Improving Cardiac Rehabilitation Outcomes Through Mobile Case Management (iCARE)

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RESEARCH STRATEGY

1. SIGNIFICANCE

1.1 Scope of the problem

Cardiovascular disease (CVD) is the leading cause of death in the world.[1] In developed nations such as the United States, the impact of CVD on the health of individuals and health care economics is unparalleled. In the US, ~85.6 million individuals currently suffer from CVD.[1, 2] In 2011, CVD accounted for ~790,000 deaths equating to one in three all-cause deaths and over two-thirds of cardiac-specific deaths in the US.[2] Coronary artery disease (CAD) is the most common type of CVD with an annual mortality of greater than 370,000 individuals. In 2014, ~635,000 Americans suffered from an acute coronary event with ~300,000 recurrent events in CAD survivors.[1] The direct and indirect economic burden of CVD totals more than $320.1 billion per year.[1] Because CVD is chronic, these data underscore the critical importance of defining logical, patient centered interventions which allow individual patients to manage their disease and the risk factors that lead to its development and progression. As such, improving behavioral risk factors (malnutrition, smoking, and physical inactivity) and conditions (hypertension, hyperlipidemia, diabetes, and obesity) are critical to blunting CVD/CAD associated morbidity and mortality.

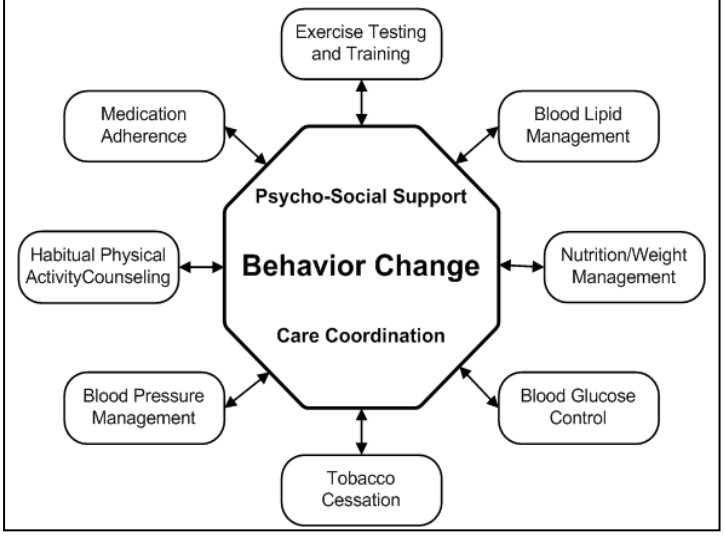
1.2 Components and Benefits of Cardiac Rehabilitation

For patients with eligible cardiac conditions **(Table 1)**, exercise based cardiac rehabilitation (CR) programs are an integral component of the standard of care. Over the past two decades, the scope of CR programs has shifted from an emphasis solely on exercise therapy to a more comprehensive multidisciplinary approach to target all risk factors and contributory conditions. To further facilitate recovery and secondary prevention in patients, this approach now encompasses wide-ranging health behavior interventions including traditional CVD/CAD risk factor reduction, habitual physical activity counseling, nutrition and weight management education, medication education, psychological and social support, as well as outcome assessment for quality improvement[3-5] **(Figure 1)**. As such, a meta-analysis of randomized trials recently demonstrated that comprehensive multifaceted CR focusing on maximizing a healthy lifestyle consistently reduces cardiovascular related mortality by 26% as well as reduces hospital readmissions.[6] This reduction in cardiovascular as well as all-cause mortality has been demonstrated by others who also report improvements in CAD risk factors, exercise capacity, psychological well-being, and quality of life.[3, 7, 8]

Table 1. Eligibility Criteria for CR

1. Myocardial Infarction
2. Acute coronary syndrome
3. Coronary artery bypass graft
4. Percutaneous coronary intervention
5. Stable angina
6. Heart valve repair/replacement
7. Ventricular Assist Device
8. Heart or heart/lung transplant

Figure 1. Components of Comprehensive CR



Based on the overwhelming evidence that participation in CR programs reduces morbidity and mortality, and in alignment with Class 1 clinical practice guidelines recommendations, the referral to such programs is now a primary performance measure for patients with CVD as recommended by the American Heart Association and American College of Cardiology.[9] Specifically, these performance measures state:

1) All eligible patients with acute coronary syndrome or whose status is immediately post coronary artery bypass surgery or post-percutaneous coronary intervention should be referred to a comprehensive outpatient cardiovascular rehabilitation program either prior to hospital discharge or during the first follow-up office visit *(Class 1 Recommendation / Level of Evidence: A)*.

2) All eligible outpatients with the diagnosis of with acute coronary syndrome, coronary artery bypass surgery, percutaneous coronary intervention *(Class 1 Recommendation / Level of Evidence: A)*, chronic angina *(Class 1 Recommendation / Level of Evidence: B)*, and/or peripheral artery disease *(Class 1 Recommendation / Level of Evidence: A)* within the past year should be referred to a comprehensive outpatient cardiovascular rehabilitation program.

In addition to the aforementioned positive outcomes associated with participation in CR, these programs have been shown to be highly cost-effective. Specifically, Ades and colleagues demonstrated that, following myocardial infarction, CR was more cost-effective than lipid lowering pharmacotherapy, thrombolytic therapy, and coronary artery bypass surgery.[10] Further, Levine et al. showed that CR participation following myocardial infarction or coronary artery bypass surgery decreased hospitalizations from 16 to 11 days, increased the rate of return to work from 38% to 53%, and resulted in an overall cost savings of $12,000 per participant over the course of 5 years of follow-up.[11] Finally, Oldridge et al. demonstrated that a 12-week CR program reduced medical costs by $739 per patient over the course of 21 months of follow-up.[12] These data clearly demonstrate the cost-effectiveness of CR in addition to the reduction in morbidity and mortality, reduction in risk factors and symptoms, and improvement in quality of life.

1.3 Referral and Utilization of Cardiac Rehabilitation

While CR has overwhelmingly demonstrated its cost-effectiveness and efficacy to improve risk factors and outcomes in patients with CVD/CAD, utilization and uptake of these services remains poor.[13] While the referral rate of patients to CR programs has increased significantly over the past 10-15 years, participation rates are still suboptimal. For example, Beatty et al have reported that between 2000 and 2007 only 56% of eligible patients were referred to CR.[14, 15] Since this time, the referral rate to CR has risen dramatically to ~81% in 2012.[14] In comparison, Fang and colleagues have recently shown that the participation rate for patients referred to CR programs is as low as 34.7% after hospitalization for acute myocardial infarction.[16] Clearly this participation rate is dramatically lower than the referral rate and thus despite the improved referral rates, a large percentage of patients are not participating in CR and are not gaining the critical benefits CR can provide with regards to reductions in morbidity, mortality, risk factors, and improvements in quality of life.

The underlying reasons for lack of participation and engagement have been examined and as such, for patients referred to conventional center-based CR programs, a number of barriers to participation in these programs have been acknowledged **(Table 2)**.[17-19] Many of the barriers have been identified as personal/patient oriented, medical, and/or healthcare system-related factors including employment conflicts, lack of transportation, geographic accessibility, and financial constraints, for example.[13, 17, 18, 20] Consequently, the lack of participation in CR likely contributes to the ~300,000 recurrent events yearly in CAD survivors.[1]

Table 2. Patient Barriers to CR Participation

1. Distance/Travel
2. Employment Factors – limited time off / self-employment / loss of salary / lack of employer provided benefits
3. Lack of transportation
4. Female sex
5. Older age
6. Racial/Ethnic minority group
7. Lack/Limited insurance coverage
8. Cost / Financial constraints
9. Low educational attainment
10. Low self-efficacy
11. Low health literacy
12. Lack of social support

Importantly, with increased referral and attempts to maximize participation rates, system-centered obstacles may pose additional challenges[18, 21, 22]. For example, Pack and colleagues recently examined individual CR program capacity and perceived obstacles to program growth to meet patient demand[23]. These authors further estimated national service utilization and potential capacity for delivering CR services. A critical finding of this work was that, on a national level, even with the most optimistic expansion of existing center-based CR programs, only about half of eligible patients could receive CR program services[23]. While this capacity limitation has several critical implications for CR program nation-wide, these findings highlight the importance of developing additional/alternative CR delivery strategies to meet patient needs that do not require patients participate center-based programs to receive the benefits of CR.

In a recent American Heart Association Presidential Advisory on the Referral, Enrollment, and Delivery of Cardiac Rehabilitation/ Secondary Prevention Programs at Clinical Centers, Balady and colleagues highlight barriers to CR participation and outline a progressive plan to expand on the conventional center-based

rehabilitation offerings **including novel methods such as the incorporation of internet-based technologies for providing services to individuals unable/unwilling to attend center-based programs.**[18] In particular, these authors point out that the boom of mobile technology and widespread access to Internet services in recent decades has served to revolutionize the process of communication and information transfer. As such, from a CR program delivery stand-point, the Internet has the potential to favorably affect the delivery of virtually all core components of cardiovascular risk reduction interventions.[18] Thus, recent advances in information and communication technologies such as Internet and smartphone access have shown great potential to bridge the gap between CR programming and patient access to services.[24] Mobile health (mHealth) options allow for implementation of personalized healthcare programming designed to meet needs of individual patients who would benefit from CR. These solutions allow patients to remotely engage with CR staff, access educational content, socially interact with other patients, record vital statistics, and track progress all within a secure environment.

This proposal will provide critical information on the use of mHealth remote CR case management technology as a new clinical care tool to improve access to, utilization of, adherence to, and completion of CR in an effort to reduce modifiable risk factors and improve patient-centric outcomes.

2. INNOVATION

Anderson and colleagues recently published a systematic review examining home-based compared to center-based cardiac rehabilitation models.[25] These authors report on mortality, exercise capacity, and health-related quality of life. In patients after myocardial infarction, revascularization, or those with heart failure, home- and center-based CR models appear to be equally effective in improving both clinical and health-related quality of life. Importantly, these authors report that the patient's choice to participate in conventional CR may reflect the availability (location) of programs as well as patient preference.[25]

These findings are an extension of a previously published systematic review by Taylor et al. who also examined home-based compared to center-based cardiac rehabilitation models.[3] Taylor and colleagues reported on a number of CVD risk factors including blood pressure, cholesterol, exercise capacity, smoking cessation among other risk factors as well as mortality and health-related quality of life. These authors found that home-based cardiac rehabilitation is equally effective for improving clinical and health-related quality of life outcomes when compared to conventional center-based cardiac rehabilitation programs.[3] However, acknowledged by the authors, this systematic review included broad heterogeneity amongst the intervention strategies in the home-based CR group including follow-up visits, letters or telephone calls from staff, or at least self-monitoring diaries. Unfortunately, in this review, there was no mention of internet- or mobile-based case management or CR delivery methods. While these findings are in support of the continued expansion of home-based programs, it is clear that additional research is needed on the efficacy of internet- mobile-based delivery methods.

Most recently, our group was part of the development of a scientific statement put forth by the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR), the American Heart Association (AHA), and the American College of Cardiology (ACC) on home-based cardiac rehabilitation[26]. Importantly, this statement specifically calls for the development of integrated practice units that can provide counseling via in-person visits or through web-based and mobile applications, telephonic coaching, handheld computer technologies, or the internet. In particular, this statement highlights three specific studies which prominently included technology in their interventions[27-29]. In each of these studies, adherence, exercise capacity, and health related quality of life was equal to or better than with center-based CR. These findings justify the need for a truly comprehensive, internet-based, mHealth CR case management platform which can be individualized to the needs of the specific patient in an effort to overcome barriers to participating in the critically important CR services. However, as the scientific statement points out, more research is needed to determine the impact of technology assisted CR on program enrollment, adherence, and outcomes.

As outlined in the Institute of Medicine's 100 Initial Priority Topics for Comparative Effectiveness Research, there is a critical gap in studies which "Compare the effectiveness of different quality improvement strategies in disease prevention, acute care, chronic disease care, and rehabilitation services for diverse populations of children and adults". This is echoed by the Agency for Healthcare Research and Quality in their Research Funding Priorities and Special Emphasis Notices in their "Interest in Research on Healthcare Delivery System

Affordability, Efficacy, and Quality" which outlines the need for alternative methods of delivering healthcare interventions and identifying systems which improve performance of existing interventions. Electronic and/or mobile case management platforms can extend effective CVD/CAD secondary prevention programs to more people and promote long-term engagement which may improve long-term outcomes and enhance patient satisfaction. However, as noted by Taylor et al., many questions remain regarding the impact of mHealth apps in larger populations, whether mobile apps will have long term efficacy, and how to integrate mobile apps into the health system.[3] Devie et al. suggest the current evidence around the efficacy of internet based rehabilitation programs has demonstrated mixed results largely due to small sample sizes, limited objective metrics, and short duration.[4] Further unanswered questions in this area center on the ability of internet based mHealth remote CR case management platforms to positively modify quantifiable metrics (such as CVD/CAD risk factors) over the time course similar to that seen with conventional center-based CR.

Thus, **two specific gaps in the current evidence persist**; **1)** the disparity between patient enrollment into center-based CR and actual patient participation/adherence to CR programming and **2)** the ability of mHealth remote CR case management to affect change in CVD risk factors and patient centered outcomes. Therefore, this proposal is innovative because it will provide critical data on the practical utility of mHealth remote CR case management alone or in addition to conventional CR on participation and adherence as well as efficacy on functional and patient-centric outcomes.

This proposal is innovative for the following reasons:

1. To our knowledge, no other study as reported assembling and utilizing a stakeholder advisory panel including patients, staff, and clinic leadership to inform the development of a novel research strategy to improve CR delivery and patient outcomes.
2. We will incorporate a prospective, three-arm, randomized controlled trial to examine the impact of a novel CR delivery model among groups of patients who are often studied in isolation or in retrospect.
3. We have identified and will address specific critical knowledge gaps necessary for the continued strategic development and subsequent clinical implementation of mHealth CR remote case management.
4. We will collect essential data necessary to answer high priority questions posed by multiple national organizations on the topic of alternative methods for delivering proven healthcare interventions.

For these reasons we believe our overall goal, aims, and hypotheses are directly aligned with the NIH criteria emphasizing innovation, impact, and significance. More specifically, this proposal is directly responsive to this Program Announcement as it tests novel strategies to increase access and adherence to CR while addressing both clinically important and patient-centric outcomes.

3. APPROACH

3.1 Research Team and Key Stakeholders

A noteworthy component necessary for the successful translation of this research to clinical practice is the development of an advisory panel who will inform the research program. With this, we have already engaged several groups of stakeholders throughout the development of this proposal. The key stakeholders outlined below have and will continue to play critical roles in the preparation, implementation, dissemination, and practical application of the proposed research. Specifically, we will assemble a stakeholder advisory panel which will convene two times per year for the duration of this study to ensure appropriate representation of the stakeholder groups. This will allow us to conduct the most patient-centric, outcomes driven research program possible which will inform key clinically important decision gaps and allow us to provide the most

Figure 2. Research Program Stakeholder Advisors

relevant treatment options for patients. Specific stakeholder engagement throughout the research design, implementation, and dissemination are described in sections below and highlighted in **Figure 2**. These stakeholders will continue to be engaged and provide feedback throughout the continued refinement of the mHealth remote case management platform.

Patients: Patients referred to cardiac rehabilitation often engage staff members in an effort to identify ways to reduce barriers to participation in CR while also minimizing the burden on their social network and allowing them to maintain employment. A number of patients have been involved with this proposal from the time of conceptualization and have expressed interest in continued participation through involvement with the Stakeholder Advisory Panel. Six individual patients will be appointed to the Stakeholder Advisory Panel (two from each study arm). As the program continues, new patients will be rotated onto the Advisory Panel to ensure new concepts and ideas are integrated into the knowledge base while maintaining overlap with previous patient advisors to ensure knowledge retention of the Panel and continuity of thought.

Core Research Team: The research team consists of a scientist, physicians, and statistician each with a deep vested interest in the success of CR and its continued development and broader dissemination to underserved populations. Two representatives from the core research team will be appointed to the Stakeholder Advisory Panel.

Clinical Support Staff: As part of the cardiac rehabilitation clinical support staff, exercise physiologists and nurse specialists work daily to provide the best possible care to all patients referred to and participating in CR. These staff members work continuously to find novel ways to engage patients to ensure positive outcomes. Two representatives from the clinical support staff will be appointed to the Stakeholder Advisory Panel.

Clinical Leadership: The Mayo Clinic cardiac rehabilitation program has a long history of studying innovation in CR dating back to the inclusion of heart failure patient in CR.[30] This extensive experience in CR clinical leadership is particularly relevant for the current application. Specifically, our group has previously examined the impact of CR on patient outcomes and readmission which demonstrated that CR participation is associated with a markedly reduced risk of readmissions (all-cause, cardiovascular, and non-cardiovascular) and death (all-cause) after incident myocardial infarction.[31] Further, we have provided leadership on the role of cardiac rehabilitation following acute coronary syndromes, percutaneous coronary interventions, coronary artery bypass surgery, valve surgery, chronic angina, as well as examining referral and participation rates, process monitoring, and quality improvement in the United States and around the world.[23, 32-38]

The cardiac rehabilitation clinical leadership team includes the Medical Director (past President of the American Association of Cardiovascular and Pulmonary Rehabilitation, past Director of the Cardiovascular Health Clinic at Mayo Clinic, and current Vice-Chair of the American Heart Association Council on Clinical Cardiology) and the Program Director (past Assistant Director of the Cardiovascular Health Clinic at Mayo Clinic). One representative from the Preventive Cardiology Clinical Leadership Team will be appointed to the Stakeholder Advisory Panel.

Division Leadership: The Mayo Clinic Division of Preventive Cardiology within the Department of Cardiovascular Medicine is dedicated to the development and implementation of new/alternative care delivery models which will complement the existing suit of telemedicine options for patient care activities. As part of this, an emergent need has been identified for implementation of new care management systems for patients unable/unwilling to attend center-based CR. One representative from the Division of Preventive Cardiology Leadership team will be appointed to the Stakeholder Advisory Panel.

3.2 Preliminary Studies and Protocol Development

During the preparation phase leading up to this proposal, a number of steps were taken to ensure close cooperation with all stakeholders outlined above. This cooperation included prioritizing research questions, development of research methods, development of a quality improvement project designed to better understand patient needs, best practices for caregiver delivery methods, and robustness of available technologies for use with this research program. As described below, the preparation phase was specifically designed to inform us as to how we can best serve our patients (key steps in this process outlined in **Table 3**).

Table 3: Planning Steps to Ensure Patient and Stakeholder Engagement

Activity	Stakeholder Engagement	Decision Making / Change

		Implementation
1. Determination of patient and staff interest in mHealth platform utilization	Survey conducted on CR patients and staff to determine interest and willingness to engage with mHealth platforms	Positive survey responses from both patients and staff lead to development of draft research plan
2. Determination of Department and Enterprise level interest in mHealth platform for CR	Discussions with Department and Enterprise leadership and Interactive Care Planning committee to gain feedback	Integration of patient/staff and Executive leadership feedback during development of research proposal
3. Determination of appropriate study design: Remote mHealth vs. Conventional CR	Discussion with staff, CR leadership, and Biostatistics on study design to ensure real world results	Decision to develop 3-arm study design to ensure adequate representation of combinations of CR / mHealth utilization
4. Determination of Specific Aims/Hypotheses to be tested and primary outcome variables	Discussion with thought leaders in the field, CR leadership, Biostatistics, patients, and staff on appropriateness of primary outcome variables for each aim	Determination that utilization, exercise capacity, and rehospitalization are key patient centric outcomes of interest
5. Recognition of importance of patient engagement and mHealth platform utilization	Discussion with leadership regarding ability to track mHealth platform utilization	Inclusion of platform utilization metrics as outcome measures for patients engaged in mHealth study arms

Patient and Staff Assessment: Initially our team developed a patient-facing survey to determine patient's level of interest in mHealth platforms. Considering the average age of cardiac rehabilitation patients is in the mid-60's, there was initial hesitation at the clinical provider level due to the stereotype that some patients may not have access to a smartphone with app capabilities or would not be responsive to an internet-based health platform. To our surprise, 92% of respondents to our survey suggested they would be "interested in engaging with a mHealth platform outside the clinical setting". With this, we also conducted a staff-facing survey to determine the interest/willingness of cardiac rehabilitation staff members to engage with an online mHealth platform for remote case management. The results were again exceedingly positive with 98% of staff members "willing to use a mHealth platform for patient care" and 94% of staff members stating that "the addition of a mHealth platform would not result in significant increase in clinical burden" beyond the initial training period.

Technology Assessment: With such positive results from both the patient and staff perspectives towards the implementation and utilization of a mHealth platform, the CR leadership began a multi-faceted pilot program to thoroughly vest platforms from multiple vendors. This included vendor presentations, committee meetings, staff and patient feedback, and ultimately the selection of three platforms which would undergo pilot testing in the clinical practice as part of a quality improvement project. Each of these three platforms was tested by 10 patients during their conventional center-based cardiac rehabilitation program (similar to the current proposal CON+ research arm). Again, patient-facing and staff-facing surveys were conducted to determine usability, patient accountability, platform flexibility, and capacity to create and modify care plans, patient-staff communication capabilities, data exchange with medical records, HIPPA compliance, and program component measurement capabilities.

Platform Selection: The platform chosen for use in this research proposal was based on a number of factors including: **a)** evidence for the platform to provide improvement in traditional risk factors, **b)** staff acceptance of its applicability and efficiency of use, **c)** patient feedback on

Figure 3a. Change in CVD risk factors

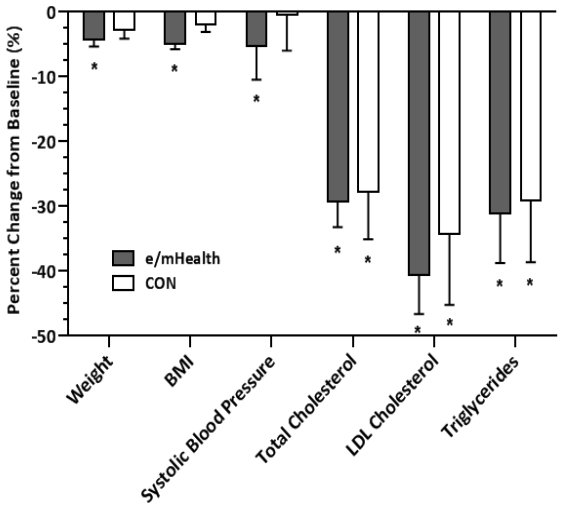
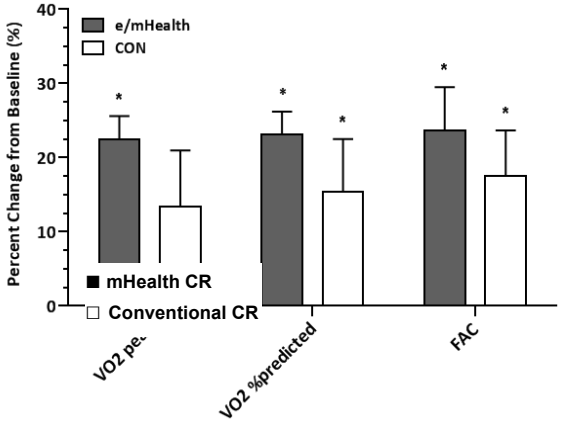


Figure 3b. Percent change in exercise capacity

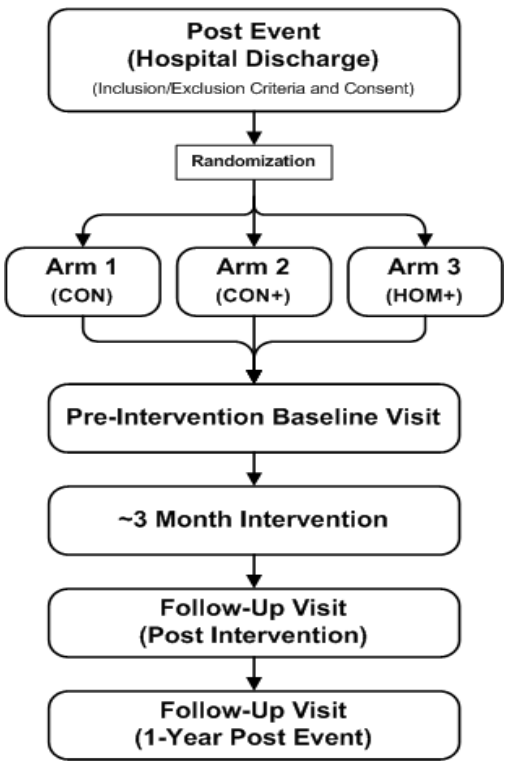


ease of use, **d)** appropriate and completeness of content, and **e)** overall patient and staff satisfaction. From the patient centered outcomes perspective, our web analytics and patient-facing survey data demonstrated that 67% of patients used the mHealth platform on a daily basis with an additional 22% using it multiple times per week. From the patient surveys, 72% of patients reported using the platform for its content and ability to record activities (daily agenda, graphs and diary). With this, 67% of patients were "satisfied" or "extremely satisfied" with the educational content provided; 78% felt the platform helped them to "better understand their health"; 89% reported the platform gave them "better control of their health"; and 89% also reported that the platform "increased their motivation to work on healthy lifestyle choices". **Figure 3a** shows the percent change from baseline to the end of CR (32±3 CR sessions) for body weight (kg), body mass index (BMI-kg/m^2), systolic blood pressure (mmHg), total cholesterol (mg/dL), low density lipoprotein cholesterol (LDL-mg/dL), and triglycerides (mg/dL) where CON represents patients enrolled in conventional center-based CR and CON+ represents patients enrolled in conventional center-based CR with the addition of mHealth platform. **Figure 3b** shows the percent change in volume of oxygen consumed during a maximal cardiopulmonary exercise test (VO_2 peak), percent of age and sex predicted VO_2 peak (VO_2 %predicted), and functional aerobic capacity as a percentage of age and sex predicted (FAC). Data are reported as mean±sd (*denotes statistically significant within group change). While pilot in nature and with a sample size of n=10 per group, these data clearly demonstrate the potential of a mHealth platform to augment conventional center-based CR.

Our data are in line with recently published studies examining the impact of various types of telerehabilitation technologies on health outcomes in CR patients. For example, Frederix and colleagues compared conventional center-based CR to conventional center-based CR plus weekly email or SMS text messaging ("telerehabilitation") which provided feedback on patients pedometer based physical activity monitor.[39] Despite the relatively limited intervention, these authors demonstrated a significant increase in exercise capacity (peak oxygen consumption) at the end of the intervention compared to the control group. Further, these authors demonstrated a trend towards reduced hospitalizations for patients in the telemonitoring group. Additionally, Avila et al. examined the impact of an exercise-based rehabilitation program between conventional center-based CR and home-based CR using weekly feedback via telephone or email to the home-based CR patients.[40] The contact moments with the home-based CR patients provided the opportunity to check for adverse events, provide feedback on exercise performed during the week, discuss the exercise program components, and discuss adherence and barriers when necessary. Again, despite the relatively limited "mHealth" intervention, these authors demonstrated a significant improvement in exercise capacity (peak oxygen consumption) in the home-based CR patients. In a more comprehensive approach but with a much smaller sample size and shorter duration, Widmer and colleagues demonstrated that the addition of a digital health intervention significantly improved specific CVD risk factors while reducing 3-month rehospitalizations.[41]

In light of previous studies, our protocol development activities formed the basis for the development of the comprehensive study protocol highlighted below. Our development process was and continues to be informed by patient feedback to ensure findings of this research are applicable to patients faced with the decision of whether to participate in CR. Our study protocol will be posted to clinicaltrials.gov prior to patient accrual.

Figure 4. Study Design Outline



3.3 Study Design

To address our specific aims we will use a single-center, prospective, three-arm, parallel group, randomized controlled trial design **(Figure 4)**. At the time of identification of eligibility for participation (See below: Patient Population), patients will be randomized to one of three arms (1:1:1 ratio): **Arm 1** consists of patients randomized to conventional CR only (CON), **Arm 2** consists of patients randomized to conventional CR with the addition of the mHealth platform (CON+), and **Arm 3** consists of patients randomized to remote case management using the mHealth platform only (HOM+). Clinical metrics will include traditional cardiovascular risk factors with additional tracking of service utilization and adherence, and quality

of life. Measures will be made at baseline (pre-intervention) and ~3-months (coinciding with completion of conventional CR). Additional follow-up will occur at 12 months post CR entry. Randomization to study arms will be done with a multidimensional dynamic allocation algorithm, minimizing imbalances in age, sex, body mass index, and race across study arms.

Description of Comparators

1) *Conventional Center-Based CR* **(CON)**:

Participants will be prescribed 36 sessions of center-based CR. This includes supervised exercise sessions, cooking demonstrations, didactic lectures, video presentations, group support, and stress management education. During sessions, participants have direct access to the medical director, case manager, registered nurse, exercise physiologist, and stress management specialists.

2) *Conventional Center-Based CR + mHealth* **(CON+)**:

Participants will be prescribed 36 sessions of center-based CR (as noted above). This includes supervised exercise sessions, cooking demonstrations, didactic lectures, video presentations, group support, and stress management education. During sessions, participants have direct access to the medical director, case manager, registered nurse, exercise physiologist, and stress management specialists.

In addition, participants will be provided access to the mHealth platform which provides “e-Learning modules” with factsheets, videos, quizzes, and questionnaires (coinciding with activities being conducted during the CON program), a Social Network Module will allow patients to communicate via a secure network with other patients who are part of their invited network. The Social Network Module also allows for secure two-way interaction with healthcare providers if patients are experiencing signs or symptoms suggestive of worsening condition.

Participants will be given a blood pressure cuff and scale with which they are asked to measure their blood pressure and weight. The device setup will be performed onsite or at home (via video visit after shipping devices to the participant’s address). This data will be uploaded to the mHealth Personal Health Record Module. This module allows patients to upload, archive, and retrieve personal health data (e.g. fitness tracker data, heart rate monitor data, blood pressure recordings, etc.) and record vital signs, symptoms, treatments, and medical history.

3) *Home-based CR + mHealth* **(HOM+)**:

Participants will be provided paper copies of educational content at the time of event/discharge.

These participants will be provided access to the mHealth platform (as noted above). The mHealth platform provides “e-Learning modules” with factsheets, videos, quizzes, and questionnaires (coinciding with activities being conducted during the CON program), a Social Network Module will allow patients to communicate via secure network with other patients who are part of their invited network. The Social Network Module also allows for secure two-way interaction with healthcare providers if patients are experiencing signs or symptoms suggestive of worsening condition.

Participants will be given a blood pressure cuff and scale with which they are asked to measure their blood pressure and weight. The device setup will be performed onsite or at home (via video visit after shipping devices to the participant’s address). This data will be uploaded to the mHealth Personal Health Record Module. This module allows patients to upload, archive, and retrieve personal health data (e.g. fitness tracker data, heart rate monitor data, blood pressure recordings, etc.) and record vital signs, symptoms, treatments, and medical history.

Participants in this HOM+ group will be encouraged to exercise three days per week while also completing the additional questionnaires and educational content provided by the mHealth platform in accordance with the CR program. Participation will be tracked using web/internet analytics. Subjects in this arm of the study will have a remote visit (either video or telephone visit) with Cardiac Rehab staff once a week for 12 weeks.

Due to recent CMS changes, Home-based CR for patients randomized to the HOM+ group will be paid for by the study.

This three arm trial will allow us to make comparisons between a hybrid program of center-based CR which incorporates mHealth remote case management technology (CON+) to a traditional center-based program

alone (CON) as well as comparisons between home-based mHealth remote case management alone (HOM+) to a traditional center-based program (CON).

3.4 *Participant Recruitment*

[[*Male and Female patients, aged 18-80 years, who are identified as eligible for conventional CR will be recruited from the Mayo Clinic Health System (MCHS) (or our subcontract site University of Minnesota Medical Center [M Physicians/Fairview Health System]) by clinical research coordinators, referring physicians, and/or CR staff. We will make every attempt to recruit equal numbers of both men and women and appropriate distribution of minority participants.****]]***

Inclusion Criteria: Patients must own, or have reliable access to, a smartphone or desktop computer with internet access, and an e-mail address. Eligible patients will have a history of one of the following: acute myocardial infarction/acute coronary syndrome, stable angina pectoris, percutaneous coronary intervention, or heart failure. Additionally, patients who underwent a surgical procedure which includes an indication for cardiac rehabilitation (coronary artery bypass surgery, heart valve repair/replacement, or heart transplant) will be enrolled but will only complete 6-minute walk test for measurement of exercise capacity per clinical practice guidelines.

Exclusion Criteria: Patients referred to CR with ventricular assist devices are not eligible. Patients who do not own, or have access to, a smartphone or desktop computer with internet access will not be recruited. Patient unable/unwilling to provide informed consent will not be enrolled.

The annual population of eligible CR patients at Mayo Clinic varies by diagnosis. As highlighted by Ades and colleagues report an annual nation-wide incidence of ~1,963,000 myocardial infarction, percutaneous coronary intervention, and systolic heart failure patients eligible for CR compared to only 395,000 coronary artery bypass surgery patients[42]. While this list is clearly not inclusive of all eligible referral diagnoses, it provides an illustration of the disproportionate number of surgical vs. non-surgical patients eligible for CR. Importantly, despite the significantly larger number of non-surgical patients eligible for CR, it has been reported that CABG patients demonstrate higher rates of participation in CR[43].

[[*Mayo Clinic has developed an in-house referral protocol for all patients meeting CR eligibility guidelines. Specifically, all patients visiting the clinic and/or hospital for one of the above inclusion criteria can be identified by our research team through the medical records, screened for eligibility, and approached to determine interest/willingness to participate in the study. This approach will maximize our potential to identify eligible individuals for screening and all patients who meet all eligibility criteria will be asked to participate. In 2018, the Rochester, MN CR program provided services for 459 new patients. Of those patients 68 were self-identified minority race or ethnicity (~15%) and 157 were women (~34%). Moreover, 365 patients were referred for non-surgical indications (~80%) which would meet the inclusion criteria of this proposal. Additionally, we have enlisted the assistance of an additional site in the Minneapolis/St. Paul metropolitan area (Hennepin County). The University of Minnesota Medical Center (M Physicians/Fairview) health network has 10 cardiac rehabilitation locations which provide cardiac rehabilitation services to ~4,000 new patients annually. Of these patients, ~3,000 receive their services within the Minneapolis/St. Paul urban area, many of which are from diverse racial and ethnic backgrounds.****]]*** We will maximize our retention by providing participants with remuneration for their time in the research program. This will include $50 for the baseline visit, $50 for the first follow-up visit at the end of the intervention, and $50 for the final follow-up visit at 1-year post event. Payments will be made at the time the participant completes the final follow-up visit or informs a study team member of their desire to withdraw from the study.

3.5 Methodology – Specific Programmatic and Functional Methods and Measurements

All metrics will be collected at baseline (within 2 weeks of beginning study arm activities) prior to participation in any arm of the research program, at approximately three-months (+/- 2 weeks) post enrollment which will coincide with 36 sessions of CR (three sessions per week for 12 weeks) for those enrolled in the CON or CON+ study arms, as well as at 1-year (+/- 4 weeks) post event.

Demographics, Anthropometrics, and Medical History: Standard demographics and anthropometrics will include age, height, weight, body mass index, waist circumference, hip circumference, and resting blood

pressure. Medical history will include current diagnoses, current medications, family disease history, and smoking history.

Body Composition: Body composition will be measured by the following standard metrics: 1) body mass index (BMI), 2) waist to hip ratio, 3) dual-energy X-ray Absorptiometry (DXA). We will measure DXA in all participants at baseline and at the first follow-up visit if available. Measurement of DXA will allow for compartmentalization of total body mass into total body lean and fat mass as well as regional distribution of these quantities. This additional detail may be useful in sub/exploratory analysis examining the impact of home-based electronic CR programing on regional fat and muscle distribution. Importantly, all participants will have height and weight measured clinically which will allow for the universally accepted assessment of BMI (weight in kilograms divided by the height in meters squared) as well as waist to hip ratio. This data can be collected at the time of enrollment in the research program and during each of the two follow-up study visits.

Blood Chemistries: All fasting blood chemistry measures will be conducted by standard clinical protocols in the Mayo Clinic laboratories. Measures will include a basic lipid panel (total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and triglycerides), blood glucose, hemoglobin, and hemoglobin A1c. These measures will be conducted at the time of enrollment in the research program and during each of the two follow-up study visits.

Physical Activity: Self-reported physical activity levels will be assessed using the International Physical Activity Questionnaire (IPAQ) and the Duke Activity Status Index (DASI).[44] [45] These activity questionnaire quantify participant's activity patterns in categories of vigorous, moderate, and leisure. This will be measured during the week immediately prior to beginning study arm activities and during each of the two follow-up study visits.

Exercise Capacity: Exercise capacity will be measured by the following standard metrics: 1) six-minute walk test (6MWT), 2) a standard 12-lead ECG monitored symptom-limited exercise stress test or cardiopulmonary exercise test to include measurement of oxygen consumption (CPET). The CPET will be the preferred measure of exercise capacity as measurement of peak oxygen consumption (VO_2peak) is considered the Gold standard measure of fitness. For standardization, the 6MWT will provide absolute distance walked and percent of age predicted distance walked as a universally accepted assessment of exercise capacity. The CPET will be conducted in the Mayo Clinic Integrated Stress Center as standard clinical protocol. These measures of exercise capacity will be conducted at the time of enrollment in the research program and during each of the two follow-up study visits.

Dietary Patterns: Dietary pattern will be obtained using a standard food frequency questionnaire at the time of enrollment and during each of the two follow-up study visits.[46]

Quality of Life: Physical and mental health-related quality of life will be assessed using the validated 9-item Patient Health Questionnaire (PHQ-9) and the validated Dartmouth 9-item Short-Form health survey at the time of enrollment and each of the two follow-up study visits.

[[*mHealth Remote CR Case Management Platform:* *The mHealth remote case management platform developed specifically for CR is an asynchronous platform consisting of several services intended to empower patients by raising their awareness about their health condition. These services give patients the opportunity to better understand, manage, and control their health condition for an improved quality of life.*

One of the main services is the learning module which provides patients the opportunity to learn about their health condition to better manage their disease by understanding how to adapt their lifestyle. This module offers a number of relevant resources that can be combined to form learning sessions organized in levels. Only the completion of a level will unlock access to the next level allowing CR staff (and research staff) the ability to track completion of specific educational content. The content will be defined and customized in line with the conventional CR programming. The different types of e-learning resources include factsheets, videos, quizzes, and questionnaires. Content modules (including didactic information and time for completion of exercise) are designed to be completed within a 45-60 minute timeframe, similar to conventional center-based programming.

This platform also includes a personal health record module which allows patients to manage their health data. Each patient can upload and archive information concerning their health. The health record section includes the ability for patients to enter general information about their health, symptoms, treatment, medical history, as well as provides a dashboard where their health data is then represented in table and graphic format. The data

patients can upload include vital signs and quality of life parameters such as pain scale, mood scale, treatment compliance, and medication compliance. The health record module also allows for recording heart rate, body weight, blood pressure, and blood glucose (as deemed appropriate for the individual patient), as well as exercise session content including duration of exercise session, type of exercise completed, heart rate during exercise, symptoms, and general comments. This content allows CR staff (and research staff) to track completion of recommended exercise sessions as well as record exercise sessions completed in addition to the individualized CR recommendations.

The social network module provides patients the ability to communicate, within a secure network, with their healthcare professionals (CR staff or research staff) who are part of their network. The network only includes patients and healthcare professionals involved in the CR program as part of the platform. Patients and care givers can have direct interactions through a chat function. Patient-caregiver (CR staff or research staff) interactions will only occur during regular outpatient clinical hours. This allows patients to ask questions, provide feedback, and communicate any possible issues that may arise. This also allows the CR staff and/or research staff to provide feedback, answer questions, provide clarification, and make changes to the individualized treatment plan (as would occur during conventional center-based CR during face-to-face conversations and interactions). Should an event or symptoms arise, patients will be instructed to go to their local emergency room and/or call 911 for assistance. The process for seeking medical attention is the same for all patients outside the center-based CR facility. Patients are automatically in contact with the care team involved in their care (medical directors, case managers, dietitians, exercise physiologists, etc.).

The platform home page has been designed to enhance the user experience. Any resource from any module can be pushed directly to the homepage by the staff to avoid excessive navigation within the platform. It can be used to view information messages, to access specific tasks, and to setup reminders to perform certain tasks. The home page is scalable in time. It also evolves with patient progress within his/her program. The goal is to provide personalized care by displaying the right information at the right time to the right patient.

All modules (e.g., services) are independent from each other and can be activated or deactivated on request. All encompass sub-modules allowing for individualized patient progress through the program. The content of the sub-modules is fully customizable so it can be easily and effectively modified based on patient needs (e.g., removing diabetes information for non-diabetics or including smoking cessation information for current smokers, etc.) and remain in-line with center-based CR program content offerings.

*<u>Website Analytics:</u> We will track and record all web-analytics associated with the usage of the mHealth remote CR case management platform for the purpose of this study. Website usage including time to first usage (onboarding to sustained login), number of times a patient visits their individual portal (per day/week/month), the amount of time a patient spends in their portal per visit, the number of times a patient views specific educational content, completion of educational content, time to completion of educational content modules, amount of time spent viewing and displaying educational content, and quantity of vital statistics recorded will be measured. This data will allow for the determination of HOM+ and CON+ patient groups CR component uptake and utilization and thus will be used as a composite marker for participation and adherence to the CR program components for comparison to the CON group.**]]***

<u>Optional Substudy:</u>

All patients, regardless of which arm they are in, will be offered the option to participate in a substudy where they are asked to wear a Fitbit to track their physical activity while participating in the main study.

3.6 *Proposed Project Timeline, Milestones, and Deliverables*

Table 4. Timeline, Milestones, and Deliverables

Proposed Timeline	**Year 1 (months)**				**Year 2 (months)**		**Year 3 (months)**		**Year 4 (months)**		**Year 5 (months)**	
	0-3	**3-6**	**6-9**	**9-12**	**12-18**	**18-24**	**24-30**	**30-36**	**36-42**	**42-48**	**48-54**	**54-60**
Finalize protocol and operating procedures/manuals	X											

(Deliverable)												
Biannual stakeholder meetings ***(Milestones)***	X		X		X	X	X	X	X	X	X	X
Obtain Institutional Review Board approval ***(Deliverable)***		X										
RAVE database creation		X										
ClinicalTrials.gov registration		X										
Participant enrollment and Intervention			X	X	X	X	X	X	X	X	X *	
Participant enrollment (n=50 in Y1 ~ 15%) ***(Milestone)***			X									
Participant enrollment (n=95 in Y2 ~ 29%) ***(Milestone)***				X	X							
Participant enrollment (n=94 in Y3 ~ 28%) ***(Milestone)***						X	X					
Interim data analysis ***(Deliverable/Milestone)***								X				
Participant enrollment (n=94 in Y4 ~ 28%) ***(Milestone)***								X	X			
Participant enrollment (n=0 in Y5 ~ 0%) ***(Milestone) (Follow-up Only)***										X		
Final data analysis ***(Deliverable/Milestone)***											X	X
Presentation/Manuscript preparation ***(Deliverable)***											X	X

* Follow-up only

[[3.7 General Statistical Considerations

Our detailed statistical approaches and power calculations are provided our Statistical Design and Power section of this application.

Data Collection and Management: *Study data will be recorded in Medidata RAVE electronic data capture and case report forms. Edit checks, electronic queries, and audit trails are built into the system to ensure accurate and complete data collection and security. Case report forms are automatically rolled out according to the visit schedule to improve staff workflow and data quality. Data are exported nightly to Mayo Clinic's secure servers. Data will be deidentified wherever possible and access is managed under a controlled and monitored access request system. Patients will be randomized using a dynamic minimization algorithm available in Medidata Balance software to minimize imbalances between groups and ensure that the distribution of both women and minorities are appropriately distributed across all cohort arms of the study. Readmission and mortality endpoints will be collected by study personnel at follow-up visits and through electronic health records.*

Briefly, ***Specific Aim 1*** *will focus on Adherence and completion related to each arm. CON and CON+ arms will be compared to determine if addition of a mHealth platform results in increased attendance of CR sessions. Number of sessions will be compared between arms using a Wilcoxon rank-sum test. Completion frequency will be compared by Pearson chi-square test. Among CON+ and HOM+ arms, the primary adherence measure is number of total portal visits (with task completion), compared by Wilcoxon rank-sum test.* ***Specific Aim 2*** *will focus on changes in modifiable risk factors across the three arms. The primary outcome is functional capacity (VO_2peak) at 3 months. Among the three treatment arms, there are two pairwise treatment hypotheses: (A) superiority of CON+ vs CON tested with two-sided alpha=0.025 and (B) non-inferiority of HOM+ vs CON tested with one-sided alpha=0.0125. This approach preserves an overall two sided alpha level 0.05 as described in the following Power and Sample Size section. Analysis of Covariance (ANCOVA) models will evaluate the relationship between the specified pairwise comparison arms and three month VO_2peak, adjusted for baseline VO_2peak. In analysis of Part A, we hypothesize superior efficacy of CON+ compared to CON. In the analysis of Part B, we first evaluate the lower bound of two-sided 0.025 confidence interval for the treatment effect difference between HOM+ and CON and compare to our pre-specified non-inferiority boundary of 2.8 mL/[min*kg] (10% relative reduction vs assumed mean of 28 mL/[min*kg] among CON patients, as specified in detail in the following Power and Sample Size section)*[39, 40, 47]*. If non-inferiority is demonstrated, we will subsequently perform a test of superiority of HOM+ compared to CON with two-sided alpha level 0.025. Secondary outcomes include measures of body composition, blood chemistries, 6MWT, and self-reported*

physical activity, dietary patterns, and quality of life, as described. For those secondary outcomes where a pre-randomization observation is available, ANCOVA will be used to reduce residual variation and compare across all three study arms. Otherwise, ANOVA methods will be used when pre-randomization data are not available. Secondary outcomes will be assessed only with respect to superiority comparisons. Regression assumptions, including normality of residual distributions and homoscedasticity will be assessed by visual assessments of residual plots. Transformations will be applied when appropriate and non-parametric tests including Kruskal-Wallis tests will be considered when appropriate. Assessments at 1 year will be compared similarly as exploratory endpoints to determine if improvements at 3 months are sustained after completion of therapy. ***Specific Aim 3*** *will focus on specific patient centered outcomes through one year post-randomization. The primary outcome is hospital readmission, compared across groups using a log-rank test. Cox proportional hazards models will estimate hazard ratios for pairwise group comparisons, with patients censored at loss to follow up or 1 year, whichever comes first. The endpoint of readmission alone will be described similarly, with cause-specific hazard ratios estimated by censoring at mortality in a Cox proportional hazards model. Mortality alone will be described using Kaplan-Meier estimates and a log-rank test, though we expect the mortality event rate to be low and any comparisons under-powered.*

3.8 Potential Limitations and Alternative Strategies

We acknowledge there may be potential limitations to our approach. First, by only including non-surgical CR eligible patients we are limiting the generalizability of our findings to the non-surgical population studied. However, we recognize that the number of non-surgical eligible CR patients is significantly greater than the number of surgical patients typically enrolled in CR and that surgical patients (e.g. CABG) already have higher rates of CR participation.[33, 42, 43, 48] Counterintuitively, this has a potential benefit in that it opens additional lines for future research examining the predictors of referral, enrollment, participation, and completion of CR programs among surgical vs. non-surgical patients. Secondly, there is sparse data available on the ability of mHealth to improve patient-centered outcomes such as mortality. While we will plan to follow our enrolled participants for one-year in an effort to examine the impact of mHealth on this important patient-centric outcome, we recognize that the number of patients who suffer fatal cardiac or non-cardiac events will likely be relatively small. In an attempt to collect meaningful patient-centric data, our primary outcome for Aim 3 will be rehospitalization over this same time period. ***[[****Lastly, although the population of patients of African descent has increased substantially over the past few years in our community, we recognize the relatively homogeneous nature of the predominately Caucasian Olmstead County population. We have engaged directly with the Center for Health Equity and Community Engagement Research within the Office of Health Disparities Research to develop dedicated strategies to maximize our recruitment of minority populations and overcome this potential limitation to ensure appropriate representation. We have also added a co-Investigator with extensive experience working with African American research participants. Moreover, we have engaged with University of Minnesota Medical Center (Minneapolis/St. Paul urban area) to assist with additional recruitment of African American patients as needed. By partnering with this additional site, we will increase the pool of eligible minority patients located outside the confines of Olmsted County. Further, we will employ a multidimensional dynamic minimization algorithm to minimize imbalances between groups and ensure that the distribution of both women and minorities are appropriately distributed across all cohort arms of the study.****]]*** ***3.9 Adverse Events (AE)***

Patients with (CAD) face negative effects of their conditions and/or surgical procedures which causes frequent Emergency Room (ER) visitation for conditions not related to the study. To better record any adverse events (AE) of this specific study, any AE notification will be notified to study PI. Which will deem its study relation by reviewing all EPIC ER documentations. Any AE will be reported to IRB and recorded in intelliTrial if the PI deems study related. In case of no study relation, a note will be put in subject folder for documentation purposes and will not be reported in intelliTrial.

[redacted]

[redacted]

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