A Smartphone-based Application Post-myocardial Infarction to Manage Cardiovascular Disease Risk
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Kaavya Paruchuri, MD, Pradeep Natarajan, MD
Statistical Analysis Plan

A. Background and Rationale:
The period between inpatient hospitalization for symptomatic coronary artery disease (CAD) and post-discharge office consultation remains a vulnerable interval for adverse outcomes. We sought to develop and evaluate a tool to help guide, reassure and educate patients during this susceptible time.

We aimed to recruit and onboard 150 patients who have undergone percutaneous coronary intervention (PCI) with a novel mobile health platform developed specifically for this population. The mobile application (app) includes educational about specific procedures (PCI) and diagnoses (coronary artery disease, acute myocardial infarction) as well as lifestyle education programs (hypertension, hyperlipidemia, diabetes, weight loss, smoking cessation). The app also utilizes live health care coaches to interact with participants virtually to facilitate adherence to outpatient follow up, enrollment in cardiac rehabilitation and achieve individually targeted goals.

B. Hypothesis:
Our overall hypothesis is that engagement with our smartphone application post PCI will correlate with increased rates of enrollment in cardiac rehabilitation amongst study participants as compared to historical controls.

C. Endpoints:
C.1. Primary: 90-day cardiac rehabilitation enrollment rates
C.2. Secondary: 30-day cardiac outpatient follow up attendance

D. General Study Design and Plan
D.1. Design: Multi-site stratified single-arm prospective study
D.2. Type of controls: Historical
  D.2.a. Control ascertainment: Query of Research Patient Data Registry (RPDR) database (a centralized clinical data registry that gathers clinical information from various Partners hospital systems with a query tool that provides users with detailed medical record information on identified patient populations that meet user-defined characteristics and criteria such as diagnoses, procedures, medications and/or laboratory results) for subjects aged 21-85 years old who underwent percutaneous coronary intervention from 01/01/2015 through 12/31/2017.
  D.2.b. Control matching: Controls matched for Age, Sex (M/F), State (MA/non-MA), PCI Type (MI/Elective), DM2 (Y/N), Partners PCP (Y/N), Insurance Type (Commercial/Medicaid/Medicare/Other), Site (MGH/BWH)
D.3. Level and method of blinding: Open-label
D.4. Randomization time point: NA
D.5. Timeframe of all study periods:
  D.5.a. Intervention arm: screening (02/2018-06/2019), baseline (02/2018-06/2019), intervention period (02/2018-09/2019), follow-up (05/2019-09/2019)

D.5.b. Historical control arm: baseline (01/2015-12/2017), follow-up (03/2015-03/2018)

D.6. Inclusion/Exclusion criteria:

D.6.a: Inclusion: 21-85 years old, fluency in English language, underwent PCI at either MGH or BWH during screening period for either symptomatic CAD or ACS, own a smartphone or tablet

D.6.b: Exclusion: Recent (<1mo) drug or alcohol abuse, in hospital AMI, pregnancy, cognitive delay/dementia, incarceration

D.7. Study variables:

Age	Age at time of enrollment into study as coded into Partners EHR
Sex	Gender as coded into Partners EHR
State	State of residence (Massachusetts vs Non-Massachusetts) at time of enrollment into study as coded into Partners EHR
PCI Type	Reason for percutaneous coronary intervention (PCI). Myocardial infarction (MI) coded as chart diagnosis of MI or positive serologic (troponin) values prior to PCI. All other PCI without evidence of myocardial necrosis coded as elective.
Partners PCP	Coded "yes" for patients with PCP in Partners EMR working primarily for Partners Healthcare system. Coded "no" for patients with PCP in Partners EMR not within Partners system or missing PCP data.
Insurance Type	Coded based on primary insurance listed in Partners EMR.
Site	Coded based on location of incident PCI procedure (either Massachusetts General Hospital [MGH] or Brigham and Womens Hospital [BWH])
Hypertension	Chart diagnosis of HTN prior to or at time of incident PCI
Hyperlipidemia	Chart diagnosis of HLD prior to or at time of incident PCI, LDL-C >129 at time of incident PCI or Triglycerides >150 at time of incident PCI
Type 2 Diabetes	Chart diagnosis of DM2 prior to or at time of incident PCI, or Hemoglobin A1c > 6.4 at time of incident PCI
Peripheral Arterial Disease	Chart diagnosis of PAD prior to or at time of incident PCI or history of peripheral arterial intervention
Smoking	Chart history of smoking (codified as current smoker, former smoker (quit >1 month prior to PCI), or never smoker). For analysis, variable was condensed into never smoker or ever smoker (either current or former).
Coronary Artery Disease	Chart diagnosis of CAD prior to or at time of incident PCI or history of CABG or prior PCI
30-day hospitalization	Admission date to a Partners hospital within 30 calendar days of incident PCI.
90-day hospitalization	Admission date to a Partners hospital within 90 calendar days of incident PCI.
Cardiac reason for hospitalization	Admission for chief complaint of cardiac etiology (ie CAD, CHF, arrhythmia), admission requiring cardiac consultation or admission to a cardiology ward unit.
30-day ER visit	Presentation to Partners ER or Urgent Care within 30 calendar days of incident PCI without subsequent hospitalization.
90-day ER visit	Presentation to Partners ER or Urgent Care within 90 calendar days of incident PCI without subsequent hospitalization.

90-day Cardiac Rehabilitation	Attendance of cardiac rehabilitation intake session at a Partners facility within 90 calendar days of incident PCI.
30-day Cardiac Follow Up	Attendance of cardiac outpatient follow up appointment at a Partners facility (with MD or NP) within 30 calendar days of incident PCI
30-day repeat PCI	Repeat percutaneous intervention on same or new coronary lesion within 30 days of incident PCI.
90-day repeat PCI	Repeat percutaneous intervention on same or new coronary lesion within 90 days of incident PCI.
90-day Stroke	Chart diagnosis of or admission for new stroke within 90 calendar days of incident PCI as noted in Partners EHR.
90-day Nonfatal MI	Chart diagnosis of or admission for myocardial infarction (without subsequent death) within 90 calendar days of incident PCI as noted in Partners EHR.
90-day CV Death	Documentation of death within 90 calendar days of incident PCI noted in Partners EHR with cause specified as secondary to CAD, CHF, Arrhythmia or other clear cardiovascular reason.
90-day All Cause Death	Documentation of death within 90 calendar days of incident PCI noted in Partners EHR.
Conversion Rate	Number of patients enrolled in Wellframe out of number of total patients eligible for study.
Days Enrolled	Number of days between patient onboarded with Wellframe app and marked done by clinical staff.
Medication Reminders	Number of medication reminders set up by patient (0 if patient has not set up any reminders).
30-day Medication Adherence	Percentage of medication reminder tasks completed within 30 days on app. (Null if no patient reminders set up)
90-day Medication Adherence	Percentage of medication reminder tasks completed within 90 days on app. (Null if no patient reminders set up)
30-day Content Completion	Percentage of content tasks (articles opened) completed within 30 days on app
90-day Content Completion	Percentage of content tasks (articles opened) completed within 90 days on app
30-day Survey Completion	Percentage of survey tasks completed within 30 days on app
90-day Survey Completion	Percentage of survey tasks completed within 90 days on app
30-day Weekly Patient Engagement	Percentage of days in which patient completed at least one task from the app checklist (survey, article, physical activity goal, encouragement) or sent a message to clinical team at least once over the previous 7 days within 30 days on app.
90-day Weekly Patient Engagement	Percentage of days in which patient completed at least one task from the app checklist (survey, article, physical activity goal, encouragement) or sent a message to clinical team at least once over the previous 7 days within 90 days on app.
30-day Daily Patient Engagement	Percentage of days in which patient completed at least one task from the app checklist (survey, article, physical activity goal, encouragement) or sent a message to clinical team within 30 days on app.

90-day Daily Patient Engagement	Percentage of days in which patient completed at least one task from the app checklist (survey, article, physical activity goal, encouragement) or sent a message to clinical team within 90 days on app.
Patient Satisfaction	Average patient response on app satisfaction via app survey function.
Patient Messages Sent	Number of total messages sent by patient within 90 days on app
Patient Messages Received	Number of total messages sent to patient within 90 days on app
Patient Messages Opened	Percentage of messages sent to patient that were opened
Patient Message Response	Percentage of messages sent to patient with at least one message response from patient
Patient Physical Activity	Percentage of days where patient met physical activity goal (default of 500 steps) within 90 days on app.
Days to First Message	Days until first message sent from care team to patient
Clinical Messages	Percentage of patients receiving at least one message from app care team within 90 days on app.

D.8. Sample size and power: We have at least 95 percent power with 150 enrolled participants, 450 matched historical controls, with alpha equal to 0.05, to detect an effect of at least 2-fold increase in the primary clinical outcome, likelihood of enrollment in cardiac rehabilitation within the 90 day study period with baseline 25% enrollment rates[6].

E. General Considerations:
    E.1. Analysis populations:
        E.1.a.: Full analysis population: All intervention subjects who downloaded the study application and 3:1 matched historical controls.
        E.1.b.: Engagement population: All intervention subjects who downloaded the study application.
    E.2. Covariates and subgroups: Sex (M/F), State (MA/non-MA), PCI Type (MI/Elective), DM2 (Y/N), Partners PCP (Y/N), Insurance Type (Commercial/Medicaid/Medicare/Other)
    E.3. Missing data: Missing data values for participants who fit inclusion criteria will default to zero or "no" for dichotomous variables. Missing data values for participants will default to "unknown" or "other" for continuous or categorical variables.

F. Summary of study data: All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by site, treatment and subject, and when appropriate by visit number within subject. All summary tables will be structured with a column for each treatment in the order (Control, Experimental) and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

G. Protocol deviations: Subjects who do not fit inclusion criteria will be removed from the data set prior to analysis. Subjects with missing data will be treated as discussed above (Section E.3.)

H. Efficacy Analyses: The Cox Proportional Hazards model will be used to assess efficacy of the intervention (use of the application) on the primary outcome. The percentage of subjects attending cardiac rehabilitation enrollment within 90 days of discharge from incident PCI hospitalization will be compared across groups. A secondary analysis between the two groups will be conducted adjusting for covariates such as age, sex, insurance type, state, diabetes, and partners PCP).

Primary analysis will verify balance in matching (unadjusted) via Chi-squared model for binary variables and ANOVA for categorical variables

I. Engagement Analyses: Overall engagement by patients in the intervention arm with the Wellframe application will be assessed by evaluating the number of days or weeks with at least one task completed (including surveys done, content read, activity goals reached and medication reminders used) within both a 30- and 90-day period. Individual task completion rates will also be assessed and reported within 30- and 90-day periods. Use of messaging between patients and health advocates will also be assessed during a 30- and 90-day period. Changes in these metrics across 30- to 90-days will be evaluated.

J. Exploratory Analyses:
We will compare subgroups (MI/elective) using linear regression across the 30-day engagement metrics above to evaluate predictors of engagement (adjusting for both 30-day engagement as well as matching covariates such as age, sex, PCI type, state, insurance, partners PCP and site).

We will use the Cox Proportional Hazards model to assess efficacy of the intervention on lowering rate of ER visits for cardiovascular reasons, ER visits for all causes and hospitalizations for all reasons.

We will use the Cox Proportional Hazards model to assess efficacy of the intervention on reducing rates of repeat PCI, stroke, non-fatal MI, cardiovascular cause of death and all cause death within 90 days of enrollment.

We will use the Cox Proportional Hazards model to assess for improvement in percentage of patients adhering to cardiovascular follow up appointments within 30 days of discharge.

K. Type I Error Control: We will control for error by limiting our primary outcome to 90-day cardiac rehabilitation enrollment. All subsequent analysis, including secondary outcomes, will be considered exploratory.

L. References:
1.Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation. 2017;135(10):e146-e603.
2. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095-2128.
3. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology

Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127(4):e362-425.

4. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2014;64(24):e139-228.

5. Tanguturi VK et al. Clinical interventions to reduce preventable hospital readmissions after percutaneous coronary intervention. *Circ Cardiovasc Qual Outcomes.*2016;9:600-604.

6. Ades PA, Keyeyian SJ, Wright JS, et al. Increasing cardiac rehabilitation participation from 20% to 70%: A road map from the million hearts cardiac rehabilitation collaborative. 2017;92(2):234-242.

FIGURES

1. Baseline Characteristics: Wellframe vs Matched Controls
   A. Descriptive: *Prove similarity of demographics* (**Table 1**)

	Enrolled	Matched Control
Age	# (SD)	# (SD)
Sex		
Male	#% (#)	#% (#)
Female	#% (#)	#% (#)
PCI Type		
MI	#% (#)	#% (#)
Elective	#% (#)	#% (#)
Site		
MGH	#% (#)	#% (#)
BWH	#% (#)	#% (#)
Ethnicity		
European	#% (#)	#% (#)
Non-Eur	#% (#)	#% (#)
Insurance		
Commercial	#% (#)	#% (#)
Medicare	#% (#)	#% (#)
Medicaid	#% (#)	#% (#)
Other	#% (#)	#% (#)
State		
MA	#% (#)	#% (#)
Non-MA	#% (#)	#% (#)
Partners PCP	#Y% (#)	#Y% (#)
Diabetes	#% (#)	#% (#)
Hypertension	#% (#)	#% (#)
Hyperlipidemia	#% (#)	#% (#)
PAD	#% (#)	#% (#)

Demographics: Wellframe vs All Control (All eligible control population) **Supplemental Fig 1**

2. Comparison of Primary Outcomes
1. Univariate Analysis (Cox Proportional Hazards): Wellframe Use
2. Multivariate Analysis (Cox Proportional Hazards): Wellframe Use + Matching Criteria
3. Multivariate Analysis (Cox Proportional Hazards): Wellframe Use + Matching Criteria + CV Risks

A. Cardiac Rehab Enrollment (Cox Proportional Hazards Model)
% of patients discharged after intervention who attend at least one session of clinic-based cardiac rehab

Outcome	Exposure(s)	Tables
CR Enrollment	Wellframe	
CR Enrollment	Wellframe + age + sex + insurance + state + DM2 + Partners PCP	
	" + CV risk factors (HTN, HLD, PAD, DM2)	

B. Outpatient Cardiology Follow Up within 4 weeks (Cox Proportional Hazards Model)
% of patients who attend at least one clinic-based cardiology follow up appointment within 4 weeks of discharge.

Outcome	Exposure(s)	Tables
OP CV F/U	Wellframe	
OP CV F/U	Wellframe + age + sex + insurance + state + DM2 + Partners PCP	

4. Comparison of Exploratory Outcomes:
30D Outcomes: All Cause Hospital, CV Hospital, All Cause ER, CV ER, CV FU and CR
A. 30 day readmission (All cause) (Cox Proportional Hazards Model)

Outcome	Exposure(s)	Tables
All Cause 30d	Wellframe	
All Cause 30d	Wellframe + age + sex + insurance + state + DM2 + Partners PCP	

B. 30 day readmission (CV related) (Cox Proportional Hazards Model)

Outcome	Exposure(s)	Tables
CV 30d	Wellframe	
CV 30d	Wellframe + age + sex + insurance + state + DM2 + Partners PCP	

C. MACE (Cox Proportional Hazards Model)

Outcome	Exposure(s)	Tables
MACE	Wellframe	
MACE	Wellframe + age + sex + insurance + state + DM2 + Partners PCP	

D. 90 day readmission (All cause) (Cox Proportional Hazards Model)

Outcome	Exposure(s)	Tables
All Cause 90d	Wellframe	
All Cause 90d	Wellframe + age + sex + insurance + state + DM2 + Partners PCP	

E. 90 day readmission (CV related) (Cox Proportional Hazards Model)

Outcome	Exposure(s)	Tables
CV 90d	Wellframe	
CV 90d	Wellframe + age + sex + insurance + state + DM2 + Partners PCP	

4. Engagement (Data from Wellframe)

Table 4.1

	90-day
Conversion Rate	
Enrolled/Total PCI	%
Enrolled/Approached	%
Average Days Enrolled	##
Average Medication Reminders	##
Average Patient Satisfaction	##
Average Clinical Messages	%
Average Days to First Message	##
Average Patient Messages Received	##
Average Patient Messages Opened	%
Average Patient Message Response	%
Average Patient Messages Sent	##
Average Patient Physical Activity	%

  i. Conversion Rate (# pt enrolled in Wellframe out of # eligible)
      a. Percentage of patients enrolled / total PCI
      b. Percentage of patients enrolled / approached

Table 4.2

	30-day	90-day
Medication Adherence	%	%
Content Completion	%	%
Survey Completion	%	%
Weekly Patient Engagement	%	%
Daily Patient Engagement	%	%

Table 4.3: Predictors of Engagement: Pearson Correlation Analysis

Outcome	Exposure(s)	Figure
Daily Engagement 30d	Age + Sex + DM2 + knownCAD + HTN + HLD + MI/Elective + PAD	Correlation Matrix
Daily Engagement 90d	"	
Weekly Engagement 30d	"	
Weekly Engagement 90d	"	

Table 4.4: Sentiment Analysis (what the messages are about)

Table 4.5: Matrix of correlation between the different engagement values given by Wellframe

FIGURES:
1. Cardiac Rehabilitation Enrollment: Bar Plot (Intervention Group vs Control Group)
2. App Engagement: Bar Plot (Percentage of Days With App Engagement)
3. Outpatient Cardiac Follow Up: Bar Plot (Intervention Group vs Control Group)
4. 30-Day and 90-Day Readmission Rates: 2 Panel Bar Plot (Intervention Group vs Control Group)
5. App/Dashboard Representative Image (From Wellframe)
6. Process Outcomes: Flow chart of recruitment/enrollment.
7. Daily Engagement and Clinical Outcomes [CR Enrollment, CVFU, 30 Day Readmission, 90 Day Readmission]: 4 Panel Bar Plot (Intervention Group vs Control Group)
8. Predictors of Engagement: Correlation Matrix (Daily/Weekly Engagement Rates vs Traditional CV Risk Factors [Age, Sex, Known CAD, MI, PAD, DM2, HTN, HLD])