

Protocol Title: Kardia – A smartphone-based care model for outpatient cardiac rehabilitation

Protocol No: Kardia

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Specific Aims and Hypothesis:

This study aims to show that a smartphone-based Cardiac rehabilitation program which provides blood pressure monitors and wearable vital signs monitors is feasible and safe in low risk post-myocardial infarction patients in Singapore.

The hypotheses are as follows:

1. Smart-phone based model for cardiac rehabilitation is safe and will improve adherence to recommendations for physical activity post-myocardial infarction
2. The uptake of this home cardiac rehabilitation would lead to improvement in the following objective outcome measures:
 - a. 6 minute walk tests
 - b. Cardiovascular risk factors
 - i. Blood pressure
 - ii. Blood tests, i.e. lipid profile, HbA1C
 - iii. Body weight/ Body Mass Index (BMI)/ Waist/hip circumference
 - iv. Smoking
 - c. Major Adverse Cardiovascular Events (MACE) and Hospitalizations (12 months)
3. This smart-phone based model will allow patients to play an active role in their own management resulting in improvement in lifestyle habits and quality of life
 - a. Physical activity
 - b. Dietary habits (Dietary Habits Questionnaire)
 - c. Psychosocial wellbeing (Kessler 10 Psychological Distress Scale; Depression, Anxiety and Stress Scale 21)
 - d. Quality of life (EQ5D)
 - e. Compliance to medications
 - f.
4. The program will result in a lasting change in patient behaviour and lifestyle.

Background and Clinical Significance

Cardiovascular disease (CVD) is the most common cause of death in Singapore, accounting for ~34% of deaths. This means 1 in every 3 deaths in Singapore is due to heart disease or stroke. Ischemic heart disease is the leading cause of mortality and accounts for 17% of all deaths attributable to life-style related risk-factors. The total burden of this disease is likely to increase given the aging population and the increase in prevalence of obesity and predisposing conditions such as diabetes mellitus, hypertension and hyperlipidaemia.

A number of modifiable environmental and patient specific factors increase the chance of developing coronary artery disease (1). These include smoking, high blood cholesterol, physical inactivity, diabetes, high blood pressure and obesity. Following myocardial infarction, acute coronary

syndromes, surgical and percutaneous interventions, cardiac rehabilitation has provided an avenue for reducing future cardiovascular risks in patients by positively influencing these factors (2-5). The eventual goal of the program is to engage patients with permanent behavioural and life-style changes. There is strong evidence for the effectiveness of cardiac rehabilitation which is given a Class 1 recommendation from the American/European Cardiology guidelines, particularly for post-myocardial infarction patients (6, 7). Several studies and meta-analyses have demonstrated a significant reduction in mortality and morbidity (2, 8, 9).

Despite the clear benefits of cardiac rehabilitation programs, the uptake of these programs has been poor due to various patient and system factors (10-13). Cardiac rehabilitation programs are traditionally carried out in hospitals and health centres under the direct personal supervision of mentoring clinicians. Patient barriers, such as time constraints and distance from treatment centres lead to poor uptake of programs among eligible patients. To overcome these barriers, home-based care models have been proposed as a viable alternative to hospital-based cardiac rehabilitation programs even in the 1980s (14). The current state of mobile phone communication and technology provides not only the capacity but an especially attractive media option to support home-based cardiac rehabilitation programs (15, 16).

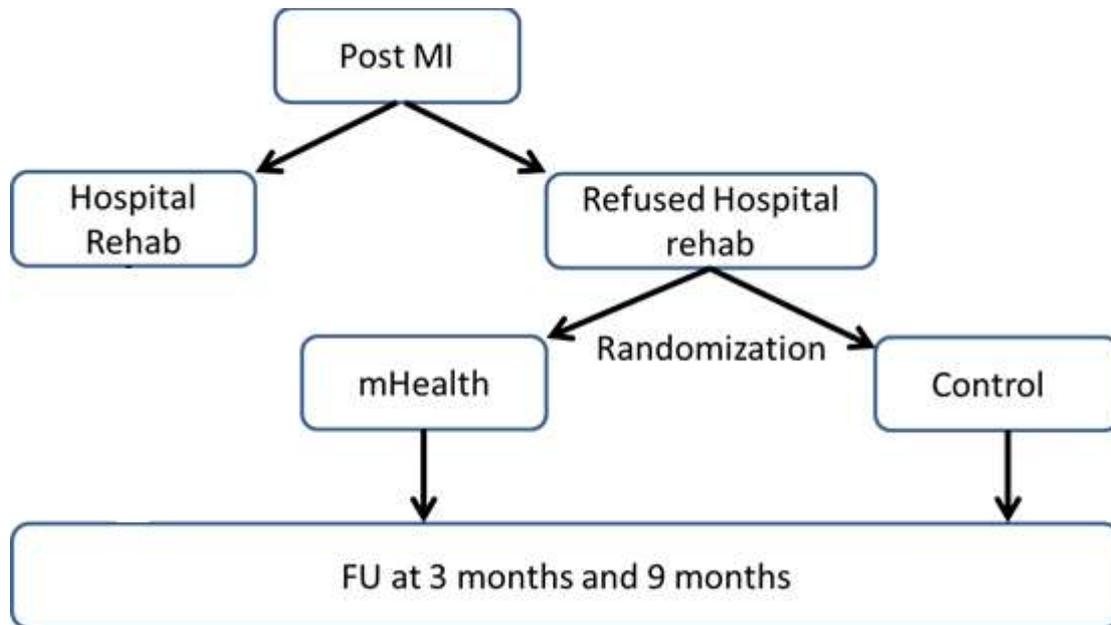
This study aims to investigate a smartphone-based cardiac rehabilitation program for patients recovering from myocardial infarction. The program focuses on providing patient centric self-monitoring platform enabling patients to take control and be actively involved in their medical care. The program (“Kardia”) is a 6-week rehabilitation program enabling patients to track their blood pressure, physical activity and medicine compliance through a mobile application. Each patient in the intervention arm is provided with a blood pressure monitor and activity tracker. The data from these devices would be automatically synced by a mobile application and uploaded to a confidential web portal which is only accessible by physician care-givers. The application also provides educational content/tasks, appropriate reminders for taking medications and daily goals on activity targets set by the care provider. This would help to engage the patients to enable behavioural change and improve compliance to medication and activity recommendations.

In Changi General Hospital, the uptake of cardiac rehabilitation among eligible patients is less than 20%. This study hopes to target the remaining 80% of patients who have refused the traditional cardiac rehabilitation program. It will be the first time that a smartphone based home cardiac rehabilitation program would be offered in Singapore. If shown to be safe and feasible, “Kardia” will help to improve patient outcomes in short to medium term. In addition, it may empower the patients to take a more active role in their medical care and promote long lasting behavioural changes in the long term. There will also be a significant operation impact if “Kardia” can be rolled out as an alternative care model to the traditional centre-based cardiac rehabilitation program, enabling greater patient access to “cardiac rehabilitation”. This is also in line with national initiatives to promote an active and healthy lifestyle, i.e. National Steps Challenge by the Health Promotion Board.

Methods/Approach

The project is a randomized controlled study of smartphone based cardiac rehabilitation program compared to routine care in patients who did not sign up for traditional hospital-based cardiac rehabilitation. 50 patients who are randomized to the intervention group (mHealth) will be enabled with remote monitoring devices (Blood Pressure and wearable vital signs monitor, Biovotion) and “Kardia” mobile application, for home-based rehabilitation program followed by review in the outpatient Cardiology clinics. The control group (50 patients) will just be monitored at fixed intervals

in the outpatient Cardiology clinics. For drop out subjects, there will not be any subject replacement. See Figure below.



Cardiac Rehabilitation program

Patients will be advised to commence the exercise program 2 weeks after the myocardial infarction

Time	Exercise Intensity	Exercise Frequency/Duration	Patient actions
Week 1	light	3x/week; 10 minutes	Exercise diary
Week 2	light	3x/week; 20 minutes	
Week 3	light	3x/week; 30 minutes	
Week 4	moderate	3x/week; 15 minutes	
Week 5	moderate	3x/week; 30 minutes	
Week 6	moderate	4x/week; 30 minutes	
Week 7	moderate	5x/week; 30 minutes	
Week 8	moderate	5x/week; 30 minutes	

Inclusion criteria:

- Age 21-85 years
- Willing and able to provide informed consent
- New onset of Post ST elevation and non-ST elevation myocardial infarction/staged PCI/ acute coronary syndrome/unstable angina
- Own and able to operate App on smartphone

Exclusion criteria:

- History of ventricular fibrillation not in the setting of acute myocardial infarction
- Documented sustained ventricular or supraventricular arrhythmia
- Unstable angina
- Awaiting staged revascularization
- Inability to perform 6MWT

Block randomization using sequentially numbered sealed envelopes would be used to assign patients to the intervention or control arms.

The primary outcome measure is compliance and adherence to the “Kardia” program. Other endpoints include 6MWT, patient wellbeing and behaviour (e.g. dietary habits, stress levels, physical activity) assessed using questionnaires, major adverse cardiovascular events (MACE), modification of cardiovascular risk profiles (i.e. LDL, BP, BMI, HbA1c, etc) and medicine compliance. The outcome measures and the corresponding measurement tools are listed in Table 1.

Table 1.

Outcome Measures	Measurement Tools
Primary Outcome Measures:	
Compliance to smart phone based cardiac rehabilitation program	Uploading of completed data (BP, activity) to web portal (90% compliance in intervention group would be considered acceptable)
Adherence to physical activity guidelines (150 minutes of moderate level exercise per week) at months 3 and 9	Questionnaire (a difference of 30% is considered significant)
Secondary Outcome Measures:	
6MWT at baseline (within 2 weeks upon discharge) months 3 (+/- 2 months) and 9 (+/- 3 months)	6MWT
Risk Factors	Blood pressure Blood tests, i.e. lipid profile, HbA1C Body weight/ Body Mass Index (BMI)/ Waist/hip circumference Smoking
MACE or hospitalization	Clinical notes
Medication Compliance	Questionnaire
Overall well being	Questionnaire (EQ5D)
Dietary habits	Questionnaire (FFQ)
Psychosocial well being	Questionnaire (K10, DASS 21)
Additional analyses:	
Reasons for non-compliance	Questionnaire
Smoking status	Questionnaire (SMOKING CESSATION SERVICE QUESTIONNAIRE)
Satisfaction and Usability	Questionnaires for patients and clinical staff in intervention group
Costs	Cost to implement <i>Kardia</i> (Staff-time, project implementation, facility cost)
Predictive analyses for re-hospitalizations, etc	Biofourmis

Sample size calculation

Previous studies have shown compliance of centre-based cardiac rehabilitation programs at about 60%. Based on that assumption, a sample size of 50 patients is necessary to show a 30% improvement in compliance in the mHealth arm, with $\alpha=0.01$ and power of 90%.

Statistical analyses

Data will be expressed as mean \pm SD for continuous variables and medians and IQR for skewed data. Statistical comparisons will be performed using paired Student's t test for within group changes over time, unpaired Students' t test for differences between intervention and control arms. Wilcoxon signed-rank test will be used to compare skewed data. Categorical variables will be expressed as counts and percentages and will be analysed using Chi-square test (or Fisher's exact test). All statistical tests will be 2-tailed and statistical significance will be based on $p<0.05$

Data Collection

Paper case record forms will be prepared. Questionnaire booklets will be provided to obtain patient responses. A research assistant will record the data and the data will be checked by the principal investigator for quality assurance. The data will be entered into an electronic database which will be password protected.

Adverse Event and Serious Adverse Event Reporting

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered investigational product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

A serious adverse event (SAE) or reaction is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity or
- is a congenital anomaly/birth defect
- is a medical event that may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Neither of the two interventions is anticipated to lead to any major adverse events. Minor troubleshooting problems will be addressed as described above and recorded. In the event the clinical staff have concerns about patient's continuation of therapy or participation in the trial, the research staff will be notified. A discussion with the primary clinician will be conducted to facilitate further therapeutic decisions. As per good clinical practice, serious adverse events will be reported

promptly to the institution representative (local SAE resulting in death), sponsor or regulatory bodies as required and appropriate.

Reporting timeline to CIRB:

- SAE that result in death, regardless of causality, should be reported immediately - within 24 hours of the PI becoming aware of the event.
- Local life-threatening (unexpected/ expected) SAE should be reported no later than 7 calendar days after the Investigator is aware of the event, followed by a complete report within 8 additional calendar days.
- Local unexpected SAE that are related events, but not life-threatening, should be reported no later than 15 calendar days after the investigator is aware of the event.
- An increase in the rate of occurrence of local expected SAE, which is judged to be clinically important, should be reported within 15 calendar days after the PI is aware of the event.
- Local expected SAE should be reported annually (together with Study Status Report for annual review).
- Local unexpected and unlikely related SAE that are not life-threatening should also be reported annually (together with Study Status Report for annual review).
- Local unexpected AE that are related events should be reported at least annually (together with Study Status Report for annual review).
- Non-local unexpected SAE that are fatal or life threatening and definitely/probably/possibly related should be reported not later than 30 calendar days after the PI is aware of the event.

Protocol Deviations

The investigator should conduct the trial in compliance with the protocol. A protocol deviation is a planned or unplanned departure from the approved study protocol. Any deviation that significantly affects the safety and/or rights of a study subject or the integrity of the data must be recorded on a deviation form.

The following is a list of reasons a deviation form should be completed for this study:

- Subject was randomized and did not satisfy eligibility criteria
- Subject received the wrong product, contrary to the randomization scheme
- Changes in procedures not pre-approved by IRB (e.g., asking subjects to fast before signing consent, taking additional blood draw or measurement not outlined in protocol/consent, etc.)
- Others that may affect the rights and safety of a subject, including errors in the informed consent process
- Others as appropriate for the study

The following deviations do not need to be recorded on a deviation form because this information will be captured elsewhere in the study data and will be summarized in the final report:

- Missed procedure(s) or questionnaire(s)
- Missed or out of window study procedures
- Other(s) as determined by the study team during the course of the trial

Ethical considerations

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Good Clinical Practice and the applicable regulatory requirements.

This final study protocol, including the final version of the Patient Information and Informed Consent Form, must be approved in writing by the Centralised Institutional Review Board (CIRB), prior to enrolment of any patient into the study.

The principal investigator is responsible for informing the CIRB of any amendments to the protocol or other study-related documents, as per local requirement.

Retention of study documents

Records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.) as well as IRB records and other regulatory documentation will be retained in a secured storage facility. The records would be accessible for inspection and copying by authorized authorities.

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