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Title: Protocol for Project Recovery: Cardiac Surgery - Leveraging Digital Platform for Efficient Collection of Longitudinal Patient-Reported Outcome Data Towards Improving Postoperative Recovery

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Abstract (287/300)

Introduction

Improving postoperative patient recovery after cardiac surgery is a priority, but our current understanding of individual variations in recovery and factors associated with poor recovery is limited. We are using a health-information exchange platform to collect patient-reported outcome measures (PROMs) and wearable device data to phenotype recovery patterns in the 30-day period after cardiac surgery hospital discharge, to identify factors associated with these phenotypes and to investigate phenotype associations with clinical outcomes.

Methods and analysis

We designed a prospective cohort study to enroll 200 patients undergoing valve, coronary artery bypass graft, or aortic surgery at a tertiary center in the U.S. We are enrolling patients postoperatively after the intensive care unit (ICU) discharge, and delivering electronic surveys directly to patients every 3 days for 30 days after hospital discharge. We will conduct medical record reviews to collect patient demographics, comorbidity, operative details and hospital course using the Society of Thoracic Surgeons (STS) data definitions. We will use phone interview and medical record review data for adjudication of survival, readmission, and complications. We will apply group-based trajectory modeling to the time-series PROM and device data to classify patients into distinct categories of recovery trajectories. We will evaluate whether certain recovery

pattern predicts death or hospital readmissions, as well as whether clinical factors predict a patient having poor recovery trajectories. We will evaluate whether early recovery patterns predict the overall trajectory at the patient-level.

Ethics and dissemination

The Yale Institutional Review Board approved this study. Following the description of the study procedure, we obtain written informed consent from all study participants. The consent form states that all personal information, survey response, and any medical records are confidential, will not be shared, and are stored in an encrypted database.

Strengths and limitations of this study

- This study will assess the patient perspective on recovery after cardiac surgery at a high frequency within the 30-day postoperative period with surveys and activity monitoring via a health information platform and wearable devices.
- Using longitudinal patient-reported outcomes measure (PROM) data, this study will define recovery patterns and factors associated with different recovery trajectories and guide the development interventions to improve recovery and support expansion of the study to additional sites.
- The study is single center and the sample size is limited.

Text (4081 words)

Background

Improving postoperative patient recovery is a priority. Readmission rates in the post-operative period are high. Moreover, in the United States, the expansion of episode-based payments and performance measures is increasing interest in the post-acute experience of patients[1, 2]. However, we generally lack systematically-collected information on the experience of patients in the post-acute period, as few studies rigorously collecting information using established patient-reported outcomes measures (PROMs). We have, for example, little information about the variation of the trajectories of recovery and the factors most strongly associated with better outcomes[3].

The assessment of the patient experience can provide important insights into the process of recovery that is not evident through clinical outcomes or intermittent clinical office visits. PROMs and wearable devices can provide complementary information by providing measurements of how the patient's experience and functional status change over time[4]. Current digital platforms allow us to efficiently collect PROMs and wearable-generated data at high frequencies and with little cost and burden. These automated data collection approaches may minimize the bias introduced by clinician-directed patient interviews[5]. Such a platform is highly suited to obtain repeated measures to characterize a time-dependent process such as recovery[6].

Cardiac surgery is an ideal area for the study of recovery. Many patients have good outcomes, but the limited existing evidence suggests a wide variation

in the post-operative experience of these patients[7]. However, these patients' experience has been poorly studied, as most studies of recovery simply assess deaths and complications.

Characterizing the recovery from the patient perspective is important for many reasons. First, shared decision-making and informed consent should be guided not only by the risk of mortality and complications but also by the recovery experience. Understanding variations in recovery could enable the early identification of people who are struggling and require additional attention. Recovery data from the patient perspective may enable remote monitoring after the procedure to selectively and preemptively intervene on those at high risk of poor recovery to improve outcomes. Characterization of recovery can also be used to identify patient, surgeon, procedural, and institutional factors that are associated with different patterns. With this information we can identify modifiable risk factors for poor recovery.

Thus, at this juncture, there are several notable gaps in knowledge. First, although recovery occurs over time, most studies of recovery included a small number of timepoints, and the recovery trajectory phenotypes remains poorly defined[3]. Cohort-level average of recovery trajectories is a common way of reporting[3] and can indicate how patients recover on average[7], but it obscures individual variation such as rapid early recovery, gradual recovery, or initial recovery followed by a decline. Second, we have limited understanding of how recovery trajectories vary by patient factors, operation types, center or surgeon

characteristics, procedural processes, and complications, which limit opportunities to identify high risk patients preemptively and intervene.

Accordingly, our overall objective is to characterize short-term trajectories of patient recovery after cardiac surgery using PROMs and wearable data. We are conducting a prospective study to characterize trajectories of postoperative recovery in multiple domains after cardiac surgery. The specific aims of this study are to: 1) leverage a digital data platform to collect PROM and wearable device data to bring forth the variable individual recovery trajectories, 2) describe distinct classes of recovery trajectories and clinical factors associated with the classes, and 3) to evaluate whether early postoperative recovery trajectory predicts later recovery trajectory. In addition, we will investigate optimal ways to manage missing data specific to these time-series data This study is a step toward using this approach to prospectively monitor and preemptively identify patients at risk of poor recovery and facilitate intervention to reduce the risk of adverse events.

Methods

Design Overview

This is a prospective cohort study of patients who are undergoing valve, CABG, or aortic surgery at a tertiary center in the U.S. We chose the operations because they are the most common cardiac operations performed[8]. We are enrolling patients postoperatively after ICU discharge in order to ensure clinical stability, and we electronically delivering surveys directly to patients every 3 days for 30 days after hospital discharge to study patient trajectories in multiple

domains characterizing recovery. The closing phone interview after 30 days, electronic medical record review, and linkage to the Society of Thoracic Surgeons database are used to confirm survival, readmission, and complications. The closing interview asks about details of readmissions if they occurred, patients' overall satisfaction with the study, and whether their experience was well captured by the summary of their PROM data. We will apply group-based trajectory modeling to the longitudinal PROM data to identify distinct categories of recovery trajectories in a data-driven fashion. We also identify predictors of protracted recovery trajectory and evaluate whether early recovery patterns (<10 days) predict the overall trajectory (30 days) at the patient-level. The Yale Institutional Review Board approved this study.

Patient Population

This study began in January 2019 and is ongoing. The study is taking place at Yale-New Haven Hospital, a tertiary center in the United States, where over 1,100 cardiac surgeries are performed annually. Inclusion criteria are patients of age 18 and older who are undergoing coronary artery bypass grafting (CABG), valve replacement or repair, or aortic operations. Exclusion criteria are those who undergo heart transplant, extracorporeal membrane oxygenation (ECMO), adult congenital operations, or ventricular assist device implantation, as these patient populations tend to have a longer course of intensive care unit stay[9], precluding the timely enrollment necessary to capture immediate postoperative recovery. We also excluded those who do not own a smartphone

or a tablet or those who do not speak or read English, because the digital platform for PROM data collection relies on patients responding to surveys displayed on web browser via email or text, and the surveys were written in English language. We do not allow proxy for survey response and consequently excluded patients who were not able to respond by themselves as determined by the research assistant.

Recruitment

Recruitment takes place postoperatively after the patient has left the intensive care unit (ICU) for the step-down or floor unit (Figure 1). We chose to enroll patients postoperatively, as opposed to preoperatively, because postoperative enrollment allows for enrollment of patients who undergo surgery under non-elective settings. Recruitment after transfer from the ICU setting ensures clinical stability. A research assistant (RA) visits the patient and after confirming the patient is eligible to participate and following the description of the study procedure, obtains written informed consent (Supplementary Material S1) from all study participants. The informed consent form states that all personal information, survey response, and any medical records are confidential, will not be shared, and will be stored in an encrypted database.

We iteratively refined the enrollment process to minimize the onboarding time, which includes obtaining informed consent and signup process directed by the RA on a tablet device to enter patient name and email address or phone number and takes approximately 10-15 minutes.

PROM instrument and administration

We use 24-item quality of recovery (QoR-24) to characterize patients' postoperative recovery in various domains. The questionnaire consists of 24 items that were developed and validated in inpatient and outpatient surgical populations[10-13]. The instrument was previously adapted into a mobile format and was successfully used to administer the survey daily for 14 days[11, 12]. We added 3 items to QoR-24 to capture the self-reported time patients went to sleep, the time they awakened, and their global perception of how much they have 'recovered' in a 0-100% scale. The resulting 27-item questionnaire takes 2-4 minutes to complete, making its frequent administration feasible (Supplementary Material S2). Among the published studies in cardiac surgery, this study will have the highest number of PROM data points collected in the first postoperative month[3].

Digital data platform

We are delivering surveys on the day of enrollment and every 3 days for 30 days. This method provides detailed longitudinal data across multiple domains of recovery (Figure 2). To facilitate data organization and scheduled survey delivery, we use Hugo (Me2Health, LLC, Guilford CT, USA) a patient-centered health data sharing platform, which has a customizable survey delivery function and reminder feature to facilitate data collection. Hugo platform allows for automated delivery of surveys without researchers having to directly contact patients, which facilitates high-frequency data collection. Additionally, it imports

data from connected wearable devices to facilitate centralization of patient health data. The patients retain access to their own data in a cloud-based account.

Identifying common reasons for low response rate

Recognizing that the survey response will be incomplete for some participants, we have conducted a phone interview with the first 22 patients to learn reasons for low responses and identify strategies to minimize the barriers toward survey response for subsequent participants. In the first 22 patients, we identified 5 with response rate of <50% and conducted recorded phone interviews. Our interview guide (Supplementary Material S3) contained questions to elucidate technical barriers, differential preferences for engagement, and or any other issues precluding survey completion. We also asked whether the length of the questionnaire or types of questions asked made it difficult to complete the survey. Two members of the research team (CB and MM) evaluated the interview recordings to identify common reasons for low response rate. This suggested the potential importance of reminder to maintain patient engagement. We modified the protocol to contact all participants approximately 10 days after enrollment.

Additional clinical data and adjudication of hospitalization and survival

Additionally, we are using the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database data specifications to retrospectively collect clinically

relevant data in this patient population. Pre-specified candidate predictors in this database will be used to identify clinical predictors of recovery trajectories (Table 1). The STS database contains patient demographics, comorbidities, presenting clinical status, operative details, and postoperative mortality and morbidity up to 30 days after the time of operation[14]. These data are routinely collected at Yale New Haven Hospital.

We will determine mortality and hospital readmissions by several approaches: review of hospital records, review of cardiac surgery clinic notes, and conducting closing phone interviews with the patient or contact person previously identified.

Patient Involvement

Prior to launching the study, we interviewed 5 patients both in pre and postoperative settings to evaluate whether the frequency of survey delivery and PROM instrument were likely to adequately capture their experience of recovery. All patients agreed that the frequency of questionnaire administration and the length of the PROM instrument were reasonable and provided face validity that the questionnaire captured aspects of recovery that were important to the patients. Additionally, this article is authored with a patient (LG) who participated in the study to reflect his perspective on the study design and experience in responding to the surveys.

Sample size

The study sample target is 200 patients. Adequate sample size for studies using group-based trajectory modeling depends on the dataset's representativeness of the population of interest[15]. Therefore, the concept of statistical power traditionally used for sample size calculation does not apply to latent class analyses. We may generate a larger simulation dataset from the measured patient trajectory data to perform a split-sample testing, evaluating whether trajectories generated from the derivation sample would allow for satisfactory categorization of the testing dataset. Additionally, the study setting is scalable to increase the sample size by increasing the enrollment period, should a larger sample size become necessary.

Analytical approach – group-based trajectory modeling

The resulting dataset is a complex time-series data, with each patient having 10 data points (one every three days) at different postoperative times for each item. A practical approach to dimension reduction is group-based trajectory modeling, which is a type of latent class analysis that groups similar patient trajectories according to a number of features derived from the time-series data[16, 17]. This approach allows for dimension reduction of the complex time-series data into several distinct classes of recovery trajectories. These trajectories can be labeled according to the observed clinical phenotype of trajectories, for example 'fast recovery,' 'average recovery,' or 'protracted recovery,'. This data-driven categorization enables additional regression modeling to identify predictors of patients belonging to a certain class of recovery path.

The dataset will be classified into distinct categories of trajectories at domain level, using group-based trajectory modeling[16, 17]. Traj package on R[18] or Proc Traj package on SAS[15], performs trajectory modeling by first extracting 24 features of patient-level trajectory, selecting a subset of features that describes the overall trajectory, and identifying optimal number of classes to group the trajectories based on the longitudinal k-means method. The 24 features include range, mean change per unit time, and slope of the linear model (Table 2), which have been demonstrated to discriminate between stable-unstable, increasing-decreasing, linear-nonlinear, and monotonic-nonmonotonic patterns of trajectories[18]. K-means method partitions the time-series data into k groups such that the mean squared error distance of each data point from the assigned cluster is minimized[19]. The optimal number of clusters is determined by the minimization of Bayesian information criterion, which signifies the balance between model's complexity and the ability to describe the dataset. This process yields distinct classes of patient trajectories in a data-driven fashion. Trajectories will be identified separately for the 5 domains and 1 global recovery measure.

Analytical approach – missing data

Because missing data are inevitable in longitudinal PROMs, there is a need employ an appropriate handling of missing data. Multiple imputation prior to latent class analysis may yield a less biased estimate of the resulting trajectories. An alternative approach used in group-based trajectory models assumes the data are missing at random (MAR) and generates the maximum likelihood of the model parameters[20]. MAR is valid when the response attrition is independent of

the group membership. However, patient attrition is oftentimes dependent on clinical characteristics and likely related to the class of trajectory itself. An extension of the model allows for modeling of attrition across trajectory groups[21], permitting dropout probability to vary as a function of covariates or observed outcomes prior to dropout and yields a more robust estimate of the probability of group membership. As such, we will perform sensitivity analysis to compare the trajectories generated via raw data vs. data preprocessed with multiple imputation vs. trajectories generated via trajectory model accounting for response attrition.

Results

Between January and May 2019, we have enrolled 22 patients who completed the 30-day follow-up. In this cohort, median age was 58.5 years (interquartile range 53.5-67.0) and 7 (32%) were women. There were 9 (41%) mitral valve repair cases and 6 isolated or concomitant CABG (27%).

Barriers to completing surveys

Of the 22 patients enrolled, 3 (14%) did not complete any surveys, 19 (86%) completed at least 3 surveys, and 17 patients (77%) completed at least 6 of 11 delivered surveys (>50% of delivered surveys). Of the 5 patients who completed less than half of the surveys, we successfully contacted 4, and 1 could not be reached after 5 attempts. All 4 reported that the major barriers precluding survey completion were their clinical conditions: 2 described readmissions as an

overwhelming event that made them feel continuing survey participation challenging, and 2 described not feeling well in general, which precluded participation. All 4 patients noted that text or email reminders might have been helpful to sustain participation. Based on these responses, we modified the protocol to contact all participants approximately 10 days after enrollment to improve engagement and resolve any patient-specific issues in completing the surveys.

Clinical outcomes

There were no deaths during follow-up. Two (9%) patients experienced at least 1 hospital readmission. Figure 2 depicts the breadth in recovery trajectories in pain, sleep, ability to take care of own hygiene, and perception of overall recovery in five patients with complete response.

Patient perspective

An author (LG) participated in this study as he underwent cardiac surgery. He noted that the length and frequency of the questionnaire was reasonable and helped him to be more aware of the recovery process because responding to the questions facilitated introspection on his progress across different domains. He recommended that the study platform feedback the data to study participants, such as a visual summary of the trajectory or response for patients to better gauge their progress. Additionally, he noted that responses may differ across the time of the day, as he was able to better function physically in the afternoon

compared with in the morning. Finally, he suggested the potential value of reviewing the questionnaire during preoperative counseling to highlight important aspects of recovery to provide better patient and family expectations. Investigators plan on providing a brochure to the clinic that contains this information.

Discussion

This study will provide time-series data on short-term recovery after cardiac surgery using PROM instruments complemented by clinical records obtained via the STS database and electronic health records. This study will provide one of the highest density of postoperative PROM data in existing cardiac surgery literature[3], and it will characterize the variability in individual recovery processes with a high temporal resolution. This study will be important in closing knowledge gaps around patient-level variations in trajectories because prior studies have mostly focused on changes in PROM scores at a limited number of time points[3] or reporting group-level aggregate of longitudinal recovery data[7, 22]. Because recovery is an individual, variable, and time-dependent process, we designed our data collection and analytical approach to capture such features important to recovery.

This study has the potential to make a variety of contributions toward improving post-acute phase of care. First, we will be able to develop a preliminary nomogram of postoperative recovery for each domain and overall perception of recovery, which would be instrumental for patients and clinicians to

gauge the breadth of possible recovery trajectories to facilitate informed shared decision-making. Second, identifying predictors of accelerated or protracted recovery, as classified by group-based trajectory model, may allow for individualized prediction of the postoperative recovery course to better inform the patients and family members. Third, early detection of recovery signals related to adverse events, such as mortality and readmission, may eventually facilitate preemptive intervention and focused monitoring of patients at an elevated risk for such events. Our design of the longitudinal PROM data collection allows for incremental update of such prediction as patients progress through the phase of recovery.

There are many challenges to the successful acquisition of patient measurements during recovery: efficient administration of PROMs in a way that does not require prohibitive amount of resources, minimizing selection bias originating from barriers to survey completion, handling of missing data that inevitably occurs in PROMs, and summarizing the complex data in a way that is interpretable to surgeons and patients[23]. Additionally, the use of wearables and device data require active patient participation in periodically charging the device, wearing them correctly, and reliably syncing the device to the server for data uploads. Moreover, there is a need to provide value to the patients for providing their recovery profile, such as giving them access to their health data in a meaningful way.

The resulting data collection, analytical, and output platforms have the potential of being implemented in the clinical setting where an integration of

incrementally increasing PROM and clinical data provides the near-real time estimate of individual patient risk of adverse post-operative events. Such a model may allow for triggering of preemptive clinical intervention. An output may assimilate a form of clinical dashboard within the electronic health record system, which may be monitored at a centralized location where a trained clinician reviews high-risk cases filtered by the algorithm to further evaluate whether the patient condition warrants an intervention. Together, this workflow has a tremendous potential to improve post-acute phase of care following surgery.

Lessons Learned from the initial experience

Through this first group of enrolled patients, we learned that most of the patients approached were willing to participate and consented to the study. By streamlining the enrollment process, the enrollment time shortened from over 1 hour on the first patient to approximately 10-15 minutes for the current enrollment. The overall response rate is acceptable, with 77% of the participants completing more than half of the delivered surveys independently without any intervention by researchers. Challenging recovery course, including readmissions may have interfered with patient engagement. While this would have resulted in an underrepresentation of those with protracted recovery or with complications, our preliminary data show we were able to capture variations in the trajectories of recovery.

To sustain patient engagement through challenging recovery course, we implemented a protocol for a research assistant to call the patient around 10

days after enrollment to troubleshoot any issues and reemphasize the importance of their participation. We believe that once the survey becomes part of clinical workflow with clinicians monitoring and responding to the PROM response, patient response rate would improve further.

We modified the enrollment protocol to reduce the enrollment time, because to some patients, the complexity and prolonged time spent for enrollment discouraged signups. Initial protocol for enrollment required patients to download an app and register. This resulted in a wide range of time spent for enrollment between 15 minutes and 90 minutes, with longer enrollment owing to technical challenges. These challenges include patients forgetting the password for app download, having to reset the password, and not having immediate email access to check account confirmation emails. Because our cardiac surgery patient population tended to be older, these technical challenges may have been pronounced. By not including the app download and allowing for the research assistant to enroll the patient via an online form with their permission, the enrollment time shortened significantly to 10-15 minutes.

Examining the initial individual data on recovery, there were wide variations in the trajectories of recovery even among only 5 patients. The variation suggests that the instrument we used was sensitive to capturing such differences. We also noted variations in improvement over time across different domains of recovery, where overall perception of recovery seemed to have a steady improvement pattern, while pain varied between consecutive measurements in some patients.

Limitations

There are several limitations to this study. First, the single-center tertiary care setting limits the sample size and applicability of the findings to patients cared for in different settings. A multi-center study following the current study would address this limitation and evaluate whether the findings at our center are comparable to findings in other centers. Additionally, group-based trajectory modeling will classify patients into distinct trajectories based on similar recovery patterns, and this analytical approach may allow for generalization of the variations in the trajectories as long as our sample represents the breadth of the possible variation in recovery.

Another limitation is the exclusion of patients who cannot participate for various reasons. The use of digital platform is advantageous in reducing the resource intensity for data collection, but leads to exclusion of patients who do not own mobile devices, which likely affects older patients disproportionately. As the number of adults using mobile devices is increasing[24], we believe this will become less of a limitation over time. Initiating this study now despite this limitation is important to establish a platform that may become the standard of postoperative care when the vast majority of patient population own digital devices in a predictably near future. Those who cannot participate due to lack of interest represent an important population that may be distinct in characteristics and risk profiles. We plan on minimizing the non-participation for the lack of interest by intermittent phone check-ins to sustain interests and identify barriers

to inform strategies to increase engagement. In following studies, we may consider other forms of incentives to participate, if this population is indeed distinct and large in proportion. Additionally, when the PROM data are integrated into routine clinical care, patient engagement will likely increase substantially because they will be more inspired to share these data if they are used by their clinicians.

Finally, postoperative enrollment and retrospective assessment of preoperative health status, as opposed to preoperative enrollment, may introduce recall bias. We decided on postoperative enrollment, because preoperative enrollment precluded standardized enrollment of patients operated on under non-elective settings. Given the retrospective assessment of baseline health status takes place on the first postoperative survey, we believe the recall bias is minimized owing to the temporal proximity.

Conclusion

This study will generate highly granular, longitudinal PROM data to characterize individual trajectories of patient recovery after cardiac surgery. Digital data sharing platforms promise to minimize the patient and researcher burden in administering and completing PROMs, allowing for characterization of granular progression of patients' state of health over time in the postoperative period. Implementation of such study is complex but feasible, and it will serve as an important platform to facilitate clinical use of PROM data to improve the overall patient recovery.

Authors contributions

MM, HMK, SD, and AG developed the study and research question. MM and HMK developed analytical strategy with inputs from BJM, GCL, and YZ. SIC and ES guided refining the enrollment strategy and interpretation of the phone interview responses. LAG provided patient perspective on the study protocol and interpretation of the preliminary results. All authors developed and approved the final manuscript before submission.

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Competing interest statement

Dr. Chaudhry is a paid reviewer for the CVS Caremark State of CT Clinical Pharmacy Program.
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Dr. Krumholz works under contract with the Centers for Medicare & Medicaid Services to support quality measurement programs; was a recipient of a research grant, through Yale, from Medtronic and the U.S. Food and Drug Administration to develop methods for post-market surveillance of medical devices; was a recipient of a research grant with Medtronic and is the recipient of a research grant from Johnson & Johnson, through Yale University, to support clinical trial data sharing; was a recipient of a research agreement, through Yale University, from the Shenzhen Center for Health Information for work to advance intelligent disease prevention and health promotion; collaborates with the National Center for Cardiovascular Diseases in Beijing; receives payment from the Arnold & Porter Law Firm for work related to the Sanofi clopidogrel litigation, from the Ben C. Martin Law Firm for work related to the Cook Celect IVC filter litigation, and from the Siegfried and Jensen Law Firm for work related to Vioxx litigation; chairs a Cardiac Scientific Advisory Board for

UnitedHealth; was a participant/participant representative of the IBM Watson Health Life Sciences Board; is a member of the Advisory Board for Element Science, the Advisory Board for Facebook, and the Physician Advisory Board for Aetna; and is the co-founder of HugoHealth, a personal health information platform, and co-founder of Refactor Health, an enterprise healthcare AI-augmented data management company.

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Tables and Figures

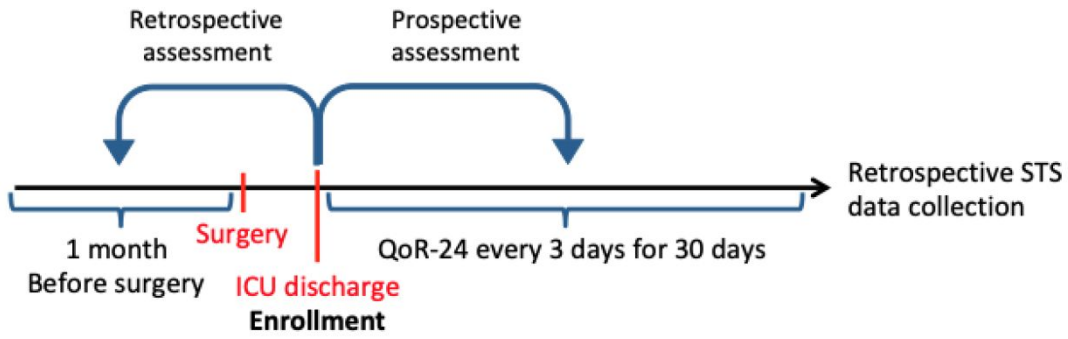
Table 1: Candidate predictors of recovery trajectory

Demographic	Comorbidity	Operative factors	Postoperative factors
Age	Diabetes	Cardiopulmonary bypass time	Length of ICU stay
Sex	Prior stroke	Cross clamp time	Length of hospital stay
Race	Congestive heart failure	Operation type	Surgical site infection
Insurance status	Chronic kidney disease	Non-elective status	Prolonged ventilation
BMI	Dialysis	Transfusion requirement	Transfusion requirement
	Prior MI	Minimally invasive approach	Stroke
	Prior cardiac surgery		Reoperation for any reasons
	Ejection fraction		Death
	Arrhythmias		Readmission
	Prior PCI		Pneumonia
	Cardiogenic shock		
	Hypertension		
	Dyslipidemia		
	Smoking status		
	Chronic lung disease		
	Endocarditis		
	Pneumonia		
	Peripheral artery disease		
	Immunocompromised		
	Mechanical circulatory support use		
	Valvular disease severity		

Table 2: 24 features of trajectory used in group-based trajectory model

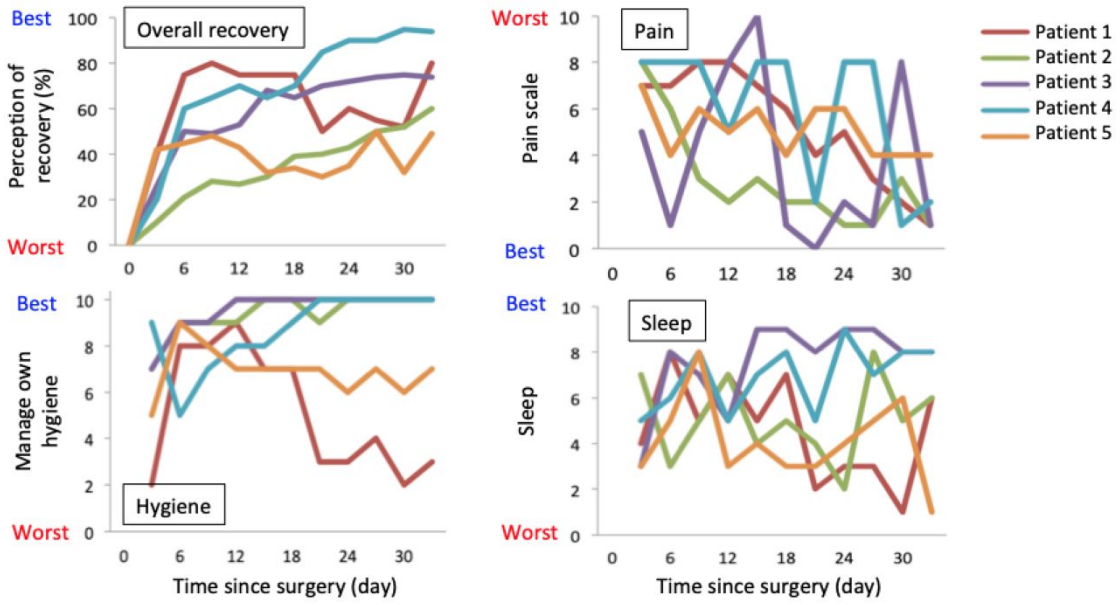
N	Features
1	Range
2	Mean-over-time
3	Standard deviation (SD)
4	Coefficient of variation (CV)
5	Change
6	Mean change per unit time
7	Change relative to the first score
8	Change relative to the mean over time
9	Slope of the linear model
10	Proportion of variance explained by the linear model
11	Maximum of the first differences
12	SD of the first differences
13	SD of the first differences per time unit
14	Mean of the absolute first differences
15	Maximum of the absolute first differences
16	Ratio of the maximum absolute difference to the mean-over-time
17	Ratio of the maximum absolute first difference to the slope
18	Ratio of the SD of the first differences to the slope
19	Mean of the second differences
20	Mean of the absolute second differences
21	Maximum of the absolute second differences
22	Ration of the maximum absolute second difference to the mean-over-time
23	Ratio of the maximum absolute second difference to mean absolute first difference
24	Ratio of the mean absolute second difference to the mean absolute first difference

Figure 1: Timing of patient enrollment and PROM administration

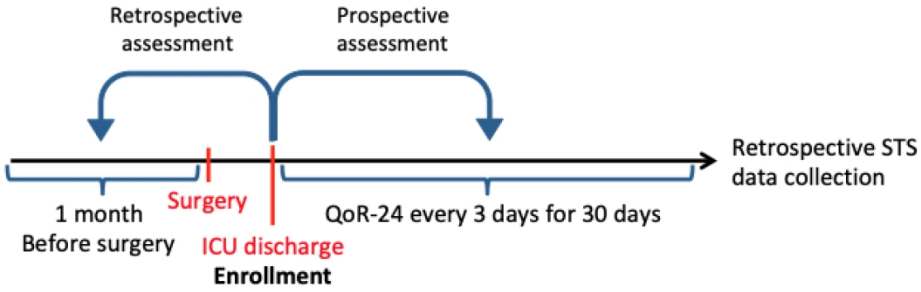


The figure shows the timing of patient enrollment and PROM administration over the clinical course. Baseline function is assessed by retrospectively asking the patient about their state of health during 1 month prior to the operation. 24-item Quality of Recovery questionnaire is administered every 3 days for 30 days following discharge from the intensive care unit.

Figure 2: Sample trajectories of recovery in 5 patients



The figures display trajectories of recovery in different domains in 5 patients. Each color corresponds to the same patient. Overall recovery is the patient's perception of overall recovery in 0 to 100% scale. Pain in surgical site is reported in 0 to 10 point scale, with 10 representing the worst pain. Being able to take care of own hygiene is reported in 0 to 10 point scale, with 10 representing complete independence in managing own hygiene. Patient's perception of sleep quality is reported in 0 to 10 point scale, with 10 being the best sleep.



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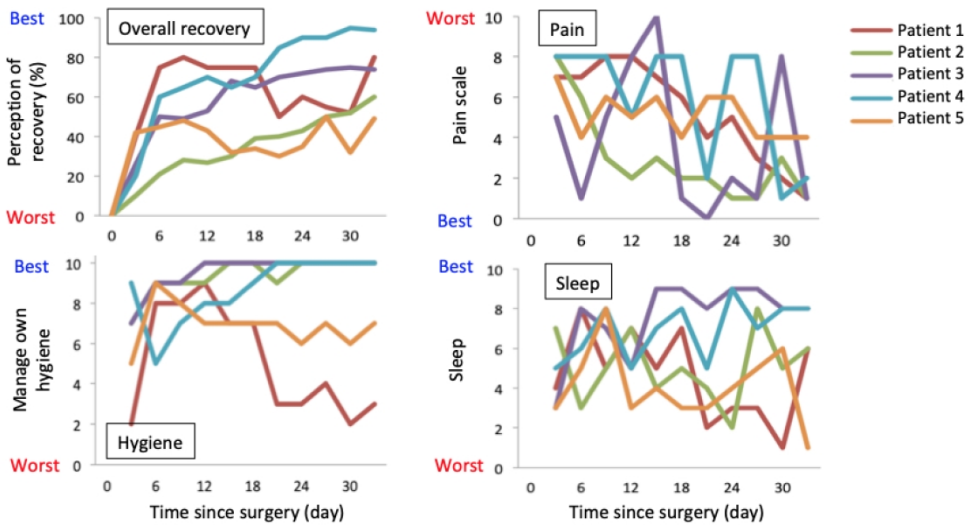

The figures display trajectories of recovery in different domains in 5 patients. Each color corresponds to the same patient. Overall recovery is the patient's perception of overall recovery in 0 to 100% scale. Pain in surgical site is reported in 0 to 10 point scale, with 10 representing the worst pain. Being able to take care of own hygiene is reported in 0 to 10 point scale, with 10 representing complete independence in managing own hygiene. Patient's perception of sleep quality is reported in 0 to 10 point scale, with 10 being the best sleep.

Modification of Quality of Recovery (QoR-24) Questionnaire

*Answered in visual analogue scale: 0 [none of the time] to 10 [all of the time]
'During the last 24 hours, I have been…'

Modified:

1. Able to breathe easily
2. Having normal bowel function
3. Able to enjoy food
4. Speaking normally
5. Able to think clearly
6. Able to remember things
7. Able to make decisions quickly
8. Able to take care of own hygiene
9. Able to write
10. Able to dress easily
11. Having pain in the surgical wound
12. Having nausea
13. Shivering or twitching
14. Feeling dizziness
15. Feeling restless
16. Feeling rested
17. Feeling depressed
18. Feeling lonely
19. Having anxiety
20. Sleeping well
21. Difficulties getting to sleep
22. What time did you fall asleep? What time did you wake up without going back to sleep?
23. How much do you think you have recovered? (0-100%)
24. Open ended question: 'Please describe what you are feeling (good and bad), what bothers you, and what has been helpful to your recovery'

HIC#:

COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT
200 FR. 4 (2016-2)
YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL

Study Title: Understanding Recovery After Cardiac Surgery

Principal Investigator: **Arnar Geirsson, MD**
Associate Professor of Surgery (Cardiac)
Yale School of Medicine
Best Contact Number: 475-201-8349

Funding Source: None

What is this study about?

You are invited to take part in a research study to understand how you recover after heart surgery. We use an app to centralize your healthcare information from multiple sources so it is easy for you and researchers to understand your health status and how you are doing after the surgery. You have been asked to take part in this study because you are planned to undergo or have undergone cardiac surgery at Yale New Haven Hospital (YNHH). If you agree to take part in this study, you will be asked to answer questionnaire through a mobile application platform called Hugo. Through Hugo, you will be asked to answer short questionnaires on your smartphone or email for up to 90 days.

This research study will examine the ability of the mobile health application, Hugo, to quickly and securely obtain healthcare information from multiple sources to monitor your outcomes after a procedure. Among the advantages of this system are that, with your permission, we will be able to access your records at multiple health systems. The risks for this study are similar to the risks associated with traditional research methods: you are sharing your personal health information with researchers and there is a risk to your privacy. However, researchers will only be able to view the heath data that you sync with the Hugo platform. There will also be audit logs of who has accessed your data via Hugo and other safeguards that do not exist with paper and faxed records. Researchers will also access your records within the YNHH electronic medical record (EMR) system. This access is to allow the researchers to confirm that your data has fully come into the Hugo, and that there are no major missing data points.

In order to decide whether you would like to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the study, which a member of the research team will discuss with you. This discussion should review all aspects of this research, especially the confidentiality risks of you having personal health information on your mobile device.

HIC#:

How is this study conducted?

Setup process

The initial set up process will take about 30 minutes in total and entails the following:

1. Using your own mobile device, a research associate (RA) will help you with the registration process for the mobile platform Hugo. Hugo will be downloaded from Google Play Store or Apple app store. Registration for Hugo will ask for basic information including first name, last name, email address, and to choose a password. You will then be prompted to accept standard terms and conditions and a privacy notice for the Hugo platform.

2. You will check your email and click the confirmation link to activate your new Hugo account.

3. The Hugo mobile application will prompt you to link your patient portal accounts by presenting a list of participating health systems. You can select the systems where you have received care and enter your patient portal credentials (all of these are password-protected).

4. You will be asked to agree to share data from Hugo. The medical record data being shared may include Medications, Problems, Allergies, Procedures, Encounters, Lab Results, Diagnoses, Vital Signs, Notes, and possibly other data that becomes available.

5. The questionnaires will be delivered to you via email or text, whichever you prefer.

6. We are asking your permission at the end of this consent form to give the researchers permission to see health information that you sync and share via the Hugo app along with your YNHH medical record.

Please note: The investigators of this study will not be watching or evaluating your symptoms as part of this study, including those that you reply to on the questionnaires. If at any point you begin to experience new symptoms or any medical issues arise, **please contact your doctor or call 911 immediately.**

Continuous Study Process

After the initial in office set up is complete you will be asked to answer questionnaires periodically until the study completion. If you have any questions or experience technical issues at any time, please reach out to the study team via email at **makoto.mori@yale.edu**:

- An RA will follow up in-person with you the day after you are transferred out of the intensive care unit to make sure your accounts and applications are working correctly, and to answer any additional questions you may have.

- Short questionnaires will be sent to your email or text, depending on your preference, initially every 3 days and eventually every 2 weeks up to 90 days following the surgery. This questionnaire should take around 4 minutes on average to complete. The RA may also call you or reach out via email to check in about any technical issues.

- You will receive reminder emails from the Hugo application 1 and 2 days after your questionnaires are sent, reminding you to complete them. These are automated messages and will be sent even if you have completed the surveys. You will also receive reminder messages to use & sync your provided devices.

New Information

You will be informed of anything that happens during the study that may cause you to re-think your decision to continue participation.

Risks and Inconveniences

The risk to patient privacy is that of any computer system that collects personally identifiable information or protected health information. The Hugo application, like many other personal health record applications, is not a considered a covered entity; this means that the HIPAA privacy rule does not apply to this platform. The Hugo platform takes all necessary precautions, including industry-standard encryption, to minimize privacy and security risks to personally identifiable information stored on behalf of study participants. Hugo makes publicly available its Security Statement (http://hugophr.com/security), its Privacy Notice (http://hugophr.com/privacy-notice), and Terms of Service (http://hugophr.com/terms-of-service/). Access to your YNHH medical record will only be within the Epic electronic medical records system; information will not be entered or removed.

You will be asked to volunteer your time to answer questions, and this is considered inconvenience.

There is no extra procedure or medications given for this study, and being on this study does not alter your care from the care you would receive had you not participated in this study.

Benefits

A possible benefit of this study is that you will have easy access to the information contained in your Yale New Haven Health and outside health records that may exist at other participating health systems. Seeing the summary of questionnaire response may also help you and the family to gain awareness and information regarding your health.

You will still be responsible for any costs associated with routine follow-ups or doctor visits, but there will be no additional follow-ups or doctor visits necessary for this study. You are responsible for data charges that may be incurred for utilizing online features of the Hugo when not connected to Wi-Fi.

HIC#:

Treatment Alternatives/Alternatives

If you decide not to participate in this study, you will still have access to your medical records as you would normally. The alternative is to not to participate.

Confidentiality and Privacy

The risk to patient privacy is no different with this study than it is with any other study that securely collects and appropriately stores personally identifiable information or protected health information. Any data transferred as part of the research protocol will be sent via secure and encrypted standard methods. Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission. When the results of the research are published, or discussed in conferences, no information will be included that would reveal your identity, unless your specific consent is obtained.

The information about your health that will be collected in this study includes:

- Electronic medical records from health systems that you import into the Hugo Health, including from Yale New Haven Health system
- Mobile questionnaires that you respond to
- Records about phone calls or emails made as part of this research
- Records about your clinical visits
- Pre-operative, intra-operative and discharge notes within Hugo or the YNHH Electronic Medical Record

Information about you and your health which might identify you may be used by or given to:

1. Representatives from Yale University, the Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
2. The Principal Investigator, along with other research staff and collaborators who are assisting with this study
3. Me2Health, the company that owns the mobile application for troubleshooting purposes
4. Health care providers who provide services to you in connection with this study

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine are required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and, therefore, may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential. In addition, note that the Hugo is not

required to comply with HIPAA but is required to maintain the confidentiality of your information as described in the privacy notice to be provided when you sign up for Hugo.

This authorization to use and disclose your health information collected during your participation in this study will never expire.

Voluntary Participation and Withdrawal

Participating in this study is voluntary and you are free to choose not to take part in this study. **Declining to participate or withdrawing will involve no penalty or loss of benefits to which you are otherwise entitled** (such as your health care outside the study, the payment for your health care, and your health care benefits). It will not harm your relationship with your own doctors or with Yale-New Haven Health or the care that you receive.

If you do become a study participant, you are free to stop and withdraw from this study at any time during its course.

To withdraw from the study, you can call a member of the research team to let them know that you would no longer like to take part. The telephone number to do this is 475-201-8349. You may also email the intent to makoto.mori@yale.edu.

When you withdraw from this study, no new health information identifying you will be gathered after that date. Information that has already been collected may still be used until the end of the research study, as necessary to ensure the integrity of the study and/or study oversight.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

HIC#:

Authorization and Permission

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

By signing this form, I give permission to the researchers to use [and give out] information about me for the purposes described in this form. By refusing to give permission, I understand that I will not be able to be in this research.

Print Name of Participant:_____

Signature:_____

Date:_____

If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919.

If you have further questions about this project or if you have a research-related problem, you may contact the Research Associate, Makoto Mori, at 475-201-8349 or at makoto.mori@yale.edu. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research participant, you may contact the Yale Human Investigation Committee at 203-785-4688.

Hugo recovery interview guide

Logistics:

- Email or call patient with response rate <50% to set up time or proceed directly with interview
- The interview likely takes 10-15 minutes
- Likely use Zoom to record interview

Before interview:

- Make clear that the intent is to learn from the interview and no hard feelings about not being able to complete the survey
- Make clear that honest opinion is most helpful for us to improve

Interview guide:

- What challenges or difficulties did you have in completing surveys?
- Did you know that surveys were emailed/texted to you? (How often do you check your email/texts?)
- What would have helped to engage you better? (better interface, better explanations of the study, why the study is important, other incentives, etc)
- Were there any technical issues with the surveys? (email/text didn't deliver, interface was not friendly, etc)
- Would reminder emails have been helpful?
- Were there too many questions?
- Did any questions feel irrelevant to you?

BMJ Open

Protocol for Project Recovery: Cardiac Surgery – A Single-center Cohort Study Leveraging Digital Platform to Characterize Longitudinal Patient-Reported Postoperative Recovery Patterns

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Cardiac surgery < SURGERY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS

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Title: Protocol for Project Recovery: Cardiac Surgery – A Single-center Cohort Study Leveraging Digital Platform to Characterize Longitudinal Patient-Reported Postoperative Recovery Patterns

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Key word: Cardiac surgery, postoperative recovery, patient-centered outcome, longitudinal, latent class

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Abstract (287/300)

Introduction

Improving postoperative patient recovery after cardiac surgery is a priority, but our current understanding of individual variations in recovery and factors associated with poor recovery is limited. We are using a health-information exchange platform to collect patient-reported outcome measures (PROMs) and wearable device data to phenotype recovery patterns in the 30-day period after cardiac surgery hospital discharge, to identify factors associated with these phenotypes and to investigate phenotype associations with clinical outcomes.

Methods and analysis

We designed a prospective cohort study to enroll 200 patients undergoing valve, coronary artery bypass graft, or aortic surgery at a tertiary center in the U.S. We are enrolling patients postoperatively after the intensive care unit (ICU) discharge, and delivering electronic surveys directly to patients every 3 days for 30 days after hospital discharge. We will conduct medical record reviews to collect patient demographics, comorbidity, operative details and hospital course using the Society of Thoracic Surgeons (STS) data definitions. We will use phone interview and medical record review data for adjudication of survival, readmission, and complications. We will apply group-based trajectory modeling to the time-series PROM and device data to classify patients into distinct categories of recovery trajectories. We will evaluate whether certain recovery pattern predicts death or hospital readmissions, as well as whether clinical

factors predict a patient having poor recovery trajectories. We will evaluate whether early recovery patterns predict the overall trajectory at the patient-level.

Ethics and dissemination

The Yale Institutional Review Board approved this study. Following the description of the study procedure, we obtain written informed consent from all study participants. The consent form states that all personal information, survey response, and any medical records are confidential, will not be shared, and are stored in an encrypted database. We plan to publish our study findings in peer-reviewed journals.

Strengths and limitations of this study

- This study will assess the patient perspective on recovery after cardiac surgery at a high frequency within the 30-day postoperative period with surveys and activity monitoring via a health information platform and wearable devices.
- Using longitudinal patient-reported outcomes measure (PROM) data, this study will define recovery patterns and factors associated with different recovery trajectories and guide the development interventions to improve recovery and support expansion of the study to additional sites.
- The study is single center and the sample size is limited.

Text (4081 words)

Background

Improving postoperative patient recovery is a priority. Readmission rates in the post-operative period are high. Moreover, in the United States, the expansion of episode-based payments and performance measures is increasing interest in the post-acute experience of patients[1, 2]. However, we generally lack systematically-collected information on the experience of patients in the post-acute period, as few studies rigorously collecting information using established patient-reported outcomes measures (PROMs). We have, for example, little information about the variation of the trajectories of recovery and the factors most strongly associated with better outcomes[3].

The assessment of the patient experience can provide important insights into the process of recovery that is not evident through clinical outcomes or intermittent clinical office visits. PROMs and wearable devices can provide complementary information by providing measurements of how the patient's experience and functional status change over time[4]. Current digital platforms allow us to efficiently collect PROMs and wearable-generated data at high frequencies and with little cost and burden. These automated data collection approaches may minimize the bias introduced by clinician-directed patient interviews[5]. Such a platform is highly suited to obtain repeated measures to characterize a time-dependent process such as recovery[6].

Cardiac surgery is an ideal area for the study of recovery. Many patients have good outcomes, but the limited existing evidence suggests a wide variation

in the post-operative experience of these patients[7]. However, these patients' experience has been poorly studied, as most studies of recovery simply assess deaths and complications.

Characterizing the recovery from the patient perspective is important for many reasons. First, shared decision-making and informed consent should be guided not only by the risk of mortality and complications but also by the recovery experience. Understanding variations in recovery could enable the early identification of people who are struggling and require additional attention. Recovery data from the patient perspective may enable remote monitoring after the procedure to selectively and preemptively intervene on those at high risk of poor recovery to improve outcomes. Characterization of recovery can also be used to identify patient, surgeon, procedural, and institutional factors that are associated with different patterns. With this information we can identify modifiable risk factors for poor recovery.

Thus, at this juncture, there are several notable gaps in knowledge. First, although recovery occurs over time, most studies of recovery included a small number of timepoints, and the recovery trajectory phenotypes remains poorly defined[3]. Cohort-level average of recovery trajectories is a common way of reporting[3] and can indicate how patients recover on average[7], but it obscures individual variation such as rapid early recovery, gradual recovery, or initial recovery followed by a decline. Second, we have limited understanding of how recovery trajectories vary by patient factors, operation types, center or surgeon

characteristics, procedural processes, and complications, which limit opportunities to identify high risk patients preemptively and intervene.

Accordingly, our overall objective is to characterize short-term trajectories of patient recovery after cardiac surgery using PROMs and wearable data. We are conducting a prospective study to characterize trajectories of postoperative recovery in multiple domains after cardiac surgery. The specific aims of this study are to: 1) leverage a digital data platform to collect PROM and wearable device data to bring forth the variable individual recovery trajectories, 2) describe distinct classes of recovery trajectories and clinical factors associated with the classes, and 3) to evaluate whether early postoperative recovery trajectory predicts later recovery trajectory. In addition, we will investigate optimal ways to manage missing data specific to these time-series data This study is a step toward using this approach to prospectively monitor and preemptively identify patients at risk of poor recovery and facilitate intervention to reduce the risk of adverse events. The purpose of this study protocol summary is to describes a new approach to studying recovery in order to address the knowledge gap as well as to prespecify our approach.

Methods

Design Overview

This is a prospective cohort study of patients who are undergoing valve, CABG, or aortic surgery at a tertiary center in the U.S. We chose the operations because they are the most common cardiac operations performed[8] while having

different patient and operative characteristics, such as the use of deep hypothermic circulatory arrest, to potentially provide insights into the recovery pattern associated with such variations. Subgroup analysis will be conducted to evaluate whether there is a distinct patient experience by operation types. We are enrolling patients postoperatively after ICU discharge in order to ensure clinical stability, and we electronically delivering surveys directly to patients every 3 days for 30 days after hospital discharge to study patient trajectories in multiple domains characterizing recovery. The closing phone interview after 30 days, electronic medical record review, and linkage to the Society of Thoracic Surgeons database are used to confirm survival, readmission, and complications. The closing interview asks about details of readmissions if they occurred, patients' overall satisfaction with the study, and whether their experience was well captured by the summary of their PROM data. We will apply group-based trajectory modeling to the longitudinal PROM data to identify distinct categories of recovery trajectories in a data-driven fashion. We also identify predictors of protracted recovery trajectory and evaluate whether early recovery patterns (<10 days) predict the overall trajectory (30 days) at the patient-level. The Yale Institutional Review Board approved this study (IRB # 2000025689).

Patient Population

This study began in January 2019 and is ongoing. The study is taking place at Yale-New Haven Hospital, a tertiary center in the United States, where over 1,100 cardiac surgeries are performed annually. Inclusion criteria are

patients of age 18 and older who are undergoing coronary artery bypass grafting (CABG), valve replacement or repair, or aortic operations. Exclusion criteria are those who undergo heart transplant, extracorporeal membrane oxygenation (ECMO), adult congenital operations, or ventricular assist device implantation, as these patient populations tend to have a longer course of intensive care unit stay[9], precluding the timely enrollment necessary to capture immediate postoperative recovery. We also excluded those who do not own a smartphone or a tablet or those who do not speak or read English, because the digital platform for PROM data collection relies on patients responding to surveys displayed on web browser via email or text, and the surveys were written in English language. We do not allow proxy for survey response and consequently excluded patients who were not able to respond by themselves as determined by the research assistant.

In order to provide the sense of patient selection resulting from these criteria, we will compare patient characteristics of those who were approached and were and were not able to participate in the study for any reasons.

Recruitment

Recruitment takes place postoperatively after the patient has left the intensive care unit (ICU) for the step-down or floor unit (Figure 1). We chose to enroll patients postoperatively, as opposed to preoperatively, because postoperative enrollment allows for enrollment of patients who undergo surgery under non-elective settings. Recruitment after transfer from the ICU setting

ensures clinical stability. A research assistant (RA) visits the patient and after confirming the patient is eligible to participate and following the description of the study procedure, obtains written informed consent (Supplementary Material S1) from all study participants. The informed consent form states that all personal information, survey response, and any medical records are confidential, will not be shared, and will be stored in an encrypted database.

We iteratively refined the enrollment process to minimize the onboarding time, which includes obtaining informed consent and signup process directed by the RA on a tablet device to enter patient name and email address or phone number and takes approximately 10-15 minutes.

PROM instrument and administration

We use 24-item quality of recovery (QoR-24) to characterize patients' postoperative recovery in various domains. The questionnaire consists of 24 items that were developed and validated in inpatient and outpatient surgical populations in terms of convergent validity with visual analogue scale, construct validity compared with length of hospital stay and sex-based difference, along with good internal consistency and test-retest reliability[10-13]. We chose QoR-24 among 5 other PROMs developed specifically to measure postoperative recovery. QoR-24 possessed many qualities advantageous for the purpose of our study, including the robust validation of psychometric property, extensive use cases in various surgical populations, ability for self-administration, and the ease of interpreting item-wise scores (Supplementary Table 1-2). The instrument was

previously adapted into a mobile format and was successfully used to administer the survey daily for 14 days[11, 12]. We added 3 items to QoR-24 to capture the self-reported time patients went to sleep, the time they awakened, and their global perception of how much they have 'recovered' in a 0-100% scale. The resulting 27-item questionnaire takes 2-4 minutes to complete, making its frequent administration feasible (Supplementary Material S2). Among the published studies in cardiac surgery, this study will have the highest number of PROM data points collected in the first postoperative month[3].

Digital data platform

We are delivering surveys on the day of enrollment and every 3 days for 30 days. This method provides detailed longitudinal data across multiple domains of recovery (Figure 2). To facilitate data organization and scheduled survey delivery, we use Hugo (Me2Health, LLC, Guilford CT, USA) a patient-centered health data sharing platform, which has a customizable survey delivery function and reminder feature to facilitate data collection. Hugo platform allows for automated delivery of surveys without researchers having to directly contact patients, which facilitates high-frequency data collection. Additionally, it imports data from connected wearable devices to facilitate centralization of patient health data. The patients retain access to their own data in a cloud-based account. Hugo does not fall under the Covered Entity that Health Insurance Portability and Accountability Act (HIPAA) regulates, but employs all the security measures that would be required by HIPAA had it been a Covered Entity.

Identifying common reasons for low response rate

Recognizing that the survey response will be incomplete for some participants, we have conducted a phone interview with the first 22 patients to learn reasons for low responses and identify strategies to minimize the barriers toward survey response for subsequent participants. In the first 22 patients, we identified 5 with response rate of <50% and conducted recorded phone interviews. Our interview guide (Supplementary Material S3) contained questions to elucidate technical barriers, differential preferences for engagement, and or any other issues precluding survey completion. We also asked whether the length of the questionnaire or types of questions asked made it difficult to complete the survey. Two members of the research team (CB and MM) evaluated the interview recordings to identify common reasons for low response rate. This suggested the potential importance of reminder to maintain patient engagement. We modified the protocol to contact all participants approximately 10 days after enrollment. We will continue to conduct this phone interview for patients with low response rate and describe engagement and barriers to participation in the final cohort. Survey response rate and time spent to complete each survey will be reported descriptively to evaluate the degree of patient engagement. This approach likely allows us to identify patients who either did not respond or completed the survey in an unrealistically short time that may not represent a meaningful response.

Additional clinical data and adjudication of hospitalization and survival

Additionally, we are using the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database data specifications to retrospectively collect clinically relevant data in this patient population. Pre-specified candidate predictors in this database will be used to identify clinical predictors of recovery trajectories (Table 1). The STS database contains patient demographics, comorbidities, presenting clinical status, operative details, and postoperative mortality and morbidity up to 30 days after the time of operation[14]. These data are routinely collected at Yale New Haven Hospital. At our program, 30-day mortality rates for isolated aortic valve replacement and isolated CABG are stable around 1%, with 30-day readmission rate of about 10%, which are slightly lower than the national average.

We will determine mortality and hospital readmissions by several approaches: review of hospital records, review of cardiac surgery clinic notes, and conducting closing phone interviews with the patient or contact person previously identified.

Patient Involvement

Prior to launching the study, we interviewed 5 patients both in pre and postoperative settings to evaluate whether the frequency of survey delivery and PROM instrument were likely to adequately capture their experience of recovery. All patients agreed that the frequency of questionnaire administration and the length of the PROM instrument were reasonable and provided face validity that

the questionnaire captured aspects of recovery that were important to the patients. Additionally, this article is authored with a patient (LG) who participated in the study to reflect his perspective on the study design and experience in responding to the surveys.

Sample size

The study sample target is 200 patients. Adequate sample size for studies using group-based trajectory modeling depends on the dataset's representativeness of the population of interest[15]. Therefore, the concept of statistical power traditionally used for sample size calculation does not apply to latent class analyses. We may generate a larger simulation dataset from the measured patient trajectory data to perform a split-sample testing, evaluating whether trajectories generated from the derivation sample would allow for satisfactory categorization of the testing dataset. Additionally, the study setting is scalable to increase the sample size by increasing the enrollment period, should a larger sample size become necessary.

Analytical approach – group-based trajectory modeling

The resulting dataset is a complex time-series data, with each patient having 10 data points (one every three days) at different postoperative times for each item. A practical approach to dimension reduction is group-based trajectory

modeling, which is a type of latent class analysis that groups similar patient trajectories according to a number of features derived from the time-series data[16, 17]. This approach allows for dimension reduction of the complex time-series data into several distinct classes of recovery trajectories. These trajectories can be labeled according to the observed clinical phenotype of trajectories, for example 'fast recovery,' 'average recovery,' or 'protracted recovery,'. This data-driven categorization enables additional regression modeling to identify predictors of patients belonging to a certain class of recovery path.

The dataset will be classified into distinct categories of trajectories at domain level, using group-based trajectory modeling[16, 17]. Traj package on R[18] or Proc Traj package on SAS[15], performs trajectory modeling by first extracting 24 features of patient-level trajectory, selecting a subset of features that describes the overall trajectory, and identifying optimal number of classes to group the trajectories based on the longitudinal k-means method. The 24 features include range, mean change per unit time, and slope of the linear model (Table 2), which have been demonstrated to discriminate between stable-unstable, increasing-

decreasing, linear-nonlinear, and monotonic-nonmonotonic patterns of trajectories[18]. K-means method partitions the time-series data into k groups such that the mean squared error distance of each data point from the assigned cluster is minimized[19]. The optimal number of clusters is determined by the minimization of Bayesian information criterion, which signifies the balance between model's complexity and the ability to describe the dataset. This process yields distinct classes of patient trajectories in a data-driven fashion. Trajectories will be identified separately for the 5 domains and 1 global recovery measure.

With the characterization of trajectories, we will then fit multinomial logistic regression models using clinical variables outlined in Table 1, including patient demographics, comorbidity, and postoperative event such as complications and ICU readmissions, to identify predictors of patients belonging to each trajectory class. As some variables interact with each other, such as history of chronic lung disease increasing the risk of postoperative pneumonia, which likely impacts the recovery experience, we plan to stratify the cohort with and without the index complications defined by the STS (prolonged ventilation, renal failure, sternal wound infection, pneumonia, stroke, all-cause reoperation). Further analyses on interaction and mediation effects likely requires a larger sample size and are of interest in the future.

Analytical approach – missing data

Because missing data are inevitable in longitudinal PROMs, there is a need employ an appropriate handling of missing data. Multiple imputation prior to latent class analysis may yield a less biased estimate of the resulting trajectories. An alternative approach used in group-based trajectory models assumes the data are missing at random (MAR) and generates the maximum likelihood of the model parameters[20]. MAR is valid when the response attrition is independent of the group membership. However, patient attrition is oftentimes dependent on clinical characteristics and likely related to the class of trajectory itself. An extension of the model allows for modeling of attrition across trajectory groups[21], permitting dropout probability to vary as a function of covariates or observed outcomes prior to dropout and yields a more robust estimate of the probability of group membership. As such, we will perform sensitivity analysis to compare the trajectories generated via raw data vs. data preprocessed with multiple imputation vs. trajectories generated via trajectory model accounting for response attrition.

Results

Between January and May 2019, we have enrolled 22 patients who completed the 30-day follow-up. In this cohort, median age was 58.5 years (interquartile range 53.5-67.0) and 7 (32%) were women. There were 9 (41%) mitral valve repair cases and 6 isolated or concomitant CABG (27%).

Barriers to completing surveys

Of the 22 patients enrolled, 3 (14%) did not complete any surveys, 19 (86%) completed at least 3 surveys, and 17 patients (77%) completed at least 6 of 11 delivered surveys (>50% of delivered surveys). Of the 5 patients who completed less than half of the surveys, we successfully contacted 4, and 1 could not be reached after 5 attempts. All 4 reported that the major barriers precluding survey completion were their clinical conditions: 2 described readmissions as an overwhelming event that made them feel continuing survey participation challenging, and 2 described not feeling well in general, which precluded participation. All 4 patients noted that text or email reminders might have been helpful to sustain participation. Based on these responses, we modified the protocol to contact all participants approximately 10 days after enrollment to improve engagement and resolve any patient-specific issues in completing the surveys.

Clinical outcomes

There were no deaths during follow-up. Two (9%) patients experienced at least 1 hospital readmission. Figure 2 depicts the breadth in recovery trajectories in pain, sleep, ability to take care of own hygiene, and perception of overall recovery in five patients with complete response.

Discussion

This study will provide time-series data on short-term recovery after cardiac surgery using PROM instruments complemented by clinical records obtained via the STS database and electronic health records. This study will provide one of the highest density of postoperative PROM data in existing cardiac surgery literature[3], and it will characterize the variability in individual recovery processes with a high temporal resolution. This study will be important in closing knowledge gaps around patient-level variations in trajectories because prior studies have mostly focused on changes in PROM scores at a limited number of time points[3] or reporting group-level aggregate of longitudinal recovery data[7, 22]. Because recovery is an individual, variable, and time-dependent process, we designed our data collection and analytical approach to capture such features important to recovery.

This study has the potential to make a variety of contributions toward improving post-acute phase of care. First, we will be able to develop a preliminary nomogram of postoperative recovery for each domain and overall perception of recovery, which would be instrumental for patients and clinicians to gauge the breadth of possible recovery trajectories to facilitate informed shared decision-making. Second, identifying predictors of accelerated or protracted recovery, as classified by group-based trajectory model, may allow for individualized prediction of the postoperative recovery course to better inform the patients and family members. Third, early detection of recovery signals related to adverse events, such as mortality and readmission, may eventually facilitate preemptive intervention and focused monitoring of patients at an elevated risk for

such events. Our design of the longitudinal PROM data collection allows for incremental update of such prediction as patients progress through the phase of recovery.

There are many challenges to the successful acquisition of patient measurements during recovery: efficient administration of PROMs in a way that does not require prohibitive amount of resources, minimizing selection bias originating from barriers to survey completion, handling of missing data that inevitably occurs in PROMs, and summarizing the complex data in a way that is interpretable to surgeons and patients[23]. Additionally, the use of wearables and device data require active patient participation in periodically charging the device, wearing them correctly, and reliably syncing the device to the server for data uploads. Moreover, there is a need to provide value to the patients for providing their recovery profile, such as giving them access to their health data in a meaningful way.

The resulting data collection, analytical, and output platforms have the potential of being implemented in the clinical setting where an integration of incrementally increasing PROM and clinical data provides the near-real time estimate of individual patient risk of adverse post-operative events. Such a model may allow for triggering of preemptive clinical intervention. An output may assimilate a form of clinical dashboard within the electronic health record system, which may be monitored at a centralized location where a trained clinician reviews high-risk cases filtered by the algorithm to further evaluate whether the

patient condition warrants an intervention. Together, this workflow has a tremendous potential to improve post-acute phase of care following surgery.

Lessons Learned from the initial experience

Through this first group of enrolled patients, we learned that most of the patients approached were willing to participate and consented to the study. By streamlining the enrollment process, the enrollment time shortened from over 1 hour on the first patient to approximately 10-15 minutes for the current enrollment. The overall response rate is acceptable, with 77% of the participants completing more than half of the delivered surveys independently without any intervention by researchers. Challenging recovery course, including readmissions may have interfered with patient engagement. While this would have resulted in an underrepresentation of those with protracted recovery or with complications, our preliminary data show we were able to capture variations in the trajectories of recovery.

To sustain patient engagement through challenging recovery course, we implemented a protocol for a research assistant to call the patient around 10 days after enrollment to troubleshoot any issues and reemphasize the importance of their participation. By the protocol, research assistant making this call does not act in clinical capacity and does not provide clinical evaluation or advise, which is an important boundary for this call to not act as an intervention to alter recovery course. We believe that once the survey becomes part of clinical

workflow with clinicians monitoring and responding to the PROM response, patient response rate would improve further.

We modified the enrollment protocol to reduce the enrollment time, because to some patients, the complexity and prolonged time spent for enrollment discouraged signups. Initial protocol for enrollment required patients to download an app and register. This resulted in a wide range of time spent for enrollment between 15 minutes and 90 minutes, with longer enrollment owing to technical challenges. These challenges include patients forgetting the password for app download, having to reset the password, and not having immediate email access to check account confirmation emails. Because our cardiac surgery patient population tended to be older, these technical challenges may have been pronounced. By not including the app download and allowing for the research assistant to enroll the patient via an online form with their permission, the enrollment time shortened significantly to 10-15 minutes.

Examining the initial individual data on recovery, there were wide variations in the trajectories of recovery even among only 5 patients. The variation suggests that the instrument we used was sensitive to capturing such differences. We also noted variations in improvement over time across different domains of recovery, where overall perception of recovery seemed to have a steady improvement pattern, while pain varied between consecutive measurements in some patients.

Limitations

There are several limitations to this study. First, the single-center tertiary care setting limits the sample size and applicability of the findings to patients cared for in different settings. A multi-center study following the current study would address this limitation and evaluate whether the findings at our center are comparable to findings in other centers. Additionally, group-based trajectory modeling will classify patients into distinct trajectories based on similar recovery patterns, and this analytical approach may allow for generalization of the variations in the trajectories as long as our sample represents the breadth of the possible variation in recovery.

Another limitation is the exclusion of patients who cannot participate for various reasons. The use of digital platform is advantageous in reducing the resource intensity for data collection, but leads to exclusion of patients who do not own mobile devices, which likely affects older patients disproportionately. As the number of adults using mobile devices is increasing[24], we believe this will become less of a limitation over time. Initiating this study now despite this limitation is important to establish a platform that may become the standard of postoperative care when the vast majority of patient population own digital devices in a predictably near future. Those who cannot participate due to lack of interest or technological barrier represent an important population that may be distinct in characteristics and risk profiles. While acknowledging the selection bias originating from this inclusion threshold, we believe there is a need to initiate collection of patient-centered outcome measures in the proposed approach, in order to further engage hospitals and programs for a broader implementation of

this approach in the context of extremely limited evidence base. We plan on minimizing the non-participation for the lack of interest by intermittent phone check-ins to sustain interests and identify barriers to inform strategies to increase engagement. While recognizing that clinical implemenation of this protocol would preclude the use of incentives, in following studies, we may consider other forms of incentives to participate, if this population is indeed distinct and large in proportion. Additionally, when the PROM data are integrated into routine clinical care, patient engagement will likely increase substantially because they will be more inspired to share these data if they are used by their clinicians.

Finally, postoperative enrollment and retrospective assessment of preoperative health status, as opposed to preoperative enrollment, may introduce recall bias. We decided on postoperative enrollment, because preoperative enrollment precluded standardized enrollment of patients operated on under non-elective settings. Given the retrospective assessment of baseline health status takes place on the first postoperative survey, we believe the recall bias is minimized owing to the temporal proximity.

Conclusion

This study will generate highly granular, longitudinal PROM data to characterize individual trajectories of patient recovery after cardiac surgery. Digital data sharing platforms promise to minimize the patient and researcher burden in administering and completing PROMs, allowing for characterization of granular progression of patients' state of health over time in the postoperative

period. Implementation of such study is complex but feasible, and it will serve as an important platform to facilitate clinical use of PROM data to improve the overall patient recovery.

Authors contributions

MM, HMK, SD, and AG developed the study and research question. MM and HMK developed analytical strategy with inputs from BJM, GCL, and YZ. SIC, CB, and ES guided refining the enrollment strategy and interpretation of the phone interview responses. LAG provided patient perspective on the study protocol and interpretation of the preliminary results. All authors developed and approved the final manuscript before submission.

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Competing interest statement

Dr. Chaudhry is a paid reviewer for the CVS Caremark State of CT Clinical Pharmacy Program.

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Dr. Krumholz works under contract with the Centers for Medicare & Medicaid Services to support quality measurement programs; was a recipient of a research grant, through Yale, from Medtronic and the U.S. Food and Drug Administration to develop methods for post-market surveillance of medical devices; was a recipient of a research grant with Medtronic and is the recipient of a research grant from Johnson & Johnson, through Yale University, to support clinical trial data sharing; was a recipient of a research agreement, through Yale University, from the Shenzhen Center for Health Information for work to advance intelligent disease prevention and health promotion; collaborates with the National Center for Cardiovascular Diseases in Beijing; receives payment from the Arnold & Porter Law Firm for work related to the Sanofi clopidogrel litigation, from the Ben C. Martin Law Firm for work related to the Cook Celect IVC filter litigation, and from the Siegfried and Jensen Law Firm for work related to Vioxx litigation; chairs a Cardiac Scientific Advisory Board for UnitedHealth; was a participant/participant representative of the IBM Watson Health Life Sciences Board; is a member of the Advisory Board for Element Science, the Advisory Board for Facebook, and the Physician Advisory Board for Aetna; and is the co-founder of HugoHealth, a personal health information platform, and co-founder of

Refactor Health, an enterprise healthcare AI-augmented data management company.

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Tables and Figures

Table 1: Candidate predictors of recovery trajectory

Demographic	Comorbidity	Operative factors	Postoperative factors
Age	Diabetes	Cardiopulmonary bypass time	Length of ICU stay
Sex	Prior stroke	Cross clamp time	Length of hospital stay
Race	Congestive heart failure	Operation type	Surgical site infection
Insurance status	Chronic kidney disease	Non-elective status	Prolonged ventilation
BMI	Dialysis	Transfusion requirement	Transfusion requirement
	Prior MI	Minimally invasive approach	Stroke
	Prior cardiac surgery		Reoperation for any reasons
	Ejection fraction		Death
	Arrhythmias		Readmission
	Prior PCI		Pneumonia
	Cardiogenic shock		
	Hypertension		
	Dyslipidemia		
	Smoking status		
	Chronic lung disease		
	Endocarditis		
	Pneumonia		
	Peripheral artery disease		
	Immunocompromised		
	Mechanical circulatory support use		
	Valvular disease severity		

Table 2: 24 features of trajectory used in group-based trajectory model

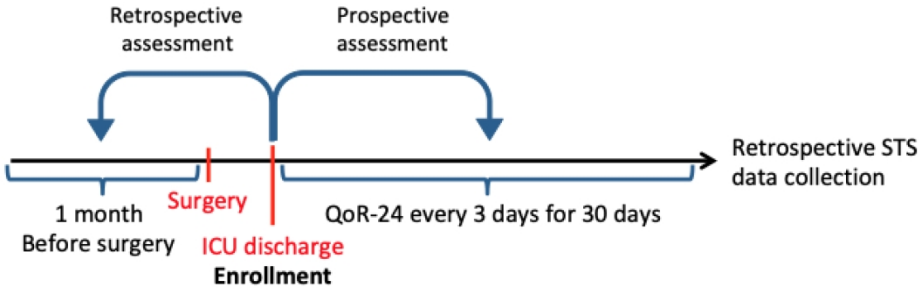
N	Features
1	Range
2	Mean-over-time
3	Standard deviation (SD)
4	Coefficient of variation (CV)
5	Change
6	Mean change per unit time
7	Change relative to the first score
8	Change relative to the mean over time
9	Slope of the linear model
10	Proportion of variance explained by the linear model
11	Maximum of the first differences
12	SD of the first differences
13	SD of the first differences per time unit
14	Mean of the absolute first differences
15	Maximum of the absolute first differences
16	Ratio of the maximum absolute difference to the mean-over-time
17	Ratio of the maximum absolute first difference to the slope
18	Ratio of the SD of the first differences to the slope
19	Mean of the second differences
20	Mean of the absolute second differences
21	Maximum of the absolute second differences
22	Ration of the maximum absolute second difference to the mean-over-time
23	Ratio of the maximum absolute second difference to mean absolute first difference
24	Ratio of the mean absolute second difference to the mean absolute first difference

Figure 1: Timing of patient enrollment and PROM administration

The figure shows the timing of patient enrollment and PROM administration over the clinical course. Baseline function is assessed by retrospectively asking the patient about their state of health during 1 month prior to the operation. 24-item Quality of Recovery questionnaire is administered every 3 days for 30 days following discharge from the intensive care unit.

Figure 2: Sample trajectories of recovery in 5 patients

The figures display trajectories of recovery in different domains in 5 patients. Each color corresponds to the same patient. Overall recovery is the patient's perception of overall recovery in 0 to 100% scale. Pain in surgical site is reported in 0 to 10 point scale, with 10 representing the worst pain. Being able to take care of own hygiene is reported in 0 to 10 point scale, with 10 representing complete independence in managing own hygiene. Patient's perception of sleep quality is reported in 0 to 10 point scale, with 10 being the best sleep.



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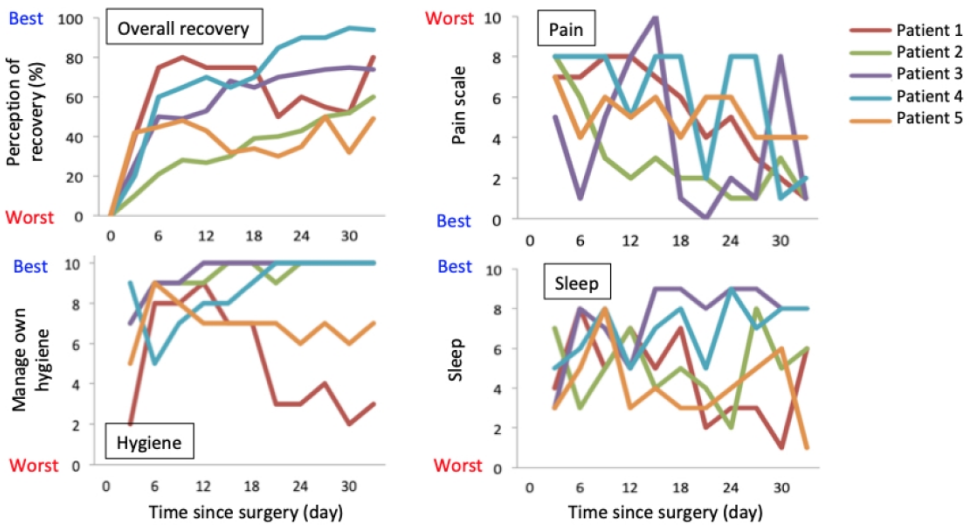

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HIC#:

COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT
200 FR. 4 (2016-2)
YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL

Study Title: Understanding Recovery After Cardiac Surgery

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Best Contact Number: 475-201-8349

Funding Source: None

What is this study about?

You are invited to take part in a research study to understand how you recover after heart surgery. We use an app to centralize your healthcare information from multiple sources so it is easy for you and researchers to understand your health status and how you are doing after the surgery. You have been asked to take part in this study because you are planned to undergo or have undergone cardiac surgery at Yale New Haven Hospital (YNHH). If you agree to take part in this study, you will be asked to answer questionnaire through a mobile application platform called Hugo. Through Hugo, you will be asked to answer short questionnaires on your smartphone or email for up to 90 days.

This research study will examine the ability of the mobile health application, Hugo, to quickly and securely obtain healthcare information from multiple sources to monitor your outcomes after a procedure. Among the advantages of this system are that, with your permission, we will be able to access your records at multiple health systems. The risks for this study are similar to the risks associated with traditional research methods: you are sharing your personal health information with researchers and there is a risk to your privacy. However, researchers will only be able to view the heath data that you sync with the Hugo platform. There will also be audit logs of who has accessed your data via Hugo and other safeguards that do not exist with paper and faxed records. Researchers will also access your records within the YNHH electronic medical record (EMR) system. This access is to allow the researchers to confirm that your data has fully come into the Hugo, and that there are no major missing data points.

In order to decide whether you would like to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the study, which a member of the research team will discuss with you. This discussion should review all aspects of this research, especially the confidentiality risks of you having personal health information on your mobile device.

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How is this study conducted?

Setup process

The initial set up process will take about 30 minutes in total and entails the following:

1. Using your own mobile device, a research associate (RA) will help you with the registration process for the mobile platform Hugo. Hugo will be downloaded from Google Play Store or Apple app store. Registration for Hugo will ask for basic information including first name, last name, email address, and to choose a password. You will then be prompted to accept standard terms and conditions and a privacy notice for the Hugo platform.

2. You will check your email and click the confirmation link to activate your new Hugo account.

3. The Hugo mobile application will prompt you to link your patient portal accounts by presenting a list of participating health systems. You can select the systems where you have received care and enter your patient portal credentials (all of these are password-protected).

4. You will be asked to agree to share data from Hugo. The medical record data being shared may include Medications, Problems, Allergies, Procedures, Encounters, Lab Results, Diagnoses, Vital Signs, Notes, and possibly other data that becomes available.

5. The questionnaires will be delivered to you via email or text, whichever you prefer.

6. We are asking your permission at the end of this consent form to give the researchers permission to see health information that you sync and share via the Hugo app along with your YNHH medical record.

Please note: The investigators of this study will not be watching or evaluating your symptoms as part of this study, including those that you reply to on the questionnaires. If at any point you begin to experience new symptoms or any medical issues arise, **please contact your doctor or call 911 immediately.**

Continuous Study Process

After the initial in office set up is complete you will be asked to answer questionnaires periodically until the study completion. If you have any questions or experience technical issues at any time, please reach out to the study team via email at **makoto.mori@yale.edu**:

- An RA will follow up in-person with you the day after you are transferred out of the intensive care unit to make sure your accounts and applications are working correctly, and to answer any additional questions you may have.

- Short questionnaires will be sent to your email or text, depending on your preference, initially every 3 days and eventually every 2 weeks up to 90 days following the surgery. This questionnaire should take around 4 minutes on average to complete. The RA may also call you or reach out via email to check in about any technical issues.

- You will receive reminder emails from the Hugo application 1 and 2 days after your questionnaires are sent, reminding you to complete them. These are automated messages and will be sent even if you have completed the surveys. You will also receive reminder messages to use & sync your provided devices.

New Information

You will be informed of anything that happens during the study that may cause you to re-think your decision to continue participation.

Risks and Inconveniences

The risk to patient privacy is that of any computer system that collects personally identifiable information or protected health information. The Hugo application, like many other personal health record applications, is not a considered a covered entity; this means that the HIPAA privacy rule does not apply to this platform. The Hugo platform takes all necessary precautions, including industry-standard encryption, to minimize privacy and security risks to personally identifiable information stored on behalf of study participants. Hugo makes publicly available its Security Statement (http://hugophr.com/security), its Privacy Notice (http://hugophr.com/privacy-notice), and Terms of Service (http://hugophr.com/terms-of-service/). Access to your YNHH medical record will only be within the Epic electronic medical records system; information will not be entered or removed.

You will be asked to volunteer your time to answer questions, and this is considered inconvenience.

There is no extra procedure or medications given for this study, and being on this study does not alter your care from the care you would receive had you not participated in this study.

Benefits

A possible benefit of this study is that you will have easy access to the information contained in your Yale New Haven Health and outside health records that may exist at other participating health systems. Seeing the summary of questionnaire response may also help you and the family to gain awareness and information regarding your health.

You will still be responsible for any costs associated with routine follow-ups or doctor visits, but there will be no additional follow-ups or doctor visits necessary for this study. You are responsible for data charges that may be incurred for utilizing online features of the Hugo when not connected to Wi-Fi.

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Treatment Alternatives/Alternatives

If you decide not to participate in this study, you will still have access to your medical records as you would normally. The alternative is to not to participate.

Confidentiality and Privacy

The risk to patient privacy is no different with this study than it is with any other study that securely collects and appropriately stores personally identifiable information or protected health information. Any data transferred as part of the research protocol will be sent via secure and encrypted standard methods. Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission. When the results of the research are published, or discussed in conferences, no information will be included that would reveal your identity, unless your specific consent is obtained.

The information about your health that will be collected in this study includes:

- Electronic medical records from health systems that you import into the Hugo Health, including from Yale New Haven Health system
- Mobile questionnaires that you respond to
- Records about phone calls or emails made as part of this research
- Records about your clinical visits
- Pre-operative, intra-operative and discharge notes within Hugo or the YNHH Electronic Medical Record

Information about you and your health which might identify you may be used by or given to:

1. Representatives from Yale University, the Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
2. The Principal Investigator, along with other research staff and collaborators who are assisting with this study
3. Me2Health, the company that owns the mobile application for troubleshooting purposes
4. Health care providers who provide services to you in connection with this study

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine are required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and, therefore, may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential. In addition, note that the Hugo is not

required to comply with HIPAA but is required to maintain the confidentiality of your information as described in the privacy notice to be provided when you sign up for Hugo.

This authorization to use and disclose your health information collected during your participation in this study will never expire.

Voluntary Participation and Withdrawal

Participating in this study is voluntary and you are free to choose not to take part in this study. **Declining to participate or withdrawing will involve no penalty or loss of benefits to which you are otherwise entitled** (such as your health care outside the study, the payment for your health care, and your health care benefits). It will not harm your relationship with your own doctors or with Yale-New Haven Health or the care that you receive.

If you do become a study participant, you are free to stop and withdraw from this study at any time during its course.

To withdraw from the study, you can call a member of the research team to let them know that you would no longer like to take part. The telephone number to do this is 475-201-8349. You may also email the intent to makoto.mori@yale.edu.

When you withdraw from this study, no new health information identifying you will be gathered after that date. Information that has already been collected may still be used until the end of the research study, as necessary to ensure the integrity of the study and/or study oversight.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

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Authorization and Permission

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

By signing this form, I give permission to the researchers to use [and give out] information about me for the purposes described in this form. By refusing to give permission, I understand that I will not be able to be in this research.

Print Name of Participant:_____

Signature:_____

Date:_____

If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919.

If you have further questions about this project or if you have a research-related problem, you may contact the Research Associate, Makoto Mori, at 475-201-8349 or at makoto.mori@yale.edu. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research participant, you may contact the Yale Human Investigation Committee at 203-785-4688.

Modification of Quality of Recovery (QoR-24) Questionnaire

*Answered in visual analogue scale: 0 [none of the time] to 10 [all of the time]
'During the last 24 hours, I have been…'

Modified:

1. Able to breathe easily
2. Having normal bowel function
3. Able to enjoy food
4. Speaking normally
5. Able to think clearly
6. Able to remember things
7. Able to make decisions quickly
8. Able to take care of own hygiene
9. Able to write
10. Able to dress easily
11. Having pain in the surgical wound
12. Having nausea
13. Shivering or twitching
14. Feeling dizziness
15. Feeling restless
16. Feeling rested
17. Feeling depressed
18. Feeling lonely
19. Having anxiety
20. Sleeping well
21. Difficulties getting to sleep
22. What time did you fall asleep? What time did you wake up without going back to sleep?
23. How much do you think you have recovered? (0-100%)
24. Open ended question: 'Please describe what you are feeling (good and bad), what bothers you, and what has been helpful to your recovery'

Hugo recovery interview guide

Logistics:

- Email or call patient with response rate <50% to set up time or proceed directly with interview
- The interview likely takes 10-15 minutes
- Likely use Zoom to record interview

Before interview:

- Make clear that the intent is to learn from the interview and no hard feelings about not being able to complete the survey
- Make clear that honest opinion is most helpful for us to improve

Interview guide:

- What challenges or difficulties did you have in completing surveys?
- Did you know that surveys were emailed/texted to you? (How often do you check your email/texts?)
- What would have helped to engage you better? (better interface, better explanations of the study, why the study is important, other incentives, etc)
- Were there any technical issues with the surveys? (email/text didn't deliver, interface was not friendly, etc)
- Would reminder emails have been helpful?
- Were there too many questions?
- Did any questions feel irrelevant to you?

Supplementary Table 1: Candidate instruments to measure postoperative recovery

Tool	Assessed interval	Population	Number of questions	Published Year	Self-administer?	Surgery type	Derivation size
Postdischarge Surgical Recovery (PSR)	Day 4	Ambulatory	18	2000	Yes	Laparoscopic cholecystectomy, hernia repair	163
Quality of Recovery (QoR)	24 h	Inpatient and ambulatory, adult	24	2000	Yes	Surgery with general anesthesia	160
Surgical Recovery Index (SRI)	Day 7, 14, 21 and 28	Inpatient	24	2004	Yes	Laparoscopic and open surgery (not specified further)	149
Functional Recovery Index (FRI)	Baseline, day 1, 3, 5 and 7	Ambulatory, adult	14	2009	Yes	Various ambulatory	324
Postoperative Quality of Recovery Score (PQRS)	Baseline, 15 and 45 min, day 1 and 3, 3 months	Inpatient, pediatrics + adults	18	2010	No	Elective surgery with general anesthesia	701
Surgical Recovery Scale (SRS)	Baseline, day 3, 7, 30 and 60	Inpatient, adult	13	2011	Yes	Elective colonic resection	150

Supplementary Table 2: Validity tested and domains assessed in instruments to measure postoperative recovery

Tool	Validity assessed	Cognitive	Nociceptive/pain	Emotive	Sleep	Activity of daily living	Physiologic	Reasons not chosen
Postdischarge Surgical Recovery (PSR)	Construct, convergent validity			Y		Y		Low number of domains
Quality of Recovery (QoR)	Convergent, construct, test-retest reliability, responsiveness		Y	Y	Y	Y	Y	-
Surgical Recovery Index (SRI)	Convergent validity		Y			Y		Low number of domains
Functional Recovery Index (FRI)	Discriminant validity		Y			Y		Low number of domains
Postoperative Quality of Recovery Score (PQRS)	Face validity	Y	Y	Y		Y	Y	Requires administer
Surgical Recovery Scale (SRS)	None			Y		Y		Low number of domains