Human Subjects Research Protocol

The Common Human Subjects Protocol Cover Form **must** be completed and **attached** to the front of this form. This Protocol form should be completed for any human subjects research proposal that does not have a specific "protocol," such as a grant application. This form must be submitted along with a copy of the complete grant proposal and all the information in this form **must** be consistent with that proposal. This protocol form, once IRB approved, will be the working protocol for that research. **When completing this document, do not refer to page numbers within your grant**. If revisions are necessary during the course of the research, amendments should refer to this protocol form, not the grant proposal. Enter responses for all sections. Check N/A if the section does not apply.

PROTOCOL SUMMARY

Project: Title (Should match the title entered on the face page of any associated grant proposal.)

Increasing Cardiac Rehabilitation Participation among Medicaid Enrollees

Principal Investigator: Diann E. Gaalema, PhD

Grant Sponsor: NIH Grant Number: #1P20GM103644-01A1 InfoED# 26835

(For grants routed through UVM, indicate the OSP Proposal ID # located at the top of the OSP Routing Form)

Lay Language Summary: *(Please use non-technical language that would be understood by nonscientific IRB members to summarize the proposed research project. The information must include: (1) a brief statement of the problem and related theory supporting the intent of the study, and (2) a brief but specific description of the procedure(s) involving the human subjects. Please do not exceed one single-spaced 8 ½ X 11" page.)*

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. Medicaid coverage and similar state-supported insurance are robust predictors of CR non-participation. There is growing recognition of the need to increase CR among patients with this form of insurance and other 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 for increasing CR participation among Medicaid patients. Financial incentives have been highly effective in altering other health behaviors among disadvantaged populations (e.g., smoking during pregnancy, weight loss). For this study we will randomize 130 CR-eligible Medicaid enrollees to a treatment condition where they receive financial incentives contingent on initiation of and continued attendance at CR sessions or to a "usual-care" condition where they will not receive these incentives. Participants in both treatment 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 incentive 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. Should this intervention be efficacious and cost-effective, it has the potential to substantially increase CR participation and significantly improve health outcomes among low-income cardiac patients.

PURPOSE AND OBJECTIVES

Purpose: *The importance of the research and the potential knowledge to be gained should be explained in detail. Give background information.*

A. **Effectiveness and Core Components of CR**: Cardiac rehabilitation (CR) is highly effective at reducing morbidity and mortality rates following a myocardial infarction (MI) or coronary revascularization, while also reducing disability and promoting a healthy, active lifestyle (Clark et al., 2004; Taylor, et al., 2004; Wenger, 2008). Participation in CR results in a 26% decrease in cardiac mortality over 3 years as well as a 31% reduction in cardiac re-hospitalizations over a 12-month horizon (Taylor, et al., 2004; Heran, et al., 2011). Thus benefits of participation accrue rapidly and limit rehospitalization costs (Heran, et al., 2011). The American Heart Association and the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) recognize that CR is an integral part of comprehensive care for patients with cardiovascular disease (Balady, et al., 2007). While some individual elements of CR may vary from program to program and from patient to patient, the core

components include prescribed exercise, medical evaluation, and coronary risk factor reduction (Wenger, 2008). Perhaps the most important element of CR is an individualized, structured, progressive exercise program (preferably initially supervised) that needs to be continued long-term (Ades, 2001). Additional elements include behavioral and pharmacological interventions for smoking cessation and counseling to help improve adherence to diet and medication recommendations while minimizing the psychological effects of coronary illness (Balady, et al., 2007). Programs vary in length but generally consist of 24-36 sessions held 2-3 times weekly over 3-4 months (Wenger, 2008). The exercise portion of programs can be started safely as soon as 1-2 weeks following hospital discharge (Suaya, et al., 2007), which is important as this allows for initiation of the intervention soon after the event, when motivation for change is highest.

B. **Need for and Benefits of CR**: There is a tremendous need for increased CR utilization in the U.S., with an estimated 3.7 million inpatient cardiovascular revascularization procedures being performed each year along with an estimated 785,000 first and 470,000 recurrent MIs (Roger et al., 2011). CR is medically indicated for each of these conditions and was recently deemed a Class 1–A recommendation for percutaneous coronary interventions and after coronary bypass surgery (Levine et al., 2011; Hillis et al., 2012). Additionally, while rates of coronary events remain high, resulting immediate mortality rates have been decreasing. From 1997 to 2007, for example, the annual death rate due to coronary heart disease (CHD) declined 26% and number of deaths declined by 13%. This leaves a growing U.S. population of individuals living with chronic CHD who are at high risk for recurrent coronary events and disability. Depending on demographics and clinical outcome, people who survive an acute MI have a risk of recurrent events and death 1.5 to 15.0 times higher than that of the general population (Thom, et al., 2001).

The benefits of CR reach beyond reduced risks for morbidity and mortality as meta-analyses indicate that CR participation also results in significant improvements in risk factors, including cholesterol levels, blood pressure, and smoking status (Taylor, et al., 2004; Clark, et al., 2004). Additionally, measures of anxiety, depression, self-confidence, and patient-reported quality of life all improve after CR (Ades, 2001). Other benefits of CR with strong empirical support include improvements in symptoms, tolerance for exercise, psycho-social well-being and stress reduction (Wenger, 2008), all of which facilitate returning to work as well as continuation of active recreational activities (Dugmore, et al., 1999).

Among CR participants, benefits extend across a multitude of demographic and clinical subgroups; improvements among those who participate appear to be similar independent of age, race, or socioeconomic status (SES) (Suaya, et al., 2009). Additionally, the health benefits of CR participation have not lessened since the introduction of newer drug therapies (e.g., beta-adrenergic blockers and lipid management). Indeed, it has been suggested that the health benefits of CR participation have actually been getting stronger (Witt, et al., 2004). The effects of CR are also dose dependent. Reductions in mortality increase with the number of sessions attended and with adherence to risk factor reduction strategies (Suaya, et al., 2009; Hammill, et al., 2010). Therefore, research interventions that attempt to increase CR participation should also focus on sustaining participation over time.

C. **CR Participation Rates are Low, Especially in Low-Income Populations**: While nearly all cardiac event survivors would benefit from CR, only 10-35% of candidates in the U.S. and Canada choose to participate (Suaya et al 2007; Cortés and Arthur, 2006; CDC, 2008; Evenson, et al., 1998; Thomas, et al., 1996), with participation being equally low in other industrialized countries (e.g. Bethell, et al., 2009; Sundararajan, et al., 2004). Women, older adults, and socio-economically disadvantaged populations are at a particularly increased risk for non-participation in CR (CDC, 2008; Suaya, et al., 2007). Low SES is an especially robust predictor of non-participation that unfortunately has received relatively little research attention in terms of methods to improve participation. Low participation rates among those with low SES can be illustrated by two studies on this topic, which examined Medicare/Medicaid databases to estimate CR participation rates. In one study, while 18% of older adults (≥65 years) attended CR as recommended, only 3-5% of those with dual Medicare/Medicaid status (i.e., low SES) did so (Suaya, et al., 2007; 2009). The second study 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 (Oberg, et al., 2009). Of the 322 patients who could have attended CR, only two (< 1%) did so within the year following their MI. That is a remarkable statistic considering that Medicaid insurance covers patient costs for CR participation.

One of the oft-cited reasons for lack of CR participation in low-income groups is perceived barriers to participation (Mochari, et al., 2006). However, just reducing financial barriers alone does not appear to be enough to ensure participation. For example, even when reimbursement of all out-of-pocket costs was offered in one study examining this issue, college graduates were still 71% more likely to participate in CR than high school graduates (Harlan, et al., 1995). Despite these many challenges to CR participation, low-SES populations are understudied, particularly as compared with other populations who have low CR participation rates (Valencia, et al., 2011; Oberg, et al., 2009). That is unfortunate as innovative approaches to encouraging CR participation in these groups are sorely needed.

D. **Incentive-Based Interventions for Low SES Populations**: Interventions employing financial incentives can be highly effective in altering health-related behaviors among disadvantaged populations. One treatment approach, which involves providing financial incentives contingent on objective evidence of behavior change, was originally developed here at the University of Vermont as a method to encourage abstinence from cocaine use among cocaine-dependent outpatients (Higgins, et al., 1991). Incentive-based treatments have subsequently been shown to be effective at increasing abstinence from a wide variety of abused drugs, regularly resulting in treatment effect sizes of 0.32-0.42 (Lussier, et al., 2005; Prendergrast, et al., 2006). In one specific example from a recent meta-analysis of treatments for smoking during pregnancy, a problem that is almost exclusively found among low-SES women, this incentive-based approach was significantly more effective at promoting smoking abstinence (RR 0.76) than any other behavioral or pharmacological treatment (RR 0.92-0.99) that has been investigated for this problem (Lumley, et al., 2009). Similar positive findings have been observed with other predominately low-SES groups. In one example, financial incentives were used to increase adherence to HIV medication regimens in a population where participants averaged less than $9,000 per year in income (Petry, et al., 2010). Even with this challenging population, the intervention was effective, significantly improving medication adherence and lowering viral loads in the intervention

condition. Similar positive outcomes in these populations have been achieved by other investigators (Rosen, et al., 2007; Haug and Sorensen, 2006). As such, financial incentives are one of the most promising approaches for motivating behavior change in low-income populations. Indeed, there is sufficient interest in this topic area that language was added in section 4108 of the Patient Protection and Affordable Care Act mandating CMS to allocate $100 million to evaluate the use of Medicaid funds as incentives to increase participation in medical prevention services (https://www.cms.gov/MIPCD/). Incentives are also the cornerstone of the international conditional cash transfer initiative to combat chronic poverty, where mothers are encouraged to have their children inoculated and enrolled in school (Ranganathan & Lagarde, 2011).
More recently this approach of systematically using financial incentives to promote behavior change has been adapted to increase a broader variety of positive health-related behaviors. As mentioned above, they have been used for increasing physical activity and weight loss (Finkelstein et al., 2008; Volpp et al., 2008), including weight loss in economically disadvantaged populations (John et al., 2011). Financial incentives have recently been shown to also be effective at changing behaviors as diverse as compliance with extended vaccine protocols (Stitzer, et al., 2010), completion of home speech therapy sessions (Günther and Hautvast, 2010), and monitoring of blood sugar levels (Raiff and Dallery, 2010). 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 (Higgins, et al., 2008). In CR, where health effects are dose-dependent (Suaya, et al., 2009; Hammill, et al., 2010), this ability to sustain participation could be of considerable benefit.

E. **Cost Effectiveness of CR**: Several studies have attempted to quantify the costs and benefits of CR participation. One comprehensive economic analysis performed in Sweden estimated that over 5 years the decreased hospitalization rate, the associated averted health costs and higher employment rates of those who attended CR actually saved 5 times as much to the Swedish system as the cost of the CR (Levin, et al., 1991). This was due in part to lower unemployment payments in the CR group. In general, however, cost effectiveness is expressed as dollars per quality-adjusted year of life saved. In more recent reviews of the subject, cost effectiveness for CR has been estimated at $7,517 - $14,458 (in 2011 dollars) per year of life saved (Lee et al., 2007; Ades, et al., 1997; Oldridge, et al., 1993; Shepard, et al., 2009). These returns on cost are better than most other post-MI treatment interventions, including thrombolytic therapy and coronary bypass surgery (Ades, et al., 1997).
While CR may be a cost-effective way to spend health care dollars, more published data on costs of new programs are necessary to make meaningful comparisons (Clark, et al., 2004). What is virtually unknown are the cost and benefits of encouraging more low-SES patients to attend CR, as they are at increased risk of costly rehospitalizations. In a population such as Medicaid recipients, where potential health gains are greater, the cost and benefits may differ favorably from that of other populations.

F. **Summary and Conclusions**: Many past approaches to increase CR use have focused on the health care provider, attempting to increase participation in CR by increasing physician referral rates. While these approaches have been successful at increasing referrals to CR (e.g. Grace, et al., 2012), actual CR initiation remains low. The problem is particularly acute in low-income populations. The number of low income and Medicaid patients who initiate CR is still extremely low (Oberg, et al., 2009; Suaya, et al., 2007, Preliminary Data, see below). Indeed, interventions to increase participation rates among Medicaid patients could have a particularly high return, as these patients already have insurance coverage for the necessary care, while also having greater needs for health improvement following a coronary event. The proposed research will evaluate the efficacy of using an incentive-based intervention to improve CR initiation rates among Medicaid and other low-income patients while measuring the associated costs of providing this treatment and the potential health cost savings of increased CR attendance. The proposed study has the potential to make a substantial contribution by helping to improve CR initiation and adherence rates among those least likely to participate but with the most to gain.

References. *Include references to prior human or animal research and references that are relevant to the design and conduct of the study.*

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Objectives: *Clearly state the primary and secondary objective(s) of the study.*

The primary objective of this study is to determine whether providing financial incentives increases participation in, and continued attendance at, a cardiac rehabilitation program. Secondary objectives are: 1) Determine if differences in attendance affect health or other quality of life measures. 2) Quantify the costs of the incentive intervention and compare to expected reductions in health care costs.

METHODS AND PROCEDURES

Study Design: *Describe the research design, including a description of any new methodology and its advantage over existing methodologies.*

This study will be a parallel condition, randomized controlled trial to assess the efficacy of a novel approach for increasing CR participation in a low-SES population. This study will last approximately 5 years, each subject's participation will last 1 year. The study population will be comprised of 140 low-income patients (10 pilot, 130 randomized) with a recent CR-qualifying acute coronary event. The experimental condition will be an intervention wherein patients earn financial incentives contingent on participating in CR, which will be compared to standard care. The main outcome measures for this project will be: CR initiation (whether even one CR session is attended) and CR adherence (expressed as # sessions completed/36). Secondary outcomes include changes over 4 months and 1 year in fitness, cognitive and quality of life measures, as well as the economic implications of this intervention.

Procedures: *Describe all procedures (sequentially) to which human participants will be subjected. Identify all procedures that are considered experimental and/or procedures performed exclusively for research purposes. Describe the types, frequency and duration of tests, study visits, interviews, questionnaires, etc. Include required screening procedures performed before enrollment and while on study. Please provide in table, list or outline format for ease of review. (describe and attach all instruments)*

Note: A clinical research protocol may involve interventions that are strictly experimental or it may involve some aspect of research (e.g., randomization among standard treatments for collection and analysis of routine clinical data for research purposes). It is important for this section to distinguish between interventions that are experimental and/or carried out for research purposes versus those procedures that are considered standard therapy. In addition, routine procedures performed solely for research purposes (e.g., additional diagnostic/follow-up tests) should be identified.

1. Baseline Assessment: During the baseline assessment patients will undergo a medical evaluation with the Medical Director (Dr. Ades) and complete an exercise tolerance test to measure peak aerobic capacity, as is standard in our CR program. Additionally, several more detailed sociodemographic, medical history, and decision-making/neurocognitive assessments will be administered. Details of the timing and content of the assessments are provided below. All study participants will receive $50 for completing the baseline assessment as remuneration for their time.

2. Usual Care Condition: Usual care patients choosing to participate in CR will proceed into the 36-session exercise program (Ades, 2001), 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. Participants will also perform 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 need to 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. Long-term maintenance of the exercise program will be recommended as per our usual clinical protocol. Smoking will be addressed using the 5 A's as is recommended practice (Fiore, et al., 2008). Regardless of CR participation all participants will be queried monthly concerning costs of obtaining treatment, quality of life and enjoyment of exercise. Additionally all participants will return for repeats of the assessment battery at 4-months and 1-year following the baseline assessment.

3. Financial Incentive Intervention: In the incentives-based intervention condition, participants will receive the usual care program described above plus financial incentives for participation in CR, paid by check upon completion of each session. Participation will be defined as attending the scheduled session and completing the recommended exercise and other activities scheduled for that day. Participation will be verified by a CR program staff person. If an unexpected medical problem arises during a session where a CR staff member recommends against completing the session, it will be rescheduled without loss of potential earnings for that day. Visits will be scheduled at 3 times a week for weeks 1-8 (24), 2 times a week for weeks 9-12 (8), and 1 time a week for weeks 13-16 (4). This will comprise the 36 visits commonly prescribed. Participation in a group orientation session will earn the participant $20. Participation in the orientation to the exercise protocol session will earn the participant $20. Participation in scheduled exercise sessions will be compensated on an escalating schedule. Participation in the first exercise session will earn a participant $4. Further participation will result in an increase of $2 earned per session. Failure to attend a session (unless 24 hour advanced notice is given) will result in no money being earned for that session and the amount possible to be earned in the next scheduled session will be reset to $4. If the participant successfully participates in two consecutive sessions following a reset, the amount earned will be 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 behaviors (Roll & Higgins, 2000). Incentives will only be available for exercise sessions completed in the 4 month period following the baseline assessment and only for the recommended 36 visits. If all 36 visits are attended within this time period a participant will earn an additional $50 bonus. The total possible incentive earnings will be $1400. Of course, some participants assigned to the incentives condition will fail to adhere to the recommended 36 sessions of CR. Based on our prior studies using financial incentives, we estimate that mean earnings in the intervention condition in the proposed study will be approximately 60% of maximal, or about $850.

3. Monthly Questionnaires: Between the baseline and 4-month assessment participants will be asked to complete 3 questionnaires on a monthly basis. Details of these questionnaires are listed below.

4. Follow-up Assessments: At 4 months and 1 year following baseline assessments, all participants from both conditions will be scheduled to undergo follow-up assessments. Details of the content of the assessments are provided below. All participants will receive $50 for follow-up assessment as remuneration for their time.

5. Cost Analyses: As part of a cost-effectiveness analysis medical billings along with direct and indirect costs will be obtained from hospital records for the one year that participants are enrolled in the study.

For research involving survey, questionnaires, etc.: *Describe the setting and the mode of administering the instrument and the provisions for maintaining privacy and confidentiality. Include the duration, intervals of administration, and overall length of participation. (describe and attach all instruments)*

☐ ***Not applicable***

Assessments will be performed at intake, after 4 months, and at one year. All assessments will be performed in a private setting at the Cardiac Rehabilitation Facility. Assessments should take approximately one hour to complete.

Assessments:
Mental health will be assessed using: A brief psychiatric screener, the Beck Depression Inventory (BDI; Beck & Beck, 1972), and the Adult Self Report (ASR), which assess aspects of adaptive functioning and problems, psychiatric illness/symptoms and current depressive symptoms. These assessments include questions about suicidal thoughts. If a subject endorses this item research staff will follow the attached suicide protocol. If any suicidal intention is expressed the subject will be taken to a private room and the staff member will sit with them and call Crises Services.

Quality of Life will be measured using: The General Health Status M.O.S. SF-36 questionnaire (Stewart et al., 1988; 1989) and the disease specific MacNew Cardiac Health Status Questionnaire (Oldridge, et al., 1998; Höfer, et al., 2004).

Executive function will be assessed using two components of the Delis-Kaplan Executive Function System (D-KEFS, http://www.pearsonassessments.com/HAIWEB/Cultures/en-us/Productdetail.htm?Pid=015-8091-108 Delis et al., 2001), the Trail Making Test and the Tower Test, the Behavioral Rating Inventory of Executive Function (BRIEF), and with two computerized assessments: Delay discounting (DD, Johnson & Bickel, 2002); measures how quickly people discount delayed hypothetical monetary rewards; Stroop task (MacLeod, 1991); measures a person's ability to inhibit incorrect responses.

General intelligence will be measured using two components of the WASI (Wechsler Abbreviated Scale of Intelligence, http://www.pearsonassessments.com/HAIWEB/Cultures/en-us/Productdetail.htm?Pid=015-8981-502 ; Axelrod, 2002): Vocabulary and Matrix Reasoning.

The Time Perspective Questionnaire- E (TPQ-E; Hall et al., 2011) measures a person's feelings about long term goals concerning exercise.

Monthly Questionnaires: Three questionnaires will be completed monthly between the baseline and 4-month assessment. These questionnaires will take approximately 20 minutes to complete and include: the EuroQual (Oldridge, et al., 2005) a measure of quality of life; PACES (Physical Activity Enjoyment Scale; Kendzierski & DeCarlo, 1991) a measure of enjoyment of exercise, and a modification of the DATCAP (French et al., 1997) a measure of the costs incurred by a patient in attending treatment.

Statistical Considerations: *Delineate the precise outcomes to be measured and analyzed. Describe how these results will be measured and statistically analyzed. Delineate methods used to estimate the required number of subjects. Describe power calculations if the study involves comparisons. Perform this analysis on each of the primary and secondary objectives, if possible.*

Study Measures: Study measures will be taken by individuals blinded to patient treatment condition.
Demographic Information: We will collect the following sociodemographic data: age, gender, educational attainment, race/ethnicity, smoking status, marital status, and health insurance status. These demographic measures will allow us to characterize the population.
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 will be 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 untoward responses, other than high threshold angina, will exclude 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. Dr. Ades will supervise these tests.
Socio-Cognitive Measures: We will assess lifetime history of depression and other psychiatric illness, general psychiatric symptoms (Brief Symptom Inventory, BSI; Derogatis, 1993), and current depressive symptoms (Beck Depression Inventory, BDI; Beck & Beck, 1972).
Quality of Life: The General Health Status M.O.S. SF-36 questionnaire will be administered with special attention to the physical function component score (Stewart et al., 1988; 1989). Quality of life measures will incorporate the EuroQual (Oldridge, et al., 2005) and the disease specific MacNew Cardiac Health Status Questionnaire (Oldridge, et al., 1998; Höfer, et al., 2004). These measures are all standardized and have adequate test-retest reliability (Kendzierski, et al., 1991; LaPier, et al., 2009).

Executive Function: Several assessments will be administered to measure executive function, which has been shown to be important in characterizing how likely populations are to engage in various health behaviors (e.g. Bickel et al., 2007; Hall, et al., 2011). To measure these characteristics we will administer the following instruments/tasks at intake: discounting of delayed hypothetical monetary rewards (DD; Johnson & Bickel, 2002); Time Perspective Questionnaire (TPQ; Hall & Fong, 2003), and versions of the Stroop (MacLeod, 1991), Trail Making and Tower Tests (From the D-KEFS, Delis et al., 2001) that have been tied to executive function. In addition, programmatic exercise has been shown to improve some cognitive measures (Smith, et al., 2010), so the Stroop task will be also be administered at the 4 month and 1 year assessments.

Statistical Analyses and Power:

Power: Sample size was determined based on having sufficient power to detect differences between treatment conditions corresponding to our primary hypotheses regarding CR participation outcomes. Results from our prior trials and the literature on financial incentives demonstrate that doubling or more of participation rates is a common outcome (e.g. Higgins, 1994; Lussier et al., 2006). Our preliminary data show that the CR participation rate in low-income groups in Chittenden County, Vermont is ~24% compared with ~50% in non-Medicaid patients. We expect to at least double that rate, which would be equivalent to bringing the low-income participation rates up to the same level as the average participation rate of the rest of the population. Given these assumptions, an adequately powered study would require 63 participants per condition. As such, the proposed sample size of 130 subjects (65/condition) will result in greater than 80% power for a chi-square test to detect the difference between participation rates of 24% vs. 48% at end-of-intervention assessment. Based on prior incentive studies we expect a similar effect size for CR adherence over time as well. 65 subjects per condition will leave us adequately powered for both initial participation as well as longer-term adherence. Thus, accrual of 140 participants (130 randomized and 10 pilot participants) over 3 years is necessary for the successful completion of this study.

Data Analysis: Treatment conditions will be compared for differences in baseline characteristics using t-tests for continuous measures and chi-square tests for categorical variables. If specific characteristics differ significantly across treatment conditions, such as gender or age, and that are predictive of treatment outcomes, they will be considered as covariates in subsequent analyses. If the number of covariates appear somewhat large in number, a propensity score approach will be implemented to adjust comparisons between groups. Primary analyses will include all subjects randomized to treatment conditions independent of early dropout, non-adherence, etc., consistent with an intent-to-treat approach to randomized clinical trials (Armitage, 1983).

The primary outcome measures in this trial will be CR participation and will be compared between the intervention and control conditions. The number of participants who attend even a single session will be examined as well as the total number of sessions each participant completes (up to 36). Attendance rates will be compared across the treatment conditions using chi square tests or Fisher's Exact tests, if small expected cell frequencies are present. Logistic regression models to compare the two groups at each time point will be employed if covariates or the propensity scoring approach are implemented. A traditional 5% significance level will be employed.

Although this study is powered for our primary outcome of participation, we will also examine fitness (maximal exercise capacity), cognitive (BSI, BDI, Stroop, GNG, DD, TPQ), and quality of life (EuroQual and MacNew) gains at 4 and 12 months, both between the two conditions, as well as between those who do and do not attend CR. 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 a repeated measures analysis implemented using a linear mixed model. Formal testing will examine the group by time interaction term to assess differential time changes between the two conditions (intervention vs. usual care). Post-hoc comparisons between the two groups will be made if significant interactions are observed.

Confidentiality Measures and Secure Storage of Data or Tissue: *Describe how the data/tissue will be collected. Will there be identifiers or will the data/tissue be coded? Describe where the data/tissue will be stored and how it will be secured. Describe who will have access to the data/tissue or the codes. If subject data/tissues with identifiers will be released, specify to whom. Describe what will happen to the data/tissues when the research has been completed.*

☐ ***Not Applicable***

All efforts will be made to maintain confidentiality. All assessments will be conducted privately. All data will be coded by identification number, with the codes known only by the investigators on this project. Names will not be connected with any results. All data from this project will be kept in a confidential form at the Tilley Dr. Cardiac Rehabilitation program. The security of these records will be maintained by keeping paper files in a locked file cabinet and by keeping computer files in a password protected file on the Fletcher Allen computer network. The results of this study will eventually be published and information may be exchanged between medical investigators, but patient confidentiality will be maintained.

The sponsor (NIH) as well as the Institutional Review Board and regulatory authorities could be granted direct access to original medical and research records for verification of clinical trial procedures and/or data. If this is required, it will be done under conditions that will protect privacy to the fullest extent possible consistent with laws relating to public disclosure of information and the law-enforcement responsibilities of the agency. Data resulting from this research will be kept for 10 years following publication as is recommended by APA.

Risks/Benefits: *Describe any potential or known risks. This includes physical, psychological, social, legal or other risks. Estimate the probability that given risk may occur, its severity and potential reversibility. If the study involves a placebo or washout period, the risks related to these must be addressed in both the protocol and consent. Describe the planned procedures for protecting against or minimizing potential risks and assess their likely effectiveness. Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Discuss the potential benefits of the research to the subjects and others. Discuss why the risks to the subjects are reasonable in relation to the anticipated benefits to subjects and others. Discuss the importance of the knowledge gained or to be gained as a result of*

the proposed research and why the risks are reasonable in relation to the knowledge that reasonably may result. If there are no benefits state so.

Risks: 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.
- If the participant were sedentary prior to embarking on this study, they may experience some mild soreness early on in the exercise program but this will be minimized by having them begin gradually.
- 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.
- There is a risk that confidential information might accidentally be disclosed. Professional standards for protecting confidential information (detailed above) will be used to minimize this risk.

Benefits: It is likely that those who complete CR will be healthier and have a higher quality of life than those who do not. However, just being in this study does not guarantee benefits.

Therapeutic Alternatives: *List the therapeutic alternatives that are reasonably available that may be of benefit to the potential subject and include in the consent form as well.*

☐ ***Not Applicable***

Cardiac rehabilitation through the aforementioned facility is the only formal recovery program for these patients in the area. The alternative would be for a patient to recover on one's own at home without the supervised exercise training, education and counseling.

Data Safety and Monitoring: *The specific design of a Data and Safety Monitoring Plan (DSMP) for a protocol may vary extensively depending on the potential risks, size, and complexity of the research study. For a minimal risk study, a DSMP could be as simple as a description of the Principal Investigator's plan for monitoring the data and performance of safety reviews or it could be as complex as the initiation of an external, independent Data Safety and Monitoring Board (DSMB). The UVM/FAHC process for review of adverse events should be included in the DSMP.*

In the proposed study, we will use the FDA's definition of AEs and SAEs. AEs and SAEs will be assessed at each subject visit by a trained staff member and copies of all reports noting AEs and SAEs will be kept in a central file as well as in the individual subject's chart. AEs will be discussed at the weekly research staff meetings.

Adverse Event and Unanticipated Problem (UAP) Reporting: *Describe how events and UAPs will be evaluated and reported to the IRB. All protocols should specify that, in the absence of more stringent reporting requirements, the guidelines established in the Committees on Human Research "Adverse Event and Unanticipated Problems Reporting Policy" will be followed. The UVM/FAHC process for review of adverse events and UAPs to subjects or others should be included in the DSMP.*

Any SAE will be brought to the attention of the Project Director and the study cardiologist as soon as possible and not longer than 24 hours. Any AE or SAE that is both unexpected and related to study participation will be reported to the IRB within 7 days of the event. That IRB will make a determination as to whether additional reporting requirements are needed. IRB actions will be reported to the funding agency by the Project Director or COBRE Director no less than annually and more frequently as recommended by the local IRB. Any SAEs will be summarized in the yearly Progress Reports to the funding agency, including a review of frequency and severity. All SAEs will be followed through ongoing consultation with the physician caring for the patient until they resolve, result in death, or stabilize and are not expected to improve. The study staff will be in close contact with participants and health care providers throughout the study to monitor for potential unanticipated problems. Any unanticipated problems will be discussed at the weekly research staff meetings and reported as required to the CHRMS using the Report of Protocol-Related Problems & Deviations Form.

Withdrawal Procedures: *Define the precise criteria for withdrawing subjects from the study. Include a description of study requirements for when a subject withdraws him or herself from the study (if applicable).*

There are no predefined criteria for withdrawal from the study. However participants may be withdrawn if the medical director (Phillip Ades, MD) determines it is not advisable that they continue on in the program. Participants may withdraw themselves at any time, for any reason. Research data gathered from such participants will be destroyed.

Sources of Materials: *Identify sources of research material obtained from individually identifiable human subjects in the form of specimens, records or data. Indicate whether the material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records or data.*

Sources of material will include:

Data from medical records. The Cardiac Rehabilitation Facility already collects medical information, performs exercise measurements, tracks staff time required, and records exercise participation as part of their clinical protocol. These data will be used in this study. In addition some data will be collected solely for research purposes. This includes: 1) data from questionnaires on demographics (age, marital status, education, etc.) and physical and mental health and quality of life; 2) data from questions about participant costs (time and financial) for attending treatment; 3) data from computerized measures of decision making and reaction time.

DRUG AND DEVICE INFORMATION

Investigators are encouraged to consult the FAHC Investigational Pharmacy Drug Service (847-4863) prior to finalizing study drug/substance procedures.

Drug (s) [X] ***Not applicable***

Drug name – generic followed by brand name and common abbreviations. Availability – Source and pharmacology; vial or product sizes and supplier. If a placebo will be used, identify its contents and source. (attach investigational drug brochure)

Preparation: Reconstitution instructions; preparation of a sterile product, compounded dosage form; mixing guidelines, including fluid and volume required. Identify who will prepare.

Storage and stability – for both intact and mixed products.

Administration – Describe acceptable routes and methods of administration and any associated risks of administration.

Toxicity – Accurate but concise listings of major toxicities. Rare toxicities, which may be severe, should be included by indicated incidence. Also adverse interactions with other drugs used in the protocol regimen as well as specific foods should be noted. Address significant drug or drug/food interactions in the consent form as well. List all with above details.

Is it FDA approved: (include FDA IND Number)

1. *in the dosage form specified? If no, provide justification for proposed use and source of the study drug in that form.*
2. *for the route of administration specified? If no, provide justification for route and describe the method to accomplish.*
3. *for the intended action?*

Device (s) [X] ***Not applicable***

Device name and indications (attach investigational device brochure)

Is it FDA approved: (include FDA IDE Number)

1. *for indication specified? If no, provide justification for proposed use and source of the device.*

Risk assessment (non-significant/significant risk) - PI or sponsor needs to assess risk of a device based upon the use of the device with human subjects in a research environment.

SUBJECT CHARACTERISTICS, IDENTIFICATION AND RECRUITMENT

Subject Selection: *Provide rationale for subject selection in terms of the scientific objectives and proposed study design.*

Participants will include individuals hospitalized at FAHC due to a recent MI, coronary revascularization, or heart valve replacement or repair who are also enrolled in Medicaid or another state-supported health insurance. Low-income individuals are being targeted as historically this population has had extremely low participation rates in cardiac rehabilitation. This study will be testing a method of increasing cardiac rehabilitation participation in low-income individuals.

Vulnerable Populations: *Explain the rationale for involvement of special classes of subjects, if any. Discuss what procedures or practices will be used in the protocol to minimize their susceptibility to undue influences and unnecessary risk (physical, psychological, etc.).*

[X] ***Not applicable***

Number of Subjects: *What is the anticipated number of subjects to be enrolled at UVM/FAHC and in the case of a multi-center study, with UVM/FAHC as the lead, the total number of subjects for the entire study.*

It is anticipated that up to 140 participants will complete the study with the expectation that 10 will be run as pilot participants in the incentives condition and 130 will be randomized into the two conditions of the study.

Inclusion/Exclusion Criteria: *Eligibility and ineligibility criteria should be specific. Describe how eligibility will be determined and by whom. Changes to the eligibility criteria at a later phase of the research have the potential to invalidate the research.*

Inclusion Criteria:

- A recent MI, coronary revascularization, or heart valve replacement or repair
- Enrolled in a state-supported insurance plan for low income individuals

- Lives in and plans to remain in the greater Burlington, VT area (Chittenden county) for the next 12 mos.

Exclusion criteria:

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

Eligibility will be determined by the PI in concert with the medical director (Phillip Ades, MD).

Inclusion of Minorities and Women: *Describe efforts to include minorities and women. If either minorities or women are excluded, include a justification for the exclusion.*

Neither women nor minorities will be excluded from this study. As eligible candidates will be identified based purely on diagnosis code and insurance type potential bias should be minimized.

Inclusion of Children: *Describe efforts to include children. Inclusion is required unless a clear and compelling rationale shows that inclusion is inappropriate with respect to the health of the subjects or that inclusion is inappropriate for the purpose of the study. If children are included, the description of the plan should include a rationale for selecting or excluding a specific age range of children. When included, the plan must also describe the expertise of the investigative team in working with children, the appropriateness of the available facilities to accommodate children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study.* ***If children are excluded*** *then provide appropriate justification. Provide target accrual for this population.*

Children will not be included in this study. This project aims to develop an efficacious intervention to increase cardiac rehabilitation among those who have experienced a recent cardiac event. As such events are exceedingly rare in children no children will be enrolled.

For protocols including the use of an investigational drug, indicate whether women of childbearing potential have been included and, if not, include appropriate justification.

n/a

If HIV testing is included specifically for research purposes explain how the test results will be protected against unauthorized disclosure. Include if the subjects are to be informed of the test results. If yes, include the process and provision for counseling. If no, a rationale for not informing the subjects should be included.

X ***Not applicable***

Recruitment: *Describe plans for identifying and recruitment of subjects. All recruitment materials (flyers, ads, letters, etc) need to be IRB approved prior to use.*

Currently patients hospitalized at FAHC due to a recent MI, coronary revascularization, or heart valve replacement or repair are already identified and approached by cardiac rehabilitation staff. Staff, if possible, meet with patients in the hospital to explain CR and schedule follow-up appointments. As this study aims to increase participation we would like to use this existing clinical interaction to also introduce the study. The PI (acting as an agent of Dr. Ades) or another member of the cardiac rehab research staff would approach eligible participants during their inpatient stay and introduce the study. Participants that expressed interest in the study would be taken through the consenting process.

FINANCIAL CONSIDERATIONS

Expense to Subject: *If the investigation involves the possibility of added expense to the subject (longer hospitalization, extra studies, etc.) indicate in detail how this will be handled. In cases where the FDA has authorized the drug or device company to charge the patient for the experimental drug or device,* ***a copy of the authorization letter from the FDA or sponsor must accompany the application. Final approval will not be granted until the IRB receives this documentation.***
There are very limited circumstances under which study participants may be responsible (either directly or via their insurance) for covering some study-related expenses. If the study participant or their insurer(s) will be billed for any portion of the research study, provide a justification as to why this is appropriate and acceptable. For example, if the study involves treatment that is documented standard of care and not investigational, state so. In these cases, the protocol and the consent should clearly define what is standard of care and what is research.

There will be no added expense to the subjects for participating in this research.

Payment for participation: *Describe all plans to pay subjects, either in cash, a gift or gift certificate. Please note that all payments must be prorated throughout the life of the study. The IRB will not approve a study where there is only a lump sum payment at the end of the study because this can be considered coercive. The amount of payment must be justified. Clarify if subjects will be reimbursed for travel or other expenses.*

☐ ***Not applicable***

Participants will receive payment for participating in this study. Both control and experimental participants will receive $50 in compensation for their time for attending each assessment. In addition experimental participants will receive $20 for attending an orientation visit and additional financial incentives for completing exercise visits. Payment for exercise sessions will occur on an escalating scale starting at $4 with a maximum of $70 possible per session. Once incentives are earned they can be requested by the participant at any time.

***Collaborating Sites**. When research involving human subjects will take place at collaborating sites or other performance sites when UVM/FAHC is the lead site, the principal investigator must provide in this section a list of the collaborating sites and their Federalwide Assurance numbers when applicable. (agreements may be necessary)*

X | ***Not applicable***

INFORMED CONSENT

***Consent Procedures**: Describe the consent procedures to be followed, including the circumstances under which consent will be obtained, who will seek it, and the methods of documenting consent.*

Note: Only those individuals authorized to solicit consent may sign the consent form confirming that the prospective subject was provided the necessary information and that any questions asked were answered.

Consent will be obtained either at the hospital, in the patient's room, or if patients are discharged before staff can reach them, at the first visit to the CR clinic, in a private room. Consent will be obtained either by the PI (Diann Gaalema, PhD), the medical director (Phillip Ades, MD), or by one of the two staff exercise physiologists (Patrick Savage, MS; Jason Rengo, MS). Participants will have no limit on the time they can take during the consenting process. Immediately after reading the consent participants will be given the consent quiz. This will serve to document consent procedures as well as test comprehension of the consent. If a question is answered incorrectly the person obtaining consent will review the question until confident the subject comprehends the question and why their answer was incorrect.

***Information Withheld From Subjects:** Will any information about the research purpose and design be withheld from potential or participating subjects? If so, explain and justify the non-disclosure and describe plans for post-study debriefing.*

X | ***Not applicable***

***Consent, Assent, and HIPAA Authorization.** Specify the form(s) that will be used e.g. consent (if multiple forms explain and place identifier on each form), assent form and/or HIPAA authorization (if PHI is included). These form(s) must accompany the protocol as an appendix or attachment.*

A consent form and a HIPPA authorization will be used in this study.

Attach full grant application, including budget information and/or any contract or draft contract associated with this application.