# Behavior, Biology, and Well-Being (BeWell) Study

1/16/2025

NCT05183867

**PROTOCOL TITLE:**

Behavior, Biology, and Well-Being (BeWell) Study

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**VERSION NUMBER/DATE:**

19.1; 1/16/2025

**REVISION HISTORY**

| Revision # | Version Date | Summary of Changes | Consent Change? |
|---|---|---|---|
| 1 | 1/20/2022 | Changes are largely editorial and to introduce word changes based on CARDS meeting. | Yes |
| 2 | 4/5/22 | Changes to sample collection window, questionnaires, subject time burden, and formatting. | Yes |
| 3 | 6/2/22 | Changes to sample collection window, recruitment methods, questionnaire timing, estimated subject time burden, NIH funding | Yes |
| 4 | 8/1/22 | Changes related to Clinical Interview in study design, research procedures, and quality control | No |
| 5 | 9/26/22 | Remove inconsistency in data sharing plans | Yes |

| | | | |
|---|---|---|---|
| 6 | 12/18/22 | Add healthy control participants at baseline only | Yes |
| 7 | 1/15/23 | Posting recruitment video on third party websites, process for emailing participants to schedule interviews | No |
| 10 | 2/19 | Remove Heather Abercrombie from staff list | Yes |
| 11 | 3/31 | Invite past participants to share recruitment materials with others | No |
| 12 | 5/16 | Assess problematic internet use | No |
| 13 | 6/29 | Assess asthma control | No |
| 14 | 8/10/23 | Recruit participants through ResearchMatch messages | No |
| 15 | 8/22/23 | Recruit participants through articles written for print or online media | No |
| 16 | 8/28/23 | Modifying inclusion/exclusion criteria to allow participants with PHQ-9 item 9 (self-harm / suicidal ideation) to enroll, if risk is determined to be low via clinical interview; modify response to imminent risk to include contacting 988 | No |
| 17 | 7/19/24 | Modifying description of where dried blood spot analyses will occur and updating data sharing details | Yes |
| 18 | 12/9/24 | Update description of video data sharing and obtaining consent to do so | Yes |
| 19 | 1/16/25 | Adding description of video analysis | No |

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## 28.0 Appendices261.0 Study Summary

| | |
|---|---|
| **Study Title** | Behavior, Biology, and Well-Being (BeWell) Study |
| **Brief Summary** | This study is a randomized controlled trial to investigate the impact of a 4-week, mobile meditation training app on symptoms of depression and psychological distress. Adults who have elevated depressive symptoms between the ages of 18 and 65 will be enrolled in the study for about 4 months. We will also recruit a sample of healthy (non-depressed) controls who will only complete baseline measures. |
| **Number of study sites** | 1 |
| **Study Design** | Participants will be randomized into one of three groups: Healthy Minds Program intervention group, active control group, and usual care group. The intervention and active control groups will use different versions of the mobile health app for four weeks. All participants will complete pre-intervention, weekly, post-intervention, and 3-month follow-up surveys and computerized tasks. Healthy control participants will not be randomized. |
| **Primary Objective** | Assess acceptability and efficacy of a 4-week mHealth meditation training program on depression symptoms. |
| **Secondary Objective(s)** | Investigate effects of the meditation training program on neurocognitive and biological processes implicated in depression and psychological distress and through which meditation training is hypothesized to operate. Understand baseline differences between participants with and without depression. |
| **Research Intervention(s)/ Investigational Agent(s)** | Healthy Minds Program (HMP) – a mobile health meditation training program |
| **Drugs/devices used on study (including any IND/IDE #)** | Healthy Minds Program (HMP) – a mobile health meditation training program |
| **Study Population** | 18-65 year olds with no significant experience with meditation |
| **Sample Size** | 1,765 participants |
| **Study Duration for individual participants** | 4 months |
| **Study Specific Abbreviations/ Definitions** | mHealth = mobile health<br>HMP = Healthy Minds Program |

## 2.0 Background

**2.1** Depression is highly prevalent and associated with extreme personal and societal costs. Meditation training reduces depression symptoms and psychological distress, but access to in-person programs is limited due to associated cost and lack of available services. The primary aim of this project is to investigate the efficacy of a 4-week mobile health (mHealth) meditation training program for adults with a wide range of depressive symptoms in an entirely remote randomized controlled trial (RCT).

**2.2** We have conducted similar mHealth studies with educators in Wisconsin (IRB Protocol: 2020-0533) and undergraduate students at UW-Madison (IRB Protocol: 2020-1454). Both studies provided evidence that a large number of participants are willing to download and regularly use the HMP app as well as stay engaged in a longitudinal study.

**2.3** Research on neurocognitive and biological mechanisms of meditation training in alleviating depression is at a preliminary stage, and an obstacle limiting research progress is over-reliance on retrospective self-report measures, which are vulnerable to a host of biases. This project will use gold-standard behavioral measures and explore novel measures of relevant neurocognitive and behavioral processes, namely pattern separation, self-referential thought, and video-based assessment of emotional well-being. Furthermore, the project will investigate effects on the gut microbiome (with stool samples) and inflammation (with dried blood spots), which reflect biological systems hypothesized to be mechanistically related to benefits of meditation and well-being training.

## 3.0 Study Objectives and Endpoints

### 3.1 Specific Aims

- Assess acceptability and efficacy of a 4-week mHealth meditation training program on candidate behavioral mechanisms of depression and psychological distress.
- Investigate effects of the mHealth meditation training program on behavioral and neurocognitive processes implicated in depression and psychological distress and through which meditation training is hypothesized to operate and improve well-being.
- Investigate effects of the mHealth meditation training program on biological processes implicated in depression and psychological distress and through which meditation training is hypothesized to operate and improve well-being.

- Compare depressed and non-depressed participants on self-report, behavioral, and biological measures.

### 3.2 Hypotheses

- The intervention participants will show larger reductions in psychological distress relative to usual care and active control participants during the intervention period and at follow-up.

- The intervention participants will show improved pattern separation behavior relative to usual care and active control participants during the intervention period at post-intervention and at follow-up.
- The intervention participants will show reduced self-referential processing (e.g., first-person pronoun use) and greater video-based indicators of well-being relative to usual care and active control participants during the intervention period at post-intervention and at follow-up.
- Speech indicators (e.g., I-talk, negative self-focused statements, and inflexible overly general thinking) evident in natural language will predict depression and task performance.
- Machine learning models will modestly predict depression (Spearman's rho ≥ .30).
- The intervention participants will show greater changes in biological processes relative to usual care and active control participants during the intervention period at post-intervention and at follow-up.
- Depressed participants will show differences on behavioral and biological markers of depression at baseline relative to non-depressed healthy controls.

### 3.3 Primary and Secondary Study Endpoints

Primary Endpoint

- Scores on the Physical Health Questionnaire depression scale (PHQ-8)

Secondary Endpoint

- Symptoms of psychological distress (GAD-7, PROMIS Sleep Disturbance and Flourishing Index)
- Performance on the behavioral pattern separation task
- Self-referential thought measured by the video recording task

### 3.4 Primary and Secondary Safety Endpoints

N/A

## 4.0 Number of Participants

### 4.1

This study will enroll 1,500 participants at UW-Madison. There will also be a pilot of up to 15 participants. We will recruit approximately 250 healthy control participants who will complete baseline measures only.

### 4.2

The expectation is that we will have 20-50% attrition resulting in roughly 750-1200 participants completing the study.

**4.3**
Participants will be considered enrolled after randomization. Participants who leave the study early will not be replaced. Healthy control participants will only complete baseline measures.

## 5.0 Inclusion and Exclusion Criteria

### 5.1 Screening
The screening survey will be accessed and completed in REDCap after potential participants learn more about the study and decide to continue with the screening process. Potential participants will be informed via a REDCap email of their eligibility up to 1 year after completing the screening surveys. This timeframe will be helpful to manage the unpredictability of participant recruitment and ensure that participants are enrolling in the study at a manageable rate for study activities that require staff time (e.g., clinical interview, sending and receiving biosample kits). If it has been 30 or more days since participants completed screening, they will be asked to complete the screening again before being invited to enroll. They will receive an email inviting them to do so. This email will be sent from the study email address (e.g., bewell@chm.wisc.edu). Screening data will be retained for all potential participants regardless of whether or not they enroll in order to keep a record of reasons individuals are not eligible for the study for reporting purposes (e.g., consort diagram). Any identifiers will be removed from the screening data of individuals who are not eligible for the study. Contact information will only be retained from individuals who are eligible for the study.

### 5.2 Inclusion Criteria
Randomized participants:
- Age 18 to 65
- Proficient in English
- Able to provide informed consent
- Have access to a smartphone that can download apps from Google Play or the Apple App Store

Indicate interest in participation after being informed of restrictions to payment
- PHQ-8 or PHQ-9 $\geq 5$

Healthy control participants:
- Age 18 to 65
- Proficient in English
- Able to provide informed consent
- Have access to a smartphone that can download apps from Google Play or the Apple App Store

Indicate interest in participation after being informed of restrictions to payment
- PHQ-8 or PHQ-9 $< 5$

**5.3 Exclusion Criteria**

Exclusion criteria apply to both randomized participants and healthy control participants.

- ○ Regular daily meditation practice for past 6 months or regular weekly meditation practice for past 12 months
- ○ Attended a meditation retreat or a yoga/body practice retreat with a significant meditation component
- ○ Previous use of Healthy Minds Program app
- ○ Current suicidal intent and/or high self-injury risk (determined from the interview)
- ○ Self-reported history of psychosis
- ○ Self-reported history of mania
- ○ Current psychopathology that interferes with study participation as assessed by interview
- ○ Living or traveling outside the US during the whole study participation period (trips outside US after the interview phase is not an exclusion)
- ○ AUDIT score ≥ 13 for women and AUDIT score ≥ 15 for men
- ○ DUDIT score ≥ 8 for women and men

**5.4 Specific Population**

We will recruit individuals with a wide range of depressive and psychological distress symptomatology. We expect the sample to be demographically representative of the overall population of the United States. The U.S. Census population estimates for July 2019 are 1.3% American Indian or Alaska Native, 5.9% Asian, 13.4% Black or African American, 18.5% Hispanic or Latino, 0.2% Native Hawaiian or Other Pacific Islander, 76.3% White, and 2.8% two or more races.

## 6.0 Special Populations

**6.1**

☐ Children/Minors

☐ Pregnant persons / fetuses (HRP-412 – CHECKLIST – Pregnant Women; HRP-413 – CHECKLIST – Non-Viable Neonates; HRP-414 – CHECKLIST – Neonates of Uncertain Viability)

☐ Prisoners

☐ Participants with impaired decision-making capacity

N/A

**6.2**

☐ Non-English speaking participants

☐ Illiterate or Low Literacy participants

☐ Participants with visual or hearing impairments

☐ Status Relationship: Individuals with a status relationship with the PI or other study team members (e.g., employees, students, family members)

N/A

**6.3**

☐ Individuals who are receiving inpatient or outpatient services for mental illness, developmental disability, or alcohol and other drug abuse (AODA)

☐ Individuals who are protectively placed by a court in a treatment facility

☐ Veterans/Military Personnel

☐ Emancipated minors

☐ Anyone especially vulnerable to manipulation or inducements for participation as a result of their illness or socioeconomic condition

N/A

## 7.0 Recruitment Methods

### 7.1 Sources of Participants

We will recruit from various sources. These sources may include the community, local and national mental health clinics, research recruitment services and from the Participant Registry at the Center for Healthy Minds (CHM; IRB Protocol: 2019-0330). We may also recruit using CHM social media and listservs.

### 7.2 Identifying Participants

Potential participants will self-identify in response to flyers, social media platforms, emails, web postings, research recruitment services (e.g., Prolific, Mturk, and/or ResearchMatch). We may send an email to individuals who have provided their contact information to CHM's Participant Registry; the email will include a link to the study page on REDCap. We may send messages to participants who have registered with recruitment services (e.g., ResearchMatch). Participants who are not eligible for the randomized portion of the study due to low depression symptoms (i.e., PHQ-8 or PHQ-9 < 5) may be invited to participate as a healthy control participant. We may write or have written articles about our study to be published in print or online media (e.g., Madison 365).

### 7.3 Recruitment Method

Recruitment materials may be shared with outside groups (e.g., universities), local and national mental health clinics and organizations (e.g., NAMI, Mental Health America), as well as posted at various local businesses (e.g., libraries, stores, and restaurants) up to several times throughout the year and shared by word of mouth. A web posting of the study may be included on CHM's website and social media ads may be placed on various social media platforms (e.g., Facebook, Twitter, Instagram) up to several times per year. We may also utilize email listservs at UW-Madison and other institutions, research recruitment services, as well as access CHM's Participant Registry to recruit participants via email up to several times per year. Our recruitment video may be posted on

third parties as well (e.g., WithPower.com). Past and/or currently enrolled participants may be invited to share recruitment materials with others. Participants will be informed that sharing recruitment materials is voluntary and unrelated to their study participation.

### 7.4 Recruitment Materials

We may use flyers, web postings, social media ads, emails and a video posted on the REDCap study page to inform potential participants about the study. Materials will include a study email address for individuals to use if they have questions about the study. Recruitment will occur on a continuous basis throughout the 3-year study.

### 7.5 Compensation

- Pre-Intervention Assessment = $0
- Week 1 Assessment = $10
- Week 2 Assessment = $10
- Week 3 Assessment = $10
- Post-Intervention Assessment = $40
- 3-Month Follow-Up Assessment = $45
- Stool sample collection = $60 ($30 for pre-intervention and $30 for follow-up)
- Dried blood spot collection = $40 ($20 for pre-intervention and $20 for follow-up)
- Bonus for Completing Above 6 Assessments = $50
- Total: up to $265

Payment will be via check and provided at the end of participation in the study (after the 3-month follow-up assessment) or via a pre-loaded and reloadable debit card issued by US Bank. The debit card will be mailed to participants after they finish the week 1 assessment. After each assessment is completed, the next payment amount will be loaded onto the debit card. If participants choose to withdraw or are taken off the study for any reason, they will receive payment for the assessments they have completed. Individuals excluded based on the interview will be paid $15 for their time spent completing the pre-intervention assessment and interview.

Individuals who have a visa will be informed in the webscreen and the consent form that due to UW-Madison limitations on payments, we can only provide monetary compensation to individuals who are US citizens or residents (green card holders). The webscreen asks individuals if they are still interested in participating after being informed about this restriction of payment.

Pilot participants will be paid up to $75: $40 for the Pre-Intervention Assessment, $10 for the Week 1 assessment, $15 for the stool sample, and $10 for the dried blood spot.

Healthy control participants will not be paid for the pre-intervention assessment, but will be paid $30 for the stool sample collection, $20 for the dried blood spot collection, and a $35 bonus for completing all study measures.

## 8.0 Consent Process

**8.1**
The consent process is a waiver of written documentation of consent. A link to the consent script will be emailed via REDCap to eligible potential participants after they complete their screening surveys. Individuals are informed in the instructions for the consent script as well as within the consent script to reach out to study staff if they have any questions before proceeding. Clicking a box will indicate one's interest in taking part in the study.

## 9.0 Process to Document Consent in Writing

**9.1**
**N/A**

**9.2**
We are waiving written documentation of consent. A consent script will be sent to eligible potential participants via REDCap after eligibility is confirmed. Individuals will check a box if they agree to participate in the study. After clicking the box, participants are informed that the next steps are to complete the initial surveys and games, a dried blood spot and stool sample kit will be mailed to them, and they will be scheduled for the interview.

This study involves minimal risk and involves no procedures for which written consent is normally required outside of the research context. The waiver will not adversely affect the rights and welfare of the participants. It will be made clear that they can withdraw at any time.

## 10.0 Setting

### 10.1 Location
Research procedures will be performed remotely.

## 11.0 Study Intervention

**11.1**
The study intervention will be the Healthy Minds Program (HMP), a 4-week mobile health meditation training augmented with depression-specific content. The HMP was developed by our affiliated non-profit organization, Healthy Minds Innovations, Inc (HMI). The HMP is designed to promote and protect psychological well-being through sustainable skills training, with instruction administered through a curriculum of high-quality guided practices. The HMP is based on research on eudaimonic well-being (e.g., environmental mastery, purpose) and brain-based skills that underlie these qualities (e.g., regulation of attention, mental flexibility). The HMP has >100 guided audio practices that address 4 constituents of well-being: awareness, connection, insight, and purpose. The intervention and active control groups will download and use a study specific version of the HMP immediately after randomization. The intervention group will have access to and instructed to listen to both the lessons and meditations (guided practices). The active control group

will have access to and instructed to listen to the lessons only (meditation practices are not included). The intervention and active control groups will use the HMP for four weeks. The active control group and the usual care group will be given the opportunity to download and use the full HMP after they finish their 3-month follow-up assessment.

The following usage data is recorded: date, time, duration, device type, lesson or practice, week, foundation (awareness, connection, insight, or purpose), and name of lesson or practice. Participants listen to lessons and/or practices and occasionally answer pre and post questions using their smartphones.

This study requested a non-significant risk (NSR) determination for the use of the HMP. Use of the HMP may mitigate symptoms of depression, anxiety and/or stress but has not shown to pose a risk to health or safety. Below is a copy of the NSR letter.

**Request for a Non-Significant Risk Determination from the IRB for an Investigational Device**

UW-Madison Health Sciences IRB:

Please accept this letter as a request for non-significant risk (NSR) determination for the investigational device evaluation described in the IRB submission titled "BeWell Study".

The FDA defines significant risk devices as follows (21 C.F.R. § 812.3(m)):

> ""(1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
>
> (2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
>
> (3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
>
> (4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject""

The Healthy Minds Program (HMP) in this study is a smartphone app that includes both didactic content and guided meditation practices. The device will be used to aid development of well-being by training skills that are based on scientific studies (the didactic content). It also includes guided meditation practices found in widely available evidence-based treatments such as mindfulness-based stress reduction, mindfulness-based cognitive therapy, cognitive behavioral therapy, acceptance and commitment therapy, and other widely used smartphone meditation apps such as Headspace and Calm.

The use of the device in this study does not meet the definition of a significant risk device as it is not an implant, is not used to sustain human life and poses no serious risk to health, safety or

welfare of a subject. The device may mitigate symptoms of depression, anxiety and stress, but has not shown to pose a serious risk to health, safety, or welfare.

Summary of prior uses: HMP has been tested by our group in two randomized controlled trials (ns = 343, 662; Goldberg et al., 2020; Hirshberg et al., 2021). In both trials, HMP was shown to produce larger reductions in psychological distress (composite of depression, anxiety, and stress) relative to a waitlist control condition. Participants in both studies were drawn from the general population, although ~75% in each sample reported elevated depression and/or anxiety symptoms at baseline. Effects were similar when restricted to those in the clinical range at baseline. No serious adverse effects were reported in either study. In support of HM''s safety, HMP was shown to produce lower rates of clinically significant increases in symptoms relative to a waitlist condition.

References:
Goldberg, S. B., Imhoff-Smith, T., Bolt, D. M., Wilson-Mendenhall, C. D., Dahl, C. J., Davidson, R. J., & Rosenkranz, M. A. (2020). Testing a multi-component, self-guided, smartphone-based meditation app: three-armed randomized controlled trial. JMIR Mental Health, 7(11), e23825. doi: 10.2196/23825

Hirshberg, M. J., Frye, C., Dahl, C. J., Riordan, K. M., Vack, N. J., Sach, J., Goldman, R., Davidson, R. J., & Goldberg, S. B. (2021). A pragmatic randomized controlled trial of a smartphone-based well-being training in Wisconsin school district employees during the COVID-19 pandemic. Manuscript submitted for publication. https://psyarxiv.com/hrvmu/

We respectively request the IRB consider this information in finding that the device does not meet the definition of significant risk. Additional information about the device can be found in the application. Please contact me if you have any questions.

Sincerely,

Dr. Richard J. Davidson

## 12.0 Study Timelines

### 12.1

This will be a 3-year project with participants randomized into 3 groups: HMP intervention group, active control group, and usual care group (see "Randomization", section 13.1.4). Participants will be involved with the study for approximately 4 months. Recruitment will start upon UW Institutional Review Board (IRB) approval and continue until study goals are reached. We estimate that we will complete primary analyses within 3 years of the end of data collection.

In order to ensure that the procedures outlined below are implemented in a feasible and functional way for the intended study participants a pilot of up to 15 participants will precede initiation of the

full study. Pilot participants will be asked to complete all aspects of the study up to and including the week 1 assessments.

A sample of healthy control participants will complete baseline measures only.

## 13.0 Procedures Involved

### 13.1 Study Design

After potential participants are informed of their eligibility, they will be invited to complete the following steps:

1. Consent Process. Individuals will read a consent script in REDCap and are given the opportunity to reach out to study staff if they have any questions or concerns about study procedures before clicking on the box indicating interest in participating in the study.

2. Pre-Intervention Assessment (Timepoint 1). A REDCap link for these surveys and games (behavioral task and video task) will be sent after consent is completed. It will take approximately 60-90 minutes to complete these measures. Potential participants will be given two weeks to complete this assessment. In order to increase study retention, only those who complete this assessment will be invited to subsequent parts of the study. A microbiome and blood spot collection kit will be mailed to participants to be completed before randomization occurs. The kit needs to be returned within one month of completing the surveys and games to continue with the randomization step.

3. Interview. The participant will undergo an interview conducted by research staff who are trained in interviewing techniques and supervised by qualified study personnel with mental health expertise. The interview will consist of the depression and related modules of the Structured Clinical Interview for DSM-5 Research Version (SCID-5-RV). The interview will be done via phone or video and will take approximately 60 minutes to complete. Participants may be sent an email to confirm their current phone number, interview time, and/or other details to assist with interview scheduling.

4. Randomization. Participants will be assigned to one of three groups: approximately two-fifths to the HMP intervention group, approximately two-fifths to the active control group, and approximately one-fifth to the usual care group. Randomization will be done in REDCap (either immediately after the interview or within a few days if consultation with a study PI or Co-I is needed; the microbiome and blood spot kit need to be returned before randomization). A REDCap alert will inform participants of group status immediately after randomization along with instructions for downloading HMP for those in the intervention and active control groups.

5. Weeks 1 to 3 Assessments (Timepoints 2, 3, 4). Participants will complete a small subset of the surveys in REDCap as well as the video task at the end of weeks 1, 2, and 3. It will take

approximately 30 minutes to complete these measures. Participants will be given one week to complete each weekly assessment.

6. Week 4/Post-Intervention Assessment (Timepoint 5). Participants will complete the same surveys and games (behavioral task and video task) in REDCap as was done for the pre-intervention assessment; the invite for these measures will be sent at the end of week 4. It will take approximately 60-90 minutes to complete these measures. Participants will be given 2 weeks to complete this assessment. Participants in the intervention or active control groups will have the option to continue using the HMP after this timepoint. We will continue to monitor app data throughout the study to learn more about its long-term impact on well-being.

7. 3-Month Follow-Up Assessment (Timepoint 6). Participants will complete the same surveys and games (behavioral task and video task) in REDCap as was done for the pre-intervention and post-intervention assessments; the invite for these measures will be sent 90 days after the date of the post-intervention invite. It will take approximately 60-90 minutes to complete these measures. Participants will be given 2 weeks to complete this assessment. Another microbiome kit and blood spot collection kit will be mailed to participants to collect samples; they will have 1 month to collect.

Healthy control participants will complete only #1 to #3.

**13.2 Schedule of Procedures**

| **Study Phase** | **Screening/Pre-Intervention** | **Intervention** | | | | **3-Month Follow-Up** |
|---|---|---|---|---|---|---|
| Visit Number | 1 | 2 | 3 | 4 | 5 | 6 |
| Informed Consent | X | | | | | |
| Review Eligibility | X | | | | | |
| Interview | X | | | | | |
| Surveys | X | X | X | X | X | X |

| | | | | | | |
|---|---|---|---|---|---|---|
| HMP or active control (Intervention and active control groups) | | X | X | X | X | X |
| Video recording task | X | X | X | X | X | X |
| Pattern Separation Task | X | | | | X | X |
| Microbiome Sample | X | | | | | X |
| Blood Spot Sample | X | | | | | X |
| Adverse Event Assessment | | | | | X | X |

**13.3 Research Procedures**

1. Clinical Interview. After being consented, participants will undergo a phone or video interview assessing the Depressive Disorders module and related modules of the Structured Clinical Interview for DSM-5 Research Version (SCID-5-RV). These interviews will be conducted by study staff trained in clinical interviewing techniques and supervised by the study PIs. The interview will last approximately 30-60 minutes and will occur after the pre-intervention surveys are completed. If participants reveal during the interview that they are at high risk for suicidality or self-harm, or it is revealed that they do not qualify for the study based on inclusion/exclusion criteria, they will be excluded. The interview is for research purposes only so individuals will not be told of any diagnoses.

   If a participant reveals suicidal ideation, self-harm or intent to harm others, the clinical research personnel will assess intent. In the circumstance that an individual indicates that self-harm or harm to others is imminent, 988 and/or 911 (or local authorities in the county/city where the participant lives) will be called. Participants who have imminent intent or an imminent plan to commit an act of self-harm will be excluded. The clinical research interviewers will consult with qualified study personnel with mental health expertise as needed. These personnel may contact the participant by phone to further assess the level of risk and provide additional referrals as needed. All interactions regarding suicide risk and referral will be carefully documented and closely tracked by the study clinician. A formal incident report will be filed with the IRB in cases in which the clinician notifies authorities. A therapeutic resource list will be provided to all individuals.

2. Surveys. Participants will complete online surveys in REDCap. It will take approximately 30-90 minutes to complete surveys depending on the timepoint (see table below). A subset of the following surveys will be completed at the various assessments (or before and following use of the HMP app):
   - ✦ Attention Checks
   - ✦ Alcohol Use Disorders Identification Test (AUDIT)
   - ✦ Asthma Control Questionnaire (ACQ)
   - ✦ Behavioral Risk Factor Surveillance System (BRFSS),
   - ✦ Adverse Childhood Experiences (ACE) Module
   - ✦ Big Five Inventory (BFI) Conscientiousness Items
   - ✦ Climate Change Anxiety Scale
   - ✦ Demographics
   - ✦ Determinants of Meditation Practice Inventory–- Revised
   - ✦ Digital Working Alliance Inventory (DWAI)
   - ✦ Decentering subscale of the Experiencing Questionnaire
   - ✦ Drug Use Disorders Identification Test (DUDIT)
   - ✦ Five Facet Mindfulness Questionnaire (FFMQ), Awareness Subscale
   - ✦ Flourishing Measure
   - ✦ General Anxiety Disorder (GAD-7)
   - ✦ General Availability
   - ✦ Growth Mindset
   - ✦ Healthy Minds Index (HMIndex)
   - ✦ Inclusion of Nature in Self
   - ✦ Lasting Effects Questionnaire
   - ✦ Life Orientation Test–- Revised (LOT-R)
   - ✦ Marlowe-Crowne Social Desirability Scale (MCSD)
   - ✦ Medication Questionnaires (Health History, Current Health and Medication use, and biospecimen collection questions)
   - ✦ Medication and Therapy Questionnaire
   - ✦ Meditation and App Usage Questionnaire
   - ✦ Mindfulness Adherence Questionnaire
   - ✦ Mindfulness-Based Program Meditation-Related Adverse Effects Scale (MBP-MRAES)
   - ✦ NIH Toolbox Loneliness
   - ✦ NIH Toolbox Meaning and Purpose
   - ✦ Patient Health Questionnaire Depression Scale (PHQ-8)
   - ✦ Patient Health Questionnaire Depression Scale (PHQ-9)
   - ✦ Problematic and Risky Internet Use Screening Scale – 3 (PRIUSS-3)

- ✦ PROMIS Sleep Disturbances–- Computer Adaptive Version
- ✦ Perceived Stress Scale (PSS-10)
- ✦ Perseverative Thinking Questionnaire (PTQ)
- ✦ Post-pattern separation task question
- ✦ Post-video task question
- ✦ Pre and Post Practice Questions
- ✦ PROMIS pain inference measure
- ✦ PROMIS pain intensity measure
- ✦ Satisfaction with Life Scale (SWLS)
- ✦ Subjective Happiness Scale
- ✦ Treatment Expectancies

| Measures | # of Items | Web Screen | Interview | Pre-Intervention | 4 Week Intervention (3 Weekly Timepoints) | Post-Intervention | 3-Month Follow-Up |
|---|---|---|---|---|---|---|---|
| Screening Questions (e.g., age, psychotic disorders, bipolar, substance use, meditation experience, device use) | | X | | | | | |
| Consent | N/A | X | | | | | |
| Attention Checks | 3 | | | X | X | X | X |
| AUDIT | 10 | X | | | | | X |
| Asthma Control Questionnaire (ACQ) | 6 | | | X | | X | X |
| Behavioral Risk Factor Surveillance System (BRFSS) Adverse Childhood Experiences (ACE) module | 11 | | | X | | | |
| Big Five Inventory (BFI) -- conscientiousness items only | 44 | | | X | | | |
| Climate Change Anxiety Scale | 22 | | | X | | X | X |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Demographics | | | | X | | | |
| Determinants of Meditation Practice Inventory–- Revised | 12 | | | X | | | |
| Digital Working Alliance Inventory (DWAI) –- app groups only | 6 | | | | X | X | X |
| Decentering subscale of the Experiencing Questionnaire | 11 | | | X | X | X | X |
| DUDIT | 11 | X | | | | | |
| Five Facet Mindfulness Questionnaire (FFMQ) – Awareness and Non-Judgment Subscales | 8 | | | X | X | X | X |
| Flourishing Measure | 12 | | | X | X | X | X |
| General Anxiety Disorder (GAD-7) | 7 | | | X | X | X | X |
| General Availability | 1 | | | X | | | |
| Growth Mindset Scale for Well-Being | 3 | | | X | | X | X |
| Healthy Minds Index (HMI) | 17 | | | X | | X | X |
| Inclusion of Nature in Self | 1 | | | X | | X | X |
| Lasting Effects Questionnaire | 2 | | | | | | X |
| Life Orientation Test Revised (LOT-R) | 10 | | | X | | X | X |
| Marlowe-Crowne Social Desirability Scale (MCSD) | 13 | | | X | | | |
| Medication Questionnaires (Health History, Current Health and Medication use, and biospecimen collection questions) | Varies | | | X | | X | X |
| Meditation and App Usage Questionnaire | 5 | | | X | | X | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Mindfulness Adherence Questionnaire informal practice items only –- app groups only | 12 | | | | X | X | X |
| Mindfulness-Based Program Meditation-Related Adverse Effects Scale (MBP-MRAES) – app groups only | 15 | | | | | X | |
| NIH Toolbox Loneliness | 5 | | | X | X | X | X |
| NIH Toolbox Meaning and Purpose | 18 | | | X | X | X | X |
| Patient Health Questionnaire -- depression scale (PHQ-8) | 8 | | X | X | X | X | X |
| Patient Health Questionnaire – depression scale (PHQ-9) | 9 | X | | | | | |
| Patient-Reported Outcome Measurement Information System (PROMIS) Computer Adaptive Version for Sleep Disturbances | Varies | | | X | X | X | X |
| Perceived Stress Scale (PSS) | 10 | | | X | | X | X |
| Perseverative Thinking Questionnaire (PTQ) | 15 | | | X | | X | X |
| Post-pattern separation question | 1 | | | X | | X | X |
| Post-video task question | 1 | | | X | X | X | X |
| Pre and Post Practice Questions | 3 | | | | X | X | |
| Problematic and Risky Internet Use Screening Scale (PRIUSS) | 3 | | | X | | X | X |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| PROMIS pain inference measure | 40 | | | X | | X | X |
| PROMIS pain intensity measure | 1 | | | X | | X | X |
| Satisfaction With Life Scale | 5 | | | X | | X | X |
| Subjective Happiness Scale | 4 | | | X | | X | X |
| Treatment Expectancies – app groups only | 6 | | | | | X | |
| SCID-5-RV | Varies | | X | | | | |
| Video Recording Measures | N/A | | | X | X | X | X |
| Pattern Separation (Mnemonic Similarity Task) | N/A | | | X | | X | X |
| Dried Blood Spot Collection | N/A | | | X | | | X |
| Microbiome Collection | N/A | | | X | | | X |
| Environmental Toxin Questionnaire | 6 | | | X | | | |

3. Behavioral Measures. Participants will receive the link for the behavioral tasks in REDCap. The behavioral task completion will take approximately 10 minutes.

✦ Pattern separation. Meditation training has the capacity to normalize the overgeneralized inflexible cognition endemic to depression, which is hypothesized to relate to alterations in the hippocampal-dependent process of pattern separation. We will use a pattern separation task sensitive to meditation training to be completed at the pre-intervention, post-intervention, and 3-month follow-up assessments via a REDCap link.

✦ Video recording measures. Participants will be asked to provide video recordings of their face and voice while responding to prompts at all time points (T1 to T6). These prompts may involve responding to a recorded prompt (e.g., cartoon image), watching brief videos of positive or negative valence (e.g., baby giggling, someone telling a sad story), or sharing information about their day or week (e.g., "tell us something positive that happened

this week"). These recordings provide the opportunity to explore indicators of self-referent, inflexible, & over-generalized thinking within natural language that can be compared to behavioral measures indicated above. Data from recordings will be used to explore novel measures that once developed can be acquired without active input from the user on mobile devices and extracted from several data streams including facial features, vocal indicators and content analysis of text. Video data will be analyzed using various machine learning methods (e.g., Google's Gemma). Data will be analyzed using models run locally which will eliminate confidentiality risks. Platforms used for video analysis will be vetted by the HIPAA security office prior to use.

4. Blood Spot Collection. A blood spot collection kit will be mailed to participants. Participants will collect approximately 5 spots of blood (approximately 50µL each) at home. The participant's finger will be sterilized and pricked using a disposable lancet, and blood collected on filter paper. Instructions will be included on how to mail samples, once dried, back to CHM. Samples will be stored at room temperature or put in biospecimen designated freezers at CHM until enough samples are collected for analyses (which will include looking at inflammatory markers and other measures of immune function). Dried blood spot samples will be used to measure two inflammatory cytokines (C-reactive protein [CRP] and interleukin-6 [IL-6]). Additionally mRNA assays will be used to detect and quantify inflammatory gene expression detect and monitor cellular immune responses. Analyses will focus on transcripts from ~200 genes known to be involved in the regulation of inflammation, and will consider key transcripts (e.g., IL-1beta, TNF-alpha) as well as summary measures reflecting the activity of transcriptional networks that coordinate inflammation (NF-kB, AP-1). We will not conduct genetic analyses of the whole human genome. Samples will be labeled with participant id.

5. Microbiome Collection. A home-kit for stool sample collection will be mailed to participants. Participants may have concerns surrounding issues of hygiene when it comes to collecting stool samples. They might also experience feelings of embarrassment around collecting the sample. In order to reduce the chances of this occurring, participants will be provided with detailed instructions and information regarding how to hygienically collect their stool sample. Genetic analyses of the microbiome of the stool sample (microorganism DNA, not that of the person) will be performed. DNA extraction with bias reduction (triplicate extraction processing) of the stool community of microorganisms will provide the sequencing data to do alpha and beta diversity analysis and phenotypic cluster assessments (similar to IRB protocol 2021-0580). Samples will be labeled with participant id.

Healthy control participants will complete only the baseline measures.

**13.4**

The data elements collected will be questionnaires, a structured interview, behavioral tasks, and biospecimens. All study materials will be uploaded to the ARROW application. Data will not be collected from any of the following sources:

- UW Health medical or billing records via ICTR's Clinical Research Data Service (CRDS)
- UW Health HealthLink Records (study team will directly access)
- Data from departmental QA or QI database
- Data from UW Health Enterprise Data Warehouse (EDW)
- Data from PACS (Picture Archiving and Communication System)
- Data from Center for Medicare/Medicaid Services
- Data from publicly available datasets (e.g., U.S. census data)
- Data from outside institutions or organizations
- Other

**13.5**

There are no current plans for long-term follow-up besides the 3-month follow-up that is part of the study procedures listed above. For those in the HMP intervention or active control groups, any data collected through the HMP app (e.g., usage data) will continue to be collected until the 3-month follow-up assessment. Additional follow-up assessments may be planned by study personnel and/or collaborators. The consent form will include language pertaining to permission for future contact.

**13.6**

N/A

## 14.0 Comparison of usual care and study procedures

N/A. All procedures are performed solely for research purposes. Individuals may elect to not enroll in this study, as it is completely voluntary.

## 15.0 Withdrawal of Participants

**15.1**

We anticipate that we will withdraw a participant from the study: 1) if we determine that participation in the study is exposing the participant to an unacceptable level of risk, 2) to maintain data integrity (e.g., if a participant is not following study procedures or may be deliberately providing false information), or 3) if the study is stopped by the sponsor or researchers.

**15.2**

When withdrawing a participant, we will: 1) thank the participant for their participation, 2) explain the reason(s) for termination, 3) explain that the participant will be paid for the portion of the study that they completed (as described in the consent form), 4) ask the participant if they have any questions or comments about the study, and 5) inform the participant that the HMP app is available to use free of charge. We will change the participant status to withdrawn in REDCap; however, we will retain and use data collected prior to withdrawal.

**15.3**

When a participant chooses to withdraw from the research, we will: 1) thank the participant for their participation, 2) determine if the participant will be fully or partially withdrawing (if partial, determine which procedures the participant will be completing), 3) explain that the participant will be paid for the portion of the study that they completed (as described in the consent form), 4) ask the participant their reason for withdrawing (if they choose to provide it), 5) ask the participant if they have any questions or comments about the study, and 6) inform the participant that the HMP app is available to use free of charge. We will remove the withdrawn participant from REDCap; however, we will retain and use data collected prior to withdrawal.

**15. 4**

Participants who withdraw or do not complete baseline may be asked why they did not continue with participation.

## 16.0 Data Management and Confidentiality

### 16.1 Quality Control

Simon Goldberg will conduct periodic checks throughout each year of the study to ensure survey, behavioral task, biospecimen and interview data are recorded as expected and to look for any missing and/or aberrant data.

**16.2**

☒Data will be coded, and the "key" linking identities to codes will be kept separately from the data.

☐ Data will be coded, and the "key" linking identities to codes will be kept on paper only. The study data will be stored electronically and labeled only with codes.

☒Only those listed as key personnel will have access to the "key."

☐ Access to the "key" will be limited to the following person (e.g., Database Administrator): _____

☒ This study is funded by the National Institutes of Health and is covered by a Certificate of Confidentiality.

☐ This study is NOT funded by the National Institutes of Health but because it will collect sensitive information, the research team apply for and received a Certificate of Confidentiality to protect data from being requested without the subject's consent as part of a legal proceeding.

☐ Other: _____

**Data Collection and Storage**

Data will be collected, protected and shared using REDCap, which is administered by ICTR at UW-Madison. This is a web-based data collection program that is HIPAA and IRB compliant, and allows for the safe and secure collection and storage of clinical assessments, questionnaires and physiological data. Participant data will be coded with participant ID numbers. All data will be managed by the study PI. Access to the data will be given only to HIPAA and CITI qualified and trained study team members. Data will be kept indefinitely on HIPAA compliant study servers. Data will also be gathered through the HMP app and a separate app participants will download for video recordings.

**Confidentiality**

We will make every effort to maintain the privacy and confidentiality of participants involved in the study. This includes taking the following steps:

- Staff will participate in initial training, follow-up training, and ongoing monitoring and supervision to ensure understanding of ethical issues involved in this research that includes, but is not limited to, courses offered by UW-Madison's Human Research Protection Program, and a training on HIPAA and measures to protect confidentiality;
- The electronic list that links the participant name with ID number will be kept in a secure electronic database file on REDCap, a database administered by ICTR at UW-Madison and will be accessible only by the PI and study staff;
- Any personal identifiers linked to data will be removed and replaced by code numbers in all records;
- The highest security features of the service used to create and implement the screening questionnaires (REDCap, administered by ICTR at UW-Madison) will be enabled. Screening data and other questionnaire data collected via these online questionnaires will be downloaded to electronic files that will be kept on the HIPAA compliant secure network drive for the Center for Healthy Minds. This is the drive on which patient and research subject data that meet the criteria for electronic private health information are stored. We do not store any electronic personal health information (including information gathered as part of the proposed study) locally on any desktop workstations. These files will be password protected and accessible only by the PI and study staff;

- Prior to signing the consent form for participation in the study, participants will be notified on the consent form that we are included in the list of mandated reporters and that by signing the consent form, they understand that in cases of suspected harm to self or other, the researcher is required by law to report to the appropriate authorities.

**16.3**

☐ Online Collaborative Research Environment (OnCore) Biospecimen Management

☒ Research Electronic Data Capture (REDCap) *Specify which instance you will be using (e.g., ICTR's, Department of Medicine's)*: ICTR's instance of REDCap

☐ Other software option that will be stored on departmental server. *Specify the department*: _____

☒ Locked filing cabinet or drawer inside a locked room. Specify the building: Center for Healthy Minds

☐ Other (describe): _____ ☐

☐ Data will not be stored or accessed on portable devices.

☒ Portable devices will be used to access secure web-based data collection sites such as ICTR's REDCap. No data will be stored locally on the device.

☒ Data stored on portable devices will be coded with the key stored separately. No identifiers will be stored on portable devices.

☐ Data stored on portable devices and therefore only encrypted devices will be used.

**16.4 Management of Identifiers**

All data will be labeled with a participant ID code (e.g., surveys, computerized tasks, and interview data will not include the participant's name). The key linking participant name with participant ID code will be stored in ICTR's instance of REDCap. Identifiers will be kept indefinitely so that we can contact participants who consented to future contact.

**16.5 Multi-Site Research**

N/A

**16.6 Data Sharing**

As part of the consent process, participants are notified that data collected as part of the study may be shared with other researchers upon request or shared publicly in an open science format. However, we clarify that the data will be deidentified. This includes standard identifiers as well as other dates and demographics that might allow for re-identification. One exception to data sharing that will involve identifiable data, is the recording of voice and face during the video measure. This

measure may be shared along with the decryption key with other researchers who sign a data use agreement with us.

The Picard Lab at MIT will analyze video records only after signing a data use agreement. The videos will be coded with a participant ID. The dried blood spot samples will be coded with a participant ID and sent to Northwestern or a similarly qualified laboratory for analysis. The similarly qualified laboratory will sign a business associate agreement before any dried blood spot samples are shared with them. Collaborators at other institutions (e.g., Weizmann Institute of Science) will not have access to identifiable study data before they have signed a data use agreement.

Data shared with collaborators outside of UW-Madison that are not currently named in this protocol will also be de-identified whenever possible (e.g., self-report, behavioral, and biomarker measures). If it is not possible to fully de-identify data (e.g., video recordings) we will share data only after a data use agreement has been signed.

We may also want to follow-up with these participants in future research studies. Future studies may include analysis of the information from this study alone or in combination with data collected in other studies. Any future research utilizing these data will be submitted as a separate application to the IRB prior to their use, if required by IRB policies and/or guidance. There is a complementary study (led by co-PI Dan Grupe; IRB 2021-1109) starting at the same time as this study that will utilize many of the same survey and behavioral task measures. We plan to share data between these two studies.

Data may be shared as Supplemental Information uploaded to a journal website and/or shared on a data sharing website. Again, these data would not include identifiers. Data sharing would not require any further participation from participants.

**To enhance the impact and understanding of our research, we plan to send a consent addendum to participants to obtain explicit permission to share their video data publicly. The addendum will emphasize that due to the nature of video data content, complete confidentiality cannot be guaranteed. Participants will be given the option to either agree or decline without any impact on their participation in the study. Additionally, no personally identifiable information, such as names or addresses, will be shared alongside the video data.**

**Future Contact**

We will ask participants via the consent form if they wish to be contacted for future studies. If they agree, their contact information (name, phone number, and address) will be kept on the Center for Healthy Minds' secure network drive indefinitely. Only study staff will have access to this information. The participant's contact information will not be stored with their data.

If future collaborations with other researchers will be conducted with this participant pool, the proper steps and approval will be taken with the IRB before conducting such research.

**17.0 Provisions to Protect the Privacy Interests of Participants**

☐ Procedures will be performed in a private area where others cannot see the procedures being performed or overhear the conversation between subjects and researchers.

☒ All members of the study team are up to date on their institutional HIPAA training.

☐ The study is not collecting information that could pose legal or reputational risks to participants.

**17.1**

All study procedures will be done remotely using their smartphone in a setting of the participant's choosing.

**17.2**

The study screener will ask questions about alcohol and other drug use and about current and/or past symptoms of various mental illnesses. The surveys and interviews include questions related to negative childhood experiences, depression, anxiety and stress. One aim of the study is to investigate whether the meditation training intervention reduces psychological distress post-intervention and again at the 3-month follow-up assessment. Current or past history of alcohol/drug use or various psychiatric disorders may confound aims of the study and thus are part of the exclusionary criteria.

**17.3**

The study description, consent form and introduction to the surveys/interview will all include language that participation is voluntary and that some questions may be of a sensitive nature.

**17.4**

N/A

**18.0 Sharing of Results**

**18.1**

All measures (surveys, games, microbiome, blood spot, and interview) are for research purposes only and individual results may not be meaningful. Participants will not be told of individual results for any measures. No study data will be shared with participants' health records.

**18.2**

Study results may be shared with the public via manuscripts and/or open source databases. The Center for Healthy Minds website and/or other social media platforms will share information on study results and/or publications.

**19.0 Data and Specimen Banking**

**19.1**
Banking of data and specimens will not be optional. Coded data and specimens from participants may be banked for future use to address research questions not included in this protocol. The code linking to identifying information will be kept on a password-protected server and ICTR's instance of REDCap with access limited to specific study personnel.

**19.2**
The code linking data and specimens to identifying information will be accessed in ICTR's instance of REDCap and on a password-protected server with access limited to specific study personnel.

**19.3**
We are not placing any limits on the intended future use of data, and any future research utilizing these data will be submitted as a separate application to the IRB prior to their use, if required by IRB policies and/or guidance. Genetic analyses are limited to the following:

- Whole genome analysis of the bacterial genome.
- mRNA analyses of dried blood spot to evaluate gene expression. Analyses will focus on transcripts from ~200 genes known to be involved in the regulation of inflammation and summary measures reflecting the activity of transcriptional networks that coordinate inflammation (NF-kB, AP-1).

Data may be requested by other researchers at UW-Madison as well as by researchers outside of UW-Madison to the study PI and/or Co-Investigators.

**19.4**
Participants may withdraw their samples and data from banking for future research. If there are any residual amounts from their dried blood spot and stool samples, they will be destroyed. Any data that has been shared in an open source format or as part of a journal database will be de-identified and thus cannot and will not be withdrawn.

## 20.0 Study Analysis

**20.1**
HMP will show greater improvements in (a) depression, (b) psychological distress, (c) well-being, (d) and performance on the pattern separation task vs. both the active control (HMP psychoeducation) and usual care conditions.

**20.2**
We plan to enroll 1500 participants in this study, assigning two fifths to HMP, two fifths to the active control, and one fifth to a usual care. Anticipating 20% dropout, this sample will provide 80% power to detect small differences between HMP and the active control ($d = 0.20$) and 80% power to detect small-to-moderate differences between HMP and the usual care ($d = 0.28$).

We plan to recruit approximately 250 healthy controls at baseline. This will allow statistical power to detect small between-group differences on baseline measures.

**20.3**
Participants will be randomized into 3 different groups: two-fifths to intervention, two-fifths to active control and one-fifth to waitlist control. All study procedures will be the same across all groups except the use or non-use of HMP.

Healthy control participants will not be randomized.

**20.4**
Group differences for the intervention will utilize linear mixed effects models to account for non-independence and to maximize use of data with missing observations.

**20.5**
Given the low risk of the intervention, no interim efficacy or safety analyses are planned.

**20.6**
Linear mixed effects analyses account for missing data in a robust manner relative to, e.g., ANOVA. If differential attrition is observed (e.g., between HMP and usual care), we may conduct sensitivity analyses to evaluate the potential impact of data missing not at random.

## 21.0 Potential Benefits to Participants

**21.1**
Participants may benefit from using the HMP, which is designed to introduce meditation practice as a way of reducing stress and developing greater balance, ease, and fuller participation in life. This meditation training teaches well-being skills which can be used in everyday life to cope with the challenges of stress, pain, illness, and everyday demands. Usual care and active control participants can use the full version of HMP after completion of the study at no cost.

**21.2**
There are no direct benefits for participants.

## 22.0 Risks to Participants

**22.1**
**Breaches of Confidentiality**
Risk of confidentiality breach is minimized due to data storage procedures employed (i.e., data coding, secure storage, trained personnel). We obtained a certificate of confidentiality due to the nature of some of the data collected.

Because there is potential for the study to capture information that could lead to reporting intention to harm self, participants will be informed in the consent form of this limit to confidentiality before they agree to participate. The researchers would report to the study psychologist on call and/or emergency services, as dictated by the specific circumstances. We have well-established protocols for handling suicidality and threat of harm to self.

**Emotional Upset**
Emotional upset due to study participation is a potential but unlikely risk of study activities. In our experience, it is rare for a participant to find self-report questionnaires to be extremely upsetting. Participants will be informed that they are free to decline answering any question for any reason.

The interview consists of the Depressive Disorders and related modules of the Structured Clinical Interview for DSM-5 Research Version (SCID-5-RV). If a participant reveals suicidal ideation, self-harm or intent to harm others, the clinical research personnel will assess intent. In the circumstance that an individual indicates that self-harm or harm to others is imminent, 988 and/or 911 (or local authorities in the county/city where the participant lives) will be called. The clinical research interviewers will consult with qualified study personnel with mental health expertise as needed. The clinicians may contact the participant by phone to further assess the level of risk and provide additional referrals as needed. All interactions regarding suicide risk and referral will be carefully documented and closely tracked by the study clinician. A formal incident report will be filed with the IRB in cases in which the clinician notifies authorities. All eligible participants will be provided with the “Therapeutic Resources” list regardless of their responses. All individuals who are excluded from the study during the screening process or interview will be given the "Therapeutic Resources - Exclusion" list which has links to the Virtual Hope Box, suicide hotline, and mental health website.

There are no physical risks involved in collecting the microbiome sample. It will be integrated as part of their regular routine, with the only difference being that this bowel movement will be collected in a plastic container. They may experience some slight psychological discomfort or embarrassment about collecting this sample.

**Physical Risks**
Some tenderness may be experienced at the site of the finger prick for the blood spot collection. Occasional bruising at the site can occur and is not permanent. In very rare cases, infection at the site can occur. Single-use lancets will minimize the risk of infection.

**22.2**
N/A

**22.3**
N/A

**22.4**
N/A

**22.5**
N/A

**22.6**
The exclusion criteria limits the number of people who are at high risk for self-harm from the study. Conducting the interview only after all of the pre-intervention surveys are completed, decreases the number of potential participants who have sensitive information collected as part of the screening process.

## 23.0 Provisions to Monitor the Data to Ensure the Safety of Participants

**23.1**
Adverse events will be tracked (including details of the incident, actions taken, and follow-up steps) by study staff and reported to the PI. The PI will be responsible for the monitoring and reporting of adverse events as necessary to the UW IRB.

Other notable incidents that occur during recruitment, consent, study assessments, but are determined to be unexpected and related to the study procedures, will be reported in a detailed log on an annual basis (at the time of continuing review). The PI will be responsible for informing the IRB immediately of any life-threatening incidents as well as take appropriate action to stop the study, release a participant from the study, or modify procedures to reduce and/or eliminate the occurrence of the risks mentioned above.

## 24.0 Economic Burden to Participants

**24.1**

Since most of the study collection will be done remotely, there is little to no expense to participating.

## 25.0 Resources Available

| | |
|---|---|
| **Will the research be conducted outside School of Medicine and Public Health or UW Hospitals and Clinics (e.g. the researcher does not have an SMPH research feasibility attestation for this study)?** | ☒ YES (complete 25.1)<br>☐ NO (remove text below, but retain this section) |

**25.1**
The Center for Healthy Minds has extensive experience running large-scale, longitudinal studies. As most studies have moved to remote data collection in the past year (IRB

protocols: 2020-0533, 2020-1454, and 2019-0893), we have been successful at recruiting a large number of participants with high retention rates.

This study will be conducted over a three-year period, with all study collection being done remotely. Each participant will be involved with the study for approximately 4 months.

Study staff will meet on a regular basis to discuss study design, implementation, processing and analyses. Any task assignments and study updates will be discussed at these meetings. The study also uses the Basecamp platform (a project organization platform) to discuss any questions, updates, and changes to the study.

All participants will be informed to contact their healthcare provider if any concerns arise when answering survey questions. A therapeutic resource list will be provided to all participants via REDCap.

## 26.0 Multi-Site Research

**26.1**
N/A

## 27.0 References

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## 21.0 Appendices

*Provide any additional information relevant to management of the study, such as instructions for specialized procedures, charts or workflow diagrams.*