PROTOCOL TITLE: Development and Testing of a Behavioral Activation Mobile Therapy for Elevated Depressive Symptoms

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1.0 Objectives / Specific Aims

Via a successfully completed Phase I STTR, our investigative team developed and preliminarily clinically evaluated Moodivate, a self-help mobile app informed by Brief BA to be utilized for depression treatment among adult primary care patients. Results of our Phase I study indicate that Moodivate is feasible and acceptable to primary care patients and that use of the app relative to TAU is associated with significantly greater decreases in depressive symptoms over time. This Phase II STTR will allow us to refine, improve, and rigorously evaluate Moodivate.

Aim 1: Refine Moodivate and develop the EHR provider portal (months 1-12). Iterative usability testing with patients (n=10) and providers (n=10) will be utilized to refine both the app and the portal. *Milestones:* 1) Development of a HIPAA-compliant Moodivate EHR portal, 2) Android expansion of Moodivate, and 3) completed app modifications consistent with feedback from Phase I participants.

Aim 2: Via a three-arm randomized controlled trial (N=695), examine the efficacy of 1) Moodivate vs. 2) Moodivate + EHR integration vs. 3) treatment as usual (TAU) for the treatment of depressive symptoms within primary care (months 12-30). Main outcomes include: 1) change in depression over time as a function of treatment and 2) patient- and provider-level treatment feasibility and acceptability. *Milestones:* 1) Determination of clinical efficacy of Moodivate and Moodivate + EHR relative to standard practice for depression treatment and 2) demonstrated treatment acceptability and feasibility, defined as ≥70% app retention across follow-up and patient and physician self-reported benefit of utilizing Moodivate.

Aim 3: Conduct a cost-effectiveness analysis of implementing Moodivate and Moodivate + EHR integration within primary care practices relative to TAU (months 30-36).
Milestones: Derivation of incremental cost-effectiveness of Moodivate and Moodivate + EHR vs. TAU.

2.0 Background

Depression is a Major Public Health Problem and the Leading Cause of Disability Worldwide. Depression is the leading cause of disability worldwide, with more than 300 million people affected[1,2]. In the United States alone, 16.2 million adults report a past year major depressive episode (MDE)[3] and an additional 38 million experience subsyndromal depression[4]. Individuals with depressive symptomatology experience significant suffering, high morbidity and mortality, and considerable social and occupational impairment[5]. As such, efficient and effective identification and treatment of depression is of critical public health importance.

Primary Care Offers a Ripe Opportunity for Depression Treatment. Most adults with depressive symptoms make at least one annual medical visit to a primary care physician (PCP)[2]. Thus, primary care offers a ripe opportunity to identify and treat adults with depressive symptoms. This is consistent with guidelines from the United States Preventive Services Task Force, which specify that depression screening should be implemented in the general adult primary care population with systems in place to ensure appropriate diagnosis, treatment, and follow-up[6]. Despite these recommendations, depression has historically been undertreated in primary care[5,7] and **more than two-thirds of U.S. adults who screen positive for depression do not receive treatment[2]**. Lack of depression treatment via primary care results in negative outcomes for patients, including prolonged depressive episodes, decreased recovery incidence, and heightened impairment and suffering[8].

Table 1: Current Primary Care Psychotherapy Market[2]

Evidence-based depression treatments that can be delivered via primary care include medications (e.g., antidepressants) and psychotherapy[6]. Although primary care patients with depressive symptoms tend to prefer psychotherapy[9,10], the vast majority (87%) of patients treated are prescribed medications[2] without therapy offered even as an option[11-13]. Of the 21.2 million U.S. adults who visit a PCP annually and screen positive for depression, only 6.6% receive therapy (***Table 1***)[2]. One key barrier is limited access to mental health specialty care[14]. Within one nationally representative survey, 66.8% of PCPs reported they were unable to get high-quality outpatient mental health services for their patients[15]. From a patient perspective, therapy barriers include problems of transportation, childcare, lack of time, stigma, and lack of available services[16,17]. There is clear need for a disseminable, evidence-based psychotherapy treatment option to meet the need for depression treatment via primary care. Such a product would not only address a public health need but would also be commercially viable.

U.S. adults	327.2 million
U.S. adults who visit a PCP ≥ 1x/year	251.9 million
U.S. adults who visit a PCP ≥ 1x/year and screen + for depression	21.2 million
U.S. adults who visit a PCP ≥ 1x/year, screen + for depression, and receive treatment	6.1 million
U.S. adults who visit a PCP ≥ 1x/year, screen + for depression, and receive antidepressants	5.3 million
U.S. Adults who visit a PCP ≥ 1x/year, screen + for depression, and receive psychotherapy	1.4 million
Current untapped market for psychotherapy via primary care within the U.S.	**19.8 million**

Mobile Health Technologies can be Leveraged to Deliver Evidence-Based Depression Treatment via Primary Care. Mobile health (mHealth) technologies offer an ideal strategy to meet the need for evidence-based psychological depression treatment via primary care. Several computerized psychological interventions for depression treatment via primary care have previously been developed and have demonstrated success[18,19]. However, mobile technologies, such as smartphones and mobile apps may be superior treatment delivery platforms as they allow continuous, patient-driven access to treatment materials while also eliminating barriers to computerized treatment (e.g. the need to have a computer at home or go to a clinic to access the treatment). Smartphone ownership in the U.S. has grown year over year and now 77% of adults own smartphones[20], with high smartphone ownership rates across age groups—92% of Millennials, 85% of Gen Xers, and 67% of Baby Boomers own smartphones[21]. Moreover, the majority of physicians report utilizing mobile apps in their clinical practices[22]. Thus, treatment access barriers could be reduced if evidence-based psychotherapy could be efficaciously delivered via smartphone. Apps delivered directly within primary care settings could provide an immediately actionable, evidence-based treatment for patients in need of services for depressive symptoms.

Brief Behavioral Activation is an Evidence-Based Depression Treatment Well-Suited for mHealth Delivery via Primary Care. To be an attractive treatment option for PCPs to recommend to their patients, a mobile app-based depression treatment must be strongly grounded in evidence-based treatment and have a research base supporting primary care implementation. Among evidence-based depression psychotherapies, brief Behavioral Activation Treatment for Depression (Brief BA)[23,24] has shown great promise and is particularly amenable to mHealth delivery within primary care. Brief BA is grounded in behavioral principles, which suggest that depression is caused by a lack of reinforcement in the environment for positive, non-depressed behaviors. Thus, the goal of Brief BA is to help the patient identify, schedule and reengage in positive activities. Brief BA accomplishes this via the following components, delivered across five to ten sessions: 1) Psychoeducation: Introduction to the Brief BA model; 2) Identification of life areas, values, and associated activities: Identification of values and goals within a variety of life areas important to the patient, including relationships, education, career, recreation, and health; 3) Daily monitoring and activity planning: Selection of activities that allow the patient to live according to his/her

values and incorporation of the activities into the patient's daily schedule; and 4) Contracts: Identification of a supportive individual to facilitate completion of difficult activities.

Brief BA was originally developed by Lejuez (study consultant) and colleagues in 2001[25] and several large-scale randomized controlled trials (RCTs) since that time have demonstrated the efficacy and cost-effectiveness of the treatment for depressive symptoms. Across studies, Brief BA is associated with reductions in depressive symptoms[26,27] including among those with Major Depressive Disorder (MDD)[28]. Brief BA treatments have been delivered successfully within primary care clinics both by mental health nurses[29] and psychologists[30]. Further, Brief BA has shown promise in a variety of other health care settings, including oncology[31,32], the Veteran's Administration health system[33], and substance use treatment[34-36]. Across studies, effect size estimates for Brief BA are in the medium to large range indicating meaningful clinical impact[37,38]. A key strength of Brief BA that makes it fitting for mobile app delivery is that it is simple, straightforward, and easily understood by patients[39].

Progress Report. The overarching goal of our Phase I STTR was to tailor the delivery of Brief BA for mHealth within primary care. We developed "Moodivate," a self-help patient-facing mobile app informed by Brief BA (***Figure 1***). Moodivate development began with a diverse team of PCPs, psychologists, and app developers (all investigators herein) to ensure psychological treatment components were faithfully translated to a mobile platform in a manner fitting the primary care environment. We utilized an agile development approach, which promotes continued collaboration across the software development lifecycle between the entire team[40].

Figure 1: Moodivate Screenshots

When users first download Moodivate, they complete a psychoeducational interactive tutorial illustrating the connection between thoughts, feelings, and behavior. This tutorial highlights that Moodivate will focus on increasing activity to improve mood and decrease the incidence of negative thoughts (***Figure 1***). Users practice generating values and activities and receive instruction regarding app use. Users are then taken to the "Life Areas" screen, where they select from five life areas (Relationships, Daily Responsibilities, Recreation, Career and Education, Health) to develop values. A value is defined as an ideal, quality, or belief in a certain way of living. For example, within the relationships life area, a user might generate a value of "Be a trustworthy friend." This value-driven framework ensures that activities will be positively reinforced over time, by virtue of being connected to what the user values as important[24]. Users generate several values within each life area. Values are then used as a framework to generate activities. For the user who generated the value of "Be a trustworthy friend", activities might include going to dinner with a friend once a week or calling a friend for 20 minutes twice a week. Users generate several activities for each value.

Once a user has generated activities across values, activities are scheduled and monitored via the Calendar. After completing an activity, the user receives reinforcement (e.g., "Nice going, you did it!"). Sometimes activities are difficult to complete individually and require help from others. For example, a user might schedule an activity to grocery shop weekly but might not have transportation. In these instances, users can enlist social support via the "Assists" screen through which they identify an individual who could help them complete the scheduled activity and schedule a time to ask that individual for help. Moodivate users can track daily mood to monitor progress. Calendar prompts remind users to rate their mood each day. Users can view a graph of fluctuations in mood overlaid upon a graph of the number of completed activities, illustrating the connection between activity and mood. Moodivate users are reinforced for treatment engagement via badges. When a user earns a badge, a pop-up displays and congratulates the user while explaining why the badge was earned. Users can view earned badges on the User Info page[41].

Table 2: Phase I STTR Participant Demographics

	All (N=52)	Moodivate (n=24)	MoodKit (n=19)	TAU (n=9)
Age (M(SD))	43.8(13.3)	44.7(14.0)	43.0(13.6)	43.1(11.9)
Gender (% Female)	84.6%	83.3%	78.9%	84.6%
Race (% White)	40.4%	41.7%	36.8%	44.4%
Ethnicity (% Hispanic)	3.8%	0.0%	10.5%	0.0%
Education (% ≥ HS)	84.6%	91.6%	78.9%	77.8%
Income (% <$50k)	61.5%	54.1%	68.4%	66.6%

To examine the feasibility and preliminary efficacy of Moodivate for depression treatment within primary care, we conducted a pilot randomized feasibility trial as part of our Phase I STTR[42]. Participants (N = 52; ***Table 2***) were recruited from one primary care clinic affiliated with the Medical University of South Carolina (MUSC) and were randomized 2:2:1 to receive: 1) Moodivate, 2) an active control Cognitive Behavioral Therapy mobile app ("MoodKit"), or 3) Treatment As Usual (TAU; no app). Because clinical data are limited on other available mobile apps that purport to treat depression[43-46], at the suggestion of NIH program staff, we opted to include the active control comparator (MoodKit) to extend the literature on efficacy data for other clinical apps. Participants completed assessments of depressive symptoms weekly for eight weeks. App analytics data were captured to examine Moodivate feasibility (similar analytics data not available for MoodKit as it was not developed by our team). Moodivate participants on average had 46.8(SD = 30.1) app sessions throughout the trial duration, spent 3.5(2.8) minutes using the app per session, and spent 120.8(101.0) minutes using the app in total throughout the trial. Participants on average generated 6.1(3.2) unique values, 14.7(10.2) unique activities, and completed 52.2(89.3) activities. Nearly 70% of Moodivate participants continued to use the app one month after trial enrollment and 50% at the end of the eight-week follow-up period. A generalized estimating equation (GEE) model examining change in depressive symptoms over time by treatment indicated a significant interaction between time and treatment (χ^2=42.21, df=14, p<.001). As compared to TAU, Moodivate participants evidenced significantly greater decreases in depression over time. Moreover, these gains were sustained across the trial period. Moodivate participants had an average(SD) 12.2(13.2) point decrease on the Beck Depression Inventory-II (BDI-II[47]; a 10-point decrease is clinically significant) from pre- to post-treatment. At study end, 52.6% of Moodivate participants (vs. 25.0% of TAU) had less than minimal symptoms of depression. Differences between the two app conditions were nonsignificant, as might be expected from a pilot feasibility study not powered to detect small effects. **In sum, this trial demonstrated that: 1) our team can feasibly recruit patients with depressive symptoms from primary care, 2) participants randomized to Moodivate utilized the app regularly throughout an eight-week period, and 3) Moodivate use was associated with clinically significant decreases in depression over time relative to TAU[48].**

To Enhance Commercialization, Moodivate Must Be Refined, Expanded, and Further Evaluated. Although these preliminary data are promising, several key issues must be resolved before Moodivate can

be commercialized. First, the patient is not the only customer. Providers and healthcare systems can benefit from more effective, efficient depression treatment[49,50]. To systematically deliver Moodivate to all patients with depressive symptoms and provide comprehensive follow-up, Moodivate must be integrated with the healthcare system (i.e., with the Electronic Health Record (EHR)) in a manner that will facilitate provider referral and treatment monitoring. Prior studies of such EHR integration for the management of other chronic diseases including diabetes and obesity indicate that integration of patient data captured via consumer technologies with the EHR facilitates more efficient workflow, improves patient-provider communication, and ultimately improves efficacy[51,52]. Herein, we will integrate the patient-facing Moodivate mobile app with the EHR. This integration will be developed in partnership with PCPs to reduce workflow burden and promote feasibility and acceptability. Via the Moodivate EHR portal, providers will be able to track their patient's Moodivate treatment utilization and response. This portal could also be used to provide additional support to patients not adherent to Moodivate, to reinforce those using the app and responding, and to track clinical outcomes across patients at the provider- and clinic-levels. Beyond potential patient-level benefits of Moodivate (i.e., improved health), systems-level integration of Moodivate with the EHR will allow clinics and health-care systems to improve rates of depression treatment, a key metric for Accountable Care Organizations (ACOs) from the Centers for Medicare and Medicaid Services (CMS). Reimbursements for ACOs by CMS are directly linked to the percent of adult patients screened and treated for depression[53]. As such, Moodivate integrated with the EHR could help rapidly disseminate depression treatment to patients who screen positive and subsequently increase reimbursement rates.

Second, our experience shows that minor product modifications are needed prior to additional clinical evaluation and commercialization. In Phase I, we developed Moodivate for iOS only to rapidly develop and test a minimum viable product (MVP). During our Phase I trial, we found that 56% of primary care patients enrolled were Android owners. For the purpose of the trial, these individuals were allowed to borrow a study iPhone to use throughout the trial. However, to commercialize Moodivate, the app must be expanded to Android. Additionally, as part of Phase I, participants randomized to Moodivate completed a qualitative interview at study end to identify modifications that would promote engagement (***Table 3***). These refinements cluster around: 1) improving the Assists component, 2) incorporating tailored suggestions for values and activities, 3) developing notifications for when activities are scheduled, and 4) offering tailored support when users record low mood.

Table 3: Suggested App Refinements as a Result of Phase I

App Feature	Participant Suggestion
Assists	"It was **difficult to understand** what I was supposed to do with the Assist."
Activities	"It might be nice to have **a bank of activities and values**. It was hard to come up with things I wanted to do. Like be a better friend, I had that value, and having suggested activities would have been helpful."
Calendar	"I would like to get **reminders to do things** 15 minutes before I scheduled an activity to occur."
Mood Rating	"When I rate my mood low, it would be helpful to offer **suggestions of activities I completed in the past that helped improve my mood**. When you're feeling down it's difficult to think of what to do to feel better."

Third, in Phase I we primarily focused on the feasibility and acceptability of Moodivate. To advance toward commercialization and collect data that may be necessary for the FDA regulatory path, a larger-scale clinical trial is needed in which the efficacy and safety of Moodivate are comprehensively evaluated.

Fourth, any downstream commercialization of Moodivate within healthcare systems requires that we first quantify its cost-effectiveness, both as a stand-alone app and as integrated with the EHR. Via our clinical trial and subsequent cost-effectiveness analyses we will determine: 1) whether there is added clinical benefit of Moodivate EHR integration and 2) the incremental cost of any added clinical benefit from a) Moodivate

+ EHR integration vs. sole provision of Moodivate, b) Moodivate + EHR integration vs. TAU, and c) Moodivate vs. TAU.

Summary of Scientific Premise and Potential to Lead to a Marketable Product. Via a successfully completed Phase I STTR, our investigative team developed and preliminarily clinically evaluated Moodivate, a self-help mobile app informed by Brief BA to be utilized for depression treatment among adult primary care patients. Results of our Phase I study indicate that Moodivate is feasible and acceptable to primary care patients and that use of the app relative to TAU is associated with significantly greater decreases in depressive symptoms over time. This Phase II STTR will allow us to refine, improve, and rigorously evaluate Moodivate. Activities proposed via Phase II will move us toward Phase III and commercialization. Outcomes of this Phase II clinical trial will position us well in the current movement across healthcare in which traditional care delivery is being replaced with patient-centric care, facilitated by digital health tools[46,54,55]. This Phase II STTR is wholly consistent with PA-18-579 (Complex Technologies and Therapeutics Development for Mental Health Research and Practice) as well as with NIMH's strategic priorities to "support development, refinement, and implementation of evidence-supported digital health technology into routine practice." Most importantly, commercialization of Moodivate will help to address the public health need for psychological depression treatment via primary care.

3.0 Intervention to be studied

Moodivate. Details of Moodivate are provided in the "Progress Report" section above. Participants randomized to the Moodivate condition will be instructed to utilize Moodivate regularly, at least once per day, for the treatment of depressed mood.

Moodivate + EHR Provider Portal. Participants randomized to the Moodivate + EHR condition will receive similar instructions as those randomized to Moodivate, but will also be instructed that their PCP will have access to metrics related to their app utilization and may choose to follow-up with them regarding treatment utilization and response. The PCP for each participant randomized to this condition will be provided EHR access to Moodivate metrics. Portal design will be developed iteratively with providers as part of Aim 1, but we expect that it will include metrics related to change in mood, frequency of app utilization, and frequency of activity completion.

TAU. TAU is designed to mimic existing standard treatment for depression. Participants in all conditions, including TAU, will be provided educational material about mood management available via the EHR with the suggestion to discuss questions with their PCP. Across conditions, participants will not be precluded from obtaining additional treatment (medication or psychotherapy), which will be tracked as a study outcome.

4.0 Study Endpoints (if applicable)

Primary outcome variables include:

Depression. The clinic-administered PHQ-2[56] will be used for preliminary EHR-based screening and the full PHQ-9[57] will be administered at final eligibility screening to assess depressive symptoms. Across all assessment timepoints (including baseline) depressive symptoms will also be assessed via the BDI-II[47]. The BDI-II is a well validated assessment of depressive symptoms and is our primary outcome measure[47].

Treatment Utilization and Retention. Moodivate utilization and utilization of the provider portal will be tracked via analytics data. As in our prior trials, Moodivate analytics will be accessed via Yahoo's Flurry Analytics system. Specifically, we will examine 1) number of app sessions, 2) average time per session, 3) total time using the app, 4) number of values created, 5) number of value-driven activities

created, 6) number of activities scheduled, 7) number of activities completed, 8) number of times mood is rated, 9) number of badges earned, 10) number of assists created, and 11) number of assists completed. Analytics will be examined within each follow-up week as well as across the entire trial. Retention will be defined as any app use within each week following enrollment. EHR portal analytics data will be accessed via reports in Epic. We utilize a similar approach in an ongoing trial of a smoking cessation electronic visit delivered to patients and reviewed by providers in Epic. This report will include: 1) whether the provider accessed the portal (yes/no) and 2) time spent reviewing the portal. Additional analytics data may be built into the report depending on the design of the portal.

Moodivate Feasibility and Acceptability. Moodivate participants will self-report metrics related to feasibility and acceptability at all study follow-ups. As in Phase I, participants will self-report: 1) ease of Moodivate use, 2) continued desire to use Moodivate, 3) perceived benefits of using Moodivate, and 4) suggested improvements.

Provider Portal Feasibility and Acceptability. Providers of patients in the Moodivate + EHR condition will be invited to complete a questionnaire following their patient's 12-week study follow-up. This questionnaire will assess: 1) provider experiences utilizing the portal with their patient and 2) suggested modifications to the portal.

We will also assess:

Depression Treatment Practices. All PCPs affiliated with MUSC's Primary Care ICCE will be invited to complete the Views about Depression Treatment Questionnaire[58] pre- and post-study, which includes four subscales assessing: 1) attitudes about depression prevalence and treatment effectiveness within primary care, 2) their skills in recognizing and treating depression, 3) the specific behaviors they implement in depression treatment, and 4) satisfaction, compensation, and adequacy of time to treat depression.

Satisfaction with Care. At baseline and Week 12, participants will self-report satisfaction with their primary care via the 10-item Patient Satisfaction Scale[59]. Questionnaire items were adapted from the Adult Primary Care Questionnaire developed by the Consumer Assessment of Healthcare Providers and Systems. All items are scored on a 7-point Likert scale and are summed, with a higher score indicative of higher patient satisfaction[59].

Treatment Mediators. Consistent with NIMH's experimental therapeutics approach, we will assess whether Moodivate engages mechanisms presumed to underlie Brief BA effects. Theorized mechanisms include hedonic capacity (i.e., ability to experience pleasure), environmental reward (i.e., increased behavior and positive affect due to rewarding experiences), and behavioral activation (i.e., goal-directed behaviors)[60,61]. Assessments will be administered at baseline, Week 4, and Week 12. Hedonic capacity will be assessed via the 14-item Snaith-Hamilton Pleasure Scale[62] (SHAPS), which has adequate psychometric properties in clinical and non-clinical samples, including convergent validity with hedonic tone and anhedonic depression[63]. Environmental reward will be assessed via the 10-item Environmental Reward Observation Schedule (EROS)[64], which measures the magnitude of reinforcing events, availability of environmental reinforcement, and ability to elicit positive reinforcement. The EROS has strong internal consistency and excellent test-retest reliability[64]. Change in behavioral activation will be assessed via the 25-item Behavioral Activation for Depression Scale (BADS)[65]. The BADS measures activation and avoidance behaviors and is valid in clinical and community samples[65,66].

Assessment Grids

Questionnaires	Screening	Final Eligibility	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 12
Screening Questionnaire	x											
PHQ-9	x	x		x	x	x	x	x	x	x	x	x
BDI-II		x		x	x	x	x	x	x	x	x	x
App Utilization Questionnaire (*Analytics data*)				x	x	x	x	x	x	x	x	x
Moodivate Usability Survey (*Feasibility/ Acceptability*)				x	x	x	x	x	x	x	x	x
System Usability Scale				x			x				x	x
Patient Satisfaction Scale			x									x
Current Use of Psychotropic Meds			x				x					x
SHAPS			x				x					x
EROS			x				x					x
BADS			x				x					x

Provider Questionnaires

Questionnaires	Pre-study	Post-study
PCP Demographics	x	x
PCP Questionnaire (*Views About Depression Treatment*)	x	x
AIM/IAM/FIM		x
EHR Usability Survey		x
System Usability Scale		x

5.0 Inclusion and Exclusion Criteria/ Study Population

Inclusion criteria:

a) Elevated depressive symptoms, defined as a score of ≥ 10 on the Patient Health Questionnaire-9 (PHQ-9)[57] and a score of ≥ 10 on the Beck Depression Inventory-II (BDI- II).
b) Age 18+
c) Currently own an iOS- or Android-compatible smartphone and runs the most up to date operating system (or willingness to update to the most current operating system)
d) Report willingness to utilize a mobile app for the treatment of depressed mood (response of "yes" on yes/no item)

e) Have a current, valid e-mail address that is checked at least once per day *or* have regular access to text messages (to access follow-up assessments)
f) Enrolled in Epic's MyChart program
g) English fluency

Exclusion criteria:

a) Current suicidal ideation at study screening, defined as a response of ≥ 2 on item nine ("I have thoughts of killing myself but I would not carry them out") of the BDI-II
b) If another household member is currently enrolled in the study
c) Severe visual impairment, which may limit ability to utilize an app

6.0 Number of Subjects

We will recruit up to 20 participants (n=10 providers and n=10 patients) for usability testing and 695 subjects for the RCT.

7.0 Setting

Study participants will be recruited from MUSC's Primary Care Integrated Center of Clinical Excellence (ICCE), which is comprised of 20 unique clinics across the Department of Family Medicine (DFM), University Internal Medicine (UIM) and Carolina Family Care (CFC) with a total patient count of ~30,000 patients treated annually. Research will be conducted remotely via REDCap and MyChart. Participants will be recruited remotely and will be MUSC patients.

8.0 Recruitment Methods

We will utilize proactive recruitment prior to primary care visits to give patients time to utilize their assigned treatment prior to their next primary care visit. For those randomized to Moodivate + EHR, proactive recruitment will ensure there is data available within the EHR for the PCP to review. Our team has previously implemented similar proactive recruitment approaches with success, utilizing EHR fields to identify intended patient populations. Herein, we will utilize available EHR data to identify Primary Care ICCE patients with depressive symptoms. As part of routine clinical care, all patients complete the Patient Health Questionnaire-2 (PHQ-2) to screen for depression during each primary care visit. Because all participants will be current Primary Care ICCE patients, they will all have completed the PHQ-2 during their last primary care visit. Information on depression is also available via the EHR within each patient's problem list and billing codes. Adult (age 18+) patients will be identified who have an upcoming visit scheduled within the next four weeks and have either: 1) a score of ≥ 3 on their last PHQ-2 assessment (the optimal cut-point to identify those symptomatic[56]), 2) depression listed on their problem list, or 3) a depression-related billing code associated with their last visit. **In the last year alone, 6,102 patients have been treated via Primary Care ICCE clinics that would meet these enrollment criteria.** With the permission of their PCP, these patients will be contacted by the study team via the patient EHR portal (MyChart) with an invitation to participate in the study. If participants do not respond to this invitation within 72-hours, we will contact them via phone, e-mail, and/or text-message (based on preferences within the EHR) to ensure they received the message. We currently implement this recruitment approach in an ongoing trial of an electronic visit for smoking cessation, and our experience has been that it is feasible and efficient to generate a recruitment report via the EHR and that all PCPs associated with the MUSC Primary Care ICCE have agreed to have their patients contacted for the purpose of our studies. If interested, participants will complete an eligibility screening via MyChart/REDCap. This eligibility screening will assess: age, sex, e-mail access, MyChart enrollment, English fluency, smartphone ownership, willingness to use a mobile app for the treatment of depressed mood, and depressive symptoms via the PHQ-9. This eligibility screening will be used solely for screening purposes, not for research purposes. Within our informed consent documents, if a participant provides informed consent to participate in the study, they will agree that their screening information can

be used for research purposes. After completing determination of eligibility, a member of the research team will complete remote electronic informed consent with the participant (see details below).

PCPs will be recruited for participation in usability testing via an email message that will be sent to all MUSC Primary Care ICCE providers.

9.0 Consent Process

Signed informed consent will be obtained from study participants. The consent process will take place via one of the following modalities: 1) Remote or in person electronic consent (e-consent) via REDCap (if remote, e-consent will be facilitated with a discussion over the phone or via video), 2) Remote consent via doxy.me facilitated with either a discussion over the phone or video connection via doxy.me, 3) Mailed (paper) consent facilitated with a discussion over the phone, or 4) in person consent (e.g., in clinic, in the investigator's lab space for usability testing).

All participants will be provided with a hard copy and/or an electronic copy of the consent form. Participants will be informed that participation in this research is strictly voluntary. Informed consent will include a detailed description of the purpose and the procedure of the study emphasizing our policy regarding privacy and confidentiality and an opportunity for the individual to ask any questions or voice concerns. Signatures on the consent form may be obtained with paper and pen OR electronically via REDCap/doxy.me. Participants who do not have access to the required technology to complete consent remotely via REDCap or doxy.me will be given the option to complete consent via mail facilitated with a discussion over the phone.

10.0 Study Design / Methods

Aim 1: Development of an EHR Provider Portal and Moodivate Refinements.

EHR Provider Portal Development and Usability Testing

Development of the Moodivate EHR provider portal will take place in two steps: 1) portal development, and 2) usability testing to determine refinements needed to promote feasibility and acceptability. PCPs will be included in usability testing if they are family medicine or primary care providers who treat adults.

Features identified in usability testing will form the basis of EHR provider portal development. As in prior projects, to develop the Moodivate EHR provider portal, we will follow an agile software development approach[40]. Key phases of development will include whiteboard design to outline all features, wireframing of user stories, graphic design, programming, and deployment. Development will be led by Mr. Kustanowitz, implemented by MPT, with iterative testing completed by the PI and co-Is.

A key consideration as we develop the Moodivate-Epic integration to promote future dissemination and commercialization will be to ensure this functionality is based on standard interfaces portable to other institutions that utilize Epic or other EHRs. As such, EHR integration will use existing connection points provided by Epic via the standard HL7 Fast Healthcare Interoperability Resources (FHIR) interface. MPT will be granted appropriate access to MUSC's Epic instance under a business associate agreement with strict security assurances. This Epic access will include appropriate credentials as well as firewall and other security access support. Mr. Bryan Rogers, Director of the Epic-EHR Research Operations Core within the Biomedical Informatics Center (BMIC) at MUSC will serve as the technical resource at MUSC to assist with Epic access. This will include assisting with setup, serving as an institutional contact for questions, and addressing any connectivity issues. MPT will coordinate with Mr. Rogers and his team to determine APIs needed, to implement a proof of concept to confirm information flows as expected, and then to proceed with full development.

Following initial portal development, we will complete usability testing with PCPs. Planned enrollment for this step is n=10, as is standard for usability testing, though we will continue testing until saturation is reached[68,69]. Usability testing procedures will largely follow the cross-sectional usability testing procedures outlined below for Moodivate refinements, although here providers will test the EHR portal rather than the patient-facing app.

Moodivate Refinements and Usability Testing

Mr. Kustanowitz and MPT will lead Moodivate refinements. These refinements will center around: 1) expansion to Android and 2) incorporation of features determined during Phase 1 qualitative interviews. Refinements will be implemented prior to usability testing which will commence during month eight. We will conduct longitudinal (i.e., field testing; n=10) usability sessions. Eligibility criteria for Moodivate usability testing will be identical to eligibility criteria for the RCT.

The goal of longitudinal usability testing is to address barriers participants may experience when utilizing the intervention in their usual environments. During longitudinal usability testing, participants will be recruited, enrolled, and provided with Moodivate in the same manner as participants who will be enrolled in the RCT. Participants will be instructed to utilize Moodivate at least once per day and that the goal of this testing stage is to provide feedback regarding barriers to utilizing Moodivate during normal life. Following longitudinal usability testing, necessary refinements will be identified and implemented by MPT to ready the product for RCT evaluation.

HIPAA Compliance

For Moodivate to be a viable commercial treatment option, it must be Healthcare Insurance Portability and Accountability Act (HIPAA) compliant. Mr. Kustanowitz has expertise in HIPAA-compliant software development and will oversee all aspects of HIPAA compliance within Phase II. It should be noted that HIPAA compliance adds measurable overhead to both the time and cost of development and operations. For example, activities that for a non-HIPAA project would be trivial (e.g., granting a developer access to the production environment) require additional controls for a HIPAA project (e.g., background check, training, access form completion, and a sanity check for "minimum required access"). Developers will not be able to simply pull production data locally to test, and scripts will be written to anonymize data for offline debugging. Operationally, server cost is higher at data centers that support HIPAA compliance, and HIPAA introduces technical requirements that surpass operational ones. For example, for a small application (<10k users), a single server could suffice, but HIPAA requires separating the database server from the front-end web server, and possibly a 3rd "hot failover" server as part of a Disaster Recovery plan. HIPAA also requires administrative activities, including but not limited to: 1) creation of a policies and procedures document and subsequent enforcement which will include staff training materials, setup of access control forms, breach report documents, and onboarding/termination procedures, 2) HIPAA-compliant server hosting, 3) enterprise antivirus protection, 4) a third-party compliance gap assessment report, 5) background checks for all employees, 6) monthly review of security reports and systems checks, and 7) an annual full-system security review and Risk Analysis.

Moodivate will use the existing standard HL7 FHIR (Fast Healthcare Interoperability Resources) interface supported by Epic. MountainPass Technology will be granted appropriate access and credentials to MUSC's Epic instance, under a business associate agreement (BAA) and strict security assurances. Mr. Buck Rogers from MUSC's BMIC Epic-EHR integration team will serve as the technical resource at MUSC to assist with Epic access. This will include assisting with initial setup, serving as an institutional point of contact for questions as they arise, and addressing connectivity issues if/when they occur. MountainPass will coordinate with Mr. Rogers and his team to determine APIs that will be needed, to implement a proof of concept, to confirm that information is flowing as expected, and then to proceed to full scale development.

Aim 2: RCT of Moodivate vs. Moodivate + EHR Provider Portal vs. TAU within Primary Care.

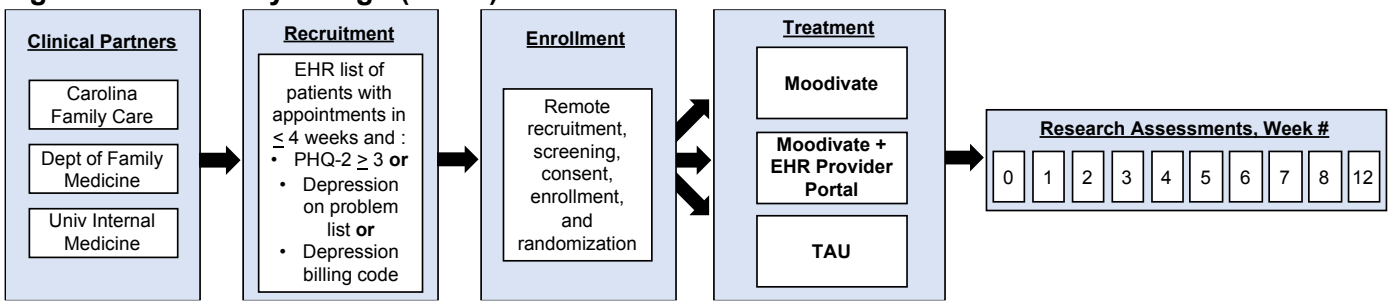
Procedures

After completing determination of eligibility and consent, the participant will complete baseline assessments remotely and be randomized via REDCap 1:1:1 to Moodivate, Moodivate + EHR, or TAU. Participants will be randomized via a mixed block design stratified by baseline depressive symptoms and concurrent depression treatment. If randomized to either of the Moodivate conditions, study staff will provide the participant with an app download code and will ensure successful download. Study staff will then give the participant a brief, scripted overview (as utilized in our Phase I trial) regarding app utilization and will provide the participant with 10 minutes to use the app and ask questions. Participants randomized to the Moodivate + EHR condition will be told that their PCP will be provided information regarding their Moodivate utilization and may discuss use and response during their next visit. Providers of Moodivate + EHR patients will be granted access to the EHR provider portal **for those patients** and it will be suggested that they review the portal during the patient's next visit. The provider portal will be developed such that it is available for providers to view only if the patient is randomized to the Moodivate + EHR condition.

Assessments

All participants will be text messaged and/or emailed a REDCap link, accessible via smartphone, to complete follow-up assessments **weekly for 8 weeks, with a final follow-up at Week 12** (***Figure 3***). We utilized a similar assessment approach in the Moodivate Phase I feasibility trial with success—80% of participants completed at least half of all follow-up assessments and >50% completed all follow-up assessments. Assessments are estimated at 20 minutes each and participants will be compensated $10 for completion of each. Participants can earn an additional $40 for completing all follow-up assessments. All PCPs affiliated with the MUSC Primary Care ICCE will be invited to complete a brief study questionnaire at the beginning and end of the trial. Providers of patients enrolled in the Moodivate + EHR condition will be invited to complete an additional questionnaire following their patient's 12-week study follow-up assessment.

Figure 3: RCT Study Design (Aim 2)



Aim 3: Cost-Effectiveness. The economic evaluation of Moodivate and Moodivate + EHR relative to TAU will be conducted from the budgetary perspective, as the primary focus herein is on the financial attractiveness of Moodivate for commercial launch. Health systems and payors in particular may be more likely to adopt Moodivate if it is established as either 1) cost-saving or 2) providing a clinical benefit cost-effectively. To examine cost-saving, we will first conduct a cost-benefit analysis by comparing changes in BDI-II scores and any reduction in all-cause and mental health-related healthcare expenditures prior to and following Moodivate implementation (or Moodivate + EHR) relative to TAU. Cost data for all inpatient, outpatient and emergency department (ED) care will be obtained from the MUSC Primary Care ICCE billings. As study participants may seek care outside of the MUSC system, we will also obtain all-payors' claims data from South Carolina's Revenue and Fiscal Affairs Office (RFA). RFA maintains data on inpatient and ED utilization across the state regardless of patients' point of care. The case for

Moodivate (with or without EHR) adoption and commercialization will be the strongest if the product reduces healthcare expenditures while also improving depressive symptoms.

11.0 Data Analysis and Data Management

Data Analytic Plan for Aim 1 Qualitative Data

Usability testing data will be analyzed using grounded theory analytical techniques[71], including inductive code identification and development, as well as associated documentation through marginal remarks and memos. Inductive coding ("open coding") involves a data-based approach to the identification of key themes (codes), their development through further exploration of the data, and systematic application. Following grounded theory analyses, we will develop a coding system for the key concepts or problems, and the key points with similar concepts will be grouped together into a category if they are raised by different participants. Each category will then be discussed and underlying themes from the coded data will be generated. Written guidelines for category classification will be used to create a response coding system. After themes are extracted, classic content analysis will be used to identify quotes and content from the feedback that fit each of these themes in the classification system[72]. The PI and two independent raters trained to criterion on the classification system will independently sort quotes by theme and then together reach a consensus on any discrepancies. Average inter-rater reliabilities will be computed prior to the resolution of coding differences. Codes developed following patient and PCP usability testing will be used to identify modifications necessary to Moodivate and to the provider portal. These modifications will be implemented by MPT prior to the RCT.

Sample Size Estimation

There are three pairwise comparisons of interest (1: Moodivate vs. Moodivate + EHR, 2: Moodivate vs. TAU, and 3: Moodivate + EHR vs. TAU), but we focus on two (each Moodivate group vs. TAU) and set α to 0.025 for each, resulting in an overall significance level of 0.05. We view the direct comparison of the two Moodivate groups *a priori* as exploratory. Although based on prior literature we expect that the provider portal addition will bolster treatment efficacy, we cannot yet estimate the magnitude of this effect. Within our Phase I trial, Moodivate participants experienced a 12.2(13.2) point decrease on average in depressive symptoms on the BDI-II, while TAU had a 7.8(15.0) point decrease[42]. Assuming, similar results here, a sample of 158 participants per group will provide 80% power to detect this difference, with a two-sided α=0.025 using a two-sample t-test. Generalized estimating equation (GEE) modeling will have higher power given the repeated nature of observations. Assuming 20% attrition, the sample size is inflated to 200 (for each group) for a total sample size of N=695.

With a sample size of 200 per group, a two-sided 95% confidence interval (CI) for binary feasibility/acceptability outcomes such as retention will extend a maximum of 0.069 in each direction from the observed proportion. For example, if the observed proportion is 50%, the 95% CI will range from 0.43 to 0.57. As the observed proportion gets further from 50%, the width of the confidence interval will decrease, providing even more precision on the observed estimate. For this study, 70% of participants are expected be in the retention group, providing a 95% CI of 0.64 to 0.76 with n=200. A sample size of n=200 in each of the Moodivate groups will provide 80% power to detect the difference between the expected proportion of 0.70 and an alternative proportion of at least 0.79, when the sample size is 200, using a one sized chi-square test of proportions with α=0.025.

For continuous measures of feasibility/acceptability, a two-sided 95.0% confidence interval for a single mean will extend 0.14 from the observed mean, assuming that the standard deviation is known to be 1.0, with a sample size of n=200.

Data Analytic Plan for Aim 2

Efficacy. Descriptive statistics (means, SDs, frequencies, percentages) will be calculated and compared for overall group differences via chi-square tests, ANOVA models, or nonparametric equivalents, as necessary, for baseline variables. Pairwise differences will be explored for variables that show a significant overall group difference. Significant baseline demographic differences between groups will be included as covariates in regression analyses. Generalized Estimating Equation (GEE) modeling will be used to examine group differences (Moodivate, Moodivate + EHR, TAU) in depression (BDI-II) over time along with the interaction between group and time adjusting for baseline differences and baseline depression. All models will include a clustering effect to account for the clinic from which the participant was recruited. Sex will be included as a covariate in all models. GEE affords examination of specific contrasts (i.e., Moodivate vs. TAU at a specific time point) as well as overall effects of group, time, and the interaction between group and time, while also accounting for repeated measures within participants and any clustering within clinics[73,74].

Missing Data. Missing data can be a concern in longitudinal studies, and GEE modeling can assist by including participants with partially complete follow-up data instead of requiring complete follow-up data from all participants. All randomized participants will be included in primary analyses, and imputation methods will be used to accommodate missing data if missing data is >10%. For small amounts of missing data (<10%), these data points will be excluded from modeling, as the sample size has been inflated to account for some attrition. Additionally, sensitivity analyses will be done using only participants with complete follow-up data, with results compared to primary analyses. Attrition will also be assessed to determine whether dropout is differential by group to identify any potential bias in group assignment.

Feasibility and Acceptability. Within both the Moodivate and Moodivate + EHR groups, retention will be defined as the proportion of participants who use the app at least once within each week following enrollment. Retention point estimates and 95% confidence intervals (CIs) will be calculated for each group separately. A one-sided, one-sample proportion test will be used to determine whether retention is at least 70% (or higher) within each group. Other metrics of feasibility/acceptability (ease of use, continued desire to use, etc.) for both patients and providers will be summarized within group via summary statistics and 95% CIs, as appropriate.

Secondary Analyses. Secondary mediation analyses will examine whether changes in hedonic capacity, environmental reward, and/or behavioral activation mediate the relationship between treatment and change in depression. Following recommendations by Preacher and Hayes[75], bootstrapping will be used to examine the indirect effect of treatment on depression via change in proposed mediators. CIs around the indirect effect estimate that do not contain zero will be considered significant. Fit indices including χ^2, the comparative fit index (CFI), the Tucker-Lewis index (TLI) and the root mean square error of approximation (RMSEA) will be examined. Model fit will be acceptable when χ^2 is nonsignificant, CFI and TLI are > 0.9[76,77] and RMSEA is < 0.05[78].

Adverse Events (AEs). AEs will be defined as a clinically significant (i.e., 10-point) increase in depressive symptoms on the BDI-II from baseline or any incidence of suicidality (response of "I would like to kill myself" or "I would kill myself if I had the chance" on the BDI-II suicidality item). We will determine the

incidence of AEs and associated 95% CIs. A chi-square test will determine if the rate of AEs is greater than 5% in any group.

Data Analytic Plan for Aim 3

The economic evaluation of Moodivate and Moodivate + EHR relative to TAU will be conducted from the budgetary perspective, as the primary focus herein is on the financial attractiveness of Moodivate for commercial launch. Health systems and payors in particular may be more likely to adopt Moodivate if it is established as either 1) cost-saving or 2) providing a clinical benefit cost-effectively. To examine cost-saving, we will first conduct a cost-benefit analysis by comparing changes in BDI-II scores and any reduction in all-cause and mental health-related healthcare expenditures for a 12-month period before and after Moodivate implementation (or Moodivate + EHR) relative to TAU. Cost data for all inpatient, outpatient and emergency department (ED) care will be obtained from the MUSC primary care ICCE billings department. As study participants may seek care outside of the MUSC system, we will also obtain all-payors' claims data from South Carolina's Revenue and Fiscal Affairs Office (RFA). RFA maintains data on inpatient and ED utilization across the state regardless of patients' point of care. The case for Moodivate (with or without EHR) adoption and commercialization will be the strongest if the product reduces healthcare expenditures while also improving depressive symptoms.

Even if the app is not cost-saving, there is a compelling case for adoption if the intervention improves outcomes cost-effectively. For cost-effectiveness analyses, we will follow gold standard procedures[79] and calculate the incremental cost effectiveness ratio (ICER), defined as the additional cost per additional outcome desired. Because there are three groups, we will order interventions from most to least costly, likely to be (a) Moodivate + EHR, (b) Moodivate, and (c) TAU. We will then calculate the ICERs for (a) vs. (b) and (b) vs. (c). Because this is an RCT, our ICER is straightforward: (cost of Moodivate + EHR – cost of Moodivate) / (BDI-II score of Moodivate + EHR – BDI-II score of Moodivate). This formula is replaced with corresponding variables when the comparison is Moodivate vs. TAU. We will assume (but verify) that the three groups have similar characteristics so that observed differences in outcomes reflect differences in the intervention. If group differences are evident, a generalized linear model will be used to adjust for between-groups differences. Any intervention that is "dominated" (i.e., is more expensive but yields less desirable result) will be eliminated from consideration. Likewise, we will also eliminate any intervention that is "extendedly dominated" (i.e., an intervention that has an ICER higher than the next most effective intervention). For example, if the ICER of Moodivate vs. TAU is higher than the ICER of Moodivate + EHR vs. Moodivate, we will eliminate Moodivate as being extendedly dominated and calculate the ICER of Moodivate + EHR versus TAU directly. All costs will be converted to net present value at standard discount rates (3% and 5%). Probabilistic sensitivity analyses using Monte Carlo microsimulations will test the robustness of results with differing ranges of costs and treatment effectiveness[80]. Ranges will be based on confidence intervals estimated in Aim 2 outcomes. For cost data, MPT will estimate ranges of app development and distribution costs. An acceptability curve of the cost-effectiveness of any non-dominated intervention will demonstrate the probability of app cost-effectiveness under different levels of willingness to pay.

Data Management

Regarding questionnaire data, data will be obtained for research purposes only. All data will be collected, stored, and managed via REDCap, which is a secure, web-based application designed exclusively to support data capture for research studies. REDCap provides secure, web-based flexible applications, including real time validation rules with automated data type and range checks at the time of entry. The underlying database is hosted in a secure data center at MUSC, a secure environment for data systems and servers on

campus, and includes redundancy, failover capability, backups and extensive security checks. The system has several layers of protection including user/group account management, "Data Access Groups" which allow data to be entered by multiple groups in one database with segmented user rights for entered data, audit trails for all changes, queries and reports, and Secure Sockets Layer (SSL) encryption. Name and relevant contact information will be obtained to provide compensation and every effort will be made to maintain subject confidentiality, in accordance with HIPAA. All data will be identified only by code numbers (participant IDs). Participant IDs will be linked to participants' names in a password-protected file that is accessible only to the PI and trained research staff.

Deidentified data from this study will be submitted to the National Institute of Mental Health Data Archive (NDA) at the National Institutes of Health (NIH).

12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects (if applicable)

This section is based on the recommendations in NIDA's "Guidelines for developing a Data and Safety Monitoring Plan" as well as NCI's "Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by the National Cancer Institute".

Summary of the Protocol
This application consists of a 3-Aim proposal. In Aim 1, both providers (n=10) and adults with depressive symptoms (n=10) will be recruited for iterative usability testing of Moodivate and the Moodivate EHR provider portal. In Aim 2, we will conduct a three-arm randomized controlled trial (n=695) to examine the efficacy of 1) Moodivate vs. 2) Moodivate + EHR integration vs. 3) TAU for the treatment of depressive symptoms within primary care. In Aim 3, we will conduct a cost-effectiveness analysis of implementing Moodivate and Moodivate + EHR integration within primary care practices relative to TAU.

Trial Management
The study will be managed from the Addiction Sciences Division within the Department of Psychiatry and Behavioral Sciences at the Medical University of South Carolina (MUSC). Recruitment, data collection, data management, and treatment provision will be coordinated and centrally managed at our research lab at MUSC and will be implemented within local Family Medicine/Primary Care clinics that are part of MUSC's Primary Care ICCE.

Data Management and Analysis
Participants will enter data in REDCap, a secure, web-based application designed exclusively to support data capture for research studies. REDCap provides: 1) an intuitive interface for data entry (with data validation); 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, Stata, R); 4) procedures for importing data from external sources; and 5) advanced features, such as branching logic and calculated fields. These procedures are effective in minimizing data entry errors (e.g., missing or errant data). All data from Moodivate will be stored on a HIPAA-compliant server and data will be transmitted securely via industry standard protocols to Epic (MUSC's EHR). Data analytic plans are outlined above.

Quality Assurance
Accuracy and completeness of the data collected will be ensured by weekly review. The REDCap system does not accept outliers, illogical response patterns, etc. The PI and research assistant will have weekly meetings to discuss any qualitative comments received during data collection and any problems in data collection. The PI will examine the database for potential irregularities monthly. Initial data analyses will

examine distributions of variable scores and comparability of baseline characteristics across conditions (for Aims 2 and 3) in case analyses need to be adjusted for these. Confidentiality procedures are outlined above.

Regulatory Issues
This study will be registered on clinicaltrials.gov. The study does not require an IND from the FDA. All serious AEs will be reported to the MUSC Committee on Human Research within 48-hours. Follow-up of all unexpected and serious AEs will also be reported. All AEs will be reviewed weekly by the PI and yearly by the IRB. Any significant actions taken by the local IRB and protocol changes will be relayed to the funding agency. We estimate the significant AE rate to be very low (< 5%). If monthly monitoring indicates the rate is above this, we will convene a meeting of the DSMB. Potential conflicts of interest (COI) will be reported using the rules of MUSC's COI committee.

Trial Safety
The potential risks and benefits and methods to minimize these risks are outlined in the "Protection of Human Subjects" section. We will determine if any AEs result in dropouts or are serious according to FDA guidelines. The PI (Dr. Dahne) will serve as the Program Manager for AEs. All unexpected AEs will be monitored while they are active to determine if treatment is needed. We anticipate that AEs will be rare given that the Moodivate app is non-invasive and that all participants will be engaged with current healthcare. Nonetheless, any AEs will be coded on a weekly basis using the FDA's COSTART rules[81] and entered into a database. For each weekly study meeting, the research assistant will prepare a summary of all AEs, including their severity, whether they caused a dropout, required treatment, and presumed relation to app utilization. The PI will review this at the weekly study meeting (or before if more urgent). At the weekly meeting (or before if urgent), the research assistant will report any premonitory symptoms to suggest emergence of a serious psychiatric condition (e.g., suicidality). Drs. Diaz and Player, board-certified Family Medicine physicians, will be available on an ad-hoc basis for on-site medical supervision for any issues that cannot be resolved by Dr. Dahne.

Study procedures will follow as much as possible the FDA's Good Clinical Practice Guidelines and our research team has found Spilker's comprehensive text on conducting clinical trials to be useful[82]. We will encourage participants to notify their physicians that a) they are in a randomized controlled research study examining a treatment for depressed mood, and b) the physician should contact the PI directly if the physician has any questions.

The research assistants will be instructed not to reveal whether a person is a participant in the study and will report to the PI any outside requests for information about a participant or any breaches in confidentiality. All requests by participant's physicians and other medical providers will be referred directly to the PI.

Trial Efficacy
The Data and Safety Monitoring Board (see below) may request a blinded interim efficacy report (blinded to the PI and research team) for review while the trial is ongoing. Final (fully unblinded) efficacy analysis will occur after all participants have completed all follow-ups.

Data and Safety Monitoring Plan Administration
The PI will be responsible for monitoring the trial, with additional oversight provided by study co-Investigators. The PI will examine monthly the outcomes database for missing data, unexpected distributions or responses, and outliers. The PI will check weekly the AE database prepared by the research assistant immediately prior to the lab meeting. A DSM report will be filed with the IRB and funding agency on a yearly basis, unless greater than expected problems occur. The report will include participant

characteristics, retention and disposition of study participants, quality assurance issues and reports of AEs, significant/unexpected AEs and serious AEs. We will report efficacy at the end of the trial.

Data and Safety Monitoring Board Plan
We will create a Data and Safety Monitoring Board (DSMB), comprised of 3 clinicians with expertise in depression treatment, primary care, and clinical trials, as well as a statistician. The DSMB will meet annually (more frequently as needed for emergent situations) to review any AEs related to the study, as well as review any data management related errors. The board may be called at any point if needed for unexpected, serious AEs, etc. Modification will be made in the procedures and/or the protocol if necessary based on the findings of the board.

13.0 Risks to Subjects

The potential risks in this study include those related to: a) depressive symptoms, b) clinical deterioration, c) confidentiality, d) potential data breach from the app database, and e) frustration. All risk mitigation strategies outlined below were approved by the MUSC IRB and implemented with success during our Phase I trial.

a) Depressive symptoms: Depressive symptoms will be monitored via the BDI-II. All participants will complete the BDI-II weekly online via a REDCap survey that is accessible via mobile phone web browsers. All participants will own smartphones. Thus, all participants should have access to the online BDI-II assessments.

b) Clinical deterioration: Dr. Dahne and her research team will monitor participant PHQ-9 and BDI-II scores for possible clinical deterioration (i.e., increasing depressive symptoms and/or the development of suicidal ideation) throughout the course of the study as participants complete the PHQ-9 and BDI-II weekly. Clinical deterioration will be defined as an increase of 10 or more points on the BDI-II from the baseline BDI-II assessment or a response of "I would like to kill myself" or "I would kill myself if I had the chance" on the suicidal thoughts or wishes item of the BDI-II. Our team has developed alerts within REDCap reports that the investigative team checks daily to determine whether a participant completed a BDI-II assessment and evidenced evidences clinical deterioration. This system has now been implemented with success across multiple studies. In the event that a participant evidences clinical deterioration, Dr. Dahne will contact the participant via phone and will provide referrals for local mental health resources for depression treatment. Dr. Dahne will suggest that the participant seek treatment and then will follow-up with the participant via phone one week later. In the event that a participant reports suicidal ideation either during study screening or during subsequent assessments, Dr. Dahne will 1) page the participant's attending primary care provider and 2) complete a risk assessment with the participant via phone. Dr. Dahne will query the participant for details regarding the suicidal ideation, including a likelihood of harming oneself imminently and a plan for committing suicide. If the participant reports an imminent likelihood of harming him/herself or a plan for committing suicide, Dr. Dahne will call emergency services and will remain on the phone with the participant until emergency services arrive. Contact information including home address will be collected during study screening and will be provided if necessary to emergency services personnel. Dr. Dahne is a licensed clinical psychologist and has more than 10 years of experience conducting suicide risk assessments. In the event that a participant evidences clinical deterioration, the participant will be allowed to continue in the trial, but we will recruit an additional participant for data collection purposes.

c) Confidentiality: Participants will be made aware of limits to confidentiality at the beginning of screening and during informed consent which includes a report of suicidal or homicidal intent or report of

abuse or neglect. If the participant reports suicidal or homicidal intent or abuse/neglect during screening or at any point during the trial, Dr. Dahne will take appropriate action as outlined by the MUSC IRB, NIH, and the State of South Carolina, which may include paging the participant's physician, contacting the authorities and/or pursuing involuntary commitment at a mental health facility. If participants present no imminent danger but also need more extensive treatment of mental health concerns, they will be given appropriate referrals.

d) Data breach: Although health information will be collected within Moodivate (e.g., daily mood ratings, activities, values), personally identifiable information will intentionally not be collected within the app (e.g., name, phone number, email address, etc.), and thus we will not collect nor will we retain protected health information (PHI). In the event of a data breach, it is important to note that health information will not be able to be tracked back to specific individual users. By refraining from collecting PHI within the mobile app, we ensure HIPPA compliance while also protecting the identities of our users. In the event of a data breach, all app users will be notified via email.

e) Frustration: Participants may become frustrated while completing questionnaires or while using Moodivate. Participants will be informed that they may refuse to answer any question(s) that they do not wish to answer and that they may discontinue use of Moodivate at any time.

Since patients will all currently be receiving medical care at MUSC, there are no additional risks associated with participation in this study.

Adequacy of Protection Against Risks

Recruitment and Informed Consent

Study participants will be recruited from local primary care/family medicine clinics associated with MUSC's Primary Care Integrated Center of Clinical Excellence (ICCE). Study recruitment will occur proactively prior to a patient's scheduled primary care visit. We will utilize available EHR data to identify Primary Care ICCE patients with depressive symptoms. As part of routine clinical care, all primary care patients complete the Patient Health Questionnaire-2 (PHQ-2) to screen for depressive symptoms during each primary care visit. Information on depression is also available via the EHR within each patient's problem list and billing codes. Adult (age 18+) patients will be identified who have an upcoming visit scheduled within the next four weeks and have either: 1) a score of ≥ 3 on their last PHQ-2 assessment (i.e., the optimal cut-point for identifying those who are symptomatic[56]), 2) depression listed on their problem list, or 3) a depression-related billing code associated with their last visit. With the permission of their attending physician, these patients will be contacted by the study team via the patient EHR portal (MyChart) to invite them to participate in the research study. If participants do not respond to this initial invitation within 72-hours, we will contact them via phone, e-mail, and/or text-message (based on patient communication preferences within the EHR) to ensure they received the MyChart message. We currently implement this recruitment approach in an ongoing trial of an electronic visit for smoking cessation and our experience has been that it is feasible and efficient to generate a recruitment report via the EHR and that all physicians associated with the MUSC Primary Care ICCE have agreed to have their patients contacted for the purpose of our studies. If interested, participants will complete an eligibility screening via REDCap to determine preliminary study eligibility. After completing determination of preliminary eligibility, a member of the research team will schedule a phone call with the participant to determine final study eligibility (no suicidal ideation reported on the BDI-II). After determining final study eligibility, a member of the research team will complete informed consent with the participant. All participants will electronically/in writing sign informed consent forms that have been IRB-approved once the study is explained to them in full and they have stated that they understand what is being asked of them. Participants will be given the opportunity to ask questions about their participation throughout the course of the study. A copy of the informed consent will be kept centrally at our study office within

locked filing cabinets and a copy will also be given to each study participant. Participants will be given a study phone number and e-mail address to contact for questions.

Protections Against Risk

All screening information will be kept in a password protected REDCap database. Only key study personnel will have access to the database. If an individual is not eligible to participate, his/her screener will include his/her first name and last initial and the reason for disqualification. Eligible participants' full name, telephone number and e-mail address will be recorded in the database. This is the only place where participants' names and subject identification numbers appear together. Eligible participants will be assigned a subject number, will complete informed consent (see procedures above), will be randomized (Aim 2), will complete baseline assessments, and subsequently will receive their randomized intervention (or will complete usability testing).

Upon completing eligibility screening, if study eligible, individuals will be provided with a verbal overview of the study, asked to review a consent form, and asked to provide informed consent. Participants will be informed of limitations of confidentiality (i.e., abuse or neglect, intention to harm self or someone else) both verbally and in writing during the informed consent process. The consent form will include the participant's name, but not his/her subject number. Consent forms will be provided in English. As utilization of Moodivate requires that participants are able to read, participants unable to read the consent form on their own will not be included.

Regarding questionnaire data, data will be obtained for research purposes only. All data will be collected, stored, and managed via REDCap, which is a secure, web-based application designed exclusively to support data capture for research studies. REDCap includes real time validation rules with automated data type and range checks at the time of entry. The underlying database is hosted in a secure data center at MUSC and includes redundancy, failover capability, backups and extensive security checks. The system has several layers of protection including user/group account management, "Data Access Groups" which allow data to be entered by multiple groups in one database with segmented user rights for entered data, audit trails for all changes, queries and reports, and Secure Sockets Layer (SSL) encryption. Name and relevant contact information will be obtained to provide compensation and every effort will be made to maintain subject confidentiality, in accordance with HIPAA. All data will be identified only by code numbers (participant IDs). Participant IDs will be linked to participants' names in a password-protected file that is accessible only to the PI and trained research staff.

Regarding user privacy while using Moodivate, users will create a username and password in order to login to their account without storing their true identity. Users will be instructed not to use identifiable information in their username (e.g., name, birthdate, etc) to protect identity. In Moodivate, we will store a one-way hashed version of the patient's email address to support password reset and unique identification, but that identification will not be traceable back to the user's true identity. We will not store any personally identifiable information (e.g., first name, last name, email address, phone number) of users in our app database. We will use a HIPAA-compliant server protected by industry-standard safeguards to prevent unauthorized access. Since we are not associating patient health information with personally identifiable information there would not be a risk of unauthorized release of patient medical data in the event of a security breach. User personal information will be contained behind secured networks and will only be accessible by the investigators, who will have special access rights to such systems. In addition, all sensitive information users supply will be encrypted via Secure Socket Layer (SSL) technology. We will not sell, trade, or otherwise transfer personally identifiable information to outside parties. Our privacy policy will be available within the app for users to view at any time. This plan is consistent with that used by our partnering app development company, MountainPass Technology LLC, in several other previous products with similar protection requirements.

Protection against risk resulting from depressive symptoms includes the following: Regarding suicidal ideation and broader mental health concerns, Dr. Dahne, a licensed clinical psychologist, will take appropriate action as outlined by the MUSC IRB, NIH, and the State of South Carolina, which may include paging the participant's referring physician, contacting the authorities and/or pursuing involuntary commitment at a mental health facility. If participants present no imminent danger but also need more extensive treatment of mental health concerns, they will be given appropriate referrals. As noted above, BDI-II data will be monitored over time in order to detect any possible clinical deterioration. BDI-II data will be monitored using only the participants' subject numbers. Should a participant evidence clinical deterioration, Dr. Dahne will then use the participant database in order to obtain contact information for the participant based on their subject number. We will also form a Data Safety and Monitoring Board (DSMB). If the percent of serious or severe AEs related to clinical deterioration appears to be greater than 5% the DSMB will be notified to make a decision on early termination of the study.

14.0 Potential Benefits to Subjects or Others

All participants in this trial will receive at minimum treatment as usual via MUSC's Primary Care ICCE clinics. We will not augment treatment as usual as provided by these clinics. The majority of participants will also receive a mobile app developed to improve depressive symptoms. The major benefit to society will be whether Moodivate and/or Moodivate + EHR integration improves depression treatment outcomes relative to TAU. Potential issues of clinical deterioration, confidentiality, data security, and frustration are a high priority and will be closely monitored throughout the study. Consequently, the risk to benefit ratio in the proposed study appears to be acceptable.

15.0 Sharing of Results with Subjects

Study outcomes will not be shared with subjects.

REFERENCES

1. World Health Organization. Depression. *Fact Sheets* 2018; https://www.who.int/news-room/fact-sheets/detail/depression. Accessed January 10, 2019.
2. Olfson M, Blanco C, Marcus SC. Treatment of Adult Depression in the United States. *JAMA Intern Med.* 2016;176(10):1482-1491.
3. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: Results from the 2016 National Survey on Drug Use and Health (HHS Publication No. SMA 17-5044, NSDUH Series H-52). In: Center for Behavioral Health Statistics and Quality, ed. Rockville, MD2017.
4. Pietrzak R, Kinley J, Afifi T, Enns M, Fawcett J, Sareen J. Subsyndromal depression in the United States: prevalence, course, and risk for incident psychiatric outcomes. *Psychol Med.* 2013;43(7):1401-1414.
5. Cassano P, Fava M. Depression and public health: an overview. *J Psychosom Res.* 2002;53(4):849-857.
6. Siu AL, Force USPST, Bibbins-Domingo K, et al. Screening for Depression in Adults: US Preventive Services Task Force Recommendation Statement. *JAMA.* 2016;315(4):380-387.
7. Tylee A, Walters P. Underrecognition of anxiety and mood disorders in primary care: why does the problem exist and what can be done? *The Journal of clinical psychiatry.* 2007;68(suppl 2):27-30.
8. Pilling S, Anderson I, Goldberg D, Meader N, Taylor C, Groups TGD. Depression in adults, including those with a chronic physical health problem: summary of NICE guidance. *BMJ.* 2009;339(oct27 1):b4108-b4108.
9. Dwight-Johnson M, Sherbourne CD, Liao D, Wells KB. Treatment preferences among depressed primary care patients. *J Gen Intern Med.* 2000;15(8):527-534.
10. van Schaik DJ, Klijn AF, van Hout HP, et al. Patients' preferences in the treatment of depressive disorder in primary care. *Gen Hosp Psychiatry.* 2004;26(3):184-189.
11. Rossom RC, Solberg LI, Vazquez-Benitez G, et al. Predictors of Poor Response to Depression Treatment in Primary Care. *Psychiatr Serv.* 2016;67(12):1362-1367.
12. Shim RS, Baltrus P, Ye J, Rust G. Prevalence, treatment, and control of depressive symptoms in the United States: results from the National Health and Nutrition Examination Survey (NHANES), 2005-2008. *J Am Board Fam Med.* 2011;24(1):33-38.
13. Stafford RS, Ausiello JC, Misra B, Saglam D. National Patterns of Depression Treatment in Primary Care. *Prim Care Companion J Clin Psychiatry.* 2000;2(6):211-216.
14. Thomas KC, Ellis AR, Konrad TR, Holzer CE, Morrissey JP. County-level estimates of mental health professional shortage in the United States. *Psychiatr Serv.* 2009;60(10):1323-1328.

15. Cunningham PJ. Beyond parity: primary care physicians' perspectives on access to mental health care. *Health Aff (Millwood).* 2009;28(3):w490-501.
16. Mohr DC, Hart SL, Marmar C. Telephone administered cognitive-behavioral therapy for the treatment of depression in a rural primary care clinic. *Cognit Ther Res.* 2006;30(1):29-37.
17. Menke R, Flynn H. Relationships between stigma, depression, and treatment in white and African American primary care patients. *The Journal of nervous and mental disease.* 2009;197(6):407-411.
18. Proudfoot J, Ryden C, Everitt B, et al. Clinical efficacy of computerised cognitive-behavioural therapy for anxiety and depression in primary care: randomised controlled trial. *Br J Psychiatry.* 2004;185(1):46-54.
19. Andrews G, Cuijpers P, Craske MG, McEvoy P, Titov N. Computer therapy for the anxiety and depressive disorders is effective, acceptable and practical health care: a meta-analysis. *PLoS One.* 2010;5(10):e13196.
20. Pew Research Center. Mobile Fact Sheet. *Pew Internet & American Life Project* 2017; http://www.pewinternet.org/fact-sheet/mobile/#. Accessed January 20, 2017.
21. Jiang J. Millennials stand out for their technology use, but older generations also embrace digital life. *Fact Tank News in the Numbers* 2018; http://www.pewresearch.org/fact-tank/2018/05/02/millennials-stand-out-for-their-technology-use-but-older-generations-also-embrace-digital-life/. Accessed July 10, 2018.
22. Franko OI, Tirrell TF. Smartphone app use among medical providers in ACGME training programs. *J Med Syst.* 2012;36(5):3135-3139.
23. Lejuez CW, Hopko DR, Hopko SD. A brief behavioral activation treatment for depression. Treatment manual. *Behav Modif.* 2001;25(2):255-286.
24. Lejuez CW, Hopko DR, Acierno R, Daughters SB, Pagoto SL. Ten year revision of the brief behavioral activation treatment for depression: revised treatment manual. *Behav Modif.* 2011;35(2):111-161.
25. Lejuez C, Hopko D, LePage J, Hopko S, McNeil D. A brief behavioral activation treatment for depression. *Cognitive and Behavioral Practice.* 2001;8(2):164-175.
26. Gawrysiak M, Nicholas C, Hopko DR. Behavioral activation for moderately depressed university students: Randomized controlled trial. *J Couns Psychol.* 2009;56(3):468-475.
27. Reynolds EK, Macpherson L, Tull MT, Baruch DE, Lejuez CW. Integration of the brief behavioral activation treatment for depression (BATD) into a college orientation program: depression and alcohol outcomes. *J Couns Psychol.* 2011;58(4):555-564.
28. Hopko DR, Lejuez CW, LePage JP, Hopko SD, McNeil DW. A brief behavioral activation treatment for depression. A randomized pilot trial within an inpatient psychiatric hospital. *Behav Modif.* 2003;27(4):458-469.

29. Ekers D, Richards D, McMillan D, Bland JM, Gilbody S. Behavioural activation delivered by the non-specialist: phase II randomised controlled trial. *Br J Psychiatry.* 2011;198(1):66-72.
30. Jakupcak M, Wagner A, Paulson A, Varra A, McFall M. Behavioral activation as a primary care-based treatment for PTSD and depression among returning veterans. *J Trauma Stress.* 2010;23(4):491-495.
31. Hopko DR, Funderburk JS, Shorey RC, et al. Behavioral activation and problem-solving therapy for depressed breast cancer patients: preliminary support for decreased suicidal ideation. *Behav Modif.* 2013;37(6):747-767.
32. Hopko DR, Armento ME, Robertson SM, et al. Brief behavioral activation and problem-solving therapy for depressed breast cancer patients: randomized trial. *J Consult Clin Psychol.* 2011;79(6):834-849.
33. Gros DF, Price M, Strachan M, Yuen EK, Milanak ME, Acierno R. Behavioral activation and therapeutic exposure: an investigation of relative symptom changes in PTSD and depression during the course of integrated behavioral activation, situational exposure, and imaginal exposure techniques. *Behav Modif.* 2012;36(4):580-599.
34. Daughters SB, Braun AR, Sargeant MN, et al. Effectiveness of a brief behavioral treatment for inner-city illicit drug users with elevated depressive symptoms: The Life Enhancement Treatment for Substance Use (LETS Act!). *J Clin Psychiatry.* 2008;69(1):122-129.
35. MacPherson L, Tull MT, Matusiewicz AK, et al. Randomized controlled trial of behavioral activation smoking cessation treatment for smokers with elevated depressive symptoms. *J Consult Clin Psychol.* 2010;78(1):55-61.
36. Magidson JF, Gorka SM, MacPherson L, et al. Examining the effect of the Life Enhancement Treatment for Substance Use (LETS ACT) on residential substance abuse treatment retention. *Addict Behav.* 2011;36(6):615-623.
37. Sturmey P. Behavioral activation is an evidence-based treatment for depression. *Behav Modif.* 2009;33(6):818-829.
38. Mazzucchelli T, Kane R, Rees C. Behavioral activation treatments for depression in adults: a meta-analysis and review. *Clinical Psychology: Science and Practice.* 2009;16(4):383-411.
39. Bolton P, Bass JK, Zangana GA, et al. A randomized controlled trial of mental health interventions for survivors of systematic violence in Kurdistan, Northern Iraq. *BMC Psychiatry.* 2014;14(1):360.
40. Martin RC. *Agile software development: principles, patterns, and practices.* Prentice Hall PTR; 2003.
41. Dahne J, Lejuez CW, Kustanowitz J, et al. Moodivate: A self-help behavioral activation mobile app for utilization in primary care-Development and clinical considerations. *Int J Psychiatry Med.* 2017;52(2):160-175.

42. Dahne J, Lejuez CW, Kustanowitz J, et al. Moodivate: A self-help Behavioral Activation mobile app for utilization in primary care—Development and clinical considerations. *The International Journal of Psychiatry in Medicine.* in press.
43. Chan S, Torous J, Hinton L, Yellowlees P. Towards a Framework for Evaluating Mobile Mental Health Apps. *Telemed J E Health.* 2015;21(12):1038-1041.
44. Leigh S, Flatt S. App-based psychological interventions: friend or foe? *Evidence-Based Mental Health.* 2015;18(4):97-99.
45. Neary M, Schueller SM. State of the field of mental health apps. *Cogn Behav Pract.* 2018;25(4):531-537.
46. Price M, Yuen EK, Goetter EM, et al. mHealth: a mechanism to deliver more accessible, more effective mental health care. *Clin Psychol Psychother.* 2014;21(5):427-436.
47. Beck AT, Steer RA, Brown GK. *Beck Depression Inventory-II (BDI-II)*. *San Antonio, TX: Psychological Corporation.* 1996.
48. Dahne J, Kustanowitz J, Lejuez CW. Development and Preliminary Feasibility Study of a Brief Behavioral Activation Mobile Application (Behavioral Apptivation) to be Used in Conjunction with Ongoing Therapy. *Cogn Behav Pract.* in press.
49. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med.* 2000;160(14):2101-2107.
50. Gonzalez JS, Peyrot M, McCarl LA, et al. Depression and diabetes treatment nonadherence: a meta-analysis. *Diabetes Care.* 2008;31(12):2398-2403.
51. Kumar RB, Goren ND, Stark DE, Wall DP, Longhurst CA. Automated integration of continuous glucose monitor data in the electronic health record using consumer technology. *J Am Med Inform Assoc.* 2016;23(3):532-537.
52. Ryu B, Kim N, Heo E, et al. Impact of an electronic health record-integrated personal health record on patient participation in health care: development and randomized controlled trial of MyHealthKeeper. *J Med Internet Res.* 2017;19(12).
53. Kaufman BG, Spivack BS, Stearns SC, Song PH, O'Brien EC. Impact of accountable care organizations on utilization, care, and outcomes: a systematic review. *Med Care Res Rev.* 2019;76(3):255-290.
54. Luxton DD, McCann RA, Bush NE, Mishkind MC, Reger GM. mHealth for mental health: Integrating smartphone technology in behavioral healthcare. *Professional Psychology: Research and Practice.* 2011;42(6):505.
55. Muñoz RF, Chavira DA, Himle JA, et al. Digital apothecaries: a vision for making health care interventions accessible worldwide. *mHealth.* 2018;4(6).
56. Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. *Med Care.* 2003:1284-1292.
57. Kroenke K, Spitzer RL. The PHQ-9: a new depression diagnostic and severity measure. *Psychiatric annals.* 2002;32(9):509-515.

58. Upshur C, Weinreb L. A survey of primary care provider attitudes and behaviors regarding treatment of adult depression: what changes after a collaborative care intervention? *Prim Care Companion J Clin Psychiatry.* 2008;10(3):182.
59. Hojat M, Louis DZ, Maxwell K, Markham FW, Wender RC, Gonnella JS. A brief instrument to measure patients' overall satisfaction with primary care physicians. *Family Medicine-Kansas City.* 2011;43(6):412.
60. Kern D, Busch A, Schneider KL, et al. Psychosocial factors associated with treatment outcomes in women with obesity and major depressive disorder who received behavioral activation for depression. *J Behav Med.* 2018:1-12.
61. Hopko DR, Lejuez CW, Ruggiero KJ, Eifert GH. Contemporary behavioral activation treatments for depression: procedures, principles, and progress. *Clin Psychol Rev.* 2003;23(5):699-717.
62. Snaith R, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P. A scale for the assessment of hedonic tone the Snaith–Hamilton Pleasure Scale. *The British Journal of Psychiatry.* 1995;167(1):99-103.
63. Leventhal AM, Chasson GS, Tapia E, Miller EK, Pettit JW. Measuring hedonic capacity in depression: a psychometric analysis of three anhedonia scales. *J Clin Psychol.* 2006;62(12):1545-1558.
64. Armento ME, Hopko DR. The environmental reward observation scale (EROS): development, validity, and reliability. *Behav Ther.* 2007;38(2):107-119.
65. Kanter JW, Mulick PS, Busch AM, Berlin KS, Martell CR. The Behavioral Activation for Depression Scale (BADS): psychometric properties and factor structure. *Journal of Psychopathology and Behavioral Assessment.* 2007;29(3):191-202.
66. Kanter JW, Rusch LC, Busch AM, Sedivy SK. Validation of the Behavioral Activation for Depression Scale (BADS) in a community sample with elevated depressive symptoms. *Journal of Psychopathology and Behavioral Assessment.* 2009;31(1):36-42.
67. Schueller SM, Neary M, O'Loughlin K, Adkins EC. Discovery of and Interest in Health Apps Among Those With Mental Health Needs: Survey and Focus Group Study. *J Med Internet Res.* 2018;20(6):e10141.
68. Van Den Haak M, De Jong M, Jan Schellens P. Retrospective vs. concurrent think-aloud protocols: testing the usability of an online library catalogue. *Behav Inf Technol.* 2003;22(5):339-351.
69. Turner CW, Lewis JR, Nielsen J. Determining usability test sample size. *International encyclopedia of ergonomics and human factors.* 2006;3(2):3084-3088.
70. Jake-Schoffman DE, Silfee VJ, Waring ME, et al. Methods for evaluating the content, usability, and efficacy of commercial mobile health apps. *JMIR mHealth and uHealth.* 2017;5(12):e190.
71. Strauss A, Corbin J. *Basics of Qualitative Research. 1998.* 1998.
72. Weber RP. *Basic content analysis.* Vol 49: Sage Publications, Incorporated; 1990.

73. Hanley JA, Negassa A, Forrester JE. Statistical analysis of correlated data using generalized estimating equations: an orientation. *Am J Epidemiol.* 2003;157(4):364-375.
74. Hardin JW, Hilbe JM. *Generalized estimating equations.* Chapman and Hall/CRC; 2002.
75. Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. *Behav Res Methods.* 2008;40(3):879-891.
76. Byrne BM. *Structural equation modeling with EQS and EQS/Windows: Basic concepts, applications, and programming.* Sage; 1994.
77. Bentler PM. Comparative fit indexes in structural models. *Psychol Bull.* 1990;107(2):238.
78. Steiger JH. Structural model evaluation and modification: An interval estimation approach. *Multivariate behavioral research.* 1990;25(2):173-180.
79. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. *JAMA.* 1996;276(15):1253-1258.
80. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes.* Oxford university press; 2015.
81. Joseph MC, Schoeffler K, Doi PA, Yefko H, Engle C, Nissman EF. An automated COSTART coding scheme. *Drug Inf J.* 1991;25(1):97-108.
82. Spilker B. *Guide To Clinical Trials.* Philadelphia, PA: Lippincott Williams & Wilkins; 2000.