Home T**el**emonitoring In **P**atients after **M**yocardial Infarction **E**xperience, HELP ME trial

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Full Title: **H**ome T**el**emonitoring In **P**atients after **M**yocardial Infarction **E**xperience, HELP ME trial.

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LIST OF ABBREVIATIONS

ACC	American College of Cardiology
AHA	American Heart Association
AMI	Acute Myocardial Infarction
CICU	Cardiac Intensive Care Unit
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ED	Emergency Department
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ITT	Intent to Treat
IRB	Institutional Review Board
LVD	Left Ventricular Dysfunction
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiovascular Events
MI	Myocardial Infarction
NP	Nurse Practitioner
PA	Physician Assistant
PHI	Protected Health Information
PI	Principal Investigator
US	United States
USA	United States of America

1. STUDY SUMMARY

Title	**H**ome T**el**emonitoring In **P**atients after **M**yocardial Infarction **E**xperience, HELP ME trial.
Methodology	Randomized, parallel-group clinical trial in acute coronary syndrome patients which have undergone coronary angiography with two study groups: **Group 1:** Discharged home with standard medical treatment. **Group 2:** Discharged home with standard medical treatment and 12 lead ECG telemonitoring device for 90 days.
Overall Study Duration	2 years
Subject Participation Duration	90 days
Single or Multi-Site	Single Site Mayo Clinic Rochester, MN
Objectives	Several retrospective studies indicate that patients with ACS post PCI have less readmissions and better survival with 12 lead ECG telemonitoring at home. So far, no prospective study was done to show this benefit. The **objective of the current study** is to evaluate the incidence of ED visits, re-hospitalizations and major adverse cardiovascular events (MACE including cardiovascular death and hospitalization for myocardial infarction, unstable angina, repeat revascularization, heart failure, stroke, arrhythmias, and cardiac arrest), and cost-effectiveness over a period of 90 (+/- 7) days after an index hospitalization for an acute myocardial infarction (MI). Our **central hypothesis** is that 12 lead ECG home telemonitoring decreases general and cardiac ED presentation and hospital readmission rates without an increase in MACE and at a lower health care utilization cost compared to patients with standard therapy alone. Three specific aims will be pursued: Aim 1: To compare the rates of ED visits and re-hospitalization rates as well as related downstream cardiovascular testing (echocardiogram, stress test or coronary CT, or invasive coronary angiogram) from discharge after index hospitalization for MI to 90 days follow-up between patients undergoing standard care alone or standard care plus the home 12 lead ECG telemonitoring device Aim 2: To compare the rates of MACE from discharge after index hospitalization for MI to 90 days follow-up between patients undergoing standard care alone or standard care plus the home 12 lead ECG telemonitoring device Aim 3: To compare health care cost utilization from discharge after index hospitalization for MI to 90 (+/-7) days follow-up between patients undergoing standard care alone or standard care plus the home 12 lead ECG telemonitoring device
Number of Subjects	240 patients in total, enrolled over one-two years

Inclusion and Exclusion Criteria	Inclusion criteria: • ≥18 years of age, • Acute myocardial infarction, both STEMI and non-STEMI • Able to use the home ECG telemonitoring • Must have smartphone device with home wi-fi/mobile internet which allows 24/7 ability to transmit ECG • Caring family member who will be able to help/perform the ECG in case the patient himself won't be able to do it • Planned to be discharged home by the treating team Exclusion criteria: • No ability to use the device at home • No smartphone device or home wi-fi/mobile internet which prevent 24/7 ability to transmit ECG • Cannot download the smartheart app • No support in home environment • Out of hospital cardiac arrest: secondary to a non-shockable rhythm, unrelated to an acute coronary syndrome, or with any level of neurologic damage. • Resident of nursing home or acute care facility • Uninterpretable ECG at discharge – left bundle branch block (LBBB), pacemaker or implantable cardioverter defibrillator (ICD) with pacing dependence. • Patients who are planned for staged PCI after the index hospitalization
Study Product, Dose, Route, Regimen	Prior to discharge patients will be 1:1 randomized to standard medical therapy or standard medical therapy + 12 lead ECG Smartheart telemonitoring device.
Duration of Administration	Patients will receive the device for the period of 90 (+/-7) days .
Reference therapy	Group 1 will serve as the reference group
Statistical Methodology	Inter-group differences in the rates of the primary combined endpoint will be analyzed by the Chi square test.

2. STUDY TEAM ROSTER

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3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this trial is to compare the rates of ED visits and re-hospitalization rates as well as related downstream cardiovascular testing (echocardiogram, stress test or coronary CT, or invasive coronary angiogram) from discharge after index hospitalization for MI to 90 (+/-7) days follow-up between patients undergoing standard care alone or standard care plus the 12 lead ECG Smartheart home telemonitoring device.

3.2 Secondary Objectives

The secondary objectives of this study are:

a) To compare the rates of cardiovascular and non-cardiovascular ED visits and re-hospitalizations rates, from discharge after index hospitalization for MI to 90 (+/-7)days follow-up between patients undergoing standard care alone or standard care plus the 12 lead ECG Smartheart home telemonitoring device.

b) To compare the rates of downstream cardiovascular testing (echocardiogram, stress test or coronary CT, or invasive coronary angiogram) from discharge after index hospitalization for MI to 90 (+/-7) days follow-up between patients undergoing standard care alone or standard care plus the 12 lead ECG Smartheart home telemonitoring device.

c) To compare the rates of MACE from discharge after index hospitalization for MI 90 (+/-7) days follow-up between patients undergoing standard care alone or standard care plus the 12 lead ECG Smartheart home telemonitoring device.

d) To compare health care cost utilization (including all cardiovascular inpatient and outpatient office visits and tests) from discharge after index hospitalization for MI to 90 (+/-7)days follow-up between patients undergoing standard care alone or standard care plus the 12 lead ECG telemonitoring device.

e) To compare quality of life (MacNew Heart Disease Questionnaire) from discharge after index hospitalization for MI to 90 (+/-7) days follow-up between patients undergoing standard care alone or standard care plus the 12 lead ECG telemonitoring device.

4. BACKGROUND AND RATIONALE

4.1 Background

Survivors of a first acute myocardial infarction (AMI) face a substantial risk of further major adverse cardiovascular events (MACE), including death, recurrent MI, heart failure, arrhythmias, angina, and stroke. The rate of rehospitalization within 30 days after acute MI is reported to range between 17 and 25 percent [1,2]. In a single-community study, Olmsted County, Minnesota, United States, of 3010 patients who were hospitalized for a first-ever MI (STEMI – 31%) rehospitalization within 30 days occurred in about 19 percent [3]. Across the broad spectrum of patients with acute myocardial infarction (MI), short-term (in-hospital or 30-day) mortality has been decreasing over the past 30 years, concomitantly with the increasing use of reperfusion strategies and proven preventative therapies such as beta blockers, aspirin, and statins [4-12]. The 30-day mortality after all acute coronary syndromes (ST-elevation myocardial infarction [STEMI], non-ST elevation myocardial infarction [NSTEMI], and unstable angina) is less than 5 percent [13]. The incidence of SCD after acute MI is the same with STEMI and NSTEMI [4,14]. Among patients who have had an MI and are followed for about four years, approximately one-half of sudden deaths occur in the first year and one-quarter in the first three months [15,16]. The risk is markedly increased in patients with a left ventricular ejection fraction ≤35 percent. Additional important aspect following acute MI [AMI] is financial, although mortality attributable to AMI has declined, 30-day post-AMI readmission rates remain high (median 19.9%) and carry a heavy economic burden, accounting for 21,000 admissions at a cost of 136 million dollars in the United States [17].

‘‘SHL’’-Telemedicine is a call center that was established in 1987 in Israel. It operates 24 hours/day, 365 days a year, and is managed by a medical staff. Each subscriber’s medical file (which also includes a full 12-lead

electrocardiogram [ECG]) is electronically stored and continuously updated. The subscribers carry a SmartHeart 12 lead ECG device by which they can transmit a full 12-lead ECG via internet by a designated smart application and call the SHL center, the archived information is uploaded within seconds on a monitor together with the real-time transmitted information, and the staff evaluates the caller's medical status according to the transtelephonic anamnesis, newly transmitted ECG data, and pertinent facts from the electronic file. By integrating computerized algorithms and clinical judgment, the staff advises the subscriber which steps to take and which action the staff will take according to predefined standing orders and protocol [18]. Several retrospective studies showed favorable clinical outcomes of patients using ''SHL''-Telemedicine and Smartheart device, including reduction in a 30-day readmission rate, shorter time lag between the onset of symptoms and contacting medical assistance and lower mortality rates[18-20].

4.2 Study Rationale

This study will be pursued as a prospective clinical trial building upon and extending the available evidence of the use of outpatient ECG monitoring after MI outlined above. We will test the clinical and economic impact of the SHL-telemonitoring cardiac device during the first 90 days after MI in a defined health care environment. The current standard of care is antiplatelet agents, beta blockers and statins alone, with a reported re-hospitalization rate of 17-25%. In addition to the standard care, patients in the intervention arm will be instructed on how to use the device and send ECG to a Mayo Clinic CICU designated study NP/PA, which will be in communication with the participant to respond to recordings taken for symptom review. Patients with a *true* acute cardiac event will be advised to seek medical assistance immediately, in case of STEMI, VT/VF or CAVB the EMS will be sent to the participant. Patients with reassuring ECG and low suspicion of acute cardiac event will be advised to postpone medical assistance and to avoid unnecessary emergency department [ED] visits. Such an approach may improve patient outcomes and reduce costs at the same time.
Additionally, the COVID-19 pandemic brought its challenges to the health systems worldwide, those are uncertain times and prevention of unnecessary ED visits and readmissions after discharge would be beneficial, in particularly for patients post AMI having comorbidities.

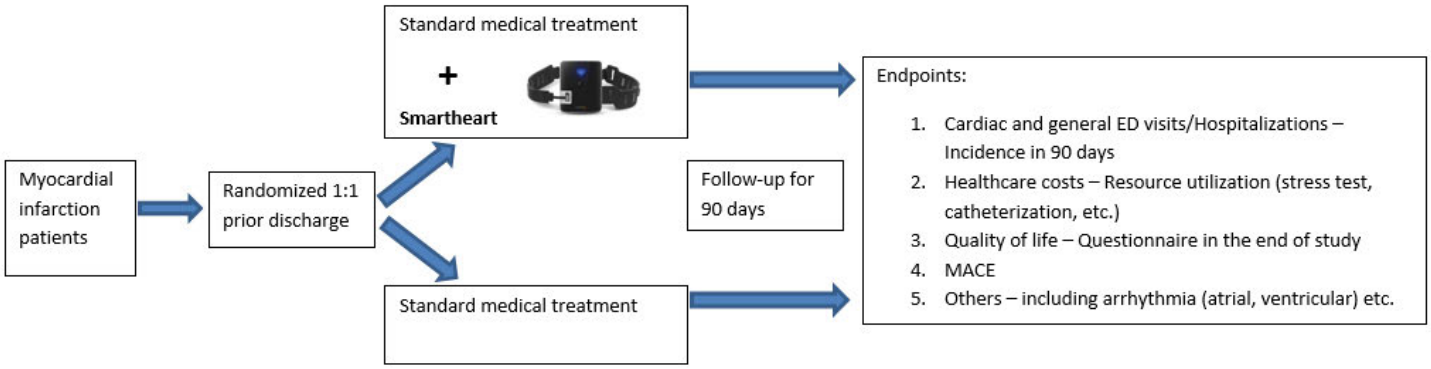
It is important to emphasize that the device is safe to use and this is a very low risk study with a large potential benefit of decrease in unnecessary readmission rates, subsequent costs and early detection of real cardiac abnormalities with prompt medical assistance could improve outcomes. This study is planned to address the importance of home telemonitoring in cardiac patients and could have future implications on the current guidelines and standard care.

5. STUDY DESIGN

This study will be conducted as a prospective, randomized pilot study in patients with acute myocardial infarction which have undergone coronary angiography with two study groups (Figure 1):

- **Group 1 (control group):** standard clinical practice medical therapy at discharge, including double antiplatelet therapy (DAPT), high potency statins and if indicated, beta blockers.
- **Group 2 (intervention group):** standard clinical practice medical therapy as above plus the Smartheart home-telemonitoring 12 lead ECG device.

Figure 1: Trial outline



Patients will be randomized at discharge to standard medical therapy (DAPT, high potency statins and beta blockers) or the standard medical therapy plus the Smartheart home-telemonitoring 12 lead ECG device. The intervention group will have instructions and explanation, prior discharge, how to use the device and will be guided to have two device testing's at home during the first two weeks after discharge. In case of any symptoms, including but not limited to chest pain, shortness of breath, sensation of irregular heart beats and near fainting during the 90 days post discharge the patient will record a 12 lead ECG at home and transmit it directly to Saint Mary's Hospital CICU designated study NP/PA, which is available 24/7, the ECG will be read by the NP/PA (with the support of the CICU consultant). Communication with the patient will be through the study designated CICU NP/PA, which will call the participant, record short history of the medical emergency and provide the patient with appropriate directions according to the ECG finding, medical urgency and study protocol. The CICU NP/PA will call the patient as soon as possible after receiving the ECG to the study email inbox.

In case of delay with conducting the phone call to the participant, >15 minutes from sending the ECG, or having any technical issues with recording the ECG, the participant will call to a study phone (number provided to the participant) carried by CICU NP/PA which is available 24/7. An alternative phone number will also be provided that will get the patient in touch with the Mayo Clinic operator who can then direct the patient to the Cardiac Intensive Care Unit (CICU) NP/PA staff. Patients will be instructed to use this if they are unable to reach the NP/PA staff directly with the previously provided phone number. In case the technical issue was not solved by the NP/PA, the recommendation for the patient will be based on the symptoms characteristics (as described in the NP/PA decision making tool). In case the participant cannot be reached by the primary phone number provided, NP/PA will call second provided phone number (of patients' related individual/significant other), in case there is no response to both phone numbers, and the participant did not call our NP/PA designated phone, further decisions will be based on the ECG tracing. If alarming findings are present, which may explain a loss of consciousness, EMS will be activated to the home address of the patient, assuming that patients will use the ECG device at home. If no alarming finding is present the patient will be reassured with a phone follow-up the next day.

Adverse Event Reporting

We will only be collecting adverse events that result in Cardiovascular Events, Emergency Department visits, and Hospitalizations, which will be looking at the outcomes, as this is a monitoring study, with no adverse events expected from the device (SmartHeart, which is FDA approved), as all other events are not relevant to the research study. To make sure assessments are consistent throughout the study, this will also be followed retrospectively.

6. SELECTION AND ENROLLMENT OF PARTICIPANTS

6.1 Inclusion Criteria

- ≥18 years of age,
- Acute myocardial infarction, STEMI and NSTEMI
- Ability to use the device at home
- Must have smartphone device with home wi-fi/mobile internet which allow 24/7 ability to transmit ECG
- Caring family member who will be able to perform the ECG in case the patient himself won't be able to do it

6.2 Exclusion criteria

- <18 years of age
- No ability to use the device at home / Unable to comply with the device instructions
- No smartphone device or home wi-fi/mobile internet which prevent 24/7 ability to transmit ECG
- Unable to download the smartheart application
- No support in home environment
- Out of hospital cardiac arrest
- Resident of nursing home or acute care facility
- Uninterpretable ECG at discharge – left bundle branch block, pacemaker dependence, implantable cardioverter defibrillator.
- Out of hospital cardiac arrest: secondary to a non-shockable rhythm, unrelated to an acute coronary syndrome, or with any level of neurologic damage.
- Patients who are planned for staged PCI after the index hospitalization

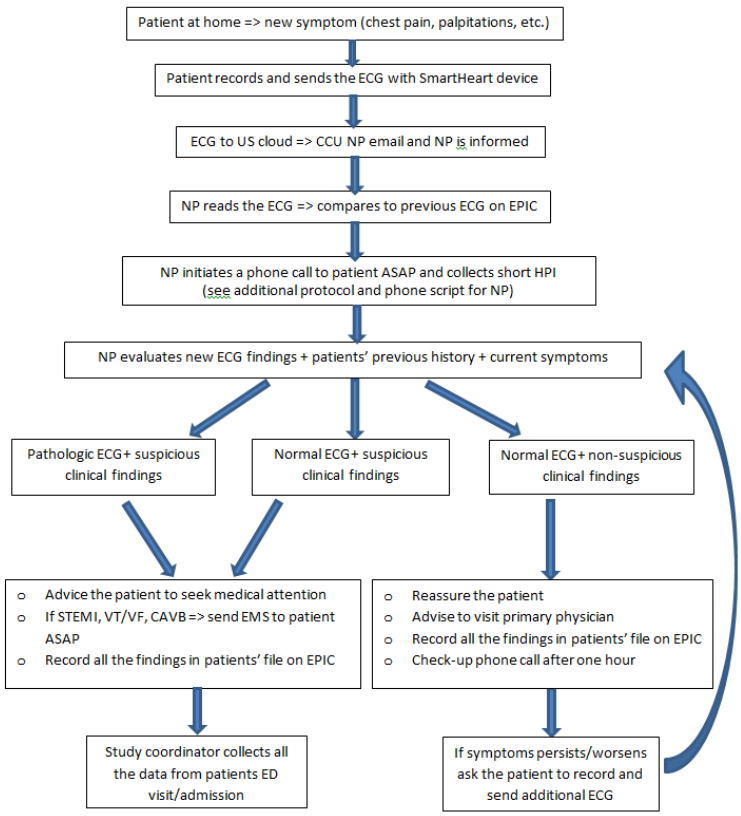


Figure 2. Call work-flow

6.2 Study Enrollment Procedures

This study will be conducted on a study platform that is already in place at the Mayo Clinic Rochester, Patients identified with a diagnosis of acute myocardial infarction and subsequent coronary angiography with will be enrolled. Any potential study candidates will be identified based on the eligibility criteria listed above. A screening log will be kept and secured electronically. Those potentially eligible will be recorded by clinic number and exclusion criteria will be checked. If any are met, the specific reason will be marked, otherwise a commentary will be entered for those who are eligible but do not wish to participate. Those patients who agree to participate will be asked to provide written consent. The study details will be outlined. It will be made clear that at this point there are no data whether the intervention approach leads to superior clinical outcomes and this very fact provides the rationale for this trial.

7. STUDY INTERVENTIONS

Interventions, Administration, and Duration

Patients will be randomized to either standard medical therapy or standard medical therapy + Smartheart home telemonitoring device. The device will be supplied be the "SHL" telemedicine for each patient in the intervention group for the period of 90 (+/-7) days from the randomization. Patients will be followed for 90 (+/-7) days. At randomization and at the end of the study period the patients will be asked to fill out quality of life questionnaire and return back the Smartheart device by mailing back the device in the padded box covered by

insurance in case it is damaged upon receipt to Mayo Clinic. Medications during the study period will be prescribed by the treating physician, no change of medications will be performed by the study team.

The SmartHeart, developed by SHL Telemedicine Ltd., was approved by the FDA on 2012 (K113514). It is a personal, hand-held device, enabling an individual to immediately transmit a 12-lead ECG from anywhere and anytime, using a smart phone application, to a physician's office, hospital or monitoring center. The ECG output from Smartheart device was compared to standard 12 lead ECG recordings and was found to be reliable. Data will be labeled with a subject's medical record number and by date of transmission. The data will be uploaded from Smartheart device to the US cloud (located in USA), and sent by email directly to designated Mayo Clinic CICU NP/PA smartphone devices email address. The smartphone device will be carried by the NP/PA 24/7 and will give a loud alert for every incoming ECG. The ECG data will be uploaded and accessible in the patient's EPIC EMR.

The smart phone application will send push notifications to the patients to remind them to perform test ECG at Week 1, Week 2, and Week 4 (optional, if patient has not performed Week 2 ECG). Patients will also be notified every other day after Week 1, if not completed.

8. STUDY PROCEDURES

8.1.1 Screening Evaluation

Acute myocardial infarctions patients identified on cardiology service will be evaluated for enrollment. These patients will be approached by a trained research member who will present the background, rationale, and details of the study. A single informed consent form will be used that describes both the screening and study procedures. Those who consent will be asked additional questions of their past medical history and their records will be reviewed to identify any exclusion criteria. If any are present, these will be charted in the screening log. For those who are eligible but refuse, a comment will be added to the screening log detailing the reason for non-participation.

8.1.2 Enrollment, Baseline, and/or Randomization

All patients who consent to the study are considered to be enrolled as of the date of the consent.

Baseline Assessments- comprises a review for any cardiovascular diseases or risk factors, home medications. Additional data will be collected: type of AMI (location: anterior, inferior, posterior, lateral), troponin levels, baseline ECG, left ventricular function by echocardiography, Canadian Classification scale (CCS) of Angina(class I, II, III IV) .

Randomization- will be done once all inclusion and exclusion criteria are reviewed and the patient meets eligibility criteria. Patient and treating cardiologist will be informed which study group the patient was assigned. Patients assigned to group 1 will be discharged with standard medical therapy as indicated by AHA/ACC guidelines in post AMI patients treated with or without PCI. Patients in group 2 will be discharged with the standard medical treatment as indicated by AHA/ACC guidelines in post AMI patients treated with or without PCI plus they will receive the Smartheart 12 lead ECG home telemonitoring device for the period of 90 days (+/-7). Those patients will have short explanation on how the device works, how to adjust it on the chest and how to transmit the ECG.

A post-study questionnaire will be administered to patients randomized to the device group to collect feedback on their experiences with the device. Participation is voluntary, and responses will be anonymized to ensure confidentiality. The inclusion of this questionnaire will not impact the primary study objectives or patient safety.

8.1 Schedule of Evaluations

Assessment	Screening, Enrollment, Randomization: pre-discharge (Day 0)	Week 1 (-3,+6 days)	Week 2 (-3,+6 days)	Week 4 (-3, +6 days)	Day 90 (Final) (+/- 7days)
Informed Consent Form	X (R)				
Demographics	X				
Medical History	X				
Vital signs	X				
Physical Examination	X				
Current Medications	X				
Blood Chemistries	X				
Electrocardiogram	X				
Echocardiogram	X*				
Inclusion/Exclusion Criteria	X (R)				
Enrollment/ Randomization	X (R)				
Providing Device + Instructions	X (R)				
Quality of Life questionnaire (day 0)	X (R)				
Follow-up ECG and training call		X (R.S.)	X (R.S.)	X (R.S.Q)	
End of participation phone call, will include:					X (R)
• ED visits/Hospitalizations/MACE data /ccs					X (R)
• Current medications and if changed lately					X (R)
• Quality of Life questionnaire (day 90)					X (R)
Device collection (patient sending by mail)					X (R)

X Performed as standard of care (not specific for research)
X* If performed after the AMI event and pre-discharge
X (R) Research related only
X (R.S.) Research – Study group related only
X (R.S.Q) Research – Study group related only, depends on the need of further training beyond the first two tests.

9. STATISTICAL CONSIDERATIONS

9.1. General Design Issues

This study will be conducted as a parallel group randomized clinical trial. The main goal is to define if Smartheart 12 lead ECG home device will decrease the rates of ED visits and rehospitalization in patients after index hospitalization for acute MI.

Our central primary hypothesis is that the Smartheart 12 lead ECG home device will decrease the ED visits and rehospitalization rates, leading to subsequent decrease in healthcare costs. Additional potential benefit is decrease in mortality by identifying any cardiac emergency at the early stage with appropriate urgent medical assistance. The quality of life of patients with the Smartheart device at home could be improved, knowing there is an easily available tool which can provide quick and reliable diagnosis.

9.2. Sample Size and Randomization

Patients will be randomized to either standard medical therapy or the medical therapy plus the Smartheart 12 lead ECG home device.

The primary combined endpoint parameter is the rate of ED visits/rehospitalizations as well as related downstream cardiovascular testing (echocardiogram, stress test or coronary CT, or invasive coronary angiogram) at 90 (+/-7) days after discharge and mortality rates during the 90 (+/-7) days of follow up. Based on the most recent in-house registry data, we have about 50 AMI patients undergoing PCI a month. Accordingly, we have at least 600 patients a year who are discharged with a diagnosis of AMI from Saint Mary's Hospital.

Our own registry data further indicate that 24% of revascularized AMI patients will present to the ED or will be readmitted within 90 days. This is in keeping with the published literature citing a rate of 20-30%. Half of these patients will present for cardiovascular complaints and may get further testing, including echocardiogram, stress test or coronary CT, or invasive coronary angiogram. Having a 12-lead ECG available and the phone triage available to direct care may impact not only emergency presentation but also downstream testing. This will be considered in this trial, and each of these will be considered as a component to the combined primary endpoint event. Assuming that patients presenting with cardiovascular concern may receive two of the outlined downstream test as they present to the ED and hospital, the estimated event rate will be 48%. With 120 patients in each arm the study we would be adequately powered (beta error <0.2) to show a statistically significant (at alpha error levels of <0.05) for a 37.5% event reduction.

9.3. Treatment Assignment Procedures

A computer-generated randomization scheme will be utilized assigning each consecutive patient enrolled to one of the two groups. The randomization scheme is 1:1. Patients and providers are to adhere to the protocol.

9.4. Interim Analyses and Stopping Rules

Due to the uncertainty in proposed rehospitalization rate of the treatment arm, a sample size reestimation (SSR) will be performed after 60 patients have finished the study in the treatment group. The rate will be estimated only for the treatment group, and the sample size will be recalculated using the new calculated rate. The results of this calculation will be the new larger sample size for the study. If the calculation proposes a sample size that is smaller, the original 120 patients per group will be used. No stopping rules are implemented for this pilot study.

As an example, there may be more rehospitalizations and ER visits than expected in the treatment group. If the rehospitalizations and ER visits were 17.5% at 90 days, this would result in the sample size being increased to 181/group. Alternatively, if the rehospitalizations and ER visits in the treatment group were 10%, the sample size required would only be 62/group. If this were to happen, the sample size for the study would be maintained at 120 per group.

9.5. Outcome measures

9.5.1. Primary trial objective

The primary aim of the trial is to compare the cardiac ED visits and hospital readmission rates as well as downstream testing at 90 (+/-7) days after hospitalization for MI between group 1 and group 2.

9.5.1.1. Primary outcome measures

The combined primary endpoint of the trial is the rate of ED visits, hospital readmission, and any of the downstream testing modalities (echocardiogram, stress test or coronary CT, or invasive coronary angiogram) from discharge after index hospitalization for MI to 90 days of follow-up between group 1 and group 2.

9.5.2. Secondary trial objective

The second aim of the trial is to compare the individual endpoints of the primary endpoint, MACE rates, heath care utilization costs and quality of life between group 1 and group 2.

9.5.2.1. Outcome measures

- Rate of ED visit and rehospitalization, overall and related to cardiovascular and non-cardiovascular causes
- Rate of downstream testing modalities (echocardiogram, stress test or coronary CT, or invasive coronary angiogram)
- Rate of MACE as defined above
- Amount of money in US dollars that was spent for any medical service related to cardiovascular and non-cardiovascular diseases in both study groups.
- Quality of life questionnaire score in both study groups at the time of enrollment and at 90 days.

9.6. Data Analyses

The primary analysis for Aim 1 (lead aim of the study) will be a comparison of the rates of the primary combined endpoint between group 1 and 2 via Chi square test for categorical data of independent samples. The test will be used for any other categorical data. For continuous data, an independent groups t-test or Wilcoxon as appropriate after testing distributional assumptions.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1. Data Collection Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A”. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use “white-out” for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

The data collection tool for this study will be investigator-designed case report forms. The investigator will maintain complete and accurate study documentation in a separate file. Study documentation may include medical records, records detailing the progress of the study for each subject, signed informed consent forms, drug disposition records, correspondence with the study coordinator study monitor/sponsor, screening and consent information, severe adverse event reports, laboratory reports, subject diaries, data clarifications requested by the sponsor, and any other documentation deemed relevant and pertinent to the study and the study subjects. Subject data necessary for analysis and reporting will be entered into a validated database or data system in accordance. Clinical data management will be performed in accordance with applicable data management vendor standards and data cleaning procedures. The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. The handling of data, including data quality assurance, will comply with regulatory guidelines (e.g., ICH GCP).

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

The investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

10.2. Data Management

All study data will be collected at Mayo Clinic with the Department of Cardiovascular Diseases as the primary coordinating and data management center.

RedCap will be used for clinical data management and randomization. These tools are institutionally supported and allow for rapid database development. The implementation of the software within a project includes training on the system's use, robust error checking, security considerations, and full audit trail. Balance, which is integrated into *RedCap*, allows for a variety of randomization and minimization algorithms.

Demographic and clinical data will be extracted from medical records including age and gender, vital signs, physical exam findings.

Data on clinical outcome/event reporting will include cardiac dysfunction and/or heart failure as well as major adverse cardiovascular events (including myocardial infarction, heart failure, arrhythmia, transient ischemic attack, and stroke).

The echocardiographic parameters that will be captured comprise systolic, diastolic LV and RV function including LVEF.

The angiographic parameters collected will include name of the coronary artery, degree of stenosis and location, number of diseased vessels and number of stents, PCI success and complications.

All individually identifiable patient records and data will be stored in a database under coded accession numbers. A password is required to gain access to this protected and privileged information. Only the approved and trained study staff will have access to the database. The sponsor will not have any access to the study data. For individuals providing data, e.g. core laboratory personnel, access will be limited to entering data only. All data are monitored regularly for entry and access, and a formal policy regarding protection of personal privacy is in place throughout Mayo Foundation. The key to identification of subjects will be maintained in a secure office environment under the direction of the investigators. The institutional commitment at Mayo Clinic to protect patients' (and study participants') privacy is a high priority.

10.3. Quality Assurance

10.3.1 Training

The study will be performed only by adequately trained personnel. This applies to the entire study team roaster. Only approved and trained study staff, experienced in trials such as these, will interact with the patients and manage the data forms and database. As part of the study data, the study team will collect data on ECG, echocardiography and other imaging tests which are ordered per routine care for the patients during their hospitalization.

10.3.2 Quality Control Committee

This study will not assemble a quality control committee.

10.3.3 Metrics

The same applies for all endpoint parameters. Computerized checks will be performed to ensure data integrity. These will be reviewed by a trained study staff for fidelity. Source document verification will be performed to ensure data fidelity as well. To ensure compliance with GCP and all applicable regulatory requirements, the sponsor or designee may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of

the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

10.3.4 Protocol Deviations

Patients will be contacted by phone for the device testing several times during the first month. The next contact will occur by phone call at the end of the study (90 +/-7 days after the randomization). If any deviation from the study protocol were noted, a record will be made on their study participation form and these patients will be flagged for review by the PI. The study team will then decide if a study deviation occurred that precludes continuation of study participation. If this were indeed the case, the patient will be notified. This individual will be removed from the study and will be replaced by another study participant.

10.3.5 Monitoring

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

The study will employ standard methods for protecting the confidentiality of research materials through the use of coded identification numbers that are specific to the study on all materials except those that are necessary for participant contact, follow-up, and ongoing linkage with data such as those from medical records, using password-protected computer data files and databases, and locked file cabinets for storing hard copies of any other study materials. Only study personnel who need to track participants for follow-up purposes have access to the identifying information for individual study participants. No personally-identifiable information (protected health information) except the minimum necessary for study purposes are shared with co-investigators, and any sharing of data is by encrypted, password-protected data files. In addition to the procedures outlined above, confidentiality and privacy are further enhanced as each institution maintains research databases behind institution-specific password-protected firewalls.

ECG recordings will be uploaded and stored in a secured data platform, accessible only to permitted Mayo Study personnel; additionally, it will be uploaded into the patient's EPIC EMR.

No preliminary or final results will be released or published with identifying information or reported on an individual level, and all epidemiologic data will be presented as statistical summaries. No statistics will be published based on fewer than 5 subjects, a practice consistent with HIPAA and most confidentiality guidelines.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

11.1. Institutional Review Board (IRB) Review

11.2. Informed Consent Forms

A signed consent form will be obtained from each participant. The consent form will describe the purpose of

the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant and this fact will be documented in the participant's record.

For patients not fluent in English, an interpreter will be present to translate the informed consent and for the discussion of the informed consent with the trained study team member. It is already a standard of care at Mayo Clinic that all patients considered not fluent enough in English will have interpreter services. Thus this study builds and extends on this practice.

11.3. Participant Confidentiality

The confidentiality of all participants will be maintained according to the Health Insurance Portability and Accountability Act (HIPAA), any special data security requirements, and record retention per the sponsor's requirements.

Any data, specimens, forms, reports, or records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NIA, and the OHRP.

11.4. Study Discontinuation

The study may be discontinued at any time by the IRB, the NIA, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12. ETHICAL CONSIDERATIONS

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject himself and the individual obtaining the informed consent.

13. COMMITTEES

This study will not convene any particular committee such as a Steering Committee or an Executive Committee, a Publication Committee, or an Adjudication Committee.

14. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Steering Committee. Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NIA prior to submission.

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SUPPLEMENTS/APPENDICES

APPENDIX A

DATA AND SAFETY MONITORING PLAN

Table 1. Enrollment by Month of Study

Month	# Expected	# Screened	# Enrolled or Randomized	# Withdrawn	# Actual (# Enrolled - # Withdrawn)	# Cumulative (Sum of # Actual by Month)
1						
2						
3						

Table 2. Demographics

Characteristics	**N**	**N%**
Gender		
Female		
Male		
Age		
Mean (SE)		
Median (min, max)		
<34 years		
34-44 years		
45-54 years		
55-64 years		
65-74 years		
75-84 years		
>84 years		
Ethnicity		
Hispanic or Latino		
Not Hispanic or Latino		
Unknown		
Race		
AIAN		
Asian		
Nat Hawaiian/Other Pac Islander		
Black or African American		
White		
Other		
More than one race		
Unknown		

Table 3. Subject Status

Pt Identifier	Date Enrolled	Date Completed Study	Study Status	Reason for Withdrawal	% Adherence to Intervention	Intervention Duration (Weeks)
Subj001						
Subj002						
Subj003						

Status:
A = Active
C = Completed
W = Withdrew
L = Lost to follow-up

% Compliance to Intervention:
(# tablets taken/total # per protocol)*100
or
(# classes taken/total # of sessions should have attended per protocol)*100

Table 5. Frequency of Specific Symptoms

Symptoms	AE Code (MedRA, CTCAE)	N%
Fatigue		
Dyspnea		
Palpitations		
(Pre-)Syncope		
Chest pain		

Table 7. Subject Deaths

Pt Identifier	DOB	Date Enrolled	Treatment Date	Cause of Death	Date of Death	Comments
Subj001						
Subj002						
Subj003						

APPENDIX B

DSMP SAMPLE STUDY REPORT OUTLINE

Study Report Outline

I. Table of Contents
II. Introduction
    A. Summary of Study Status and Issues or Problems
    B. Report Preparation Procedures
III. Study Description
    A. Project Organization Chart, Personnel
    B. Brief Statement of Purpose of Trial
    C. Projected Timetable and Schedule
    D. List of Any Resource Centers
IV. Study Administration
    A. Recruitment Status
        i. Enrollment by Year/Month
        ii. Comparison of Targeted to Actual Enrollment
    B. Retention Status
        i. Overall Subject Status
        ii. Individual Subject Status
V. Study Data Reports/Tables or Figures
    A. General Information
        i. Enrollment (see Appendix B, Table 1)
        ii. Demographic/Baseline Data (see Appendix B, Table 2)
        iii. Subject Status (see Appendix B, Table 3)
    B. Safety Assessment
        i. Treatment Duration for All Subjects (see Appendix B, Table 3)
        ii. AE Data
            a. Overall Listing (see Appendix B, Table 4)
            b. Specific Symptom Listing (see Appendix B, Table 5)
            c. SAE Listing (see Appendix B, Table 6)
            d. Subject Deaths (see Appendix B, Table 7)