Healthy Hearts Healthy Minds: A PPRN Demonstration Pragmatic Trial

ClinicalTrials.gov Identifier: NCT03373110

Healthy Hearts Healthy Minds: A PPRN Demonstration Pragmatic Trial

Andrew Nierenberg, MD (Principal Investigator)

Department of Psychiatry, Massachusetts General Hospital
Harvard Medical School

I. BACKGROUND AND SIGNIFICANCE

Depression and cardiovascular disease (CVD) frequently occur together, exacerbate each other, and when combined, are among the leading causes of disability and death. Compared to people without depression, those with **depression have two times the risk of myocardial infarction**[1, 2] **and are four times more likely to die from coronary heart disease**[3, 4]. Mostly because of cardiovascular comorbid conditions, people with major depressive disorder (lifetime prevalence of about 17%) [5-7], or bipolar disorder (prevalence of about 4.5%)[7] die 8 to 25 years earlier than the general population [8, 9]. **Conversely, people with CVD (overall prevalence over 33% of adults**[10]**) have three to four times the rate of depression compared to the general population** [11, 12], and die at twice the rate if they have comorbid depression compared to those without depression [13-15]. Depression and CVD interact in a vicious cycle and are responsible for a large proportion of morbidity and mortality [16].

Why Exercise may be the key to breaking the vicious cycle: **The impact of exercise on CVD is clear and clinically meaningful**. Exercise improves virtually all risk factors for CVD as well as the disease itself. For example, exercise positively benefits hypertension as well as risk of metabolic syndrome and diabetes[17]. A walking study of 8,436 male and 33,586 female participants found that this physical activity remarkably lowered the risk of CVD mortality by 35%, ischemic heart disease mortality by 31%, diabetes mortality by 91%, and 34% for hypertensive diseases[18]. Recently, a 15-year study investigating the role of exercise in preventing and treating CVD in healthy adults (N=8,662) found that people exercising regularly were 0.35 (0.13–0.98) times less likely to die from CVD compared to those not exercising regularly[19]. Given these data the US Preventive Services Task Force (USPSTF) recently published a guideline recommending "*referring adults who are overweight or obese and have additional CVD risk factors to intensive behavioral counseling interventions to promote a healthful diet and physical activity for CVD prevention."*

The impact of exercise on depression is also clear and clinically meaningful. Two recent meta-analyses found that exercise for depression was superior to no treatment at all as well as to similarly efficacious psychotherapies[20, 21]. The treatment effect size for exercise across 11 well controlled trials was large (Hedge's g = 1.39, for a random effects analyses), indicating that it has powerful antidepressant properties[21]. Exercising 3 days/week for 45-min over four months is as effective in reducing depressive symptoms as an antidepressant (i.e., sertraline) for individuals with unipolar depression[22, 23, 24]. Other studies have found that exercise improves bipolar depression[25, 26], one's stress reactivity[27] and cognition[28]. Similar to the risk for CVD, there is a dose-response relationship between exercise and depression highlighting the direct impact of exercise on one's mental health[28, 29]. Exercise may also address the underlying mechanisms for the vicious cycle of depression and CVD. Recent evidence suggests that depression is linked to inflammatory processes (indicated by C-reactive protein and interleukins) [30] and inflammation is a key feature of

atherosclerosis and CVD. The most robust way to combat inflammation is to exercise[31-34]. In sum, exercise is key to reducing the impact of these co-occurring conditions, which increases morbidity and mortality in the US population. **It is less clear, however, how to best help people make this important behavioral modification.**

The proposed study is particularly poised to further target high-risk populations as individuals with lived experience of depression and/or heart disease will co-design two online interventions with clinicians and researchers. We will also leverage existing knowledge about facilitating exercise amongst people with depression and individuals who are at risk for, or have, CVD online, through the positive role of others (e.g., online communities) and utilizing the rich experience of the field of online education to keep people engaged in the two chosen web-based, empirically-validated interventions to enhance exercise[51-54]. The proposed study also seeks to disseminate two targeted, empirically-based interventions for individuals with depression at risk for or with CVD. By bringing together MoodNetwork and Health eHeart (UCSF, CHR #12-09993), we have the immediate opportunity to serve the participants currently enrolled in our two networks (>4100 in MoodNetwork and >80,000 in Health eHeart) across 50 states, 5 territories, and 33 countries. Potential dissemination, however, is much wider. Thus, **the impact of this study is increasing access to empirically-supported treatments that are specifically tailored by partnering with patients to enhance exercise in depressed individuals who are at risk for, or have, CVD.**

This study will utilize the National Institutes of Health-funded Eureka mHealth Research Platform (UCSF, CHR #16-19397), a platform that enables investigators to conduct mobile, online, and wireless health research in a less costly, more streamlined manner, in order to recruit participants, collect and store study data, and manage study participants. The research platform will accelerate our ability to access a large cohort of volunteers who have agreed to participate in research, and provide a quick, affordable means for collecting their health data through mobile and wireless technologies.

II. SPECIFIC AIMS

The purpose of this research is to compare the effectiveness of web-based cognitive behavior therapy (CBT) and use of a fitbit device, web-based mindfulness-based cognitive therapy (MBCT) and use of a fitbit device, and use of a fitbit device with no adjunctive therapy for increasing physical activity in people with a history of depression and who have or are at risk of having cardiovascular disease.

A. Primary Aims

Aim 1: To determine if 1) web-based CBT or web-based MBCT, supported by use of Fitbit technology for self-tracking of activity, improves physical activity, and 2) How these two therapies compare to a Fitbit-only control group.

Hypothesis 1a: Because CBT (compared to MBCT) is the more directive intervention, we hypothesize that CBT will be superior to MBCT in increasing daily steps over the course of 8-weeks of treatment and at follow-up.

Hypothesis1b: Both forms of therapy-based treatment will be superior to the Fitbit only control group in increasing daily steps over the course of 8-weeks of treatment and at follow-up.

Aim 2: Explore the heterogeneity of treatment effects (HTE) to both interventions. This aim will allow us to *explore* who will benefit from either CBT+ Fitbit, MBCT+ Fitbit, or Fitbit alone (predictors) and to determine the factors that can help match patients to each intervention (moderators or who will have better outcomes with CBT+Fitbit, MBCT+Fitbit, or Fitbit only).

III. INTERVENTION MODULES AND OVERVIEW

Participants in both therapy-based interventions will access materials (e.g., client vignettes, videos, activities) that illustrate ways to increase physical activity (e.g., walks, runs, climbing stairs, etc.). They will be guided to gradually increase their daily steps (physical activity) at their own pace. Both CBT and MBCT will be provided online and will guide participants through the elements of each treatment which are geared to address the barriers against exercise that individuals with mood disorders at risk for or with CVD face (fear of the physiological signs of exertion as they may mean a heart attack, etc.). Besides structured guidance towards exercise, the main focus of both treatments will be on addressing these obstacles that prevent individuals from engaging in exercise. Participants in both of these groups will receive Fitbit devices to measure their steps (main outcome) throughout the study. In addition to the two treatment-based intervention group there will also be a group of participants who serve as controls. This group will receive a Fitbit device, but no form of therapy and will not have access to the online therapy material. By including this control group, we will be able to ensure that any treatment effect is not due to wearing a Fitbit.

Cognitive-behavioral therapy (CBT): CBT will be based on previous work using CBT to enhance exercise [53, 55-57] in individuals with mood disorders which includes the following elements: (1) identifying and setting realistic exercise-based goals and intermediate goals (to maximize success to increase motivation); (2) behavioral scheduling to optimize when to exercise, identify rewards for exercising, and problem solve obstacles to exercising; and (3) identify dysfunctional, maladaptive thoughts about exercise (which decrease motivation) and skills to identify more adaptive, positive thoughts (to overcome thoughts of being too tired or too stressed to exercise). These aspects follow the core components of CBT[58], or to change dysfunctional thoughts and behaviors to change a problem behavior (i.e., sedentary behavior). Evidence shows that adjunctive CBT for exercise helps patients improve their planning to exercise, motivation to exercise, and self-efficacy (or one's belief in their ability) to exercise [56, 59, 60]. Two hundred participants will be randomized to this group.

The CBT Program can be added to an individual's regular course of treatment (such as medications), but should not replace ongoing treatment with his/her own doctor. Throughout participation in this study, the participant should continue any medications or treatments that his/her own doctor feels will best treat the symptoms of depression and/or cardiovascular disease.

Mindfulness-based Cognitive Therapy (MBCT): MBCT will be based on previous work with individuals with mood disorders [44-46]. A central aspect of MBCT is the concept of awareness. Participants practice a variety of meditation types (e.g. breath awareness) and learn to bring mindfulness to everyday situations. Awareness will be directed to elements in participants' lives that interfere with living a more productive, physically active life (e.g. thoughts and feelings that interfere with becoming more physically active; stressful situations and circumstances that prevent them from engaging in exercise). The program guides participants to a mindful consideration about how to "respond" to factors that interfere with a healthy lifestyle. In addition participants bring mindfulness to actual physical activity and the pleasant after effects (to enhance motivation). Compared to CBT, mindfulness, takes a more explorative, self-guided approach of raising awareness rather than a more directive and prescriptive approach adopted by CBT. The fundamental difference between CBT and MBCT is that CBT focuses on goal setting, planning, behavioral contingencies and re-conceptualizing of dysfunctional thoughts that interfere with goal achievement, whereas MBCT strives for gradually increasing awareness towards personal and situational factors that interfere with a healthy, more physically active lifestyle, and developing personalized ways to respond to these factors as well as changing the experience of exercise itself. Although participants cannot choose the intervention, we will explore treatment preferences as a potential source of heterogeneity effects. Two hundred participants will be randomized to this group.

The MBCT Program can be added to an individual's regular course of treatment (such as medications), but should not replace ongoing treatment with his/her own doctor. Throughout participation in this study, the participant should continue any medications or treatments that his/her own doctor feels will best treat the symptoms of depression and/or cardiovascular disease.

Fitbit-Only Control Group:
Participants assigned to the Fitbit-only control study group you will not be receiving therapy. However, they will receive a Fitbit, which they will be asked to wear over the course of 16 weeks as well as to complete the same schedule of assessments as the therapy arms. One hundred participants will be randomized into this group.

Participation in this study can be added to an individual's regular course of treatment (such as medications) but should not replace ongoing treatment with his/her own doctor. Throughout participation in this study, the participant should continue any medications or treatments that his/her own doctor feels will best treat the symptoms of depression and/or cardiovascular disease.

IV. RESEARCH DESIGN AND METHODS

Overview

Given that majority of participants screened will not be eligible, we plan to screen 5000 individuals with the expectation that 10% will be eligible. We propose to recruit 500 eligible

patients from the ongoing MoodNetwork and the Health eHeart Alliance studies who self-report a history of depression and are at elevated risk for cardiovascular events. 40% of participants (2000) will be recruited from MoodNetwork, while 60% (3000) will be will be recruited from Health-eHeart. Participation will take a total of 16 weeks. During the first 8 weeks, participants will receive online CBT and a fitbit device to track activity, online MBCT and a fitbit device to track activity, or a fitbit device to track activity but no adjunctive therapy. The second 8 weeks are a follow-up period where participants will be asked to continue wearing their fitbit device, but receive no other form of treatment, regardless of which group they were initially randomized to. Participants will use desktop computers, laptops, tablet devices, or phones to participate in this study. These procedures are described in detail below.

Accessed through a links managed by MoodNetwork.org and Health-eHeart.org, interested participants will sign an online consent form waiver, found in a web portal hosted by the Eureka mHealth Research Platform. Eureka is a multi-tenant system (architecture in which a single instance of a software application serves multiple customers), which is housed on a HIPAA compliant Amazon cloud database. Once the participant has read and electronically signed the waiver of consent form, participants will register for Eureka and then complete a short battery of assessments to determine eligibility. The assessments will consist of 3 standard psychological assessments (The Patient Health Questionnaire [PHQ-9], the Altman Self-Rating Mania Scale [ASRM], and the Mini International Neuropsychiatric Interview [MINI], and 2 cardiac health assessments (The Duke Activity Status Index [DASI], and the International Physical Activity Questionnaire [IPAQ]). They will also be asked to complete a standard demographic form, and their medical and psychiatric histories. If they are not eligible, they will be thanked for their interest and informed that unfortunately, they are not eligible. If found eligible, they will provide their mailing address information so that we can ship them a Fitbit device. Once they receive their Fitbit device, they will return to the study portal to sync their fitbit with our system so that we can collect their step data complete a series of questionnaires, including the World Health Organization Composite International Diagnostic Interview for Bipolar Spectrum Disorders (CIDI), The Patient Health Questionnaire (PHQ-9), The Altman Self-Rating Mania Scale (ASRM), The Sheehan Disability Scale (SDS), The World Health Organization-5 Well-Being Index (WHO-5), the Self Efficacy for Exercise (SEE), the International Physical Activity Questionnaire (IPAQ), the Seattle Angina Questionnaire-7 (SAQ-7) and the Perceived Stress Scale (PSS). Once completed, participants will be randomized to CBT + Fitbit, MBCT + Fitbit, or the Fitbit-only control group. Those who are randomized to one of the two therapy-based treatment groups will be sent to a portal on MoodNetwork.org to access the interventions. Those randomized to the Fitbit-only treatment group will be brought to a page thanking them for their participation, reminding them to wear their fitbit for the next 16 weeks, and informing them that they will be emailed reminders when they need to return to the portal to complete surveys. All participants, regardless of study group, will be asked to return to Eureka in weeks 2, 4, 6, 8, and 16 to complete a battery of assessments and asked questions about adverse events that may have occurred since beginning the study (detailed in Table 1 below).

Participants in the two therapy-based intervention groups will receive either online CBT or online MBCT through a portal in MoodNetwork for 8 weeks. The therapy will consist of 25-40 minutes of weekly material. After this 8-week period, they will enter an 8-week follow-up phase during which no new treatment material will be administered, but they can access the material already presented during the treatment phase. If randomized to the control group, participants will wear the Fitbit device for an 8-week period and follow the same schedule of assessments as the treatment groups. Throughout the 16-week study, Fitbit data will be pulled into the Eureka mHealth Research Platform database, which is housed on a HIPAA compliant Amazon cloud database**,** using Fitbit's secure application programming interface (API). Coordinated and approved of by the Partner's Clinical Trial Office, Fitbit and MGH have agreed to a collaboration wherein Fitbit will share data (heart rate variability data and sleep data) with the study team that is collected with the devices, which is not available through their public API. Additionally, Fitbit will donate half of the devices needed for the study (275). In return, the study team will share de-identified assessment and summary data with Fitbit. Data will be transferred in a secure file sharing area (S3 Bucket) in Amazon cloud services. This has been documented in a donation agreement and a data use agreement.

Participant Selection and Recruitment

Participants (N = 5000) will be recruited from MoodNetwork.org and health-eheartstudy.org. Participation will take 16 weeks and will involve (1) 8 weeks of receiving online CBT and use of a fitbit, MBCT and use of a fitbit, or use of a fitbit with no adjunctive therapy and (2) 8 weeks of follow-up. Participants will use desktop computers, laptops, tablet devices, or phones to participate in this study. An IRB approved electronic alteration of a written Informed Consent will be obtained from all patients before protocol-specified procedures are carried out. Patients will be recruited according to the following criteria:

a. Inclusion Criteria

- Ability to give informed consent
- Fluent in English
- Between the ages of 18-65
- Lives in the United States
- Self-report of having experienced depression as assessed by the Mini International Neuropsychiatric Interview (MINI)
- Self report an elevated risk for or of having cardiovascular disease (< 150 minutes of physical activity a week)
- Registered a personal account with Fitbit prior to enrollment in the study

b. Exclusion Criteria

- Unwilling/unable to comply with study procedures
- Pregnant

- Responds to item 9 (Suicidal ideation) on the PHQ-9 with a 3 (i.e., "Thoughts that you would be better off dead or of hurting yourself in some way nearly every day ")
- Contraindications to exercise or diet interventions as assessed by the DASI
- Already uses a fitbit device or other activity monitor
- Suffers from repeated episodes of "blacking out" or "fainting"
- Survived a cardiac arrest
- Has recurrent chest discomfort with activity that goes away within 10 minutes of rest or with nitroglycerin
- Has heart failure
- Has been hospitalized recently (within past 6 weeks) for a cardiovascular problem

c. Diagnostic and Clinical Assessments

Diagnostic and Clinical Assessments:

The Mini International Neuropsychiatric Interview (MINI) The MINI can assess for current 17 Axis I diagnoses, exploring lifetime diagnoses where clinically relevant (i.e., previous manic episode for a diagnosis of bipolar disorder). Diagnoses can be ruled out by answering no to one or two screening questions. Positive responses to screening questions are followed by further exploration of other diagnostic criteria. The MINI shows good specificity and sensitivity for most psychiatric diagnoses and concordance with other structured diagnostic interviews.

The World Health Organization Composite International Diagnostic Interview for Bipolar Spectrum Disorders (CIDI) is a 12-item fully-structured lay-administered diagnostic interview that was validated as being capable of generating conservative diagnoses of both threshold and sub-threshold bipolar disorder.

The Duke Activity Status Index (DASI) is a 12- item self-administered questionnaire that utilizes self-reported physical work capacity to estimate peak metabolic equivalents and has been show to be a valid measurement of functional capacity.

The Patient Health Questionnaire-9 (PHQ-9) is a brief self-report instrument used to screen, diagnose, monitor, and measure the severity of depression. The first 8 questions incorporate DSM-IV diagnostic criteria as well as other major depressive symptoms, and Question 9 assesses for the presence and duration of suicidal ideation.

The Altman Self-Rating Mania Scale (ASRM) is a brief (5-item) self-report questionnaire that helps measure the severity or intensity of manic or hypomanic symptoms.

The Sheehan Disability Scale (SDS) measures functional impairment resulting from depressive, panic, anxiety, or phobic symptoms. Patients rate the extent to which their work/school work, social life/leisure activities, and family responsibilities/home life are affected on a 10-point scale. Patients also indicate the number of days lost and number of days underproductive due to symptoms.

The World Health Organization-5 Well-Being Index (WHO-5) is a brief self-report (5-item) of positively-worded statements related to positive mood (good spirits, relaxation), vitality (being active and waking up fresh and rested), and general interests (being interested in things) over the prior two weeks.

The Perceived Stress Scale (PSS) is the most widely used psychological instrument for assessing perception of stress. This scale measures the extent to which situations in one's life are labeled as stressful.
Self Efficacy for Exercise (SEE) is a 13-item instrument that focuses on self-efficacy expectations related to the ability to continue exercising in the face of barriers to exercise.
International Physical Activity Questionnaire (IPAQ) The IPAQ was developed to assess cross-national monitoring of physical activity and inactivity. It is validated in 12 countries and is available in both a long and a short form.
Cardiac Events (CE) is a two - question survey designed to monitor participants who may develop contraindications to exercise or who are at elevated risk for a cardiac event over the course of the study.
Seattle Angina Questionnaire – 7 (SAQ-7) is a well-validated and widely used 19-item instrument that measures patient-reported symptoms, function and quality of life for patients with coronary artery disease.
Adverse Event Questions (AEQ) two-question survey designed to assess if participant has experienced any adverse events, related to the study, since starting to participate.

Table 1. Schedule of Assessments

Weeks	0	1	2	4	6	8	16
	Pre				Mid	Post	Follow-Up
Demographics	X						
Medical/Psych Hx	X						
Mini International Neuropsychiatric Interview (MINI)	X						
World Health Organization Composite International Diagnostic Interview for Bipolar Spectrum Disorders (CIDI)		X					
Duke Activity Status Index (DASI)	X						
The Patient Health Questionnaire (PHQ-9)	X	X	X	X	X	X	X
Altman Self-Rating Mania Scale (ASRM)	X	X	X	X	X	X	X
Sheehan Disability Scale (SDS)		X		X		X	X
Well-Being Index (WHO-5)		X	X	X	X	X	X
Perceived Stress Scale (PSS)		X		X		X	X
Self Efficacy for Exercise (SEE)		X					

International Physical Activity Questionnaire (IPAQ) short form	X	X					
Cardiac Events	X	X	X	X	X	X	X
Seattle Angina Questionnaire – 7 (SAQ-7)*		X				X	X
Adverse Event Questions			X	X	X	X	X

*The SAQ-7 will only be re-administered to those who respond affirmatively to having angina (coronary artery disease), heart attack, coronary bypass surgery coronary stent or angioplasty procedure or if participant has recurrent chest discomfort with activity that goes away within 10 minutes of rest or with nitroglycerin

d. Targeted Enrollment

We expect to recruit a representative sample of the US. We expect that our sample will resemble the general population given the recruitment sites, or MoodNetwork and Health eHeart.

Table 2. Expected Enrollment by Race, Ethnicity and Gender

Race	**Male (N)**	**Female (N)**	**Total (N)**
American Indian/Alaska Native	6	7	13 (2.5%)
Asian	12	13	25 (5%)
Black/African American	87	88	175 (35%)
Hawaiian/Pacific Islander	2	3	5 (1%)
White	137	138	275 (55%)
Multiracial	3	4	7 (1.5%)
Ethnicity	**Male (N)**	**Female (N)**	**Total (N)**
Hispanic (Latino/Latina)	50	50	100 (20%)
Non-Hispanic	200	200	400 (80%)
Age	**Male (N)**	**Female (N)**	**Total (N)**
17 years or younger*	----	----	0%
18 to 44 years	125	125	250 (50%)
45 to 64 years	125	125	250 (50%)
65 years or older*	---	---	0%

V. POTENTIAL BENEFITS

The proposed research study involves an intervention that holds the potential for direct individual benefit such as weight loss, increased healthy lifestyle choices and habits, and decreased medical burden. This research will further our knowledge about medical

burden in depression and the feasibility of psychosocial treatment to reduce this burden. Risks of discomfort associated with the treatment should be offset by the potential physical and mental health benefits. Thus, this study has the potential to not only improve the treatment of depressed patients, but also advance the field by developing a treatment that can be used in future treatment studies of depression.

Subjects will not receive monetary compensation. Subjects will, however, receive the online therapy modules at no cost (if randomized to one of the two therapy-based intervention groups). All participants, regardless of which group they are randomized to, will receive a fitbit device at no cost. For completing the bi-weekly assessments, participants can earn up to $60 worth of Amazon gift cards. Lastly, participants will have the opportunity to be part of the cutting edge of clinical research.

VI. RISKS AND DISCOMFORT

The risks that this trial poses to participants are reasonable in relation to the anticipated benefits because bipolar disorder is associated with a disproportionately high medical burden as well as chaotic mood swings and a high rate of functional impairment.

The risk of loss of privacy in our study hosted by the Eureka Research Platform and the MoodNetwork will be present for all persons participating. Loss of privacy could occur by compromise of either of the technical systems, or if either are required by law to disclose data to authorities, e.g. to prevent serious harm to the participant or others.

Potential Risks to Subjects

Participants may experience some discomfort or anxiety from discussing personal material and completing self-report questionnaires. If a subject feels uncomfortable responding to a question, he or she will not be required to give a response.

As with any type of physical activity, there is a small risk of physical injury. In order to minimize this risk, we take several steps. First, we ask individuals to participate only if they are healthy enough for mild to moderate physical activity. We ask that if they are not sure, that they check with a physician before continuing with this study. Second, we ask that they do not engage in any exercise practices that cause any physical discomfort or place them at risk of falling. If, for some reason, they do experience an injury while participating in this study, we ask that they contact their primary care physician or visit their local emergency room.

A further risk is a breach of confidentiality. This breach could occur when PII is accidentally made visible to other researchers or to the public. The potential harm from this risk is psychological or social harm from having personal data made public.

Protection Against Risks

We will implement the following procedures to protect participants against risks:

1. Screening procedures will exclude any individuals who are not clinically suitable for the study protocol. For example, individuals will be excluded if they endorse a 3 on item 9 (Suicidal ideation) of the PHQ-9 (i.e., "Thoughts that you would be better off dead or of hurting yourself in some way p nearly every day") during study intake. Lastly, to protect participants against risks, we will exclude individuals who have any contraindication to exercise or who are at elevated risk for a cardiac event as assessed by the DASI and Cardiac Events questionnaire.

2. Throughout the study, participants will be closely monitored for exacerbation of mental health conditions with the Patient Health Questionnaire (PHQ-9) and Altman Self-Rating Mania Scale (ASRM). Participants who score greater than a total score of a 20 on the PHQ-9 (indicative of "very severe" depression) and/or a total score of a 16 on the ASRM (or indicative of "very severe" mania) will be sent an automated message stating that their response on these assessments suggests that follow-up care with a local provider is warranted. If item 9 (Suicidal ideation) on the PHQ-9 is a 2 or higher (i.e., "Thoughts that you would be better off dead or of hurting yourself in some way on more than half the days"), then an automatic message will also be generated alerting the individual that their response warrants follow-up care with a local provider. Specifically, via embedded web links, we will refer participants to the MoodNetwork resource page and the DBSA "Find a Pro" link, and will encourage people to contact the National Suicide Prevention lifeline number (1-800-273-TALK) and/or online chat service if needed. When automated messages are sent, a flagged email will be sent to the PI, Dr. Nierenberg. Based off the patient responses from the assessments, Dr. Nierenberg and his fellow study clinicians will determine if it is safe for the participant to continue participating in the study.

3. Patients will complete the brief, bi-weekly survey of potential cardiovascular symptoms (CE) to monitor participants throughout the study. The survey will ask patients whether they have been hospitalized for any of a variety of cardiac conditions. Patients who respond affirmatively to any of the components of the CE (specifically any of the choices 1-7 in question 1) will be automatically prompted to stop engaging in any excessive physical activity (including activity related to study) and to seek medical attention from their primary provider before proceeding. Study staff will be alerted in these situations and may follow-up directly with the participant.

4. Subjects may be withdrawn from the study for any of the following: 1; 1) Elevated risk for a cardiac event as confirmed by Cardiac Events assessment 2) Clinically significant or serious adverse event not consistent with continuation in study, as determined by subject or study clinicians; 43 Subject's decision to withdraw. Any subjects that are withdrawn for the study will be asked to contact their treating physician for any follow up care.

Ensuring Confidentiality

To minimize risk of loss of privacy, MoodNetwork and the Eureka mHealth Research Platform takes the following steps:

For MoodNetwork, the database and the web portal will be housed on the Partners Research Computing Cloud Infrastructure (DIPR and RFA). The Discovery Information Platform for Research (DIPR) provides a set of virtual services within the Partners secure data center and within the Partners network which consist of virtual servers for web or application hosting, file storage and database management. All systems are secured behind the Partners firewall and follow Partners Healthcare Information Security policies for authenticated, minimum access. All systems are patched, monitored and scanned routinely for vulnerabilities and intrusions by the systems administrator and PHS Information Security. The web server and database server are hosted within the Partners Firewall. The web server makes use of standard 128-bit Secure Socket Layer (SSL) encryption to protect data in transit.

Unique identifiers (UIDs), or strings of letters and numbers continuing no PHI, will be used to de-identify the data. MGH will securely store a linking list document, which allows the UIDs from this project to be linked to the UIDs used by the MoodNetwork and Eureka, allowing access to historical medical data stored in these databases. However, no data generated by this project will be inserted into MGH or Partners Healthcare medical records.

The Eureka mHealth Research Platform is hosted on Amazon Web Services (AWS), a cloud-based server system and computing services, similar to those that protect websites used by banks and electronic health record systems. The platform is HIPAA compliant and Eureka follows security guidelines of the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). Specifically, all research data are stored behind a secure firewall, guarded by intrusion detection software, and encrypted at rest and in transit in our Amazon Virtual Private Cloud. Identifying information (name and email address) will be stored in separate (but linked) data tables so that health-related data can be viewed by approved staff as needed without inadvertent association with identifiers when such linkage is not required. In summary, data are coded, the data key is kept separately and securely; electronic data are protected with a password, and all data are stored on a secure network.

We will include the MoodNetwork and Eureka Privacy Policy and Data Security Measures that will be referenced in study onboarding and viewable at any time (please see attached documents to this submission). The statement will inform patients of the risks of loss of privacy, including via technical compromise or legal requirements. We will also make them aware that they are responsible for keeping their login credentials secure.

VII. DATA COLLECTION

All data collection will adhere to HIPAA regulations. Data will be obtained specifically for research purposes and managed using a secure and HIPAA compliant Amazon cloud database managed by the Eureka mHealth Research Platform. All data will be managed

and shared between MGH and USCF per the subcontract agreement. Both teams have separate statistical analysis and engineering teams. Teams can work both together and individually to manage the needs of data gathering, quality assurance, and data management.

These data will be used to evaluate treatment feasibility and acceptability, treatment integrity, efficacy, and possible mechanisms of change.

All data will be managed and shared between the study team and Fitbit per the data-use agreement.

a. Safety and Monitoring

The PI (Dr. Nierenberg) and the study staff will discuss participant safety in person or via conference call on a regular basis. They will discuss and resolve any safety issues, as such issues arise - for example, the occurrence of adverse events, possible participant withdrawal from the study, or a score of full depression, hypomania/mania or suicidal ideation. Dr. Nierenberg will be responsible for preparing a written report that summarizes these discussions and any decisions that are made pertaining to participant disposition. He will also be responsible for determining whether the research should be altered or stopped.

In addition, there will be a Data Safety and Monitoring Board (DSMB) for this study composed of (1) three Massachusetts General Hospital clinical researchers experienced in conducting randomized clinical trials for depression (2) an expert in assessing and treating cardiovascular disease; (3) an expert in biostatistics; and (4) a patient stakeholder with cardiovascular disease. This DSMB will monitor safety issues, including the review of adverse events, the PI's quarterly report of the study's progress, all IRB amendments, and the adequacy and integrity of accumulating data. The purpose of this process is to assess scientific integrity and patient safety issues, and ensure the ethical conduct of the trials. The DSMB will approve the initiation of the study and subject enrollment, and determine if study procedures should be altered or stopped due to evidence of benefit or harm to trial subjects that may be attributable to the study or reasons related to scientific integrity. The PI will submit quarterly reports to the DSMB detailing any study changes, adverse events, subject recruitment and retention, reasons for early termination, and ongoing data reports. The PI will also respond to all DSMB issues and queries.

b. Adverse Events

Researchers will follow all ethical and professional reporting requirements for adverse events. Reporting of adverse events will occur as follows (procedures below are consistent with requirements of the Partners IRB):

1) Serious adverse events that are reportable according to the guidelines of the Office for Human

Research Protections (OHRP) and FDA (e.g., death, suicide attempt, inpatient hospitalization) will be reported by telephone within 2 business days to the IRB of MGH.

A full written report of the event will be sent to the MGH IRB within 1 week of the event's occurrence.

2) Any other unanticipated problems occurring will be reported to the IRB within 2 weeks, in
accordance with guidelines of the Office for Human Research Protections (OHRP) and FDA.

3) All adverse events will be summarized in the PCORI and IRB annual progress reports.

VIII. DATA ANALYSIS

Baseline demographic and clinical characteristics will be examined by the PI in collaboration with Steve Faraone, Ph.D., Professor of Biostatistics. Measures of central tendency and variability will be estimated on each continuous measure; proportions estimated for categorical variables. Transformations will be used when distributional assumptions are not fulfilled for inferential tests. Dropouts and completers will be compared on baseline variables using Mann-Whitney or chi-square tests. Following FDA guidance for clinical trials, we will not correct our single primary outcome for multiple comparisons. We have 61 additional secondary/exploratory analyses. These will be corrected for multiple comparisons using the Bonferroni method, which yields an alpha level of 0.0008.

A. Data Management: Amazon Cloud

Using 128 bit RSA Secure Socket Layer (SSL) encryption, approved users will be logged-in to machines using secured browsers behind the Partners Healthcare Systems IS corporate firewall or the RIH firewall. Staff will have a unique identifying key that will link them to the electronic study forms. This unique ID will be used in addition to a randomly generated secure password that only the staff person will have. Additional confidentiality procedures are detailed in the Human Subjects section.

B. Statistical Analyses Plan for Research Aims

Each of the statistical tests below will use a two-tailed alpha-level of 0.05.

Aim 1: Hypothesis 1a and 1b: *CBT will be superior to MBCT in increasing daily steps over the course of 8-weeks of treatment and after 8 additional weeks of follow-up, and both forms of treatment will be superior to the Fitbit-only, control group.* The primary hypothesis, or Hypothesis 1a, is that the CBT group will do better than the MBCT group at increasing the number of daily steps. A secondary hypothesis, or Hypothesis 1b, is that the CBT and MBCT groups will do better at increasing the number of steps as measured by the FitBit over the 16-week study compared to the FitBit-only group. Since the data for Hypotheses 1a and 1b both use repeated measures on subjects, we will conduct analyses for both hypothesis using general linear mixed models that account for the covariance of observations within subjects. For both hypotheses, we will model a random intercept and slope for subjects and site and fixed effects for treatment, time, and potentially confounding covariates. The treatment by time interaction for both hypotheses will be used to assert the statistical significance of treatment effects. Canonical links will be used to correctly model the distribution of dependent variables: for count data (e.g. steps) Poisson regression

models will be fit with the Poisson family and the log link and for normally distributed data linear regression models will be fit with the Gaussian distribution and identity link. To choose the correct model for the hypotheses, we will use the Shapiro-Wilk test to assess for normality as well as the deviance statistic, the Akaike information criterion and the Bayesian information criterion to assess the best fitting model. We will compare nested models with the likelihood ratio chi-square statistics for both hypotheses. When a treatment effect is significant for either Hypothesis 1a or 1b, we will clarify its clinical significance by computing, for each time point, effect size statistics that convey the magnitude of treatment group differences. For effect size of both hypotheses, we will use the standardized mean difference for continuous variables. Our primary analyses for Hypotheses 1a and 1b will use daily steps as measured by Fitbit (primary outcome), and then self-reported physical activity, weight, perceived stress, PHQ-9, Altman Mania Scale Scores, and Sheehan disability scores as secondary outcome measures

Aim 2: Exploratory Aims (Phase II). *Hypotheses*: Between treatment group effects sizes (and 95% CI) will be calculated. To supplement this, Mann-Whitney tests will compare treatment groups on medical burden (as measured by FRS) (*Hypothesis 2a*) and on improvement in symptoms (PHQ-9, ASRM) and functioning (SDS) (*Hypothesis 2b*) based on change from baseline.

C. **Rate of Attrition**

Some attrition (i.e., 20%) is expected and this can result in bias and reduce power, precision and generalizability[70]. Consistent with the Intent to Treat principle[71], we will continue with the assessments for the study duration, even among those who fail to comply with the treatment[72].

D. **Power Analysis**

Following FDA guidance for clinical trials, we will not correct our single primary outcome for multiple comparisons. We have 61 additional secondary/exploratory analyses. These will be corrected for multiple comparisons using the Bonferroni method, which yields an alpha level of 0.0008.

IX. REFERENCES

1. Abramson J, Berger A, Krumholz HM, Vaccarino V. Depression and risk of heart failure among older persons with isolated systolic hypertension. *Arch Intern Med.*;161(14):1725-1730.

2. Pratt LA, Ford DE, Crum RM, Armenian HK, Gallo JJ, Eaton WW. Depression, psychotropic medicarion, and risk of myocardial infarction. Prospective data from the Baltimore ECA follow-up. *Circulation.* 1996;94(12):3123-3129.

3. Jiang WW, Krishnan RR, O'Connor CM. Depression and heart disease: evidence of a link, and its therapeutic implications. *CNS Drugs.* 2002;16(2):111-127.

4. Wulsin LR, Singal BM. Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. *Psychosom. Med.* 2003;65(2):201-210.

5. Kessler RC, Berglun P, Demler O, et al. The epidemiology of major depressive disorder - Results from the National Comorbidity Survey Replication (NCS-R). *JAMA: The Journal of the American Medical Association.* 2003;289(23):3095-3105.

6. Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of 12-Month DSM-IV Disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry* 2005;62(6):617-627.

7. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-Month prevalence of Bipolar Spectrum Disorder in the National Comorbidity Survey Replication. *Archives of General Psychiatry.* 2007;64(5):543-552.

8. Musselman DL, Evans DL, Nemeroff CB. The Relationship of Depression to Cardiovascular Disease: Epidemiology, Biology, and Treatment. *Archives of General Psychiatry.* 1998;55(7):580-592.

9. Carney RM, Rich MW, Freedland KE, et al. Major depressive disorder predicts cardiac events in patients with coronary artery disease. *Psychosomatic Medicine.* 1988;50(6):627-633.

10. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics-2015 update: a report from the american heart association. *Circulation.* 2015;131(4):e29.

11. Baune BT, Stuart M, Gilmour A, et al. The relationship between subtypes of depression and cardiovascular disease: a systematic review of biological models. *Translational Psychiatry.* 2012;2(92).

12. Elderon L, Whooley MA. Depression and Cardiovascular Disease. *Progress in Cardiovascular Diseases.* 2013;55(6):511-523.

13. Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction: impact on 6-month survival. *JAMA: The Journal of the American Medical Association.* 1993;270(15):1819-1825.

14. Melle JPv, de Jonge P, Spijkerman TA, et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosomatic Medicine.* 2004;66(6):814-822.

15. Frasure-Smith N, Lesperance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. *Circulation.* 1995;91(4):999-1005.

16. Walker E, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: A systematic review and meta-analysis. *JAMA Psychiatry.* 2015;72(4):334-341.

17. Brown Y, Avenell A, Edmunds LD, et al. Systematic review of long-term lifestyle interventions to prevent weight gain and morbidity in adults. . *Obesity Reviews.* 2009;10:627-638.

18. Williams PT. Dose-response relationship of physical activity to premature and total all-cause and cardiovascular disease mortality in walkers. *PLoS One.* 2013;8(11):e78777.

19. Dhaliwal SS, Welborn TA, Howat PA. Recreational physical activity as an independent predictor of multivariable cardiovascular disease risk. *PLoS One.* 2013;8(12):e83435.

20. Lawlor DA, Hopker SW. The effectiveness of exercise as an intervention in the management of depression: Systematic review and meta-regression analysis of randomized controlled trials. *British Medical Journal.* 2001;322(7289):763-766.

21. Stathopoulou G, Powers MB, Berry AC, Smits JAJ, Otto MW. Exercise interventions for mental health: A quantitative and qualitative review. *Clinical Psychology: Science and Practice.* 2006;13(2):179-193.

22. Blumenthal JA, Babyak MA, Moore KA, et al. Effects of exercise training on older patients with major depression. *Arch Intern Med.* 1999;159(19):2349-2356.

23. Babyak M, Blumenthal JA, Herman S, et al. Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. *Psychosom Med.* 2000;62(5):633-638.

24. Blumenthal JA, Babyak MA, Doraiswamy PM, et al. Exercise and pharmacotherapy in the treatment of major depressive disorder. *Psychosom Med.* 2007;69(7):587-596.

25. Ng F, Dodd S, Berk M. The effects of physical activity in the acute treatment of bipolar disorder: A pilot study. *Journal of Affective Disorders.* 2007;101(1-3):259-262.

26. Hays AE. Effect of an acute bout of aerobic exercise on Dehydroepiandrosterone Sulphate (DHEAS) in clinically diagnosed bipolar subjects. *Dissertation Abstracts International: Section B: The Sciences and Engineering.* 2008;68:5779.

27. Edenfield TM. Exercise and mood: Exploring the role of exercise in regulating stress reactivity in bipolar disorder. *Dissertation Abstracts International: Section B: The Sciences and Engineering.* 2008;68(8-B):5566.

28. Greer TL, Grannemann BD, Chansard M, Karim AI, Trivedi MH. Dose-dependent changes in cognitive function with exercise augmentation for major depression: Results from the TREAD study. Cognition as a target in schizophrenia, bipolar disorder and depression. . *Eur Neuropsychopharmacol.* 2015;25(2):248-256.

29. Heesch KC, van Uffelen JG, van Gellecum YR, Brown WJ. Dose-response relationships between physical activity, walking and health-related quality of life in mid-age and older women. . *Epidemiol Community Health.* 2012;66(8):670-677.

30. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol.* 2006;27(1):24-31.

31. Colbert LH, Visser M, Simonsick EM, et al. Physical activity, exercise, and inflammatory markers in older adults: findings from the Health, Aging, and Body Composition Study *J Am Geriatr Soc.* 2004;52(7):1098-1104.

32. Jefferis BJ, Whincup PH, Lennon LT, Papacosta O, Goya Wannamethee S. Physical Activity in Older Men: Longitudinal Associations with Inflammatory and Hemostatic Biomarkers, N-Terminal Pro-Brain Natriuretic Peptide, and Onset of Coronary Heart Disease and Mortality. *J Am Geriatr Soc.* 2014;62(4):599-606.

33. Martinez-Gomez D, Gomez-Martinez S, Ruiz JR, et al. Objectively-measured and self-reported physical activity and fitness in relation to inflammatory markers in European adolescents: the HELENA Study. *Atherosclerosis.* 2012;221(1):260-267.

34. Hamer M, Sabia S, Batty GD, et al. Physical activity and inflammatory markers over 10 years: follow-up in men and women from the Whitehall II cohort study. *Circulation.* 2012;126(8):928-933.

35. Diabetes, Prevention, Program, Research, Group. Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin. *N Engl J Med.* 2002;346:393-403.

36. Diabetes, Prevention, Program, Research, Group. The Diabetes Prevention Program: Design and methods for a clinical trial in the prevention of type 2 diabetes. *Diabetes Care.* 1999;22(4):623-634.

37. Svetkey LP, Harsha DW, Vollmer WM, et al. PREMIER: A Clinical Trial of Comprehensive Lifestyle Modification for Blood Pressure Control: Rationale, Design and Baseline Characteristics. *Annals of Epidemiology.* 2003;13:1-10.

38. Brownell KD. *The LEARN Program for weight management 2000*. Dallas: American Health Publishing Company; 2000.

39. Daumit GL, Dickerson FB, Wang N, et al. A Behavioral Weight-Loss Intervention in Persons with Serious Mental Illness. *N Engl J Med.* 2013;DOI: 10.1056/NEJMoa1214530.

40. Casagrande S.S., Jerome GJ, Dalcin AT, et al. Randomized trial of achieving healthy lifestyles in psychiatric rehabilitation: the ACHIEVE trial. *BMC Psychiatry.* 2010;10:108.

41. Baker A, Kay-Lambkin FJ, Richmond R, Filia S, Castle D, Jill Williams6 TJL, 7. Study protocol: a randomised controlled trial investigating the effect of a healthy lifestyle intervention for people with severe mental disorders. *BMC Public Health.* 2011;11:10.

42. Stauffer VL, Lipkovich I, Hoffmann VP, Heinloth AN, McGregor HS, Kinon BJ. Predictors and correlates for weight changes in patients co-treated with olanzapine and weight mitigating agents; a post-hoc analysis. *BMC Psychiatry.* 2009 9:12.

43. Velligan DI, Bow-Thomas CC, Huntzinger C, al. e. Randomized controlled trial of the use of compensatory strategies to enhance adaptive functioning in outpatients with schizophrenia. *Am J Psychiatry.* 2000;157:1317-1323.

44. Miller WC. How effective are traditional dietary and exercise interventions for weight loss? . *Medicine and Science in Sports and Exercise.* 1999;31(8):1129-1134.

45. Malone M, Alger-Mayer SA, Anderson DA. The lifestyle challenge program: a multidisciplinary approach to weight management. *Ann Pharmacother.* 2005;39(12):2015-2020.

46. Lehman AF, Goldman HH, Dixon LB, al. e. *Evidence-Based Mental Health Treatments and Services: Examples to Inform Public Policy.* New York, NY: Milbank Memorial Fund; 2004.

47. Druss BG, Rohrbaugh RM, Levinson CM, Rosenheck RA. Integrated medical care for patients with serious psychiatric illness: a randomized trial. *Archives of General Psychiatry.* 2001;58:861–868.

48. Cossman JS, James WL, Cosby AG, Cossman RE. Underlying causes of the emerging nonmetropolitan mortality penalty *Am J Public Health.* 2010;100(8):1417-1419.

49. Ezzati M, Friedman AB, Kulkarni SC, Murray CJ. The reversal of fortunes. *pLoS Med.* 2008;5(4):e66.

50. Lee K, DeVallance E, Fournier S, et al. The Effects of a Community-Based Multi-Lifestyle Intervention on CV Health in Rural Populations. *The FASEB Journal.* 2015;29(1).

51. Rogerson MC, Murphy BM, Bird S, Morris T. "I don't have the heart": A qualitative study of barriers to and facilitators of physical activity for people with coronary heart disease and depressive symptoms. *Int J Behav Nutr Phys Act.* 2012;9(140):doi: 10.1186/1479-5868-1189-1140

52. Vickers KS, Nies MA, Patten CA, Dierkhising R, Smith SA. Patients with diabetes and depression may need additional support for exercise. *Am J Health Behav.* 2006;30(4):353-362.

53. Sylvia LG, Nierenberg AA, Stange JP, Peckham A, Deckersbach T. Development of an integrated psychosocial treatment to address the medical burden in bipolar disorder. *Journal of Psychiatric Practice.* 2011;17(3).

54. Sylvia LG, Salcedo S, Bernstein EE, Baek JH, Nierenberg AA, Deckersbach T. Nutrition, exercise, and wellness treatment in bipolar disorder: feasibility, acceptability, and preliminary efficacy *Int J Bipolar Disord.* 2013;1(1):doi:10.1186/2194-7511-1181-1124/2194-7511-1181-1124

55. Gary RA, Dunbar SB, Higgins MK, Mulsselman DL, Smith AL. Combined exercise and cognitive behavioral therapy improves outcomes in patients with heart failure. *Journal of Psychosomatic Research* 2010;69(2):119-131.

56. Norris SL, Engelgau MM, Narayan VKM. Effectiveness of self-management training in type 2 diabetes: A systematic review of randomized controlled trials. *American Diabetes Association.* 2001;24(3):561-587.

57. May AM, Van Weert E, Korstjens I, et al. Improved physical fitness of cancer survivors: A randomised controlled trial comparing physical training with physical and cognitive-behavioural training. *Acta Oncologica.* 2008;47:825-834.

58. Beck AT, Rush AJ, Shaw BF, Emery G. *Cognitive Therapy of Depression*. New York, NY: Guilford Press; 1979.
59. Damush TM, Perkins A, Miller K. The implementation of an oncologist referred, exercise self-management program for older breast cancer survivors. *Psycho-Oncology* 2006;15:884-890.
60. Sylvia LG, Bernstein EE, Hubbard MS, Keating L, Anderson EJ. Practical guide to measuring physical activity. *Journal of the Academy of Nutrition and Dietetics.* 2014;114(2):199-208.
61. Sylvia LG, Ametrano RM, Nierenberg AA. Exercise treatment for bipolar disorder: potential mechanisms of action mediated through increased neurogenesis and decreased allostatic load. *Psychother Psychosom.* 2010;79(2):doi: 10.1159/000270916.
62. Segal ZV, Williams JMG, Teasdale JD. *Mindfulness-based cognitive therapy for depression*: Guilford Press; 2012.
63. Deckersbach T, Hölzel B, Eisner L, Lazar SW, Nierenberg AA. *Mindfulness-Based Cognitive Therapy for Bipolar Disorder*. New York: Guildford Press; 2014.
64. Caldwell KL, Baime MJ, Wolever RQ. Mindfulness based approaches to obesity and weight loss maintenance. *Journal of Mental Health Counseling.* 2012;34(3):269-282.
65. Salmon P, Hanneman S, Harwood B. Associative / dissociative cognitive strategies in sustained physical activity: Literature review and proposal for a mindfulness-based conceptual model. *Sport Psychologist.* 2010;24(2):127-156.
66. Roberts KC, Danoff-Burg S. Mindfulness and health behaviors: Is paying attention good for you? *Journal of American College Health* 2010;59(3):165-173.
67. Trivedi MH, Greer TL, Grannemann BD, Chambliss HO, Jordan AN. Exercise as an augmentation strategy for treatment of major depression. *Journal of Psychiatric Practice.* 2006;12(4):205-211.
68. Richardson CR, Avripas SA, Neal DL, Marcus SM. Increasing lifestyle physical activity in patients with depression or other serious mental illness. *J Psychiatr Pract.* 2005;11(6):379-388.
69. Sylvia LG, Kopeski L, Brown C, et al. Feasibility of incorporating exercise into a partial hospital program: Preliminary data that exercise enhances treatment. 2010;*Under editorial review*.
70. Leon AC, Mallinckrodt CH, Chuang-Stein C, Archibald DG, Archer GE, Chartier K. Attrition in Randomized Controlled Clinical Trials: Methodological Issues in Psychopharmacology. *Biological Psychiatry.* 2006;59(11):1001-1005.
71. Lachin JM. Statistical considerations in the intent-to-treat principle. *Control Clin Trials.* 2000;21(167-89).
72. Lavori PW. Clinical trials in psychiatry: should protocol deviation censor patient data? . *Neuropsychopharmacology.* 1992;6(1):39-48.
73. Leon AC, Demirtas H, Hedeker D. Bias Reduction with an Adjustment for Participants' Intent to Dropout of a Randomized Controlled Clinical Trial. *Clinical Trials: Journal of the Society for Clinical Trials.* 2007;4(5):540-547.