Comparison of Depression Interventions after Acute Coronary Syndrome (CODIACS)

STUDY PROTOCOL

Version 1.4

Funded by the National Institute of Heart, Lung and Blood (NHLBI)
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1. SUMMARY

This multi-center, single-blind, parallel-group feasibility/vanguard trial is designed to assess the feasibility and estimate the effectiveness of a Stepped Care intervention relative to Referred Care (usual care) for depressive symptoms in patients hospitalized for an acute coronary syndrome (ACS) event who have elevated depressive symptoms 3-months after the event. The basic eligibility criteria are: 1) age at randomization of at least 18 years, 2) fluency in English or Spanish, 3) persistent depression, and 4) diagnosis of acute coronary syndrome (ACS) defined as either unstable angina or myocardial infarction.

Patients with an ACS event and comorbid depressive symptoms will be recruited from a network of hospitals connected with five field centers (Columbia University, Washington University, University of Pennsylvania, Emory University, and Yale University). The study will randomize 150 participants over a 9-month period. The Stepped Care (SC) intervention involves offering patients the choice of receiving psychotherapy and/or antidepressant treatment, and a stepped algorithm in which treatment is adjusted as needed according to predetermined decision rules. Referred Care (RC) involves physician notification of elevated depressive symptoms and subsequent treatment as determined by the patient’s physician. The duration of the intervention will be 6 months.

The primary endpoint is non-fatal myocardial infarction, hospitalization for unstable angina, or all-cause mortality over the 6-months of treatment. As this is a vanguard for a larger trial, we do not have the power for this outcome. Rather, we are testing all procedures to propose an adequately powered trial. In addition, patients will be evaluated for secondary endpoints including depressive symptoms. Compliance with the protocol and unanticipated events will be assessed periodically throughout the study.

2. SPECIFIC AIMS

The primary aim of the study is to:

1. Determine the feasibility and effectiveness of the interventions by conducting a 5-site randomized controlled trial (RCT) comparing Stepped Care to Referred Care for elevated depressive symptoms in post-ACS patients, and to evaluate yield, acceptance, retention, and depression improvement for use in planning a large Phase III clinical trial.

3. BACKGROUND AND SIGNIFICANCE

3.1. Background

Despite significant advances in the prevention and treatment of coronary heart disease (CHD) over the past 10 years, CHD remains the leading causes of death in industrialized nations, and mortality rates are expected to rise as the population ages. Consequently, ACS—the acute manifestation of CHD—remains a key focus for improving public health.

Systematic reviews have concluded that elevated depressive symptoms or depression defined either by self-report measures or by structured psychiatric interviews, increases the risk of morbidity and mortality in ACS (Carney 2008). Depressive symptoms more than double the risk of all-cause mortality, and Major Depressive Disorder (MDD) poses an even higher risk (Lesperance 2002; Carney 2008). Depressive symptoms and depressive disorders are better predictors than CHD
severity of overall health status and quality of life outcomes (Ruo 2003). The risk remains apparent in the most recent studies and meta-analyses, despite continual improvement in cardiac interventions and medications (Carney 2008), and it persists for many years after post-ACS depression is detected (Thombs 2008). It is largely independent of, and as strong as, some of the more traditional risk factors and has a dose-response relationship with medical outcomes (Carney 2008). The risk is particularly high for patients with persistent depression, especially those who receive ineffective treatment (Taylor 2005).

ENRICHD (Berkman 2003), CREATE (Lesperance 2007), and SADHART (Glassman 2002), three previous randomized controlled trials, found that depression can be safely treated in ACS patients. Unfortunately, none of these interventions had a very strong effect on depression, and none conferred cardiac benefits, although they suggested a possible benefit of SSRI antidepressants. Therefore, improving the effectiveness of treatment for post-ACS depression and determining whether effective treatments can reduce the risk of further morbidity and mortality remain critical public health priorities.

Summarizing the major findings and conclusions from these recent studies:

*Transient* depressive adjustment reactions to ACS are common. Only a subset of patients who are depressed during ACS hospitalization need treatment. Previous studies enrolled patients with transient depression, which made it difficult to detect effects of treatment on persistent elevated depressive symptoms and on subsequent cardiac outcomes. Furthermore, many depressed patients are too medically unstable and debilitated to begin depression treatment during the first few weeks after ACS.

ENRICHD showed that the depression-associated mortality risk did not increase until 3 months after the index cardiac event. There is mounting evidence that post-ACS depression is associated with excess morbidity and mortality only if it continues long after hospital discharge. Consequently, randomization and treatment can be initiated weeks or even months after ACS, at a time when the patient is medically stable, adjustment reactions have remitted, and depression treatment acceptance and adherence increases. Hence, randomization should be delayed for approximately 3 months after ACS, and elevated depressive symptoms should be added to the eligibility criteria for the next trial.

Many ACS patients have never been depressed before, and some object to being identified as “depressed”, particularly when only elevated depressive symptoms are present. These patients differ from those who present for psychiatric treatment meeting criteria for major depression. In prior trials, acceptance of standard depression treatments has been low, and this has contributed to non-adherence and attrition. The next trial should avoid psychiatric labeling and offer choices of effective treatments to increase trial acceptance and adherence with the treatment regimen.

Monotherapy is ineffective for more than half of all depressed patients. The STAR*D trial showed that many patients who do not respond to an initial antidepressant do respond to switching or augmentation strategies. A stepped care approach that includes more aggressive treatments for those who do not respond to the initial treatment is the best available strategy for treating depression to remission.

Recent trials have found several different antidepressants to be safe for post-ACS patients. At the time of the ENRICHD trial, only one antidepressant with demonstrated safety was available.
Side effects and adverse events have to be monitored proactively in the next trial. With expanded use of SSRI antidepressants, recent observational studies have reported drug-drug interactions with certain cardiac medications, and excess bleeding and related complications for some classes of antidepressants. Potential drug-drug interactions can be identified before prescribing, and possible side effects should be monitored closely and proactively to assure patient safety.

### 3.2. Previous depression trials in post-ACS patients

The Enhancing Recovery in Coronary Heart Disease (ENRICHD) (Berkman 2003) study was the first large, Phase III clinical trial designed to test whether depression treatment after acute myocardial infarction (MI) reduces the risk of recurrent MI or death. Utilizing the most efficacious treatments available at the time, ENRICHD yielded only modest effects on depression and no effect on the primary medical outcome. Progress since then includes the STAR*D trial (Rush 2006) which demonstrated that aggressive, stepped-care delivery of existing therapies achieves better depression outcomes, and several Phase II clinical trials which demonstrated better depression outcomes in cardiac populations. With this progress, leading experts have concluded that it is time to conduct a feasibility study for the next Phase III comparative effectiveness trial.

We therefore propose a multicenter feasibility project comparing the effectiveness of two interventions for post-ACS elevated depressive symptoms. The project will culminate in proposing a well-designed, well-organized multicenter Phase III clinical trial. The multidisciplinary investigative team includes cardiologists, psychiatrists, clinical health psychologists, statisticians, and clinical trials specialists. The feasibility project is based on the COPES RCT (Burg 2008; Davidson submitted). COPES tested the acceptability and efficacy of Stepped Care, a patient preference-driven, stepped care depression intervention for post-ACS patients, to Referred Care, in which depression screening was followed by physician notification of elevated depressive symptoms and encouragement to implement a physician-preferred depression treatment (Lichtman 2008). This was a 6-month RCT in patients 3 months after their index ACS event. Treatment acceptability was higher in the Stepped Care group (54%) than in the Referred Care group (18%). The change in depression between groups yielded an effect size of .59, considerably higher than reported for other depression interventions for CHD patients. Although COPES was underpowered to detect effects on major adverse cardiac events (MACE), the incidence of MACE was lower in the Stepped Care (4%) than in the Referred Care arm (13%). The COPES RCT was a small efficacy trial. The present multicenter study will test the feasibility of using the COPES protocol at multiple sites.

### 4. STUDY DEFINITIONS

#### 4.1. Unstable Angina

Patients will be defined as meeting our criteria for unstable angina if they have the presence of ischemic chest pain lasting \( \geq 20 \) minutes with recent onset or with an accelerating pattern or episodes at rest or with minimal effort, and troponin values that are elevated above the 99th percentile.

#### 4.2. Myocardial Infarction (MI) defined as one of the following:

a. **ST elevation MI** - Typical rise and gradual fall (troponin) or more rapid rise and fall (CKMB) of biochemical markers of myocardial necrosis (see definition of *Biochemical evidence of MI* below) with new or presumed new ST segment elevation at the J point in 2 or more contiguous leads with the cutoff points greater than or equal to 0.2 mV in lead V1, V2, and V3, or greater than or equal to 0.1 mV in other leads. Patients with elevated CKMB and normal cTn values will not be considered to have AMI (Thygesen 2007).
b. **Non ST elevation MI** - Typical rise and gradual fall (troponin) with one of the following (in the absence of ST elevations):
   i. ST segment depression
   ii. T wave abnormalities
   iii. Ischemic symptoms without ST segment depression or T wave abnormalities, in the presence or absence of chest discomfort (unexplained nausea and vomiting or diaphoresis; persistent shortness of breath; unexplained weakness, dizziness, lightheadedness, or syncope).

c. **Bundle Branch Block/Uncertain Type MI** - Typical rise and gradual fall (troponin) with:
   i. Left BBB (new or old) or paced rhythm
   ii. Initial ECG findings are not available or the patient presents beyond the time of ST segment changes (e.g. greater than 24 hours).

### 4.3. Biochemical Evidence of MI

Actual values for biochemical markers of myocardial necrosis are based on established cutoffs at the various sites. All sites will be encouraged to obtain and review troponins for evaluation for MI.

a. Troponin: Maximal concentration of cardiac troponin I or T greater than the 99th percentile of a reference population with a rising and/or falling pattern during the first 24 hours after the index clinical event.

## 5. STUDY DESIGN

### 5.1. Overview

This single-blind, parallel groups, feasibility trial will determine whether the superiority of Stepped Care over Referred Care for depression in post-ACS patients found in the COPES trial is replicable at other centers around the country.

Patients will be screened for medical eligibility during an outpatient visit 2-4 months after their ACS. Those who meet the study’s depression criteria and who do not meet any exclusion criteria will complete a baseline evaluation and if their depressive symptoms persist for 2 weeks, they will be randomly assigned to the Stepped Care intervention or to Referred Care. The intervention phase will be 6 months. Hospitalization information will be collected over the same period and reviewed by an independent medical event adjudication committee to identify cardiac events and mortality using prespecified criteria. Interim telephone measures of depression will be obtained at 2 and 4 months post-randomization.

The SC intervention is based on the COPES protocol (Burg 2008) in which the SC intervention included a choice of psychotherapy and/or one of several study-approved antidepressants, and a stepped care algorithm in which treatment is adjusted as needed according to predetermined decision rules.

### 5.2. Study Population

One hundred fifty men and women greater than 18 years of age with persistent depression will be recruited 2-4 months following diagnosis of ACS.

### 5.3. Eligibility criteria

#### 5.3.1. Inclusion criteria

- Hospitalized for ACS defined as unstable angina or MI
5.3.2. **Exclusion criteria**

- Presence of non-cardiac condition likely to terminate fatally within 1 year
- Inaccessibility for intervention or follow-up (e.g., plans to move from the area)
- Cognitive impairment
- Need for immediate psychiatric intervention (i.e., requiring hospitalization or psychiatric intervention within 72 hours)
- Suicidal ideation
- Major psychiatric co-morbidity (current or by history) including active psychosis, bipolar disorder, or overt personality disorder
- Active substance abuse or dependency
- Renal impairment (serum creatinine ≥ 2.0) or moderate/severe liver disease (e.g., esophageal varices, portal hypertension, encephalopathy, GI bleeding)
- Participation in another clinical trial for the treatment of depression.

These exclusion criteria have been set for safety concerns, evidence that depression improvement will not occur because of a psychiatric illness, or the likelihood that the participant will be unable to provide usable outcome data. If a participant is found to be ineligible, he/she will be referred back to his/her primary medical physician for further care, except where immediate psychiatric attention is warranted, in which case a study psychiatrist or psychologist will consult and refer.

5.3.3. **Rationale for eligibility criteria**

**Established ACS eligibility criteria:** Patients with acute ST-elevation MI, non-ST-elevation MI, or documented unstable angina (UA) will be enrolled. Enrolling both MI and UA patients increases the generalizability and reach of this trial. Depression is prevalent in both subgroups and poses similar risks. Acute ST-elevation MI is defined by the presence of ischemic chest pain lasting ≥ 20 minutes, ST elevations (1 mm or more) in ≥ 2 contiguous ECG leads, and acute rise in serum cardiac markers meeting the criteria of the Redefinition task force (Thygesen 2007). Non-ST-elevation MI will be defined by an episode of angina with recent onset or with an accelerating pattern or prolonged (≥ 20 minutes) or episodes at rest or with minimal effort, and elevated levels of cardiac enzymes [preferably troponin using the criteria advocated by Task Force for the Universal Definition of AMI (Thygesen 2007)] with or without ischemia ECG changes (ST-depression > 0.5 mm or T-wave inversions > 2 mm). Patients will be defined as meeting our criteria for unstable angina if they have the presence of ischemic chest pain lasting ≥ 20 minutes with recent onset or with an accelerating pattern or episodes at rest or with minimal effort, and troponin values that are elevated above the 99\textsuperscript{th} percentile value.

One of the cardiologist consultants on this grant, Allan Jaffe, MD, will be responsible for quality assurance of these criteria which will be applied at eligibility and for event adjudication. Each site will be asked to provide the name of the troponin assay used locally and the cut off value used at that center for the diagnosis of MI.

**Elevated Depressive symptom Criteria:** A BDI score ≥ 10 on two occasions, or a BDI ≥ 15 on one occasion will serve as the depressive symptom inclusion criterion for this trial. Depressive symptoms will be assessed 3 months (+ 1 month) after the index ACS, and again 2 weeks later if the BDI score is between 10 and 15. The second screening assessment can be conducted by telephone.
5.4. Recruitment and follow-up schedule

Figure 1. Patient enrollment, randomization, and treatment flow

ACS patients aged ≥ 18y

Assessed for eligibility 2-4 months post-ACS (n=1125)

Excluded (n=955)
- Not meeting inclusion criteria (65%)
- Refused to participate (15%)
- Other reasons (5%)

Randomized (n=170)

Allocated to referred care (n=85)

Allocated to stepped care (n=85)

Lost to follow-up (n=10, 11%)

Included in analysis of depression change (n=75)
Included in analysis of MACE (n=85)
Table 1. Schedule and Timing of Measurements and Procedures

<table>
<thead>
<tr>
<th>Study Month Type of Contact</th>
<th>Screening (2-4 months after ACS)</th>
<th>Baseline (Visit)</th>
<th>2 month (Phone) follow-up</th>
<th>4 month (Phone) follow-up</th>
<th>6 month (Visit) follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent</td>
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<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Hospitalization Release</td>
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<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>BDI (+ Suicidality form if indicated)</td>
<td>x</td>
<td>x*</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Alcohol abuse screening tool</td>
<td>x</td>
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<tr>
<td>Substance abuse screening tool</td>
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<tr>
<td>Psychosis screening tool</td>
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<tr>
<td>Medical History</td>
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</tr>
<tr>
<td>Demographic</td>
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<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Patient Contact/update</td>
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<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Physical Exam</td>
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<td></td>
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<td></td>
<td>x</td>
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<tr>
<td>Eligibility and randomization</td>
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<td>x</td>
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<tr>
<td>Depression treatment</td>
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<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>SF-12 (QOL)</td>
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<tr>
<td>Satisfaction with depression care</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Unanticipated events checklist</td>
<td>x</td>
<td>x</td>
<td>x</td>
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</tr>
</tbody>
</table>

*Administered if necessary (e.g., if first BDI score is between 10 and 15).

5.4.1. Recruitment

Patients will be recruited from different sources: cardiology and primary care practices and hospitals of participating institutions. Patients will enter the enrollment phase of the study, during which their eligibility will be confirmed. Patients who meet the inclusion criteria and do not meet exclusion criteria, but have a BDI between 10 and 14, will be phoned 2 weeks later, and those meeting the depression criteria will be randomized to SC or RC. All other patients will be followed for endpoints and managed by the primary care provider according to that provider’s usual standard of care.

From previous studies in similar patient populations, we estimate that each site will need to identify 225 medically eligible patients (e.g., meeting ACS criteria) to meet the goal of randomizing 30 per site. Among the pool of 225 medically eligible patients, we expect 86% will not meet the depression inclusion criteria, will refuse to participate, or will have medical/psychiatric or other reasons excluding them from participation (see Figure 1).

Patients at outpatient cardiology services, primary care clinics and hospitals will have their charts screened for ACS criteria (under HIPAA Form D). If a patient is found potentially eligible, their attending health care provider will mail a letter to their home explaining the study. At the next outpatient visit, if this falls in the window from 2-4 months, the health care provider and the study coordinator will explain the study, and seek consent. If consent is obtained, screening for all eligibility criteria occurs. Health care providers can refer their patients to one of the study physicians, but we will ask that the referring physician/health care provider send out a letter on our behalf. Finally, for patients who are walk-ins/add-ons, we will ask the physician/health care provider to discuss the study with the patient during their office visit; we will later approach those patients who are interested in the study.

5.4.2. Screening visit

We will obtain consent and HIPAA authorization from eligible patients at the time of the screening. After consent is obtained, we will collect demographic and contact information. In some cases, patients will be informed that if they meet further eligibility in 2 weeks, they will be randomized.
5.4.3. Treatment phase

The assessment staff will be blinded to group assignment. Patients will be consented and screened between 2 and 4 months after the index ACS. Patients who are classified as depressed (BDI ≥ 10) on two occasions two weeks apart, or ≥ 15 on one occasion and who meet all of the trial’s eligibility criteria will then undergo a brief interview to determine whether any psychiatric exclusion (such as suicidality or bipolar disorder) are met. Through informed consent, both arms of the trial will be described with equipoise. Patients who consent to randomization will be enrolled in the treatment trial. We expect to screen 225 patients at each site to yield 45 eligible patients.

5.4.4. Follow-up evaluations

Of the 45 patients (per site) eligible at the screening visit, we expect 15 will not be found to be eligible at the baseline visit (due to withdrawal of consent or failure to meet persistent elevated depressive symptom inclusion criteria). Telephone calls will be conducted at 2 and 4 months. A final visit will occur 6 months after randomization. Relative contacts will be collected, in case a patient moves during the 6 month period of the trial. At each assessment, SC and RC patients are assessed for depressive symptoms with the BDI and asked if they had been hospitalized since the previous visit. For each reported hospitalization, documentation will be requested from hospital records. Hospital systems will also be actively surveyed for events. A medical event adjudication committee, blinded to treatment status, will classify and adjudicate each hospitalization. For patients who cannot be contacted or who are reported deceased by a relative, the Social Security Death Index will be searched to verify vital status and death certificates will be obtained. Patients in each arm will receive the same number and length of assessment contacts.

5.5. Project schedule

The study timeline and tasks are shown in Table 2 and milestones in Table 3.

Table 2. Timeline

<table>
<thead>
<tr>
<th></th>
<th>Year 1</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finalization of trial design, MOP, forms</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Training of screening, intervention, and core staff</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Enrollment</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Intervention</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Preparation for Phase III trial submission</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Final data analysis; manuscript submissions</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Month → 3 6 9 12 3 6 9 12
Table 3. Milestones

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>October 2009</strong></td>
<td><strong>October 2010</strong></td>
</tr>
<tr>
<td>• Grant awarded</td>
<td>• Annual IRB renewal submitted</td>
</tr>
<tr>
<td>• Subcontract paperwork initiated</td>
<td>• First center closed to initial enrollment (intervention continues)</td>
</tr>
<tr>
<td>• IRB distributed to all sites for submission</td>
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<tr>
<td>• DSMB members identified</td>
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<tr>
<td>• #1 Steering committee in-person meeting</td>
<td></td>
</tr>
<tr>
<td><strong>November 2009</strong></td>
<td><strong>November 2010</strong></td>
</tr>
<tr>
<td>• Clinical trial protocol, Manual of Operations, Forms finalized</td>
<td>• #1 Event adjudication meeting</td>
</tr>
<tr>
<td>• #1 Steering committee in-person meeting</td>
<td>• #4 Steering committee in-person meeting</td>
</tr>
<tr>
<td><strong>December 2009</strong></td>
<td><strong>December 2010</strong></td>
</tr>
<tr>
<td>• #2 Steering committee in-person meeting</td>
<td>• Core status reports</td>
</tr>
<tr>
<td>• Field/screening staff training</td>
<td>• Clinical trial protocol and manual of operation completed for Phase III trial</td>
</tr>
<tr>
<td>• #1 DSMB in-person meeting</td>
<td>• Forms completed for Phase III trial</td>
</tr>
<tr>
<td>• IRBs approved/modified if needed</td>
<td></td>
</tr>
<tr>
<td><strong>January 2010</strong></td>
<td><strong>January 2011</strong></td>
</tr>
<tr>
<td>• Formal Review of Milestones and Deliverables</td>
<td>• Formal Review of Milestones and Deliverables</td>
</tr>
<tr>
<td>• Data management system training</td>
<td></td>
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<tr>
<td>• Initial patients (n=3) run through protocol</td>
<td></td>
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<tr>
<td>• Core labs run patients (n=3)</td>
<td></td>
</tr>
<tr>
<td>• Data entered on patients (n=3)</td>
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<tr>
<td><strong>February 2010</strong></td>
<td><strong>February 2011</strong></td>
</tr>
<tr>
<td>• First patient enrolled at all 5 sites</td>
<td>• #3 NHLBI in-person meeting to formally propose Phase III trial (in conjunction with #5 Steering committee meeting)</td>
</tr>
<tr>
<td>• #1 NHLBI teleconference meeting to plan for Phase III trial</td>
<td>• Last patient completes intervention</td>
</tr>
<tr>
<td>• Review by all RCT members of mock protocol issues</td>
<td>• Final data cleaning</td>
</tr>
<tr>
<td><strong>March 2010</strong></td>
<td><strong>March 2011</strong></td>
</tr>
<tr>
<td>• Intervention staff training</td>
<td>• data analysis of yield, acceptance, retention estimates</td>
</tr>
<tr>
<td>• Core staff training</td>
<td>• #2 DSMB in-person meeting</td>
</tr>
<tr>
<td>• Event adjudication committee trained</td>
<td></td>
</tr>
<tr>
<td>• Patients randomized at all centers</td>
<td></td>
</tr>
<tr>
<td><strong>April 2010</strong></td>
<td><strong>April 2011</strong></td>
</tr>
<tr>
<td>•</td>
<td>• #2 Event adjudication meeting</td>
</tr>
<tr>
<td>•</td>
<td>• #6 Steering committee in-person meeting to outline R01s, cores, and finalize budget</td>
</tr>
<tr>
<td>•</td>
<td>• NHLBI over 500k letter submitted</td>
</tr>
<tr>
<td><strong>May 2010</strong></td>
<td><strong>May 2011</strong></td>
</tr>
<tr>
<td>•</td>
<td>• R01 application preparation*</td>
</tr>
<tr>
<td>•</td>
<td>• Final data analysis of yield, acceptance, retention estimates</td>
</tr>
<tr>
<td><strong>June 2010</strong></td>
<td><strong>June 2011</strong></td>
</tr>
<tr>
<td>•</td>
<td>• Phase III trial R01 submitted (June 5)</td>
</tr>
<tr>
<td><strong>July 2010</strong></td>
<td><strong>July 2011</strong></td>
</tr>
<tr>
<td>• #3 Steering committee in-person meeting</td>
<td>• Preparation of Ancillary study applications</td>
</tr>
<tr>
<td>• Preparation of trial design manuscript</td>
<td></td>
</tr>
<tr>
<td><strong>August 2010</strong></td>
<td><strong>August 2011</strong></td>
</tr>
<tr>
<td>• #2 NHLBI teleconference meeting to discuss Phase III trial planning</td>
<td>• Feasibility Study Manuscript preparation</td>
</tr>
<tr>
<td><strong>September 2010</strong></td>
<td><strong>September 2011</strong></td>
</tr>
<tr>
<td>• Trial design manuscript submitted</td>
<td>• Feasibility Study Manuscript submission</td>
</tr>
<tr>
<td>• Last patient randomized</td>
<td></td>
</tr>
</tbody>
</table>

*Actual writing of R01s will not be paid for by NIH funds for PI effort, to be in compliance with NIH rules.
5.6. Project Goals

The major goals and technical risks to the successful conduct of these proposed activities are shown in Table 4. Slow enrollment is considered our first major technical risk. We have estimated our patient accrual rates from the COPES trial. We will discuss with centers if one can increase recruitment, or if another site has to be added, should this risk be realized. The second risk is that major alterations to the future Phase III trial proposal could be needed. This risk may result in a later submission of the final set of linked R01s. Finally, data analyses could reveal a different yield, retention rate, or other rate than was found with COPES. These changes will be incorporated into the final power analysis.

### Table 4. Expected Measurable Outcomes/Deliverables and Risks

<table>
<thead>
<tr>
<th>Year</th>
<th>Measurable Outcome /Deliverable</th>
<th>Technical Risk/ Decision Point</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-3 months</td>
<td>Subcontracts executed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All forms, adverse events to be assessed, protocol, manual of operations finalized.</td>
</tr>
<tr>
<td></td>
<td>4-6 months</td>
<td>IRBs/HIPAAas approved at all sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Certificate of confidentiality approved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All training completed</td>
</tr>
<tr>
<td></td>
<td>7-9 months</td>
<td>Mock patients and forms completed at all sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any protocol modifications approved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>First patient randomized</td>
</tr>
<tr>
<td></td>
<td>10-12 months</td>
<td>First draft of Phase III protocol completed &amp; discussed with NHLBI staff</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trial design manuscript submitted</td>
</tr>
<tr>
<td></td>
<td>1-3 months</td>
<td>Feasibility study enrollment closed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All forms, adverse events to be assessed, protocol, manual of operations for Phase II trial finalized.</td>
</tr>
<tr>
<td></td>
<td>4-6 months</td>
<td>Formal presentation of Phase III trial to NHLBI for feedback</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Feasibility study interim analyses</td>
</tr>
<tr>
<td></td>
<td>7-9 months</td>
<td>End of follow-up period</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Final data analyses completed for Feasibility study</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase III linked R01s submitted</td>
</tr>
<tr>
<td></td>
<td>10-12 months</td>
<td>Manuscript preparation and submission</td>
</tr>
</tbody>
</table>

6. INTERVENTIONS

6.1. Background

The STAR*D trial demonstrated that the efficacy of behavioral and pharmacological treatments for depression, such as those used in ENRICHD and SADHART, can be improved by following an aggressive, stepped care algorithm. Several single-site depression efficacy trials in cardiac populations, most notably COPES (Davidson) have yielded larger effect sizes than were observed in the ENRICHD and SADHART multicenter trials. Whether the COPES intervention can be delivered as intended in multiple clinical centers is a key question that this feasibility study aims to address. Of all of the depression interventions tested to date in cardiac patients, the COPES protocol is both one of the most efficacious and the one best suited for large-scale clinical application. A definitive test can only be achieved if this apparently effective depression intervention can be delivered to a sufficiently large sample of ACS patients.
ENRICHD and several other trials yielded only modest differences in depression between the treatment and control arms. Plausible reasons include: 1) the interventions were not very efficacious, 2) the treatments were not well accepted, 3) the control conditions improved depression more than expected, 4) the appropriate patient population was not studied, and 5) the adverse effects of post-ACS depression may emerge later than the effects of the ACS itself. There is evidence to support each of these possibilities:

1) Previous trials utilized interventions that had modest effects on depression. (Carney 2008) Recent systematic reviews of pharmacological (Kirsch 2008) and behavioral monotherapies in other patient populations have shown small to medium effect sizes. While multimodal interventions have produced larger effect sizes, the best results have involved stepped depression care algorithms. Stepped depression care for ACS patients was tested in COPES and found to be highly efficacious.

2) Treatments must be acceptable to patients because willingness to engage in, comply with, and continue depression treatment predicts treatment success. Most empirically-supported depression interventions were originally tested on treatment-seeking psychiatric outpatients, not on medically ill patients whose depression is identified by others through screening. The acceptability of depression interventions increases when patient preference is taken into account, and when the interventions are designed to eliminate the stigma associated with traditional psychiatric care. Problem solving therapy, a key component of the COPES intervention, has higher acceptability and a lower dropout rate than other psychological interventions.

3) Improvement in the control arm has been problematic in both ACS (Carney 2008) and non-ACS depression trials (Kirsch 2008). This may in part be due to the increasing recognition and treatment of post-ACS depression in routine medical care (Lichtman 2008), to the attention received as part of trial participation, or to the enrollment of patients with transient depressive reactions that spontaneously remit. It has become clear that both premature classification of patients as “depressed” and premature intervention invite Type II errors in post-ACS depression trials. COPES included 2 depressive symptom assessments, 3 months apart, reduce the risk of Type II error, a strategy that was very successful.

4) Most cohort studies have found depression-associated MACE/ACM risk with a Beck Depression Inventory (BDI) score $\geq 10$. In addition, hospitalization for ACS is a stressful event that can precipitate a transient depressive reaction that in many cases remits as soon as the patient returns home and resumes normal daily activities. Although persistent depression after ACS predicts adverse medical outcomes, transient depressive reactions may not. Previous trials did not exclude patients with transient depressive reactions. Consequently, some of the participants were probably not at increased depression-related risk of MACE or ACM. COPES targeted patients with persistently elevated BDI scores 3 months after hospitalization for ACS, regardless of whether they met diagnostic criteria for a depressive disorder.

5) The adverse effects of post-ACS depression lag those of the ACS itself by several months. Clinical outcomes are predicted by depressive symptoms for up to 5 years after the index ACS event (Carney 2004). In ENRICHD, there was slightly more improvement in depression at 6 months in the intervention than in the UC arm, but both groups improved significantly (Berkman 2003). There was no overall between-group difference in time to reinfarction or death, but patients who responded to the intervention had better survival than those whose depression did not improve, and this was also the case for the 25% of those randomized to usual care who received antidepressants from their own physicians. Furthermore, only 1/3 of
the intervention patients who were eligible for antidepressants accepted them. Participants who did receive an antidepressant after failing CBT survived longer than those who did not, even though they were likely to be more severely depressed at baseline. Similar findings have been reported in secondary analyses of four smaller post-ACS trials, suggesting that successful treatment of depression can improve cardiac outcomes.

6.2. Rationale for intervention selection

**Stepped Care:** We systematically reviewed the available interventions and depression care algorithms. After careful consideration, we chose an intervention of patient preference-driven stepped care that was tested in the COPES trial (see Figure 2 for algorithm). SC participants will be given a description of the choices available in this arm, including a variety of antidepressant medications and telephone-based, Problem-Solving Therapy (PST). If the patient is randomized to Stepped Care, their physician will be informed that depression treatment is being provided by the trial.

**Figure 2. Stepped Care (SC) Treatment Algorithm**

Patients will select their preferred treatment approach. Depression symptoms will be monitored to determine whether the patient is improving relative to his/her baseline score. The intervention manual defines depression cutoff scores for defining improvement (see manual of operations). If the improvement criterion is not met within 6 weeks of randomization (4 weeks of receiving treatment for antidepressant choice), additional or alternative treatments will be initiated by patient choice. Additional treatment modifications will be made again 6-8 weeks later, with the objective of treating the depression to remission by the end of the intervention. Relapse monitoring and maintenance therapy will continue for the duration of the study.

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* If history of SSRI intolerance/unresponsiveness, another antidepressant class is considered.
As demonstrated by STAR*D (Rush 2006) the majority of treatment-seeking, previous treatment failure depressed patients do not have an adequate response to antidepressant monotherapy, and they require stepped depression care. Furthermore, many ACS patients, and especially those recovering from ACS, have strong depression treatment preferences, with some willing to accept pharmacotherapy, others preferring psychotherapy, and still others preferring a combination. For these reasons, we chose the COPES Stepped Care algorithm as it provides patient choice.

**Referred Care:** Many different depression treatments or algorithms could be tested against the Stepped Care algorithm. A recent advisory from the American Heart Association that was also endorsed by the American Psychiatric Association recommended assessing, referring, and treating depression when detected in patients with coronary disease (Lichtman 2008). Specifically, it recommends administering a self-report depression screening questionnaire to CHD patients and referring those who screen positive to a professional qualified to diagnose and manage depression. The advisory notes that cardiologists should be aware that depressed patients are at increased risk of cardiac morbidity and mortality, and that they should aggressively manage depressed patients' compliance, engagement in cardiac rehabilitation, and lifestyle modification plans. As this standard of depression care is recommended for all CHD patients, we will use it as our active comparator. Immediately after the initial post-ACS screening, the patient’s physician will be notified in writing if the patient is depressed according to the BDI. Depending upon the physician’s own evaluation of the patient, he or she may elect to defer depression treatment, initiate it, or to refer the patient to a mental health specialist. Non-study depression treatments will be systematically documented for patients in both arms of the trial.

6.3. **Study Drugs**

**Sertraline:** An antidepressant, of the selective serotonin reuptake inhibitor class, indicated for treatment of unipolar major depressive disorder, obsessive compulsive disorder, premenstrual dysphoric disorder, social phobia, post-traumatic stress disorder, and panic disorder, See “Potential Risks” section for additional details.

**Citalopram:** An antidepressant of the selective serotonin reuptake inhibitor class, indicated for treatment of unipolar major depressive disorder. See “Potential Risks” section for additional details.

**Buproprion:** An antidepressant, other; indicated for the treatment of major depressive disorder and for smoking cessation assistance. See “Potential Risks” section for additional details.

7. **DATA ANALYSIS**

7.1. **Introduction**

Estimates of recruitment yield and retention rates, and minority/gender representation will be used to guide selection of the number and type of sites needed for the future larger phase III trial. If yield is low, consideration will be given to relaxing the eligibility criteria in the larger phase III trial. Retention rates and reasons for drop-out will be compared between treatment groups to determine whether there is differential drop-out which could lead to selection bias in the future phase III trial. Treatment acceptance rates will be compared between groups across field sites to identify potential variation in implementation of the intervention protocol for the Stepped Care. If our feasibility experience establishes a correlation between acceptance rates and adherence to the treatment protocol, it would serve as a useful tool for monitoring field site performance in the future phase III trial. For example, inclusion of a site in the larger phase III trial may require acceptance rates of at least 40% in the Stepped Care group, and rates above 30% in the Referred Care or Standard Care might warrant closer monitoring of the field site.
7.2. Analyses relating to assessment of feasibility

The final yield, patient consent, retention, and depression improvement in the feasibility study will be compared across sites and to the COPES trial. In COPES, only 5% of consenting patients refused treatment after randomization, and only 6% more were lost to follow-up. The feasibility sites will be compared to the COPES trial standards as to yield, patient agreement to all three consents, retention, and improvement in depression.

The feasibility sites vary with respect to such attributes as centralization of care, service delivery approaches, rural/urban mix, availability of electronic medical records, and demographic characteristics. Differences in these characteristics among the feasibility sites will be examined to determine whether they account for any differences in yield, acceptance, retention, or depression improvement. This information will be used to fine-tune staff training procedures, to improve the implementation of the intervention across sites, and to guide the development of procedures for future Phase III site selection and start-up.

We will use the feasibility clinical event data primarily for training and QA procedures. This will ensure that the sites are prepared to submit complete and accurate documentation of clinical events, as there is a learning curve to this site function. Site variability in event rates will be examined. The results will be used, along with the published results of much larger trials, to inform the power analysis for the future Phase III trial.

We will also address two fundamental questions for the feasibility study. The first is whether successful implementation of the COPES depression algorithm generalizes to 5 field centers selected for diversity in patient population and clinical practice. QA metrics for the COPES intervention (see Intervention manual) will be used to characterize variability across sites in treatment delivery. The treatment delivery compliance data will be used to revise the training manuals for the future Phase III trial, and to establish therapy delivery QA thresholds below which retraining or field site termination is required. Second, we will assess whether patients are benefiting from the Stepped depression treatment at the feasibility centers. We will calculate the BDI pre-post delta for each site, and examine therapy QA and site characteristics to determine whether variability can be reduced, and thus training for the larger trial improved. We are not proposing an a priori depression effect size below which a site would be excluded from the future Phase III trial, or below which the Phase III trial would not be proposed. Both of these contingencies could possibly occur (a site excluded or a Phase III trial not submitted) but the purpose of this feasibility study is to determine the generalizability of COPES, whether there is excessive variability among sites, and if so, whether it is remediable. A wide range of variables will be used to determine if the COPES approach is feasible, generalizable, and worthy of testing in a larger trial.

7.3. Power

Although the feasibility study is underpowered to detect differences in MACE, and detecting such a difference is the aim of the larger trial, we present here an exploratory power analysis for a depression difference for descriptive purposes. The proposed sample size of 170 patients will allow an 80% chance of detecting a difference in depression scores between groups of 0.46 SD-units (e.g., approximately 4-point difference in BDI). An intent-to treat approach will be used to compare depression scores at 2, 4, and 6 months follow-up. Missing depression data will be imputed using the conditional (e.g., age- and sex-adjusted) mean of the missing value in the control group. Group differences in depression outcome will be determined in the feasibility study to compare the estimated effect size of a multicenter implementation of the COPES intervention with that reported by the single site COPES trial. Clinical endpoint data will be used to help project the length of follow-up and
number of participants and associated events that will be needed to have good power (> 90%) to see a 20% difference between groups in the future phase III study.

Selection of sample size was to reflect the sample size for COPES, while meeting the logistical constraints of a 2-year funding period with recruitment conducted across 5-sites.

8. DATA MANAGEMENT

8.1. Introduction

A web-based data management systems (DMS) will be used to key interviews directly as they are administered. This direct (paperless) data entry approach has become the gold standard in research today because of the possibility of identifying errors in real time, allowing resolution in a timely fashion by the primary data collector. In addition, upgrades or changes to a web-based DMS (e.g., form version change, or addition of a standardized report) that are during the course of the study can be installed locally at the DCC without the need to involve field center staff. A more thorough treatment of the advantages of direct data entry are described elsewhere (Meadows 2003).

Key features of the DMS include data validation upon entry, ID/password authentication, encryption of sensitive data (e.g., personal identifiers), transaction auditing, tailored reporting, and a tool for randomization.

8.2. Data collection and recording

The Data Coordinating Center will provide each field center with a laptop computer for data collection. At the time of entry, the user is notified of data values failing field-specific validation. If the user chooses to over-ride the validation, the value is stored but flagged as over-ridden in the database. Users can update (change) data values unless the record is flagged as complete (locked). An audit trail of all updates to the database is maintained. The system includes context-sensitive help.

The DMS provides each field center with the ability to generate a variety of reports to allow monitoring of the center’s performance and to facilitate timely identification and resolution of problems in data collection. These include reports showing the number of patients screened and randomized, and the state of data collection forms (e.g., completed, pending, incomplete, or permanently missing).

8.3. Participant scheduling

A schedule of participant visits and data to be collected at each visit (“Participant Calendar”) can be generated through the DMS. Frequently subjects are unable to adhere strictly to prescribed schedules as set for them by the study protocol. The schedule shows allowable time ranges for the visits within the specifications of the protocol (allowance of a 1 month window around the scheduled “6-month follow-up visit”). These upper and lower time bounds can be used to provide warnings to the field center personnel and for timely data entry reports.

The DMS scheduling tool can provide reminders to study personnel to facilitate appointment tracking. The reminders will provide a checklist of forms to be administered (or procedures to be performed) for each participant, based on that participant's calendar. Optionally, reminders of future appointments can be sent to participants, i.e. via mailed letters.

8.4. Consolidated database

Data from all field centers comprise the study’s consolidated database. The consolidated database is stored in a SQL Server database and managed on the DCC Novell Local Area Network (LAN).
Standard transaction validity checks are applied to all updates to the database (e.g., to prevent the addition of records with duplicate keys, etc. Updating of the consolidated database by any means other than the DMS or imported data transfer files is disallowed. Thus, audit logs from the DMS, and processing logs produced by the update program provide complete documentation for changes to the consolidated database. Backups of the consolidated database as well as imported files and processing reports are made daily.

8.5. Database closure

Periodically the consolidated database goes through a series of closure checks to ensure the completeness and correctness of data collection and processing. These checks are performed on a ‘frozen’ version of the database defined by a specific time cut point. Typical closure checks include classifying the universe of IDs, assuring all expected forms were received and assuring all queries generated were resolved.

Data are frozen after completion of baseline data collection and resolution of all data queries and again after completion of each subsequent measurement period.

8.6. Data retrieval and statistical computing

Data are retrieved from the consolidated database and converted to SAS datasets. The resulting SAS datasets are permanently archived on magnetic tape cartridge.

All statistical computing is done using the SAS system, and is documented using the Coordinating Center’s statistical computing request system. This system requires the project statistician to produce a written specification of each analysis to be done. The specification, the resulting analysis program, and the output produced are all cataloged and archived (in paper and electronic format) to provide complete documentation of each computing task.

8.7. Data security and confidentiality

All paper data collection forms are stored at the Field Centers. They are stored and handled like confidential medical records. Access to the files of forms is restricted to study staff. Each user of the DMS at the Field Centers needs an individual user ID and password to use the DMS. Individually identifying fields within the database are encrypted, and decrypted only for display on-screen.

All data received from the Field Centers are stored, processed, and analyzed within the Data Coordinating Center’s office space. At the Data Coordinating Center, all access to office space containing data is controlled through manned reception areas. Visitors are screened by the receptionists and cannot move about without a Coordinating Center escort. All office space is locked after working hours. Access to computer data files is controlled by passwords released only to those Coordinating Center personnel who use the files. In addition, critical data files are encrypted.

A backup of the consolidated database is made daily to a separate file server on the Data Coordinating Center LAN. Magnetic tape backups of the database are made weekly (using a father/grandfather cycle with five generations). Once a month, the current backup tape is removed from the cycle and permanently archived at the Data Coordinating Center’s off-site data storage facility.

Each participant will be assigned a unique ID. Output mailed to Field Center staff identifies participants only by ID number. No individually identifiable information is distributed.

When printed material containing confidential information is to be discarded, it is stored under supervision until the material can be recycled into paper pulp.
Policies regarding the confidential nature of the data collected, processed, and stored at the Data Coordinating Center, are explained to all personnel upon employment, who must then sign a “confidentiality certification” before being allowed access to confidential information. In addition to this initial training, the Data Coordinating Center reinforces the need for careful and confidential handling of data at staff meetings.

8.8. Data quality assurance

Many of the features of the web-based data management system described above are designed to ensure the quality and completeness of the study data. In addition, the Data Coordinating Center has an ongoing quality assurance program including routine generation of reports regarding the frequency of missing or overdue forms, and outstanding queries that facilitate timely corrective action and resolution of data quality issues.

8.9. Installation, maintenance, and support

The Data Coordinating Center purchases the required hardware and software for the Field Centers.

The Data Coordinating Center provides all the necessary documentation, user support, and user training of the DMS. Training includes instruction, demonstration, and hands on practice with data collection instruments. All Field Center staff participating in the Data Coordinating Center training sessions are evaluated and certified for use of the DMS.

The Data Coordinating Center Project Manager is the primary contact for support concerning the DMS. This staff member can call on the programming staff for technical support as needed.

8.10. Data sharing

In compliance with NIH regulations, we will provide a data archive that will contain raw study data (no personal identifiers will be provided). The archive will reside on a server on which machine-readable data are acquired, manipulated, documented, and finally distributed to the scientific community for further analysis. The data will be accessible via a website, which we are in the process of developing now (for other purposes as well as data sharing). Appropriate firewalls and other forms of protection of the data will be installed for maximum security. Prospective users will have to register on the website. All NIH regulations and restrictions will be observed.

9. ORGANIZATION AND ADMINISTRATION

9.1. Overview

CODIACS is divided into three phases. Phase A (Oct 1, 2009 - Dec 31, 2009) includes planning and protocol development. Phase B (Jan 1, 2010 - Jan 31, 2011) is the pilot trial. Final data analyses, preparation of manuscripts, closeout activities, and archiving of data will take place during 6-month Phase C.
9.2. Participating Institutions

9.2.1. Clinical Coordinating Center (CCC)

The CCC is located at Columbia University. Under direction of Drs. Davidson and Bigger, the CCC will be responsible for executing the Operations Committees decisions about the trial’s conduct in coordination with the Data Coordinating Center and the NHLBI staff, training screening staff and interventionists, and offering clinical site support, such as recruitment procedures, and contributing to the operations manual sections and administrative functions that support these critical activities. The CCC will coordinate the screening staff and therapy staff training, and will host a 2-day workshop on these activities. They will then support the field centers on a regular, ongoing basis in the problem-solving and operational functioning of the centers as needed.

9.2.2. Data Coordinating Center (DCC)

The DCC is located at the University of North Carolina. Under the direction of Dr. Catellier, the CC will be responsible for finalization of the protocol and manual of operations, development of a system for data collection and data management, randomization and quality control procedures, study communications (newsletter, website, webcasts, conference calls, IRB and HIPAA templates) meeting coordination and preparation of reports for the Steering Committee and DSMB, and reporting of adverse events to the DSMB. In addition, the DCC will be responsible for outcome ascertainment by an independent Medical Event Classification Committee (MECC). The DCC will train sites to abstract relevant material from the medical records of hospitalizations, after which the DCC will blind the material and distribute to the MECC for validation of MACE.

9.2.3. Field centers/sites

Listed below are names of the field centers willing to participate in the trial and their principal investigators.
9.2.4. Depression Assessment Core

Dr. Freedland, the principal developer of the Depression Interview and Structured Hamilton (DISH), will be responsible for organizing and managing the Depression Assessment Core (DAC) at the Washington University center. He will oversee coordinators who will locally screen for the psychiatric exclusion criteria, and will ensure training and quality control for this aspect of the protocol.

9.2.5. Therapy Quality Assurance Core

Quality assurance procedures will include, 1) the digital voice recording of all therapy sessions, 2) the secure transfer of digital files of recorded sessions, and 3) the secure centralized storage of files. The core will also conduct bi-weekly phone based conference calls with site therapists concerning therapy issues and participant progress, and engage in quality assurance sampling of audio files to insure that site therapists are conducting the intervention according to protocol, providing feedback to site therapists as required.

9.3. Steering Committee

This committee consists of Principal Investigators of the field centers and the Data Coordinating Center, and the NHLBI Project Officer. The committee is chaired by Dr. Davidson. Each of the five participating field centers, the DCC, and NHLBI has one vote on the Committee.

The Steering Committee oversees all aspects of the design, execution, and publication of the study. The Steering Committee will have in-person meetings as necessary - but at least once per year, and convene by conference call throughout the study. These meetings will monitor the development of the protocol, study logistics, progress of the trial, possible changes to the protocol, and new developments in the field. The Steering Committee will establish subcommittees as needed to provide guidance and recommendations to the Steering Committee.

9.4. Operations Committee

This committee consists of the Steering Committee Chair (Davidson), study co-PIs (Carney, Bigger), the PI of the Data Coordinating Center (Catellier), and the NHLBI Project Officer (Czajkowski). The Operations Committee oversees the day to day management of the study between Steering Committee conference calls.

The major responsibilities of the Operations Committee include monitoring the study timeline, recruitment and other indicators of study progress, resolving issues that are urgent but do not require discussion by the full Steering Committee, and preparing the agenda for Steering Committee meetings and calls. The Operations Committee in consultation with the Steering Committee will select and recruit additional centers, as part of the plan for the larger trial.

9.5. Data and Safety Monitoring Board (DSMB)

A Data and Safety Monitoring Board (DSMB) will oversee the study in terms of safety, ethics, and science. This committee is advisory to NHLBI and established by the Steering Committee. The
DSMB will have expertise in cardiology, psychiatry, and biostatistics. The approval of the DSMB will be required for any significant changes in protocol recommended by the Steering Committee during the course of the study. The Data Coordinating Center will be responsible for preparing and presenting up-to-date statistical reports on the progress of the study for the DSMB. The DSMB will be convened by conference call or meeting at least once per year. Presentations to the DSMB will be made by the Chair of the Steering Committee, the PI of the Data Coordinating Center, the NHLBI Project Officer, and other individuals proposed by the Project Office or requested by the DSMB. The NHLBI Project Officer, Steering Committee Chair, and Data Coordinating Center PI are ex-officio members of the DSMB. An Executive Session (excluding all study investigators) will be held at each meeting.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Potential risks

The first of three potential risks to the participant is the potential for violation of privacy. Participants are protected by the customary constraints on confidentiality of participant data. Data are stored in the study database using an identification (ID) number, with the linkage between name and ID kept in a secure location at the field center. Forms and electronic data are protected by reasonable security procedures including locked rooms and/or file cabinets for paper documents and coded security access for electronic data. Access to identifying information is limited to study personnel with a need for such access. Personnel involved in the study must agree not to disclose any information which might be protected by confidentiality policies to persons who do not work for the study or who do not have a need to know the information. No published data will include information which would permit readers to identify any individual participant in the study. When the study database is made available to the program office, it will not include actual identities and contact information for participants. Such information will be retained under lock and key at the individual Field Centers and at the Data Coordinating Center for use in the event the future follow-up of the study participants is necessary. The Data Coordinating Center will also maintain confidentiality of participant data as explained above.

The second potential risk is the possibility of discovering during the screening visit that a participant is experiencing suicidal ideation that warrants immediate treatment. If this occurs, the safety procedures outlined in Section 10.5.1 will be followed. We may also discover that participants have cognitive or alcohol/drug impairments that disqualify them from participating in the study. Should participants screen positive on the measures of cognitive impairment or alcohol/drug abuse, we will notify participants’ physicians of the results of the screens (with participants’ consent).

The final set of risks concern those subjects who are randomized to Stepped Care and choose an antidepressant medication. There is no evidence that treatment of depression symptoms in the post ACS period improves outcome, therefore randomization to the Referred care arm is not viewed as a risk. Because the relative efficacy of PST and antidepressant therapy is similar, approximately 40% of the patients with elevated depressive symptoms in this study are expected to fail either pharmacologic or non-pharmacologic treatment. The most observed side effects (Physician’s Desk Reference 2000) associated with the discontinuation of medications to be used in this trial include: asthenia (1.6%), sweating (1%), nausea (3.2%), somnolence (2.3%), tremor (1.1%), nervousness (1.1%), and ejaculatory disturbance (1.6%), dizziness (1.9%), insomnia (1.5%), asthenia (1.3%), and nervousness (1.2%).

According to the FDA, there is a small risk of increased suicidal ideation associated with beginning antidepressant therapy. With respect to cardiac risk, there is a limited amount of data that suggests
that Buproprion might occasionally be associated with an increase in blood pressure. Sertraline and Citalopram were compared to placebo in heart disease patients in the SADHART and CREATE trials, respectively. Neither active drug was associated with any cardiovascular adverse events.

Although Citalopram has been shown to be safe in patients with coronary disease, it can cause side effects including: nausea, dry mouth, insomnia, and increased sweating. Other side effects that occur less frequently include: trembling, diarrhea, tiredness and sexual problems. The side effects will disappear once the medication is discontinued.

The most common side effects of Sertraline include: upset stomach, trouble sleeping, diarrhea, dry mouth, sexual side effects in men and women, feeling unusually sleepy or tired, tremors, indigestion, sweating, decreased appetite, feeling agitated,

The most common side effects of Bupropion are nervousness, constipation, trouble sleeping, dry mouth, headache, nausea, vomiting, and shakiness (tremor).

Lastly, the risk of cardiac events during therapy with the medications to be used has not been fully evaluated in depressed patients. Although cardiac events are not the main outcomes of the RCT, careful attention must be paid to the safety of this group of patients.

10.2. Consent process

Each Field Center must file its own separate Federalwide Assurance (FWA) of Protection of Human Subjects with the Department of Health and Human Services (DHHS) Office of Human Research Protection, providing written, informed consent using procedures reviewed and approved by each Field Center’s local Institutional Review Board. These procedures must meet the requirements of 45 CFR 46, Protection of Human Subjects, including purpose of the study, guarantees of confidentiality and privacy, statement of possible risks, and resource for grievances. Protection is assured in accordance with the ethical principles of (a) respect for persons, (b) beneficence, and (c) justice. All provisions of the federal Privacy Act apply, as appropriate.

Consent forms will be worded in language that a person with an 8th grade education can understand. All staff involved will have completed and passed GCP and HIPAA training for their site, and will have been provided with materials and instruction in the proper and ethical manner in which consent should be obtained. At the time of enrollment, the staff member will give a complete description of the study to the patient in clear, easy-to-understand language. After reading the consent form and having an opportunity to have questions answered, those who choose to participate will sign and date the consent form in the presence of a staff member who will then countersign and date the form. A model consent form is included in the appendix.

10.3. Elements of consent

Consent must include all of the elements listed below:

1. Participants must be advised that the study involves research. The following items must be addressed: purpose of the research; expected duration of the subject’s participation; and a description of the procedures to be followed.
2. Anticipated benefits of the study must be explained to the participant.
3. Attendant discomforts and risks reasonably to be expected must be described.
4. The extent, if any, to which confidentiality of records identifying the participant will be maintained must be described.
5. Prospective participants must be advised of the availability or non-availability of treatment or compensation for physical injuries incurred as a result of participation in the study, and, if available, what they consist of, or where further information can be obtained.

6. The informed consent must include the name of a contact person who can answer questions about the research, the participant’s rights, or information on what to do if a research related injury should occur.

7. Participants must be told that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled, and the participant may discontinue participation at any time without penalty or loss of benefits to which he or she is otherwise entitled.

10.4. Spanish-speaking patients

To reduce the barriers to recruitment and retention of Hispanic/Latino participants, the consent form, HIPAA form, and study forms have been translated into Spanish. We are not seeking IRB permission at this time for these materials, but will submit them as an amendment.

10.5. Procedures for monitoring and reporting adverse events

NIH guidelines indicate that an adverse event (AE) is “any untoward medical occurrence in a study participant.” A serious adverse event (SAE) is “any event that is life-threatening, requires an inpatient hospitalization, results in significant disability, results in congenital anomaly, results in death, requires intervention to prevent impairment or damage, or is an otherwise important medical event.” The field center PI will ensure that an AE is appropriately treated and the event is reported to the local IRB in accordance with local IRB policy. These events will also be reported to the DCC, which will collect and disseminate the information to the DSMB. We will finalize the list of Unanticipated events to be collected and distributed with consultation with the DSMB.

If immediate psychiatric intervention is warranted (e.g., suicidal intent, etc), a study psychiatrist, study physician, or study advanced nurse practitioner will promptly arrange appropriate psychiatric care. Appropriate study personnel will contact the study psychiatrist/physician/advanced nurse practitioner, if any problems arise with a study patient. The study psychiatrist/physician/advanced nurse practitioner will manage the side effects of antidepressant therapy.

After the final follow-up is conducted, those remaining with elevated depressive symptoms will be provided with mental health referral information that is close to their home address.

10.5.1. Procedures for determining safety in suicidal participants

Patients who are found to be actively suicidal, will be ineligible for participation in the trial and will be immediately referred for further clinical assessment and treatment. Patients with psychosis, bipolar disorder, alcohol or drug dependence, or cognitive impairment or other overt psychiatric disorders will also be ineligible and their health care providers will be notified of these conditions, so that appropriate treatment can be offered.

A score of 2 or greater on the BDI item #9 (which concerns suicidality) initiates the safety protocol. When initiated, this protocol requires that a psychologist/psychiatrist be notified, and based on the patient’s presentation and history, a determination be made as to whether the patient is safe to participate in the study, or whether the patient’s physician should be notified. These protocols are followed for both patient screening/recruitment contacts and participant follow-up contacts. Figure 4 illustrates the safety protocols we intend to follow for this project.
### 10.6. Potential benefits of the research

There are no direct benefits to the participants in this study, however some may benefit from amelioration of their depressive symptoms. The research will provide important information about the possible appropriate treatment for comorbid depression in ACS patients. In light of the anticipated knowledge to be derived from the study, the risks to participants appear reasonable.

### 10.7. Compensation

**10.7.1. Screening**

Potential subjects will receive $10 for completing the screening interview.

**10.7.2. Trial**

Subjects may receive up to $105 if they are randomized. They will receive the following payments for each completed study visit:

- **Baseline:** $25
- **5-month (phone):** $15
- **7-month (phone):** $15
- **9-month (office):** $50

In addition, any subjects who must travel to the study offices will be compensated $10 towards travel expenses for each visit.
11. REFERENCES


