

VERMONT CENTER ON BEHAVIOR AND HEALTH

University of Vermont

Healthy Lifestyle Program (HeLP)

Incentives and Case Management to Improve Cardiac Care

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Study Protocol

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Abbreviations

- MI: Myocardial Infarction
- SES: Socioeconomic status
- CR: Cardiac rehabilitation
- AHA: American Heart Association
- ACC: American College of Cardiology
- EF: Executive function
- CM: Case management
- FI: Financial incentives
- ED: Emergency department
- PVO₂: Maximal oxygen consumption or peak oxygen uptake
- PCI: Percutaneous coronary intervention (stent placement)
- CHF: congestive heart failure
- CABG: Coronary artery bypass grafting
- PHQ-2: Patient health questionnaire
- MRSA: Methicillin-resistant Staphylococcus aureus
- VRE: Vancomycin-resistant enterococci
- MMSE: Mini-mental state examination
- METS: Metabolic equivalent
- ETT: Exercise tolerance test
- CO: Carbon Monoxide
- ECG/EKG: Electrocardiogram
- BRIEF: Behavior Rating Inventory of Executive Function
- ASEBA: Achenbach System of Empirically Based Assessment
- TPQ: Time Perspective Questionnaire
- WASI: Wechsler Abbreviated Scale of Intelligence
- BDI: Beck Depression Inventory
- D-KEFS: Delis-Kaplan executive function system
- SST: stop signal task
- DD: Delay discounting
- MOS SF-36: Medical outcomes study short form health survey
- TCAP: Client Drug Abuse Treatment Cost Analysis Program
- CPR: Cardio-pulmonary resuscitation
- HIPAA: Health Insurance Portability and Accountability Act
- ANOVA: Analysis of variance
- ANCOVA: Analysis of covariance
- DSMB: Data Safety Monitoring Board
- SAE: Serious adverse event
- AE: adverse event
- FDA: Federal Drug Administration
- IRB: Institutional Review Board
- PI: Principal Investigator
- LCOM: Robert Larner, MD College of Medicine
- VCBH: Vermont Center on Behavior Health
- TCORS: Centers of Tobacco Regulatory Science
- COBRE: Centers of Biomedical Research Excellence
- UVM: The University of Vermont
- UVMCMC: The University of Vermont Medical Center

HeLP Protocol

1. Background and Significance

1.A. Cardiovascular Disease is the Deadliest and Most Costly Disease in the US

Cardiovascular disease continues to be the number one killer in the US, responsible for 800,000 deaths per year, more than all types of cancer combined.^{1,2} One in three deaths in the US is attributable to cardiovascular disease.² Decreases in quality of life and disability as a result of cardiovascular disease are also concerning, with disability adjusted life years increasing steadily over the last 10 years.³ Heart disease is also costly, dominating all other diagnoses in direct health expenditures, estimated at \$116 billion a year.² If indirect costs are included, costs attributed to cardiovascular disease are estimated at over \$200 billion a year. Costs are projected to keep increasing with costs attributable to cardiovascular disease expected to more than double over the next 20 years. The vast majority of that increase will be due to costs associated with initial and subsequent hospitalizations.² Rehospitalizations after a cardiac event are a major concern, as there are more than 305,000 recurrent myocardial infarctions (MI) each year.² In one study, 30% of those hospitalized for an MI were readmitted within 90 days.⁴ These hospitalizations are extremely costly. A recent study estimated the average cost of the first rehospitalization after a myocardial infarction (MI) at \$20,000.⁵ If a vascular or cardiac surgery procedure is needed, the costs are even higher, ranging in 2012 from \$70,027 to \$149,480.² Interventions that successfully prevented rehospitalizations could significantly reduce health-care costs.

1.B. Lower-SES Patients Suffer a Disproportionate Burden of Cardiovascular Morbidity and Mortality

The burden of cardiovascular disease is not spread evenly across the population. Certain groups, such as those of lower-socioeconomic status (SES) shoulder a higher proportion of the morbidity and mortality resulting from this disease.⁶ These disparities can be seen both in the development of cardiovascular disease and in outcomes after serious cardiac events. First, cardiovascular disease is significantly more prevalent among persons of lower-SES.⁷ Second, lower-SES patients also have higher rates of MI that are also more severe at presentation.^{8,9} Third, outcomes after a cardiac event also differ by SES. Lower-SES patients have worse outcomes after MI, with in-hospital mortality rates of those on Medicaid nearly double those with commercial insurance¹⁰ and 1-year death rate following discharge of 5% compared to 2% among more affluent patients.^{8,9,11}

However, these disparities by SES are largely accounted for by modifiable behaviors, including smoking, diet, physical activity, and adherence to medication. Disparities by SES in developing coronary heart disease as well as disparities in outcomes following a serious cardiac event are significantly attenuated or become non-significant when controlling for these risk-factor behaviors.^{8,9,11-15} Thus, the increased morbidity and mortality following a serious cardiac event in lower-SES individuals should be modifiable by promoting behavior change. A promising platform for cardiac-related behavior change is cardiac rehabilitation (CR).

1.D. Cardiac Rehabilitation Reduces Morbidity and Mortality

Cardiac rehabilitation, a structured secondary prevention program consisting of supervised exercise and risk-factor control interventions, is standard of care following a major cardiac event such as MI or coronary revascularization.¹⁶ Attendance at CR following a major cardiac event results in a 26% reduction in cardiovascular mortality and a 31% reduction in one-year hospital readmissions.^{17,18} Consequently, attendance at CR is given the highest level of recommendation and strength of evidence in the secondary prevention guidelines established by

the American Heart Association and the American College of Cardiology (AHA/ACC). Yet, despite proven benefits of CR, attendance rates for appropriate patients has been disappointingly low ranging from only 18–34%.^{19,20} Leaders in the field, as part of the Million Hearts CR Collaborative, have called for programs to employ strategies to increase rates of attendance at CR in an effort to prevent one million cardiac events over the next five years.²¹

Attendance at CR is also commonly associated with improvements in fitness and other health-related behaviors. Patients who participate in CR experience significant improvements in exercise capacity,²² lipid control,²³ medication compliance,^{24,25} body composition,²³ as well as improvements in quality of life.^{26,27} It is likely that the increased fitness and adherence to other health-related behaviors accounts for the demonstrated reductions in morbidity and mortality. It has been shown that increases in fitness garnered during CR reduces future mortality, especially among those who have low levels of fitness at intake.^{22,28}

In the general population, CR has repeatedly been shown to be cost-effective. One comprehensive economic analysis in Sweden estimated that over 5 years decreased hospitalization rates and associated averted health costs, as well as higher employment rates of those who attended CR actually saved 5 times as much to the Swedish system as the cost of CR.²⁹ In general, however, cost effectiveness is expressed as dollars per quality-adjusted year of life saved. In more recent reviews of that subject, cost effectiveness for CR has been estimated at \$7,517 - \$14,458 (in 2011 dollars) per year of life saved.³⁰⁻³³ These returns on cost are better than most other post-MI treatment interventions, including thrombolytic therapy and coronary bypass surgery.³¹

1.E. Lower-SES Patients Have Low Rates of CR Attendance and High Risk for Cardiovascular Events

Despite the significant health gains associated with CR, lower-SES patients have extremely low rates of attendance. Several studies have demonstrated this association, using education or insurance type to define SES. Looking in detail on the state level, Oberg et al tracked the Medicaid claims of all patients who were enrolled in the Washington State Medicaid system during 2004 and were discharged alive following an MI.³⁴ Of the 322 patients eligible to attend CR, only two (< 1%) did so within the year following their MI. In a national study of Medicare data, while overall 18% of older adults (≥ 65 years) attended CR as recommended, only 3-5% of those with dual Medicare/Medicaid status (i.e., lower-SES) did so.^{19,35} A recent meta-analysis concluded that those with limited educational attainment were a third less likely to attend CR.³⁶ Additionally, in the most recent comprehensive data on the subject, a national survey demonstrated that those with less than a high-school education were half as likely to attend CR compared to college graduates (23 vs. 46%).²⁰ Overall these studies paint a bleak picture of lower-SES CR attendance.

The lack of attendance at CR is troubling especially as lower-SES patients are higher-risk for subsequent cardiovascular events, entering CR with low fitness levels and higher rates of smoking, obesity, and diabetes.^{8,37} Given the relatively high-risk profiles of lower-SES patients, and their increased risk of morbidity and mortality from cardiovascular disease,^{8,9,11} they stand to benefit greatly from CR. The few studies examining gains from CR participation by SES support this idea, demonstrating that lower-SES patients who complete CR make similar gains in fitness and risk factor reduction as higher-SES patients.³⁸⁻⁴⁰ Indeed, increasing CR participation among lower-SES patients has the potential for an even greater return than among more affluent populations given the high-risk profiles of lower-SES patients. We note these high-risk profiles locally as well. Lower-SES patients from our prior studies had higher-risk profiles such as lower fitness and rates of smoking as high as 40% vs. ~7% in higher-SES patients (Preliminary data) and high rates of morbidity, being hospitalized as many as 6 times and visiting the ED up to 16 times within a year (Preliminary data).

1.E.1 SES is Associated with Executive Function which Predicts Adherence to Medical Regimes

CR attendance can be challenging for lower-SES patients. Attending requires creating time in your schedule to attend, remembering to attend, organizing coverage for responsibilities you may have elsewhere as well as obtaining transportation to attend, a set of behaviors that require complex planning. Additionally, attending entails engaging in behaviors (exercise) or inhibiting others (smoking) that, while beneficial in the long term, may be unpleasant in the short term. These sets of behavior (planning and execution of complex behaviors and behaving or inhibiting behavior for long-term benefit) can be considered aspects of a construct known as executive function (EF) which has shown to be useful in understanding health-related behaviors.⁴¹ EF has been demonstrated to predict adherence to a variety of medical regimes including appropriate medication dosing and exercise interventions in older adults.^{42,43} Especially relevant, EF was shown to predict success in heart failure management, which included a variety of complex tasks including taking medications appropriately, keeping medical appointments, and adhering to recommendations for diet and exercise.⁴⁴ Additionally, in our prior trial, two measures of executive function were significant predictors of completing the CR program (Preliminary data). Executive function has also been shown to be correlated with SES⁴⁵ and in our prior trial, lower-SES patients reported significant EF challenges during CR (Preliminary data).

1.F. Interventions Needed for Lower-SES Patients to Attend CR

While there appears to be broad agreement that CR participation rates need to be increased, the literature on interventions to improve CR participation is limited.²¹ One area where interventions have been successful is in improving CR *referral* rates. Automatically referring eligible patients and providing in-hospital liaisons to meet with patients can double referral rates and increase enrollment.⁴⁶ Other approaches, such as providing more flexible hours, having a nurse call the patient after discharge, having patients sign participation contracts, and allowing patients to exercise at home have also led to enrollment improvements of 10-25%.⁴⁷⁻⁵¹ However, the most challenging aspect of improving CR utilization appears to be increasing longer-term adherence. Considering that the health benefits of CR increase with number of sessions attended^{35,52} adherence is critical. In a Cochrane review of interventions designed to improve CR uptake and adherence, none of the three studies examining interventions to improve adherence to CR sessions demonstrated a significant improvement.⁵³ As such, strategies to increase CR adherence rates are sorely needed. Also, as lower-SES populations are at increased cardiac risk and have significantly lower adherence to CR than higher-SES populations, interventions targeting them are especially needed. However, to our knowledge, not a single study, other than the trial on financial incentives reported in our preliminary data, has focused on increasing CR participation in lower-SES patients. Ideally, interventions to improve attendance in CR among low-SES patients would promote attendance while addressing the specific challenges this population faces. Two interventions have these qualities: case management (CM) and financial incentives (FI).

1.G. Case Management is a Promising Approach for Supporting CR Attendance and Improving Outcomes among Lower-SES Patients

Case management involves an individual, often a nurse, who is assigned to a patient with the goal of improving health outcomes through coordinated care. CM programs involve several activities including individual-based assessment, planning and coordination of care, coordination of other services, and patient monitoring and evaluation. Outside of cardiac populations, a series of studies conducted by our research group has demonstrated that case management is

efficacious for promoting adherence to medical treatment (abstinence from cocaine) when offered as a single treatment or when combined with incentives.⁵⁴⁻⁵⁸ Supporting its use within the cardiac population, case management has been demonstrated to be successful at reducing cardiovascular risk, and reducing rehospitalizations in cardiac patients,⁵⁹⁻⁶² even in lower-SES patients,⁶³ with improvements sustaining even after the intervention was completed.⁶⁴ CM has also been successful in reducing psychological distress, which is common in lower-SES patients as well as being a barrier to participation.⁶⁵ CM has been efficacious in other aspects of cardiac care, such as precipitating clinically significant reductions in depression in patients who have undergone bypass surgery.⁶⁶ Indeed, there is evidence that CM can be helpful in CR specifically, increasing referral rates as well as improving health outcomes.⁵⁹

CM is considered a promising strategy to improve rates of CR enrollment and participation, especially among those from particularly vulnerable subgroups. Specifically, approaches using strength-based case management, which focus on helping patients identify individual strengths and how they might be used to overcome obstacles, has had good success engaging traditionally disenfranchised medical populations in on-going care.⁶⁷ Through its multifaceted approach tailored towards patients' individual needs, CM can overcome a wide array of barriers that impede lower-SES patients' participation in CR such as psychological stressors, difficulties in managing appointments, and transportation issues.^{68,69} After a comprehensive individual-based assessment of health- and social-related needs of the patient, the designated case manager can assist by facilitating entry into the CR program, connecting patients to available resources in the community, collaborating with the patient's health care team, and scheduling subsidized transportation services. Case managers can also help sustain participation by providing timely information about recommended care for the cardiac condition, emphasizing the importance of CR in recovery from a cardiac event and managing appointments and transportation needs.^{66,70,71} Finally, case managers can help prevent unnecessary ED visits and hospitalizations⁵⁹ by serving as a first line review of patient symptoms, determining which can be managed outside of the ED setting.

1.G.1 Case Management Supports those with Executive Function Deficits

One of the aspects of EF is the ability to plan and execute complex patterns of behavior. Given the challenges of coordinating appointments, taking new medications, and executing other areas of risk factor control (e.g. changes in diet, smoking and physical activity) it is not surprising that patients with EF challenges would struggle with post-cardiac event care. Addressing EF challenges can take two general forms, a remedial approach, which seeks to improve EF directly, or a compensatory approach, which seeks to create environmental supports that improve quality of life by reducing cognitive burdens and stress.⁷² Case management is an example of the latter. In comprehensive case-management a case manager performs a functional needs assessment to characterize a patient's ability to initiate and perform necessary self-care activities. Armed with this information, the case manager can work with the patient to identify the patient's strengths and create an individualized plan of environmental supports, while providing timely education about the patient's illness and regularly interacting with the health-care providers, to maximize the patient's engagement with care and quality of life.^{66,67,72}

1.H. Incentives are also a Promising Avenue for Promoting CR Attendance in Lower-SES Patients

Incentive-based interventions can also be highly effective in altering health-related behaviors among disadvantaged populations. One treatment approach, termed contingency management, involves providing financial incentives contingent on objective evidence of behavior change, and was originally developed here at the University of Vermont as a method to encourage

abstinence from cocaine use among cocaine-dependent outpatients.⁵⁷ This incentives-based model was subsequently shown to be effective at increasing abstinence from a wide variety of substances, regularly resulting in treatment effect sizes of 0.32-0.42.^{73,74} In a specific example from meta-analyses of treatments for smoking during pregnancy, a problem almost exclusive to lower-SES women, patients treated with this incentive-based model had 3.79 (95% CI: 2.74-5.25) greater odds of quitting smoking than those treated without incentives⁷⁵ and this treatment is significantly more effective at promoting smoking abstinence (RR 0.76) than any other behavioral or pharmacological treatments (RR 0.92-0.99).^{76,77} Similar positive findings have been observed with other health-related behaviors in predominantly lower-SES groups.^{78,79} Overall, financial incentives are one of the most promising approaches for motivating behavior change in lower-SES populations. Additionally, the use of incentives to promote health-related behaviors has become widely accepted in the private sector with the majority of large private employers include financial incentives as part of their employee wellness programs.⁸⁰

More recently, financial incentives to promote behavior change has been adapted to increase a broader variety of health-related behaviors. Incentives have been used for increasing physical activity, medication adherence,⁸¹ and weight loss,^{82,83} including weight loss in economically disadvantaged populations.⁸⁴ Financial incentives are also highly efficacious at increasing treatment completion and adherence rates. For example, in a notoriously challenging population (cocaine dependent outpatients), adding incentives to a comprehensive treatment program approximately doubled treatment completion rates.⁸⁵ In CR, where health effects are dose-dependent,^{35,52} this ability to sustain participation could be of considerable benefit. Indeed, our prior work suggests that incentives can increase CR adherence and may also be improving health (Preliminary Data).⁸⁶

1.H.1 Incentives Help Overcome Executive Function Challenges

In line with the challenges faced by lower-SES populations, the use of incentives can help overcome EF challenges. One aspect of executive function, often referred to as delay discounting, is the weighing of future outcomes when considering current behaviors.⁸⁷ Those with EF challenges may overvalue the immediate (continued smoking, not exercising) and devalue the future (improved health) consequences when engaging in health-related behaviors.⁸⁸ Incentives can harness this bias towards the immediate outcome by providing an immediate positive outcome (earning an incentive) following the desired behavior (completing CR session).^{89,90}

1.I. Summary and Conclusions

Lower-SES cardiac patients are at disproportionate risk for increased morbidity and mortality after a cardiac event. Much of this risk is attributable to lack of adherence to secondary prevention behaviors which are addressed at CR. Lower-SES patients who attend CR show significant improvement in health-related outcomes and subsequent reductions in risk. However, the number of lower-SES patients who attend CR is remarkably low.^{19,34} Interventions to increase participation rates among lower-SES patients could have a particularly high return, as these patients, along with dismal CR participation rates, also have remarkably high levels of ED visits and rehospitalizations. This study has the potential to make a substantial contribution to reducing health disparities by improving health outcomes among those who are the most at risk but also with the most to gain. Additionally, this randomized, controlled study will add important data on the cost effectiveness of increasing CR attendance in lower-SES populations, which may differ in important ways from the analyses based on the general population. Given their high rate of costly rehospitalizations and the greater potential for health gains, the cost and benefits may differ even more favorably than those observed in more affluent populations. Accordingly, improved CR attendance could also have a substantial positive impact on health care costs by preventing costly rehospitalizations¹⁷ which, during an interim analysis, averaged over \$26,000 each in our prior

trial. Preliminary data suggests that financial incentives are an efficacious approach to increase adherence to CR. Additionally our supporting data from trials of treatment for cocaine dependence, as well as evidence from the literature, suggests that case management should also be an efficacious intervention for promoting CR attendance and that these two interventions combined could promote attendance in an additive manner. Identifying efficacious treatments will significantly reduce cardiovascular disease disparities and costs in lower-SES cardiac patients.

Project Summary

Participation in outpatient cardiac rehabilitation (CR) decreases morbidity and mortality for patients hospitalized with myocardial infarction, coronary bypass surgery or percutaneous revascularization. Unfortunately, only 10-35% of patients for whom CR is indicated choose to participate. Lower socioeconomic status (SES) and Medicaid coverage are robust predictors of CR non-participation. There is growing recognition of the need to increase CR among economically disadvantaged patients, but there are no evidence-based interventions available for doing so. In the present study we propose to examine the efficacy of using financial incentives and case management, alone and in combination, for increasing CR participation among low-income patients. Financial incentives and case management have both been shown to be highly effective in altering other health behaviors among disadvantaged populations (e.g., smoking during pregnancy, weight loss). Additionally, case management and financial incentives have properties that might compensate for executive function deficits, which often impede healthy behavior change and are overrepresented in lower-socioeconomic status populations. For this study we will randomize 200 CR-eligible lower-socioeconomic status patients to a usual care control condition or to an experimental condition where they receive financial incentives contingent on initiation of and continued attendance at CR sessions, a case-manager assigned at the hospital, or to a combination of these two interventions. Participants in all conditions will complete, and be compensated for, pre- and post-treatment assessments. Treatment conditions will be compared on attendance at CR and end-of-intervention improvements in fitness, decision making and health-related quality of life. Cost effectiveness of the treatment conditions will also be examined by comparing the costs of the intervention and usual care conditions with their effects on increasing CR initiation and adherence. Furthermore, we will model the value of the intervention based on increases in participation rates, intervention costs, long-term medical costs and health outcomes after a coronary event. This systematic examination of promising interventions will allow us to test the efficacy and cost-effectiveness of approaches that have the potential to substantially increase CR participation and significantly improve health outcomes among lower-SES cardiac patients.

Study Design

This study is a four parallel-condition, randomized controlled trial to assess the efficacy of the use of incentives and case management for increasing CR participation in a lower-SES cardiac population. The study population will be comprised of 200 lower-SES patients with a recent CR-qualifying coronary event (including congestive heart failure). The experimental conditions will be: 1) an intervention where patients are assigned a case manager (CM) in hospital or in an outpatient clinic setting to coordinate their care 2), an intervention wherein patients earn financial incentives (FI) contingent on participating in CR, or 3) a combination of these two interventions (FI+CM). These intervention conditions will be compared to a usual care control (i.e., referral to CR). The main outcome measure for this project will be CR participation and adherence (% who complete 30+ sessions, # of sessions completed). Secondary outcomes will include improvements in executive function, fitness (PVO2), and quality of life over four months and at a one-year follow-up, as well as rehospitalizations and emergency department visits through one-year follow-up. A comprehensive cost effectiveness analysis of the interventions will be conducted, incorporating rehospitalization rates and the cost of both delivering and receiving the treatment.

Recruitment and Consent Procedures

Participants

Study participants will be men and women who are receiving care as an outpatient, or who have been hospitalized, due to a recent CR-qualifying coronary event (including congestive heart failure). Qualifying cardiac events include myocardial infarction (MI), stable angina, congestive heart failure (CHF) percutaneous intervention (PCI, i.e. stent placement), coronary artery bypass grafting (CABG) or valve repair/replacement procedures. Eligible participants will also be of lower-socioeconomic status. Low-SES will be determined by insurance status (i.e. Medicaid), educational attainment of less than high school graduation, or indication of receiving some other type of needs/income-based assistance (i.e. food stamps).

Recruitment

We will approach 240 patients with the goal of randomizing 200 (recruitment is slated to last for 45 months beginning in month 4 and ending in month 48).

Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Individuals receiving care as an outpatient, or who have been hospitalized at UVMMC, due to a recent MI, stable angina, coronary revascularization, diagnosis of congestive heart failure or heart valve replacement or repair.
2. Enrollment in a state-sponsored insurance plan for low income individuals or receiving other state benefits based on financial need (housing subsidy, food stamps, etc.), or having received less than a high school education.
3. Residing in (and plans to remain in) the greater Burlington, VT area for the next 12 months.
4. Copley Hospital (Morrisville, VT) transfer patient (enrolled in a state-supported insurance plan for low income individuals or receiving other state benefits that are based on financial need).

Exclusion Criteria:

1. Dementia (MMSE<20) or current untreated Axis 1 psychiatric disorder other than nicotine dependence as determined by medical history.
2. Advanced cancer, advanced frailty, or other longevity-limiting systemic disease that would preclude CR participation.
3. Rest angina or very low threshold angina (<2 METS) until adequate therapy is instituted.
4. Severe life threatening ventricular arrhythmias unless adequately controlled (e.g. intracardiac defibrillator).
5. Class 4 chronic heart failure (symptoms at rest).
6. Exercise-limiting non-cardiac disease such as severe arthritis, past stroke, severe lung disease.
7. Previous successful attendance at cardiac rehabilitation (defined as completion of 6+ sessions).

Informed Consent Process

The informed consent process will take place in-person at UVMMC in patient hospital rooms prior to discharge or in an outpatient Cardiology/Cardiac Rehabilitation setting. In the case that the patient cannot make a decision on enrollment while still in the hospital, this process would

take place either at the patient's home, a mutually agreed upon meeting point, or in a private office at the Cardiac Rehabilitation Clinic at Tilley Drive. Study information will be presented and written consent will be required prior to moving on to the screening.

Demographic Measures

Following the informed consent process, demographic information will be collected by the interviewer prior to randomization. Demographic information collected at screening includes: age, gender, educational attainment, race/ethnicity, smoking status, marital status, and health insurance status. Additionally, the researcher will ask the participant about the frequency of depressed mood and anhedonia over the two weeks prior using the PHQ-2 questionnaire. All data will be directly entered into REDCap unless the patient is on contact precautions (MRSA, VRE), in which case data will be collected on paper forms and then directly entered into REDCap following the informed consent process.

Allocation

Stratified random allocation of participants will be used to assign individuals to groups, using two dichotomous variables to stratify the sample: age (<57 years of age vs. ≥57) and smoking status (current smoker vs. former/non-smoker). Current smoking status and age were significant predictors of CR attendance in our prior trial. Participants will be allocated to groups using a 2:2:2:1 routine, whereby for every two individuals assigned to one of the three treatment groups (CM only, FI only, and CM + FI), one individual will be assigned to the control group (UC). Following the random allocation, the assigned case manager or research assistant will become a point of contact for the patient. The CM will complete a follow up questionnaire with the patient, and schedule an initial assessment call to be done following discharge. The research assistant will assist in scheduling a CR introductory group meeting, if one has not already been made by hospital staff.

Assessment Procedures

The intake study assessment will take place within 2-3 weeks following discharge date (depending on surgical vs. non-surgical diagnosis). Intake assessment may be delayed if the patient is transferred to subacute rehabilitation following discharge or is receiving home health care that would preclude immediate enrollment in cardiac rehabilitation. The intake appointment will begin with a consult by a medical professional prior to either Exercise Tolerance Test (ETT) or clinical consult/6 minute walk test (depending on mobility level). Clinical measures will be collected and entered directly into REDCap by clinical staff blinded to treatment condition.

Clinical Measures

CO level

Carbon Monoxide level (CO) will be collected using a coVita carbon monoxide measuring device. The participant will be required to breathe slowly through a cardboard tube to obtain this measurement. This measurement will quantify recent exposure to carbon monoxide (e.g. smoke/secondhand smoke/car exhaust/heater emissions).

Maximal Exercise Capacity

Maximal exercise capacity will be assessed on a treadmill using measurements of peak oxygen uptake, duration of treadmill exercise and maximal exercise intensity in METS. A continuous modified-Balke protocol will be used, with exercise increasing gradually at 1 MET increments at 2-minute intervals. Exercise is EKG monitored and stopped prior to exhaustion if the patient develops progressive angina, > 2mm ST segment depression, exercise induced hypertension (230 systolic, 105 diastolic), severe arrhythmias, dizziness or symptomatic hypotension. The occurrence of any concerning responses, other than high threshold angina, excludes a patient from the training protocol unless effective therapy is instituted. Patients will perform the maximal stress test taking their usual medications at a standardized time of day. The clinical staff at UVMMC have extensive experience measuring peak exercise capacity in patients in the CR setting.⁹¹

Executive Function Assessment

The participant will meet with an executive function staff member after finishing the physical/ETT component of the assessment. During this portion of the visit, the EF researcher will guide the participant through a battery of socio-cognitive measures (subjective measures) as well as computerized tasks (objective measures).

Self-Report Measures

1. Behavior Rating Inventory of Executive Function (BRIEF)
2. Achenbach System of Empirically Based Assessment (ASEBA)
3. Euro-Qual
4. Time Perspective Questionnaire (TPQ)

EF-administered Tasks/Measures

1. Wechsler Abbreviated Scale of Intelligence (WASI)
2. Trail Making Test (subtest of D-KEFS)
3. Digit Span

4. Stop Signal Task (SST)
5. Delay Discounting (DD)

Additional Questionnaires

The participant will complete the following questionnaires directly in REDCap:

1. Beck Depression Inventory (BDI)
2. MacNew Cardiac Health Status Questionnaire
3. ISEL – Interpersonal Support Evaluation List

Finally, the RA will administer the TCAP (Treatment Cost Analysis Program) questionnaire and enter data directly into REDCap.

End of Treatment Assessment (4-month follow up)

At the four-month follow-up assessment, independent of CR attendance, participants will complete all of the tasks and questionnaires detailed above with the exception of the WASI. Participants allocated to the either case management condition will be asked about how useful the CM was to them over the 4-month period in achieving their health and/or personal related goals. Finally, if a participant dropped out of the CR program at any point, additional data on drop-out date and reason will be collected.

End of Study Assessment (1-year follow up)

The final assessment occurs at one year from the intake assessment. Participants will complete all of the tasks and questionnaires done at the 4-month follow-up.

Ongoing Adverse Event Monitoring

For all participants, the research assistant will screen for adverse events every two weeks by contacting participants, either in person or over the phone. For the current study AEs are defined as seeking out advice or treatment from a medical professional for any health-related symptom or issue of concern as well as endorsing suicidal ideation on the BDI. Information on adverse events will be directly entered into an Adverse Event form in REDCap and includes duration, associated MedDRA code, outcome, action taken, severity, and attribution. The study PI will sign off on all AEs as they arise.

Serious adverse events (hospital admission - both study related and unrelated) will be brought to the attention of the PI as soon as possible. A formal write-up detailing the event will be submitted to the members of the DSMB within 72 hours of research staff becoming aware of the event. Medical Director Philip Ades, MD (Sherrie Khadanga, MD providing coverage as needed) will determine SAE study relatedness prior to submission of this write-up.

Study Conditions

Usual Care

Usual care patients choosing to participate in CR will proceed into the 36-session exercise program,¹⁶ with each session eventually including 25 min of treadmill walking at an intensity of 70-85% of peak exercise heart rate (HR) from baseline testing. Sessions will also include 5-10 minutes on a cycle ergometer, arm ergometer, or rower for a total exercise duration of 45 minutes. As patients improve their fitness, they will increase their exercise intensity to maintain their exercise heart rate in the desired range. Participants will also attend weekly educational sessions at the CR program, including stress management (5 sessions), healthy nutrition (2 sessions), medication use, symptom recognition, and the importance of risk factor control. Smoking cessation will be addressed using the 5 A's as is recommended practice.⁹² Regardless of CR participation, all participants will return for follow-up testing at 4-months and 1-year following the baseline assessment.

Incentives Intervention

In the incentives condition, participants will receive financial incentives (FI) for participation in cardiac rehabilitation sessions, paid upon completion of each of the 36 sessions. Participation will be defined as attending the scheduled session and completing the recommended exercise and other activities scheduled for that day by clinical staff. Participation will be verified by a program staff person. Visits will be scheduled 2-3 times a week over a period of 4 months to comprise the 36 visits commonly prescribed. Participation in an introductory group meeting will earn the participant \$20. Participation in subsequent exercise sessions will be compensated on an escalating schedule. Participation in the first exercise session earns a participant \$10 with each subsequent session increasing the amount earned by \$2 per session up to a maximum of \$40 per session. Failure to attend a session (unless advanced notice is given) results in no earnings for that session and the amount possible to be earned in the next scheduled session is reset to \$10. If the participant successfully participates in two consecutive sessions following a reset, the amount earned is returned to the amount it was prior to the reset. This schedule of escalating value incentives combined with a reset contingency for failure to meet the targeted goal has been experimentally demonstrated to sustain continuous periods of adherence for other health-related behaviors. The total possible incentive earnings is \$1220, however, some participants assigned to the incentives condition will fail to adhere to the recommended 36 sessions. Based on our prior studies using financial incentives, we estimate that mean earnings in the intervention condition will be approximately 70% of maximal, or \$854. Incentives will be earned in the form of vouchers exchangeable for retail goods (e.g. gift cards) which has been shown to be a form of incentives that can be clinically useful. Participants will be encouraged to use their incentives to further health-related goals or overcome barriers (e.g. healthy groceries, new walking shoes, transportation costs, etc.).

Case Management Intervention

In the CM condition patients will receive the usual care program described above but will also receive case management, initiated in the hospital or in an outpatient setting after consent. The case manager will subsequently be available by phone daily between the hours of 0900 and 1900 during the week and 0900 and 1200 on Saturday. The case manager will work with the patient to identify the patient's strengths and create an individualized management plan. The designated case manager will support CR attendance by facilitating entry into the program, connecting patients to available resources in the community, collaborating with the patient's

health care team, and scheduling subsidized transportation services as needed. Case managers will also sustain participation by emphasizing the importance of CR in recovery from a cardiac event, and managing appointments and transportation needs. To maximize benefits from case management, supporting patient's engagement with care and quality of life, the case manager will also provide timely education about the patient's illness, answer questions on cardiac self-management, regularly interact with health-care providers, and provide plans of environmental supports. Finally, case managers will serve as a first line review of patient symptoms, preventing unnecessary ED visits and hospitalizations by determining which can be managed outside of the ED setting.

Financial Incentives and Case Management Intervention

In the combined condition (FI +CM), participants will receive both the case management and financial incentives program as described above.

Statistical Methods and Power

Power

Sample sizes were calculated to provide sufficient power to calculate differences in our primary outcome (CR adherence, as measured by % completing 30+ sessions) between the control condition and any of the three intervention conditions as well as between the combined intervention and either of the interventions delivered alone. Of most relevance, preliminary data from a previous trial on the use of incentives to increase CR rates among lower-SES individuals show that 54% of those receiving incentives completed the 30+ sessions compared to 28% of those receiving usual care. Using these proportions and the likelihood ratio test for two proportions in SAS POWER, 56 individuals per condition would be needed to detect a significant difference between conditions with 80% power. A seminal set of studies, conducted by Co-I Higgins, that systematically determined the efficacy of case management and incentives, alone and in combination, on cocaine abstinence, provided additional data for the power estimates.⁵⁴⁻⁵⁸ Using effect sizes from these five studies, the maximum estimated number of participants needed per condition is 50 to detect a significant difference in treatment adherence in combined intervention vs. single intervention with 80% power. Comparing any of the interventions singly or combined to usual care at four months post-treatment is estimated to require at most 25 participants per condition. Supporting these estimates, additional studies on the use of case management or incentives for adherence to other health-related behaviors have demonstrated effect sizes comparable to the studies referenced above^{66,67,73,93,94} As such, the proposed sample size of 200 randomized subjects (56/intervention condition, 32 control) will allow us to conduct all pre-planned pairwise comparisons of the primary outcome measure (program adherence) with 80% power.

Data Analysis

Treatment conditions will be compared for differences in baseline demographic characteristics using one-way Analysis of Variance (ANOVA) (or a nonparametric alternative, such as the Kruskal-Wallis Test) for continuous measures and chi-square tests (or Fisher's Exact Test) for categorical variables. If specific characteristics differ significantly across treatment conditions and are predictive of treatment outcomes, they will be considered as covariates in subsequent analyses. Primary analyses will include all subjects randomized to treatment conditions independent of early dropout or non-adherence, consistent with an intent-to-treat approach for randomized clinical trials.⁹⁵ The primary outcome measure in this trial will be CR adherence (% completing 30+ sessions) compared between the control condition and any of the three intervention conditions as well as between the combined intervention and either of the interventions delivered alone. Proportions completing all CR sessions will be examined across conditions using the test for differences between two population proportions (z), with 95% confidence intervals on effect sizes. To look at other measures of attendance, Cox proportional hazard models will be used to test differences in number of CR sessions completed (i.e., time to dropout) between conditions. Purposeful selection of covariates will be used to build models.⁹⁶ Once final models have been derived, we will generate estimated hazard ratios with 95% confidence intervals and graphs of covariate-adjusted survival functions. Across all tests, statistical significance will be defined as $p < 0.05$ (2-tailed).

Although this study is powered for our primary outcome of adherence to CR, we will also carefully examine improvements in fitness, and other health outcomes (quality of life, maximal exercise capacity, weight, waist measurements) between conditions, using the pre-planned comparisons outlined for the primary outcome. Additionally, we will examine changes in executive function measures and socio-cognitive status at 4 and 12 months. Changes in these scores will also be examined for possible gender interactions. Since multiple observations for each

participant will be obtained, the general analytic approach will consist of analysis of covariance (ANCOVA) at 4 months and repeated measures analysis of variance (ANOVA) at 12 months. Formal testing will examine the condition by time interaction term to assess differential time changes between treatment conditions. Post-hoc comparisons between conditions will be made if significant interactions are observed.

Dr. Donald Shepard, a Health Care Economist at Brandeis University, will lead the economic evaluation of the program. We will collect data on the costs associated with program implementation from the clinical site and from participants at each follow-up interview (including travel costs). Operating costs under each arm will be collected through a customized cost assessment tool that Dr. Shepard developed using some of our own programmatic data for cardiac rehabilitation and lifestyle modification⁹⁷ and counseling services.^{98,99} To assess costs to participants (e.g. travel expenses, time spent, and out-of-pocket expenses), we will use a tool created for our prior study that adapted the Client Drug Abuse Treatment Cost Analysis Program (DATCAP; www.datcap.com/client.htm) for use in cardiac rehabilitation. Direct nonmedical and indirect costs include the value of time of participants attending the program, waiting, traveling, or exercising, as well as transportation expenses.

Quality-adjusted life years (QALYs)¹⁰⁰ for each condition will be calculated using the health-related quality of life (HRQL) measure.¹⁰¹ The ratio of cost per QALY will be modeled incorporating meta-analysis data from randomized-controlled trials of CR after a coronary event^{18,166} to estimate the cost-effectiveness of incentives encouraging CR compared to standard CR. This cost-effectiveness model will also include hospitalization costs averted and possible increases in ambulatory costs if CR use, associated testing, and ambulatory services increase for those in treatment conditions.³³ Similar to another recent cost-effectiveness study of CR, we will perform the analysis with two contrasting time perspectives – the period of follow-up alone and a lifetime perspective – based on a carefully calibrated model of project utilization and costs.¹⁴ The former provides a more conservative, short-term analysis closely tied to the observed data. The latter provides a long-run perspective.

Data and Safety Monitoring Plan

Entities Conducting Monitoring

The IRB at the University of Vermont will review this protocol and all procedures and will provide oversight in communication with the PI (Gaalema).

What is Monitored

All research procedures will be monitored to ensure that they conform to the approved protocol. In addition, monitoring will be done of all adverse events that might arise and affect safety. This will include all reports of serious adverse events (SAE) as defined by FDA. An SAE is defined as any adverse experience occurring that results in any of the following outcomes: life-threatening, death, new or prolonged hospitalization, persistent or significant disability/incapacity, or congenital anomaly/birth defect. Additionally, other significant adverse events (adverse events that lead to drop out by the participant or termination by the investigator) and other expected and unexpected adverse events resulting from the study will be monitored.

Frequency of Monitoring

Cardiac-related symptoms will be rated at baseline and monitored during each participant contact (in person and by telephone) using scales that are operationally-defined, have good-to-excellent inter-rater reliability and are widely used in clinical and research settings. In addition, participants will be asked about their general health, symptoms and adverse events weekly during the study. Any clinically-significant symptom exacerbations noted during the study (i.e., changes in severity of existing symptoms, presentation of new symptoms) will trigger review and contact with the participant by the Medical Director Dr. Ades. Any serious adverse event and any unexpected and apparently related adverse event will trigger immediate review and contact with the participant by Medical Director Ades and will be reported by the PIs to the IRBs. Participants will be given study contact cards so that they can inform us of events that occur in between study visits. Monitoring by the PI is conducted on an ongoing basis and monitoring by the IRB is conducted at the continuing reviews as scheduled by the IRB and upon receiving reports of adverse events from the PIs.

Reporting Plan

Serious and unexpected adverse events that are related to the study will be reported to the IRB and to NIH. Any actions taken by the IRB other than acceptance will be reported to the sponsor along with any changes or amendments to the protocol requested by the IRB in response to these reports. Proposed changes or amendments to the protocol in general must first be requested in writing to the IRB, which will then grant or deny permission to make the requested change in protocol. The NIH will be informed of any changes or amendments in the approved protocol.

Data and Safety Monitoring Board (DSMB)

Charge of DSMB

The DSMB will be charged with monitoring and evaluating two aspects of the clinical trial. These include: a) monitoring study progress; i.e., screening, recruitment, and retention data, to assure that the study can be completed in the time proposed, and b) reviewing safety data, especially serious adverse events (SAEs). SAEs, study or non-study related, will be reported to the DSMB, as well as to NIH, by the PI within 72 hours of the PI learning of the event. The DSMB will review all adverse events.

DSMB Members

Our DSMB will consist of four individuals. The DSMB will include members with experience in cardiac rehabilitation, lower-SES patients, conduct of clinical trials, and data analysis. It will include at least one physician and one researcher. The chair will have served on prior DSMBs.

Meetings

The DSMB will meet approximately every 6 months either in-person or by teleconference call. Meetings of the DSMB will be coordinated by the PI (Gaalema) and Lead Statistician (J. Priest). Three members will constitute a quorum. Members who are unable to attend will be contacted and given an opportunity to provide input on the issues at hand. Interim data reports will be supplied to the DSMB by the PI at least two weeks prior to each meeting. Data will be supplied in tabular and electronic forms per request of the DSMB. Examples of acceptable interim reports will be made available to investigators to facilitate their interaction with the DSMB. In addition, any new information from external sources that could alter the DSMB's perception of the trial, for example, relevant findings published from other trials on improving CR participation in lower-SES patients, will be assembled and summarized with respect to the PI's perception of its importance.

Meeting Procedure

Prior to each formal meeting, it is the responsibility of the chair of the DSMB to assure that the required data have been submitted with appropriate explanations. This material will be sent to Board members at least two weeks prior to the DSMB meeting. The formal meeting of the DSMB for the trial shall consist of three parts. The first part is an open session in which members of the research team, including the Principal Investigator and the study statistician, will attend. Outcome results must not be discussed during this open session. Minutes from the open session will be taken by project staff. Following the open session, the DSMB will hold a closed session. The study statistician will be available to discuss the results with the DSMB during the closed session. Minutes from the closed session will be taken by the chair or her/his designate. The third phase of each meeting is a final executive session involving only voting DSMB members and may be held to allow the DSMB to discuss general conduct of the trial and all outcome results, including adverse events, to develop recommendations, and to take votes as necessary. Following the meeting, the DSMB Chair will provide a summary of the DSMB's recommendations to the PI. Study investigators will also have the opportunity to ask questions to clarify the recommendations.

Reports of DSMB Deliberations

Clerical support will be provided by research staff as requested by the chair of the DSMB. Following each DSMB review, the chair shall prepare a written report to be finalized within 20

working days following the formal meeting and be sent to the PI. The report will review the two main aspects of the trial for which the DSMB is responsible as noted in section 2 above (i.e., study progress and safety). In addition, following each study review, the DSMB will recommend either: a) continuation of the trial using the current protocol and statistical plan, b) Continuation of the project with modifications as outlined by the Board, c) Immediate suspension of the trial for safety reasons with a recommended plan of follow-up to minimize subject harm (requires unanimous vote), d) placing a clinical hold on the trial. This should include freezing further accrual. Subjects may continue on their assigned treatments until clarifications requested by the Board are resolved (requires unanimous vote), e) Termination of the trial because of: 1) treatment effectiveness demonstrated earlier than expected (“early stopping”); 2) futility of further accrual to meet the trial’s goal; 3) discovery of new information that precludes completion of the trial; and/or 4) structural problems in trial execution that are not amenable to correction (requires unanimous vote).

Discussion of Confidential Material

No communications, either written or oral, of the deliberations or recommendations of the DSMB will be made outside of the DSMB except as provided by written policy. Study data are strictly confidential and must not be divulged to any non-member of the board except as indicated by policy.

Human Subjects Considerations

Potential Risks of Participation

1. Exercise Testing: Exercise testing is a common procedure with minimal risks, but the test is monitored by a physician and will be stopped if problems occur. These include fainting, dizziness, chest pain, irregular heartbeats, or a heart attack, although the latter is extremely rare. The risks of this test are roughly 1 death in every 10,000 tests performed and serious adverse effects such as a heart attack or serious irregular heart beat (arrhythmias) requiring hospitalization occur in less than 1 in 1,000 tests. Blood pressure, heart rate and rhythm and breathing are closely and constantly monitored by a physician and exercise technician trained in CPR, exercise testing and emergency treatment of cardiac arrhythmias. This team has a specific, well-practiced protocol that includes contacting emergency services and providing interim medical support if needed.
2. Survey Questionnaires: The participant may feel uncomfortable answering some of the questions. We will work with them to minimize this discomfort and no one has to answer any question that they do not wish to answer. There is a risk that participants will express suicidal thoughts or actions as we will be using the Beck Depression Inventory which queries suicidality. A suicidality protocol will be used in the case of a participant endorsing a suicidality item.
3. Breach of Confidentiality: There is a risk that confidential information might accidentally be disclosed. Professional standards for protecting confidential information will be used to minimize this risk.

Adequacy of Protection against Risks

Study consent forms and the linkage between the participants' names and study IDs will be stored in a locked file cabinet and maintained by the research assistant. All study data will be entered and stored in REDCap, which is housed on the University of Vermont Medical Center's HIPAA-compliant computing system.

a. Recruitment and Informed Consent

All participants will provide written informed consent after having a face-to-face discussion of the research with the PI or research staff designated and trained to represent the PI in this function. That discussion is conducted in a private setting and permits the prospective participants ample opportunity to raise questions and seek clarifications regarding the research. A consent quiz will be administered to verify that the participant fully understands the implications of participating in this study. If any questions are answered incorrectly they will be reviewed with the participant until the participant fully understands the question. The study site operates in full compliance with HIPAA regulations. All participants in the proposed study will receive a HIPAA authorization form upon entry into treatment and be fully informed regarding their rights with respect to the release of personal health information. Further, as mandated by NIH, all personnel funded by this project will complete the NIH required course on Human Subjects Research as well as a course on Good Clinical Practices.

b. Protection against Risk

We will take the following actions to protect against the potential risks noted above:
(a) All written study files will be stored in locked filing cabinets. Subject IDs will be used in place of names to identify study records. All data entry will take place on password protected and encrypted databases/ computers.

- (b) Participants will have the opportunity to meet with the PI and/or other investigators to discuss any discomfort they may experience. Participants will also be offered the opportunity to obtain feedback on their assessment data following completion of the study.
- (c) Highly trained, well-equipped clinical staff are available during all exercise sessions to respond to any potential complications.
- (d) Exercise tests will be closely monitored by an experienced Cardiologist and are normally performed at entry into CR programs.
- (e) We conduct our use of incentives in a manner to minimize the potential risk of coercion. First, incentives will be provided in the form of vouchers exchangeable for retail goods (e.g. gift cards, checks to pay bills). Case managers will work with patients to purchase goods with the incentives that will further the patient's health goals (e.g. purchasing healthy food, paying co-pays on medications, obtaining appropriate walking shoes). Secondly, incentives of this overall value and type have been widely used in NIH-supported and IRB-approved studies at the University of Vermont and a multiple of other institutions for more than two decades.⁵⁴⁻⁵⁸

Potential Benefits of the Proposed Research to the Subjects and Others

We believe that the aforementioned risks are reasonable in relation to the anticipated benefits to participants and others. There is direct benefit to the study participants from a comprehensive CR program and all participants will receive access to this program. Based on the literature, we believe that participants will benefit from participation in any arm of the trial as they will all receive at a minimum a strong referral to CR and periodic monitoring. All study participants will be encouraged to communicate the results from the study to their primary care providers.

Participant Compensation

All study participants are compensated \$100 for the three study assessments (Intake, 4mo, 12mo). Additionally, if they live over 30 minutes away or demonstrate significant issues with transportation, they receive an extra \$50 travel compensation. If allocated to one of the two incentives group interventions, participants can earn up to \$1220 in financial incentives (gift cards) for attending cardiac rehabilitation exercise sessions.

Importance of Knowledge to be gained

Despite the known health benefits of attending CR, only 10-35% of eligible patients attend even one CR session. Participation is even poorer among low-SES populations with CR rates being only half (or less) than that of higher-SES populations. To date, interventions to increase participation in cardiac rehabilitation programs have mostly focused on increasing physician referral rates and none have specifically targeted improving participation among lower-SES populations except for a prior study conducted in our lab. Developing efficacious interventions to increase participation, especially among lower-SES populations, who are at increased cardiac risk, is an important public health priority.

Inclusion of Women and Minorities

Women and men will be recruited equally for this project. Women make up 38% of the pool of patients in the U.S. with an acute coronary event (Roger, et al., 2011) but they are on average almost 10 years older than men at diagnosis. Thus, women at diagnosis are characterized by having more medical co-morbidities than men (dementia, severe frailty) that

might exclude them from enrolling in a program such as the one proposed. As our project is aimed at increasing participation through, among other things, reducing barriers to participation, it is likely that the proportion of women who attend should be proportionate to the 38% in the general cardiac population, as women report facing a disproportionate share of participation barriers as compared to men. In our prior trial, where we also recruited lower-SES cardiac patients, we recruited 37.7% women, suggesting that our recruitment methods are successful at including women at representative numbers.

There will be no exclusion criteria concerning race or ethnicity. In Burlington, Vermont, minorities comprise 7% of the general population. We anticipate a representative number of minorities in the proposed study as our recruitment methods will target lower-SES individuals. In our prior study, we recruited 8% minorities suggesting our recruitment methods are appropriate for recruiting minorities in representative numbers. We shall do all that we can to assure that minorities and women continue to be included in the research in proportion to their representation in the local community. There will be no bias in recruiting as participants will be selected purely based on qualifying medical conditions and insurance status as drawn from their medical record.

Inclusion of Children

This project aims to develop an efficacious intervention to increase participation in cardiac rehabilitation programs among those who have a qualifying cardiac condition. As such events are exceedingly rare in children, no children will be enrolled.

Scientific Environment

The facilities and other resources available to the PI and Co-Is at the University of Vermont (UVM) Robert Larner, MD College of Medicine, and the University of Vermont Medical Center (UVMMC), the University of Vermont's affiliated teaching hospital, include everything necessary for the successful completion of the proposed research. The University of Vermont Medical Center is a tertiary care hospital that serves a population of over 1,000,000 patients in Vermont and northern New York State. The PI is an Assistant Professor in the Department of Psychiatry and the Co-I/Medical Director, Dr. Philip Ades is a Professor of Medicine and Director of the CR program at UVMMC. The facilities and resources at the University of Vermont, UVM Medical Center, and the Vermont Center on Behavior and Health (VCBH) that are instrumental to the proposed study are described in detail below. These factors, combined with the ready access to top-notch core facilities, create a scientific and intellectual environment that facilitates the success of the proposed research.

The Robert Larner, MD College of Medicine (LCOM) at the University of Vermont

The University of Vermont is home to over 10,000 undergraduates, 1,460 graduate students, 461 medical students and more than 1,600 full- and part-time faculty. The Robert Larner, MD College of Medicine (LCOM) has a longstanding reputation for educating and training superb physicians and scientists, fostering groundbreaking research to improve patients' lives, and actively engaging with the community of Vermont and the region. Established in 1822, it is the nation's seventh oldest medical school in the US and is the only medical school in Vermont. Today the LCOM enjoys over \$90M in external grant funding, an award-winning integrated curriculum, and international recognition for research-based expertise, clinical and teaching excellence, and strong community partnerships. Over the past 10-15 years the LCOM has built or renovated more than 100,000 sq ft of new space for science education, research faculty offices and conference rooms, and laboratory and core space to a total of 550,000 sq ft of research space. A state-of-the-art educational facility, the Larner Learning Commons, interconnects the UVMMC hospital and ambulatory care facility with all the research buildings, and contains the Dana Medical Library, as well as sophisticated classrooms and lecture spaces that support active, team-based learning, simulations, and flipped classrooms. A major strength of the LCOM is the collaborative and interactive nature of its environment, which allows for interdisciplinary research that cuts across all departments. The VCBH is the latest example of that collaborative approach. This collaborative atmosphere is a longstanding and distinguishing characteristic of the LCOM and UVM generally, and will continue to be one of the driving forces for the ongoing success of the institution and the VCBH.

The University of Vermont Medical Center (UVMMC)

The University of Vermont Medical Center (UVMMC) is the academic medical center allied with the LCOM. UVMMC is a full-service, sophisticated tertiary care, vertically integrated health care system that serves as a regional referral center – providing advanced care to approximately 1,000,000 people in Vermont and northern New York. The UVMMC main campus (Burlington, VT) is adjacent, and interconnected to the Larner College of Medicine, and the hospital's activities are closely aligned with those of the College. UVMMC, the only teaching hospital within a wide radius, trains approximately 300 residents and fellows in 16 residency and 23 fellowship programs. UVMMC consists of 562 licensed hospital beds and over 30 satellite clinics.

The Vermont Center on Behavior and Health (VCBH)

The Vermont Center on Behavior and Health (VCBH) was established in 2013, sponsored in part by a Centers of Biomedical Research Excellence (COBRE) Award from the National Institute on General Medical Sciences and a Centers of Tobacco Regulatory Science (TCORS) Award from the National Institute on Drug Abuse. The VCBH resides within the College of Medicine at UVM, with the director and administrative offices being located within the Department of Psychiatry, and participating investigators, collaborators, and advisors across 15 academic departments in the College of Medicine and 7 colleges within UVM and 5 other universities. The VCBH is further strengthened by interdisciplinary collaborations with key community healthcare leaders and distinguished scientific advisory panels. The focus of the VCBH is on investigating relationships between personal behaviors and risk for chronic disease and premature death, understanding mechanisms underpinning risk, and developing effective interventions and policies to promote healthy behavior. The center is supported by two training grants and numerous other NIH research grants for a total of 8 pre-doctoral fellows, 8 post-doctoral fellows, over 20 faculty at UVM, and 17 affiliated faculty at other institutions who serve as co-investigators, external advisors or consultants. The VCBH has an Administrative Core which provides support for obtaining appropriate resources for training as well as support for manuscript and grant writing, a Behavioral Economics and Intervention Science Core which provides consultation on the cost effectiveness and econometric modeling of interventions and health outcomes, and as a Collaboration, Dissemination and Education Core which hosts a monthly lecture series bringing in some of the top researchers in behavior and health and yearly conference on behavior and health. In the four years since its inception, VCBH researchers have published more than 100 peer-reviewed journal articles, including papers in *JAMA*, *JAMA Psychiatry*, and *Nature*. The PI and all the Co-I's are associated with the Center, creating additional opportunities for collaboration and mutual support.

The University of Vermont Cardiac Rehabilitation Program

The Cardiac Rehabilitation Facility of the UVMCC is located in the Outpatient Cardiology building of the Division of Cardiology, 3 miles away from the Medical School and the Medical Center Hospital. The Outpatient Cardiology building comprises a total clinical space of 16,000 square feet of which 3,000 sq feet are the Cardiac Rehabilitation Program and associated exercise testing laboratory and office space. It is there that Dr. Philip Ades has his full time research and clinical office. Dr. Gaalema has office space here as well as in the College of Medicine. On the clinical side, this program is one of the busier programs in the U.S. seeing well over 400 new patients annually. The UVM Cardiac Rehabilitation Exercise Testing and Training Facility is one of the preeminent CR research centers in the world. Research topics that have been investigated include resistance training in older cardiac patients and patients with chronic heart failure, methods of weight reduction in overweight cardiac patients, and methods such as financial incentives to increase CR participation in low SES cardiac patients. Behavioral counseling services for weight reduction and stress management are provided. The facility includes both clinical areas for examining patients and exercise testing and training areas along with research space. It is equipped with an exercise-testing laboratory with a Mortara Stress ECG system and a MedGraphics Ultima expired gas analysis system. Exercise training equipment includes 10 Quinton treadmills, 6 cycle ergometers, 4 supine ergometers, 6 Concept 2 Rowing ergometers, a Body Masters multi station resistance training apparatus and a variety of dumbbells. An automatic defibrillator is on site as are ECG monitors. In addition to ample equipment for exercise there is dedicated facility space and equipment for individual and classroom education and counseling. This cardiac rehabilitation facility will serve as the primary study site for this proposal.

The LCOM Biostatistics Unit (Taka Ashikaga, PhD, Director)

The Biostatistics Unit provides a comprehensive, coordinated program of research support covering biostatistics, statistical genetics, and epidemiology for biomedical and health-related research activities. The faculty of the Biostatistics Unit includes biostatisticians, epidemiologists, and behavioral scientists. The Department staff currently consists of 5 Ph.D. Biostatisticians, 3 M.S. Biostatisticians, and 2 Data Analysts. Data Analysts carry out data processing and analysis as well as assist in the development of databases. The Unit maintains a library of specialized statistical software programs designed for biomedical research data. Additionally, the Biostatistics Unit supports the preparation of individual research grant proposals, including study conceptualization and planning, research design, preparation of a proper statistical methods section and power calculations for the applications. The bioinformatics staff has access to a sophisticated computer facility with extensive capabilities.

Equipment and Other Resources

In addition to standard equipment for cardiac rehabilitation exercise training, described in the facilities and resources section, the exercise testing laboratory has specialized equipment for the measurement of expired gas analysis at peak exercise. This equipment includes a Mortara Stress EKG system and a MedGraphics Ultima expired gas analysis system. The room is also equipped with a cardiac defibrillator.

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