INtegrating DEPrEssioN and Diabetes treatmENT (INDEPENDENT) Study

Trial Protocol

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INtegrating DEPrEssioN and Diabetes treatmENT (INDEPENDENT) Study: Trial Protocol

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Abbreviations and Acronyms

AE	Adverse Event
ACE-i	Angiotensin Converting Enzyme – Inhibitors
AIIMS	All India Institute of Medical Sciences
AUDIT-10	Alcohol Use Disorders Identification Test (10 item)
BMI	Body Mass Index
BP	Blood Pressure
CC	Care Coordinator
CARRS	Center for Cardio-metabolic Risk Reduction in South Asia
CVD	Cardiovascular Disease
DAST-10	Drug Abuse Screening Test (10 item)
DKA	Diabetic ketoacidosis
DSMB	Data Safety Monitoring Board
DTSQ	Diabetes Treatment Satisfaction Questionnaire
ECG	Electrocardiogram
DS-EHR	Decision Support and Electronic Health Record System
FBG	Fasting Blood Glucose
HbA1c	Glycated Hemoglobin
HDL	High-Density Lipoprotein Cholesterol
HUI-3	Health Utility Index Mark-3
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
LDL	Low-Density Lipoprotein Cholesterol
LAR	Legally Acceptable Representative
MDRF	Madras Diabetes Research Foundation
MoCA	Montreal Cognitive Assessment
PHQ-9	Patient Health Questionnaire (9 item)
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SCL-20	Symptoms Checklist (20 item)
SDSCA	Summary of Diabetes Self-Care Activities
WHO	World Health Organization

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Study Title:

INtegrating DEPrEssioN and Diabetes treatmENT (INDEPENDENT) Study

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1 Study Objective

The objective of this study is to evaluate the sustained effectiveness of an integrated depression and diabetes care intervention (health worker-led participant-activation and decision-supported team reviews) compared to enhanced usual care (notifying the participant's usual provider of depressive symptoms) for diabetic participants in India who have clinically-significant depressive symptoms (Patient Health Questionnaire [PHQ-9] ≥10) AND one or more poorly-controlled CVD risk factor (HbA1c ≥8.0%, SBP ≥140 mmHg, or LDL-c ≥130 mg/dl) in a randomized controlled implementation trial of 400 participants at four clinic research sites over 36 months (12-month active intervention with 24-month extended phase to evaluate sustainability).

1.1 Primary Outcome

The sustained (24 month) difference in the proportion of trial participants in each arm achieving combined improvements in depressive symptoms and CVD risk factors (≥50% reduction in the Symptoms Checklist-20 items [SCL-20] score AND one or more of the following: ≥0.5% reduction in HbA1c, ≥5 mmHg reduction in SBP, or ≥10 mg/dl reduction in LDL-c).

1.1.1 Hypothesis

Compared to the control group, a higher proportion of intervention participants (30% vs. 15%) will achieve combined improvements in depressive symptoms and CVD risk factor levels (≥50% reduction in SCL-20 score AND one or more of the following: ≥0.5% reduction in HbA1c, ≥5 mmHg reduction in SBP, or ≥10 mg/dl reduction in LDL-c) at 24 months.

1.2 Secondary Outcomes

To evaluate global, individual, and economic effects of our multi-condition strategy, we will report a number of secondary outcomes ***for each study arm*** at ***12, 24 and 36 months***:

1) measures of "common effect," i.e., whether the intervention had a similar beneficial effect on all four main targets (SCL-20, HbA1c, SBP, LDL-c);[1]
2) proportion of participants achieving all 3 CVD risk factor targets in the two groups;
3) mean reductions in four main targets (SCL-20 score; HbA1c; SBP; LDL-c);
4) proportion of participants achieving treatment targets or significant reductions in individual outcomes (reduced depressive symptoms [≥50% reduction in SCL-20], glycemic control [HbA1c ≤7.0% or ≥0.5% reduction], BP control [SBP ≤130 mmHg or ≥5 mmHg reduction], lipid control [LDL ≤100 mg/dl or ≥10 mg/dl reduction]);
5) mean utility, quality of life, and participant treatment satisfaction scores; and
6) mean health expenditures and within-trial cost-utility.

2 Background

2.1 Burdens of Mental and Cardio-metabolic Illnesses Globally and in India

Mental health conditions (depression, psychoses, substance abuse) are associated with huge morbidity, social, and economic burdens;[2] and depression is the leading cause of disability worldwide.[2] Diabetes accounted for 4.6 million deaths in 2011[3] and CVD caused a third of global mortality.[2]

Mental health and cardio-metabolic illnesses (e.g., diabetes) also interact and there are several large meta-analyses showing bi-directional relationships between them.[2] For example, depression is a risk factor for development of type 2 diabetes,[4, 5] adversely affects self-care for diabetes,[4, 6] and worsens glycemic control[7] and quality of life;[2] and diabetes is associated with increased risk of developing depression.[8] In addition, risks of debilitating complications and mortality are all compounded when cardio-metabolic and mental illnesses co-exist or are poorly controlled.[2]

Depression affects 12.1% to 15.1 of adults[2] and diabetes affects over 65 million people in India.[2] Prevalence of depression is higher among those with pre-existing CVD risks (e.g., 19.7% of people with diabetes)[2] or CVD complications (e.g., neuropathy).[9, 10] Therefore, the absolute number of those affected by both conditions is sizeable and constitutes a group at elevated risk and in whom intervention may have considerable synergistic benefits.[2] In particular, better organized, more effective, and more responsive care delivery may reduce morbidity and mortality.[2]

2.2 Gaps in Implementation

For most cardio-metabolic diseases, current evidence-based guidelines recommend comprehensive medical management (i.e., treating all CVD risk factors together)[2] combined with lifestyle modifications (regular physical activity, healthier diet, tobacco avoidance and cessation).[2] Mental health conditions such as depression also require long-term, participant-empowered, and self-guided care[11] in collaboration with providers.[12] However, this type of comprehensive care is limited by prohibitive costs, weak health care systems, poor coordination, and shortage of skilled personnel, especially in low-and-middle-income countries. In India, where depression, diabetes, and CVD remain under-diagnosed and sub-optimally treated as individual conditions and incombination,[2]≥60% of people with diabetes are not routinely achieving risk factor control targets and care for people with mental health disorders has been described as generally suboptimal,[2] with anti-depressants used by only half of all eligible subjects.

2.3 Rationale for Integrated Care

Both mental health and cardio-metabolic diseases are chronic, complex, progressive, and costly to care for.[2] Identification is a key initiating step towards clinical- and self-care for these conditions, and in both behavioral activation and motivation are critical for adherence to management plans. In addition, care is hampered by major barriers at the patient (e.g., stigma, motivation),[2] provider (e.g., clinical inertia to intensify treatment), and system (e.g., organization of care) levels, all of which interact with each other.

Given the similarities in course of disease and barriers to care, as well as the adverse interactions between these groups of conditions, integrated care that combines mental health management with cardio-metabolic risk reduction may provide efficient opportunities to reduce morbidity and improve physical and social functioning among patients experiencing these conditions together.[2] This is particularly important as an opportunity to identify previously-unrecognized depressive symptoms among people with diabetes as they may be contributing to poor control and fueling a vicious cycle. There are data to indicate that optimizing therapy for depression, HbA1c, SBP, and LDL-c together is associated with better outcomes than focusing on any one condition alone.[2] As an example of how this works in practice, exercise, weight loss, and better glycemic control — which are routinely employed for diabetes care— also lower depressive symptom burdens in people affected by both diabetes and depression.[2]

The gaps in implementation of evidence-based recommendations may be due to low awareness of one's conditions or what to do about them or low motivation at the patient-level, while at care provider and systems levels, lack of decision-support tools limit implementation of evidence-based guidelines (e.g., intensification plus follow-up of treatment regimens). The evidence suggests that targeting different levels

of barriers to care at the same time (e.g., patient motivation and provider inertia) using patient-centered care models[2] can enhance health outcomes and satisfaction for people with diabetes and depression.[2]

2.4 Experiences in Integrated Care and Preliminary Data

Drs. Katon and Unutzer are pioneers in structuring care for multiple conditions (stepped-care interventions led by trained nurses). They have developed a chronic disease-focused depression treatment model[2] that:

- targets symptoms of depression, motivation, and hopelessness with medication and behavioral therapy;
- targets CVD risk factor control by optimizing medication intensification and helping patients self-manage their conditions better (empowerment, coping mechanisms, and overcoming perceived barriers to self-care); and
- helps patients adopt positive self-management behaviors (e.g., smoking cessation, medication adherence).

This model of care has been associated with a significantly enhanced response to depression treatment as well as enhanced medical control of diabetes (better adherence; reductions in depressive symptoms; more depression-free days;[2] intervention costs offset by savings for medical care;[2] and sustained incremental improvements in HbA1c (-0.58%), SBP (-5.1mmHg), and LDL-c (-6.9mg/dl) compared to usual care controls).[2] Importantly, these findings have stimulated adoption of collaborative care models by health payers and managed care providers in the United States (US), advocacy by major health agencies, and similar research in other countries.[2] This integrated care model emphasizes how combined depression and medical therapies can increase each other's benefits.

The INDEPENDENT study leverages previous work in this area, merging and adapting models of integrated care delivery from the US (TEAMCare)[2] and India (CARRS Translation Trial)[13] to improve psychosocial and metabolic outcomes, respectively, among participants in India who have diabetes and poorly controlled CVD risks and are also suffering from depressive symptoms. The study builds on existing Indo-US collaborations and a robust platform of information technology (experiences of developing decision-support software), skilled teams, trial logistics expertise, and local expertise.

2.5 The INDEPENDENT Study

This study will develop and test an integrated depression and diabetes care model in four ambulatory diabetes clinics in India. Our evaluation plan will generate usable evidence regarding effectiveness, quality of life, and costs.[2]

The collaborative care intervention in this study will incorporate unique aspects of Indian culture gathered from focus group discussions and in-depth interviews with participants, family members, and health care providers at all clinic research sites. We will endeavor to make the intervention more participant-centered, develop locally-understandable educational materials for participants in India, and identify ways to overcome stigma of mental health disorders while facilitating trustful therapeutic relationships between nurse managers and the participants and their families.

Several additional benefits will emerge from this study, including: (a) identifying unrecognized depressive symptoms among several hundred diabetic patients and working with their regular providers to manage this appropriately; (b) training a cadre of care coordinators (CC) who can motivate better self-care for high-risk individuals; (c) offering a toolbox of therapeutic options (family-centered or other culturally-sensitive activation models such as spirituality, yoga, or meditation) in order to customize care according to the individual's preferences; and (d) developing software technology that prioritizes participants for review,

prompts treatment plan recommendations and modifications, and makes case review meetings efficient by providing an overview of key participant indicators in one place (the "dashboard").

3 Study Design

The study is a four site, single-blind, individually randomized controlled implementation trial. Blinding outcome assessments and randomization will limit biases and evenly distribute participant characteristics.

3.1 Study Timeline

INDEPENDENT Study						
Activities	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**
Design and Planning						
Refining intervention components						
Recruitment of care coordinators and training						
Installation of decision-support software and on-site training						
Data Collection						
Participant screening, recruitment, enrollment, randomization						
12-month intervention and 24-month follow-up of participants (Total participation = 36-months)						
Analysis						
Data analysis and reporting of outcomes						

4 Selection and Enrollment of Participants

4.1 Sample Size

The study is powered on between-arm differences in the proportion achieving the primary outcome [*combined depression and CVD risk factor improvements* (≥50% reduction in SCL-20 **and** ≥1 of: ≥0.5% reduction in HbA1c **or** ≥5mmHg reduction in SBP **or** ≥10mg/dl reduction in LDL-c)] at 24 months post-randomization. The sample size estimation is guided by: (1) studies in India [14, 15] and elsewhere [16, 17] showing that <50% of all people with diagnosed diabetes routinely achieve single or multiple CVD risk factor targets; and (2) published results by Katon [18] demonstrating a 30% between-group absolute difference [60% (TEAMCare) vs. 30% (usual care)] in proportions of subjects achieving ≥50% reduction in SCL-20 score at 12 months and 15% absolute difference [37% vs. 22%] in the proportion of subjects achieving significant reductions or target control for all three CVD risk factors [HbA1c, SBP, LDL-c]. It is anticipated that a 15% absolute difference [30% of intervention arm participants will achieve combined and sustained reductions in depressive symptoms plus ≥1 CVD risk factor at 24-months post-randomization, compared to 15% of usual care participants]. Using a two-sample test of equality of proportions and a normal approximation with a continuity correction in Stata Version 12.0., we calculated that n=268 provides 80% power, and n=335 allows additional 20% for loss to follow-up. The aim is to recruit an enhanced sample of 360 participants, assigned equally to the two arms with the goal of randomizing 120 participants across the four clinic sites.

4.2 Participant Screening

The population for this study will be Asian Indian, clinic-attending diabetes participants 35 years of age or older, with depressive symptoms (a PHQ-9 score ≥10) and at least one poorly controlled CVD risk factor (HbA1c ≥ 8.0%, SBP ≥ 140 mmHg, or LDL-c ≥ 130 mg/dl).

Project coordinators at each diabetes clinic research site will review existing electronic records or paper charts to identify participants with diabetes and one or more poorly controlled CVD risk factor (HbA1c ≥8.0%, SBP ≥140 mmHg, or LDL-c ≥130 mg/dl) in the previous six months. The coordinator will contact these participants and invite them to visit the clinic or complete the initial screening assessment by phone. During this interaction, participants will provide verbal consent, and respond to the nine-item PHQ-9 depression scale (see Appendix A) as a screener for depressive symptoms and additional questions to identify presence of other exclusion criteria (recent cardiovascular events or life-threatening cancer or kidney disease). Based on the prevalence of depression among people with diabetes and previous studies,[2] we anticipate screening 7,500 participants to recruit and randomize 400 participants.

The PHQ-9 helps ascertain presence of depression symptoms and functional impairments, and provides a gauge of depression severity (0-3 scoring for each item). The PHQ-9 is based on criteria for major depressive disorder in the Diagnostic and Statistical Manual Fourth Edition (DSM-IV) and has high sensitivity and specificity for depression symptoms.[2] This scale is an open source tool, has been translated into multiple languages,[19] and has been used extensively and successfully in our past US and India studies.[2] PHQ-9 scores ≥10 have been shown to be associated with chronicity of depression[46] and predictive of adverse outcomes (dementia, mortality).[2] Individuals with scores of 10-12 benefit from intervention as much as those with scores of 14-15.[2]

4.3 Eligibility: Inclusion and Exclusion Criteria

Individuals who are eligible after the initial screening (PHQ-9 score ≥10 indicating newly-identified with depressive symptoms and one or more poorly-controlled CVD risk factors in the previous 6 months) will have study details fully explained to them and be invited to the clinic for written informed consent and complete eligibility testing. During this final phase of screening, a detailed medical history; questionnaires to rule out psychoses, alcohol and substance use, and reduced cognitive function [e.g., dementia]; physical examination; and laboratory tests will be conducted by a blinded outcomes assessment officer (likely to be a physician or research nurse at each site). For ALL participants who screen positive for co-morbid diabetes and depression, their status will be explained to them. The consent form will include approval to notify the participant's usual care provider of this co-morbid status.

To be eligible for the study, participants must meet all of the following inclusion criteria in the final phase of screening: (1) age ≥35 years; (2) confirmed diagnosis of diabetes (documented in the charts); (3) PHQ-9 score ≥10; (4) one or more poorly-controlled CVD risk factors (HbA1c ≥8.0%, SBP ≥140 mmHg, or LDL ≥130 mg/dl) regardless of medications used; and (5) willingness to consent to randomization.

Individuals will be excluded from participation if any of the following are present: (1) a "3" is reported for the PHQ-9 questionnaire suicide item (item #9), which reflects very high suicide risk, or the evaluating physician deems that the patient is suffering severe depression requiring immediate referral; (2) currently under a psychiatrist's care or using antipsychotic or mood stabilizer medication or have diagnosed dementia or bipolar disorder or schizophrenia; (3) have diabetes secondary to uncommon causes (e.g., chronic pancreatitis); (4) are pregnant or lactating; (5) had a documented CVD event (MI, stroke) in past 12 months; (6) have end-stage renal disease (on dialysis or requiring a transplant); (7) have malignancy or life-threatening disease with death probable in 3 years; (8) currently abuse alcohol or drugs; (9) current chronic steroid use; or (10) no fixed address or contact details. Any participant reporting a "2" on the PHQ-9 suicide

item (item #9) will be given a self-harm risk assessment and if considered too high risk, the participant will be excluded from enrollment in the trial and referred for more intensive psychiatric care.

4.4 Informed Consent

Most of the participants will be literate in the local language or English (90.3% literacy in Chennai, 86.3% in Delhi, 80.5% in urban Andhra Pradesh, and 75.5% in Bangalore)[20] so the participant information sheet (PIS) and informed consent form will be available in Tamil, Hindi, Telugu, Kannada and English. For those who cannot read, study details will be explained and informed consent obtained by thumbprint signature and recording verbal consent in the presence of a friend or family member.

The information sheet and consent form will be given to the potential participant and details of both documents will be explained by the consenter (the blinded outcomes assessor), including the purpose of the trial, screening and study procedures, benefits and risks, confidentiality terms, rights of the participant, and trial contact information and any concerns or questions will be addressed. The consenter will ask questions to ensure that the potential participant understands the PIS and consent form information. The potential participant will be given as much time as needed to review the documents and will be allowed to take them home to discuss with family or friends.

Participation is purely voluntary and there will be no coercion by the consenter. Participants will not receive material compensation to join the study. All participants will be assured that they have the right to voluntarily withdraw from the study at any time and that withdrawal will not affect their future medical care. Participants will also be told that their diabetes care provider will be notified of their depressive symptoms.

If the individual agrees to participate in the trial, one copy of the signed consent form will be signed by the participant and the Lead Site Investigator. For those who cannot read, a thumbprint and proxy signature by a legally acceptable representative (LAR) will be obtained. In addition, a recording will be made of the verbal consent process. In the absence of a LAR, a literate third party (non-study staff) may act as witness. One photocopy of the signed consent form will be given to the participant to keep and another copy will be kept in locked storage at each clinic research site.

These consent procedures have been reviewed and approved by each site's ethics committee (Madras Diabetes Research Foundation [Chennai], All India Institute of Medical Sciences [Delhi], Endocrine and Diabetes Center [Visakhapatnam], Diacon Hospital [Bangalore]) as well as the institutional review board (IRB) of Emory University.

4.5 Randomization and Blinding

To prevent "contamination" (i.e., contact between care coordinators [CC] and subjects randomized to usual care), all baseline eligibility testing and six-monthly outcome assessments will be completed by an independent outcomes assessor who is blinded to the participant's trial arm assignment.[21] This blinded outcomes assessor will document findings from evaluations by entering them into the web-enhanced decision-supported electronic health record (DS-EHR) system. The software will automatically interface with an interactive web response system for computer-generated randomization. For individuals randomized to the intervention, the DS-EHR will automatically email the CC that a new participant has been assigned to the intervention, instruct the CC to contact the participant for the initiation visit, and will give the CC access to the participant's record. For control participants, the system will generate a record (not accessible by CCs), which will be updated at six-monthly evaluations by the blinded outcomes assessor (Figure 1). The system will remind the blinded outcomes assessor to contact each participant (whether control or intervention arm) when their six-monthly visit is due and provide a 10-week window of time (four weeks before and six weeks after the exact 6 months elapsing) for data to be entered regarding that visit.

As mentioned, the participant's symptoms and severity of depression, as well as the levels of control of cardio-metabolic risk factors, will be reported to their usual care provider. We will create information tools that can help usual care providers who are not familiar with management of depression. Therefore, the usual care (control) group will, in effect, receive enhanced usual care, assuming their provider proactively manages the psychological and metabolic illnesses concurrently.

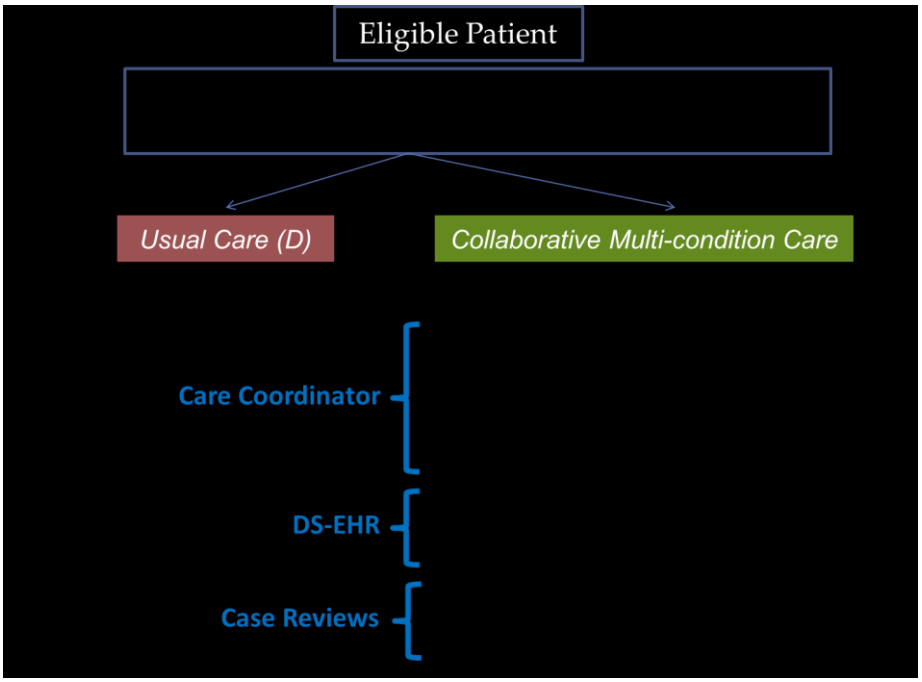


Figure 1: Usual Care vs. Intervention

5 Study Interventions

Participants randomized to the intervention will receive care coordinator-led and decision-supported care. Participants randomized to the control arm will receive the existing standard care and treatment for their diabetes that is provided routinely at each site with the exception that their care provider will be notified regarding their depressive symptoms.

5.1 Program of Care for Intervention Arm Participants

Participants randomized to the intervention will receive care coordinator-led and decision-supported care (Figure 1) comprised of: (1) behavioral activation to motivate effective self-care; (2) proactive follow-up (helping participants solve problems and adhere to medications); (3) evidence-based care prompts that modify therapy responsively; and (4) team-based reviews to check treatment adjustments and ensure accountability (Table 1). This integrated multi-condition care model is focused on improving patient self-care and facilitating better monitoring and treatment intensification by provider care teams. Each of the components described is a part of the participant's continued progress reviews and follow up (Figure 2).

Table 1: Components of Integrated Depression and Diabetes Care

Activation of participants	*GOAL = stimulate self-care* Meet to identify measurable goals Collaborate with participant's family to problem-solve
Care Coordinator-led coordination	*GOAL = support self-care* Proactive and individualized follow-up Empower and motivate adherence
Web-enhanced decision-support software	*GOAL = support clinical decision-making* Track participant health indicators Prioritize participants (new, poorly-controlled) for review Prompt intensification of medication regimens
Multi-disciplinary team treat-to-goal reviews	*GOAL = enhance care continuity and accountability* Active monitoring of PHQ-9, HbA1c, SBP, LDL-c Responsive adjustments of medication regimens based on software prompts and clinical judgment

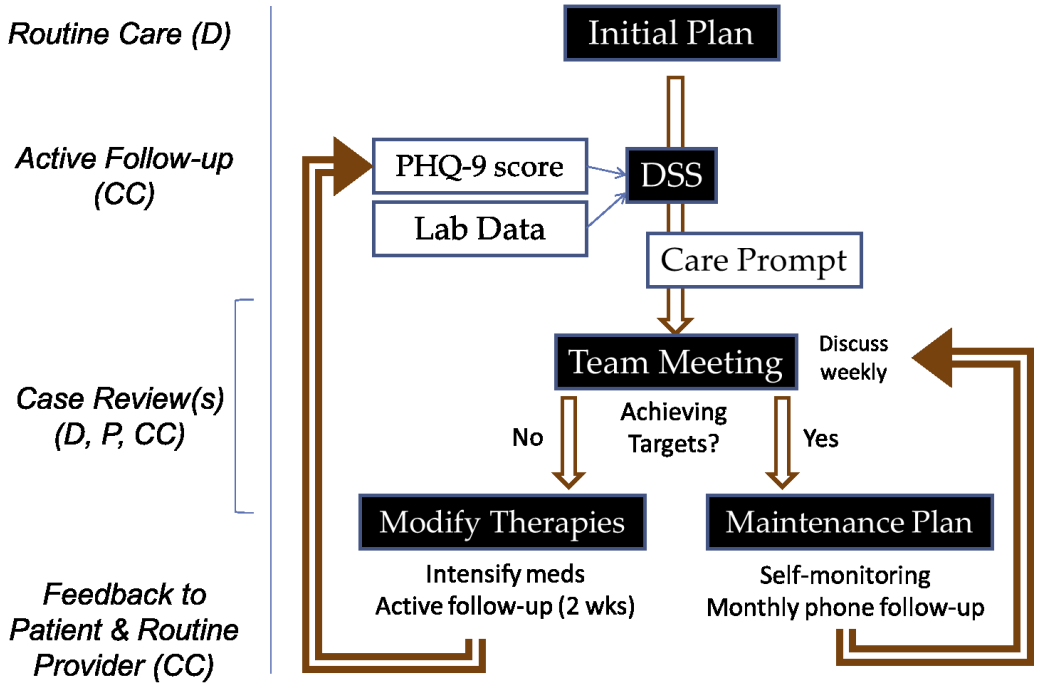
Better Self-care: Participant Education and Behavioral Activation –Participant education materials and behavioral activation techniques that are adapted for the Indian population will be used to stimulate and motivate sustained and effective self-care. Behavioral activation strategies are brief, structured psychological interventions that are based on extensive theoretical[2] and clinical literature [2], can be delivered by non-specialist providers, can be combined with antidepressant medications, and emphasize reinforcing behaviors to produce improvements in thoughts, mood, and quality of life.[22]

Supporting Self-Care: Proactive Follow-up by Care Coordinators (CC) – We will train two or more Care Coordinators at each of the diabetes clinic research sites in enhanced depression-diabetes care (INDEPENDENT care). Individuals eligible to perform the tasks of the CC will be educators, social workers, nutritionists, psychologists, or lay health workers who have good communication, motivation, and organizational skills. The CC will complete training and certification in multi-condition care (led by the University of Washington team):

- General instruction regarding all aspects of the intervention
- Refresher courses in follow-up and management of high-risk diabetes
- Specific instruction (didactic and role play) in behavioral activation and motivational and brief negotiation strategies
- Practicing cases under observation

Once trained, CCs will: (a) meet with intervention arm participants and collaboratively set treatment goals; (b) provide verbal education regarding diabetes and depression self-care (self-monitoring; adherence to medication, diet, exercise; and cessation of smoking); (c) use motivational interviewing (therapeutic approach designed to help individuals explore and resolve ambivalence and foster commitment to behavior changes in a non-confrontational manner) and self-efficacy enhancement strategies (e.g., structured feedback) to promote monitoring of depressive symptoms, glucose, and blood pressure; (d) proactively follow-up participants (phone calls or clinic visits) to externally monitor depressive symptoms (regular PHQ-9's) and CVD indicators (laboratory and home monitoring); (e) enter updated participant indicators into the DS-EHR (as "interim visits") and utilize software outputs to prioritize participants for review; (g) convene case review meetings with supervising physicians; (h) communicate physician-recommended treatment changes to participants and their usual care providers; and (i) update the DS-EHR based on whether the case review meeting agreed with the physician and software system's care prompt or not, and provide a reason. CCs will attend re-training meetings on behavioral activation, motivational interviewing, and brief negotiation strategies with members of the study team on an as-needed basis.

Oversight by Psychiatrist and Diabetologist Reviews – At each site, a senior psychiatrist and endocrinologist/diabetologist will be involved in weekly or bi-weekly offline (participants do not attend) case review meetings with CCs (Figure 2). Case review meetings will be structured and involve discussion of all participants. The DS-EHR "dashboard" of participant indicators will help identify participants whose depression, glucose, BP, or lipid levels remain poorly controlled (for example, elevated PHQ-9 scores 6 weeks or more after most recent treatment changes, or continued poor HbA1c, glucose, BP, or LDL-c control in past 4 weeks). Using the most recent indicators in the DS-EHR "dashboard" and current therapies, the DS-EHR will provide care plan prompts (based on evidence-based algorithms developed by senior physicians in our team) to usual care physicians when the CC and participant visit the usual care physician. The recommended treatment changes (initiation, increases, or simplification of medication regimens, or higher or lower frequency of follow-up or behavioral therapy) can be accepted or modified by the usual care physician. The usual care physician's care plan will be communicated to participants by the CC. Within 14 days of this, the care prompt and the physician's treatment plan will be reviewed at the weekly or bi-weekly case review meeting and a recommendation will be made as to whether to continue with or modify treatment. If the case review team recommends modifying the treatment the CC will communicate this to the usual care physician who has the ability to accept or modify the care plan. Any change in the care plan will be communicated by CCs to participants. It is the responsibility of the participant to obtain new medications if necessary.



Abbreviations: DSS=decision support system; D=diabetologist; CC=care coordinator; P=psychiatrist

Figure 2: Intervention Arm Participant Flow

Supporting Case Reviews and Treatment Intensification: decision-support electronic health record (DS-EHR) –The DS-EHR will store participant indicators, produce reporting "dashboards" to monitor single participants and whole clinic populations, and provide care prompts based on an evidence-based treatment algorithm. The DS-EHR has: (1) a summary dashboard (updated PHQ-9, HbA1c, FBG, LDL-c, SBP, and DBP on a single screen) to monitor participants' progress; (2) depression care and diabetes care prompts derived from algorithms based on recommended guidelines, Indian formularies, and help from the research study investigators; (3) functionality that permits checking single participant and clinic-level

indicators for case review meetings; (4) processes that promote accountability (physicians must justify rejecting electronic care prompts); (5) accountability by case review members of whether care prompts were appropriate and why or why not; and (6) separate access controls for CCs and outcomes assessors at each clinic to ensure outcomes assessors are blinded to the participants' intervention status.

5.2 Intervention Visits

Initial visit: CCs will schedule a consultation with every intervention arm participant and use a semi-structured interview to: explain CC roles; build rapport; get a detailed history of depression, diabetes, current and prior treatments; assess barriers to care; set measurable goals with participants; and provide educational materials. The CC will introduce behavioral activation[2] to engage participants regarding their self-care. For example, they might discuss self-management behaviors (e.g., increased physical activity), graded behavioral goals to promote self-efficacy, mood improvements, and better CVD risk factor control. CCs will encourage participants to adopt responsibility for intermittently monitoring BP and glucose (where very poorly controlled, clinics will provide glucometers and/or home BP cuffs).

At follow-up ("interim") visits (which may be in-person or over the phone), CCs (Figure 2) will add guided activities, self-monitoring using activity and mood rating records which help participants make the connection between behaviors and changes in mood; "booster" sessions (delivered by telephone, participants are trained in how to maintain self-care behaviors and recognize medical illness as a stressor). Table 2 shows an example follow-up schedule. Frequency of participant contact will depend on individual risk. Any of these interim visits, data collected from participants in the form of completed PHQ-9 scores, or blood glucose, BP, or lipid levels will be entered into the DS-EHR, which will update the participants' record.

Table 2: Care Program: Schedule of Follow-ups for Intervention Arm Participants

Week	Medication Intervention	Behavioral Intervention	Community Linkage
0	Baseline Interview and randomization		
1	Initial visit with CC and family; evaluation of control, medications, and adherence.	CC provides rationale for behavioral activation; introduces activity monitoring.	
2	Follow-up visit with CC after physician reviews (for new or modification of existing prescriptions).	CC helps participant prioritize self-care goals/behaviors; 1st behavioral experiment	CC facilitates linkages to community resources (e.g., counseling, rehabilitation, or behavior change programs).
3-7	Follow-up visits with CC (in-person or telephone): review of PHQ-9, CVD risk factor control, and adherence.	Review of behavioral activation progress. Continued motivational enhancement and behavioral activation (guided activity).	
8	Follow-up visit with diabetes physician – *If depressive symptoms or poor control persists*, more intensive psychotherapies or doses.	Review of behavioral activation progress. Continued motivational enhancement and behavioral activation (guided activity).	Scheduled follow-up CC telephone calls.
10-16	As needed follow-up visits with CC (in-person or phone): review of control and adherence.	Review of behavioral activation progress. Continued motivation; behavioral activation.	
25-52	Monthly tailored follow-up (in-person or phone): support maintenance / relapse prevention.	Individual booster behavioral activation sessions.	

Each intervention participant will be enrolled in the integrated depression and diabetes care program (proactive follow-up and case reviews) for 12 months. All participants (intervention and control) will undergo outcomes assessments for months 0-36 (visits at 0, 6, 12, 18, 24 and 36 months following randomization). The focus of the 13-36 month assessments is to evaluate if effects of the intervention are sustained.

5.3 Program of Care for Control Arm Participants

Participants randomized to the control arm will receive the existing standard care and treatment for their diabetes that is provided routinely at each site and their care provider will be notified regarding their depressive symptoms. As mentioned in Section 6.2, the physicians treating the control arm will also be provided with trainings regarding identification and care for people with depression. The control participants will have no contact with CCs and will only be contacted at 6-monthly intervals for assessment by the blinded outcomes assessor.

6 Study Procedures and Measures

Participants in both arms will be invited for outcomes assessments ("study visits" at 0, 6, 12, 18, 24 and 36 month time-points) by a blinded outcomes assessor at each site to collect biochemical and participant-reported measures (Table 4). Biochemical measures (glucose, HbA1c, cholesterol subfractions) will be collected via blood draws while BP and anthropometric measures will be collected using an automated sphygmomanometer, weighing scale, tape measure, and clinic-based stadiometers. Participant-reported outcomes will be collected via questionnaires.

Although the PHQ-9 will be used to identify and efficiently monitor depressive symptoms and severity, regular use of the PHQ-9 leads to test-retest bias. As a result, we will use the Symptoms Checklist (SCL-20) depression scale as our main depression outcome measure.[23] This tool is very sensitive to changes in depression among people with diabetes and will be used for baseline, 6-monthly and 36 month measures only. It has also been used successfully in prior studies.[2] The PHQ-9 will still be administered at the 6-monthly study visits.

Data regarding health utilization, costs, and quality of care will be collected through clinic chart reviews and questionnaires. We will collect data on self-reported direct medical costs (inpatient, outpatient, prescription medication, and diagnostic services), and pharmacy use plus clinic administrative records to identify unit costs. Since out-of-pocket health expenditures predominate in India, we will also use questionnaires developed for previous studies in India.[24] The questionnaire will capture direct non-medical (participant time spent traveling to and attending appointments) and indirect costs (lost productivity associated with illness or premature mortality). Data regarding patient-centered outcomes such as treatment satisfaction, quality of life and utility (reflects participants' judgments regarding different health states on a continuum from 0.0 [representing death] to 1.0 [perfect health]) will be collected using the instruments described in Table 3.

All data will be labeled with unique participant identifying numbers that cannot be discerned without access to the coding sheet and are meaningless to study staff and lay persons.

Table 3: Study Procedures and Measures for All Participants

Variable and Tool	Method
Demographic and Anthropometric	
Age / Sex / Marital Status / Education / Occupation / Income / Migration	Q
Height / Weight / Body Mass Index / Waist Circumference	E
Depressive symptoms	
SCL-20 depression scale; PHQ-9 (Patient Health Questionnaire)	Q
Other Psychiatric Conditions	
GAD-7 (anxiety); MoCA (cognitive function); AUDIT-10 (alcohol use); DAST-10 (substance abuse)	Q
Risk Factor Control	
Glycated Hemoglobin (HbA_1c)	B
Blood Pressure (BP)	E
Venous Fasting Lipid panel (HDL- and LDL-cholesterol, Triglycerides)	B
Tobacco Use	Q
Incidence of Complications	
Hospitalization / ER visits / Revascularization / Surgery / Dialysis	Q
Self-efficacy	
Summary of Diabetes Self-Care Activities (SDSCA)[25]	Q
Quality of Life / Utility / Satisfaction	
Health Utilities Index (HUI-3)	Q
Diabetes Treatment Satisfaction Questionnaire	Q
Costs and Quality of Care	
Costs of Care (direct, indirect costs); Health Utilization; Unit Costs	Q; R
Processes of Care (e.g., annual eye exams)	Q; R

Q = Questionnaire; E = Examination; B = Blood test; R = Records.

6.1 Schedule of Evaluations

VISIT 1–PHQ-9 Screening; Eligibility Screening and Baseline Randomization; 6-monthly Visits for All

Table 4: Schedule of Evaluations

PHASE	Screening	Eligibility testing & baseline (0 month study visit)	Intermediate visits (Intervention Grp)	6-monthly study visits	Sustained effectiveness visits
MONTH	Max -4 weeks	-4 to 0 weeks		6, 12, 18	24 and 36 month visits
Verbal consent	X	X			
Signed informed consent		X			
PHQ-9	X	X	X	X	X
SCL-20		X		X	X
Assess Eligibility + Enrollment	X	X			
Demographics (age, sex, socioeconomic status)		X			
Medical history	X (basic)	X (full)	X (interval)	X (interval)	X (interval)
Family history		X			
Social History (lifestyle/habits)		X	As needed	X	X
Questions regarding Bipolar Disease / Psychosis		X		X	X
Anxiety (GAD-7)		X		X	X
Alcohol use (AUDIT-10) and drug use (DAST-10)		X			X
Cognitive function (MoCA)		X			X
Self-care (SDSCA)		X		X (partial)	X
Quality of Life(HUI-3)		X			X
Diabetes Treatment Satisfaction (DTSQ)		X			X
Costs of Care (records, questionnaire)		X			X
[*]Acceptability: physician interviews		Likely			Likely
Blood pressure (BP) and heart rate	X	X	As needed	X	X
Height, Weight, BMI (calculated), Waist Circumference		X	As needed	X	X
General Physical Examination		X	As needed	X	X
Eye Examination		X	As needed	As needed	X
Foot Examination		X	As needed	As needed	X
ECG		X	As needed	As needed	X
Urine Microalbuminuria		X			X
Albumin:creatinine ratio (urine analysis)		X			X
[†]Serum Creatinine Serum Sodium, Potassium and ALT		X	As needed		X
Venous fasting blood glucose (FBG)		X	As needed	X	X
Glycated hemoglobin A1c		X	As needed	X	X
Lipids (TC, HDL, LDL [calculated], TG)		X	As needed	X	X
Glucose-lowering, blood-pressure lowering, and cholesterol-lowering medications		X	As needed	X	X
Other concomitant medications		X	As needed	X	X
Tobacco use		X	As needed	X	X
AE/ SAE Intake (ongoing)			X	X	X

[*]Qualitative interviews of physician sub-samples will be administered by Coordinating Center staff.
[†]Follow-up serum potassium and creatinine levels if high and started on ACE-i; follow-up ALT if started on statin.

6.2 Evaluation Schedule

The first visit is for participant screening and the second visit for confirming eligibility and documenting baseline status. Randomization will be computer-generated and CCs at each site will be notified of participants who are assigned to the intervention arm only. The CCs will then contact the intervention participants and schedule their initial and subsequent intervention visits directly with participants. Reviews by the team (diabetologist, psychiatrist, and CC) will happen weekly and the intensity of discussion on each participant will depend on CC and DS-EHR prompts and needs of the participants (well-controlled participants will require minimal discussion, while poorly-controlled participants may require more intensive discussion).

For the **intervention arm:** The CC will motivate and monitor participants' progress. The CC will update the participant's medications and labs plus PHQ-9 values in the DS-EHR and will provide a dashboard printout of participants' progress and suggested treatment plans and/or modifications for physicians to review at every case review meeting. The **usual care physician** will assess the participant and accept or modify the prompt (providing a reason if he/she chooses to modify the prompt). The case of this same participant will then be discussed, along with all other participants at the site weekly or bi-weekly case review meeting and the case review team will continue with or recommend modifications to the physician's and DS-EHR's care plan for the patient. If the case review team recommends modifications to the care plan these will be accepted or modified in a final review step by the usual care physician. The CC will update the participant and the DS-EHR system; address any barriers to care and motivate him/her to achieve risk factor management goals and confirm the next appointment dates. The CC will continue to facilitate the participant's adherence to appointments and self-management using DS-EHR reminders and phone calls.

For ALL participants: The blinded outcomes assessor at each site will independently contact all participants (intervention and control) to schedule post-randomization visits for study assessments. All other intermediate visits by the participants will be documented as they routinely are in participant's clinical case notes.

For all randomized participants, the post-randomization follow-up period will be 36 months. The study staff at each site involved in executing the study procedures includes:

- **Lead Site Investigator/Co-investigator/Sub-investigator:**
    - Site PI: Oversee all trial-related procedures (recruitment, screening, enrollment, randomization, and follow-up of participants for medical evaluation)
    - Co-investigator or coordinator to support recruitment and retention activities
- **Blinded Outcomes Assessor:**
    - **Screening and Outcomes Assessments**: a research physician or nurse that will perform screening evaluations, baseline and six-monthly history and physical examination and enters data into DS-EHR system, which randomizes participants into trial arms.
- **Care Coordinator:**
    - Motivates intervention participants to self-manage and self-monitor their conditions;
    - Monitors intervention participants and enters PHQ-9 and blood testing (glucose, HbA1c, BP, and cholesterol levels) data from clinic report forms regularly into DS-EHR and follows prompts regarding case reviews
    - Coordinates with diabetologist and psychiatrist to conduct case review meetings for intervention participants on a weekly or bi-weekly basis

- Supplies the intervention participants' management plans (generated from the DS-EHR) to study physicians at case review meetings
- Conveys any treatment plan changes to intervention participants and continues monitoring until 36 months post-randomization

- **Usual Care Physicians (diabetes or primary care physicians at each site):**
  - Routine care for participants, whether control or intervention arm
  - Attend continued education training on managing diabetes and depression
  - For intervention participants, assess output prompts from DS-EHR system and accept or reject implementation of this care plan, providing reasons for any rejection
- **Case Review Specialists (psychiatrist and diabetologist at each site):**
  - Discuss all participants' cases in the intervention arm on a weekly or bi-weekly basis
  - Recommend treatment maintenance or changes based on the outputs of the DS-EHR and clinical judgment

6.2.1 Screening (Pre-randomization)

Based on clinic records, any eligible subjects (those with poorly controlled HbA1c, BP, or lipids within the previous six months and no other obvious exclusion criteria) will be contacted for depression screening. Screening with PHQ-9 (maximum of 4 weeks before randomizing) for all potential participants will be conducted in-person or via the phone. Eligible participants from the first screening visit will be advanced to a more detailed screening visit. The second screening visit is the first time participants are required to present at the clinic.

Screening Visit 1

Potentially eligible participants will interact with a site screening officer via in-person or phone visit. The visit will include:

- Verbal consent to screen and also to notify participant's usual care provider if he/she is found to have co-morbid depression and diabetes
- Collecting contact information
- Assessing basic medical history (general Inclusion/Exclusion Criteria items)
- PHQ-9 assessment

The participants who do not meet eligibility criteria for the trial will be notified of their status. The participants who are still eligible for the study after this 1st visit will be asked to present fasting (minimum of 8 hours) for detailed screening visit (including laboratory tests and questionnaires).

Screening Visit 2 – detailed assessment (by blinded outcomes assessor)

Within 4 weeks after Screening Visit 1 (PHQ-9), the participant will be invited to present to the clinic in a fasting state for informed consent (by the site investigator or a co-investigator) and detailed screening and baseline visit (please see Table 44):

- Urine sample for urine albumin:creatinine ratio

- Blood sample for measurement of Hemoglobin A1c and blood chemistries (serum creatinine, sodium, potassium, and ALT) to determine if existing medical conditions would exclude an individual from participating in the study
- Baseline Symptoms Checklist (SCL-20) depression questionnaire
- Questionnaires to exclude other psychiatric illnesses (e.g., bipolar disorder, psychosis, reduced cognitive function)
- Fasting venous blood sample for glucose and lipids (triglycerides, total cholesterol, HDL cholesterol, and LDL [calculated])
- Blood pressure and heart rate
- Height, weight, BMI (calculated), waist circumference
- Data will be entered into DS-EHR for randomization

Those potential participants who do not meet eligibility criteria will be notified of their status at the clinic and will not undergo further testing. Those individuals still meeting the inclusion/exclusion criteria will be told that they will either be contacted by a CC if assigned to intervention arm or to continue visiting the clinic as guided by their usual care physicians.

For all participants, the outcomes assessor will:

- Complete **data entry for each participant into the DS-EHR**, which includes medical and family history, medications, and mental health evaluations.

6.2.2 Follow-up Study Visits (0, 6, 12, 18, 24, and 36 months post-randomization)

All participants (intervention and control) will be invited to present for the 6-monthly follow-up visits. All participants will have to obtain all investigations: venous FBG, HbA1c, lipid profile, serum creatinine, and other blood biochemistries if necessary, SCL-20, and any complication screenings deemed necessary (urine albumin:creatinine ratio, eye exam, and ECG) prior to the visit. All participants will be required to present the lab results at the visit, if the site does not have a system in place to obtain the laboratory results independently. Participants will be contacted by a study coordinator or the outcomes assessor and scheduled for a full assessment and blood draws.

The outcomes assessor will obtain the following data from the participants:

- Interval history, hypoglycemic events, any adverse events or serious adverse events, other complications developing or changes experienced
- Measures: Blood pressure and heart rate, height, weight, BMI (calculated), waist circumference
- Investigations: values from lab reports; reports of ECG, eye and/or foot exams
- Social/lifestyle habits and questionnaires: self-care (SDSCA), health utilities (HUI-3), diabetes treatment satisfaction (DTSQ), and frequency/costs of care
- SCL-20 and PHQ-9 depression questionnaires
- GAD-7 anxiety questionnaire
- Questionnaires to exclude other psychiatric illnesses (e.g., bipolar disorder, psychosis, reduced cognitive function)

Scheduling:

Follow-up of participants after they have stopped participation in the intervention will be conducted and will include monitoring and reporting any adverse experiences or outcomes. Potential reasons for early termination of study participation can be found in Section 9.7: Non-Compliance

Non-compliance is the failure to follow national, state, or local regulations governing human subject research, institutional policies related to human subject research, or the requirements or determinations of the IRB. This may pertain to the principal investigator, research staff, or any member or component of the human research protection program.
Examples of non-compliance:

- Performing human subject research without first obtaining ethics committee approval or an ethics committee declaration of exemption
- Deviating from or violating the provisions of an ethics committee-approved protocol
- Failing to secure ethics committee approval of a protocol due for periodic continuing review prior to its expiration date
- Permitting a protocol's ethics committee approval to lapse without stopping all research-related activities and submitting a closing progress report to the ethics committee, or in the event of an overriding safety concern or ethical issue such that it would be in the individual subject's best interest to continue study participation, not arranging with the ethics committee to continue those activities

6.2.3 Serious Non-compliance

Serious non-compliance is non-compliance that creates an increase in risks to subjects, adversely affects the rights, welfare and safety of the research subjects or adversely affects the scientific integrity of the study. Willful violation of policies and/or federal regulations may also constitute serious non-compliance.

6.2.4 Continuing Non-compliance

Continuing non-compliance is a pattern of non-compliance that if allowed to continue is likely to increase risk to subjects, adversely affect the rights, welfare and safety of research subjects, or adversely affect the scientific integrity of the study.

6.2.5 Reporting of Serious Non-compliance

Serious non-compliance should be reported to the Research Coordinating Centre and the local, site-specific ethics committee within 5 business days of event occurrence, or from when the Site Principal Investigator first learned about the event. The MDRF and Emory ethics committees should be notified by the Research Coordinating Centre within 10 business days of event occurrence, or from when the Site Principal Investigator first learned about the event. Serious non-compliance that results in increased risks to subjects will be promptly reported to NIMH.

Criteria for Discontinuation.

7 Study Participant Risk, Privacy and Burden

All participants will be approached at each data collection time-point, unless they voluntarily withdraw from the studies. All data collection tools will be well established, including validated questionnaires in local languages or English, clinical interview, and clinical assessment techniques. The collection of biological samples is minimally invasive and minimally painful. Data collection will be conducted in non-threatening settings by trained professional clinical staff (either physicians or research nurses) at participating diabetes clinics where these participants routinely access care. All questionnaire, examination, and laboratory data will be entered in each participant's unique electronic health record (the DS-EHR) that can only be accessed by the outcomes assessor, the CC, and/or the trial

Coordinating Center (each of whom have unique logins permitting different levels of access to data). For data analysis, all participant identifiers will be removed when datasets are compiled.

7.1 Expected Risks for Participants

The potential risks from involvement in this trial are considered to be minimal. No invasive procedures will be performed, except for collection of venous and capillary blood samples (which are minimally-invasive procedures). However, there is a risk of bruising or discomfort with blood draws and, very rarely, the procedure can result in inflammation or infection of the arm veins. For all data collection, trial participants will be provided with in-clinic facilities that afford appropriate privacy and hygiene. Appropriate precautions will be taken to avoid inflicting harm or risk to participants. It is also unlikely, although possible, that trial questionnaires may cause distress to the participant. Risks are considered minimal, and participants will be informed of all possible risks in the consent form. If the participant deems the risks too large, he or she may refuse to take part in the study or withdraw at any time.

Adverse events and serious adverse events will be monitored. Further details are available in Section 9.4: Adverse Events and Serious Adverse Events.

7.1.1 Measures to Minimize Risk

Appropriate precautions will be taken to avoid harming the well-being of participants. Any potential adverse effects will be monitored and reported by the study investigators immediately to the relevant clinic research site ethics committees, the Madras Diabetes Research Foundation Institutional Ethics Committee (IEC), and Emory University Institutional Review Boards (IRB) for appropriate action.

Even though the potential for injury to research subjects due to the risks of the proposed procedures is judged to be minimal, all reasonable efforts will be made to minimize these risks through the exclusive use of properly trained and educated research personnel. Individuals who are injured by study procedures will be informed of their rights to and be offered treatment of the injury as part of the informed consent procedure and the prevailing local health policy. Specifically:

- Participants will be informed of their right to refuse to answer any survey question that makes them uncomfortable.
- Any undiagnosed disease or condition or abnormal test results that present during study testing will be brought to the attention of the Site Lead Investigator and the participant.
- The participant will be referred for emergency care for emergencies or to their personal physician or a community hospital or clinic (if he or she does not have a personal physician) for non-emergencies.
- Where mild injury / discomfort is caused to the participant, e.g. vasovagal attacks, needle-stick injury, etc., appropriate procedures will be followed to attend to this by study and medical staff
- The study will have trial insurance to cover any major injuries or discomfort encountered by participants if the harm is judged to be attributable to study procedures

Suicide/Self-Harm Risk:

We have established a suicide protocol that is specific to each clinic research site. Potential participants who indicate a high risk of suicide (a “3” on the PHQ-9 suicide item [#9]) at the screening visit will not be eligible for the study and will be immediately referred for intensive psychiatric care. Individuals scoring a “2” on the PHQ-9 suicide item at the screening visit will be administered a self-harm risk assessment. Potential participants assessed to be at high risk for self-harm will be immediately referred for intensive psychiatric care and will not be eligible for the study. Potential participants assessed to have a low risk for self-harm will be eligible to be enrolled in the study. Study participants

who score a 3 on the PHQ-9 suicide item during the study will be similarly referred for care. During the study, those reporting a 2 on the suicide item will be treated and followed intensively, in accordance with the suicide protocol. If there is heightened concern by the study team, the participant may be removed from the study into specialist care.

We will provide two continuing medical education presentations on recognition of depressive symptoms, treatment approaches, and particularly, recognition of severe depression (e.g., suicidal risk) so that all physicians and nursing staff at each site can be attentive to these occurring in both intervention and usual care participants. Assessment tools (PHQ-9 and SCL-20) will be used by study personnel to determine the risk of participant self-harm and study personnel will be trained, and given refresher courses every 6 months, in procedures to handle emergencies of this sort. Study personnel and site physicians will always be able to contact psychiatry specialists from our study team in emergencies: Dr. Radha Shankar (Chennai), Dr. Rajesh Sagar (Delhi), Dr. Bodepudi Sarath (Visakhapatnam) and Dr. Pooja Rai K. (Bangalore). In addition, each site has identified mental health providers who are skilled at managing severe forms of depression. Participants will be referred to them in an emergency.

Usual Care Participants: Study protocols regarding management of risk will apply to both intervention and usual care arm participants. All participants assigned to usual care will *be notified of their elevated depression scores and abnormal CVD risk indicators by the screening investigator, who will also obtain verbal consent to contact the participant's usual care provider*. We will convey the participant's symptoms and severity of depression as well as the levels of control of cardio-metabolic risk factors to his/her usual care provider. We will create information tools that can help usual care providers who are not familiar with management of depression. As such, the usual care group will really receive enhanced usual care. Mental health services will not be withheld from usual care participants who happen to seek additional psychological or pharmaceutical therapies for their condition. Providers will not be prevented from referring usual care participants to mental health or alternative therapy providers.

7.2 Protection of Participant Privacy

We will utilize the following additional protections:

a) Validated and previously approved protocols and instruments will be adapted to suit the research plans and context, and will be internally and externally reviewed (by appropriate IRBs). Our experienced local India investigators will additionally provide critical appraisal of all study tools to ensure cultural sensitivity regarding privacy prior to use.

b) All interventionists (CC) and study personnel will be trained in procedures to minimize the potential for breaches of confidentiality, including but not limited to ensuring that all files are closed, that interviews are conducted in private settings, and that no conversations about individual study participants occur in public settings.

c) Names and other easily recognizable identifiers will be removed from all questionnaires prior to data entry and will not be included in any electronic databases. Numeric study identifiers will be included so that data from the several instruments may be linked; however, these will not be meaningful to anyone not having access to the original study logs. All data files will be maintained under password protection at all times, at each participating site and at the Coordinating Center.

    1) As the intervention is delivered in a personal, one-to-one manner, CCs will interact with participants by name, and may even review cases with the remainder of the case review team using the participant's name. Also, logs or information collected for the interim care (between outcomes assessment visits) of intervention participants will be kept separate and only accessible by CCs – any data accessible to the research team will be de-identified.

d) Based on previous collaborative studies in India in how to maintain confidentiality of study data, this study too will employ password-protection for computer data files, and locked file cabinets in restricted-access buildings (at each participating clinic and at the Coordinating Center at MDRF) for storage of hard copies of interview questionnaires and other study materials. An additional off-site server for data back-up will also be secured in a restricted access building. Regular data back-up schedules and appropriate server security procedures (to ward off unauthorized data retrieval attempts) will be instituted.

e) The Health Information Portability and Accountability Act (HIPAA) privacy and security regulations are a part of US law and do not apply to India. However, we will still make every effort to uphold participant privacy by ensuring that study staff at each location will only have access to the data that is relevant to their roles. Each of the roles (CC, outcomes assessor) will have unique access to the DS-EHR, whereby certain functions are limited (e.g., the Coordinating Center team has 'full administrative rights' status, while CCs cannot view data collected by outcomes assessors for the 6-monthly visits). If data are entered incorrectly and submitted by CCs, they can contact the Coordinating Center team to modify the data. All study-related computers will be in access-controlled settings and are password-protected. Identification information will be stored separately from all assessment data. Data will be audited on an ongoing basis to ensure confidentiality safeguards and data integrity are maintained.

f) Analysis of data and publication of manuscripts will be limited to aggregate data such that identification of individuals will be impossible.

7.3 Participant Burden

The initial screening questionnaire will require 5 minutes of explanation and opportunity for questions and 10 minutes to complete the PHQ-9 questionnaire, while the travel time to the clinic will vary by distance to the clinic. The more detailed screening assessment to identify reasons that would make a participant ineligible will take approximately 60 minutes to complete. This baseline assessment visit requires traveling to the clinic and undergoing detailed explanation and documentation of informed consent, detailed medical history, clinical examination, anthropometric measurements, and collection of biochemical specimens. All participants enrolled in the trial (whether enrolled in the intervention arm or usual care arm) will also be requested to return to the clinic for follow-up assessments at 6, 12, 18, 24 and 36 months and unscheduled visits are recommended if the participants are not well or it is deemed necessary by the usual care physicians or the case review specialists (these "interim" visits will be shorter than the baseline visit and will be completed by the CC for intervention arm participants and the usual care physician for control participants – documentation in the DS-EHR is required for intervention arm participants, but not control arm participants). At full six-monthly visits, the outcomes assessor will administer detailed questionnaires regarding medical history, self-care activities, depressive symptoms, quality of life, satisfaction, and costs of care, in addition to clinical examination and biochemical measures collected at the clinic laboratory (Table 4). Each visit will require travel to the clinic and approximately 30 minutes to complete questionnaires and 15 minutes to complete the laboratory sample collection. The study will pay all costs associated with these 5 visits (0 (baseline) plus 6, 12, 18, 24 and 36 month time-points) for all participants (intervention arm and usual care), including consultation fee for nurses and research staff, and all measurement tools and laboratory costs. Participants will be provided with 200 rupees to cover their travel and refreshment expenses per visit.

Participants randomized to the usual care group will have no additional direct contact with the study staff. The routine care providers of usual care participants will be provided with written guidance on how to manage depressive symptoms and provide the most updated evidence-based guidelines for care of diabetes and CVD (e.g., American Diabetes Association guidelines). As such, the usual care providers may request usual care participants to visit the clinic more frequently or may intensify treatments. We will assess these changes at outcomes assessment visits.

Participants randomized to the intervention group will have additional visits and follow-up with the CC interventionist. These "interim" visits will involve an initial visit and at least 4 visits over the course of the 12-month active intervention. There may also be more visits and more phone contact, lasting from 10 minutes for brief progress checks to more detailed 60-minute visits to use behavioral activation or motivational interviewing techniques to encourage better self-care. Participants will not be compensated for these visits and phone calls. If additional tests or changes to treatment plans are required based on guidance from the DS-EHR, the usual care physician, or our case review team, the costs for these intermediary tests or treatment adjustments will be borne by participants as this is an implementation trial. As mentioned, all study-related outcome assessment visit costs (the six-monthly "study visits") are borne by the study team.

Throughout the screening and study process, potential participants will be treated with respect and reassured that they have the right to withdraw from the screening process or the study at any time without any consequence for their usual care. All clinic interactions and activities will be conducted in a private room and the in the preferred language(s) of the local regions to assure participants' comfort.

8 Study Benefits

The intervention is a preventive health study that is helping implement existing, evidence-based guidelines for diabetes and depression care. The control group will follow the existing usual care provided by their Routine Care Physicians at each clinic research site, while the intervention is designed to improve quality of care delivery (better control of depressive symptoms and CVD risk factors via regular examination of lab and PHQ-9 parameters and implementing responsive therapies suggested by a "smart" software technology and overseen by Specialist Case Review Physicians).

8.1 Potential Benefits of Participation

All participants in this implementation trial (whether in the intervention or the usual group) will benefit from greater awareness of their depressive symptoms and individual CVD risk, provision of evidence-based self-management guidelines, 6-monthly biochemical and preventive) investigations at no cost to the individual concerned, and potentially superior continuity of care where all participant health information is recorded by an electronic system. In addition, participants randomized to the intervention group will receive structured and customized multi-condition care led by a CC with support from a physician case review team, individualized attention and follow-up, and motivation for better lifestyle choices and treatment adherence. It has been shown that this model of care is associated with better health and participant-reported outcomes (e.g., quality of life, patient satisfaction). Participants randomized to the usual care arm may also benefit, as all physicians at the four recruiting clinics will have the benefit of CME courses in recognition and treatment of depression and raised awareness of all clinic staff to better control glycemia, blood pressure, and lipids. We will also provide updated guidelines for treating depression and CVD risk to all physicians at the clinics. Whether or not subjects experience therapeutic benefit in the study, all participants have the opportunity to express their satisfaction or opinions about medical and mental health services received. Overall, the study itself may have important implications for models of improving mental health disorder detection and care as well as better care of CVD risk factors.

8.1.1 Importance of Knowledge to be Gained

We anticipate that the benefits of an integrated multi-condition depression and diabetes control implementation trial are extensive. Individualized care of these participants may infrequently uncover previously unknown health problems that, with treatment, will result in better future health for participants. This study aims to fill deficiencies in knowledge regarding delivery of depression and diabetes care in India. Other collateral benefits include greater awareness of depression, risk factor control, environmental and behavioral risk factors, quality of care, and creating

a stimulus for auditing and more in-depth health services research, increasing awareness of quality of care among the region's physician community.

Enhancing the roles and skills of diabetes educators or nutritionists that are trained to be CC's will strengthen local health-services capacity. Trained CCs offer a cadre of health workers that fill an existing void in co-morbid disease control. If successful, the training tools from the study can help Public Health Foundation of India develop a program that builds human resources capacity for India's national mental health and CVD control programs.

Other tools [updated evidence-based guidelines and already-tested software (incorporating easy-to-use dashboards of participant indicators; risk stratification; decision prompts)] developed for this study may be adaptable for use in other low and middle income countries. Cost-utility analyses and user-friendly data regarding human and financial resources required to implement this intervention may motivate health resource allocation toward more quality improvement strategies and inform health policy development.

9 Study Monitoring Plan

An external data safety and monitoring board (DSMB) with no conflict of interest will monitor for any potential adverse effects and report these to both the study investigators and ethics committees (or institutional review boards) at the research clinic sites, Emory University, and National Institute of Mental Health (NIMH). Special efforts will be made to ensure that all study participants are monitored carefully. The Coordinating Center team will monitor study enrollment, loss to follow up, adherence and satisfaction, as well as adverse effects. These matters will be regularly communicated to the DSMB and the study's PIs (Mohan, Ali, Chwastiak). Serious adverse events (e.g., risk of suicide) that occur during the intervention or present during study testing will be brought to the attention of study physicians and participants will be referred to emergency care. In the event of significant risks to human participation or decreased likelihood of study completion, provisions will be made to consider premature discontinuation of the trial where deemed necessary or as recommended by external review boards (IRBs, DSMB) or by consensus of the investigator group.

9.1 Data Safety and Monitoring Board

Four India-based, independent, respected professionals, who are not affiliated with any of the institutions in our research group, will serve on a DSMB for this trial. The members will consist of one clinical trials specialist, one statistician, one senior psychiatrist, and one senior diabetologist. The DSMB will be charged with external oversight, to monitor the conduct of the study for feasibility, data integrity, and safety. DSMB members will be chosen for their relevant expertise.

The DSMB will review the protocol and plans, and will monitor participant flow, screening, and recruitment procedures, and the occurrence of adverse events related to participation in the study. The following adverse events will be monitored: death, suicide attempts, dropout, psychiatric hospitalizations, clinical deterioration, CVD or diabetes complications hospitalizations, revascularizations, other major surgical procedures (e.g., amputation), suicidal ideation or plans, development of serious substance abuse, emergence of new psychiatric or medical diagnosis posing significant risk to subjects.

The PIs will convene DSMB meetings in years 3, 4, and 5 to review study progress and safety. The meetings will largely be via teleconference with one or two in-person meetings. The PIs and Coordinating Center team (project manager, data manager, analyst) will compile all reports and information requested by the DSMB in a timely fashion and will respond to all DSMB queries and suggestions. Following DSMB meetings, the PIs will compile the suggestions and discussion into a report and share this with each site plus the Emory IRB and NIMH.

Even though we have judged the potential for injury to research participants from the proposed procedures to be minimal, all reasonable efforts will be made to further minimize these risks through the exclusive use of properly trained and educated research personnel and high-quality materials. As part of the informed consent procedure, individuals will be informed of their rights regarding injury sustained during study procedures and will be offered treatment for the injury according to prevailing local health policies. Detailed procedures for the notification of any abnormal findings of clinical relevance as well as non-emergency and emergency referrals will be developed and implemented.

9.2 Specification of Safety Parameters

The integrated care delivery strategies in this intervention are not implementing any new drug or invasive procedure that requires specific monitoring of safety parameters. All routine clinical care precautions will be used (e.g., checking liver function in the first few months following initiation of statin use), but all of these are common in routine practice and involve well-tested, established medications and procedures.

9.3 Monitoring Procedures

This is an implementation trial to improve care delivery for people with diabetes and depression with no direct risks anticipated for participants. Site monitoring visits will occur on at least 3 occasions in the first year and on at least two occasions in the subsequent year. Sites will provide 3-monthly progress reports with information on participant recruitment/retention, adverse events, and any protocol deviations or issues. The Steering Committee is comprised of all study investigators and the Coordinating Center manager. The Steering Committee provides annual reports to the DSMB, ethics committees, and NIMH who will review the progress of the study and make recommendations as necessary.

The annual report will include:

1) A list and summarization of adverse events;
2) Whether adverse event rates are consistent with pre-study assumptions;
3) Reason for dropouts from the study;
4) Enrollment of participants, by site, age, gender, other characteristics;
5) Whether all participants met entry criteria;
6) Whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and
7) Conditions whereby the study might be terminated prematurely.

The DSMB will convene regularly to review the report and other issues pertaining to the trial's progress and safety. The annual report will be signed by the DSMB chairperson and forwarded to the MDRF IEC and the Steering Committee of Investigators. Minutes of the DSMB recommendations will be provided to NIMH within 30 days of convening.

9.4 Unanticipated Problems

Unanticipated problems (UP) are events that are assessed by the PI as unexpected, related to study participation, **and** involving risk for participants or others.

- To be considered unanticipated, an event should be unexpected, not described in the study documents, or presenting with increased severity, duration, or frequency.

- To be related to study participation, an event should be probably or possibly related to study participation, due to drug effect, or as a consequence of a study procedure (even if, in the case of the control arm, the procedure is considered standard of care). If an event could be explained by the underlying medical condition, it is not considered related.
- To involve risk for participants or others, the event may affect subjects' risk. Even if the event did not result in harm, if the subject could have been affected by the event (safety, rights, welfare), the event is reportable.

Other unanticipated information that changes the risk-benefit ratio, or that indicates participants or others might be at greater risk of harm than was previously known may also be considered a UP. Examples:

- Any change to the protocol taken without prior ethics committee approval in order to eliminate apparent immediate hazards to participants
- Any publication in the literature, DSMB report, or interim result that indicated an unexpected change to the potential risks of the study

9.5 Adverse Events and Serious Adverse Events

9.5.1 Classification of Adverse Events

Definition of an Adverse Event: "An **adverse event (AE)** is *any untoward medical occurrence in a subject temporally associated with participation in the clinical study or with use of the experimental agent being studied*. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these." All adverse events will be assigned a severity, attribution to the study, and a status (anticipated or unanticipated) as described below:

Classification of AE Severity: AEs will be labeled according to severity, which is based on their impact on the participant. An AE will be termed 'mild' if it does not have a major impact on the participant, 'moderate' if it causes the participant some minor inconvenience and 'serious' if it causes a substantial disruption of the participant's wellbeing.

AE Attribution Scale: AEs will be categorized according to the likelihood that they are related to the study intervention. Specifically, they will be labeled either definitely, probably, possibly, or unrelated to the study intervention based on the professional judgment of the site PI Events categorized as probably or possibly related to study participation due to a drug effect or as a consequence of a study procedure will be considered related to study participation. An event is not considered related if it can be explained by a participant's underlying medical condition.

Unanticipated Status: AEs will be classified as anticipated or unanticipated. Unanticipated AEs are assessed by the PI and must be unexpected, related to study participation, and involve risk to the participants or others. Unexpected events are events that do not appear in the list of anticipated events give below. The AE attribution scale will be used to determine if events are related to participation in the study. Events are considered to involve risk to the participant or others if their safety, rights, or welfare are affected (even if the event did not result in harm).

List of Non-Serious Adverse Events:

1) Mild hypoglycemia not requiring medical attention
2) Side-effects of medications (e.g. hepatic dysfunction or myopathy due to statins; dry cough due to ACE-I; negative effects of drugs on biochemical parameters such as hypo- or hyper-kalemia, hyperuricemia; and others per Investigator discretion)
3) Peripheral vascular disease: intermittent claudication, rest pain

4) Allergic reactions/reactions on basis of drug interactions
5) Infection (skin infections, soft tissue infections)
6) Weight gain
7) Worsening of pre-existing conditions other than dyslipidemia, hyperglycemia and systemic hypertension
8) Clinically significant biochemical evaluations as per the PI's discretion
9) Mild to moderate retinopathy without diabetic macular edema
10) Common AEs from depression treatments include headache, dry mouth, insomnia, constipation, dizziness, fatigue, somnolence, diarrhea, and hyperhidrosis (excessive sweating); most are mild to moderate
11) Other AEs associated with depression treatment are flu-like symptoms, anxiety, sexual dysfunction, sleep disturbance, dizziness, appetite changes, and blurred vision

9.5.2 Serious Adverse Events

Definition of a Serious Adverse Event: "A **serious adverse event (SAE)** is any adverse event that results in one or more of the following outcomes: death; a life-threatening event; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability/incapacity; a congenital anomaly or birth defect; or an important medical event based upon appropriate medical judgment." SAEs are AEs in which the severity has been classified as serious. SAEs will be further assessed by the PI for study attribution and anticipated status using the criteria described above.

List of Serious Adverse Events:

1) Severe hypoglycemia requiring medical attention/hospitalization (a hypoglycemic episode associated with transient central nervous system dysfunction without other apparent cause in which the individual was unable to treat him/herself and had help from another person to administer glucose or glucagon)
2) Acute hyperglycemia (e.g., diabetic ketoacidosis [DKA])
3) CVD events: angina, non-fatal MI / unstable angina, revascularization procedure (angioplasty or CABG), TIA, stroke (non-fatal), arrhythmia
4) Gangrene or amputation due to diabetes-related peripheral neuropathy and peripheral vascular disease
5) Major bleeding (e.g., intracerebral or gastro-intestinal)
6) Renal: end-stage renal disease requiring renal replacement therapy (dialysis or transplantation)
7) Eyes: severe diabetes-related eye disease (defined as the requirement for retinal photocoagulation or similar treatment and development of diabetes-related blindness in either eye in a participant known not to have this condition at study entry)
8) Major infection: requiring hospitalization and/or parenteral antibiotics (UTI, skin infections, soft tissue infections, lower respiratory tract infections/physician-diagnosed pneumonia)
9) Inpatient hospitalization or prolongation of existing hospitalization
10) Suicidal ideation
11) Death
12) Any other major health conditions/events (important medical event based upon appropriate medical judgment)

9.5.3 Reporting of AEs and SAEs

Information about the occurrence of any AEs or SAEs will be sought at all scheduled visits and any intermediate visits between CCs and intervention participants. AEs and SAEs will then be classified as anticipated or unanticipated.

Unanticipated SAEs will be reported promptly. Death (whether anticipated or unanticipated) will follow the same prompt reporting procedure. The Lead Site Investigator will ensure that there is adequate follow-up of each participant who has a serious adverse event. Also, the Lead Site Investigator should ensure that all regulatory requirements specified by the local, site-specific IRB are completed. The DSMB will regularly review all such events and provide recommendations to the Steering Committee of Investigators. Documentation of all such SAEs will be retained in the participant's trial folder for at least 3 years.

Prompt reporting of a death or unanticipated SAE requires the responsible Lead Site Investigator to report the event to the Coordinating Center within 24 hours of the Lead Site Investigator's knowledge of the event by completing a serious adverse event document by fax, email, or online submission and with notification by telephone. The clinic research site must report the death or unanticipated SAE to the local, site-specific ethics committee within 7 calendar days.

The Coordinating Center will report deaths or unanticipated SAEs to the DSMB, Emory IRB, and MDRF IEC within 7 calendar days, with appropriate follow-up reports and final resolution forms with supporting documents as per evolution of the disease. Unanticipated SAEs will be reported to NIMH within 10 business days. Deaths related to study participation will be reported to NIMH immediately (no later than 5 business days) from when the site PI learns of the event. Anticipated deaths will be reported to NIMH as part of the annual report. Death or unanticipated SAEs that occur within 15 days after the end of the scheduled follow-up visit will be reported in the same way as those that occur before the end of follow-up. In addition, any AE that occurs after the completion of the scheduled follow-up, and that the investigator deems due to the study intervention, will be reported in the same way.

Anticipated SAEs or those unrelated to the study intervention will be reported to the same individuals/entities on a monthly basis. Anticipated AEs and SAEs will be reported to NIMH in the annual progress report.

9.6 Protocol Deviations and Protocol Violations

9.6.1 Protocol Deviations

A "protocol deviation" is any change, divergence, or departure from the ethics committee approved protocol. Although every effort should be made to follow the protocol as written, it is common for studies to have protocol deviations. These deviations may result from human error, subject non-compliance, or confusing and/or ambiguous details. Protocol deviations may not alter the course of the study and do not pose a safety risk to the participant.

Examples include:

- Lab draws off schedule
- Office or phone visit off schedule
- Baseline laboratory values out of enrolment window
- Out of window or missed visit, or out of window or missed lab draw

9.6.2 Protocol Violations

A "protocol violation" is a protocol deviation that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. Major protocol deviations are considered substantive and adversely affecting one of the following:

- Rights or welfare of subjects

- Safety of subjects
- Willingness of subjects to continue with study participation
- Integrity of the research data

Examples include:

- Enrolment of ineligible subject
- Lack of valid consent form
- Failure to report an SAE
- Lapse in IRB approval
- Improper breaking of the blind
- Mishandled samples
- Materially inadequate record keeping
- Intentional deviation from the protocol, Good Clinical Practice, or government regulations by study personnel
- Subject repeated non-compliance with study requirements

9.6.3 Reporting of Protocol Deviations and Protocol Violations

When encountering a situation determined to be a protocol deviation, the site coordinator should complete a Protocol Deviation Assessment Form and submit it to the Coordinating Center. Protocol deviations do not need to be reported to the local ethics committee or the Emory IRB.

Protocol violations are **promptly** reportable. Prompt reporting is done by sending a Protocol Violation Assessment Form to the Coordinating Center and the local, site-specific ethics committee and should occur within 5 business days of event occurrence, or from when the Site Principal Investigator first learned about the event. The Emory ethics committee should be notified by the Coordinating Center within 10 business days of event occurrence, or from when the Site Principal Investigator first learned about the event. Protocol violations will be documented in the annual progress report to NIMH.

The Coordinating Center will log all protocol deviations and violations to identify possible trends that may indicate a substantive problem.

9.7 Non-Compliance

Non-compliance is the failure to follow national, state, or local regulations governing human subject research, institutional policies related to human subject research, or the requirements or determinations of the IRB. This may pertain to the principal investigator, research staff, or any member or component of the human research protection program.

Examples of non-compliance:

- Performing human subject research without first obtaining ethics committee approval or an ethics committee declaration of exemption
- Deviating from or violating the provisions of an ethics committee-approved protocol
- Failing to secure ethics committee approval of a protocol due for periodic continuing review prior to its expiration date
- Permitting a protocol's ethics committee approval to lapse without stopping all research-related activities and submitting a closing progress report to the ethics committee, or in the event of an overriding safety concern or ethical issue such that it would be in the individual subject's best interest to continue study participation, not arranging with the ethics committee to continue those activities

9.7.1 Serious Non-compliance

Serious non-compliance is non-compliance that creates an increase in risks to subjects, adversely affects the rights, welfare and safety of the research subjects or adversely affects the scientific integrity of the study. Willful violation of policies and/or federal regulations may also constitute serious non-compliance.

9.7.2 Continuing Non-compliance

Continuing non-compliance is a pattern of non-compliance that if allowed to continue is likely to increase risk to subjects, adversely affect the rights, welfare and safety of research subjects, or adversely affect the scientific integrity of the study.

9.7.3 Reporting of Serious Non-compliance

Serious non-compliance should be reported to the Research Coordinating Centre and the local, site-specific ethics committee within 5 business days of event occurrence, or from when the Site Principal Investigator first learned about the event. The MDRF and Emory ethics committees should be notified by the Research Coordinating Centre within 10 business days of event occurrence, or from when the Site Principal Investigator first learned about the event. Serious non-compliance that results in increased risks to subjects will be promptly reported to NIMH.

9.8 Criteria for Discontinuation of Intervention

Criteria for discontinuing the intervention **for a participant** include:

1) Moves away from proximity of the clinic research site
2) If the Lead Site Investigator finds the participant to be incompatible with the intervention. For example, if the participant is unable to engage in the intervention due to major stroke, is in a vegetative state, or cannot communicate with the care coordinator.
3) In-trial development or diagnosis of a major psychiatric illness (i.e. mania, bipolar disorder, schizophrenia, schizoaffective disorder), which may complicate treatment within a non-psychiatric health facility and/or greatly confound the health outcomes for the individual.

If any member of the local study team encounters a participant that meets any of the criteria for discontinuation, he/she must inform the Lead Site Investigator, who will report the incident to the Coordinating Center by completing a Participant Discontinuation Form.

Reasons for discontinuation of the study intervention **at a clinic research site** include:

1) Infrastructure unable to handle intervention (determined by quality monitoring).
2) Discontinuation recommended by steering committee or sponsor
3) Low-recruitment rate: less than 6 participants per month recruited

Discontinued participants will continue to be followed with their permission if the study intervention is discontinued at the clinic research site.

Discontinued participants will be followed up annually for 2 years from their date of enrollment for adverse events and serious adverse events/clinical outcomes of (1) death from any cause; (2) major macrovascular event: a composite of non-fatal MI, non-fatal stroke and death from any cardiovascular cause (based on investigator diagnosis); (3) microvascular events; and/or (4) major psychiatric event.

Secondary outcomes which will be followed include:

1) MI (non-fatal and fatal or revascularization procedure (angioplasty or CABG));

2) Stroke (non-fatal and fatal)
3) Requirement for renal replacement therapy (dialysis or transplantation);
4) Death from renal disease
5) Development of severe diabetes-related eye disease (defined as the requirement for retinal photocoagulation or similar treatment and development of diabetes-related blindness in either eye in a participant known not to have this condition at study entry); and
6) Major hypoglycemia episode (a hypoglycemic episode associated with transient central nervous system dysfunction without other apparent cause in which the individual was unable to treat him/herself and had help from another person to administer glucose or glucagon)
7) Acute hyperglycemia (e.g., DKA)
8) Amputation due to diabetes-related peripheral neuropathy and peripheral vascular disease
9) Major infection requiring hospitalization (e.g., pneumonia)
10) Any other health conditions/events.

9.9 Data Safety

The respective site coordinators and all study staff at each participating clinic research site will complete training in the protection of human subjects, including training in data handling and confidentiality. The project managers will administer all transfers, organization, storage, and back-up of study data. They will work closely with participating clinic investigators to ensure all data is secured and any edits can be tracked using: password-protected access; automated edit tracking; audit trails; validation tools for data-entry (split screen views); and encrypted transfer facilities.

10 Data Analysis

10.1 Primary and Secondary Health Outcomes

Participants in both arms will be invited for 6-monthly assessments [0, 6, 12, 18, 24 and 36 month time-points] for blinded outcomes assessors. Data for health outcomes analyses will include demographic (age, sex, marital status, education, occupation, income, migration status), anthropometric data (height, weight, waist circumference), depression (SCL-20 and PHQ-9), and risk factor levels (fasting blood glucose, HbA1c, BP, lipid levels, and tobacco use). Data regarding patient-centered outcomes such as treatment satisfaction, quality of life and utility [reflects participants' judgments regarding different health states on a continuum from 0.0 (representing death) to 1.0 (perfect health)] will be collected using the Summary of Diabetes Self Care Activities, Diabetes Treatment Satisfaction Questionnaire, and Health Utilities Index-3.

Data Analysis: Recruitment and retention of trial participants will be assessed by examining: number screened, number eligible to be randomized, number enrolling in the study, and dropout from regular testing at the completion of 36 months. We will test for differences in baseline characteristics to assess randomization using appropriate statistical tests for sample proportions [χ^2] or means [t-tests]. Between-group differences in primary and secondary outcomes will be assessed at 12, 24 and 36 months, using the following indicators:

- **Primary Outcome:** At each time-point, we will test the unadjusted difference in the proportion achieving the primary outcome, which jointly evaluates depressive symptoms and CVD risk reduction.

- **Secondary Outcomes:** Given the objective of assessing the cumulative benefits of a multi-component intervention, a "common treatment effect" will be tested on all four main targets [SCL-20, HbA1c, SBP, LDL-c] jointly using a scaled marginal model.[1] Each target, measured continuously, is scaled by its standard deviation and a single parameter is estimated representing the "common effect" on all targets. The advantage of this approach is that all targets can be measured continuously, thereby improving power, and a "common effect" in standard deviation units is produced. Katon[18] used this approach in a similarly designed trial [the model is estimable using the SAS PROC GENMOD procedure [26] described by Roy].[1]
- Additional secondary outcomes that will be evaluated include: (1) a measure of "common effect," i.e. whether the intervention had a similar beneficial effect on all four main targets [SCL-20, HbA1c, SBP, LDL-c];[1] proportion of participants achieving all 3 CVD risk factor targets; (2) mean reductions in four main targets [SCL-20 score; HbA1c; SBP; LDL-c]; (3) proportion of participants achieving treatment targets or significant reductions in individual risk factors (depression control [≥50% reduction in SCL-20]; glycemic control [HbA1c≤7.0% **or** ≥0.5% reduction]; BP control [SBP≤130 mmHg **or** ≥5mmHg reduction]; lipid control [LDL≤100 mg/dl **or** ≥10mg/dl reduction]; (4) mean utility, quality of life, and depression- and diabetes-specific patient satisfaction scores; and (5) mean health expenditures and within-trial cost-utility.

All analyses will be conducted with both intention to treat (ITT) and per protocol analytical approaches. All treatment effects (primary and secondary outcomes) will be assessed using multivariate regression models adjusted for baseline characteristics. Generalized linear models will be estimated with appropriate link functions and error distributions for each outcome [e.g., logit models for dichotomous outcomes]. Heterogeneity in treatment effects across sites will be tested with interaction terms between site and the treatment variable. Similarly, heterogeneity in treatment effect by baseline age, gender, socioeconomic status, SCL-20, HbA1c, SBP, and LDL-c will also be evaluated. Robust standard errors will be estimated to account for within-site clustering [design effects].

10.2 Economic Analyses

Data regarding health utilization, costs, and quality of care will be collected through clinic chart reviews and questionnaires. Data on direct medical costs [inpatient, outpatient, prescription medication, and diagnostic services] will be collected, primarily using chart reviews [health service utilization] and pharmacy plus clinic administrative records [unit costs]. Since out-of-pocket health expenditures predominate in India, we will use a questionnaire to capture that data. The questionnaire also captures direct non-medical [value of participant time spent traveling to and attending appointments] and indirect costs [lost productivity associated with illness or premature mortality].

Economic Analyses: Health expenditures and within-trial cost utility of the intervention compared to usual care will be calculated using a health care system perspective as the base-case analysis and societal perspective for secondary analyses. Only direct medical costs in analyses with a health system perspective will be used, while societal perspective analyses will include direct medical and nonmedical, and indirect costs.

To compare health expenditures between the intervention and usual care arms, costs will first be classified as: direct medical costs based on clinic- and pharmacy-reported data for health utilization and unit costs; patient-reported direct nonmedical costs; patient-reported indirect costs; and costs of the intervention from the clinic and study expenditures [e.g., labor costs for NCMs, costs for educational materials, and overhead costs (facility, administrative, and technology infrastructure) minus costs attributable only to research activities]. Costs associated with identifying individuals with comorbid depression will be summarized. Incremental costs of intervention [implementation, side-effects of multi-condition care, and medical care associated] will be identified. Since in-patient costs over a 36 month study can vary greatly [outliers = a few random disease events], health expenditures will be estimated in two ways: (1) limited to outpatient costs, and (2) combined inpatient and outpatient costs. Because private and government-

funded clinics are included in the trial, mean expenditures will be reported for the intervention arm relative to usual care participants by site and cumulatively.

To compare the within-trial cost-utility of intervention to usual care, an incremental cost-utility ratio will be calculated [net costs to net utility: $costs_{intervention} – costs_{control}$ / $utility_{intervention} – utility_{control}$]. To calculate utility for each arm, 6-monthly health utility and mortality data will be used. The chosen measure of utility is the closest option to a global measure, the quality adjusted life year [QALY] and is calculated as the sum of mean survival time [life years] x utility scores at 6, 12, 18, 24 and 36 months. Twelve, 24 and 36 month costs per QALY will be reported.[27]

If the trial is successful, we will consider comparing modeled long-term cost-utility of the intervention and usual care using Markov Chain Monte Carlo estimation techniques [controlling for age, gender, baseline risk and disease control].[28] This will be compared to reference points from the literature – e.g., ceiling ratios for costs per QALY that are less than three times GDP per capita [29-31] are considered cost-effective [India's 2011 GDP per capita was $3,700; threshold: ≤$11,100 per QALY][32]. Sensitivity analyses will be used to examine the effects of varying discount rates, costs of the intervention, and effectiveness.

11 Study Coordination

11.1 Coordination Plans

The trial has a designated Coordinating Center (at the Madras Diabetes Research Foundation) to oversee the successful design and conduct of the trial. The Steering Committee will support and guide Coordinating Center staff, providing the scientific leadership for the trial. The Executive Committee serves as the operational arm, for day-to-day management, and making any recommendations to the Steering Committee. The Executive Committee will be comprised of the Coordinating Center manager and co-Principal Investigators of the Study.

The Coordinating Center, with input from the Steering Committee, is responsible for developing the protocol; certification of clinic research sites; developing and distributing procedural manuals; training trial personnel in the standardized protocol implementation and data collection; collecting and managing all trial data; quality control; analyzing data; and preparing reports for the Data Safety Monitoring Board, Steering Committee, and NIMH. The Coordinating Center staff will conduct visits to each site to monitor and assure high performance during the trial.

11.2 Laboratories

Central Coordination: The Coordinating Center and laboratory at the Madras Diabetes Research Foundation will coordinate the external quality assurance methods for all clinic research sites.

Clinic Research Site Laboratories: The site laboratories will undergo external quality control checks arranged by the Coordinating Center for cross-site standardization.

11.3 Administrative Clauses

The administrative clauses relating to this protocol are covered by Clinical Trial Agreements (CTA) between the clinic research sites and the Coordinating Center plus the Trial Steering Committee.

Appendix A – PHQ-9 Checklist

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you had any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the number of days	Almost every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself down or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you ticked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

‡

‡ Available at: http://www.lphi.org/LPHIadmin/uploads/.PHQ-9-Review-Kroenke-63754.PDF.

Appendix B – SCL 20 Questionnaire

SCL-20

Overall, in the past **2 weeks** how much were you distressed by….

		Not at all	A little bit	Mod-erately	Quite a bit	Ex-tremely
1.	Feeling lonely or blue	0	1	2	3	4
2.	Feeling hopeless about the future	0	1	2	3	4
3.	Feeling no interest in things	0	1	2	3	4
4.	Inability to take pleasure in things	0	1	2	3	4
5.	Poor appetite	0	1	2	3	4
6.	Overeating	0	1	2	3	4
7.	Trouble falling asleep	0	1	2	3	4
8.	Awakening in the early morning	0	1	2	3	4
9.	Sleep that is restless or disturbed	0	1	2	3	4
10.	Thinking, speaking and moving at a slower pace	0	1	2	3	4
11.	Feeling so restless you couldn't sit still	0	1	2	3	4
12.	Thoughts of death or dying	0	1	2	3	4
13.	Thoughts of ending your life	0	1	2	3	4
14.	Feeling low in energy or slowed down	0	1	2	3	4
15.	Feeling everything is an effort	0	1	2	3	4
16.	Blaming yourself for things	0	1	2	3	4
17.	Feelings of worthlessness	0	1	2	3	4
18.	Feelings of guilt	0	1	2	3	4
19.	Trouble concentrating	0	1	2	3	4
20.	Difficulty making decisions	0	1	2	3	4

IF Q 13=3 or 4, Invoke self-harm protocol

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