eIMPACT Trial:
Modernized Collaborative Care to Reduce the Excess CVD Risk of Older Depressed Patients
(ClinicalTrials.gov ID: NCT02458690)

Trial Protocol
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Jesse C. Stewart, Ph.D.
Principal Investigator
Department of Psychology
Indiana University-Purdue University Indianapolis
402 N. Blackford Street, LD 100E
Indianapolis, IN 46202

Christopher M. Callahan, M.D.
Co-Investigator
Department of Medicine
Indiana University School of Medicine
HITS Suite 2000
Indianapolis, IN 46202

John I. Nurnberger, Jr., M.D., Ph.D.
Co-Investigator
Department of Psychiatry
Indiana University School of Medicine
791 Union Drive
Indianapolis, IN 46202

Samir K. Gupta, M.D., M.S.
Co-Investigator
Department of Medicine
Indiana University School of Medicine
Emerson Hall, Room 421
545 N. Barnhill Dr.
Indianapolis, IN 46202-5124

Richard J. Kovacs, M.D.
Co-Investigator
Department of Medicine
Indiana University School of Medicine
Krannert Institute of Cardiology, Room E300
1801 N. Senate Blvd., Suite E4000
Indianapolis, IN 46202

Robert V. Considine, Ph.D.
Co-Investigator
Department of Medicine
Indiana University School of Medicine
Gatch Clinical Building, Room 455
1120 W. Michigan Street
Indianapolis, IN 46202

Sujuan Gao, Ph.D.
Co-Investigator
Department of Biostatistics
Indiana University School of Medicine
410 West 10th Street, Suite 3000
Indianapolis, IN 46202

Bruce L. Rollman, M.D., M.P.H.
Consultant
Professor of Medicine, Psychiatry,
Clinical and Translational Sciences, and Biomedical Informatics
University of Pittsburgh School of Medicine
230 McKee Place, Suite 600
Pittsburgh, PA 15213

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1.0 Background

Significance

CVD and depression are top public health concerns; they are highly prevalent, deadly, and costly.
CVD is highly prevalent and disproportionately affects older adults.[1] A total of 15.4 and 6.8 million Americans suffer from coronary artery disease (CAD) and cerebrovascular disease (CBV).[1] CVD is also deadly. CAD and CBV are the first and fourth leading causes of death in the U.S.[2] Finally, the economic burden of CVD is substantial. For 2009, total cost in the U.S. was estimated to be $312.6 billion, which is greater than all cancers.[1] Furthermore, due to the rapidly growing elderly population, the prevalence of CAD and CBV are projected to increase by 18-22% by 2030, and the total cost is expected more than double.[1]

Depression is also a top concern. In the U.S., major depressive disorder (MDD) has a lifetime prevalence of 16.2%,[3] and the point prevalence of depressive disorders in primary care is 16-19%.[4,5] Depression is the leading cause of disability,[6] and the annual total cost of depression is over $83.1 billion.[7] By 2020, CVD and depression are projected to be the #1 and #2 causes of disease burden worldwide.[6]

Depression is an independent risk and prognostic factor for CVD.
Thirty years of evidence indicates that depression is an independent risk and prognostic factor for CAD and CBV.[8,9] Meta-analyses have shown that adults with a depressive disorder or symptoms have a 64% greater risk of CAD onset[10,11] and that depressed CAD patients have a 59% greater likelihood of a future CVD event than their nondepressed counterparts.[9] The depression-CVD relationship is comparable in strength to conventional CVD risk factors[12] and has been detected in men and women and in various age and racial/ethnic groups.[8,13-15] Although other emotional factors have been linked to CVD,[16] the depression association is the most consistently observed[16] and seems to be independent of anxiety and hostility/anger.[17] CVD risk increases with depression severity,[10] indicating a dose-response relationship. Finally, depression has been linked to several atherogenic factors, which supports the biological plausibility of these prospective associations.

Because depression satisfies 8 of Hill's 9 criteria for causation,[18] it is reasonable to conclude that depression is an independent, and potentially causal, risk factor for CVD. Experimental animal research also supports a causal relationship between depression and atherogenesis.[19] The lack of experimental evidence in humans, however, prevents one from drawing a causal inference, as the possibility that a third factor (e.g., genetic variants related to inflammation) explains the depression-CVD association has not been ruled out.[20]

The Problem: Attempts to improve CVD outcomes of depressed patients have been unsuccessful.
Despite this strong evidence base, the few trials that have evaluated whether depression interventions reduce the likelihood of CVD events generally have not observed the anticipated benefits. A key study was the Enhancing Recovery in Coronary Heart Disease (ENRICHD) Patients trial, in which 2,481 post-MI patients with depression and/or low social support were randomized to cognitive-behavioral therapy (CBT) or usual care. After 29 months, no difference in nonfatal MI or death was found.[21] In the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART), depressed CAD patients randomized to selective serotonin reuptake inhibitor (SSRI) treatment had a numerically lower rate of CVD events than patients randomized to placebo.[22] This suggestive trend was not confirmed in the Myocardial Infarction and Depression Intervention Trial (MIND-IT), in which depressed post-MI patients were randomized to a staged pharmacologic intervention or usual care.[23] Follow-up studies of ENRICHD, SADHART, and MIND-IT confirmed the absence of intervention effects on medical outcomes.[24-26] Interestingly, some post hoc analyses of these trials revealed that patients whose depression improved had better long-term medical outcomes.[24,25,27] However, other researchers have suggested that these relationships may be due to confounding, as early improvements in medical status after a CVD event may predict both later improvements in depressive symptoms and a reduced likelihood of recurrent CVD events.[28,29] This would explain the null intervention effects in these trials.

There are two intriguing exceptions to these negative trials; however, methodological factors cloud interpretation. The first is the TeamCare trial,[30] in which depressed patients with diabetes or CAD were randomized to usual care or blended collaborative care for depression and diabetes/CAD risk factor control. At 12 months, the intervention group exhibited greater improvements in glycated hemoglobin, cholesterol, and blood pressure but not hospitalization rates. Unfortunately, it is unclear whether the depression or diabetes/

CAD components were responsible for these improvements. The second is the Coronary Psychosocial Evaluation Studies (COPES) trial,[31] in which 6 months of the IMPACT intervention was delivered to persistently depressed CAD patients. At 6 months, intervention patients had fewer CVD events (3 vs. 10), although only 13 total events occurred. Unfortunately, this interesting trend was not maintained in a recent follow-up of this trial.[32] In sum, the critical problem is the absence of interventions to improve CVD outcomes of a large cohort of (depressed) patients at elevated risk of CVD onset, poor CVD prognosis, and high healthcare costs.

A Viable Solution: Treating depression before clinical CVD may yield cardiovascular benefits.
Shimbo et al.[33] and others[28,34] have summarized possible reasons for why past depression trials did not detect cardiovascular benefits, including (a) depression differences between treatment and control arms may have been too small to improve CVD outcomes (perhaps due to weak intervention effects, high spontaneous remission rates, or high treatment rates in the control groups), (b) treatment was not initiated while the patient was hospitalized, and (c) the interventions may have been too short (≤6 months). A novel explanation, however, is that the late timing of depression treatment in the natural history of CVD may have played a role. Critically, the past trials all involved patients with preexisting CVD. For several reasons (see b1), we previously hypothesized that treating depression before, versus after, clinical CVD onset could reduce CVD risk.[13]

As a first step, we conducted a follow-up study[35] of Indiana sites of the IMPACT trial,[36] in which older depressed patients were randomized to collaborative care or usual care. We found that IMPACT patients without baseline CVD had a 48% lower risk of a hard CVD event than usual care patients, whereas there was no treatment effect among patients with baseline CVD. Our findings (a) provide preliminary support for our hypothesis that initiating depression treatment before clinical CVD onset may reduce CVD risk and (b) suggest a complement or alternative to the current paradigm of initiating depression treatment after clinical CVD onset to improve CVD prognosis. These unique results strengthen the case that depression is a CVD risk factor and suggest that depression treatment may bring about a clinically relevant reduction in CVD risk.

The IMPACT trial, however, was not designed to test our hypothesis. Consequently, our findings are post hoc and observational, CVD outcomes were not pre-specified endpoints, and virtually no mechanistic data were collected. To address these key limitations, there is a current need for a well-powered, prospective trial.

Establishing that depression treatment reduces CVD risk would have a substantial positive impact.
In the scientific domain, a positive trial would vertically advance the field of behavioral medicine in three ways. **(1)** It would expand the focus of this research area to include delivering depression treatment before, instead of only after, CVD onset. **(2)** It would remove a critical barrier to progress (past null intervention effects on CVD outcomes) and pave the way for the next step project: a multisite, event-driven Phase 3 trial to confirm eIMPACT's efficacy in reducing CVD risk. Specifically, a positive Phase 2 trial would generate the mechanistic rationale (biological plausibility of intervention effects), efficacy evidence (first support of our central hypothesis from a well-powered, prospective trial), and effect size estimates (intervention effects on FMD, candidate mechanisms, and CVD events, which would be combined with estimates from other relevant studies) needed to justify and design a Phase 3 trial. Moreover, a positive Phase 2 trial would further establish the feasibility of our recruitment, intervention, and assessment approaches. **(3)** The proposed trial will address two long unanswered questions: (a) Is depression a causal risk factor for CVD? (b) What mechanisms underlie the depression-CVD relationship? The lack of experimental evidence, which this trial could generate, prevents depression from being labeled a causal CVD risk factor. In addition, although several plausible mechanisms have been proposed, little direct support has been generated. Elucidating the mechanisms underlying the cardioprotective effect of eIMPACT would allow us to optimize our intervention for CVD risk reduction by adding adjunctive treatments directly targeting the identified mechanisms (e.g., anti-inflammatory medication). In the clinical domain, demonstrating that depression treatment reduces CVD risk, the main expected outcome of this overall line of research, would have a positive impact for three reasons. **(1)** It would identify a novel target for CVD prevention, likely leading to the inclusion of depression in risk management guidelines. **(2)** It would equip primary care providers with a new tool (eIMPACT) to simultaneously treat depression and manage the CVD risk of a large cohort of high-risk patients. This tool would also be of use to specialists working with patient groups in which depression is prevalent and CVD risk is high, such as those with diabetes and HIV.[37,38] **(3)** Positive results, combined our practical intervention, should facilitate the dissemination of eIMPACT, possibly resulting in higher rates of quality depression care. Even though addressing depression in medical settings is a priority, it goes untreated in many patients. Data from a nationally representative sample suggests

that that only 22% of MDD cases receive adequate care.[3] Demonstrating that a depression intervention reduces CVD risk should move depression treatment up the priority list of both the patient and provider and should encourage healthcare administrators to divert more resources to depression care. In addition, because using a computerized CBT reduces dependence on trained therapists, eIMPACT is more disseminable and scalable, easier to deliver with high fidelity, and likely more cost effective and sustainable than current collaborative care models. Furthermore, eIMPACT has the potential to reach patients with logistical barriers to treatment, such as those in rural areas. eIMPACT's properties (disseminable, scalable, cost-effective, sustainable, and accessible) maximize the public health impact of this line of research.

These three practice changes (identifying a novel treatment target, equipping providers with a new tool, and facilitating intervention dissemination) should reduce CVD morbidity, mortality, and costs, as our preliminary results suggest that treating 1,000 depressed patients may prevent 164 hard CVD events over 5 years.[35] Recently, the American Heart Association set its 2020 Impact Goal, which is "to improve the cardiovascular health of all Americans by 20%, while reducing deaths from CVDs and stroke by 20%." In addition, NHLBI expressed a commitment to reducing socioeconomic status (SES) disparities in CVD in its strategic plan.[39] Given that depression is highly prevalent, especially in low SES groups,[40] depression treatment could play a key role in achieving AHA's goal and in reducing health disparities. Although our preliminary results suggest that a negative trial is unlikely, its importance should not be overlooked. Such an outcome would indicate a need to shift our focus to designing and evaluating alternative approaches to reducing the excess CVD risk of depressed patients (e.g., intervening directly on the underlying mechanisms).

Innovation

Depression treatment will be delivered before clinical CVD onset, a promising complement or alternative to current paradigm of treating depression in CVD patients to improve CVD outcomes. We propose and report preliminary evidence that treating depression before, versus after, the onset of clinical CVD could yield more pronounced cardiovascular benefits, an idea that is plausible for several reasons.

One, earlier treatment of another CVD risk factor, hypercholesterolemia, produces larger benefits,[41-43] perhaps by slowing atherosclerotic progression.[44] Combining data from trials and prospective studies, Law et al.[42] estimated that the risk reduction in CAD events of a 1.8 mmol/l decrease in LDL cholesterol (achievable with statins) was greater among patients in their 50s (77%) than those in their 60s (61%) and 70s (49%). Other evidence suggests that earlier treatment may slow atherosclerotic progression, as younger age at initiation of statin treatment predicted smaller increases in carotid intima-media thickness over time in children with familial hypercholesterolemia.[44] A recent meta-analysis of genetic studies also bolsters the earlier treatment rationale; it was found that lower LDL cholesterol beginning early in life (due to a mutation) confers a 3 times greater reduction in CAD risk than the same lowering of cholesterol later in life (due to statin treatment).[41] Altogether, these findings raise the possibility that earlier treatment of other modifiable CVD risk factors, including depression, may also slow atherosclerotic progression and prevent CVD events to a greater degree. We are not the first to argue for earlier treatment of CVD risk factors;[45-50] we are just the first to apply this rationale to depression. Steinberg et al. stated that "much of the same reasoning [for hypercholesterolemia] applies to obesity, cigarette smoking, hypertension, diabetes mellitus, and other reversible risk factors" (p. 627).[48]

Two, our past work[15,17] and other studies indicate that depression exerts a cardiotoxic influence early in CVD pathogenesis. Depression is reliably associated with endothelial dysfunction[51] and predicts progression of subclinical atherosclerosis in humans[15,17,52,53] and early atherogenesis in primates.[19] Intervening earlier, when depression is exerting a deleterious effect, would minimize exposure to this CVD risk factor.

Three, depression treatments may have greater antidepressive efficacy before clinical CVD onset. Most trials of depressed CVD patients have reported relatively small effect sizes for depression outcomes (0.20-0.38).[54] Similarly, the depressive symptoms effect size observed in our IMPACT follow-up study was 0.06 among depressed patients with baseline CVD; however, it was much larger (0.69) among patients without baseline CVD (see c2.2). A possible explanation is that subgroups of depressed CVD patients in the past trials were experiencing vascular depression[55] (which responds poorly to treatment[56,57]) or an adjustment reaction related to CVD diagnosis and treatment (which is more likely to spontaneously remit[58,59]). Consistent with the latter idea, two trials have reported medium effect sizes in CVD patients with persistently elevated depressive

symptoms.[31,60] Because we will enroll depressed patients without clinical CVD, our sample should have few patients from the subgroups thought to be contributing to the smaller effect sizes of past trials.

Four, conventional prognostic factors, such as CVD event severity or cardiovascular interventions (e.g., revascularization procedures), may override the effect of depression during the later stages.[16,61]

We will examine multiple candidate mechanisms of eIMPACT's hypothesized effect on CVD risk. As we have done previously,[15] we will conduct formal statistical mediation tests to examine the leading candidate mechanisms through which depression treatment may reduce CVD risk – i.e., decreases in depressive symptoms, autonomic dysfunction, systemic inflammation, and platelet activation. We will also explore atherogenic behavioral factors, conventional CVD risk factors, and depression care variables as potential mechanisms (see c3.5). Although many plausible mechanisms have been proposed previously, testing for mediation is rare in this field,[62] particularly in the favorable context of a RCT, which allows for stronger inferences. The proposed study would be the first prospective trial to examine candidate mechanisms underlying the hypothesized cardioprotective effect of depression treatment initiated before CVD onset.

eIMPACT is a novel intervention and an appropriate selection for the proposed trial. Although collaborative depression care has been examined in CVD patients,[31,60,63] no trials in this area have incorporated computerized psychotherapy into this framework. The original IMPACT intervention is an established, collaborative, stepped care program involving a multidisciplinary team delivering evidenced-based treatments (antidepressants and psychotherapy) consistent with patient preference.[36,64,65] We will modernize the IMPACT intervention (a) by adding a computerized CBT, Beating the Blues (BtB), as the first-line psychotherapy and (b) by delivering other components, including Problem Solving Treatment in Primary Care (PST-PC), via telephone. BtB is a stand-alone CBT program for depression designed for primary care patients and appropriate for adults with lower reading levels and computer experience.[66] BtB uses an interactive, multimedia format to deliver 8 weekly sessions, the structure and content of which mirror face-to-face CBT. We will also deliver PST-PC via telephone, which Davidson et al.[60] recently found to be feasible and efficacious.

In addition to being novel, there are two reasons why eIMPACT is an appropriate selection. First, the eIMPACT components are efficacious and acceptable. In the IMPACT trial,[36] 45% of intervention patients versus 19% of usual care patients had >50% reduction in depressive symptoms, and satisfaction was high. In our IMPACT follow-up study,[35] we observed a moderate to large effect size for depressive symptoms (see c2.1). BtB has more empirical support than any other computerized psychotherapy, including a positive RCT of 274 primary care patients.[67,68] BtB has been found to be a potent intervention,[67-75] with effect sizes comparable to face-to-face CBT.[76] In our pilot trial, we observed a large BtB effect size for depressive symptoms (see c2.2). BtB has been shown to be acceptable to patients[66,74,75] and was recently found to be effective, acceptable, and preferred to usual care among older adults.[77] In 2006, NICE recommended BtB for managing depression in the English National Health Service.[78] Early studies in the U.S. are promising,[79] and large trials are underway (including Dr. Rollman's trial; NCT01482806). Because we are retaining the key elements of the IMPACT model and our pilot data support the efficacy of BtB in the target population, we expect eIMPACT to achieve an effect size as large as the original IMPACT intervention with fewer human resources.

Second, eIMPACT fits very well with our long-term goal of developing, optimizing, and disseminating treatments to improve the CVD outcomes of a large cohort of patients at elevated risk of CVD onset, poor CVD prognosis, and high healthcare costs. To achieve this goal, large-scale dissemination and adoption must be possible. Because eIMPACT uses a stand-alone computerized CBT, it is more disseminable and scalable, easier to deliver with high fidelity, and likely more cost effective[80] and sustainable than current collaborative care models. Given that components of eIMPACT are computer and telephone delivered, it also has the potential to reach patients with logistical barriers. Finally, implementation tools for the IMPACT intervention are available (see impact-uw.org) and could be leveraged to facilitate dissemination and adoption of eIMPACT.

Our trial design is not ideal for determining the differential efficacy of the eIMPACT components. If that was our goal, we would have chosen a 2 Antidepressants (yes, no) x 2 CBT (yes, no) design. While such a study would be valuable, our trial is the preferable next step in our view. First, we selected a flexible and efficacious treatment model to achieve our broader objective of determining whether successfully treating depression earlier in the natural history of CVD reduces CVD risk. Second, dismantling eIMPACT could neutralize some

key strengths (i.e., stepped care, patient choice, and treat to target), potentially compromising its efficacy. Third, justifying the higher cost of a dismantling study is difficult when the intact treatment has not been shown to reduce CVD risk in a prospective trial. Based on our IMPACT follow-up study,[35] we expect eIMPACT patients to receive both antidepressants and CBT (50%), antidepressants only (26%), CBT only (12%), or neither component (12%). To generate hypotheses, we propose supplemental analyses to explore which components are most strongly related to the outcomes (see c3.5).

Brachial flow-mediated dilation (FMD) is an innovative and appropriate primary outcome.
The proposed trial would be the first to examine the effect of depression treatment, delivered before clinical CVD onset, on endothelial dysfunction. Endothelial dysfunction, the impaired ability of the vascular lining to maintain normal homeostasis,[81] is an early precursor to and plays a central role in atherosclerosis.[82] FMD is a noninvasive technique that uses high-resolution ultrasound to measure changes in brachial diameter in response to stimuli,[83] with results correlating closely with coronary endothelial function.[84,85] Measurements are made before and after endothelium-dependent and endothelium-independent stimuli.[86] The endothelium-dependent stimulus is hyperemic blood flow triggered after the release of an inflated blood pressure cuff around the forearm. The shear stress from the increased blood flow causes endogenous vasodilators (e.g., nitric oxide) to be released from the endothelium, which relaxes the vascular smooth muscle. This dilation of the brachial artery is thus a measure of the endothelium's ability to respond normally to hyperemic shear stress. Nitroglycerin, the endothelium-independent stimulus that directly relaxes smooth muscle, is then applied to assess the smooth muscle's functional capacity. If FMD is low and nitroglycerin-mediated dilation is normal, the endothelium (and not the smooth muscle) can be safely assumed to be dysfunctional.

FMD is the best choice for the primary outcome of the proposed trial for several reasons. One, endothelial dysfunction is considered a barometer of total CVD risk and the final common pathway through which CVD risk factors promote atherosclerosis.[87-89] Endothelial dysfunction (a) has been observed in adults with CVD risk factors but no detectable disease,[83,90-97] (b) is related to other vascular disease measures,[98-100] and (c) is an independent predictor of CVD events among initially healthy persons, at-risk individuals, and CVD patients.[101-112] Two, intervention-related improvements in FMD predict a reduced incidence of CVD events,[113-115] indicating that FMD is a predictor of clinical benefit. In contrast to anatomic measures such as coronary calcification and carotid thickness, FMD also responds within weeks of pharmacologic and behavioral interventions,[87] making it well suited to evaluate if a new treatment approach holds promise. Three, FMD is a continuous measure of CVD risk that provides greater statistical power than dichotomous outcomes. Thus, trials with FMD as the primary outcome require much smaller samples and shorter follow-ups than CVD event-driven trials. Four, a recent meta-analysis[51] and our pilot findings (see c2.3) demonstrate that depressed adults exhibit evidence of endothelial dysfunction as measured by FMD relative to their nondepressed counterparts.
Although results of some surrogate endpoint trials have not been confirmed in subsequent event-driven trials,[116] this risk is minimized here. First, we have already detected a beneficial effect of a similar intervention on CVD events in our post hoc analysis of the IMPACT trial,[35] increasing the likelihood that we will see a comparable effect in a prospective, event-driven Phase 3 trial. Second, in the proposed Phase 2 trial, we will collect event data and explore whether eIMPACT patients show a clinically relevant reduction in events.

Using a statewide information exchange to identify CVD events is unique and has advantages.
We will leverage this unique resource to identify CVD events. The Indiana Network for Patient Care (INPC),[117,118] the nation's largest clinical data repository (see Facilities and Other Resources), was an NIH-funded expansion of the Regenstrief Medical Record System,[119] which has been used extensively for clinical research. The INPC contains 4.7 billion bits of standardized clinical data for 14.7 million patients from 19,000 physicians, 90 hospitals, and 110 clinics and other sites. The participating systems deliver registration records; coded diagnoses and procedures; laboratory, pathology, and vital signs data; emergency department, inpatient, and outpatient encounter data; and pharmacy data. INPC also gathers data from Indiana Medicaid and other commercial payers, as well as death data from the Indiana State Department of Health.

Advantages of our approach include minimal attrition and an observation period that can be easily extended. As in our IMPACT follow-up study,[35] we anticipate having event data for nearly all randomized patients, given that (a) we will identify most CVD events through INPC searches (no patient participation required) and (b) we have developed procedures (e.g., follow-up calls) to identify the few events that may occur outside of the INPC

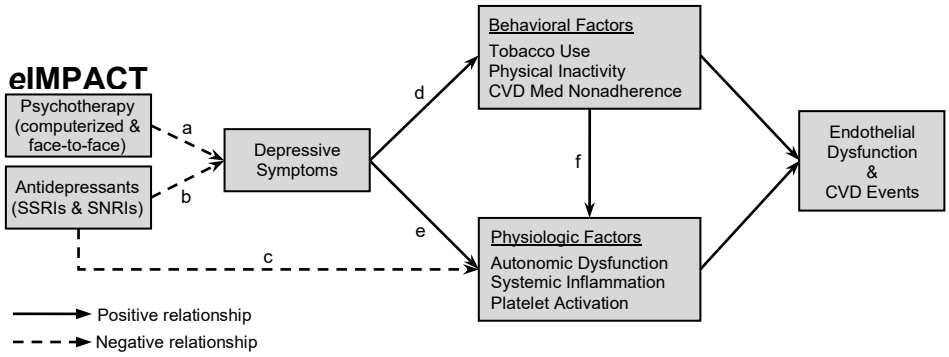
catchment area. Extending the observation period to capture more CVD events would also require few resources, as it would involve the data manager re-running INPC search programs.

Proposed Research and Conceptual Framework

We will conduct a Phase 2 randomized controlled trial of 220 primary care patients aged 50+ years with a depressive disorder and CVD risk factors but no clinical CVD. Patients will be randomized to 12 months of eIMPACT or usual care and will be followed for a mean of 4 years. The conceptual framework guiding our trial is shown in Figure 1. Our central hypothesis is that eIMPACT will improve endothelial dysfunction by decreasing depressive symptoms, autonomic dysfunction, systemic inflammation, and platelet activation.

The atherogenic physiologic and behavioral factors in Figure 1 are the leading candidate mechanisms through which depression treatment may reduce CVD risk. Substantial literatures indicate that depression is reliably associated with each factor,[120-126] as well as endothelial dysfunction.[51] Although far fewer in number, some studies have reported more direct evidence. We and others have observed that the strength of the depression-CVD association is attenuated after adjusting for autonomic function indices,[127,128] inflammatory markers,[128-130] physical activity,[130-133] and smoking.[15,130,131,133] Finally, evidence suggests that CBT and SSRIs decrease autonomic dysfunction,[134-137] inflammation,[138-143] platelet activation,[144-147] and smoking.[148,149] While we propose that treatment-related reductions in depressive symptoms (paths a and b) will result in decreases in the atherogenic factors (paths d and e), we also hypothesize that SSRIs and SNRIs will reduce CVD risk via their direct effects on inflammation and platelet activation (path c).[33,147,150] We chose the physiologic factors as secondary outcomes, given that they represent likely pathways through which behavioral factors increase CVD risk (path f). This conceptualization is in line with current models of the depression-CVD relationship[151] and empirical findings.[152-155] We will examine behavioral factors as mechanisms in exploratory analyses.

Figure 1. **Conceptual Framework of the Proposed Clinical Trial**



2.0 Rationale and Specific Aims

Cardiovascular disease (CVD) is a top public health concern in the U.S. CVD is highly prevalent and is the number one killer of Americans. Moreover, its economic burden is substantial and on the rise.[1,2] Thirty years of evidence indicates that adults with depression are at increased risk of CVD events and poor CVD prognosis;[8,9] however, attempts to improve the CVD outcomes of depressed patients have been unsuccessful. The few trials[21-23,30-32] that have evaluated whether depression interventions reduce the likelihood of CVD events generally have not observed the anticipated benefits. The reasons for these null results have been the subject of debate.[34] We recently proposed a novel explanation: the depression interventions in these trials, all of which involved patients with preexisting CVD, may have been delivered too late in the natural history of CVD.[13] We hypothesized that treating depression before, versus after, the onset of clinical CVD could reduce CVD risk because: (1) earlier treatment of another CVD risk factor, hypercholesterolemia, yields more pronounced benefits,[41-44] (2) depression exerts a cardiotoxic influence early in CVD pathogenesis,[17,19,51,53] (3) depression treatments appear to have greater antidepressive efficacy prior to clinical CVD onset,[36,54] and (4) conventional prognostic factors may override depression's harmful effect during the later stages of CVD.[16,61]

As a first step, we conducted an 8-year follow-up study[35] of Indiana sites of the Improving Mood-Promoting Access to Collaborative Treatment (IMPACT) trial,[36] in which older depressed patients were randomized to a collaborative care intervention or usual care. Results supported our hypothesis. Intervention patients without baseline CVD had a 48% lower risk of myocardial infarction (MI) or stroke than usual care patients. There was no treatment effect among patients with baseline CVD. Although these results are unique and potentially significant, the IMPACT trial was not designed to test our hypothesis. Thus, our findings are post hoc and observational, CVD outcomes were not pre-specified endpoints, and virtually no mechanistic data were collected. To address these key limitations, there is a current need for a well-powered, prospective trial.

Our long-term goal is to develop, optimize, and disseminate treatments to improve CVD outcomes of a large cohort of patients at elevated risk of CVD onset, poor CVD prognosis, and high healthcare costs. This project's objective is to test whether our modernized IMPACT intervention (eIMPACT), delivered before CVD onset, reduces CVD risk. We propose a Phase 2 randomized controlled trial of 220 primary care patients (≥50 years, 40% African American) with a depressive disorder and CVD risk factors but no clinical CVD. Patients will be randomized to 12 months of eIMPACT (a collaborative stepped care program including antidepressants and computerized and telephonic cognitive-behavioral therapy) or usual care (usual primary care for depression). Patients will be followed for a mean of 4 years. The primary outcome is endothelial dysfunction assessed by brachial flow-mediated dilation (FMD),[81] which is considered a barometer of CVD risk.[88] Critically, intervention-related improvements in FMD predict a reduced incidence of CVD events.[113-115] Our central hypothesis is that eIMPACT will improve endothelial dysfunction in depressed patients by decreasing depressive symptoms, autonomic dysfunction, systemic inflammation, and platelet activation, which are leading candidate mechanisms. We will test our central hypothesis by carrying out these specific aims:

Aim 1: Determine whether eIMPACT reduces the excess CVD risk of depressed patients. Depressed patients randomized to eIMPACT, versus usual care, will exhibit a clinically and statistically significant improvement in the primary outcome of endothelial dysfunction at the 12-month post-treatment visit (Hypothesis 1). We will also explore whether eIMPACT patients, versus usual care patients, show a clinically relevant reduction (25% lower relative risk[156,157]) in CVD events (exploratory outcome) over a mean observation period of 4 years (1-year intervention period plus 3-year follow-up period).

Aim 2: Examine candidate mechanisms underlying the effect of eIMPACT on CVD risk. Depressed patients randomized to eIMPACT, versus usual care, will exhibit greater decreases in the secondary outcomes of depressive symptoms (Hypothesis 2), autonomic dysfunction (Hypothesis 3), systemic inflammation (Hypothesis 4), and platelet activation (Hypothesis 5) at the 12-month post-treatment visit. We will also explore whether decreases in these four candidate mechanisms (a) are associated with improvements in endothelial dysfunction and (b) are partial mediators of eIMPACT's hypothesized cardioprotective effect.
A positive trial would generate the mechanistic rationale, efficacy evidence, and effect size estimates needed to justify and design a multisite, event-driven Phase 3 trial to confirm eIMPACT's efficacy in reducing CVD risk. Conversely, a negative trial would indicate a need to evaluate alternative approaches to reducing the excess CVD risk of depressed patients. Demonstrating that depression treatment reduces CVD risk, the main expected outcome of this line of research, would have a substantial positive impact. It would identify a novel target (depression) for CVD prevention efforts, and it would equip providers with a new disseminable and scalable tool (eIMPACT) to treat depression and manage the CVD risk of a large cohort of high-risk patients. These clinical practice changes should translate into reduced CVD morbidity, mortality, and costs, as our preliminary results suggest that treating 1,000 depressed adults may prevent 164 CVD events over 5 years.[35]

3.0 Inclusion/Exclusion Criteria

Inclusion criteria

- Primary care patients
- Age ≥ 50 years
- Current depressive disorder
- Elevated CVD risk

To identify patients with a current depressive disorder, ResNet assistants will administer the PHQ-9,[158] a validated diagnostic measure designed for primary care patients.[159-162] We will consider patients to have a depressive disorder if (a) they have a PHQ-9 ≥10[158] and (b) they meet criteria for a PHQ-9 depressive disorder diagnosis (2 or more of the 9 depressive symptoms, including depressed mood or anhedonia, present in the past two weeks).[160] The cut point of ≥10 has 88% sensitivity and 88% specificity for MDD diagnosed by a clinical interview.[158] The combination of a PHQ-9 ≥10 and a PHQ-9 depressive disorder 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,[31,60,163] and (c) we observed evidence of a signal of depression treatment on endothelial function and inflammation in our pilot trial, in which we used the PHQ-9.

Elevated CVD risk will be defined as ≥1 (if 60+ years) or ≥2 (if 50-59 years) of the following risk factors in the medical record in the past 5 years but no clinical CVD: hypertension, hypercholesterolemia, diabetes, or current smoking. According to the Framingham risk calculator for primary care patients,[164] the odds of a CVD event of a 50-year-old man/woman with 2 risk factors is about equivalent to that of a 60-year-old man/woman with 1 risk factor.

Exclusion Criteria

- History of clinical cardiovascular disease
- Presence of the following chronic disorders: HIV/AIDS, chronic kidney disease, or active cancer/current cancer treatment
- History of bipolar disorder or psychosis
- Continuous (e.g., daily) treatment for a systemic inflammatory condition (e.g., rheumatoid arthritis, lupus, Crohn's disease, and ulcerative colitis) in the past 3 months. Nonsteroidal anti-inflammatory drug (NSAID) use is allowed, given its high prevalence in the target population.
- Current use of anticoagulants (Aspirin and cholesterol and blood pressure medications are allowed.)
- Acute risk of suicide
- Severe cognitive impairment (≥3 errors on 6-item cognitive screen[165])
- Current pregnancy
- Ongoing depression treatment with a psychiatrist outside of the Eskenazi Health/Midtown system (ongoing depression treatment with a Eskenazi Health/Midtown psychiatrist is allowed, as we will be able to collaborate and coordinate depression care)

A history of clinical CVD will be defined as any of the following in the medical record before enrollment: CAD (ICD-9 410-414, 429.2) or CBV (ICD-9 430-434) diagnosis, acute MI (CK-MB >3.0 ng/ml or troponin >0.3 µg/L), percutaneous coronary intervention (ICD-9 00.66, 36.03, 36.06, 36.07, 36.09; CPT 92980-92984, 92995, 92996), or *c*oronary artery bypass graft *(*ICD-9 36.10-36.19; CPT 33510-33536).

4.0 Enrollment/Randomization

We will use the 3-stage process of our past trials to recruit patients. First, the Regenstrief Medical Records System,[166] one of most comprehensive electronic medical records, will be searched in accordance with HIPAA to generate lists of eligible patients. Next, ResNet assistants will obtain permission to approach from each patient's provider. ResNet, Indiana University's primary care practice-based research network, is the sole mechanism through which patients in the targeted clinics can be contacted for research. ResNet also maintains a patient registry, which will also be used by ResNet to identify potentially eligible patients. Finally, ResNet assistants will conduct high-intensity in-clinic and telephone screening and will enroll eligible patients (see Appendix 1 for Screening Interview). ResNet assistants will use a paper copy or a REDCap version of the Screening Interview. Through administering the eligibility interview refined in our pilots, ResNet assistants will assess cognitive function, medical/psychiatric status, and depression status; will obtain consent and authorization; and will implement the suicidal ideation protection protocol.

We estimate that ≈4,320 patients (45/week) will need to be approached, consistent with the IMPACT trial.[36] We will be able to start recruitment immediately, as the infrastructure, personnel, and protocols are in place from the PI's recent trials. At the Indiana sites of the IMPACT trial, 6.4% of approached patients were randomized. We conservatively estimate that 5% of approached patients will be randomized (9/month) in the proposed trial. Patients who meet inclusion/exclusion criteria and consent will be scheduled for the pre-treatment visit. Because only patients who attend this visit will be randomized, it will serve as a prerandomization compliance screening.[167]

In the unanticipated event of slower-than-projected recruitment, we will first request direct referrals from providers in the targeted clinics. Next, we will pursue expanding recruitment to another healthcare system in Indianapolis, such as the VAMC or Community Health Network. Finally, we will extend the recruitment window up to a year if the benefits to the primary outcome of endothelial dysfunction (ample power due to a larger sample) outweigh the costs to the exploratory outcome of CVD events (shorter observation period).

At the end of the pre-treatment visit described below, the randomization procedure will be initiated. To balance the groups on two strong FMD correlates,[91] randomization will be stratified by sex and age (50-59 and 60+ years) using random number sequences.[168] Sequentially numbered sealed envelopes containing group assignment will be prepared by the study statistician (Dr. Gao).

5.0 Study Procedures

Overview, Visits, and Setting

We will conduct a Phase 2 randomized controlled trial of 220 primary care patients aged 50+ years with a depressive disorder and CVD risk factors but no clinical CVD. Patients will be randomized to 12 months of eIMPACT, our modernized IMPACT intervention, or usual care and will be followed for a mean of 4 years.

The timing of activities is shown in the table below. We will strive to schedule patients within two weeks of enrollment, although some visits will fall outside of that window due to conflicts in the patients' schedules and no-showed or rescheduled appointments. Patients will attend a 3-hour pre-treatment visit at the Indiana CTSI Clinical Research Center. To minimize the effect of extraneous factors on FMD,[169,170] patients will be told to fast and to avoid tobacco and exercise for ≥8 hours before their visit. The exam room will be kept at 68-71°F, and premenopausal women will be scheduled within 2 weeks of menstruation onset. Patients will have their height, weight, and BP measured; will complete self-report scales on a secure SurveyMonkey website designed for this study visit; and will undergo FMD and heart rate variability assessments and a blood draw (standard venipuncture). To end this visit, the randomization procedure will be initiated, the patient and the treatment team will be notified of the assignment, and the mid-treatment call and post-treatment visit will be scheduled. If the patient is randomized to the eIMPACT intervention, the depression clinical specialist will conduct a brief session over FaceTime to orient the patient to intervention materials and to schedule the initial assessment. The FaceTime session will not be recorded. Within 2 weeks, the depression clinical specialist will call eIMPACT patients to initiate treatment, and a research assistant will send a letter to the primary care providers of usual care patients to notify them that their patient has a depressive disorder and to encourage follow-up. Approximately six months after randomization, research assistants will contact all patients to complete the 45-min mid-treatment call. First, a brief questionnaire used in our pilot trials will be administered to assess for the occurrence of CVD events since enrollment. As we have also done in our pilot projects, the self-reported scales completed at pre-treatment will then be readministered. Approximately twelve months after randomization, patients will return to the Clinical Research Center for the post-treatment visit, during which all factors measured at pre-treatment will be reassessed. Finally, research assistant will contact patients annually after their post-treatment visit to complete the follow-up calls, with the last call coming within 2 weeks of the study end date. These calls will follow the same procedures as the mid-treatment call.

The schedule of participant reimbursement is as follows: $100 for the pre-treatment visit, $25 for the mid-treatment call, $100 for the post-treatment visit, $20 for each of the annual follow-up calls, and up to $10 per visit to cover parking or transportation costs.

	Year 01					Year 02					Year 03					Year 04					Year 05				
Recruitment & Pre-Treatment Visits																									
Treatment																									
Mid-Treatment Calls																									
Post-Treatment Visits																									
Annual Follow-Up Calls																									
Analysis & Manuscript Submission																									

The setting, which is identical to the IMPACT trial, is the primary care clinics of two healthcare systems affiliated with Indiana University: Eskenazi Health and Indiana University Health. Eskenazi Health, a safety net

healthcare system, provides care for ≈20% of the population of Indianapolis. The Eskenazi Health Center for Senior Health, where elderly patients receive primary care, is included in the targeted clinics. About 90% of Eskenazi patients are underinsured or uninsured, and 50% are African American. Therefore, these patients provide special opportunities to research diseases that disproportionately affect lower SES and minority populations, such as CVD.[1,171] Indiana University Health, a large academic medical center, is Indiana's most comprehensive healthcare system.

Treatment Groups

eIMPACT
eIMPACT is a collaborative stepped care intervention involving a multidisciplinary team delivering evidenced-based treatments consistent with patient preference. We will modernize the IMPACT intervention (a) by adding a computerized CBT as the first-line psychotherapy and (b) by delivering some of the other components via telephone or FaceTime (see below). None of the computerized, telephonic, or FaceTime sessions will be recorded. Other than restricting the list of antidepressant medications to maximize CVD risk reduction, the remaining IMPACT components will not be altered.

Beating the Blues (BtB; Ultrasis PLC) is a widely used, empirically supported, stand-alone CBT program for depression designed for primary care patients and appropriate for adults with little computer experience and a 5th-6th grade reading level.[66] In prior trials, we have used the UK and US versions; we will use the US version in the proposed trial (see www.beatingthebluesus.com for a brief video tutorial). BtB utilizes an interactive, multimedia format to deliver eight 50-minute, weekly sessions, the structure and content of which mirror face-to-face CBT. Although sessions are tailored to each patient's problems, general topics include challenging dysfunctional thoughts, activity scheduling, problem solving, graded exposure, task breakdown, sleep management, and relapse prevention. Patients are also assigned tailored homeworks.

To minimize treatment barriers (e.g., transportation issues) and attrition, to reduce subject burden, and to ultimately facilitate implementation of *e*IMPACT, BtB sessions will occur in a private room at the Clinical Research Center, at Dr. Stewart's laboratory, at the patient's primary care clinic, or in a location selected by the patient where s/he can access a computer with internet, such as the patient's home, the patient's work, a family member's/friend's home, or a public library. Patient preference will drive the location decision. Patients will be offered with ear bud headphones if they plan to use them at remote locations and do not already own a pair that they would rather use. All patients completing BtB will be provided with a BtB binder that contains printouts of all BtB worksheets.

To begin each in-person BtB session, an assistant will collect the homework. The patient will then work alone through the BtB session at his/her own pace, with the assistant providing help only with technical issues. To end the session, the assistant will give the patient the printed homework.

Remote BtB sessions will scheduled, just like in-person sessions. To begin each remote BtB session, an assistant call the patient to instruct the patient to put last week's homework in the BtB binder, to address any technical issues, and to ensure that the patient has launched the correct BtB session for that day. The patient will then work alone through the BtB session at his/her own pace, with the assistant monitoring progress remotely on the secure BtB website set up for this trial. To end the session, the assistant will call the patient back to address any questions and ensure that the patient has identified the correct printed homework in the BtB binder.

Problem Solving Treatment in Primary Care (PST-PC) is a manualized, empirically supported CBT developed for use by healthcare professionals in primary care.[172-177] The focus of the 6-10 30-minute sessions is teaching patients approaches for solving current problems contributing to depression. PST-PC was the first-line therapy in the IMPACT trial; however, it is our second-line therapy. We will deliver PST-PC primarily via telephone or FaceTime (although in-person sessions are also allowed), which Davidson et al.[60] found to be feasible and efficacious in the recent CODIACS Vanguard trial. Our consultant (Dr. Rollman) also completed the Bypassing the Blues trial in which his team delivered collaborative depression care to cardiac patients via telephone and observed positive results.[63]

The IMPACT treatment manual provides guidelines for using antidepressants, such as selecting a medication, titrating, switching to another medication, managing side effects, and avoiding drug interactions.[65] To optimize eIMPACT for CVD risk reduction, we have restricted the IMPACT list of antidepressants to SSRIs, duloxetine, bupropion, and mirtazapine. These medications are FDA approved for the treatment of depression and are the safest from a cardiovascular perspective.[178,179] We are prohibiting the use of most serotonin-norepinephrine reuptake inhibitors (SNRIs) and all tricyclics due to their potential adverse effects on cardiovascular parameters.[178,179] We do not expect this change to have a negative effect on depression outcomes, as antidepressants not on our list of allowed medications are typically used only as second- or third-line treatments and also have contraindications.[65]

At the first session, the depression clinical specialist (DCS), a Master's-level licensed mental health counselor (LMHC), will review depression materials and discuss treatment options. The DCS will then work with the patient's primary care provider to develop a plan that follows the IMPACT algorithm[65] with modifications noted above. Our modernized algorithm recommends a Step 1 treatment of 8-12 weeks of BtB or an antidepressant depending on the patient preference. Providers will manage prescriptions. In addition to delivering PST-PC, the DCS will help the patient adhere to antidepressant therapy and schedule pleasurable activities. If the patient is taking an antidepressant at baseline, the dose will be increased, BtB will be added, or the antidepressant will be discontinued and another one will be prescribed or BtB will be delivered. If the patient wants psychotherapy but has a strong preference for traditional treatment, PST-PC will be offered at Step 1. The DCS will have weekly team meetings with the supervising psychiatrist (Dr. Nurnberger) and primary care expert (Dr. Callahan), during which new cases and those requiring plan changes will be discussed. Fidelity to the eIMPACT algorithm will be continually assessed and recorded by the supervisors at these team meetings, and adjustments needed to ensure high fidelity will be made.

The DCS will follow patients for 12 months, while monitoring response.[158] At the start, the DCS will attempt to have telephone sessions or contacts at least every 2 weeks. For patients who achieve remission (≥50% PHQ-9 reduction and <3 MDD symptoms[36]), the DCS will develop a relapse prevention plan and follow up monthly. Step 2 treatment – which involves either augmenting Step 1 treatment with an antidepressant or psychotherapy or switching to another antidepressant or psychotherapy – will be delivered to patients who do not achieve remission. If a patient does not respond after 6-10 more weeks, Step 3 treatment will be initiated, which consists of additional medications and psychotherapy, hospitalization, or other services. In the IMPACT trial,[36] intervention patients had 9.2 ± 6.2 in-clinic sessions and 6.1 ± 5.1 telephone contacts with a DCS during the 12 months of treatment. At the end of the 12 month treatment phase, the participant will receive a certificate indicating completion of eIMPACT treatment. We expect similar numbers in our trial, although most sessions/contacts will be via telephone. Based on our experiences, one DCS can manage 80-100 patients. The maximum number of patients in treatment at any given time in this trial will not exceed 80.

Usual Care

This arm was modeled after the IMPACT trial control group.[36] At the pre-treatment visit, patients will be informed of their depression diagnosis and group assignment, will be provided with a list of local mental health services (with contact information) available to Eskenazi patients, and will be encouraged to follow-up with their primary care provider regarding their depression. These patients will also be reminded (from the informed consent statement) that, although we will pass along information to their primary care provider, participants in this group do not receive any depression treatment from the study team; instead, all depression treatments that participants in this group receive during the study are delivered by their usual providers. The patient's PCP will also receive a letter indicating that their patient has a depressive disorder and was randomized to usual care. This letter will encourage the PCP to follow-up with their patient to address their depression, will note that there are no restrictions on the care that these patients can receive, and will provide the same list of Eskenazi mental health services given to patients. Although this feedback could result in treatment that would not have occurred naturally in primary care, informational support alone is unlikely to improve depression outcomes.[180] Moreover, our pilot trial indicates that depression outcomes achieved with usual care in targeted clinics remain suboptimal (see c2.2). Patients in both arms will continue to have access to services that are part of usual care in the targeted systems. There will be no restrictions on the care received, although new depression treatments received outside of the trial are discouraged in the eIMPACT group.

<u>Assessments</u>

	Pre-Treatment* (0 months)	Mid-Treatment† (6 months)	Post-Treatment* (12 months)	Annual Calls† (2-4 calls)
Endothelial Dysfunction (Primary Outcome)	X		X	
Atherogenic Physiologic Factors (Secondary Outcomes)	X		X	
Depressive Symptoms (Secondary Outcome)	X	X	X	X
CVD Events (Exploratory Outcome)		X	X	X
Atherogenic Behavioral Factors	X	X	X	X
Conventional CVD Risk Factors	X		X	
Miscellaneous Factors	X	X	X	X

*Clinical Research Center Visit. †Telephone Call.

Endothelial Dysfunction (Primary Outcome)

Patients will undergo FMD assessments at Dr. Gupta's laboratory in accordance with consensus guidelines.[81] Dr. Gupta as well as Ms. Grounds and Ms. Scott (our vascular ultrasonographers) have undergone certified training through the University of Wisconsin Brachial Artery Reactivity Testing Symposium. Our group has performed 700+ FMD assessments in the past 10 years. We utilize a GE Logiq E ultrasound system with AccessPoint 2011 software. To illustrate the reproducibility of our results, we performed paired FMDs over 1-4 weeks in 11 healthy volunteers in 2013. Intraclass correlations for baseline diameter, reactive hyperemia, and FMD were 0.98, 0.98, and 0.70, which compare favorably to other laboratories.[181-183]

After a 10-minute supine rest, high-resolution baseline images of the brachial artery will be obtained from 3 consecutive cardiac cycles. Next, the forearm cuff will be inflated to 250 mmHg for 5 minutes and then rapidly deflated. At 60 and 90 seconds post deflation, images from 3 consecutive cardiac cycles will be acquired. Brachial diameters will be measured at peak R wave. FMD values will be computed as % increase in diameter at 60 or 90 seconds post deflation[196,197] (the larger of the two values). Percent change in reactive hyperemic flow velocities will also be computed to ensure that sufficient shear stress triggers were induced.

Atherogenic Physiologic Factors (Secondary Outcomes)

To quantify autonomic function, we will assess high-frequency heart rate variability, a parasympathetic index, following established guidelines.[184,185] See our paper[186] for complete details. Briefly, using an electrode arrangement recommended by Qu et al.,[187] a HIC-2000 impedance cardiograph, and MindWare software, estimates of high-frequency heart rate variability (ln of ms^2/Hz) will be derived by spectral analysis (bandwidth: 0.15-0.40 Hz) from 1-minute epochs of ECG data obtained during the last 5 minutes of a 10-minute rest period. To control for the influence of respiration rate on high-frequency heart rate variability, participants will complete a paced-breathing computer task set to a normal resting rate of 12 breaths/minute during ECG data collection. Values will be corrected for respiration.[188,189] Blood samples obtained by research nurses from the median cubital vein will be centrifuged within 20 minutes. Plasma aliquots will be frozen at -80°C until the time of assay at the Indiana CTSI Clinical Research Assay Laboratory directed by Dr. Considine. To quantify systemic inflammation, we will measure IL-6 and CRP levels using R&D Systems ELISA kits. To quantify platelet activation, we will measure levels of platelet-specific release products, β-thromboglobulin (BTG) and platelet factor 4 (PF4),[190] using R&D Systems ELISA kits. The remaining plasma aliquots will saved for possible future assays. Assistants scoring the autonomic data and performing the assays will be blind to assignment.

Depressive Symptoms (Secondary Outcome)

Like the IMPACT trial,[36] we will assess depressive symptoms with 20 depression items of the Symptom Checklist-90 (SCL-20), a reliable and valid measure.[191-194] We will examine total score and % remitted. We also added an item (”Sleeping too much") to the SCL-20 to measure this symptom of atypical depression that was not including in the original questionnaire. We will also administer the PHQ-9 to assess depressive symptoms.

CVD Events (Exploratory Outcome)

Our exploratory outcome, modeled after the JUPITER trial,[195] is time to first major CVD event, defined as: CVD death (ICD-10 I20-I25 or I60-I69 the first-listed cause of death); nonfatal MI (CK-MB >3.0 ng/ml, troponin >0.3 µg/L, or ICD-9 410); nonfatal stroke (ICD-9 430-432, 433.01, 433.11, 433.21, 433.31, 433.91, 434.01, 434.11, 434.91); unstable angina requiring hospitalization (inpatient admission ICD-9 411.1); and revascularization – i.e., percutaneous coronary intervention (ICD-9 00.66, 36.03, 36.06, 36.07, 36.09; CPT 92980-92984, 92995, 92996) or coronary artery bypass graft (ICD-9 36.10-36.19; CPT 33510-33536). Because recruitment will occur during Years 01-02, the mean observation period will be 4 years (1-year intervention period plus 3-year follow-

up period), with a range of 3-5 years. The Regenstrief programmer who worked on our IMPACT study[35] will identify candidate CVD events by searching the INPC every 6 months (blind to assignment), with the last search performed on the end date. To capture the small number of events that may occur outside of the INPC catchment area, patients will complete a CVD questionnaire at mid- and post-treatment and during the follow-up calls. If a reported event is not in the INPC, we will request medical records from the patient to confirm the event. Our cardiologist (Dr. Kovacs), also blinded, will use standardized criteria to adjudicate all CVD events for this exploratory outcome. Dr. Kovacs has served on endpoint committees for past trials. When needed, Dr. Kovacs will consult with the cardiologist on the DSMB (also blinded). Given that we are coding "harder" events and that many events will be positive for multiple markers, it is unlikely that coded events will be misclassified. We may fail to detect (and thus initially misclassify) a few events through INPC, which is why we are obtaining patient reports and medical records.

Atherogenic Behavioral Factors
The BRFSS Tobacco Use Questionnaire, International Physical Activity Questionnaire, and the Morisky Questionnaire (MMAS-8) will assess tobacco use, physical activity, and adherence to cholesterol and blood pressure medications, respectively. Each scale possesses strong psychometric properties.[196-198]

Conventional CVD Risk Factors
SBP and DBP will be the mean of the last 2 of 3 readings.[199] Fasting cholesterol, glucose, insulin, and HbA1c will be quantified using standard methods. BMI will be computed from measured height and weight.

Miscellaneous Factors
Standard questions from our pilot studies will be used to assess demographics, medical history/update, psychiatric history/update, and current medications. Depression care variables (e.g., dose and duration of antidepressants, # and type of psychotherapy sessions) will be extracted from the treatment notes for eIMPACT patients. To obtain additional depression care data, all patients will complete a brief interview at the mid- and post-treatment visits and during the follow-up calls. Consistent with approved Authorization Form for this study, we will also periodically extract relevant depression treatment data (e.g., dose and duration of antidepressants) from the electronic medical record for all patients. We will also assess anxiety symptoms using the Generalized Anxiety Disorder-7 (GAD-7),[200] hostility/anger using the Buss-Perry Aggression Questionnaire,[201] trait positive affect using the Positive Affect subscale of the Positive and Negative Affect Schedule (PANAS),[202,203] and sleep quality using the Pittsburgh Sleep Quality Index,[203] all of which are widely used and validated instruments. We will also assess depression treatment satisfaction using an item employed in other recent depression trials conducted on the IUPUI campus and for the occurrence of any potential adverse events using a brief questionnaire. Finally, the Regenstrief programmer will identify potential adverse events by searching the INPC every 6 months (before DSMB meetings) for emergency department visits, hospitalizations, and deaths.

All items of the questionnaires to be administered at the pre-treatment visit (see Appendix 2), mid-treatment visit (see Appendix 3), post-treatment visit (see Appendix 4), and annual follow-up calls (see Appendix 5) can be found in the appendices.

Suicidal Ideation Protection Protocol

For the entire protocol, see Appendix 6.

6.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

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

Data and Safety Monitoring Plan:

- If an adverse event occurs, its severity will be promptly graded using the following scale:
  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

- After grading severity, the attribution of the adverse event will be graded using the following scale:
  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 adverse events that meet the IUPUI IRB prompt reporting requirements (i.e., unexpected, related or possibly related to participation in the research, and suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized) will be reported the IUPUI IRB, CRC Research Subject Advocate, and NIH immediately. All other adverse events will be reported to these entities at the time of continuing review.
- A summary of adverse event data (frequency, types, and corrective actions) will be provided to the IUPUI IRB, CRC Research Subject Advocate, and NIH at the time of continuing review.

Data and Safety Monitoring Board:

- A 4-member, independent Data and Safety Monitoring Board (DSMB) will be formed to provide independent oversight. The DSMB will consist of a psychiatrist (from the Indiana University Department of Psychiatry), a cardiologist (from the Indiana University Krannert Institute of Cardiology), a clinical trialist (from the Indiana University Department of Biostatistics), and a medical ethicist (from the Indiana University Center for Aging Research), all of whom will not be part of the study team.
- Adverse events that are severe, life-threatening, or unanticipated will be immediately reviewed by the DSMB. At 6-month intervals, the DSMB will prepare a formal report of participant recruitment, accrual, retention, data quality, and adverse events. At that time, the DSMB will also determine whether the study should continue unchanged, be modified, or be stopped. The IUPUI IRB, CRC Research Subject Advocate, and NIH will receive copies of all DSMB reports at the time of continuing review.

7.0 Study Withdrawal/Discontinuation

All participants will be considered enrolled at the end of the ResNet interview. 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. The schedule of participant reimbursement is as follows: $100 for the pre-treatment visit, $25 for the mid-treatment call, $100 for the post-treatment visit, $20 for each of the annual follow-up calls, and up to $10 per visit to cover parking or transportation costs. 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 his/her 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, in the assessment of the eIMPACT psychiatrist, exhibits evidence of a psychotic disorder or bipolar disorder (both of which are exclusionary conditions and could interfere with treatment delivery/effectiveness) during the 1-year 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 CVD events) 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.

For Usual Care patients who score in the "severe depression" range (20-27) on the PHQ-9 at the mid-treatment (6 months), the DCS (a) will contact the patient's primary care provider in person, by phone, or through the electronic medical record to notify the provider of the patient's high depressive symptoms and to urge the provider to follow-up and (b) will provide a list of local mental health services, including referral to a psychiatrist outside of the study team. In addition, 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. Finally, for participants in both treatment groups who score in the "severe depression" range (20-27) on the PHQ-9 during an annual follow-up call, the DCS (a) will contact the patient's primary care provider in person, by phone, or through the electronic medical record to notify the provider of the patient's high depressive symptoms and to urge the provider to follow-up and (b) will provide a list of local mental health services, including referral to a psychiatrist outside of the study team.

8.0 Statistical Considerations

Sample Size and Power Considerations

Endothelial Dysfunction
Using the effect size of depression treatment on FMD from our pilot trial, we need 88 patients (44 per arm) to detect a group difference in FMD of 1.7% (d = 0.61) at 12 months, assuming a power level of 0.80 and a Type I error of 0.05. This would be a clinically relevant difference. Assuming a conservative attrition rate of 20%,[204] we will have 172 completers (220 x .80) for FMD, yielding power levels of 0.98 for d = 0.61 and 0.80 for d = 0.43.

Candidate Mechanisms
We expect at a power level ≥0.80 for the candidate mechanisms (Hypotheses 2-5), as we will be able to detect effect sizes as small as d = 0.43 with 172 completers. In our IMPACT study[35] and pilot trial, effect sizes for depressive symptoms (d = 0.69 and 1.33), IL-6 (d = 0.43), and CRP (d = 0.78) were in the medium-to-large range. In other studies, effect sizes of 0.52 were found for psychological interventions on heart rate variability,[205-207] 1.00 for SSRIs on IL-6,[143] 0.74 for SSRIs[143] and 0.85 for CBT[138] on CRP, 0.91[146] and 0.46[144] for SSRIs on BTG, and 0.87 for SSRIs on PF4.[144]

CVD Events
Over the mean observation period of 4 years, we anticipate a cumulative CVD event rate of 20% (39 events) and a 25% lower relative risk (HR ≤ 0.75) in eIMPACT versus usual care. These estimates are reasonable, as we observed a CVD event rate of 24% and a 46% lower relative risk (event rate: 18% vs. 31%) in our IMPACT secondary analysis that had a 4-year observation period. Our high-risk sample will differ from the typical sample of a risk reduction trial in that (a) all patients will have depression and ≥1 CVD risk factor and (b) many will be of low SES and/or African American, two groups at elevated risk for CVD event.[1,171] Although we expect to have CVD event data for nearly all patients, we assume a conservative attrition rate of 10%, leaving 194 completers. As is typical of Phase 2 trials, our trial is not designed to detect a statistically significant difference in clinical events; however, a 25% relative risk reduction would be a clinically relevant signal (statin therapy reduces risk by ≈30%[156]) and has been used to power recent event-driven Phase 3 cardiology trials.[157]

Statistical Analyses

We will use the intent-to-treat approach.[208] All tests will be two-tailed with p <.05 considered significant. Supplemental analyses of completers will be performed. We will assess for differences in all baseline factors. Due to randomization, we do not expect baseline group differences. Even so, any differences will be taken into account when interpreting results, and any baseline factors that differ between the groups will be included as covariates in sensitivity analyses. Aim 1: We will test our hypothesis that eIMPACT patients will exhibit greater improvement in endothelial dysfunction (Hypothesis 1) by performing a two-sample t-test with FMD at 12 months as the dependent variable. If there is a group difference in baseline FMD, analyses of covariance (ANCOVAs) adjusting for baseline level will also be performed. We will also explore whether eIMPACT patients show a clinically relevant reduction (25% lower relative risk) in CVD events by running a Cox proportional hazards model with treatment group predicting time to first CVD event. Patients will be censored at non-CVD death or the end date. We expect to observe a HR ≤ 0.75. Aim 2. We will test our hypotheses that eIMPACT patients will exhibit greater decreases in the candidate mechanisms (Hypotheses 2-5) by performing two-sample t-tests with SCL-20 score, high-frequency heart rate variability, IL-6, CRP, BTG, and PF4 at 12 months as the dependent variables. If baseline group differences are found, ANCOVAs adjusting for baseline level will

also be performed. To explore whether decreases in the candidate mechanisms are associated with improvements in endothelial dysfunction, we will compute correlations between 12-month change in each mechanism and in FMD. To explore whether decreases in the candidate mechanisms are partial mediators of eIMPACT's hypothesized cardioprotective effect, we will conduct exploratory mediation analyses using MacKinnon's approach, which has greater power than others.[209] First, to quantify the treatment effect on each mechanism ("a" coefficients), we will perform linear regressions with treatment group predicting 12-month level of each mechanism. Second, to quantify the effect of each candidate mechanism on endothelial dysfunction ("b" coefficients), we will perform linear regressions with 12-month level of each mechanism predicting 12-month FMD in the presence of treatment group. Third, the significance of each mediation effect will be tested using MacKinnon and Lockwood's product of coefficients ("ab") method employing asymmetric confidence limits.[209,210] If this test is significant, the selected mechanism is a partial mediator of the treatment effect on 12-month FMD. Of note, we will also explore (a) if changes in depressive symptoms are correlated with changes in the atherogenic physiologic factors and (b) if changes in FMD predict CVD events.

Supplemental, Hypothesis-Generating Analyses

(1) We will explore atherogenic behavioral factors, conventional CVD risk factors, and depression care variables as potential mechanisms of eIMPACT's effect on FMD by repeating Aim 2 analyses. (2) To explore the separate effects of intervention components (which likely have shared and unique pathways; Figure 1), Aim 1 and 2 analyses will be repeated after coding the treatment variable as follows: eIMPACT both components, eIMPACT antidepressants only, eIMPACT psychotherapy only, eIMPACT neither component, and usual care. (3) We will explore sex and race/ethnicity as moderators of the treatment effect on the outcomes. (4) We will estimate the cost per patient of providing eIMPACT, including charges for BtB, DCS, psychiatrist and primary care expert supervision, materials, and a telephone line.

9.0 Privacy/Confidentiality Issues

Participants will be screened and consented in the privacy of their homes via telephone and/or in private rooms at the targeted primary care clinics or the CRC. All procedures will take place in private rooms at the CRC, Dr. Stewart's Cardiovascular 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 the follow-up calls and the telephonic and computerized components of the eIMPACT intervention). All research material will be kept strictly confidential. All study personnel have completed Collaborative Institutional Training Initiative (CITI) courses in human subjects research 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.

10.0 Follow-Up and Record Retention

For Usual Care patients who score in the "severe depression" range (20-27) on the PHQ-9 at the mid-treatment (6 months) or post-treatment (12 months) assessments, the DCS (a) will contact the patient's primary care provider in person or by phone to notify the provider of the patient's high depressive symptoms and to urge the provider to follow-up and (b) will provide a list of local mental health services, including referral to a psychiatrist outside of the study team. In addition, 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 is five years, all study documents will be kept up to seven 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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