (trajectories) across the various patterns of missing data.[18]

Sample Size and Power Calculations

Power calculations for each aim were calculated assuming effect sizes as estimated from the preliminary data collected in 55 subjects in the PI's pilot RCT. Calculations were conducted in R using the pwr and powerMediation packages. All tests were conducted at level α=0.05. In the preliminary data, a Cohen's d of 0.616 was observed for the change in depression scores after treatment between WELL and EUC. Under this effect size, there is an estimated 96.3% power to detect differences in changes in depression among treatment groups in Aim 1.

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