HSR #17-4351: Development of an Integrated Depression and Behavioral Risk Factor Reduction Intervention for Secondary Prevention Following Acute Coronary Syndrome

Significance

Acute Coronary Syndrome (ACS) and Behavioral Risk Factors

More than 1 million Americans survive an Acute Coronary Syndrome (ACS; unstable angina, ST and non-ST elevation myocardial infarction) each year.[1] ACS survivors are at risk for recurrent events and early mortality. Thus, secondary prevention following ACS is a major public health issue. Modifiable behavioral risk factors (e.g., smoking, inactivity, poor diet) contribute significantly to occurrence of ACS.[2,3] Thus it is not surprising that these behavioral risk factors frequently occur post-ACS. For example, 31-37% of ACS patients smoke cigarettes[45-47] and without intensive treatment, most return to smoking within a year following ACS.[48-50] An estimated 57% of post-ACS North American patients fail to meet physical activity recommendations and 53% fail to meet dietary recommendations.[8] Further, there is clear evidence that medications (e.g., statins, beta blockers, etc.) improve post-ACS survival. However, 40-75% of patients do not take medications as prescribed.[6,7] Improving the behavioral risk factor profile of post-ACS patients is imperative. Modifiable behavioral risk factors predict morbidity/mortality post-ACS in an additive manner;[3,8] thus interventions targeting only one risk factor may be inefficient.

Depression Symptoms and ACS

Twenty percent of ACS patients meet criteria for clinical depression immediately following ACS (3x the point prevalence in the US population), and an additional 11% experience significant but subclinical depression symptoms.[9,10] Additional patients who are not depressed at the time of ACS develop depression in the following weeks.[51,52] Clinical depression and sub-clinical depression symptoms at the time of ACS and in the weeks following independently predict post-ACS morbidity and mortality.[10-12] The most recent meta-analysis of this issue found that depression was associated with an increased risk of 2.3x for all-cause mortality, 2.7x for cardiac mortality, and 1.6x for cardiac event reoccurrence over 2 year follow-up.[11] These relationships are only slightly attenuated when controlling for known cardiac risk factors.[10,11]

Interaction of Depressed Mood and Behavioral Risk Factors Post-ACS

In the general population, depression is associated with a higher smoking rate, [53,54] lower levels of physical activity[55,56], poor diet[57] and obesity[58], and poor adherence to prescribed medications.[59,60] Further, depression symptoms predict failure of interventions targeting behavioral risk factors. For example, depression symptoms predict smoking cessation failure.[61,62] Likewise, depression predicts drop out, poor adherence, and poor outcomes in interventions targeting physical activity, diet, and/or weight loss.[63-68] Specifically among post-ACS patients, those with depression smoke more,[13] exercise less,[14,15] eat a less healthy diet,[16] and adhere less well to prescribed medications.[14,15] Recent work has demonstrated that at least part of the relationship between depressed mood and post-ACS morbidity/mortality is explained by a poor profile of modifiable behavioral risk factors among those with depression,[14-17,69-72] suggesting that depressed mood contributes to morbidity/mortality both directly and indirectly through interference with post-ACS improvement in behavioral risk. However, successful treatment of depression alone does not have automatic serendipitous effects on behavioral risk factors.[18] Thus, an integrated treatment targeting depression and multiple behavioral risk factors may have unique potential to reduce long-term mortality for those with post-ACS depression.

Existing Treatments for both Mood and Behavioral Risk Reduction Post-ACS

To our knowledge, only one treatment targeting depression and multiple behavioral risk factors post-ACS has been tested. This treatment ("MoodCare"[21,73]) provided 10 phone counseling sessions utilizing Cognitive Therapy and Motivational Interviewing. MoodCare targets several behavioral risk factors (e.g., physical activity, diet, sleep, alcohol consumption). This study demonstrated the feasibility of combining depression treatment and behavioral risk factor change post-ACS. They found evidence for the efficacy of MoodCare on depression symptoms at end of treatment, but mixed results at 1-year follow-up. They did not report the effect of MoodCare on risk factors or on cardiac health. MoodCare has several weaknesses we considered when deciding to develop a new treatment: 1) Cognitive Therapy and Motivational Interviewing both require substantial training and supervision to implement with fidelity, thus limiting dissemination potential; 2) No data on behavioral risk factor changes were reported,

thus we do not know if MoodCare had any effect on these; and 3) MoodCare focuses on a broad array of behavioral risk factors, rather than focusing on those that have specifically been implicated in explaining the relationship between depression and post-ACS mortality (tobacco use, physical activity, medication adherence, and diet have been implicated[14-17,69-72]).

Behavioral Activation and Behavioral Risk Reduction

Behavioral Activation (BA) is a well-established counseling treatment for depression.[28] BA is easier to train than other empirically-supported counseling treatments.[29,32,74-76] BA can be effective in relatively few sessions[77] and can be delivered with fidelity by bachelor's level providers.[33,78] BA aims to ameliorate depression and decrease avoidance behaviors (which can include smoking, overeating, and inactivity) by reengaging patients with healthy sources of positive reinforcement in their environment. This is accomplished through individually-tailored "activation goals" that are collaboratively set and explicitly scheduled during counseling sessions. Behavioral risk factor changes can be explicitly scheduled as activation goals. The efficacy of BA was originally established for the treatment of clinical depression in psychiatric settings.[25,26] Importantly, BA now has support for the treatment of depression in a variety of medical populations, including patients with cancer,[24] macular degeneration,[79] stroke,[22] and obesity.[23] Research suggests that BA counseling can facilitate behavioral risk factor change among those with depressed mood,[34-40] including pilot data from the PI's K23 award (see preliminary studies below). To our knowledge, BA for depression has not been tested as a stand-alone treatment in post-ACS patients. However, there is evidence to support its use in this population. First, the core target of BA, greater engagement in pleasant/valued life activities, is independently associated with improved post-ACS mood trajectories.[80-83] Second, low levels of pleasant/valued life activities have been linked to higher levels of established ACS risk factors, including inflammation and hypertension.[84-86] Finally, BA techniques have been included as components of successful collaborative care interventions for post-ACS depression.[41-44] The proposed study will develop a treatment targeting secondary prevention post-ACS that integrates BA based treatment for depression and modification of behavioral risk factors post-ACS (Behavioral Activation for Health and Depression; BA-HD).

Approach

Aim: Conduct an open trial (N=20) of BA-HD to test the feasibility and acceptability of our procedures and obtain initial indications of efficacy.

Inclusion criteria: 1) ACS diagnosis (diagnosis of unstable angina, ST and non-ST elevation myocardial infarction) documented in medical record in the preceding 2-12 months, 2) Depression diagnosis listed on patient problem list in patient's medical record, a clinically administered PHQ-9 score of 10 or greater in the past 12 months indicated in the patient's medical record, or a Center for Epidemiologic Studies Depression scale (CESD) score ≥10 (indicating "likely major depressive disorder"); CESD will be administered by phone during screening if there is no indication of depression or PHQ-9 score within 12 months in the patient medical record, 3) current non-adherence to ≥ 1 of four behavioral risk factors (see below), 4) willing to make immediate changes to ≥ 1 relevant behavioral risk factors, 5) age of 18-75, 6) lives within 1.5 hours of Hennepin Healthcare, and 7) fluent in English.. Exclusion criteria: 1) Limited mental competency (as indicated in medical chart), 2) presence of current exacerbation of psychosis/serious mental illness or suicidality, 3) in hospice care, 4) currently attending regular counseling targeting depression or any health behavior change, and 5) currently attending a cardiac rehabilitation program (those excluded for being in rehabilitation will be re-contacted after completion). We will attempt to obtain a sample of at least 45% women, which is representative of the gender distribution of discharged ACS patients.[1]

We will define non-adherence as follows: Tobacco non-adherence = use of any tobacco product in the last week. Physical activity non-adherence = engagement in < 90 minutes of moderate or greater physical activity per week.[104] Medication non-adherence = non-adherence based on Heart and Soul study criteria i.e., taking medication as prescribed 75% of the time or less, forgetting medications at least 1x/week, or skipping a medication at least 1x/week. Diet non-adherence = following a "healthful eating plan" 4 or fewer days per week, eating 5 or more servings of fruits and vegetables 4 or fewer days per week, or eating high fat foods 3 or more days per week.

Recruitment: Participants will again be recruited through review of electronic medical records at Hennepin Healthcare. We will pull records of recent ACS hospital discharges, screening for depression where available. The ACE team may identify names from EPIC to facilitate this. We will also review records of outpatient cardiology (clinic and cardiac rehab to identify potential patients, (a flyer will be provided to patients and providers. Flyer attached). Opt out letters will be sent to all participants identified through chart review and

a research assistant will call patients on this list to screen for eligibility using the above criteria. Those that qualify by phone screen will be invited to an in person meeting to provide informed consent and then complete a baseline assessment. If study staff are unable to reach potentially qualifying patients by phone, study staff will work with care providers in clinic or cardiac rehab to introduce the study during a clinical visit, where research assistant will screen in person. The research assistant will then schedule the patient for a first session of BA-HD coaching at the Berman center, other Hennepin Healthcare facility, or in patient's home when needed; (Note that "Home" can be a nursing home, assisted living, rehab center, or other institution.). We may recontact patients who have completed primary outcome in other Busch Lab studies.

Behavioral Activation for Health and Depression (BA-HD)

Consistent with successful BA manuals, we plan to conduct up to 10 sessions of treatment over 12 weeks (the recommendation will be to do at least 8 sessions; scheduling of sessions will be flexible and conform to patient preference). The initial two sessions will be about 50 minutes long and later sessions will be 20-30 minutes long. Sessions can be done on site or over the phone. The recommended treatment will have 2 sessions in person followed by phone sessions. Home visits will be offered for sessions 1-2 if a participant cannot travel to on-site sessions. Study treatment will be conducted by an exercise physiologist who is a cardiac rehabilitation provider, a HHRI employed licensed social worker, or a licensed clinical health psychologist with clinical privileges at Hennepin Healthcare.

BA has its underpinnings in the behavioral model of depression,[75] which purports that depression results from reduced engagement in positively reinforcing activities. According to BA theory, depression and related problem behaviors can be reduced by reconnecting patients with healthy sources of positive reinforcement. The core components of all BA treatments are 1) Assessment of participant values, 2) self-monitoring of mood and behavior between sessions, and 3) Between session goal setting. We will integrate behavioral risk factor improvement into these core components.

Assessment of participant values is accomplished through a structured values assessment. The results of this assessment will be used to guide content of goals for increasing pleasant/valued activities in order to improve depression. Personal values will also be used to maintain motivation for behavioral risk factor changes. Patents will be asked to self-monitor mood and behavior between sessions in order to gather idiographic data on the relationship between mood and daily activities. Participants will also monitor the behavioral risk factors currently being targeted (see below). This will allow for discussion of the relationship between mood and behavioral risk factors. Participants will be provided with standard BA self-monitoring forms, with added sections for tracking behavioral risk factors. Between session goal setting is accomplished though collaboratively defined, between-session "activation goals" (i.e., explicitly scheduled between session activities). Goals are pleasurable and/or value driven, but specific content is individualized. Several aspects of BA facilitate the completion of activation goals. Specifically, goals are collaboratively determined, set in manageable increments (to increase self-efficacy through early success), and reviewed in detail during subsequent sessions in order to identify and problem-solve any barriers encountered.[75,107] In addition, all activation goals are explicitly written down (e.g., to-do list, daily planner) or otherwise scheduled (e.g., entered into cell phone calendar). With the participant's permission, study staff will send an automated email or text message between sessions to remind the patient to complete their goals (in our pilot RCT (see section 3.2) >80% of participants were willing and able to receive goal reminders by text or email). There is emerging evidence that such text messages can improve post-ACS adherence.[108] Texting and emailing are included in the informed consent document. Further, when obtaining contact information, we will confirm with patients what email address we can use and what phone numbers they give us permission to text message to.

Behavioral risk factor change goals will be set alongside depression focused goals (see below) and the content of goals will be integrated to maximize both mood improvement and risk factor change. For example, for a participant trying to quit smoking, the interventionist will ensure that goals don't involve increased contact with smoking triggers. Likewise, the interventionist will encourage pleasant/valued activity content that is consistent with risk factor targets (e.g., walking, cooking healthy a meal with spouse) and discourage content inconsistent with risk factor goals (e.g., outings for ice cream).

Risk factors will be targeted sequentially. First, the interventionist and participant will collaboratively choose the first risk factor to target. This will primarily be based on what the participant is most motivated to change. If the participant is equally motivated to change two or more risk factors on which they are non-adherent, the priority order will be: 1) tobacco, 2) medication adherence, 3) physical activity, 4) diet. This priority order is based on strength of data implicating each as a mechanism of the depression to post-ACS mortality relationship. [14-17,76-79] Next, the interventionist will provide brief education regarding the importance of that risk factor post-ACS, the recommended level of that risk factor for secondary prevention, and how their

current behavior compares to recommendations. This information will be based on the latest clinical guidelines.[109-111] The interventionist will then collaboratively set an attainable goal regarding that risk factor until the next session and ask the participant to self-monitor engagement in the risk factor. A second and/or third risk factor could be targeted later in treatment if the participant makes sufficient progress on the first. The detailed content of coaching for each of the behavioral risk factors has been developed by the investigative team and is informed by clinical guidelines and our Aim I qualitative findings.

We will provide relevant educational content to support health behavior change. Content will be produced by, or closely adapted from the American Heart Association, and in-line with current guideline-based care (patients will receive a packet with this information). The behavioral targets for improving health behavioral will be as follows: **1)** For tobacco use, we will focus on quitting tobacco completely during the study period. We will allow goals to partially reduce tobacco use, but only in the context of "cutting down to quit" (i.e., we will support tobacco reduction goals that are first steps towards a goal of quitting completely; we will not support reduction itself as a long-term goal). **2)** For physical activity, we will focus on increasing overall walking steps per day. **3)** For medication adherence, we will focus increasing days that participants are adherent to their currently prescribed medications. We will encourage participants to resolve issues (e.g., cost, side effects) in discussions with their clinical providers. **4)** For diet, we will focus on making small, concrete changes to diet, consistent with the "small changes approach". For example, we might set goals like, "eat one more fruit per day" or "limit fast food to 2x per week". We will not focus on weight loss as a short term goal. As we have done in our previous studies (K23HL107391, AHA 12CRP9840018), we will also provide tools to facilitate behavioral risk factor change that are cost effective and widely used in clinical care. Specifically, we will: **1)** provide courses of the nicotine patch and/or lozenge to tobacco users who are willing to make a quit attempt in the next 30 days when medically indicated. Nicotine replacement is medically indicated for the vast majority of smokers with few exceptions (e.g., pregnancy). If nicotine replacement is provided the dose will be determined in consultation with study team (i.e., Dr. Busch: psychologist/tobacco expert; Dr. Ayenew: cardiologist; Dr. Vickery: family physician). Non-daily tobacco users will only be offered the nicotine lozenge.The patient's primary provider will be informed through EPIC messaging that nicotine replacement was provided to the participant. The study MDs/PhD may talk to the participant to obtain more information in order to assess appropriateness of nicotine replacement. Participants will be encouraged to contact staff if they have any side effects or concerns. Providing nicotine replacement is important because recent data indicate that smokers with depression symptoms experience more nicotine withdrawal post-ACS.[112] **2)** Provide wearable accelerometers/pedometers to those attempting to increase physical activity. Accelerometers/pedometers will facilitate physical activity monitoring and goal setting. Physical activity promotion will focus on increasing step counts on accelerometers/pedometers by walking more. It is safe for the vast majority of post-ACS patients to start a walking program. If the interventionist has any concern regarding the safety of walking Dr. Ayenew and Dr. Vickery will be available for consultation. The participant may want to work on more intense exercise, especially later in the treatment protocol. If this is the case the interventionist will discuss with the patient if they have been cleared by their medical team to engage in the desired activity. If there is any concern regarding clearance for exercise, the interventionist may contact the patient's providers and/or consult with Dr. Ayenew and Dr. Vickery. **3)** Provide a variety of pill boxes with and without reminder alarms. We will also offer reminder devices that replace pill bottles if participants prefer. We will also encourage those targeting medication adherence to set a cell phone alarm for every daily dose. Interventionists will assist participants in setting these cell phone/pill box/pill bottle top alarms. **4)** Provide those targeting diet change with American Heart Association-supported cookbooks and/or simple measurement and healthy cooking tools to facilitate healthy cooking.

BA-HD will have the following structure: **Session 1** will be offered in our clinic or at home (based on participant need and preference). Session 1 will include the following: **1)** review patient history, **2)** review status of 4 health behavior targets, **3)** discussion of rationale for BA-HD, **4)** choice of initial behavioral risk factor target, **5)** brief education and history regarding chosen health behavior, **6)** introduction of self-monitoring of mood and behaviors (including relevant health behaviors), **7)** collaboration to set one activation goal to be completed before the next session, **8)** problem-solving of barriers to completion of goals, and **9)** offering an automated email or text message reminder of goals. Participants will be provided with a packet of educational materials to keep at session 1. If applicable, interventionist will engage providers and the study team (including study cardiologist) to assess for safety of physical activity or use of nicotine replacement.

Session 2 will be scheduled in person if possible. **Session 2** will include the following: **1)** follow-up on between session self-monitoring and any planned activities, **2)** a structured values assessment[107] and a

discussion of how resulting values relate to risk behaviors (e.g., "How will continued smoking detract from grandparenting?"), **3)** provision of tools to aid risk behavior change, **4)** collaboration to set 1-4 activation goals to work on before the next session, **5)** problem-solving of barriers to completion of goals, and **6)** offering an automated email or text message reminder of goals.

Sessions 3-10 will be conducted by phone and will follow the same basic format: **1)** assess depressed mood, activity, and relevant behavioral risk factors between sessions, **2)** review adherence to activation goals from the previous session; **3)** choose 1-4 activation goals that are pleasant and/or in line with the participant's values and explicitly schedule these; **4)** problem-solve barriers to completion of new goals, and **5)** offer an automated email or text message reminder of goals. Starting in session 4 the interventionist and participant will collaboratively discuss if the next relevant behavioral risk factor should be added to goals. During the final coaching call (session 10 if full protocol completed), rather than assigning new activation goals, the interventionist will guide the participant in completion of a written guide which provides a structure for continuing to work towards goals independently.

Measurement

Participants will complete self-report, interview, and anthropomorphic measures at enrollment and at end-of-treatment (i.e., following 12 weeks of BA-HD coaching). In addition, at end-of-treatment a 30-45 minute qualitative interview will be conducted. Participants will be compensated $30 per assessment and an extra $20 for completion of the qualitative interview. Thus, Aim II participants could receive $80 total for assessments. Transportation will also be provided or reimbursed as well.

Variables assessed at baseline only: Socio-demographics, including age, gender, ethnicity, employment, and income will be collected. Medical history will be assessed through self-report and chart review and will include ACS diagnosis and treatment, and a detailed history of cardiac disease, events, and procedures. Co-Morbid conditions will also be assessed.

Outcomes: Acceptability will be assessed only during the end-of-treatment assessment using the 8-item Client Satisfaction Questionnaire.[94] Feasibility will be assessed by rate of recruitment/retention, session attendance, and completion of between session goals. Depression symptoms will be assessed using the CESD and the 9-item self-report Patient Health Questionnaire (PHQ-9).[97] Composite Behavioral risk factor adherence: The Medical Outcomes Study Patient Adherence Questionnaire[106] has validated items measuring all four of the behavioral risk factors targeted (tobacco, physical activity, diet, medication adherence) and has been used in large studies of post-ACS risk factor change.[113] Thus, we will use the total score of these items as a composite outcome across the 4 risk behaviors. We will calculate the total score for the 10 more general items related to cardiac health [135]. We will also administer brief validated questions regarding time spent engaging in physical activity, medication adherence, and diet quality. Change in tobacco use will also be measured continuously with cigarettes/other tobacco product use per day and dichotomously using 7-day point prevalence abstinence (i.e., no use at all in past 7 days). A breath sample will be used to verify abstinence.[117,118] Participants who report using smokeless tobacco products or e-cigarettes containing nicotine will be considered tobacco users. **Secondary outcomes**: We will also include established self-report measures of affect,[119] health related quality of life[121], exercise capacity,[122] and hypothesized BA mediators.[123,124] Weight/height, waist circumference, and resting systolic and diastolic blood pressure will be collected using standard procedures.

Analysis

Qualitative Data: We will again analyze recordings of end-of-treatment qualitative interviews using the Framework Matrix Analysis procedures described for Aim I above. However, analysis of follow-up interviews will explicitly focus on acceptability and suggestions for improving BA-HD.

Feasibility and Acceptability Data will be examined descriptively. Client Satisfaction Questionnaire score, rates of recruitment/retention, sessionattendance, and completion of between session goals will be compared to relevant previous trials. Clinical outcome analyses will focus on determining if BA-HD had clinically meaningful effects. For example, we will examine within participant effect size and response rates (using standard cut offs) on the PHQ-9. We will examine within participant change in our composite of behavioral risk factors in a similar manner. We will analyze data in an intent-to-treat manner.

Design Considerations

Choice not to use cardiac rehabilitation. Cardiac rehabilitation is the gold standard for targeting behavioral risk factors post-ACS and also improves depression symptoms. However, only a minority of ACS patients complete cardiac rehabilitation and those with depression are particularly unlikely to attend or complete.[123] Thus, if we conducted our treatment in a rehabilitation setting we would miss many of those with depression post-ACS. Choice to enroll participants 2-12 months after ACS. We considered enrollment of patients while in the hospital for ACS. We chose not to because: 1) there is a high rate of spontaneous recovery of hospital assessed

depression in the first month post-ACS,[124] 2) there is a high rate of development of new depression symptoms in the initial months following ACS,[9,51] 3) depression assessed 3 months post-ACS has specifically been linked to poor adherence to behavioral risk factors,[14] and 4) many patients will not be cleared to increase physical activity immediately post-ACS. Choice to complete an open trial rather than an RCT. We considered conducting an RCT as part of the proposed R03. However, our primary purpose is to get as much patient feedback on the BA-HD manual as possible, making an open trail a better fit. Choice of a sequential intervention. We considered targeting depression and all relevant behavioral risk factors simultaneously. However, simultaneous targeting of multiple risk factors is cognitively demanding for the patient and associated with increased drop-out.[125] Given that those with depression have concentration and memory deficits, and are already more likely to drop-out of risk factor reduction treatments, we chose to target risk factors sequentially. Choice to provide free behavior change aids. Those with depression struggle with motivation, concentration, memory, and self-regulation, thus we provide reminder and goal tracking aids (e.g., wearable accelerometers, medication reminder alarms, diet measurement/tracking tools) to help address these deficits. We provide nicotine replacement treatment because smokers with depression symptoms experience more nicotine withdrawal post-ACS.[112]

PROTECTION OF HUMAN SUBJECTS

1. Risks to Human Subjects

Note: The design of Aim II will be adjusted based on the results of Aim I. Thus, the protections below will be reviewed and updated as needed following the design of Aim II.

1a. Human Subjects Involvement, Characteristics, and Design

AIM II Inclusion criteria: 1) ACS diagnosis (diagnosis of unstable angina, ST and non-ST elevation myocardial infarction) documented in medical record in the preceding 2-12 months, 2) Depression diagnosis listed on patient problem list in patient's medical record, a clinically administered PHQ-9 score of 10 or greater in the past 12 months indicated in the patient's medical record, or a Center for Epidemiologic Studies Depression scale (CESD) score ≥10 (indicating "likely major depressive disorder"); CESD will be administered by phone during screening if there is no indication of depression or PHQ-9 score within 12 months in the patient medical record, 3) current non-adherence to ≥ 1 of four behavioral risk factors (see below), 4) willing to make immediate changes to ≥ 1 relevant behavioral risk factors, 5) age of 18-75, 6) lives within 1.5 hours of Hennepin Healthcare, and 7) fluent in English.. Exclusion criteria: 1) Limited mental competency (as indicated in medical chart), 2) presence of current exacerbation of psychosis/serious mental illness or suicidality, 3) in hospice care, 4) currently attending regular counseling targeting depression or any health behavior change, and 5) currently attending a cardiac rehabilitation program (those excluded for being in rehabilitation will be re-contacted after completion). We will attempt to obtain a sample of at least 45% women, which is representative of the gender distribution of discharged ACS patients.[1]

We will define non-adherence as follows: Tobacco non-adherence = use of any tobacco productin the last week. Physical activity non-adherence = engagement in < 90 minutes of moderate or greater physical activity per week.[104] Medication non-adherence = non-adherence based on Heart and Soul study criteria i.e., taking medication as prescribed 75% of the time or less, forgetting medications at least 1x/week, orskipping a medication at least 1x/week. Diet non-adherence = following a "healthful eating plan" 4 or fewer days per week, eating 5 or more servings of fruits and vegetables 4 or fewer days per week, or eating high fat foods 3 or more days per week.

We are recruiting ACS patients who are depressed and struggle with at least one behavioral risk factor post-ACS because this population will be the target of our intervention. We require patient willingness to change at least one risk factor because the treatment is designed for patients with some motivation to change. We limited enrollment to ages 18-75 because young children and geriatric patients may need tailored interventions. Fluency in English is required because (at this time) the BA-HD manual and forms are only in English and clinical supervisors are mono-lingual English speakers. Those with limited mental competency, a severe mental illness that would interfere with participation, or suicidality are excluded because these groups likely require different counseling strategies and/or a higher level of counseling care than provided by the proposed intervention. Our treatment manual was not designed for use in these populations. Those in hospice are excluded because the BA-HD manual does not address end of life issues. Those currently attending counseling for depression or health behavior change are excluded because these concurrent treatments would confound primary outcomes.

For **both Aims I and II**, we will enroll individuals of all racial and ethnic backgrounds. We plan to enroll ratios of minority groups that are consistent with the population of Minneapolis, MN. According to latest United States Census data, the racial composition of individuals living in Minneapolis, MN is 63.8% White, 18.6% Black or African American, 5.6% Asian, 2.0% American Indian/Alaska Native, 0.0% Native Hawaiian/Other Pacific Islander, and 4.4% two or more races. The ethnic composition of individuals living in Minneapolis MN is 10.5% Hispanic/Latino and 86.0% Non-Hispanic/Latino. Thus, we expect that 36.2% of the sample will be members of a racial minority group, and 10.5% of the sample will be of Hispanic/Latino ethnicity. We expect to enroll a sample that is 45% women which is representative of the gender distribution of ACS patients.[1,45] Please see the Targeted/Planned Enrollment Table for a detailed distribution.

Enrollment, Aim II: Participants will again be recruited through review of electronic medical records at Hennepin Healthcare. We will pull records of recent ACS hospital discharges that also have depression listed as a diagnosis. The Analytics Center of Excellence (ACE) team may identify names from EPIC to facilitate this. We will also review records of outpatient cardiology and ask outpatient cardiology providers to direct us to records of patients who might qualify. A research assistant will call patients to screen for eligibility using the above criteria. In addition, patients will be invited to call a research assistant themselves via use of a recruitment flyer will be provided to cardiology patients and providers (See attached). This flyer will be given to providers for distribution to interested patients and posted in clinic waiting rooms.

Those who qualify by phone screen will be invited to an in person meeting to provide informed consent

and then complete a baseline assessment. The research assistant will then schedule the patient for a first session of BA-HD coaching at the Berman center or other Hennepin Healthcare facility (or in patient's home when needed).

Procedure, Aim II: Following informed consent, participants will complete self-report, interview, and anthropomorphic measures at enrollment and at end-of-treatment (i.e., following 12 weeks of BA-HD coaching). In addition, at end-of-treatment a 30 minute qualitative interview will be conducted. Qualitative questions will focus on the participants experience throughout the study (e.g., How was the screening process? How was the consent and enrollment process? What did you like and dislike about the coaching program?, etc). Data will also be pulled from the medical chart. Participants will be compensated $30 per assessment and an extra $20 for completion of the qualitative interview. Thus, participants completing could receive $80 total for assessment completion. Transportation will also be provided or reimbursed as well.

Consistent with successful BA manuals and our Aim 1 qualitative data, we plan to conduct a 10 session treatment over 12 weeks (weekly for the first 8 sessions and bi-weekly for the final two). The initial two sessions will be about 50 minutes long and later sessions will be 20-30 minutes long. We plan a treatment that is primarily over the phone, but allowing for the 1st and 2nd sessions in person and in home if needed per patient preferences. Dr. Busch, a Hennepin Healthcare employed exercise physiologist, and/or an HHRI employed social worker will conduct all treatment in the proposed study.

1b. Sources of Materials

All data collection will follow IRB and HIPAA guidelines. Data will be collected directly from participants and from medical records. Data will include participant responses to interviews and self-report questionnaires(including screening questions), expired air samples (aim II for those focused on tobacco cessation only, i.e., carbon monoxide testing), physical measurements (aim II only, e.g., blood pressure, height, weight), and datapulled from medical charts. Coaching sessions (aim II only) and qualitative interviews (aim I only) will also be audio recorded (explicit permission to do so will be obtained).

As participants will be recruited via chart review (medical records will be screened in order to identify patients who may meet inclusion criteria), we will apply for a Protected Health Information (PHI) waiver from our IRB. All data will be treated as confidential and will never be stored or reported in association with identifying information. Participant responses to interviews and self-report questionnaires and information obtained from medical charts will be entered directly into a secure electronic database. Only the PI, Co-Is, and study staff that have completed training in the ethical conduct of research will obtain or have access to identifiable information. All data will be de-identified and filed according to participant ID numbers in secure storage. Any forms with identifying information (e.g., signed informed consent forms) will be stored separately. Only de-identified data will be published.

1c. Potential Risks

Nicotine replacement side effects (Aim II only): All subjects in Aim II who are tobacco users, ready to quit in 30 days, and cleared for use by the study team will be offered a free course of nicotine patches and/or the nicotine lozenge. Nicotine replacement treatment has been in clinical use for 20 years. It is available over the counter and has been judged to be generally safe and efficacious with very few contraindications. Nicotine replacement has been found to be medically safe for use with cardiac patients,[126] including specifically among ACS patients.[127,128] Nicotine replacement is medically indicated for the vast majority of smokers with few exceptions (e.g., pregnancy). However, there are some reports indicating that nicotine replacement use poses risk to some subgroups of ACS patients in some situations[129]. Thus, if nicotine replacement is provided, the dose will be determined in consultation with study team (i.e., Dr. Busch: psychologist/tobacco expert; Dr. Ayenew: cardiologist; Dr. Vickery: family physician). The patient's primary provider will be informed through EPIC messaging that nicotine replacement was provided to the participant. The study MDs/PhD may talk to the patient to obtain more information in order to assess appropriateness of nicotine replacement. Initial dosing will follow FDA instructions/clinical guidelines, but lower doses may be provided if recommended by Drs. Busch, Ayenew, or Vickery. Staff will be trained to explain the purpose of nicotine replacement, use, and side effects. Common side effects of the patch include local skin irritation at the site of the patch and disturbed or vivid dreams. Common side effects of the nicotine lozenge include mouth problems, indigestion, and sore throat. Less common reactions to both the patch and lozenge includes allergic reactions. If the dose of nicotine replacement is too large or if the participant continues to smoke at a high level while using the nicotine replacement, they may experience symptoms of nicotine overuse including nausea, irregular heartbeat or palpitation, and dizziness. The risk of using nicotine replacement in the current study is judged to be very minor.

Nicotine Withdrawal Symptoms After Quitting (Aim II only): There is a strong likelihood that most study

participants who quit smoking will experience some nicotine withdrawal symptoms, including anxiety, restlessness, anger, irritability, sadness, problems concentrating, appetite change and weight gain, insomnia, and decreased heart rate. Generally, these reactions are temporary and pose no serious health risks.

Injury from increasing physical activity (Aim II only): It is possible that physical activity post-ACS could trigger a recurrent cardiac event or cause other injury. The risk of injury from increasing physical activity in the current study is judged to be very minor, given that we will focus on increasing walking (rather than more intense exercise).

Confidentiality or loss of privacy. We will collect potentially sensitive information about participants; if released inappropriately, participants may experience embarrassment or distress. The seriousness of the consequences would depend on the nature of the information revealed and to whom the information was revealed. Given the numerous steps we take to protect participant confidentiality, we think the risk of a breach of confidentiality is low.

Discomfort or distress when completing assessment and treatment procedures. Some participants may feel uncomfortable or distressed answering personal or private questions during assessment or treatment. Some participants may also feel uncomfortable or distressed due to the collection of physical measures (e.g., weight). In our previous studies, when individuals did report discomfort in these situations, it was mild.

Worsening of depression and emergent suicidality. The post-ACS period can be a high stress time. Although not likely resulting from trial participation, it is likely that a minority of participants will experience worsening of depression or episodes of suicidality during this study.

2. Adequacy of Protection Against Risk

2a. Recruitment and Informed Consent

Participants who appear to meet inclusion/exclusion criteria, based on review of their electronic medical records, will be called by study staff. At first contact, all participants will first be given a brief verbal overview of the study. If participants agree to be screened and pass the screening questions based on inclusion/exclusion criteria they will be invited to participate. Written informed consent (including a description of the nature, purpose, risks, and benefits of the study) will be obtained from participants before initiating assessment. The voluntary nature of the study and the participant's right to withdrawal at any time will be stressed during the consent process; this information will be provided to participants in written form at the time of consent. As part of the consent process for Aim II, we will also ask five questions about the study. The staff member will clarify any misunderstandings that emerge during this process. Those who answer fewer than four questions correctly (after two tries) will be considered to lack the capacity to consent to the research. Research assistants and study interventionists will obtain consent.

2b. Protections Against Risk

Minimization of nicotine replacement side effects: Nicotine replacement is generally safe for patients with stable cardiac disease[126] and with post-ACS patients.[132,133] However, there are some reports indicating that nicotine replacement use poses risk to some subgroups of ACS patients in some situations[129]. **Thus, we will minimize the occurrence of any serious medical side effects by having the** study provider team (i.e., Dr. Busch: psychologist/tobacco expert; Dr. Ayenew: cardiologist; Dr. Vickery: family physician) review if the patient is appropriate for nicotine replacement and if so what the dose should be. Initial dosing will follow FDA instructions and clinical guidelines, but lower doses may be provided if recommended by the study team. Participants will agree to consult with their outpatient medical providers regarding the safety of using nicotine replacement if their medical status changes after nicotine replacement is initially provided. Further, staff will be trained to explain the purpose of nicotine replacement, procedure for use, and side effects, as well as how to use nicotine replacement in a manner that minimizes risk.

To minimize skin reactions related to the nicotine patch, participants will be instructed to move the site of patch placement each day and to not repeat site use for at least one week. Smokers will be instructed to remove the patch before bed if it significantly interferes with sleep. To minimize lozenge side effects, participants will be instructed in proper use in detail (i.e., do not chew the lozenge).

Nicotine replacement dose may be adjusted downward if there is significant nausea or other reactions. Participants with severe side effects will be asked to discontinue nicotine replacement use and discuss with study team and/or their providers before continuing.

Only participants who are ready to quit within 30 days will be provided with nicotine replacement. Participants will be allowed to use the nicotine lozenge to reduce smoking in preparation for a quit day (i.e., consistent with a "cut down to quit" approach).

Minimization of nicotine withdrawal symptoms after quitting: Participants who decide to use the nicotine replacement will be told that it will reduce but not entirely eliminate withdrawal symptoms. Participants will be instructed to call their outpatient physician in the case of severe withdrawal reactions. Withdrawal symptoms typically abate within 1 to 2 weeks of quitting and are not medically dangerous.

Minimization of potential for injury from increasing physical activity. BA-HD focuses on increasing self-paced walking (i.e., goals well be stated in steps per day on wearable accelerometers/pedometers), which is safe for the vast majority of patients who are ≥3 months post-ACS. If the interventionist has any concern regarding the safety of walking Dr. Ayenew and Dr. Vickery will be available for consultation. The patient may want to work on more intense exercise, especially later in the treatment protocol. If this is the case the interventionist will discuss with the patient if they have been cleared by their medical team to engage in the desired activity. If there is any concern regarding clearance for exercise, the interventionist may contact the patient's providers and/or consult with Dr. Ayenew and Dr. Vickery.

Minimization of loss of confidentiality/privacy: All data and records will be safeguarded according to the strict privacy/confidentiality policies of Hennepin Healthcare Research Institute's Institutional Review Board (IRB). Confidentiality will be maintained by numerically coding all data, disguising identifying information, and keeping data in secure electronic locations or locked in file drawers. All electronic data will be numerically coded and stored on a password protected computer in a secure research space. All paper forms will be stored in locked file cabinets in a locked room. Names of participants will be stored separately. Participant information will be accessible only to research staff, who are pledged to confidentiality and complete training in the ethical

conduct of research (i.e., both HIPAA and CITI trainings). Dr. Busch will also personally train staff on maintenance of participant confidentiality. Identifying information will not be reported in any publication.

Minimization of discomfort or distress when completing assessment and treatment procedures: We will take three specific steps to reduce the possibility of discomfort or distress:

Study will be clearly explained. A detailed explanation of the study, including what study participation would involve, the nature of the questions participants will be asked to answer, the nature of measurements, and the right to withdrawal from the study at any time without penalty, will be provided to the participants, both verbally and in writing (through the informed consent form). Participants will be encouraged to ask questions about the study. Individuals who are uncomfortable answering these types of questions, assessments, or interventions likely will not choose to participate. Those who choose to participate but are very uncomfortable with the questions, assessments or interventions will likely refuse these assessments or choose to withdrawal from the study.

Private setting. To help ensure clients' comfort, they will answer survey questions and complete physical measurements in a private setting. Thus, they should not be concerned that another individual would be able to observe these assessments.

Staff Training. All staff interacting with participants will be trained by Dr. Busch to ask questions and complete assessments in a sensitive manner and be supportive to any participant experiencing discomfort or distress.

Minimization of risk from worsening of depression and emergent suicidality. **There is no evidence indicating that participation in this trial will worsen depression or cause suicidality.** However, given that post-ACS period can be a high stress time, it is likely that a minority of participants will experience worsening of depression during this study. A smaller minority may experience episodes of suicidality. Thus, we will monitor and respond to these issues in an ethically sensitive manner.

For aim II, we are only enrolling participants who are not currently in counseling for depression. Participants taking an anti-depressant medication at baseline and during the study will be allowed to participate. For ethical reasons, once enrolled we will not restrict anti-depressant medication treatment seeking in any way during the study (i.e., we will not ask participants to refrain from starting antidepressant medication during the study). We will carefully track antidepressant medication seeking outside of the study and will control for outside treatment in analyses as appropriate.

All participants will be assessed for depression using the PHQ-9 at all assessments. If a participant continues to report significant depression (i.e., PHQ-9 ≥10) at the end-of-treatment assessment, staff will 1) encourage the participant to discuss these symptoms with his or her medical providers and 2) provide a list of community psychiatric treatment referrals.

If a participant reports active suicidality (i.e., any recent suicidal attempts, suicidal gestures, or self-injurious behavior; any current plan or intent to engage in suicidal or self-injurious behavior) to any study staff at any time point, the participant will be assessed by Dr. Busch (a licensed clinical psychologist). Dr. Busch will assess the participant and respond in an appropriate and ethical manner according to the standards of care for suicide prevention (e.g., referral to immediate emergency psychiatric care if danger to self is imminent).

3. Potential Benefits of the Proposed Research

Potential benefits for Aim II participants include free treatment with the potential to increase the likelihood of behavioral risk factor reduction, which could in turn extend their lives. Aim II participants will also receive free depression coaching, which can improve their quality of life. By participating in the research, all participants (both Aims I and II) will also benefit from knowing they may ultimately be helping others as they will have helped us develop and test an intervention. The costs of participating in the research will be minimized through our extensive efforts to maintain confidentiality, reduce discomfort or distress, and minimize medical complications. Overall, it is expected that the potential benefits to participants in the proposed study will outweigh potential risks.

4. Importance of the Knowledge to be Gained

The results of the proposed study will further our knowledge regarding 1) the relationship between behavioral risk factors and mood in post-ACS patients and 2) the utility of integrating Behavioral Activation based depression treatment with behavioral risk factor reduction for cardiac patients. This knowledge could lead to a reduction in post-ACS mortality rates. As discussed above, we expect that these benefits will outweigh potential risks to participants.

5. Data and Safety Monitoring Plan

We expect the proposed trial to be considered minimal risk by Hennepin Healthcare Research Institute's IRB. Given that the proposed Aim II research is a single site trial and our expectation of a minimal risk designation, the proposed trial does not meet NIH criteria requiring establishment of a formal Data and Safety Monitoring Board. However, we have a detailed data and safety monitoring plan for aim II to ensure the safety of all participants and the validity and integrity of the data. (Note: If our Institutional Review Board or the study sponsor unexpectedly decides that the proposed study includes more than minimal risk to participants, we will convene a Data and Safety Monitoring Board before recruitment begins.) The Data and Safety Monitoring plan is provided in a separate attachment.

6. ClinicalTrials.gov Requirements

The proposed clinical trial will be registered at www.clinicaltrials.gov.

Amendment 2: H³ Study Issued Cell Phone Protocol

If at time of recruitment or any time during treatment/follow-up study staff determine that the participant does not have access to or has lost access to regular phone access, the participant may be offered use of a H³ provided cell phone. Participants who are issued a study phone will complete the H³ Study Issued Cell Phone Agreement form. Patient will be instructed to return the H³ provided phone to staff upon completion of the 12w outcomes visit or at any time if it is determined that the participant no longer qualifies for the study or is not adhering to the guidelines outlined in the H³ Study Issued Cell Phone Agreement. Upon return of the device, participants will qualify for a $20 stipend.

See Appendix A: Study Issued Cell Phone Agreement.

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