PROTOCOL

for The "improving ATTENDance in cardiac rehabilitation trial" = iATTEND Trial"

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iATTEND: The improving ATTENDance in cardiac rehabilitation Trial

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Table of Contents

List of Abbreviations.

6MW =	Six minute walk
AE =	Adverse event
AHA =	American Heart Association
ACC =	American College of Cardiology
AACVPR =	American Association of Cardiovascular and Pulmonary Rehabilitation
CPX =	Cardiopulmonary exercise
CBCR =	Center based cardiac rehabilitation
CVD =	Cardiovascular disease
COOP =	Cooperative functional assessment
DSMB/P =	Data safety monitoring board/plan
HYCR =	Hybrid Cardiac rehabilitation
iPAQ =	International Physical Activity Questionnaire
METs =	Metabolic equivalents of task
PAST =	Past-day Adult Sedentary Time Questionnaire
PHQ-9 =	Patient health questionnaire
PMT =	Project management team
QOL =	Quality of life
REDCap =	Research Electronic Data Capture
RPE =	Ratings of perceived exertion
SAE =	Serious adverse event
SF-12 =	Short form health survey -12
SC =	Steering committee
SRRSA =	Subject recruitment and retention and staff adherence committee
TM =	Telemedicine
VO_2 =	Oxygen uptake

1. Overview of iATTEND

The benefits of cardiac rehabilitation are well known. However, despite center based cardiac rehabilitation (CBCR) representing guideline-based care for patients with cardiovascular disease, most patients do not complete the maximum number of sessions allowed by third party insurance payers. As such, many patients may not be receiving the full clinical benefit ascribed to CR. Several studies suggest that the number of CR sessions completed is directly and independently associated with lower mortality (an ~1% to 2% observed decrease in risk for each additional session of CR completed). The barriers to attendance in CBCR include those at the patient, program, policy, and system-levels. Among African Americans, participation and attendance to CR and adoption of healthier lifestyle changes are less likely. The iATTEND (improving ATTENDance to cardiac rehabilitation) Trial will assess the effectiveness of an innovative approach to CR delivery on attendance. The intervention group combines CBCR and remote-/home-based CR (i.e., Hybrid CR, HYCR) and is tailored to the individual needs of each patient, accomplished with the assistance of an easy-to-access telecommunications methodology (telemedicine). iATTEND is also unique because it focuses on patients residing within (or proximal to) Detroit, MI., representing a predominately at-risk cohort (e.g., 79% African American) that often cannot regularly attend CR due to social (e.g., dependent care) and economic challenges. In addition to being understudied and likely associated with disparity in CR utilization, our cohort provides an opportunity to examine the adoption and effectivenss of an innovative model to deliver CR, one that otherwise mimics traditional CBCR in terms of delivered content and expected outcomes. During the R61 start-up phase of iATTEND (year one), we will prepare to operationalize a clinical trial, including finalizing protocol, developing and finalizing the manual of operations, establishing data safety monitoring board, confirming partnerships, and demonstrating the ability to screen and enroll patients in to the trial. During the R33 clinical trial phase (years 2-5) we will assess the effect of a HYCR program on patient attendance, exercise capacity and quality of life. The design of iATTEND is a single-site, prospective, controlled Phase II clinical trial that will randomize 270 urban patients to CBCR only or HYCR. Both groups will be scheduled to attend 36 CR sessions within 6 months. Patient assessments will be conducted at baseline, within 10 days after completing CR, and 6 months after completing CR. To strengthen the generalizability of iATTEND, for both study groups we plan to (a) deliver the same secondary prevention elements and (b) measure the common program outcomes expected of traditional CBCR.

2. Specific Aims

2.1 Primary Aim

R61 Phase (Year 1, Formative Phase): In conjunction with study investigators, stakeholders, and NHLBI staff, prepare and operationalize a clinical trial that evaluates the effect of a HYCR program on attendance to CR. This includes finalizing the protocol, obtaining any institutional review board approved amendments, developing the manual of operations,

establishing data safety monitoring board, hiring and training CR and research staff, and demonstrating the ability to screen and enroll patients into the trial.

R33 Phase - Primary Aim (Years 2 – 5, Trial Phase): Assess the effect of HYCR on over-all patient attendance.

Primary Hypothesis: The number of CR sessions completed within 6 months will be significantly greater in patients randomized to HYCR vs. patients randomized to traditional CBCR (usual care).

Hypothesis 2: The percentage of patients completing 36 CR sessions within 6 months will be significantly greater among patients randomized to the HYCR program vs. patients randomized to the CBCR program.

2.2 Secondary Aims

R33 Phase: Assess the effect of HYCR on exercise capacity and quality of life.

Hypothesis 3: The improvement in exercise capacity, as measured by distance walked during the six min walk (6MW) test, in patients randomized to HYCR will be equivalent (not inferior) to patients randomized to CBCR.

Hypothesis 4: The improvement in exercise capacity, as measured by peak oxygen uptake (VO_2), in patients randomized to HYCR will be equivalent (not inferior) to patients randomized to CBCR.

Hypothesis 5: The improvement in quality of life (QOL), as measured by the Dartmouth COOP, in patients randomized to HYCR will be equivalent (not inferior) to patients randomized to CBCR.

2.3 Exploratory Aims

At 6 months after completing CR, explore the effect of a HYCR on (a) exercise capacity, (b) QOL, (c) self-engaged purposeful exercise, and (d) total physical activity habits, Also, explore the cost effectiveness of a HYCR program

3. Background

Although the age-standardized death rate attributable to cardiovascular disease (CVD) has decreased over the past decade (1), it remains our nation's number one killer. In 2017, almost 700,000 American's will have a new coronary heart disease-related event (myocardial infarction [MI] or death) with another 325,000 people experiencing a *recurrent* coronary heart disease *(*CHD) related-event. In addition, there are approximately 960,000 new cases of heart failure diagnosed annually, ~53% of which are due to reduced ejection fraction (1). Among survivors

of the above cardiac-related events, most go on to experience increasing disability, a reduction in quality of life (QOL), and morbidity (11-13). For example, re-hospitalization rates for patients that survive an MI or an index hospitalization for heart failure range from 10% to as high as 20% or 30% (12-15). Finally, in addition to the burden that CVD places on health, functional capabilities and QOL, the recurrence of CVD-related problems carries a heavy economic burden as well. The cost of re-hospitalization after an MI can exceed $19,000 (16) and if a procedure is required, the cost is increased further.

There are numerous effective therapies that target secondary prevention following an initial CVD-related event including lipid- and blood pressure lowering-drugs, exercise training, after-load reduction and/or beta-adrenergic blockade agents, smoking cessation programs, and anti-platelet drugs (17,33). However, despite secondary prevention guidelines advanced by the American Heart Association (AHA), The American College of Cardiology (ACC), and the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) (17,18), greater than 15% of patients still smoke cigarettes, compliance to cardioprotective drugs is not optimal (31% stop taking $\geq$ 1 drug), regular exercise is only 40%, and obesity is common (1,10,19-22,91). Additionally, the simultaneous adherence to proven secondary prevention strategies is reported to be less than 10% (22); yet most all of these strategies are addressed through a comprehensive cardiac rehabilitation (CR) service and its use of disease management, clinical surveillance, supervised exercise, and patient education.

3.1. Secondary Prevention in Vulnerable, at Risk Patients with Cardiovascular Disease

Patients of lower socio-economic status (SES) experience a disparate or disproportionate level of morbidity and recurrent events following an initial heart problem, a portion of which can be explained by poorer engagement in secondary preventive strategies (e.g., cigarette cessation, blood pressure and lipid control, physical activity, and compliance to prescribed medication) (1,10,20,23,24). Additionally, following a cardiac event annual mortality is lower among Caucasians versus others (4,6).

Much of the research to date that pertains to CR has involved patients that were healthier and socially and financially better able to adhere to CR and; therefore, able to participate in CR-related research. Limited prior research suggests lower participation rates and fewer CR sessions completed among minorities and people of lower SES (3,9). The cardiovascular health care needs of these patients are real (and grossly understudied). Advancing and evaluating CR and its associated secondary prevention strategies (17,18) in a predominately urban, vulnerable cohort of at-risk patients represents an ideal opportunity to potentially impact their health care outcomes ... and is worthy of further investigation (3).

3.2. Cardiac Rehabilitation as a Secondary Prevention Therapy… Role and Clinical Effectiveness

Today, more so than ever before, the majority of CR programs in the US no longer represent an “exercise-only” intervention. CR is now a multidisciplinary and multifaceted secondary prevention service that addresses the core components of CR as defined by the AHA, AACVPR and ACC (17,18). Therefore, the deliverables from CR should be the same, regardless

if provided in center-based CBCR or a combination of CBCR and remote-/home-based CR ("hybrid" CR, HYCR).

The evidence supporting the clinical effectiveness of traditional, CBCR is well-established and as a result, CR is a class 1 recommendation following MI, coronary artery bypass surgery, or percutaneous coronary intervention (25-29). Additionally, CR is recommended for patients who have undergone cardiac transplantation or heart valve surgery and those with chronic stable angina and stable chronic heart failure with reduced ejection fraction (30-33). Briefly, CR is associated with a 10% to 24% reduction in total mortality over 1 to 3 years and an ~ 30% decrease in re-hospitalizations over 1 year (3,4,25,34-39). We recently estimated that if CR participation was increased to 70% among eligible patients, ~25,000 lives would be saved and 180,000 hospitalizations would be prevented annually (25). In addition, quality of life and functional capacity are improved (25,39,40,83) and much of the abnormal physiology that accompanies CVD is improved [e.g., coronary artery endothelial function, autonomic function, insulin resistance] (25,41-43). Finally, mood is also favorably influenced (44,45). Taken in sum, CR is a cost effective means to deliver and advance secondary prevention to patients with known CVD via a multidisciplinary and patient-centered approach.

3.2.1. *Relationship between Number of Cardiac Rehabilitation Sessions Completed and Outcomes.*

Most patients attend 25 or fewer CR sessions (2-5,9), less than what is typically allowed by the majority of health insurers (e.g., Medicare allows 36 visits), potentially diminishing the functional and clinical benefits ascribed to CR. Hammill and co-workers (6) observed that a 6 session increase in number of CR sessions completed was associated with an ~ 6% decrease in risk of mortality (HR: 0.94, $p < 0.001$). Martin et al (7) reported a 1% decrease in risk for each additional CR session attended (HR: 0.99, 99% CI: 0.98-0.99). Finally, Doll et al. (8) reported a 13% reduction in risk for mortality for each increase of 5 CR sessions (HR: 0.87, 95% CI: 0.83–0.92). We previously showed, that (a) the number of sessions completed is associated with the magnitude of the increase in exercise capacity (45) and (b) higher achieved MET level at discharge from CR is related to a reduction in risk for mortality (HR:0.60; 95% CI: 0.51–0.70) (46).

Last year the Centers for Medicare and Medicaid Services (CMS) recognized the importance of the relationship between the number of visits completed and outcomes, when they proposed a model that linked level of reimbursement to the number of CR attended. Although that project was rescinded (47), it did indicate that CMS acknowledged the value associated with maximizing the number of CR sessions attended. Finally, there is biologic plausibility underpinning the concept that more visits in CR are related to improved outcomes. Hundreds of exercise trials over the past 30 years involving healthy people and patients with CVD demonstrate that, to an extent, the "dose" of regular exercise delivered is related to the magnitude of the improvement (48).

3.3. Alternate Delivery Methods …. And Home-Based Cardiac Rehabilitation

Million Hearts is a national initiative led by the Centers for Disease Control and Prevention and CMS (49), with an aim to improve use of evidence-based practices (e.g., aspirin use, blood pressure to goal), especially in priority populations. Recognizing the important role of CR in secondary prevention, in 2015 Million Hearts established the CR Collaborative, which set a target goal to increase participation in CR to 70% by 2022 and advocated that "patients complete all 36 sessions of the CR protocol …" (25). Consistent with the above, two AHA advisories (50,51) called for *the development and deployment of new delivery models to improve the utilization of CR services*. Both advisories recognized that the CBCR programs of today are insufficient to meet the needs of CR nationally. In fact, Pack et al (52) estimated that if all CBCR programs currently in the U.S. operated at full capacity, such an accomplishment would accommodate <50% of qualifying patients.

Various types of home-based CR have been evaluated (53-75). What has not been fully investigated is an industry-standard, hybrid CR model, one that tailors program offerings to the individual needs of each patient, while at the same time demonstrating generalizability by operating within (not separate from) a CBCR program. Helping patients overcome barriers to regular attendance in CBCR is possible through a patient-centered HYCR model and; therefore, has the potential to increase the number of CR visits attended.

Home-based CR has not flourished to date, likely for two reasons. First, and of great importance, is that home-based CR is not a covered benefit by health insurers (e.g., Medicare or commercial payers such as Blue Cross and Blue Shield) across the U.S. Therefore, home-based CR is not viewed by health systems as financially favorable. That said, the technology used today for the remote or home delivery of telehealth (e.g., video synchronized telemedicine), which is insurance covered in most states in the US, has not been applied and tested on a larger scale as a means to secure reimbursement for remote-based CR.

Second, most research studies that tested home-based CR were conducted using additional or assigned clinical research staff that operated independently or outside of the daily function of CR. This can be a source of frustration for existing CBCR programs who are unsure how to integrate schedules, allocate and parse limited staff, and remotely deliver patient education. CR programs that strive to "improve patient attendance" by offering a HYCR program need to be assured of not only equivalency of outcomes (between CBCR and HYCR) but ease of adoption within their setting as well.

To help the field of CR take an evolutionary step forward, we believe it is important to test a HYCR model that addresses all of the industry-standard elements of contemporary CR, and does so by leveraging existing video telemedicine technology that (a) operates via the virtual private network (VPN) within the electronic medical records (EMR) that serve hospitals today (e.g., EPIC, Cerner, Allscripts) and (b) only requires hardware that is already accessible by most patient's. This approach represents a model for CR to meet existing telemedicine (TM) statutes for reimbursement in most States (like Henry Ford has tested in Michigan)

(http://cchpca.org/state-laws-and-reimbursement-policies). [TM is defined here-in as video synchronized telecommunications for the remote delivery of patient care.]

3.3.1. *Telemedicine (TM) Today.* TM uses devices and technology to deliver patient care when the patient and provider are separated by distance. TM is used by many specialties including behavioral health and primary care to improve access to care, cost effectiveness, and quality of care (76). Patient satisfaction ranks high with TM, evidenced by a recent survey of 1700 U.S. adults in which 94% reported being "very satisfied" with all aspects of their TM visit and only ~ 1% rated the experience confusing/complicated (77). Current estimates are that 63% of health care providers use some form of TM, and that 44% of health systems indicate TM is a "top priority" (78) in their strategic planning. Currently, 48 states provide Medicaid reimbursement for TM via some form of live, synchronized video (79) and 31 states have "Parity Laws" requiring commercial insurers (e.g., Blue Cross/Blue Shield) to reimburse for TM at the same rate as in-person encounters (80).

3.3.1.a. Within Henry Ford Health System in Detroit, TM visits are conducted with the patient using a mobile device (smart phone or tablet) and software integrated within their patient portal of our EMR [EPIC (i.e., MyChart/Vidyo, VidyoMobile, Vidyo, Inc. Hackensack, NJ)], ensuring a secure, two-way, real time video interaction between the patient and the provider. The other commercial EMR's offer similar capabilities.

3.4 Impact of Changes in Program Operations on Adherence

To date, three studies systematically assessed the effect of changes in CR programmatic operations on number of CR visits completed (**Table 1**). Pack et al. (81) used as tailored welcoming video and non-monetary motivational incentives and showed that both incrementally increased the number of sessions completed. Among Medicaid beneficiaries, Gaalema et al. (82) showed that the use of monetary incentives resulted in the completion of more CR sessions. An *Australian-based* study is (74) particularly relevant because it *employed synchronized TM*, and reported a greater number of sessions with home CR versus CBCR. I ATTEND is the first large, US-based, prospective randomized trial to use TM and assess the effect of a comprehensive, individualized HYCR program on the number of CR sessions attended. If iATTEND successfully demonstrates the effectiveness of a HYCR program using TM on a larger scale, then it can be advanced as a model to CR programs in other health systems, as well as to health insurers in other states.

Table 1: Comparison of Studies Using an Administrative or Programmatic Intervention to Increase Attendance in CR

	Design	Sample	Intervention	Primary Finding

Pack et al (81) 2013	Retrospective	N=1103, Age=64+13, 70% men, 92% Caucasian	• Policy change defining completion at ≥ 30 sessions • Monetary motivational incentives for patients and staff (e.g. packing pass, t-shirt) • Descriptive video	• Overall completion rate increased • The addition of each intervention associated with a 3-4 visit increase in number of visits
Gaalema et al (82) 2016	Convenience group compared to historical controls	N=10 Age=59 ± 10 yr, 69% men, 80% Caucasian	Increasing financial incentives per each session attended	• 31 sessions for incentivized patients vs 13.6 sessions for controls
Hwang et al (74) 2017	Randomized parallel (non-inferior), home-based vs center-based	N=53, mean age 67±12 yr, 75% men, 75% Caucasian	Real-time video teleconferencing	• 20 visits for home-based vs 14 visits for center-based • Equivalent gains in six minute walk

Securing insurance reimbursement for HYCR via synchronized TM has the potential to attenuate concerns from hospital administrators who avoid home-based CR because it is viewed as a negative financial endeavor. Importantly, HYCR may help overcome common attendance barriers by providing care in one's home or closer to where they live, and at a mutually agreed upon time.

3.5 Applying HYCR to a Vulnerable, at Risk Patients with Cardiovascular Disease

Per the 2016 US census, the City of Detroit, MI is a major city in the US, with >670,000 residents. The main demographics for Detroit are: 79% African American (AA), 8% Hispanic; 13% age 65 yr or older; and a median annual household income < $27,000… representing a priority population that is vulnerable to some of the social and economic challenges that HYCR

is aimed at overcoming. In 2016, ~ 80% of the patients cared for in the Henry Ford Hospital CR program in Detroit were AA, indicating that the patient population we serve at our Detroit site is indeed consistent with the population of the City. Unfortunately, AA are less likely to use CR (3,9) and adopt lifestyle changes aimed at the secondary prevention of CVD (10); iATTEND will provide them with improved access to CR and its secondary prevention capabilities using a convenient approach to increase attendance.

3.5.1 *Patient access to the needed technology and home exercise equipment*

To test the effectiveness of our HYCR model requires that all patients studied have the device technology and exercise equipment needed to conduct the trial. To minimize project costs, reflect "real-world" operations in CR, minimize CR staff burden, and still test effectivenss, iATTEND will enroll patients referred to the Hospital's Detroit-based program that have access to the needed equipment; specifically, (a) a smart phone or tablet (via self or a "willing to assist" family member/friend) with internet access and (b) stationary exercise equipment (treadmill, elliptical or bike) at home, work, place of worship, or in the community; and would be willing to periodically use both for their CR efforts.

3.6. Safety of home-based CR

It is important to emphasize that the level of incremental risk for major unexpected adverse events (death, events requiring hospitalization) that are probably related to a subject's participation in this project will likely be extremely low. Specifically, center-based cardiac rehabilitation (CR) is known to be safe for patients that participate, with reported rates of 1 major event per 750,000 to 900,000 patient-hours of training (88). *Concerning home-based CR, it is important to first emphasize that most all patients that participate in center-based programs today are already asked to "exercise on their own on non-rehab days"; therefore, iATTEND is mainly giving some structure and supervision to that recommendation.* Numerous studies have looked at the safety of home based CR and have shown no apparent increased risk (53-62,64,66-68,72-74).

The Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) Study is the largest study to assess the safety of exercise training, with the vast majority of the exercise training completed outside of center-based CR (38). In HF-ACTION, patients with stable, chronic heart failure and NYHA class II to IV symptoms (n-2331) were enrolled. In that study, participants were prescribed 9 or more months of home based CR. A heart rate monitor (chest/wrist heart rate-watch) and daily exercise records were used to guide and monitor exercise intensity at home. No significant difference was reported between the exercise and usual care groups for the overall rate of hospitalization (1.9% vs 3.2%, respectively) or death (0.4% versus 0.4%, respectively) during or within 3 hours after exercise. Furthermore, the investigators identified 1,053 patients from the HF ACTION trial who had an implantable cardioverter defibrillator (ICD) at baseline and were randomized to the exercise intervention vs. control. Study participants had a median ejection fraction of 24% at baseline. During 2.2 years of follow-up, 20% of the 546 exercise patients experienced a shock vs. 22% of the 507 usual care patients. Exercise training was not associated with the increased occurrence of ICD shock (HR 0.9, 95% CI, 0.7 – 1.2) (89).

4. Investigational Plan

4.1. Overview.

The iATTEND Trial is a single-site, prospective, randomized controlled Phase 2 clinical trial that will assess the effectiveness of a patient-individualized HYCR program, one that is provided either remotely (home and/or in the community) and includes 1 or more sessions of CBCR. iATTEND tests this paradigm in a vulnerable, urban cohort that often cannot maintain participation in CR due to personal (e.g., dependent-care) and financial challenges. To strengthen the generalizability of our findings, in both study groups we plan to (a) deliver the same key secondary prevention elements and (b) measure the same program outcomes that are expected of an industry-standard CR program. Clinical operations at the Henry Ford Detroit CR site are to be revised (including its staffing matrix) in a manner that allows the site to offer both CBCR only and HYCR, using existing CR staff (research staff will not be involved in direct patient care). Therefore, the only difference between the two study groups will be the method of program delivery (CBCR vs. HYCR). HYCR will be delivered with the periodic use of synchronous TM, which will be billed to and is covered by Blue Cross and Blue Shield of Michigan and Health Alliance Plan of Michigan [or billed to the project's budget, if the patient's health insurer (e.g., Medicare) has not yet agreed to cover HYCR delivered via TM.]

4.2. R61 – Year 1 – Formative or Start-Up Phase.

The first 12 mo of iATTEND will transition from starting the project and finalizing the protocol to subject screening and starting enrollment.

Month 1 of year 1. The PI, several of the co-investigators, and the Project Manager (Matt Saval) will meet to discuss potential collaborations and begin to finalize the scientific aspects of the study protocol (e.g., recruitment, retention). Any amendments to the protocol will be drafted and submitted to the institutional review board (IRB) for approval. Hospital administration will be engaged to secure the approvals to post the research staff positions.

Months 2-4 of year 1. Constitute and conduct meetings of the Steering Committee and the Project Management Team (PMT), begin the development of case report forms for data collection, draft the manual of operations around study protocol, establish the trial's dataset template using the REDCap system, and interview and hire the research staff.

Involving patients currently in the Detroit CR program, conduct a survey to describe access to a telecommunications device (smart phone, tablet) and exercise equipment, as well as ascertain willingness to participate in a trial like iATTEND, best hours of accessibility, and potential barriers with usage. Using this information, develop/test strategies aimed at preventing interruption in CR operations during the R33 phase. If survey data indicates potential difficulty recruiting subjects over the 30 month enrollment period, additional strategies aimed at boosting recruitment will be conceptualized and tested. For patients who do not have the needed technology or equipment, develop and test messages that empowers to "think through" other

options for accessing the equipment (i.e. willing to assist family member, fellow church parishioner, friend, community center). Codify any learnings for use by the research staff.

Months 5-9 of year 1. Train all Detroit CR staff to work within a framework of having some patients in a CBCR only model and others in the HYCR model. In conjunction with feedback provided by the CR staff, modify program orientation materials, class sizes and format (e.g., open gym), computers, and staff matrixes to allow both the CBCR and HYCR program models to operate in an integrated manner. Because some patients will now be receiving their CR care remotely, the number of sessions held at our Detroit center will decrease proportionately. This increased availability of staff time will be used by CR staff to conduct HYCR visits based on an established schedule, with the new delivery model "stress tested" within mock environments to ensure that all disciplines of the staff are sufficiently trained on the technology and procedures associated with simultaneously offering both CBCR-only and HYCB with TM. Procedures will be revised based on user feedback and the manual of operations near-finalized. Any forms, training, or procedures associated with subject testing and follow-up will be finalized and codified. Finally, the data safety monitoring plan will be developed, including the appointment of the internal data safety monitoring board (DSMB).

Months 8 and 10 of year 1. Interface the in-patient and out-patient processes that refer patients to the Detroit CR program with the screening and recruiting processes for iATTEND. Register the trial on clinicaltrials.gov. Secure all approvals of the trial's protocol.

Months 9-12 of year 1. Begin subject screening, recruitment, consenting, and baseline testing, and enroll subjects (~4% of 270 total). Hold the first of annual in-person meetings with NHLBI to review progress and scientific and protocol integrity; revise milestones as needed. Secure approval to proceed to R33 phase.

4.2.1. *Implementation Science and Practices for the R61 Phase*

Under the guidance of co-investigator Jack Jordan, recruit several patients currently in CR to assist the PMT as patient stakeholders, as a means to ensure 360 degree input. Using a problem-solving approach, identify patient markers that might be associated with discontinuing the use of CR, including any patients that might link their discontinuation to difficulties with the methods of adopting or using TM. Also, identify what data will be regularly captured in real-time going forward, including but not limited to patient satisfaction, duration of patient engagements, language barriers, adoption/sustainability of TM in CR by patients and staff, and reliability of TM operations.

4.3. R33 – Years 2-5 – Clinical Trial Phase.

4.3.1. *Study Population*

270 patients with an index event that qualifies for CR will be recruited (a) prior to discharge from the hospital, (b) soon after hospital discharge with documented referral to CR, or (c) from screening appointment schedules for physicians that will be seeing patients in an

ambulatory care setting. The inclusion and exclusion criteria are not overly restrictive, such that we expect a sufficient number of patients eligible and enrolled in CR to consent to trial participation.

4.3.1.a. Inclusion Criteria

1) Has agreed to participate in CR and has experienced a cardiac event (myocardial infraction, coronary revascularization, heart valve surgery, or cardiac transplant in the past 6 months; diagnosed with chronic, stable AHA/ACC stage B or C heart failure or Canadian class 0-2 stable angina pectoris)

2) Lives in or plans to remain in the greater Detroit, MI area for the next year

3) Age 18-85 years of age

4) Agrees to attend at least one CBCR session

5) Agrees to scheduling at least 2, up to 3, CR sessions (either CBCR or HYCR)/wk

6) Has demonstrated to research staff their ability to access and connect to the internet via smart phone or tablet and already has access to satisfactory home- or community-based exercise equipment

4.3.1.b. Exclusion Criteria

1) Received a left ventricular assist device, receiving continuous inotropic support (e.g., milrinone), or undergoing hemodialysis

2) Angina at rest or with a low functional capacity (< 2 METs)

3) Advanced cancer, advanced risk for falling, limiting cognitive impairment, or other advanced disorder that limits participation in CR

a. Advanced risk for falling will be assessed by 5X sit-to-stand test, with a cut-off score of >15 seconds

b. Cognitive assessment will be completed using the Mini-Cog instrument, with a cut-off score < 3 used to exclude potential subjects.

4) Severe arrhythmia unless adequately treated (e.g., implantable cardiac defibrillator)

5) Pregnant or plan to become pregnant in the next year.

6) Major cardiovascular procedure or hospitalization planned in the next 6 months

7) Exercise testing results that preclude safe exercise training, including abnormal blood pressure response, early ischemic changes or unexpected life-threatening arrhythmia

8) Participation in another clinical trial that interferes with iATTEND participation, follow-up, data collection, exercise capacity or quality of life.

9) Participation in a cardiac rehabilitation program within one year.

4.3.2. *Background Therapies*

Guideline based medical, device and surgical care for a patient's cardiovascular disease will be managed solely by their physician and any changes in therapy will remain at the discretion of said physicians. While a patient is participating in the iATTEND trial we recognize that some patients may be or become candidates for current or new therapies that could impact exercise capacity or quality of life. Patients in whom their physician considers a procedure or placement of a device to be probable within 6 months should be excluded from trial entry until after such device has been placed or procedure completed.

4.3.3. *Subject Enrollment*

4.3.3.a. *Screening … from in-patient and EMR*

Using census data from the EMR for in-patient cardiology units, as well as the out-patient preventive cardiology unit work que in the EMR, potential subjects will be identified/screened by the CR and research staff that visits or calls patients. The names of potential candidates will be forwarded to the research staff who will then conduct a detailed screening of eligibility using the EMR and a telephone call. If the patient meets the enrollment criteria and agrees to participate after having discussed study purpose, procedures, risks and responsibilities, a baseline appointment will be made, ideally on the same day the patient will be scheduled to attend CR orientation; 7-14 days after discharge if hospitalized. Patients stating interest in the research study will meet with the research coordinator, the project PI, or the project manager to undergo further screening and receive a verbal explanation of the trial and sign informed consent.

4.3.3.b. *Baseline Clinic Visit*

The baseline testing required in this protocol should be completed as soon as possible after signed consent, but may be completed up to 4 weeks after consenting, if necessary. All baseline testing will be completed prior to a patient's first session in CR. For any study visit that includes a QOL assessment and a symptom-limited cardiopulmonary exercise (CPX) test, the quality of life (QOL) instrument(s) (Dartmouth COOP, and/or EuroQOL-5D) must be completed prior to the CPX test. Also, the 6 min walk (6MW) test must be completed, per standardized procedures (84), 1 hour or more before the CPX test; therefore, during any clinic visit the order of these tests is as follows: (a) 6MW, (b) QOL tools and other assessments (PHQ-9, Rate your Plate, mini-cog), (c) 5x repetition sit-to-stand test, and (d) CPX test. The 6MW and the CPX test will be completed per procedures as specified and overseen by the Henry Ford Clinical Exercise Physiology Core Laboratory ("Exercise Core Lab); and case report forms for 6MW and QOL surveys and data collected from the CPX test will be forwarded to the Exercise Core lab or data entry/management as indicated.

4.3.3.c. *Baseline Testing*

The written questionnaires (EuroQOL-5D, Dartmouth COOP, Rate Your Plate, and PHQ-9) will be administered per the standardized instructions associated with each instrument. Advanced risk for falling will be assessed by the repetition 5X Sit-to-Stand test and cognitive status will be assessed by the Mini-Cog screening tool. Those patients meeting the exclusion criteria based in advanced risk for falling or cognitive status will be excluded from participating in the trial, but still allowed to participate in CR.

The Exercise Core Lab will oversee staff training, quality control, procedural conduct, and all data analysis for both the 6MW and CPX test. The primary modality for CPX testing will be the motor driven treadmill; however, a stationary bike can be used if indicated. Patients must use the same testing and exercises protocol for all CPX testing completed during the trial. For any bike tests, a ramped protocol will be used that starts at 0 watts and work rate is increased 10 watt/min. For all treadmill tests, the modified Naughton protocol will be used for testing:

Table 2.

Stage	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Time (min)	2	4	6	8	10	12	14	16	18	20
Speed (mph)	1.0	1.5	2.0	2.0	2.0	3.0	3.0	3.0	3.0	3.5
Grade (%)	0	0	3.5	7	10.5	7	10	12.5	15	14
Estimated METs	2.3	3.3	4.5	5.5	6.5	7.5	8.5	9.5.	10.5	11.5

Patients will be excluded from the study if exercise testing results preclude safe exercise training in CR as defined by ACC/AHA guidelines, including abnormal blood pressure response, early ischemic changes and unexpected life-threatening arrhythmia. If an exercise-induced arrhythmia is identified as life-threatening, the exercise test will be stopped. If the patient is performing a baseline exercise test, he/she will <u>not</u> be randomized in to the study. If the patient is performing a follow-up exercise test immediately after CR or at 6 month, he/she will be asked to stop any exercise training and his/her physician will be notified of the results; these patients will be followed per protocol for the duration of the study and no further exercise testing will be performed. Patients who have a non-life-threatening arrhythmia that stops the test can re-take the test or re-start CR after it is treated.

For patients taking a beta-adrenergic blocking agent, they should participate in exercise testing and training between three hours and 10 hours after taking their last dose of the drug. All CPX tests will be sign- and symptom-limited, with strong encouragement to achieve a respiratory exchange ratio >1.10 and a Borg rating of perceived exertion >16; however, neither of these criteria will serve as a stopping criteria for the test. Ventilatory threshold, peak oxygen uptake (VO_2), and other test variables will be determined per Core lab procedures. After the baseline CPX test, intentional attempts will be made to blind the person supervising all subsequent follow-up tests to a patient's study group assignment through isolation of test materials, patient instructions, and restricted conversation with testing staff. The exercise testing lab will undergo quality control testing every 6 months in accordance with Core lab procedures.

4.3.4. *Randomization*

After a patient has satisfied all enrollment criteria, informed consent obtained, and they complete all of the written and exercise assessments, the patient will be randomized to usual care CR or Hybrid CR. **Generally, randomization should occur the same day of the final screening test (i.e., CPX).** A one-to-one randomization scheme will be computer generated and will be balanced on random accrual points and stratified by race and gender.

4.3.5. *Study groups*.

Patients in both arms of iATTEND will receive CR. Participation in CR will begin as soon as possible after randomization, with a goal of initiating training no more than 10 days after randomization.

4.3.5.a. Usual care. Patients in this arm of the trial will receive the following:

1. Industry standard, facility-based CR, in accordance with current Henry Ford policies and procedures; attending CR 2-3 days per week. Briefly, transportation issues will be resolved per current practices using family and community resources. Individual treatment plans (ITPs) will be established upon enrollment into CR; revised per patient progress; and uploaded in to the EMR upon entry and 30, 60, and 90 days and upon completion of CR. Current guidelines for prescribing exercise (type, frequency, duration, intensity) will be in accordance with Unit procedures, as adapted from published guidelines (85). Any ECG telemetry or blood pressure measurement during exercise will be used as clinically indicated, and in accordance with program policies and procedures. Health insurance coverage will be verified per Unit protocol and CR visits billed in accordance with a patient's policy and per hospital practices. To avoid any effect that co-payments or differing co-payment amounts might have on attendance (and thus induce a potential source of bias between groups), all co-payments will be charged to the project. For those patients without health insurance, their CR sessions will charged to proposed project budget. CBCR subjects will be encouraged to engage in purposeful exercise ad libitum on their own each week.

2. Upon (a) completion of 36 sessions, (b) having stopped attending CR due to medical/ personal reasons or non-compliance (defined per current Henry Ford polices and procedures), or (c) 6 months of elapsed time from their first CR session, subjects will be deemed having "completed" CR and <u>follow-up visit 1</u> of project testing (QOL, CPX test, 6MW test, and all standard CR surveys) will be scheduled and completed within 10 days after such designation.

3. After completing CR and then follow-up visit 1, <u>all subjects will also be contacted by the research coordinator by telephone at 2 months and 4 months within the 6 month follow-up period</u>. The main reason for these telephone calls at months 2 and 4 after CR is to facilitate continued subject retention/engagement in the trial. The coordinator will remind patients about their scheduled follow-up visit 2 (at 6 months). The coordinator will also equally speak with subjects in both groups about any barriers/issues they might be experiencing relative to proper self-care or disease management behaviors, and assist with resolution strategies using an open,

problem-solving approach. Subjects that were administratively "dropped" from CR will still be contacted and scheduled to complete follow-up testing visits 1 and 2.

4. Follow-up visit 2 will be completed at 6 months after completing CR, including project testing (QOL, CPX test, 6MW test, and all standard CR survey) will be scheduled and completed.

4.3.5.b. Intervention Group (HYCR)

This group of iATTEND involves a hybrid design, with the frequency of CBCR visits and HYCR visits individualized and modified based on the subject's personal preferences and their family, transportation and work constraints. Per study eligibility criteria, patients in HYCR will engage in at least one CBCR visit. For those with no preferences as to their number of TM visits, they will be scheduled to complete 12 of their 36 visits as HYCR-TM, with the remainder being home-based without TM (up to one time per week) and/or CBCR 1 or more per week. Immediately following CR visit 1 (which will be CBCR), patient in HYCR will have the video app loaded to their smart phone or tablet (or that of a "willing to assist" family member or friend). HYCR patients receive a chest strap/wrist heart rate device to document HR before, during, and/or after exercise during the TM session. After CBCR visit 1, if the patient opts to complete the remainder of the CR session as HYCR, they will be provided with a home blood pressure unit for the regular reporting of resting blood pressure prior to each HYCR visit. HYCR subjects will be encouraged to engage in purposeful exercise ad libitum on their own each week.

Since both Blue Cross and Blue Shield of Michigan and Health Alliance Plan already cover CBCR and HYCR, only the co-payments will be covered by the project's budget. For patients randomized to HYCR that have an insurer that <u>does not</u> yet cover CR delivered using TM (e.g., Medicare), their CR visits will be covered by the project's budget. For all patients randomized to CBCR, their co-payments will be covered by the project's budget.

Program education for patients in HYCR will be delivered using the twenty-eight, 7-15 min audio PDF's that are free to access from the Health System's web site. For patients in the HYCR group, 1-3 of the audio PDF's will be "assigned" (based on their ITP) for viewing before their next CR visit, with content discussed with the appropriate CR staff person during their next remote or center-based visit.

The following table (Table 3) provides a descriptive summary of the CR protocol for subjects in the two study groups of iATTEND.

Table 3. Summary of the CR protocol for subjects in the two study groups of iATTEND.

	Hybrid CR	**Center-Based CR**
Staff : Subject ratio (contact time, setting)	1:1 (12 to 15 min, individual setting)	4:1 (60 min, group setting)

Programming for CR session	• 2 to 3 sessions each week • At least 1 and no more than 12 of the sessions will be center-based • Remainder of 36 sessions will be remote-/home-based with TM	All sessions will be center-based sessions, 2 to 3 sessions each week
Recommended total number of sessions	36	36
Exercise intensity range (85)	60%-80% of heart rate reserve or RPE 11-14	60%-80% of heart rate reserve or RPE 11-14
Recommendation for purposeful exercise outside of formal CR	Encouraged, ad libitum	Encouraged, ad libitum
Patient monitoring	ECG telemetry and resting and exercise blood pressure monitoring for 1-6 center-based visits, with HR monitors provided for all home/remote telemedicine visits.	ECG telemetry and resting and exercise blood pressure monitoring for 3-6 center-based visits. Additional monitoring based on clinical indications
Patient education	28, 7-15 min audio PDFs	8, 45-60 min group lectures
Completion of individual treatment plan	At baseline; 30, 60 and 90 days; at discharge	At baseline; 30, 60 and 90 days; at discharge
Outcomes routinely assessed before and after CR, and used for iATTEND	• Nutrition: Rate Your Plate • QOL: Dartmouth COOP • Functional Capacity: MET level* • Depression: PHQ-9	• Nutrition: Rate Your Plate • QOL: Dartmouth COOP • Functional Capacity: MET level* • Depression: PHQ-9
RPE = ratings of perceived exertion; COOP = cooperative functional assessment; TM=telemedicine *Change in MET (metabolic equivalent of task) level during training from week 1 to final week of CR		

4.4. Program Operations.

One concern with any home-based CR program that periodically incorporates some form of synchronized communications might be that "the use of staffing resources per patient encounter is less efficient". To minimize potential inefficiencies in iATTEND, a schedule for HYCR at Henry Ford Main Campus will be adopted that allocates up to 4, one hour blocks of

time each day (up to 3 patients per block), with 1 hour blocks allotted to the early morning, late-morning, mid-afternoon and the early evening. This approach will provide staff coverage for up to 20 hours (4 hours per day, 5 days per week; 0.5 FTE) of HYCR each week (or up to 60 synchronized HYCR visits/week). Assuming 1 to 3 TM visits per patient per week, this allows CR staff to comfortably care for 20 HYCR patients during any given week. Additionally, in concert with the Henry Ford Virtual Care Department, technology and operational solutions will be sought that allow for 2 HYCR visits to occur simultaneously with a CR staff person.

Also, since iATTEND is targeting an at-risk, urban population, another concern relative to program operations might be that our patients do not have at their disposal the equipment needed to engage in a remote synchronized video TM CR visit. During the R61 phase of the trial, focus group and administrative surveys will be used to identify strategies that best facilitate helping patients identify confirmed and regular access (via self or a "willing to assist" family member or friend) to both the technology (smart phone, tablet with internet access) and exercise equipment (elliptical, treadmill, bike) needed to exercise while using a synchronized video.

Regarding contingency plans for the few patients that might lose access to exercise equipment during the intervention period (up to 36 CR sessions), the research staff will work closely with these few patients to identify and secure a nearby and safe alternate option such as an outdoor walking path, indoor path (mall, school hallway), school track, park, or public community-center for them to conduct their planned exercise (e.g., walking) sessions regardless of the weather; this includes the identification of a partner support person to assist with safety and transportation (if needed). For the few patients for which free-walking in a community setting is needed for their exercise plan, maintaining a video link via the internet during free-walking may be difficult. For these individuals a standard audio phone call will be established while they walk. Concerning the video synchronized visits, for the rare occasion where the video link is lost due to a poor Wi-Fi connection, we will simply rely on the audio portion or connected via a standard phone call.

4.5. Adherence.

Since adherence is the primary end point for this trial (defined as the number of scheduled CR sessions completed within 6 months after starting CR), careful instruction will be provided to all staff that surrounds ensuring no differential overt or covert attempts are undertaken to overly or unduly influence attendance in either study group. A five person sub-committee of the Project Management Team (called the Subject Recruitment and Retention and Staff Adherence [SRRSA] sub-committee) will monitor the above to ensure that only normal and customary program procedures that are normally used to enhance attendance are uniformly engaged across all patients. These normal and customary procedures include (a) calling those patients who miss one or more scheduled CR appointments, (b) providing patients with a calendar of all future scheduled appointments, and (c) administratively discharging those patients that exhibit no CR appointment activity for 6 weeks.

4.5.1. *Family/Friend Involvement*

In addition to the above normal and customary, and because spouses, partners, significant others, or friend who support patients in an exercise program influence attendance, patients in both study groups will be encouraged to bring such a person(s) to the orientation session/first CR session and this person will be viewed and relied upon as a primary source of social support.

4.5.2. *Logistical Assistance and Incentives.*

Patients will be thoroughly interviewed and screened to identify potential barriers to adherence. The study coordinator will ensure that participants have sufficient logistical assistance to attend the screening visits, baseline testing, CR sessions, and follow-up visits. Common barriers/issues that impact attendance will be addressed for resolution per standard CR program practices (equally in both study groups) and include the following; (a) transportation (countered by use of alternate transportation strategies such as Lyft, taxi, and GoRide), (b) return to work conflict (countered by requesting initial part-time or temporary flexible hours), and (c) family care needs (countered by identifying home support person(s) to assist with such and offering convenient hours of operation).

No structured system for providing patients with incentives to attend CR sessions will be used. To facilitate delivery, all patients HYCR will be given a chest strap/wrist HR monitor; patients in HYCR that are scheduled to attend less than one CR session per week will also be given a home blood pressure monitoring unit. Gas cards will be made equally available to patients in both study arms to facilitate retention to scheduled study baseline and follow-up appointments.

4.6. Retention

Retention for iATTEND is defined as compliance with scheduled testing sessions (baseline and follow-up visits 1 and 2), as well as compliance with scheduled follow-up telephone calls with the study coordinator (at months 2 and 4 after completing CR). A main reason for the telephone calls at months 2 and 4 of follow-up is to facilitate continued subject retention/engagement in the trial. The coordinator will remind patients about their scheduled follow-up visit 2 (at 6 months). Also, the coordinator will equally speak with subjects in both groups about any barriers/issues they might be experiencing relative to proper self-care or disease management behaviors, and assist with resolution strategies using an open, problem-solving approach. Subjects that are administratively "dropped" from CR will still be contacted and scheduled to complete follow-up testing visits 1 and 2.

Relying on data provided by the SRRSA, the PMT will regularly review reports detailing subject retention to follow-up testing and telephone calls and in conjunction with the Steering Committee, enact measures (telephone calls by research and clinical staff, email, and U.S. mailed letters) to help ensure fidelity to the specified protocol for testing. Project budgeted gas cards ($10 each) can be provided to help defray subjects' travel costs associated with baseline testing and follow-up visit 1 and 2 testing.

The SRRSA sub-committee will (a) track and report on project issues that impact patient retention to the above testing events and follow-up telephone calls, as well as (b) staff compliance to protocol procedures. The later includes the SRRSA committee periodically (every 6 months) conducting shadow-evaluations (using video and observation) of CR staff for the uniform conduct of patient assessments and the uniform delivery of CR per protocol standards.

4.7 Drop outs.

4.7.1. *Drop out recovery.*

Relative to study retention, the following definitions will be applied:

1. *Integrated* subjects are those attending all appointments as scheduled, or re-scheduling any missed appointments or cancellations
2. *Poorly compliant* subjects are those who cancel, do not show and fail to reschedule 2 of their 4 follow-up responsibilities (follow-up visit 1 or 2 and telephone encounter 1 and 2).
3. *Refusals/drop-outs* are those that state, in no uncertain terms, that they do not want to participate any longer in the trial, and refuse any further contact with study staff.

iATTEND will use a systematic approach in an attempt to recover poorly compliant subjects, especially those that either (a) inquired about or expressed interest in dropping or (b) or appear to be "moving toward" dropping out based on poor compliance data. Since most drop outs are due to life changes (e.g., divorce, illness of family member, change in jobs) and/or misunderstandings with research staff, a planned recovery approach will be used that addresses the following.

1. Be sure that subjects are NOT pushed to the point that they refuse to participate/all contact
2. Stay in touch with the patient though email, phone calls or being present at planned clinic visits they may have with their physicians. All of this is aimed at showing support, as well as provides an opportunity to garner subject concerns such that problem solving and barrier resolution techniques can be applied to I prove participation.
3. To foster continued, planned contact with the research staff… even if it is something as simple as to schedule another contact on a specific day and time.

Engaging patients at risk for dropping out using barrier identification and problem resolution techniques is a dynamic endeavor that also can vary with time, especially among those subjects where challenging life circumstances (e.g., transportation, work, family care) change improve… such that it then becomes more feasible for them to re-engage in the project.

4.7.2. *Other important* d*rop out recovery considerations.*

A. Attempts to re-integrate a participant should be discontinued as soon as an adamant refusal is communicated.

B. A patient will be considered "lost to follow-up" only after all means of contact have failed. The status of the patient at the last visit or contact will be used for the final analysis. The vital status of these patients will be followed by appropriate national database.

C. For patients that formally withdraw consent, vital status will be followed by appropriate national database.

4.8. Subject Follow-Up

After completing CR or a subject's last CR visit, follow-up visits 1 and 2 will be scheduled, the former scheduled within 10 days of last CR visit and the latter scheduled at 6 months ± 15 days after last CR visit. Data collected at follow-up visit one will be nearly the same as that gathered during baseline. This includes both QOL instruments (Dartmouth COOP, EQOL), a CPX test, the 6MW, PHQ-9, Rate your Plate, and 5x sit-to-stand. Data collected at follow-up visit two includes both QOL instruments (Dartmouth COOP, EQOL), a CPX test, the 6MW, PHQ-9, Rate your Plate, and frailty assessment.

Table 4. Schedule of Trial Events and Time line

Patient Care Event	**Screening and Baseline**	**Weeks 1-26 or CR visits 1-36***	**F/up visit 1 within 10 d after last CR visit**	**2 mo after last CR visit**	**4 mo after last CR visit**	**F/up visit 2 at 6 mo after last CR visit**
Testing						
CPX	X		X			X
6MW	X		X			X
Dartmouth COOP	X		X			X
EuroQOL-5D	X		X			X
Rate your plate	X		X			X
Mini-cog	X					
5x sit-to-stand	X		X			X
iPAQ	X		X	X	X	X
PAST	X		X	X	X	X
Training						
Exercise sessions		X				
Telephone calls				X	X	

*Patients will have 6 mo to complete 36 visits; iPAQ=International Physical Activity Questionnaire; PAST = Past-day Adult Sedentary Time Questionnaire

5. Trial Endpoints

5.1. Primary endpoint

R61 Phase. In conjunction with study investigators, stakeholders, and NHLBI staff, prepare and operationalize a clinical trial that evaluates the effect of a HYCR program on attendance to CR. This includes finalizing the protocol, obtaining any institutional review board approved amendments, developing the manual of operations, establishing data safety monitoring board, hiring and training CR and research staff, and demonstrating the ability to screen and enroll patients into the trial.

R33 Phase. The number of CR sessions completed within 6 months

5.2. Secondary Endpoints.

R33 Phase only.

1. Percentage of patients completing 36 CR sessions within 6 months

2. Change in exercise capacity upon completion of CR

    a. Peak VO_2

    b. Six minute walk distance

3. Change in quality of life upon completion of CR

4. Exploratory endpoints

    a. Change in exercise capacity at 6 mo after completion of CR

        i). Peak VO_2

        ii). Six minute walk distance

    b. Change in quality of life at 6 mo after completion of CR

    c. Change in sedentary behavior and physical activity habits (home, work, recreation), the latter of which does not include exercise in CR

    d. Economics and resource utilization associated with of CR.

    Home- or hybrid approach to CR (with or without telemedicine) is often viewed as a "negative" financial business model due to lack or revenue (and increased patient care expenses and staff time). The cost effectiveness, economics and resource utilization of the HYCR program will be determine and compared to the similar data for CBCR. In both CR models we will collect and calculate costs associated with program implementation (staff time, HR monitors, and upgrading desk tops for telemedicine) as gathered from both administrative data within the CR unit and from the Health System's Corporate Accounting/Financial Services Department. We will also collect costs from participants at follow-testing, including direct nonmedical and medical costs (including value of time of the participants attending a program, waiting, and travel). In a subset of

our his project's full cohort, for patients insured Health Alliance Plan or Blue Cross and Blue Shield of Michigan, we will identify and compare reimbursement and health care utilization during CR and for the 6 month period of time after CR is completed

6. Safety

Consistent with what is known today about the practice of cardiac rehabilitation, the level of incremental risk for major unexpected adverse events (death, events requiring hospitalization) that are probably related to a subject's participation in this project is anticipated to be extremely low.

6.1. Safety assessment.

Safety assessments will consist of the recording and monitoring of all safety related events. Results from patient assessments (e.g., CPX results, ECG rhythm strips [if any]) that include safety parameters performed as part of the patient evaluation or trial protocol will be maintained in the patient's research chart and considered to be source documents.

6.1.1. *Adverse and Serious Adverse Events or Experience*

An adverse event (AE) is defined as any untoward medical occurrence (new onset or change in disease state) in a patient that is unfavorable and unintended (e.g., new onset chest pain, near syncope, new onset atrial fibrillation), regardless of whether or not it is considered to be related to the intervention. A serious adverse event (SAE) is defined as any untoward medical occurrence that results in any of the following: death; persistent or significant disability/incapacity; hospitalization; stroke; fall requiring medical attention; is life threatening; or requires or is considered serious such that the patient may require medical or surgical intervention to prevent any of the previously listed events.

For the purposes of iATTEND, the project will follow all policies and procedures set forth by Henry Ford Hospital, its Office of Research Administration, and its Institutional Review Board (IRB). SAEs and AEs of interest will be collected after randomization and through follow-up visit 2 and recorded on a CRF. The project management team (PMT) will forward this safety data to the DSMB on a regular basis (e.g., quarterly), which will perform routine evaluations of such.

Additionally, although likely very rare, unexpected SAEs that are possibly attributable to rehabilitation, as determined by the trial PI (e.g., occurring during or within 3 hours after exercising), will be reported to the IRB and DSMB within 10 days of occurrence.

6.1.2. *Assessment of Actionable Events Immediately Proximal to CR*

A secondary analysis is planned of actionable events (both AE and SAE) sustained immediately prior to, during, or immediately after (during recovery) an exercise training session. These represent both major events that may require hospitalization (e.g., myocardial infarction, fall) or an emergency room visit, as well as events that often occur in CR and may lead to with-

holding a patient from starting exercise, stopping a patient from continuing to exercise, or requiring notification of the patient's a physician (e.g., symptomatic hypoglycemia requiring oral glucose supplementation, new onset or worsening angina/ischemia, falls, persistent hypotension).

7. Study Organization

7.1. Steering Committee

The Steering Committee (SC) is responsible for overseeing and maintaining the scientific and operational integrity of the project. Duties include approving the final trial protocol; overseeing the scientific direction of the trial; review and approval of case report forms, assessment questionnaires and manual of operations; review and approval of main analysis plan; review and vote on any proposed protocol amendments; review, comment on and vote on any presentations, publications or recommendations of the Publications sub-committee; and act on any recommendations from the DSMB

The SC will meet annually.

7.1.1. *Publications Sub-Committee*

A Publications subcommittee will be established, comprised of up to 4 individuals (two of which will be from the SC) who will initially meet quarterly to give direction and timelines to the expected writings, publications, presentations and pronouncements from this project. The publications committee will be responsible to review and comment on proposals for papers made by investigators, review trial press releases, approve secondary databases analyses, address any issues pertaining to authorship of publications and presentations, and ensure that NHLBI publications approval procedures are followed. It will also assist the research staff with registering the project with clincaltrials.gov and establish a schedule for the submission of trial results to clinicaltrials.gov (within 12 months after study completion).

7.2. Project Management Team (Plan)**.**

Under the guidance and leadership of the SC, the PMT will plan and implement/conduct the project in a manner that adheres to the approved protocol and manual of operations. The PMT will be established during month 1 or 2 of year 1 and meet in-person or via teleconference every 1-3 weeks. It will be led by the Project Manager (to be determined), in concert with the project PI. Any and all financial and operational issues that might require input from the full PMT will be added to the agenda for the next meeting of the PMT. The agenda will follow a standardized format for each meeting to address on-going business (screening report, enrollment report, retention report, assessments, process initiatives, and financial issues), new business, and action items.

Responsibilities for the PMT include, but are not limited to, telecommunication issues, patient education, data collection and entry, retention and adherence, maintenance of staff skills for testing, effective integration of both the center-based and hybrid programs, project

assessments, and protocol fidelity. Other PMT members will include the PI, the project's to-be-hired research coordinator, the Coordinator for CR at the Detroit campus, the registered dietician for the Detroit CR program, the hospital's Director of the Office of Performance Excellence and Quality or h/er designee, a behavioral medicine specialist, a former (recent) patient from our Detroit-based CR program, and a staff person from the System's Virtual Care Unit. *To ensure that the objectives of the trial are being met, the PMT will adopt an approach that is both proactive and rapid-response reactive*. The former approach will actively survey/identify potential "pinch-points' for trial operations (based on team planning discussions and experience gained from the years of operating CR, clinical trials in CR, and home-based CR) and design accordingly the study operations and schedule staff for the effective achievement of objectives. The latter approach (i.e., rapid-response reactive) involves both the regular review of operational report data (e.g., weekly enrollment reports, retention to follow-up testing, time elapsed between data collection and data entry) and collecting CR staff feedback on trial operations and milestone achievement. If problems are identified that threaten achievement of study objectives, the PMT will adjust trial procedures using a rapid-cycle, data-driven methodology.

7.2.1. *Subject Recruitment and Retention and Staff Adherence [SRRSA] sub-committee*

During month 11 of the project staff will begin the real-time tracking of key indicators of patient engagement in the study (e.g., adherence to testing). This will be done equally in both study groups to aid in identifying favorable/unfavorable implementation issues; it may include surveying and tracking the adoption and acceptability of changes to CR delivery by staff and patients, as well as assessing sustainability of the over-all model. A sub-committee of the PMT (called the *Subject Recruitment and Retention and Staff Adherence [SRRSA] sub-committee*) will be convened and charged with the above duties, as well as track, report and help intervene on other global project issues such as: ensuring convenient hours for testing, ensuring available hours for delivery of both CBCR and HYCR, ensuring equivalent delivery of educational content, and the timely completion of the patient's individual treatment plans. The SRRSA will also periodically (every 6 months) shadow-evaluate (using video and observation) CR staff for the uniform conduct of patient assessments and the uniform delivery of CR per protocol standards. Finally, the SRRSA committee will conduct a systematic, standardized rapid-cycle review of any patient (from either study group) that did not complete follow-up visit 1 testing or follow-up visit 2 testing. Learnings gathered from such will be applied to in a manner to avoiding future retention issues.

7.3. Data Safety Monitoring Plan/Board (DSMB) (See also Appendix A for additional details)

The Data Safety Monitoring Board (DSMB) for this trial will be an "internal DSMB", comprised of 4 individuals that are independent of the NHLBI, trial investigators and trial management. The NHLBI will approve the membership of the DSMB and the DSMB serves in an advisory capacity to both the NHLBI and the trial's Steering Committee. The DSMB will be comprised of two senior staff from within Henry Ford Health System, one of which will be a senior physician-scientist with NIH funding and the other will be a clinical cardiologist experienced with clinical trials from the Division of Cardiovascular Medicine (who will also serve as chairperson). The third DSMB member will be an external (to HFHS) cardiac

rehabilitation professional (clinical exercise physiologist) that is actively working in the field of CR. The fourth member will be a biostatistician (other than Dr. Peterson) from the HFHS Department of Public Health Sciences. It will be the responsibility of the study coordinator and project manager, in conjunction with the Dr. Keteyian, to ensure that unexpected SAEs associated with exercise training (defined as occurring during or within 3 hours after exercising) will be reported to the IRB and DSMB within 10 days of occurrence. The DSMB will meet bi-annually, of which a portion of each meeting will be with study investigators.

The primary endpoint for this study is number of CR sessions attended (versus a clinical endpoint such as death or re-hospitalization); therefore, the DSMB will not have to address the issue of trial continuation relative to clinical endpoint futility. All subjects will be evaluated for the specified duration of the trial for all primary and secondary outcomes measures. A subject's participation in the trial can also be stopped upon their formal request for withdrawal. The number of subjects that withdraw consent from trial participation will be tracked and reported to the DSMB.

The monitoring for unexpected major SAE's, as well as patient withdrawals, will occur continuously through the study by the project manager and research coordinator. The DSMB will meet every six months during the trial, and at the end of the trial, to review all trial-related reports and study findings. All records of AE and SAE will be available to the DSMB chair and the entire DSMB at any time, upon request.

All relevant unexpected and major SAE that occur during or within 3 hours after exercise will be collected, summarized and reported within 10 days to the local IRB and to the DSMB. Although the occurrence of these SAE's is extremely rare in the CR setting, any such events that do occur will be investigated and discussed jointly between the principal investigator and the DSMB or its chair. Any policy or procedural changes that arise from such discussion will be incorporated into a revised study protocol. Subjects that withdraw consent from trial participation will also be tracked by the study coordinator and reported to the DSMB.

The primary and secondary analyses will be conducted by Dr. Peterson (biostatistician) from Public Health Sciences and he will possess a copy of the treatment codes for randomization.

8. Data Management

8.1. The data needed to test the primary hypothesis from this proposed project will be gathered from 270 subjects. The final data set will be comprised of demographic and clinical data gathered from questionnaire, electronic medical record, clinical CR care, and laboratory assessments. The three main time points for laboratory assessments are upon entry in to the trial, immediately after the patient completes CR (follow-up visit 1), and at 6 months after completing CR (follow-up visit 2). The primary outcome measure is attendance to CR; secondary outcome measures are quality of life and exercise capacity.

Data from the above mentioned sources will be collected on case report forms (CRFs) and entered in an ongoing manner (and within 2 weeks of collection) by the research assistant or staff from the Henry Ford Clinical Exercise Physiology Core Laboratory, and they will follow entry and validation processes that are consistent with the Health System's Department of Public Health Sciences (Research Informatics Unit). Study data will be collected in and then managed using REDCap (Research Electronic Data Capture, Vanderbilt University, Tennessee) electronic data capture tools (90). A thorough, study-specific data dictionary, defined by all members of the research team in an iterative, self-documenting process, will be compiled. The baseline data form and the final visit (follow-up visit 2) data forms will require the signature of Dr. Keteyian.

The final data base will be stripped of identifiers (de-identified) and secured and hosted on a HIPAA-compliant server managed by the Department of Information Technology at the Corporate Data Center of Henry Ford Health System. REDCap will be used for generating the shared dataset. It will be used to remove identifiers, export data in a format that SAS can read, and create the SAS code needed to read the data in SAS. REDCap will also export PDF's of the case report forms and the data dictionary (codebook). The data base will be made available to the NHLBI. It will also be made available to others (upon request), under the auspices of a data sharing agreement that includes a commitment to (a) use the data for research purposes only, (b) not attempt to identify any one individual, and c) secure the data using appropriate computer technology and back-up. The dataset (and an accompanying data dictionary and other documentation) will be prepared to share in accordance with NHLBI data repository requirements, and consistent with other repository (BioLINCC) and NHLBI policy requirements.

9. Manual of Operations

A manual of operations (MOO) will be developed for all key aspects of the trial and will provide objectives, scope, design and operational policies and procedures beyond that spelled out in this clinical protocol. The manual will detail instructions for completing CRFs (e.g., baseline medical history data), baseline and follow-up questionnaire and clinical assessments, retrieval of primary endpoint data, and exercise training in CBCR and HYCR. The MOO will detail the follow-up testing/assessment schedule and survey tools, the follow-up phone calls to be completed at 2 and 4 months after completing CR, trial level contact information, and data queries. With regards to the CPX test and the 6 min walk test, quality assurance assessments/training, data handling/transfer, and any variable-specific data calculations or manipulations will be addressed in the existing manual of operations/procedures found within the CPX Core lab.

10. Statistical Analysis Plan

Dr. Peterson (biostatistician) will oversee and conduct the data analysis for this trial. He will also assist with the development of enrollment and retention reports sent to the NHLBI and will also assistant with preparing materials for the DSMB meetings that are held every 6 months.

10.1. Randomization Procedure

Using computer generated randomization, the randomization process will be stratified by race and sex and blocked to ensure balance at random accrual points. Lists were compiled for the 4 sex-race specific strata. As new participants are added to the study they will be assigned the next available treatment assignment (CBCR, HYCR) based on the lists provided. The project manager will be responsible for treatment assignment as all other staff involved in the study will be blinded as to the randomization lists to avoid bias.

10.2. Sample size and power calculations.

We propose to enroll a total of 270 patients evenly randomized into two groups of 135 patients each. To determine power for **Hypothesis 1**, we will use a Student's t-test approach. From recent data from our administrative CR data base, we believe that the CBCR group will complete 21 ±13 (mean + sd) visits over the course of the study. The test, with a two-sided 0.05 alpha level, will have 80% power to detect an increase of 4.5 visits. We believe this to be a clinically significant difference (5).

Also, for **Hypothesis 2**, our recent administrative data indicates that 24% of patients in our CBCR program complete 36 visits. A chi-squared test with a two-sided 0.05 alpha rate and 135 subjects per group will have 80% power to detect an **increase to 39.8% or more in the HYCR group** (effect size=15.8 percentage point increase).

Hypothesis 3, 4 and 5 require longitudinal measures six months after CR is completed, so it is possible that some lost to follow-up will occur at follow-up testing point number 2. If we assume that no more than 20% will be lost, our sample size for this analysis will be at least 108. We anticipate a standard deviation of the change in meters walked in the 6-minute walk to be 107 meters (based on data from the Henry Ford Core Exercise Laboratory) When the sample size in each group is 108, a two group 0.05 one-sided t-test will have in excess of 90% power to reject the null hypothesis that the CBCR and HYCR groups are not equivalent (the difference in means is 50 meters or farther), in favor of the alternative hypothesis that the means in the two groups are equivalent.

The measured of peak VO_2 should have a standard deviation near 6 (86). With a sample size of 108 per group, a two-group one-sided t-test will have greater than 80% power to reject the null hypothesis that the CBCR and HYCR groups are not equivalent (the difference in means is 2.0 mL/kg/min or farther), in favor of the alternative hypothesis that the means in the two groups are equivalent.

Based on Campbell, et al. (87), we anticipate that the standard deviation of the Short Form Health Survey (SF-12) physical component summary will be 22 and the mental component summary will be 18. When the sample size in each group is 108, a two-group 0.05 one-sided t-test of the physical component scale will have 80% power to reject the null hypothesis that the

CBCR and HYCR are not equivalent (the difference in means is 7.5 or further from zero in the same direction), in favor of the alternative hypothesis that the means of the two groups are equivalent. The power for the mental component summary will exceed 90%.

10.3. Data Analysis Plan.

Data analysis will begin with prepatory activities such as checking for complete data entry, identification of outliers, and other such data cleaning tasks. Once the above tasks are completed, the data base will be "locked" for analyses. The Statistical Analysis System, (SAS, version 9.4) will be used for data analysis. A detailed descriptive analysis of all quantitative data will be performed involving the summarization of data and the use of inferential and graphical exploratory analytic techniques. The information obtained from this preliminary investigation will be used to: 1) describe univariate and bivariate sample distributions of the data; 2) identify the interrelationships between variables (i.e., need for covariate adjustment); and 3) check for violations of assumptions underlying identified statistical techniques (e.g. independence, linearity, homoscedasticity, normality). In the event that statistical assumptions are severely violated, data transformations or nonparametric methods will be employed. An intention to treat approach will be utilized for all analyses. For hypothesis 1 the number of visits completed before lost to follow up will be used and for hypothesis 2 a yes/no response will be generated based on the observed data.

R33- Primary Aim*: Assess the effect of a HYCR program on over-all patient attendance*

For the **Primary Hypothesis** (number of sessions completed), if the distribution of the number of sessions completed is normal then a Student's t-test will be used for comparison of the two groups. In the likely event it is skewed a two-sample Wilcoxon with a Fligner-Policello correction for unequal variances will be used. **Hypothesis 2** (percentage of patients completing 36 CR sessions) will be addressed using a Chi-squared test for comparison of proportions.

R33- Secondary Aim: Assess the effect of HYCR on exercise capacity and quality of life.

Hypotheses 3 and 4 (both address measures of exercise capacity) and **Hypothesis 5** (QOL) all involve assessing if the two group responses are equivalent. A two one-sided test approach will be used to demonstrate equivalence between the two groups.

There are several identified **exploratory aims** for this project, including but not limited to:

(a) short-term (6 month) retention of CR-related outcomes [e.g., exercise capacity, QOL, and self-engaged (not CR) purposeful exercise and total physical activity habits]

(b) program cost effectiveness.

Analyses of the exploratory aim associated with the short-term retention of CR-related outcomes will be analogous to the analyses described above, such that Student's t-test, Chi-squared tests or their nonparametric alternatives will be utilized.

Concerning cost effectiveness, we have included it as an exploratory aim because some view a home- or hybrid approach to CR (with or without telemedicine) as a "negative" financial business model due to lack or revenue (and increased patient care expenses and staff time). The cost effectiveness of the HYCR program will be explored to determine the cost differential between the two CR approaches. In both CR models we will collect and calculate costs associated with program implementation (staff time, HR monitors, and upgrading desk tops for telemedicine) as gathered from both administrative data within the CR unit and from the Health System's Corporate Financial Services Department. We will also collect costs from participants at follow-testing, including direct nonmedical and medical costs (including value of time of the participants attending a program, waiting, and travel). In collaboration with our colleagues at both Health Alliance Plan and Blue Cross and Blue Shield of Michigan, the two Michigan–based insurers that agree to cover hybrid CR for their subscribers in this project, we also have the unique opportunity to partially track and compare the potential impact of HYCR and CBCR on health care utilization and costs during the 6 months after CR is completed (and afterwards).

Finally, the CR-outcomes and behaviors that Henry Ford normally assesses before and immediately after CR (e.g., Rate Your Plate, Dartmouth COPOP for QOL) will again be assessed at the 6 month post-program follow-up 2 visit (for short-term retention). In addition, reasons for stopping program attendance before completion of the study recommended 36 visits will be gathered from all subjects for subsequent secondary analysis.

11. Institutional Review Board and Ethics and Good Clinical Practice

This study must be carried out in accordance with the approved protocol and all Henry Ford Health System and study operating procedures. Compliance with such protocols and procedures will ensure adherence to good clinical practice.

Before implementing the study, the final protocol, the proposed informed consent and other subject information documents must be reviewed and approved (initially and then annually) by the System's Institutional review Board (IRB). A signed and dated document that the protocol and informed consent have been approved by the IRB must be in-place before study initiation. Any amendments to the protocol, other than administrative, must be approved by the IRB.

11.1. Informed Consent (IC)

The principal investigator or his designee must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procerus involved, the

expected duration, the potential risk and benefits involved and any discomforts it might entail. Each subject must be informed that participation is voluntary and that s/he may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent treatment or relationship with their treating physician.

The IC should be given by means of standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating, and should be given a copy of the signed document. If written consent is not possible, oral consent can be obtained if witnessed by a signed statement from one or more person not involved in the study that mentions why the patient was unable to sign the form. No patient can enter the study before his/her IC has been obtained.

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Appendix A

DATA SAFETY MONITORING PLAN

The data safety monitoring plan will adhere to all policies and procedures set forth by Henry Ford Hospital, its Office of Research Administration, and its Institutional Review Board (IRB). Additionally, all defined unexpected adverse events and unanticipated problems will be reported to the system's IRB, data safety monitoring board (DSMB), and other applicable regulatory agencies.

To help ensure subject safety, the following procedures will be followed:

a) Based on review of the System's EMR and/or in-person interview/examination with study staff, potential subjects will be carefully "screened-out" during the trial's screening processes for known contraindications to exercise testing and exercise training (e.g., receiving continuous inotropic support therapy).

b) All study-eligible subjects will complete a symptom-limited graded cardiopulmonary exercise (CPX) test at baseline, prior to randomization. This test has the ability to identify and screen patients for rare exercise-induced contraindications to exercise training (e.g., abnormal blood pressure response, significant dysrhythmia).

Concerning home-based CR, it is important to emphasize that most all patients that participate in center-based programs today are already asked to "exercise on their own on non-rehab days"; therefore, this study is mainly giving some structure and supervision to that recommendation.

c) All subjects will also attend at least one exercise session in center based CR, during which their gait, balance and stability on their preferred exercise modality will be evaluated to ensure the patient will be safely able to use the equipment on their own.

d) Published guidelines for prescribing exercise in the CR setting will be followed, such as progressing exercise duration and frequency before intensity, reinforcing proper warm-up and cool down procedures, the periodic screening for exercise-related signs or symptoms, and progressing and maintaining exercise training intensity to stay within prescribed levels based on heart rate or rating of perceived exertion.

e) At the beginning of each remote telemedicine CR session, we will document the patient's exact current street address/location (e.g. home, community fitness center, workplace), for the rare instance that an untoward event occurs that requires intervention by emergency medical services.

<u>The Data Safety Monitoring Board (DSMB).</u> For this trial the DSMB will be an "internal DSMB", comprised of 4 individuals that are independent of the NHLBI, trial investigators, and trial management. The NHLBI will approve the membership of the DSMB and the DSMB is advisory to the NHLBI and the trial's Steering Committee.

The primary endpoint for this study is number of sessions attended (not a clinical outcome such as mortality). However, trial safety is always a concern. Therefore, rare, untoward, unexpected major events related to exercise training or exercise testing (i.e., during or within three hours) may occur and will be monitored, such as death or events requiring hospitalization (e.g., myocardial infarction, syncope, arrhythmia, fall). These events will be reported to both the IRB and DSMB per existing institutional and protocol requirements (i.e., within 10 days) and documented in the subject's study file.

Monitoring of events. A DSMB meeting will be held in-person (with teleconference capabilities) every six months, during which a comparison will be made of any excess, untoward events. If needed, the DSMB will advise the NHLBI and Steering Committee accordingly. Minor events, such as falls not requiring emergency care, angina, and ST segment changes during testing that are suggestive of myocardial ischemia will be documented in the subject's study file.

Relative to suspending or discontinuing a specific subject's participation in CR and/or the trial assessments due to a clinical indication (worsening symptoms, compromising arrhythmia), Dr. Keteyian will consult with co-investigators Drs. Lanfear or Nour to ensure that all applicable and relevant Henry Ford Hospital and Preventive Cardiology Unit program- and patient-level clinical policies and procedures are followed. With the subject's permission, and to assist with their care, their own physician will be contacted regarding the relevant clinical findings. The Steering Committee will be informed of the above.

Since a clinical endpoint such as death or re-hospitalization does not represent a trial endpoint or outcome measure for this project, the DSMB will not have to address the issue of trial continuation relative to endpoint futility. All subjects will be evaluated for the specified duration of the trial for all primary and secondary outcomes measures. The number of subjects that withdraw consent from trial participation will be tracked and reported.

The monitoring for unexpected major adverse events and minor events, as well as patient withdrawals, will occur continuously through the study by the project manager and research coordinator. Major events will be discussed within the project management team.

It will be the responsibility of the study coordinator, in conjunction with Dr. Keteyian, to ensure that unexpected serious/major adverse events that occur within 3 hours of exercise are collected, summarized and reported within 10 days to the local IRB and to the DSMB. Although the occurrence of an unexpected, major adverse events is not anticipated and felt to be extremely rare, any such events that do occur will be investigated and discussed jointly between the principal investigator and the DSMB or its chair. Any policy or procedural changes that arise from such discussion will be incorporated into a revised study protocol. Subjects that withdraw consent from trial participation will also be tracked by the study coordinator and reported to the DSMB.