eIMPACT-DM Pilot Trial:
Depression Treatment to Reduce the Excess Diabetes Risk of People with Depression and Prediabetes

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1.0 Background & Rationale

A. Significance

A1. Diabetes, prediabetes, and depression are highly prevalent, disabling, and deadly.

Diabetes and prediabetes affect 31 million (12%) and 82 million (34%) U.S. adults, respectively.[1,2] The ramifications of diabetes include CVD, renal disease, amputations, blindness, neuropathy, reduced functional status, and death.[1,3,4] These statistics highlight the need for new prevention targets and approaches, especially for T2D, to augment current efforts.[5] The lifetime prevalence of major depressive disorder (MDD) is 16%.[6] Depression is the 2nd leading cause of disability[7] and predicts multiple chronic diseases[8-12] and death.[13]

A2. Depression is an independent, clinically important, and robust risk factor for diabetes.

Twenty years of evidence shows that depression is a diabetes risk factor, independent of established diabetes risk factors. A 2013 meta-analysis[14] (23 studies) found that depressed adults have 56% (unadjusted) and 38% (adjusted for established risk factors) greater risk of developing diabetes than nondepressed adults. This risk conferred by depression is clinically important, as it is on par with established diabetes risk factors, such as smoking.[15-17] In addition to clinical diabetes onset, a 2013 meta-analysis[18] (18 studies) revealed that depression is associated with insulin resistance, a sign of prediabetes. This finding supports intervening on depression at the prediabetes stage. Finally, the depression-diabetes relationship is robust, as it has been observed in major demographic groups.[8,10,14] A 2008 meta-analysis[10] found that risk ratios for depression predicting diabetes were comparable for women (1.26), men (1.57), older adults (1.50), younger adults (1.96), samples with higher minority representation (1.79), and samples predominantly White (1.65).

A3. The depression-to-diabetes relationship is biobehaviorally plausible.

Although the exact pathways through which depression contributes to diabetes development have yet to be determined, several candidate mechanisms have been identified. The leading biological mechanisms are HPA axis hyperactivity, autonomic dysfunction, and systemic inflammation. Substantial literatures indicate that depression is accompanied by HPA axis hyperactivity[19,20] and autonomic dysfunction.[21] Depression-related dysfunction in these two systems that normally exert anti-inflammatory effects could explain why depression is also reliably associated with elevated inflammatory markers.[22-25] Moreover, HPA axis hyperactivity, autonomic dysfunction, and systemic inflammation are all implicated in the pathogenesis of insulin resistance and T2D.[26-30] The leading behavioral mechanisms are increased adiposity, poor diet, physical inactivity, smoking, and medical nonadherence. Compared to nondepressed adults, depressed adults have a 58% greater risk of future obesity,[9] a major T2D risk factor.[31] Maladaptive behaviors common in depressed people – i.e., high calorie diets,[32-35] physical inactivity,[36] smoking,[36,37] and nonadherence to medical regimens[38,39] – also promote insulin resistance and T2D.[14,17,18,40] Of note, current conceptual frameworks[27] view systemic inflammation as a final common pathway through which many candidate mechanisms promote insulin resistance and T2D.

Our team's published studies further support the biobehavioral plausibility of the depression-to-diabetes relationship. We have found that: (1) depression is positively associated with the inflammatory markers interleukin-6 (IL-6) and C-reactive protein (CRP) and predicts inflammatory marker increases over 6 years;[41-43] (2) depression predicts future obesity development;[44] (3) depression is linked with poorer adherence to primary prevention recommendations;[45] and (4) depression is positively associated with insulin resistance and

predicts insulin resistance increases over 6 years, and CRP and BMI are mediators of these relationships.[46,47]

A4. Many patients have a modifiable diabetes risk factor that is going underdetected or undertreated.

In primary care, the prevalence of depression is 16-19%.[48,49] Depression is receiving increased, but still limited, attention in settings where diabetes prevention occurs, including primary care. Because depression screening is not routine, first-line interventions other than antidepressants are often not available, and the outcomes achieved are suboptimal,[50] there is a large cohort of primary care patients with an underdetected or undertreated diabetes risk factor. This status quo could represent a major missed opportunity to prevent T2D.

A5. There is a need to evaluate if depression treatment is a new diabetes prevention strategy.

The state of the science (see A2 and A3) and the status quo (see A4) create the current need for a pilot RCT to begin to evaluate the utility of depression treatment as a new diabetes prevention strategy. Because no such trial has been conducted, it is unknown if depression treatment improves A1c and prevents T2D in people with prediabetes. Even so, three smaller studies provide initial indirect support for such an approach. In 20 depressed patients without diabetes, 3 months of antidepressant treatment was linked with improved insulin resistance.[51] In two RCTs of 80 and 51 depressed inpatients without diabetes, depression remission after antidepressant treatment was associated with improved insulin resistance.[57,58] Our post hoc analysis also provides initial indirect support. In 18 depressed patients without diabetes, we found that those randomized to computerized CBT for depression, vs. usual care, exhibited improvements in fasting glucose (see C1). Unfortunately, none of these studies was designed to test our hypotheses. First, some used pre/post designs with no randomization or control group,[51] while others randomized patients to different antidepressants but did not have a control group.[52,53] Second, none targeted patient groups with the greatest need for diabetes prevention, such as those with prediabetes. Third, none had A1c, an indicator of high clinical relevance, as an outcome. These key limitations, combined with the strong state of the science and the problematic status quo, create the need for the proposed pilot RCT of 64 depressed patients with prediabetes (1) to determine the preliminary efficacy of our depression intervention (eIMPACT-DM) on A1c and insulin resistance and (2) to explore whether somatic depressive symptoms moderate the intervention effect on A1c and insulin resistance.

The scientific premise of the proposed trial is strong, as: (a) current diabetes prevention approaches have only partial effectiveness;[5,54-56] (b) the depression-to-diabetes relationship is independent of established diabetes risk factors, is clinically important (i.e., of sufficient magnitude that effective intervention could meaningfully lower diabetes risk), is robust, and is biobehaviorally plausible (see A2 and A3); (c) many patients have a modifiable diabetes risk factor (depression) that is going underdetected or undertreated (see A4); (d) initial evidence, including our post hoc analysis, suggests that depression treatment can improve insulin resistance and fasting glucose (see A5 and C1); and (e) our preliminary data suggests that depressed people with somatic depressive symptoms are a subgroup at particularly elevated diabetes risk (see C3).

A6. Establishing that depression treatment reduces diabetes risk would have a major positive impact.

A positive pilot trial would pave the way to an R01-level RCT by yielding three expected outcomes: (1) generating critical proof-of-concept data (depression treatment can improve A1c) to support the premise; (2) providing preliminary effect sizes for eIMPACT-DM on diabetes risk markers to help justify future power analyses; (3) identifying a potentially important moderator

(somatic depressive symptoms) of eIMPACT-DM efficacy. If evidence of moderation by somatic depressive symptoms is observed, it would have implications for recruitment (enroll 50% with and 50% without these symptoms), randomization (stratify on presence of these symptoms), and the sample size (ensure sufficient power to detect 3-way interactions) of the future RCT.

Ultimately, demonstrating that depression treatment reduces diabetes risk would have a major positive impact. In the scientific domain, it would identify depression as a causal diabetes risk factor. In the clinical domain, it would identify a novel target for prevention efforts, likely leading to the inclusion of depression in diabetes guidelines. Moreover, it would equip healthcare providers with a new intervention (eIMPACT-DM) to simultaneously treat depression and lower diabetes risk for a large cohort of high-risk patients. Finally, positive results – combined with our practical, scalable intervention – would facilitate dissemination and implementation of eIMPACT-DM. These three clinical practice changes should reduce diabetes morbidity, mortality, and costs.

B. Innovation

B1. Our trial would be the first to evaluate depression treatment as a diabetes prevention strategy.

This RCT would be the first to test the effect of a depression intervention on A1c in depressed people with prediabetes. Our focus on a psychological factor is a major departure from current prevention efforts.[5]

B2. eIMPACT-DM has innovative aspects that support broader dissemination and implementation.

Although collaborative care for depression in primary care is an established approach,[57] only one trial[58] besides our eIMPACT Trial (see C2) has incorporated computerized CBT. Moreover, no trials have used an antidepressant algorithm optimized for diabetes risk reduction. To achieve our long-term goal, large-scale dissemination and implementation must be possible. eIMPACT-DM fits very well in primary care, where behavioral health staff and space are limited, as it harnesses technology to minimize personnel and space requirements. In addition, because eIMPACT-DM uses computerized CBT, it is more scalable, easier to deliver with high fidelity, and likely more cost effective[59] than current collaborative care models. Finally, eIMPACT-DM can reach patients with logistical barriers, as many components are internet or phone delivered. Pew data show that 89% of adults (87% for non-Hispanic Blacks; 81% for lower income households) use the internet.

B3. Using a statewide information exchange to identify incident T2D is unique and has advantages.

The Indiana Network for Patient Care (INPC),[60,61] the nation's largest clinical data repository, is a secure statewide health information exchange operated by Regenstrief Institute. In addition to extensive data provided by healthcare systems, INPC gathers data from Indiana Medicaid and commercial payers and death data from the Indiana State Department of Health. Advantages of using INPC seen in our past studies[62-64] are an easily extended follow-up and minimal attrition (no patient participation required).

C. Preliminary Studies

C1. The Beating the Blues for Your Heart Trial (PI: Stewart; ClinicalTrials.gov Identifier: NCT01605552)

This small pilot RCT provides initial proof-of-concept data. Although its primary outcome was a CVD risk marker, it allowed for a diabetes-related post hoc analysis. 29 Eskenazi Health

primary care patients with depression were randomized to Beating the Blues (BtB) – an empirically supported computerized CBT – or usual primary care for depression. 22 patients (76%) attended the 3-month post-treatment visit. For this analysis, we selected the 18 patients free of diabetes to parallel the targeted prediabetes population. BtB patients (-3.6 mg/dL), vs. usual care patients (+3.2 mg/dL), exhibited greater improvements in fasting glucose (see table). While this difference fell short of significance due to low power, the effect size of d=0.90 is large.[65] BtB patients also showed large improvements in SCL-20 depression score, moderate-to-large improvements in CRP, and moderate improvements in IL-6 (see table).

The major limitation of these data is the fasting glucose outcome, which is a point estimate of glycemia highly susceptible to acute influences.[66] Unfortunately, we did not bank whole blood samples to assess A1c. NIH reviewers previously noted that an R01-level RCT is premature due to our lack of preliminary data showing a promising effect of depression treatment on A1c. Another limitation of these data is post hoc selection of patients free of diabetes. These key limitations underscore the need for the proposed pilot RCT.

	Beating the Blues Mean (SD)	Usual Care Mean (SD)	P-value	d
Pre-Treatment Level				
Fasting Glucose, mg/dL	105.7 (10.2)	107.6 (10.7)	0.72	---
SCL-20 (range: 0-4)	1.47 (0.64)	1.67 (0.98)	0.66	---
CRP, mg/L	4.90 (2.19)	3.17 (2.66)	0.19	---
IL-6, pg/mL	4.15 (2.55)	4.42 (5.34)	0.91	---
Post-Treatment Level				
Fasting Glucose, mg/dL	102.1 (12.6)	110.8 (9.8)	0.10	0.90
SCL-20 (range: 0-4)	0.79 (0.47)	1.48 (0.78)	0.06	1.03
CRP, mg/L	2.91 (3.11)	3.94 (2.83)	0.16	0.76
IL-6, pg/mL	3.88 (1.78)	5.14 (3.17)	0.41	0.46

P-values and effect sizes (d's) are adjusted for pre-treatment level.

C2. eIMPACT Trial (PI: Stewart; R01HL122245; ClinicalTrials.gov Identifier: NCT02458690)

This phase II RCT provides data supporting the feasibility of recruitment, intervention, and assessment and the efficacy of eIMPACT-DM for depression. The eIMPACT Trial's objective is to determine if treating depression, before CVD onset, reduces CVD risk. We randomized Eskenazi primary care patients with depression and CVD risk factors to eIMPACT or usual primary care for depression. eIMPACT is identical to the proposed intervention, except the antidepressant algorithm is optimized for CVD risk reduction. We are now in Year 4. We have met our recruitment goal by randomizing 216 patients (56% non-White) and have executed the intervention/usual care procedures with high fidelity and minimal impact on clinic operations. Attrition has been low, with 93% of the intervention arm and 91% of the usual care arm attending the 12-month post-treatment visit. Checks indicate that the data are of high quality with minimal missingness. To evaluate eIMPACT efficacy, we selected all 135 patients whose post-treatment visits have come due. eIMPACT patients (-7.0 points), versus usual care patients (-3.5 points), showed significantly greater and moderate-to-large improvements in PHQ-9 depression score (see table). The clinical response data yielded similar results – 51% of eIMPACT patients, versus 20% of usual care patients, had a 50% PHQ-9 reduction.

While these results establish the feasibility of our approaches and the efficacy of our intervention for depression, this ongoing trial is not appropriate for achieving our aims for three reasons: (1) the sample is problematic (~1/3 have diabetes), (2) the antidepressant algorithm (optimized for CVD risk reduction) includes medications that could increase weight and A1c, and (3) we cannot assess A1c (no whole blood samples).

	eIMPACT Mean (SD)	Usual Care Mean (SD)	P-value	d / OR
Pre-Treatment Level				
PHQ-9 score (range: 0-27)	15.0 (5.1)	15.4 (4.6)	0.62	---
Post-Treatment Level				
PHQ-9 score (range: 0-27)	8.0 (6.4)	11.9 (5.8)	<0.001	0.68
50% Reduction in PHQ-9	50.8%	20.3%	0.001	4.06

P-values and effect sizes (d's) are adjusted for pre-treatment level.

C3. Somatic Depressive Symptoms and Elevated Diabetes Risk

Our evidence suggests that depressed people with the somatic symptoms of hyperphagia (increased appetite/weight) and/or hypersomnia (increased sleep) may be a subgroup at particularly elevated diabetes risk. First, in our analysis of the NESARC data (N=17,787), we found that depressed adults with hyperphagia and hypersomnia had a greater odds (OR=1.51; p<.001) of developing obesity and exhibited greater increases in BMI (+0.40 kg/m^2; p=.009) over the 3-year follow-up than depressed adults without these symptoms.[44] Obesity is a major T2D risk factor.[31] Second, in the eIMPACT pre-treatment data, we found that hyperphagia (β=0.348, p=.004), but not the other depressive symptoms, is associated with greater insulin resistance. The cohort for this analysis was the 135 depressed patients with post-treatment visits due minus those with baseline diabetes (final n=78, 63% with hyperphagia and/or hypersomnia). The outcome was the Homeostatic Model of Assessment 2 (HOMA2) Score[67] computed from fasting glucose and insulin from banked plasma samples. Together, our results raise the intriguing possibly that depressed adults with hyperphagia and/or hypersomnia may show greater improvement in diabetes risk markers after depression treatment due to their higher baseline diabetes risk. We will explore this possibility in the proposed RCT.

2.0 Objectives

Diabetes and prediabetes are top public health priorities in the U.S. Diabetes affects 31 million (12%) adults, and another 82 million (34%) adults have prediabetes, a precursor to frank diabetes.[1,2] The ramifications of diabetes are grave and include cardiovascular disease (CVD), renal disease, amputations, blindness, neuropathy, reduced functional status, and death.[1,3,4] While these statistics highlight the importance of diabetes prevention, current approaches have only partial effectiveness.[5,54-56] This has created a clear need for new primary prevention targets and approaches, especially for type 2 diabetes (T2D; 90-95% of diabetes cases in U.S. adults[1]). Thus, our focus is on augmenting the overall effectiveness of diabetes prevention efforts by identifying and treating novel primary prevention targets that are unaddressed in current approaches.

Depression, another top priority, is a diabetes risk factor. A 2013 meta-analysis[14] found that depressed adults have 56% (unadjusted) and 38% (adjusted for established diabetes risk factors) greater risk of diabetes than nondepressed adults. The risk conferred by depression is on par with established diabetes risk factors,[15-17] and the depression-to-diabetes relationship has been observed in major demographic groups.[8,10,14] Plausible biobehavioral mechanisms have also been identified.[27] Collectively, these literatures form the scientific premise for the proposed pilot trial by demonstrating that the depression-to-diabetes relationship is independent of established diabetes risk factors, is clinically important (i.e., of sufficient magnitude that effective intervention could meaningfully lower diabetes risk), is robust, and is biobehaviorally plausible. However, research has yet to determine whether depression treatment can prevent the development of T2D in people with prediabetes.

Depression is receiving increased, but still limited, attention in settings where diabetes prevention occurs, such as primary care. Thus, there is a large cohort of primary care patients with an underdetected or undertreated diabetes risk factor (depression). This status quo could represent a major missed opportunity to prevent diabetes. Together, the state of the depression-

to-diabetes science and this status quo create the need for a pilot RCT to evaluate the utility of depression treatment as a new diabetes prevention strategy.

The long-term goal of our transdisciplinary team is to develop, evaluate, and disseminate new diabetes prevention strategies targeting novel psychosocial risk factors. This project's objective is to perform a preliminary evaluation of the efficacy of our existing primary care-based intervention for depression (eIMPACT-DM) in improving diabetes risk markers. eIMPACT-DM is a modernized collaborative stepped care intervention consisting of (1) computerized and telephonic cognitive-behavioral therapy (CBT) for depression and (2) select antidepressant medications included in an algorithm optimized for diabetes risk reduction. Our preliminary data (see C2) establish the feasibility and antidepressive efficacy of eIMPACT-DM. We propose a pilot RCT of 64 primary care patients with a depressive disorder and prediabetes. Patients will be randomized to 6 months of eIMPACT-DM or the active control (depression education, symptom monitoring, and primary care for depression). The primary outcome is hemoglobin A1c – the gold standard glycemic outcome,[68] a strong predictor of diabetes development,[69,70] and a potent indicator of improvement in diabetes endpoints.[5,69,71,72]

Primary Aim: Determine the preliminary efficacy of eIMPACT-DM in improving diabetes risk markers among depressed primary care patients with prediabetes. Depressed patients randomized to eIMPACT-DM, versus the active control, will exhibit greater improvement in A1c (primary outcome; H1) and insulin resistance (HOMA score; secondary outcome; H2) from pre-treatment to post-treatment 6 months later.

Exploratory Aim: Explore whether the effect of eIMPACT-DM on diabetes risk markers is greater among patients with a somatic presentation of depression at pre-treatment (baseline) than among patients without such a presentation. A somatic presentation of depression at baseline is defined as having hyperphagia (increased appetite/weight) and/or hypersomnia (increased sleep) at pre-treatment. Our preliminary data (see C3) suggest that, in people with depression, those with hyperphagia (increased appetite/weight) and/or hypersomnia (increased sleep) are a subgroup at particularly elevated diabetes risk. Because our findings raise the intriguing possibly that this subgroup may show greater improvement in diabetes risk markers after depression treatment, we will explore if effect sizes for eIMPACT-DM on A1c and insulin resistance are larger for patients with versus without hyperphagia and/or hypersomnia.

There is a tight fit between our aims and PA-18-405, which requests applications for pilot therapeutic trials that will "lay the foundation for larger clinical trials related to the prevention and/or treatment of diabetes" by "acquiring data to support the rationale and/or feasibility of a definitive study and to develop and/or refine power calculations." These trials could "test a new disease prevention strategy" and/or "explore the differential responses to interventions amongst subpopulations." A positive pilot trial would pave the way to an R01-level RCT by: (1) generating critical proof-of-concept data (eIMPACT-DM can improve A1c) to support the premise of the definitive trial; (2) providing preliminary effect sizes for eIMPACT-DM on diabetes risk markers to help justify future power analyses; (3) identifying a potentially important moderator of eIMPACT-DM efficacy that may need to be incorporated into the definitive trial. Ultimately, demonstrating that depression treatment reduces diabetes risk would have a substantial positive impact. It would identify a novel target (depression) for diabetes prevention efforts, and it would equip healthcare providers with a new practical, scalable, and disseminable intervention (eIMPACT-DM) to help lower diabetes risk for a large cohort of high-risk patients.

3.0 Outcome Measures/Endpoints

Primary Outcome (A1c)

The primary outcome is 6-month change in hemoglobin A1c. A1c will be measured at pre- and post-treatment by an immunoturbidimetric method on a Randox Daytona Clinical Analyzer in the Translation Core Analyte Lab of the Indiana CTSI. A1c is the best choice for our primary outcome for many reasons. First, A1c is considered the gold standard assessment of glycemic control and is a common surrogate endpoint in diabetes trials.[16] Also, A1c ≥6.5% is diagnostic of diabetes.[86] Second, A1c strongly predicts future diabetes.[17] A systematic review[18] found that the 5-year incidence of diabetes increased sharply with A1c, from <9% incidence for A1c 5.0-5.5% to 9-25% incidence for A1c 5.5-6.0% and 25-50% incidence for A1c 6.0-6.5%. The diabetes incidence rate for A1c 5.0-5.5%, 5.5-6.0%, and 6.0-6.5% was approximately 2 times, 5 times, and 20 times greater than for A1c <5.0%, respectively.[18] Third, interventions producing A1c improvements have been shown to also improve clinical diabetes endpoints,[19,20] and diabetes prevention interventions targeting glycemic control result in reduced rates of progression from prediabetes to T2D.[8,17] Thus, A1c is associated with clinical benefit. Fourth, A1c has statistical advantages. As a continuous measure, it provides greater statistical power than clinical events and thus requires smaller samples and shorter follow-ups. Also, because A1c reflects average glucose over the preceding 90-120 days,[139] it is more stable than alternative measures, such as fasting glucose and oral glucose tolerance tests.[86] For all of these reasons, A1c is well suited to evaluate if a new intervention approach holds promise, and it is appropriate and feasible for pilot trials.

Secondary Outcome (HOMA Score)

The secondary outcome is 6-month change in insulin resistance, as indicated by HOMA score. HOMA scores[80] will be derived from fasting glucose (glucose oxidase method on a Randox Daytona Clinical Analyzer) and insulin (two antibody immunoassay on a Roche cobas e411 Analyzer). Fasting glucose and insulin assays will be performed in Translation Core Analyte Lab of the Indiana CTSI. HOMA score is an established index of insulin resistance that correlates highly with the more invasive euglycemic clamp (r=0.85-0.88) and is appropriate for assessing change.[111-114]

Exploratory Outcome (Incident Diabetes)

The exploratory outcome is time to T2D onset, defined as the first occurrence of the following between the participant's enrollment date and five years after their post-treatment visit date: T2D diagnosis (ICD-10 E11), fasting glucose ≥126 mg/dL, A1c ≥6.5%, or death due to T2D. The Regenstrief programmer will identify incident T2D cases by searching INPC – the statewide health information exchange (see B3) – blinded to group assignment. Our endocrinologist (Dr. Saeed), also blinded, will use standardized criteria to adjudicate all incident T2D cases. As we are doing in the eIMPACT Trial, we will obtain authorization from participants to conduct INPC searches to identify incident diabetes until five years after their post-treatment visit date. We will assess this outcome annually, with the first assessment at post-treatment. Because only a large Phase III trial would be powered for clinical events, incident T2D is an exploratory outcome. Based on our prediabetes inclusion criterion and the review described above,[70] we expect a diabetes incidence rate of ≥25% over 5 years. Dr. Stewart will use his faculty development funds ($4K/year) and/or his research account ($50K) to cover INPC searches after the project period.

Somatic Depressive Symptoms

Total depressive symptoms will be assessed by the 20 depression items (response options: 0-4) of the Symptom Checklist-90 (SCL-20), a reliable and valid scale,[115-118] at the pre-

and post-treatment visit. Patients with a score ≥2 to the hyperphagia item and/or hypersomnia item at pre-treatment will be coded as "yes" for the presence of somatic depressive symptoms. All others will be coded as "no."

Other Factors

Weight, height, blood pressure, heart rate, respiration rate, and temperature will be measured by CRC nurses (pre, post). Validated questions/scales will assess demographics, medical/psychiatric history, current medications, alcohol use (AUDIT),[73] tobacco use (BRFSS Tobacco Use Questionnaire),[119,120] physical activity (International Physical Activity Questionnaire),[121] OHA adherence (Morisky Medication Adherence Scale-8),[122-124] depressive symptoms (PHQ-9),[74,75] anxiety (GAD-7),[125] hostility/anger (Buss-Perry Aggression Questionnaire),[76] trait positive affect (Positive Affect subscale of the PANAS),[77,78] life satisfaction (Satisfaction with Life Scale),[79] insomnia symptoms (Insomnia Severity Index),[80] sleep quality (PSQI),[126] eating behaviors (Dutch Eating Behavior Questionnaire),[81]quality of life (SF-20)[82] (all pre, post), and expectancy of benefit[83] (pre). Attention will be determined from the intervention database for eIMPACT-DM patients and from EMR chart review for AC patients (post). Depression care variables (e.g., antidepressant dose/duration and psychotherapy session number/type) will be determined from the treatment delivery database for eIMPACT-DM patients and from EMR chart review for Active Control patients (post). Patients will complete a brief interview to assess depression care received outside of the trial (post). We will assess depression treatment acceptability (post). Diabetes prevention care received outside the trial will be assessed by EMR chart review (post) and a brief interview (post). We will also assess for the occurrence of any potential adverse events using a brief questionnaire and will administered the Techniques for Overcoming Depression Questionnaire[84] (post).

Type	Name	Time Frame	Brief Description
Hemoglobin A1c	Primary	Baseline, 6 months	The primary outcome is 6-month change in hemoglobin A1c, which will be measured at pre- and post-treatment by an immunoturbidimetric method on a Randox Daytona Clinical Analyzer in the Translation Core Analyte Lab of the Indiana CTSI. A1c is the gold standard glycemic outcome,[16] a strong predictor of future diabetes development,[17,18] and a potent indicator of improvement in clinical diabetes endpoints.[8,17,19,20]
HOMA score	Secondary	Baseline, 6 months	The secondary outcome is 6-month change in insulin resistance, as indicated by HOMA score. HOMA scores[80] will be derived from fasting glucose (glucose oxidase method on a Randox Daytona Clinical Analyzer) and insulin (two antibody immunoassay on a Roche cobas e411 Analyzer). Fasting glucose and insulin assays will be performed in Translation Core Analyte Lab of the Indiana CTSI. HOMA score is an established index of insulin resistance that correlates highly with the more invasive euglycemic clamp (r=0.85-0.88) and is appropriate for assessing change.[111-114]

4.0 Eligibility Criteria

Inclusion Criteria

- Current primary care patient in Eskenazi Health: a clinic visit in the past two years at one or more of the 8 Eskenazi primary care clinics (Clinics: Blackburn, Cottage Corner, Forest Manor, Grassy Creek, North Arlington, OCC, Westside, W. 38th St, Center for Senior Health)
- Age ≥18 years
- Current depressive disorder: During screening, ResNet assistants will administer the Patient Health Questionnaire-9 (PHQ-9),[81] a validated depression diagnostic measure designed for primary care patients.[82-85] We will consider patients to have a depressive disorder if (a) they have a PHQ-9 ≥10[81] and (b) they meet criteria for a PHQ-9 MDD diagnosis (2 or more of the 9 depressive symptoms, including depressed mood or anhedonia, present in the past 2 weeks).[83] The PHQ-9 cut point of ≥10 has 88% sensitivity and 88% specificity for MDD diagnosed by a clinical interview.[81] The combination of a PHQ-9 ≥10 and a PHQ-9 MDD diagnosis helps to ensure that false positives will not be enrolled. In addition to its diagnostic validity, we chose a PHQ-9 case finding approach because: (a) it is feasible in primary care and is how depressed patients will likely be identified in clinical practice, (b) recent successful trials have used similar approaches,[106,132,133] and (c) we observed initial evidence of a signal of depression treatment on fasting glucose levels in our pilot trial, in which we used PHQ-9 ≥10 as the depression inclusion criterion (see C1).
- Prediabetes: (a) a prediabetes diagnosis (ICD-10 code R73.03) ever in the patient's EMR before enrollment or the most recent A1c in the past 2 years between 5.70-6.49% in the patient's EMR before enrollment and (b) a finger-stick A1c <6.5%[86] at the start of the pre-treatment visit

Exclusion Criteria

- History of diabetes: a self-reported type 1 or 2 diabetes diagnosis during screening or any of the following in the patient's EMR before enrollment: type 1 or 2 diabetes diagnosis (ICD-9 250.X; ICD-10 E10.X or E11.X), fasting glucose ≥126 mg/dL, A1c ≥6.5%, or insulin prescription. Patients with a pre-treatment A1c ≥6.5% will also be coded as having a history of diabetes, and their PCP will be notified. Of note, OHA use is not exclusionary, as practice guidelines recommend OHAs for prediabetes in some situations.[86]
- HIV/AIDS
- Chronic kidney disease
- Active cancer/current cancer treatment
- Ongoing treatment for an inflammatory condition (e.g., rheumatoid arthritis, lupus, Crohn's disease, and ulcerative colitis) in the past 3 months (daily use of NSAIDS is allowed)
- Current pregnancy: Women able to become pregnant will complete a urine pregnancy test at the pre-treatment visit, and those with a positive pregnancy test will not continue in the trial.
- Severe cognitive impairment: ≥3 errors on a validated 6-item cognitive screen[87] during screening
- Acute risk of suicide: Patients will be coded as at acute risk of suicide if: (a) they trigger the Suicidal Ideation Protection Protocol (see 16.0 Appendix) during screening or at the start of the pre-treatment visit and (b) after the situation is properly handled, the patient's PCP or other clinical provider considers the patient to be at acute risk of suicide.

- History of bipolar disorder or psychosis or current use of an atypical antipsychotic medication: a self-reported diagnosis of bipolar disorder or a psychotic disorder during screening or a bipolar disorder diagnosis [ICD-9 code 296.X (all); ICD-10 codes F30X (all), F31X (all), F34.0] in the patient's EMR before enrollment or a psychotic disorder diagnosis [ICD-9 code 295.X (all); ICD-10 codes F20.X (all), F21, F22, F23, F24, F25.X (all), F29] in the patient's EMR before enrollment or current use of aripiprazole, aripiprazole lauroxil, asenapine, asenapine transdermal, brexiprazole, cariprazine, clozapine, iloperidone, lumateperone, lurasidone, olanzapine, paliperidone, paliperidone palmitate, pimavanserin, quetiapine, risperidone, or ziprasidone in the patient's EMR at screening.
- Participation in the eIMPACT Trial: All patients who participated in the eIMPACT Trial will be removed from the recruitment lists of eligible patients. Thus, none will be contacted during screening.

Inclusion of Women and Minorities

None of the inclusion/exclusion criteria of the proposed pilot RCT pertain to sex, gender, race, or ethnicity, except that pregnant women will be excluded due to the potential influence of pregnancy on depression and diabetes risk markers. We conducted a preliminary EMR search and identified 47,361 demographically and medically eligible Eskenazi primary care patients with no history of diabetes (63% women, 48% non-Hispanic Black, 20% Hispanic/Latino), of whom 9,876 (21%) fell on the high priority list (positive for a prediabetes marker). Moreover, in our eIMPACT Trial involving older Eskenazi primary care patients, we have had success recruiting and retaining racial/ethnic minorities with a depressive disorder, as 49% of the 216 randomized patients identify as non-Hispanic Black, 4.6% as Hispanic/Latino, and 3.2% as multiracial. Because <3% of Indianapolis residents are American Indian/Alaskan Native, Asian, or Native Hawaiian/Other Pacific Islander (see www.stats.indiana.edu), we do not expect these racial groups to be well-represented in the proposed trial. Based on these data, we anticipate that participants in the proposed trial will be 64 primary care patients aged ≥18 years with a depressive disorder and prediabetes, of whom 60% will be women, ≥40% will be non-Hispanic Black, ≥10% will be Hispanic/Latino. We expect that, due to randomization, groups based on sex, gender, race, and ethnicity will be approximately equally represented in the two trial arms. It is worth noting that the inclusion of a high percentage of women and racial/ethnic minorities will enhance the external validity of the findings of the proposed trial.

Inclusion of Children

Participants in the proposed pilot RCT will be 64 primary care patients aged ≥18 years with a depressive disorder and prediabetes. Children (<18 years) will not be eligible because a separate, age-specific study of children is warranted and preferable for at least two reasons. One, evidence indicates that depression is experienced and expressed differently in children and adolescents (e.g., with increased irritability and suicidal ideation) versus in adults. Two, the major components of our modernized collaborative stepped care intervention for depression called eIMPACT-DM – namely, Good Days Ahead (computerized cognitive-behavioral therapy), Problem-Solving Treatment in Primary Care (telephonic cognitive-behavioral therapy), and our antidepressant algorithm optimized for diabetes risk reduction – were designed for adults and have not been fully evaluated in children. Thus, the appropriateness, acceptability, and effectiveness of eIMPACT-DM in children are unknown.

5.0 Enrollment/Randomization

Participants will be 64 primary care patients (≥18 years, 50% minority) with a depressive disorder and prediabetes but no history of diabetes.

Recruitment Plan

We will use the successful 3-stage process of our R01-funded eIMPACT Trial to recruit patients. In the eIMPACT Trial (see C2), we met our recruitment goal of randomizing 216 Eskenazi primary care patients with a current depressive disorder and CVD risk factors (78% women, 56% non-White) but no history of clinical CVD. First, a Regenstrief Institute data manager will search the Eskenazi EMR in accordance with HIPAA and IRB regulations to generate lists of potentially eligible patients. To optimize recruitment, we will have high and low priority lists. Patients will be placed on the high priority list and screened first if there is a prediabetes marker (A1c 5.70-6.49% or prediabetes ICD-10 code R73.03) present in their EMR in the last 2 years. All others will be placed on the low priority list and screened second. To ensure that patients who participated in the eIMPACT Trial are not enrolled, we will remove all such patients from these recruitment lists prior to screening. Second, ResNet personnel will obtain permission to approach for screening from each patient's PCP. ResNet, Indiana University's primary care practice-based research network, is the sole mechanism through which primary care patients can be contacted. Third, ResNet personnel will conduct high-intensity phone screening. Through administering the eligibility interview refined in the eIMPACT Trial, they will assess depression status, medical/psychiatric status, and cognitive function. For patients who are eligible and remain interested in participating, ResNet personnel will provide a brief summary of key information from the informed consent statement at the end of the call. Specifically, they will summarize: the voluntary nature of participation, the study rationale, the structure and duration of study visits/contacts, the potential risks and benefits of participation, and payment for participation. Written informed consent and authorization will be obtained from each participant at the start of the pre-treatment visit.

Using the 4.8% randomization rate from our eIMPACT Trial, we estimate that we will need to screen ≈26/week to randomize 64 patients over the 1-year recruitment period. In the eIMPACT Trial, which has similar but more restrictive eligibility criteria, 4.8% (216/4539) of approached patients were randomized. Most ineligible patients did not meet the current depressive disorder inclusion criterion. We conducted an EMR search and identified 47,361 demographically and medically eligible Eskenazi primary care patients with no history of diabetes (63% women, 48% non-Hispanic Black, 20% Hispanic/Latinx), of whom 9,876 (21%) fell on the high priority list (positive for a prediabetes marker). ResNet leadership agrees that our approach and our randomization rate and target are feasible. We will be able to start recruitment immediately because personnel and protocols are in place from the eIMPACT Trial.

Randomization

1:1 randomization[88] will be stratified by A1c (≤6.09%, 6.10-6.49%) and somatic depressive symptoms (yes, no) at pre-treatment using random number sequences.[88] Sequentially numbered, opaque, sealed envelopes containing group assignment will be prepared by the study statistician (Dr. Saha).

Blinding

All outcomes assessors will be blinded to group assignment to ensure unbiased results. The investigators and interventionists will have no data collection responsibilities, and the patients will be explicitly instructed not to reveal their group assignment to the outcomes assessors.

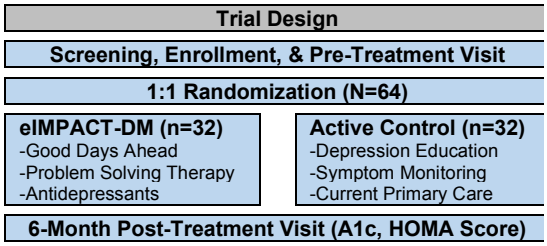
Retention Plan

We will use the successful practices of our eIMPACT Trial to retain participants over the 6-month study period. First, we will implement Mason's procedures for minimizing attrition – e.g., collecting extensive contact information for patients and at least two secondary contacts, stressing the study timeline and scientific importance of study completion at enrollment, and

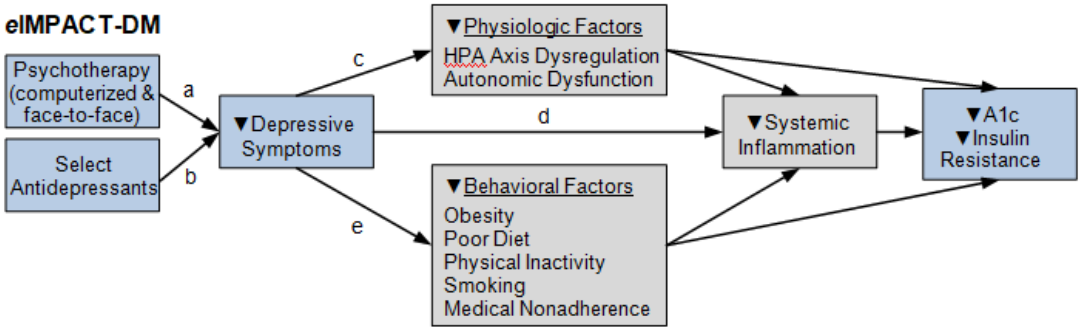
providing consistent incentives ($75 for attending the pre-treatment visit and $75 for attending the post-treatment visit). Second, we will make reminder calls and/or send reminder texts before the pre- and post-treatment visits according to patient preference (e.g., one day before, one week before, or both). Third, for all study visits, we will cover parking or transportation expenses, including arranging taxis or ride shares (e.g., Uber and Lyft) and providing bus vouchers. Fourth, we will maintain at least monthly contact with participants in both arms throughout the study period. Fifth, we will mail a mid-treatment newsletter to participants in both arms with study updates. The low attrition observed in the eIMPACT Trial indicates that our retention practices are effective, as 93% of participants in the intervention arm and 91% of participants in the usual care arm have attended the 12-month post-treatment visit.

6.0 Study Design

We propose a pilot RCT of 64 primary care patients with a depressive disorder and prediabetes. Patients will be randomized to 6 months of eIMPACT-DM (our modernized collaborative stepped care intervention for depression) or the active control (depression education, symptom monitoring, and primary care for depression). The primary outcome is hemoglobin A1c – the gold standard glycemic outcome,[68] a strong predictor of diabetes development,[69,70] and a potent indicator of improvement in diabetes endpoints.[5,69,71,72] The secondary outcome is HOMA score, an established index of insulin resistance that correlates highly with the more invasive euglycemic clamp (r=0.85-0.88) and is appropriate for assessing change.[85-88] We will also explore whether the presence of somatic depressive symptoms moderates the effect of eIMPACT-DM on diabetes risk markers (A1c and HOMA score).



In line with current conceptual frameworks,[27] we predict that eIMPACT-DM will improve A1c and insulin resistance by decreasing depressive symptoms and downstream factors (see figure). These downstream factors (grey boxes) are the leading candidate mechanisms by which depression treatment could reduce diabetes risk. First, substantial literatures indicate that depression is associated with each downstream factor (see A3). Second, intervention studies indicate that depression treatment (CBT or antidepressants) is related to improvements in autonomic dysfunction,[89-92] smoking,[93,94] inflammatory markers,[95-98] and insulin resistance.[51-53] Third, our post hoc analysis suggests that computerized CBT is associated with improvements in inflammatory markers and fasting glucose (see C2). While we expect that intervention-related reductions in depressive symptoms (paths a and b) will result in decreases in downstream factors (paths c, d, and e), some antidepressants could reduce A1c and insulin resistance via their direct effects on inflammation[99] and weight loss.[100,101] We are not testing mechanisms in the proposed RCT (mechanistic trials are not allowed under PA-18-405); however, we plan to do so in the future definitive trial. Blue boxes indicate factors to be assessed in the proposed trial.



7.0 Study Procedures

Trial Overview

Patients will attend the pre-treatment visit at the Clinical Research Center (CRC). They will fast and avoid tobacco and exercise for ≥8 hours. A finger-stick blood sample will be obtained to ensure patients have an A1c of <6.5%. Those with an A1c outside of this range will not continue. Women able to become pregnant will also complete a urine pregnancy test, and those with a positive pregnancy test will not continue in the trial. Patients will complete questionnaires, an interview, anthropometric measurements, vital signs assessments (blood pressure, heart rate, respiration rate, and temperature), and standard venipuncture (to test A1c, HOMA scores, and insulin levels). Finally, randomization will occur. Six months after randomization, patients will return to the CRC for the post-treatment visit following the same procedures as the pre-treatment visit.

Trial Setting

The setting is the 8 primary care clinics of our clinical partner, Eskenazi Health, which is affiliated with Indiana University and is the second largest safety net healthcare system in the U.S. Eskenazi provides special opportunities to study diseases, like T2D,[1] that disproportionately affect lower SES (~90% are underinsured/ uninsured) and minority (~50% are racial/ethnic minorities) populations.

Participants

Please see sections 4.0 and 5.0 above.

Treatment Groups

1:1 randomization[102] will be stratified by A1c (≤6.09%, 6.10-6.49%) and somatic symptoms (yes, no).

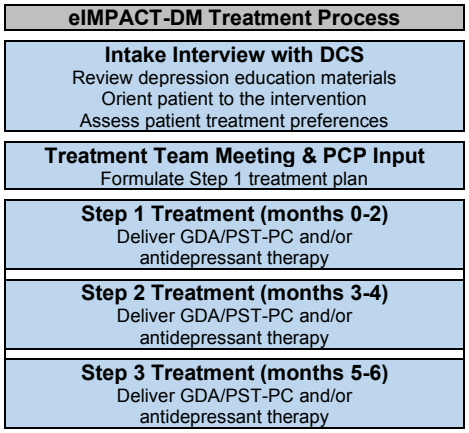
eIMPACT-DM is our eIMPACT intervention (see C2), except that Good Days Ahead has replaced Beating the Blues and the antidepressant algorithm has been optimized for diabetes risk reduction. It is a collaborative care intervention in which a multidisciplinary team delivers established depression treatments consistent with patient preference. It uses a stepped, flexible, treat-to-target approach that modernizes the IMPACT intervention[50] by harnessing technology to minimize staff and space requirements. Interventions are Good Days Ahead (GDA), Problem Solving Treatment in Primary Care (PST-PC), and antidepressants. Critically, each intervention has a strong evidence base supporting its efficacy, and the IMPACT results[50] and our data (see C2) support efficacy of the intervention structure. Our treatment team consists of a depression clinical specialist (DCS; Ms. MacDonald), a supervising psychiatrist with expertise in primary care (Dr. Bateman), and the patients' PCPs. The PI will monitor treatment fidelity.

(1) GDA (Empower Interactive; video tutorial) is an empirically supported, HIPAA compliant, computerized CBT for depression appropriate for primary care patients and people with little computer experience.[103] GDA was created by Dr. Jesse Wright (University of Louisville), Dr. Andrew Wright (University of Washington), and Dr. Aaron Beck (University of Pennsylvania). Dr. Beck is widely recognized as the father of CBT. Dr. Jesse Wright is also a co-founder of Empower Interactive. GDA uses an interactive, multimedia format (including video, exercises, calls to action, newsfeeds, and customized feedback) to deliver 9 45-minute sessions, the structure and content of which mirror face-to-face CBT. Although session content is tailored to each patient, general topics include identifying and modifying automatic thoughts, using behavioral activation and other behavioral methods, identifying and modifying schemas, using effective coping strategies, and employing other core CBT methods. Characters appearing in GDA represent diverse racial, ethnic, age, and cultural backgrounds. GDA includes a clinician portal to allow clinicians to track progress, view completed exercises, and check comprehension. GDA is empirically supported – it is acceptable to patients,[104] achieves superior depression outcomes to waitlist comparators (effect size = 1.60),[105] and yields equivalent (noninferior) depression outcomes to standard face-to-face CBT (effect size = 0.05).[105,106] GDA is being evaluated further in ongoing trials in new settings.[103]

To minimize time/transportation barriers, GDA sessions will occur at the PI's lab or a location with internet access selected by the patient (e.g., patient's, family member's, or friend's home). In our eIMPACT Trial, most patients have elected to complete BtB remotely. For those with lower confidence in using GDA, the DCS and patient will work through the first few sessions together over the phone, via IU Zoom Health, or in the PI's lab. IU Zoom Health is a HIPAA-aligned version of Zoom for use by individuals who host Zoom meetings where Personal Health Information (PHI) is shared or discussed. It is currently in use at many medical centers. Patients can install it for free onto their smartphones, tablets, or computers.

(2) PST-PC is an established, manualized, empirically supported CBT developed for primary care.[107-112] During the eight weekly 30-minute sessions, patients are taught skills for solving problems contributing to depression. We will deliver PST-PC by phone or IU Zoom Health, which we (see C2) and others[113] have found to be feasible and efficacious.

(3) Antidepressants. We first considered all FDA-approved antidepressants and excluded those with weight gain effects (tricyclics, paroxetine, mirtazapine[73,74]) and those rarely used in primary care (MAOIs[114]). Then, we used existing evidence to inform the structure. We made bupropion (an aminoketone) and fluoxetine (an SSRI) our first-line and second-line antidepressants, as meta-analyses indicate that their use is associated with weight loss.[100,101] We made other SSRIs (escitalopram, sertraline) and SNRIs (desvenlafaxine, duloxetine, venlafaxine) our third-line antidepressants, given their negligible effects on weight.[100,101] As we did in the IMPACT and eIMPACT trials, our team will make recommendations to the patient's PCP, who will write prescriptions. Our team and the PCP will then collaboratively manage pharmacotherapy.



Treatment Process. At the end of the pre-treatment visit, our DCS will speak to the patient for 20 minutes via IU Zoom Health to orient them to depression materials and schedule the intake interview. Future DCS contacts will be over the phone or via IU Health Zoom, consistent with patient preference. Our DCS will contact the patient for the intake interview. At meetings every 2 weeks, the DCS will present cases to our team, who will formulate a Step 1 plan with PCP input. The DCS will work with the PCP to implement this plan. Step 1 will be 2 months of psychotherapy or an antidepressant. GDA and PST-PC are our first- and second-line psychotherapies; bupropion and fluoxetine are our first- and second-line antidepressants (others are third-line). For patients on an antidepressant at entry, the dosage may be increased, psychotherapy may be added, or a different antidepressant may be prescribed. For patients who want psychotherapy but have major barriers to GDA, PST-PC will be offered at Step 1. Our DCS will follow patients for 6 months, while monitoring response and staffing cases with the team at least every 2 months. At the start, the DCS will have sessions at least every 2 weeks. For patients who achieve remission (≥50% PHQ-9 reduction and <3 symptoms[50]), the DCS will develop a relapse prevention plan and follow-up monthly. Step 2 – augmenting Step 1 with psychotherapy or an antidepressant or switching to another psychotherapy or antidepressant – will be delivered to patients not in remission. If remission is not achieved after Step 2, Step 3 will be initiated, which will involve additional psychotherapy and/or antidepressants.

PHQ-9 Score	Action (within 24 hours)
<10 (minimal)	Results will be reported in a note added to the EMR.
10-19 (minor/ moderate)	RA will encourage patient to seek treatment at their primary care clinic and will notify the patient's PCP and the embedded behavioral health clinician.
20-27 (severe)	RA will strongly encourage patient to seek treatment at their primary care clinic and will notify the patient's PCP, the embedded behavioral health clinician, and the affiliated psychiatrist.

Active Control (AC) consists of depression education (study staff), symptom monitoring (study staff), and primary care for depression (clinical staff). (1) At the end of the pre-treatment visit, the RA responsible for Active Control delivery (a clinical psychology PhD mentee of the PI) will speak to the patient for 20 minutes via IU Zoom Health to review depression materials,[115] including their PCP's role in its management and treatment options. In addition, patients will be provided with a list of Eskenazi mental health services, and the RA will encourage patients to follow-up with their PCP. To engender expectancy of benefit, the RA will stress that our notifications should prompt PCP actions and that the available treatments are effective. We will then send an EMR message to the PCP indicating that their patient has a depressive disorder and was randomized to the AC group. This message will encourage the PCP to address their patient's depression, note that there are no care restrictions, and provide the same list of Eskenazi services. (2) The RA will call AC patients every 4 weeks (i.e., at the end of Months 1, 2, 3, 4, and 5) to assess depressive symptoms (PHQ-9) and will notify clinical staff to encourage additional care when indicated (see table). (3) AC patients will receive current primary care for depression. The Eskenazi primary care clinics utilize a team care approach for behavioral health issues, as PCPs are supported by embedded behavioral health clinicians and affiliated psychiatrists available for brief counseling and antidepressant management.

We chose an AC comparator[116] for several reasons. (1) Because we plan to use an AC group in the R01-level RCT, we need to use it here to obtain accurate effect size estimates. Other approaches (no comparator or usual care comparator) could overestimate effect sizes. (2) Our AC group will help to ensure that the groups have similar expectancy of benefit and clinical

attention. We will assess expectancy[83] and attention and will adjust for them in a sensitivity analysis. (3) Our AC group is feasible. As eIMPACT-DM uses a flexible approach, each patient will have their own treatment path within the intervention structure. Thus, it is not possible to develop a comparator that exactly parallels the attention for each eIMPACT-DM patient.

Type	Name	Description
Behavioral (e.g., Psychotherapy, Lifestyle Counseling)	eIMPACT-DM (intervention)	eIMPACT-DM is a 6-month, modernized, collaborative, stepped care intervention consisting of (1) computerized and telephonic cognitive-behavioral therapy for depression and (2) select antidepressant medications included in an algorithm optimized for diabetes risk reduction. It is a collaborative care intervention in which a multidisciplinary team delivers established depression treatments consistent with patient preference. It uses a stepped, flexible, treat-to-target approach that modernizes the IMPACT intervention by harnessing technology to minimize staff and space requirements. Interventions are Good Days Ahead, Problem Solving Treatment in Primary Care, and select FDA-approved antidepressants. The treatment team consists of a depression clinical specialist, a supervising MD with expertise in primary care and IMPACT, and the patients' PCPs.
Behavioral (e.g., Psychotherapy, Lifestyle Counseling)	Active Control (comparator)	Active Control (AC) consists of depression education (study staff), symptom monitoring (study staff), and primary care for depression (clinical staff). (1) The RA (a clinical psychology PhD mentee of the PI) will have a 50-minute call with AC patients to review depression materials, including their PCP's role and treatment options. We will send an EMR message to the patient's PCP to encourage the PCP to address their patient's depression. (2) The RA will call AC patients every 4 weeks to assess depressive symptoms and will notify clinical staff to encourage additional care when indicated. (3) AC patients will receive current primary care for depression. The Eskenazi primary care clinics utilize a team care approach for behavioral health issues, as PCPs are supported by embedded behavioral health clinicians and affiliated psychiatrists available for brief counseling and antidepressant management.

Potential for Crossover Effects: Because randomization will occur at the patient level, it is possible that a PCP could have patients in both the eIMPACT and Active Control groups. Even so, crossover effects (i.e., diffusion of treatment) are unlikely for several reasons. One, PCPs do not attend eIMPACT treatment team meetings and do not have access to the eIMPACT treatment protocol, including the antidepressant algorithm. Instead, if treatment with an antidepressant is pursued for a particular patient, the PCP will receive a specific medication recommendation from the eIMPACT-DM treatment team via the DCS. Two, the behavioral health clinicians embedded in the targeted primary care clinics do not have the capacity or resources to deliver the intensity or modes (computerized) of psychotherapy of the eIMPACT treatment team. Three, we have not observed any evidence of crossover effects in our ongoing eIMPACT Trial, which utilizes a similar design. Moreover, our preliminary data from that trial (see C2) – i.e., 51% of eIMPACT patients, versus 20% of usual care patients, had a 50% reduction in depressive symptoms – argue against the existence of meaningful crossover effects. For these reasons, we believe that crossover effects (i.e., diffusion of treatment) are not a threat to the internal validity of the proposed pilot RCT.

Justification for Intervention and Comparator Components: We chose to incorporate only components addressing depression specifically into our intervention and active control groups. We chose not to incorporate components directly targeting factors known to improve A1c (e.g., diet, physical activity, or weight) into our intervention or active control groups, as doing so would severely cloud interpretation and undermine our ability to determine whether improving depression lowers A1c and other diabetes risk markers – the primary aim of the proposed research.

Training and Treatment Fidelity: Before launch, the treatment team will complete training with the PI on the eIMPACT-DM model and antidepressant algorithm. The DCS will also complete trainings for GDA with Empower Interactive and PST-PC with the AIMS Center. The PI will provide annual refresher trainings. At bi-monthly treatment team meetings, fidelity to eIMPACT-DM will be assessed by the PI. In addition, the PI will also audit a random subset of 20% of eIMPACT-DM and Active Control patients every 6 months and perform an assessment of treatment fidelity using our adherence checklists. We have developed a treatment delivery REDCap database for the eIMPACT Trial, which we will use here. This database, which will include the DCS's de-identified notes and EMR messages, will allow for assessments of treatment fidelity. To maintain high fidelity, the PI will provide timely feedback to the DCS and any needed training. Our approaches are in line with the NIH Treatment Fidelity Workgroup recommendations.[138]

Assessments

Please see sections 3.0 above.

8.0 Study Calendar

The timeline for study activities is shown below. In Quarter 1 of Year 1, we will complete trial start-up tasks, including obtaining regulatory approvals from the Indiana University IRB, the Indiana CTSI Clinical Research Center, and Eskenazi Health Research Committee; forming the DSMB and obtaining the board's feedback on the trial protocol; finalizing all trial manuals, protocols, questionnaire batteries, databases, and meetings; and registering this study on ClinicalTrials.gov. Of note, through the eIMPACT Trial, we have already developed many materials (treatment manuals, safety protocols, questionnaire batteries, and REDCap databases), processes (treatment team meeting structure and preferred methods of communicating with PCPs), and relationships (Eskenazi leadership, PCPs, and clinic staff). We have also obtained permission from the IMPACT PI (Dr. Unützer) to modify the IMPACT intervention and manuals. During the 1-year recruitment period (Quarter 2 in Year 1 through Quarter 1 in Year 2), we will recruit and randomize (at the end of the pre-treatment visit) 64 primary care patients with a depressive disorder and prediabetes. During the 1.5-year treatment period (Quarter 2 in Year 1 through Quarter 3 in Year 2), the eIMPACT-DM and Active Control interventions will be delivered. The post-treatment visits will begin 6 months after the first pre-treatment visit and will be completed from Quarter 4 in Year 1 through Quarter 3 in Year 2. Upon completion of the last pre-treatment visit, we will begin data management and analysis in Quarter 2 of Year 2, which will run through Quarter 4 of Year 2. Finally, in Quarters 3 and 4 of Year 2, we will prepare the R01 application to support the definitive RCT for which this pilot trial is designed to generate preliminary data.

	Year 1				Year 2			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Trial Start-Up Phase								
Recruitment & Pre-Treatment Visits								
Intervention Delivery								
Post-Treatment Visits								
Data Management & Analysis								
R01 Preparation								

9.0 Reportable Events and Data Safety Monitoring

We have developed a Data and Safety Monitoring Plan and Board to ensure the safety of participants and to monitor participant recruitment, accrual, randomization, and retention; treatment delivery and fidelity; and data collection and quality.

Data and Safety Monitoring Plan (DSMP)

Adverse Event Monitoring

As we are doing in our ongoing eIMPACT Trial (see C2), we will systematically identify potential adverse events (AEs): (a) by conducting Eskenazi Health EMR searches every 6 months (before DSMB meetings) for all emergency department visits, hospitalizations, and deaths that occurred among randomized patients and (b) by reviewing responses on a self-report questionnaire assessing for the occurrence of any potential adverse events since the pre-treatment visit administered at the post-treatment visit. The eIMPACT-DM depression clinical specialist will also receive alerts through the Eskenazi Health EMR when any randomized patient has a new emergency department visit or hospitalization, which will provide real-time monitoring. Finally, any potential adverse events spontaneously reported by participants (e.g., during a study visit or call) will be evaluated. We will fully investigate, rate, and prepare a Case Report Form for those events that are plausibly related to depression, depression treatment, suicidal ideation, or any study procedures and for all deaths. For all other captured events (emergency department visits or hospitalizations typically for chronic medical conditions that are unrelated to study involvement), we will provide frequency counts for the eIMPACT-DM and Active Control arms. We will fully investigate these events only if there is evidence of group imbalance. It is worth noting that that: (a) we are delivering safe and established depression interventions, (b) we are not delivering any new or experimental interventions or restricting usual care, and (c) all study procedures are noninvasive (except for the blood draw) and standard.

Adverse Event Rating and Reporting

All events plausibly related to depression, depression treatment, suicidal ideation, or any study procedures and all deaths will be promptly rated using the anticipation, severity, and attribution scales below. These ratings will be included in the Case Report Form for the adverse event signed by Dr. Stewart (principal investigator) and Dr. Bateman (trial psychiatrist).

Anticipation

1. Anticipated
2. Unanticipated

Severity

1. Mild: Awareness of sign or symptom but easily tolerated
2. Moderate: Interference with normal daily activities
3. Severe: Inability to perform normal daily activities
4. Life-Threatening: Immediate risk of death from the reaction as it occurred

Attribution

1. Definite: Adverse event clearly related to study involvement
2. Probable: Adverse event likely related to study involvement
3. Possible: Adverse event may be related to study involvement
4. Unlikely: Adverse event doubtfully related to study involvement
5. Unrelated: Adverse event clearly not related to study involvement

All AEs that meet the IUPUI IRB prompt reporting requirements (unanticipated; definitely, probably, or possibly related to study involvement; and suggest that the research places participants or others at a greater risk of harm than was previously known or recognized) will be immediately reported the IUPUI IRB, DSMB, CRC Research Subject Advocate, and NIH. All severe or life-threatening AEs will be immediately reported to and reviewed by the DSMB. All other AEs will be reported to these entities at the time of continuing review. A summary of AE data (e.g., frequency, types, and corrective actions) will be provided to the IUPUI IRB, DSMB, CRC Research Subject Advocate, and NIH at the time of continuing review.

Data and Safety Monitoring Board (DSMB)

As we did in our ongoing eIMPACT Trial (see C2), we will form a DSMB to provide independent oversight. None of the DSMB members will be involved in the proposed trial other than serving on this board. The DSMB will consist of a psychiatrist, an endocrinologist, and a clinical trialist from the Indiana University School of Medicine. All AEs that are severe/life-threatening or that raise questions about the risks posed to other participants will be immediately reviewed by the DSMB. In addition, every 6 months, Dr. Stewart (principal investigator) will submit a written report to the DSMB describing study updates; participant recruitment, accrual, randomization, and retention; treatment delivery and fidelity; data collection and quality; suicidal ideation protection protocol triggers; any adverse events; any protocol deviations; and any IRB amendments. At that time, the DSMB will have a closed meeting to determine whether the trial should continue unchanged, be modified, or be stopped, and the DSMB Chair will provide a written response with all recommendations. The IUPUI IRB, CRC Research Subject Advocate, and NIH will receive copies of all DSMB reports and responses at the time of continuing review.

10.0 Study Withdrawal/Discontinuation

All participants will be considered enrolled at the start of the pre-treatment visit after written informed consent and authorization are obtained. The informed consent statement describes the possibility of and the procedures for withdrawing from the study. A participant may notify either the principal investigator or any member of the research team at any time via email, phone, or in-person that s/he wants to withdraw from the study for any reason. If a participant withdraws before the pre-treatment assessment visit, no payment will be provided.

Other reasons for study withdrawal/discontinuation are: (a) the participant's primary care provider or another provider seeing the participant (e.g., a psychiatrist outside of the study team) no longer believes that the patient is appropriate for this trial after a triggering of the Suicidal Ideation Protection Protocol or any other reason, (b) the participant develops acute or serious illness that precludes completion of the main study visits within the allowed timeframes, and (c) the participant exhibits evidence of a psychotic disorder or bipolar disorder (both of which are exclusionary conditions and could interfere with treatment delivery/effectiveness) during the 6 month treatment phase of the trial. In the case of situation (b), the patient will not complete any future study visits or calls. However, if the patient provides permission, electronic medical record data (e.g., incident diabetes) will still be obtained going forward, consistent with our Authorization Form. In the case of situation (c), patients with a psychotic disorder or bipolar disorder would likely benefit from psychotropic medications, such as antipsychotic medications or mood stabilizer, that are beyond what are provided in this trial.

11.0 Statistical Considerations

Sample Size Justification and Power Analysis

This pilot RCT is not designed to detect statistically significant differences. We chose N=64, as it is sufficient to yield the expected outcomes and is feasible within the R21 constraints. Assuming an attrition rate of ≤20%,[117] we will have ≥50 completers (25/arm). With 50 completers and type I error rate=5%, we will have 55%, 68%, 79%, and 88% power to detect a d=0.60, 0.70, 0.80, and 0.90, respectively. We observed a d=0.90 for CBT for depression on fasting glucose in depressed primary care patients (see C2).

Primary Aim Analytic Plan

Analyses will use the intent-to-treat approach.[118] Tests will be two-tailed with p<.05 considered statistically significant. Supplemental analyses of completers and analyses employing multiple imputation (SAS mi and mianalyze) will be performed. We will assess for group differences in baseline factors. Due to randomization, we do not expect differences. Even so, baseline differences will be taken into account when interpreting results, and baseline factors that differ between groups will be added as covariates in sensitivity analyses. We will also add expectancy and attention as covariates in sensitivity analyses.

We will evaluate H1 and H2 (eIMPACT-DM patients will exhibit greater improvement in A1c and HOMA score) using linear mixed modeling (SAS proc mixed) with an unstructured covariance matrix. Subject will be a random effect, and treatment group, time, and their interaction will be fixed effects. Separate models will be run for the primary (A1c) and secondary (HOMA score) outcomes. Treatment group x time interactions would indicate statistically significant treatment effects. For both A1c and HOMA score, we will report the group means and standard errors; regression coefficients, 95% CIs, and p-values; and effect sizes (d's). We will consider an absolute group difference in post-treatment A1c of ≥0.3% (d=0.50) to be clinically important (e.g., 5.9% for eIMPACT-DM group versus 6.2% for AC group; d=0.50). This A1c difference corresponds to annualized diabetes incidence rate of 4.0% for the eIMPACT-DM group versus 7.0% for the AC group.[70] Because there is no absolute cut point distinguishing between normal and abnormal HOMA scores,[119] we will consider a d≥0.50 (moderate effect size[65]) as clinically important. If we find that the eIMPACT-DM produces clinically important improvements in A1c and HOMA score (d's ≥0.50), it would pave the way to an R01-level RCT by (1) generating critical proof-of-concept data to support the premise and (2) providing preliminary effect sizes for eIMPACT-DM on A1c and HOMA score. Of note, the effect size estimate used in the primary power analysis for the future RCT will be based on the minimal clinically important difference in A1c instead of solely on this RCT's results, as pilot studies tend to overestimate or underestimate true effect sizes.[120] We will use this RCT's results, along with other relevant data, to make a strong case that the selected effect size estimate is plausible and achievable.

A set of planned subgroup analyses will be performed including only participants with pre-treatment A1c values between 5.70%-6.49%. Another set of planned subgroup analyses will explore whether history of COVID-19 infection (defined as history of a positive COVID-19 test at trial entry) moderates the effect of eIMPACT-DM on A1c and HOMA score.

Exploratory Aim Analytic Plan

To explore whether somatic depressive symptoms moderate the effect of eIMPACT-DM on A1c and HOMA score, we will rerun the Primary Aim models stratified by somatic symptoms group. We expect ~60% of patients to have hyperphagia and/or hypersomnia and thus be coded as "yes" on the somatic symptoms group variable (see C3). The remaining patients will be coded as "no." We anticipate larger effect sizes for the somatic symptoms group. We will consider an effect size difference between groups of d≥0.50 to be clinically meaningful (e.g.,

d=0.75 vs. 0.25). We will compute effect sizes of treatment group x somatic symptoms group x time interactions for A1c and HOMA score; however, we expect these to be nonsignificant due to lower power. If we find clinically important effect size differences between those with vs. without somatic depressive symptoms, we will modify the design of the R01-level RCT as follows – recruitment: enroll 50% with and 50% without these symptoms; randomization: stratify on presence of these symptoms; and sample size: ensure sufficient power to detect 3-way interactions.

A set of planned subgroup analyses will be performed including only participants with pre-treatment A1c values between 5.70%-6.49%. Another set of planned subgroup analyses will explore whether history of COVID-19 infection (defined as history of a positive COVID-19 test at trial entry) moderates the effect of eIMPACT-DM on A1c and HOMA score.

Incident Diabetes

We will also explore whether eIMPACT-DM patients show a clinically relevant reduction (≥25% lower relative risk) in incident diabetes by performing a Cox model with treatment group predicting time to diabetes onset.

Sex as a Relevant Biological Variable

In exploratory analyses, we will examine sex as a moderator of treatment effects on all outcomes by testing treatment group x sex x time interactions in the Primary Aim models. In addition, we will examine whether there is sex difference in the likelihood of being classified as having a somatic presentation of depression (i.e., those with hyperphagia and/or hypersomnia) at baseline. If a sex difference is found, it would influence the design of the future definitive RCT – e.g., we would likely additionally stratify randomization by sex.

12.0 Statistical Data Management

Research materials that will be directly obtained from the participants are: (1) questionnaires; (2) standard measures of height, weight, and waist circumference; (3) blood samples; and (4) urine specimens to determine pregnancy status (women only). Only members of the research team directly involved in the proposed trial will have access to individually identifiable private information about the participants. All research material collected during the proposed project will be used for research purposes only and will be kept strictly confidential. The only research materials that will be obtained from other sources are the recruitment data: potential participants' medical records will be accessed in accordance with HIPAA and IRB regulations when the Eskenazi EMR is searched to generate a list of patients who satisfy the study inclusion/exclusion criteria.

REDCap software will be used to obtain the questionnaire data and other data (e.g., height, weight, waist circumference, and urine pregnancy test results). Blood samples will be transferred from the Indiana CTSI Clinical Research Center (CRC) to Translation Core Analyte Lab of the Indiana CTSI for secure storage until the time of assay. An Excel file reporting assay results will be securely sent to Dr. Stewart from the Translation Core Analyte Lab. SPSS statistical software will be used for all data merging, cleaning, and reduction tasks.

13.0 Privacy/Confidentiality Issues

Participants will be screenedco in the privacy of their homes via phone or the Indiana CTSI Clinical Research Center (CRC). All procedures will take place in private rooms at the CRC, Dr. Stewart's Cardiometabolic Behavioral Medicine Laboratory, the targeted primary care clinics, or a location selected by the patient, such as their home or a family member's/friend's home (for calls and the computerized and telephonic components of the treatment groups). All

research material will be kept strictly confidential. All study personnel have completed the required Collaborative Institutional Training Initiative (CITI) courses and will make every effort to ensure confidentiality. All electronic and hard copy data will be identified using only the unique participant number assigned when each individual is enrolled in this study (participant identifying information will not be included). All electronic data will be saved on password-protected and encrypted computers and secure servers, and all hard copy data will be stored in secure and locked file cabinets. The key linking participant names with the participant numbers will be kept in a separate secure and locked file cabinet. Data will be analyzed and reported as an aggregate, with no individual identifying information. Any leftover blood samples will be stored in Dr. Considine's laboratory.

14.0 Follow-up and Record Retention

Participants in both treatment groups who continue to exhibit elevated depressive symptoms (PHQ-9 ≥10) at post-treatment will be will urged to follow-up with their primary care providers regarding their depression. Their providers will also receive a letter from the study team indicating that their patient has completed participation in the treatment phase of the trial and continues to have elevated depressive symptoms. This letter will also urge physicians to follow-up with their patients and will provide a list of local mental health services.

While the study duration (i.e., project period) is 2 years, all study documents will be kept up to 7 years after study completion. After this time, we will permanently delete patient identifying data and shred all paper records, per Indiana State law. This process prevents any opportunity for a breach of confidentiality to occur.

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16.0 Appendix: Suicidal Ideation Protection Protocol

Suicidal ideation protection protocols very similar to the one described below have previously been approved by the Indiana University IRB and were successfully implemented in three other depression trials conducted by our team (IRB #'s 1105005448, 1110007119, and 1411802537). Those suicide management plans were constructed with input from Sandra Eskenazi Mental Health Center leadership (Dean Babcock, Associate Vice President, and Michael Hughes), who concluded that the plans provide a high level of protection while minimizing disruption to usual clinical activities. The informed consent form for this trial contains a section describing the steps that will be taken if an enrolled patient reports suicidal ideation on a questionnaire or spontaneously.

ResNet Phone Screening Interview

If a potential participant reports having thoughts of being better off dead or of hurting him/herself (i.e., responds with a 1, 2, or 3 to PHQ-9 Item #9 or spontaneously reports suicidal ideation) during a ResNet telephone interview, the interview will be immediately stopped, and the ResNet research assistant will interview the potential participant to complete the Patient Suicidality Form. If the potential participant answers "no" to the clarifying question, the interview will proceed as normal. If the potential participant answers "yes" to the clarifying question, the participant will be asked the three suicide questions. If the potential participant answers "no" to all three suicide questions or if the patient answers "yes" only to Question 3 (previous attempt) and the most recent attempt was ≥ 10 years ago, the interview will proceed as normal, and the completed Patient Suicidality Form will be given to the principal investigator. If the potential participant answers "yes" to any of the three questions (for Question #3 the previous attempt must be within the past 10 years), the ResNet research assistant will inform the patient that the interview must be stopped and that a behavioral health clinician must be contacted according to the study protocol. The patient will also be told that the behavioral health clinician will call them back before the end of that day. The ResNet research assistant will then contact a behavioral health clinician, who will contact the patient before the end of that day to determine the appropriate course of action (e.g., referral to the psychiatrist or to the Crisis Intervention Unit) and will notify the patient's primary care provider. After the situation is handled, the ResNet research assistant will contact the behavioral health clinician. If the behavioral health clinician considers the patient to be at acute risk of suicide (an exclusion criterion), the patient will be coded as ineligible. If the behavioral health clinician considers the patient ***not*** to be at acute risk of suicide, ResNet will attempt to contact the patient again to readminister the screening interview.

In-Person Study Visits

Suicidal ideation will be assessed using Item #9 of the PHQ-9 at the pre- and post-treatment visits. The PHQ-9 may also be administered periodically in person by the depression clinical specialist during the treatment phase. Suicidal ideation will also be assessed using items #3 "thoughts of ending your life" and #14 "thoughts of death or dying" on the SCL-20 at pre- and post-treatment visits.

If an enrolled patient reports having thoughts of being better off dead or of hurting him/herself (i.e., responds with a 1, 2, or 3 to PHQ-9 Item #9; responds with a 1, 2, 3, or 4 to SCL-20 Item #3 or #14; or spontaneously reports suicidal ideation) during an in-person study visit, the visit will be immediately stopped, and the research assistant or depression clinical specialist will interview the participant to complete the Patient Suicidality Form. If the potential participant answers "no" to the clarifying question, the visit will proceed as normal. If the

potential participant answers “yes” to the clarifying question, the participant will be asked the three suicide questions. If the participant answers “no” to all three suicide questions or if the patient answers “yes” only to Question 3 (previous attempt) and the most recent attempt was ≥ 10 years ago, the visit will proceed as normal, and the completed Patient Suicidality Form will be given to the principal investigator. If the participant answers “yes” to any of the three questions (for Question #3 the previous attempt must be within the past 10 years), the research assistant or depression clinical specialist will immediately contact Dr. Stewart. If Dr. Stewart cannot be reached, contact Dr. Bateman. Dr. Stewart (a clinical psychologist) and Dr. Bateman (the trial psychiatrist) will review the case as soon as possible, but no later than the same day, to determine the appropriate course of action (e.g., interview the patient to obtain further information, immediately contact the patient’s primary care provider and/or behavioral health clinician to involve them in the decision-making process, consult with clinicians at Sandra Eskenazi Mental Health Center, escort the patient to the Crisis Intervention Unit, and/or contact the police if the patient is at imminent danger of harm and is refusing all care). The depression clinical specialist will also notify the participant’s primary care provider if s/he was not involved in the decision-making process. Regardless of the exact course of action, the study team will ensure that the participant is connected to the appropriate existing clinical services. If the patient’s primary care provider no longer believes that the patient is appropriate for this trial following a situation, s/he will be withdrawn.

Study Calls

Suicidal ideation will be assessed using Item #9 of the PHQ-9 during most study calls completed by the depression clinical specialist responsible for intervention delivery and during most study calls competed by the research assistant responsible for active control delivery.

If an enrolled patient reports having thoughts of being better off dead or of hurting him/herself (i.e., responds with a 1, 2, or 3 to PHQ-9 Item #9 or spontaneously reports suicidal ideation) during a study calls, the research assistant or depression clinical specialist will immediately interview the participant to complete the Patient Suicidality Form. If the potential participant answers “no” to the clarifying question, the call will proceed as normal. If the potential participant answers “yes” to the clarifying question, the participant will be asked the three suicide questions. If the participant answers “no” to all three suicide questions or if the participant answers “yes” only to Question 3 (previous attempt) and the most recent attempt was >10 years ago, the call will proceed as normal, and the completed Patient Suicidality Form will be given to the principal investigator. If the participant answers “yes” to any of the three questions (for Question #3 the previous attempt must be within the past 10 years) or prematurely terminates the call, the research assistant or depression clinical specialist will immediately contact Dr. Stewart. If Dr. Stewart cannot be reached, contact Dr. Bateman. Drs. Stewart and Bateman will review the case as soon as possible, but no later than the same day, to determine the appropriate course of action (e.g., interview the patient to obtain further information, immediately contact the patient’s primary care provider and/or behavioral health clinician to involve them in the decision-making process, consult with clinicians at Sandra Eskenazi Mental Health Center, refer the patient to the Crisis Intervention Unit, and/or contact the police if the patient is at imminent danger of harm and is refusing all care). The depression clinical specialist will also notify the participant’s primary care provider if s/he was not involved in the decision-making process. Regardless of the exact course of action, the study team will ensure that the participant is connected to the appropriate existing clinical services. If the patient’s primary care provider no longer believes that the patient is appropriate for this trial following a situation, s/he will be withdrawn.

Patient Suicidality Form

Interviewer:_____ Date: _____

Patient's Name: _____ Hospital ID: _____

Patient's Address: _____

Patient's Phone Number: _____ Patient's PCP: _____

****

Clarifying Question
Over the past 2 weeks, have you been having thoughts of hurting yourself in some way?

Yes ____ No ____
(Continue) (Stop, no SIPP trigger)

Comments:

****

I'm going to ask you a few questions that are part of the study protocol, because we have seen that in some patients with these symptoms, these are important concerns.

1. Do you have a suicide plan?

Yes ____ No ____

Comments:

2. Have you been struggling against thoughts about committing suicide? In other words, are you afraid you might act on these thoughts?

Yes ____ No ____

Comments:

3. Have you attempted suicide in the past?

Yes ____ No ____

If YES, in what year was the most recent attempt? _____

Comments:

If the patient answers "yes" to any of the three questions (for Question #3 the previous attempt must be within the past 10 years), you must carefully follow the procedures described in the Suicidal Ideation Protection Protocol.